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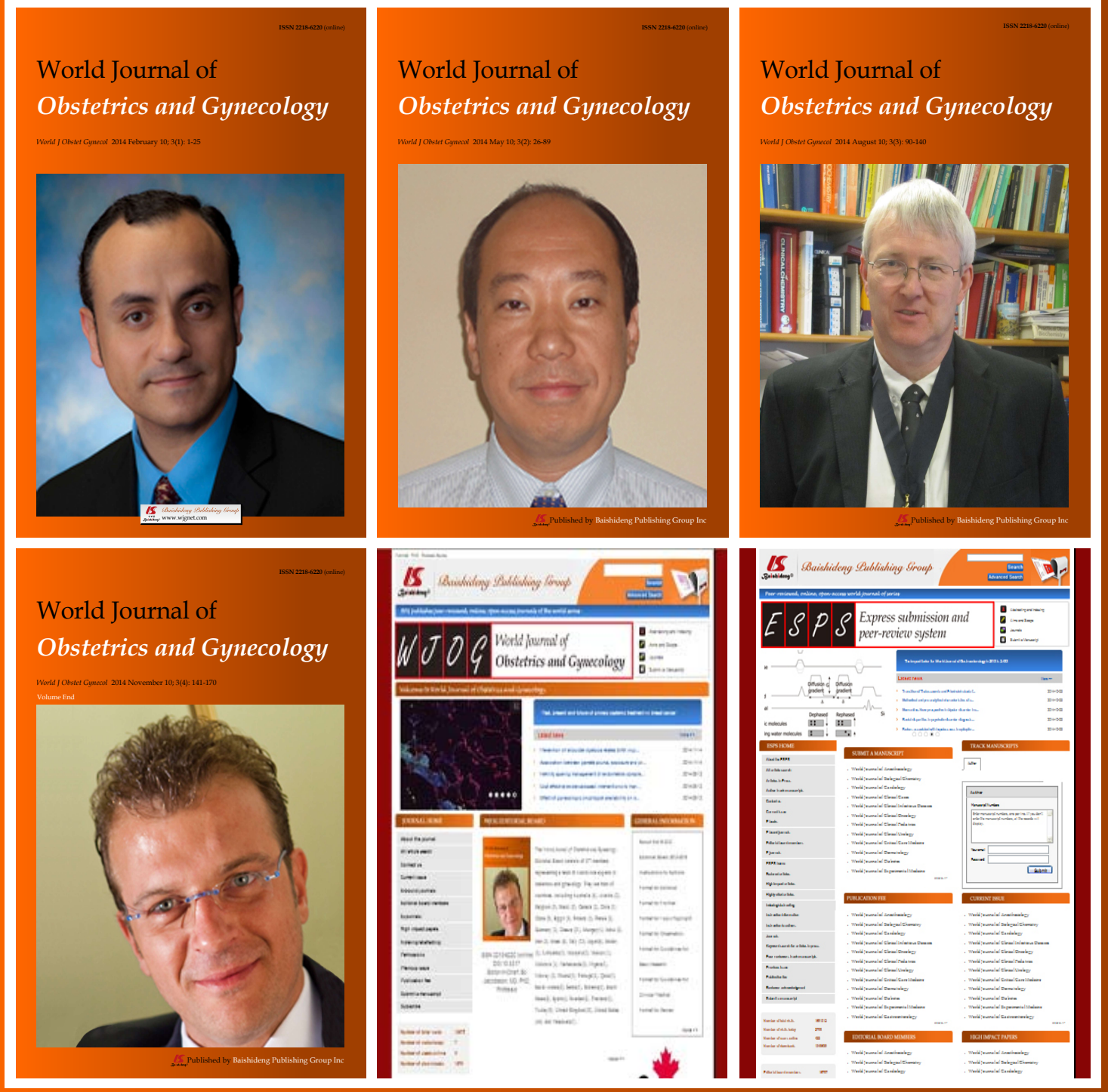

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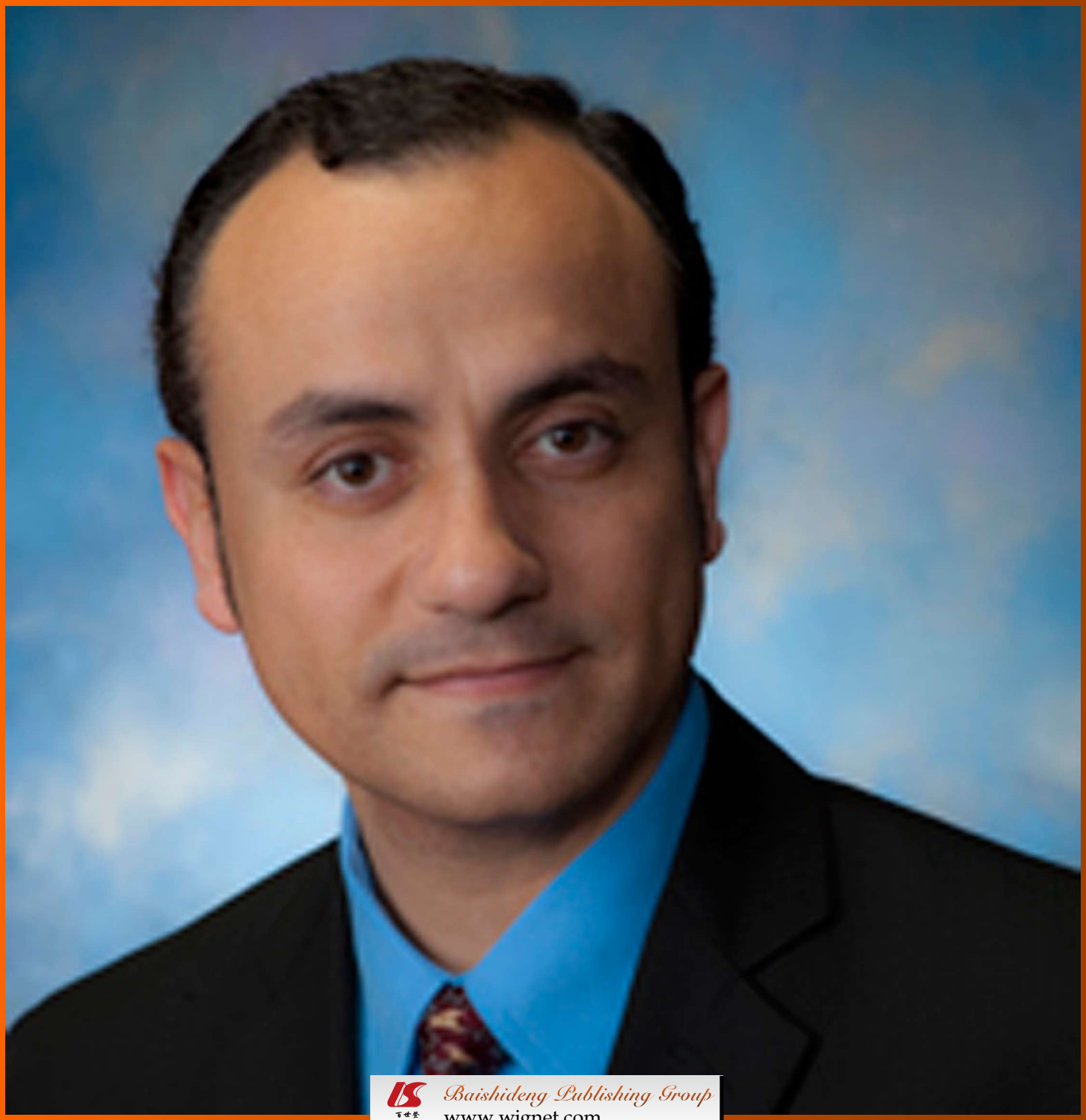

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EDITORIAL

Centers of excellence in minimally invasive gynecology: Raising the bar for quality in women's health

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Abstract

The "Center of Excellence" concept has been employed in healthcare for several decades. This concept has been adopted in several disciplines; such as bariatric surgery, orthopedic surgery, diabetes and stroke. The most successful model in surgery thus far has been the bariatric program, with a very extensive network and a large prospective database. Recently, the American Association of Gynecologic Laparoscopists has introduced this concept in gynecologic surgery. The "Center Of Excellence in Minimally Invasive Gynecology" (COEMIG) designation program has been introduced with the goals of increasing safety and efficiency, cutting cost and increasing patient awareness and access to minimally invasive surgical options for women. The program may harbor challenges as well, such as human and financial resources, and difficulties with implementation and maintenance of such designation. This commentary describes the COEMIG designation process, along with its potential benefits and possible challenges. Though no studies have been published to date on the value of this concept in the field of gynecologic surgery, we envision this commentary to provoke such studies to examine the relative value of this new program.

Key words: Excellence; Minimally-invasive; Gynecology; Surgery; American Association of Gynecologic Laparoscopists; Outcomes

Core tip: There are a number of benefits and potential challenges inherent to the "Center Of Excellence in Minimally Invasive Gynecology" (COEMIG) program. With an understanding of these challenges, organizations pursuing COEMIG may find advantages in efficiency, marketing and growth for both the institution and practice as a whole. There may also be reductions in complications, improvement in patient satisfaction and potentially reductions in cost that can arise as a result of COEMIG.

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INTRODUCTION

A program has recently been implemented whereby surgical facilities and gynecologic surgeons can earn the designation of "Center Of Excellence in Minimally Invasive Gynecology" (COEMIG). The COE programs are focused on improving the safety and quality of surgical care, and lowering the overall costs associated with successful treatment. They are designed to expand patient awareness of - and access to - surgical procedures per-

formed by surgeons and facilities that have demonstrated excellence in the specialty-specific techniques[1]. Under the direction of the American Association of Gynecologic Laparoscopists (AAGL) and administered by the Surgical Review Corporation (SRC), surgeons, hospitals and ambulatory surgery centers around the world that provide minimally invasive gynecologic surgical care may now pursue designation as a "Center of Excellence in Minimally Invasive Gynecologic"[2]. Though the nomenclature and its application vary, centers of excellence have been shown to improve outcomes and reduce costs[3]. The implementation of strict guidelines including procedure volumes, complication rates, readmissions, and mortality has helped to refine what exactly constitutes a standard center of excellence[4]. Recently, the University of Florida minimally invasive gynecologic surgery program has been designated as a COEMIG site. Herein we attempt to provide a concise description of the COEMIG program, including both its potential benefits and challenges. In doing so, we hope to stimulate research pertaining to this relatively new and uninvestigated process.

CENTER OF EXCELLENCE IN MINIMALLY INVASIVE GYNECOLOGY

COE concept dates back to the 1960s and generally describes a facility or organization which creates value that exceeds the norm in the locale of interest[3]. Similarly, the National Institutes of Health designate centers of excellence to institutes that have made concerted progress in a given area of research[5]. In the case of COEMIG and similar COE programs like that of bariatric surgery and cardiovascular service, COE refers to a specialty that works to incorporate the highest standards of practice into their entire scope of operations[6]. In the most fundamental sense of the term, a center of excellence should strive to fulfill several basic goals, including the presence of an integrated program, a comprehensive array of services, diverse ability to handle complications, high levels of patient satisfaction, a lower cost based on improved safety and efficiency, and a commitment to the continual measurement and comparison of care quality[7]. Our organization utilizes several methods for extracting patient satisfaction, including paper and electronic methods. Ideally, monitoring patient satisfaction scores and comparing data over time to the baseline scores before COEMIG designation may provide insight into the effect of the program on patient satisfaction.

The American Society for Bariatric Surgery (ASBS) recognized the need for this framework of care delivery and assessment in bariatric surgery and in 2003 they formed the nonprofit accreditation agency, surgical review corporation (SRC)[7]. The bariatric surgery center of excellence program has been shown to improve surgical outcomes[8]. This positive performance may be related in part to the fact that center of excellence programs are typically found in higher volume facilities (> 100 cases per year) with literature supporting volume as a metric by which accreditation occurs[9]. Compared to low volume facilities, patients who underwent gastric bypass at high-volume hospitals had a shorter length of hospital stay (3.8 d *vs* 5.1 d, $P < 0.01$), lower overall complications (10.2% *vs* 14.5%, $P < 0.01$), lower complications of medical care (7.8% *vs* 10.8%, $P < 0.01$), and lower costs ($10292 *vs* $13908, $P < 0.01$), further compounding this notion[10]. Additionally, centers of excellence in knee and hip replacement have also shown statistically significant lower risk of complications with an odds ratio of 0.80 ($P = 0.002$)[11].

The AAGL was inspired by the success of the bariatric and knee and hip center of excellence programs and partnered with SRC in 2010 to launch the COEMIG program. Like other center of excellence programs, COEMIG focuses on improving outcomes, reducing costs, increasing access to minimally invasive procedures and advancing the field.

The ten-year-old accreditation methodology used for the bariatric centers of excellence program has proven efficacious in improving surgical outcomes and lowering readmission rates[8,12]. COEMIG utilizes a similar system to promote a potentially transformative mechanism for surgeons, healthcare organizations and the discipline of minimally invasive gynecologic surgery as a whole[1]. SRC reports that this transformation includes processes to improve safety and efficacy, promote practice development, contain costs and improve patient satisfaction[1].

COEMIG adoption may also prove beneficial for the discipline of gynecologic surgery in general. For individual practices, SRC also asserts that through the effective marketing and communication of COEMIG status, healthcare organizations and surgeons may be able to use their position for personal and organizational benefit and likely impact contract negotiations, reimbursement rates and referral patterns[1].

SRC incorporates three committees, including boards for Standards, Review and Outcomes[13]. Each of these committees is comprised of a host of the industry's leading surgeons, each working to monitor and ensure an alignment of missions between the AAGL and organizations seeking COEMIG status. As of the date of this publication, 75 institutions and 282 gynecologic surgeons have earned the COEMIG designation. An additional 6 institutions and 45 surgeons are in the final stages of being designated[14].

COEMIG works to foster excellence in the field through the establishment of a live outcomes database, much like the bariatric outcomes longitudinal database (BOLD) of the BSCOE program. The goal of this database is to help establish a standard resource of information for the accumulation and analysis of improvements or areas of need within the field. This large, prospective database will also enable the development of new "standards" of care through monitoring outcomes for issues that have long been debatable due to the lack of large prospective trials. The BOLD is now the world's largest and most comprehensive repository of related clinical

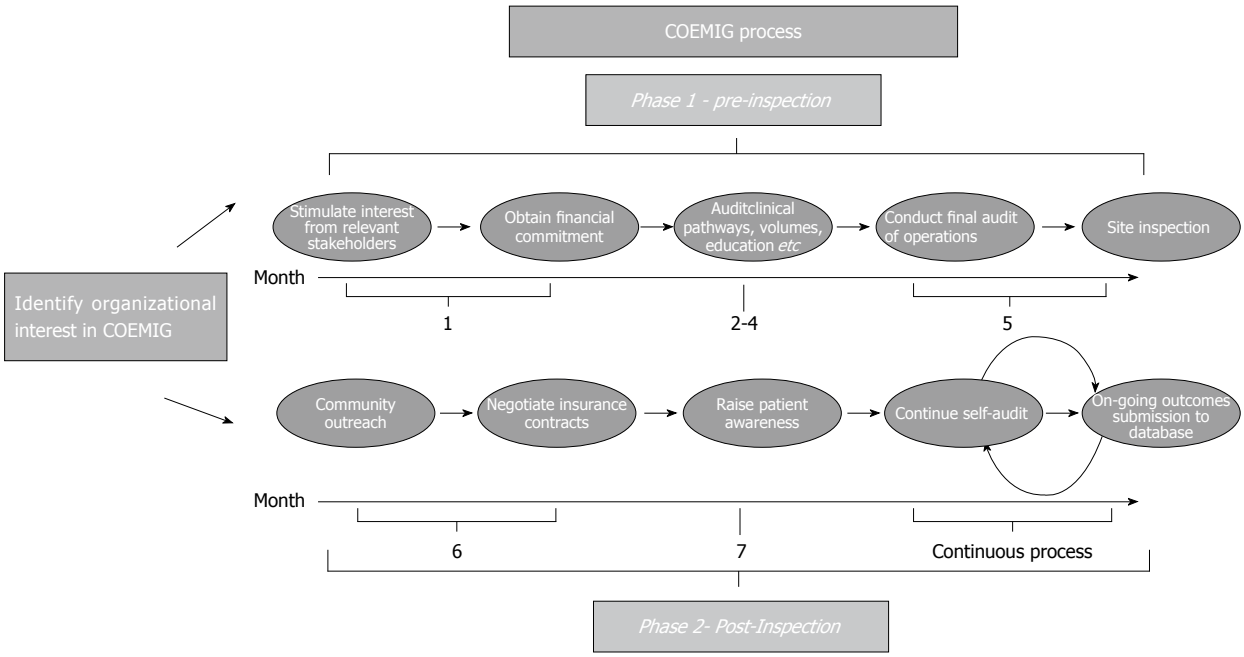

Figure 1 A visual depiction of the center of excellence in minimally invasive gynecology process. COEMIG: Center Of Excellence in Minimally Invasive Gynecology.

bariatric surgery patient information, a vital resource that the COEMIG database will likely try to emulate for minimally invasive gynecologic surgery[15].

COEMIG designation is promoted by the American Association of Gynecologic Laproscopists and the Surgical Review Corporation, through their website, e-mails, webinars, meetings, periodicals, journals and direct mail to the membership. Through the COEMIG initiative, the AAGL and SRC provide the opportunity to surgeons, practices, and hospitals of varying size and scope to pursue the designation and contribute to the potential growth and enhancement of the field.

The University of Florida Minimally Invasive Gynecologic Surgery (MIGS) program found it desirable to pursue designation, to strengthen the multidisciplinary team approach to the care of the minimally invasive surgical patient and to streamline our processes and procedures. The application process proved transformative for us and produced a level of organizational examination and introspection that have led to significant benefit. The process itself, outlined in Figure 1 was not a short one; a significant amount of effort and time was required for successful preparation and completion. In addition to workload, pursuit of COEMIG demanded a high level of consistent, clear communication among multiple units of the organization, displayed in Figure 2. Through an organized and focused approach, coupled with a fluid, communicative relationship among all involved, our pursuit of COEMIG was ultimately successful.

Certain aspects of the COEMIG application process in particular have encouraged a positive transformation in our practice. The augmentation of existing clinical pathways for example, has been an excellent method for analyzing organizational processes and ensuring their effectiveness, consistency and efficiency. Clinician and staff education requirements also provided an effective platform for bringing together the MIGS team and confirming and growing their knowledge base and synergy level. To maintain this synergy, quarterly staff education sessions on topics pertaining to minimally invasive gynecologic surgery, as well as in-services on equipment, are required for designation. Additionally, participating surgeons will need to maintain continued medical education credits in topics pertaining to minimally invasive surgery while also participating in staff education and quarterly team meetings.

Detailed review of volumes pointed out opportunities for improvement in coding and documentation, though formal percentages of error were not recorded. Some procedural volumes CPT codes provided by SRC were not congruent with the codes used within our organization. These challenges did not impact safety and efficiency; however they did add an additional layer of difficulty to the application process. The use of a prospective database will strive to alleviate this obstacle, as retrospective data collection will no longer be necessary. The creation of resource manuals for each unit that MIGS patients visit worked to ensure a consistent and reliable reference. Our resource manual includes call schedules, consultants, equipment specifications, patient education material, clinical pathways, standard operating procedures and consent information. Through the creation of these manuals, we were able to establish a more refined and identifiable source for information within our department.

The application process requires linked facility and surgeon(s) applications. Neither a surgeon nor a facility can apply independently. Hence, collaboration and building a unified goal between the facility and the applicant surgeon(s) are paramount. Surgeon requirements include demonstration of adequate surgical experience in lapa-

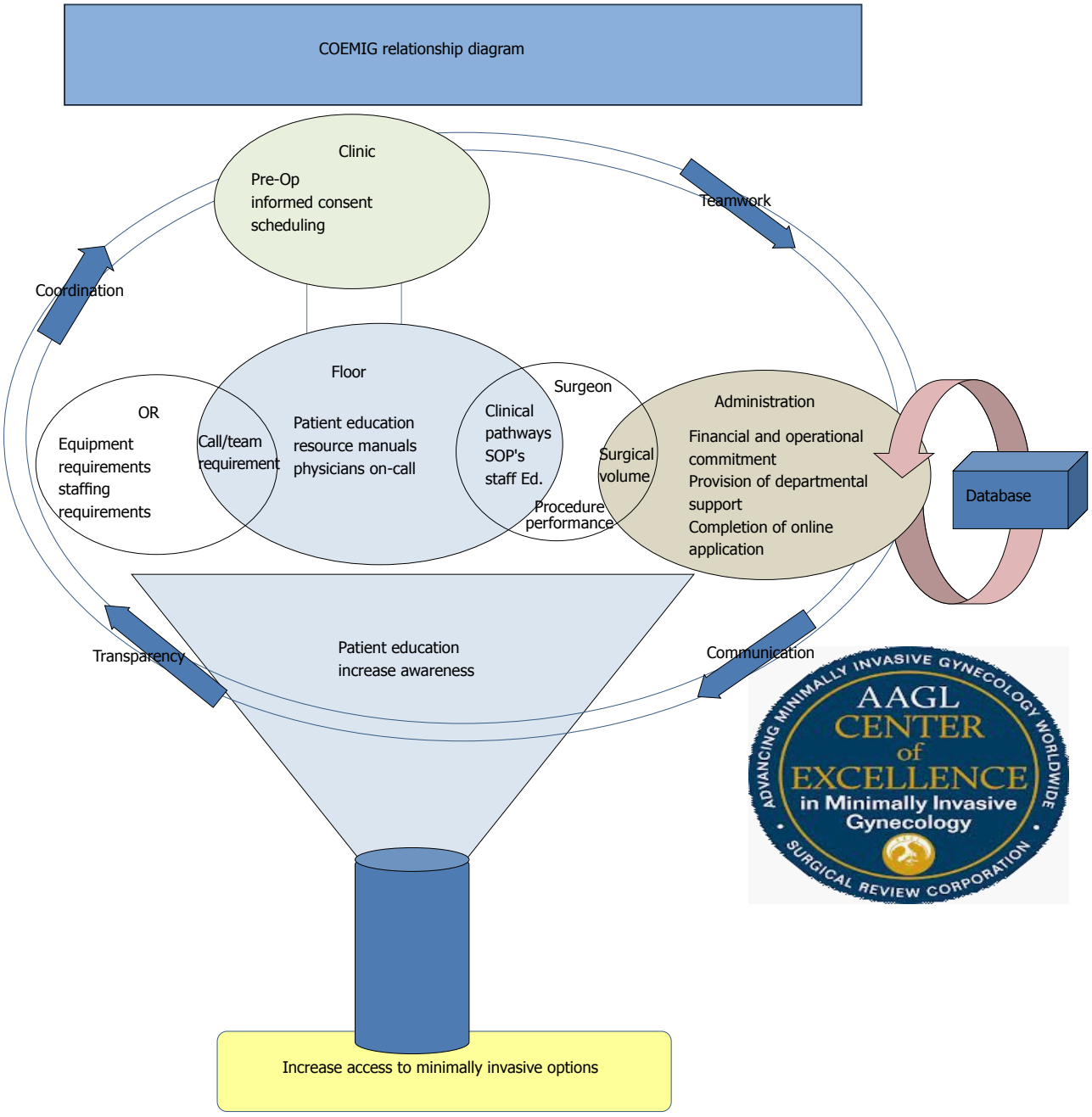

Figure 2 A visual depiction of the interconnected nature of the relationships within the center of excellence in minimally invasive gynecology process. COEMIG: Center Of Excellence in Minimally Invasive Gynecology.

roscopic and/or hysteroscopic procedures, a physician program director, qualified call coverage, consistent utilization of clinical pathways and standard operating procedures, informed patient decision making and consents for procedures commonly performed, and continuous assessment of quality goals[16]. The facility requirements include an institutional commitment to excellence in minimally invasive gynecology, surgical experience and volumes, a physician program director leading a multidisciplinary team, surgeons and qualified call coverage, and 24/7 consultant availability, advanced equipment and instruments, clinical pathways and standard operating procedures. Additional requirements include consistent, trained surgical team and support staff, documentation of informed patient decision making and consent and continuous assessment of quality and safety goals, defined by operative time, estimated blood loss, rate of complications, length of stay, reoperations, readmissions and mortality[17]. Specific difficulties in addressing these requirements within our organization dealt with the scope of the institution and the intricate navigation that occurs while trying to collect information and resources in a relatively short period of time. We found it beneficial and efficient to ensure brief but focused communication sessions at regularly scheduled intervals between a close group of relevant parties for the delegation and assurance of timely duty completion.

COEMIG requirements embrace similar criteria to

other quality programs such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Staff education requirements and physician CME requirements foster the environment of safety that is promoted by other quality programs. It is important to note that an additional program is available in minimally invasive gynecologic surgery and is administered through the American Institute of Minimally Invasive Surgery (AIMIS). The requirements of this program are parallel to those of COEMIG. Individual institutions and surgeons can choose the program that fits their style or environment. The programs should be viewed as complimentary rather than competitive, with the overarching motivation to improve safety in a larger number of institutions and improve patient access to minimally invasive surgical procedures in institutions and by surgeons that have met minimum criteria for designation.

Additional surgeons in our organization began seeking COEMIG designation within 5 mo, interested in the potential benefits of our pursuit of designation as a center of excellence. Although all of the surgeons within an organization may not initially choose to pursue COEMIG, this is not a reflection of their quality of practice. Moreover, the overarching benefits to the entire institution help improve the organization as a whole and may stimulate other surgeons' interest in meeting the criteria to be designated. We envision this designation to incrementally increase volume, safety and efficiency of our processes and increase patient awareness and access to minimally invasive surgical options, and consequently, improve patient outcomes and satisfaction. Though a formal definition has not been implemented, efficiency will be monitored and measured through the recording of operative times, length of stay and complications. Each of these metrics coordinates directly with the cost of care and monitoring these changes over time may reflect changes in the level of efficient operation within a COEMIG applicant institution. These benefits illustrate a potentially positive transformational process within one organization, but the overarching implications of these changes may be considered for the practice of minimally invasive gynecologic surgery as a whole.

The execution of the center of excellence designation process does possess challenges and potential pitfalls. While physicians may foresee the possible benefits of creating a center of excellence, aligning the goals with hospital leadership may prove more challenging. A financial commitment is required for participation in the program, as with many other designation processes. The required fees include a COEMIG application fee of $7500, COEMIG surgeon application fee of $650 and site Inspection fee of $1850. Annual COEMIG institution participation fee of $3975 and an annual COEMIG surgeon participation fee of $650 are required. There are also significant effort, staffing and time commitments involved in the process. Staff education, standardized clinical pathways and operating procedures are some of the core requirements that can demand time, effort and consensus-building among participating surgeons. Another designation requirement is commitment to submit all surgical data into a prospective database, a task that will require ongoing support and accuracy, with potential added cost. It is conceivable that COEMIG pursuit may harbor personal interests and pose ethical issues; however, COEMIG designation is available to any facility that meets the requirements, including small and large practices, community and academic institutions as well as outpatient surgery centers[18].

COEMIG designation will vary based on the institution's size and practice type. In larger institutions, the disparate locations and motivations of departments and key stakeholders may make it challenging for the completion of certain aspects of the application. Conversely, smaller organizations may reach consensus easier, but may find it challenging to demonstrate adequate volume and to make the financial and personnel commitments required to achieve COEMIG designation. COEMIG applicants may also see a challenge in gaining interest from non-applicant surgeons; however, it is important to maintain that this does not mean those surgeons are not "excellent" in practice. It may be beneficial for organizations and the center's leadership to ensure that this fact is communicated to its surgeons so as not to create an exclusionary environment within their facility. Another foreseeable pitfall of designation is potentially misleading the patients to believe that every practicing surgeon in the facility is COEMIG-designated, while this is not true in most institutions. The Surgical Review Corporation has developed safeguards against this in the institutional agreements. Marketing of COEMIG will be important to the impact of its implementation. However, surgeons and organizational leaders must remain focused on the core purpose of COEMIG, which is to examine and improve the operations of an institution and ultimately improve patient care.

COEMIG designation remains in effect as long as the center is in good standing and verifiable compliance with all current requirements and program criteria, monitored every three years as part of a renewal cycle. At the three-year re-inspection visit, or sooner through monitoring the prospective database, surgeons who are not meeting the criteria will be moved back to a provisional status. Provisional status prohibits the surgeon from communicating his/her COEMIG designation in any fashion. If the surgeon is able to rectify the deficiency, she/he is moved back to the designated status. Conversely, if the deficiency is not rectified, the surgeon will lose his or her designation and is required to reapply in the future if she/he so desires. It is imperative for institutions interested in COEMIG to weigh the challenges and benefits when deciding whether this pursuit is appropriate for their organization.

It is important that COE programs make every effort to be inclusive, so that to build partnership with every institution and individual surgeon that can provide consistent, safe and efficacious minimally invasive surgi-

cal options for women. The driving purpose for this is to increase awareness and access to patients, and encourage the increased training of surgeons and staff and utilization of minimally invasive approaches. By elevating the level of practice, sharpening the operations of individual organizations and establishing an ongoing outcomes database for review and analysis, the COEMIG process generates a possible platform for advancing an entire arena of practice. The value of a large, prospective national and international database cannot be underestimated, not only for clinical research and advancing the field, but also for monitoring surgeons' and hospitals' progress over time and for anonymous comparison to peer surgeons and institutions. Though the COEMIG process is not without challenges, this incarnation of quality will and should serve to augment organizations, the field and most importantly, the standard of patient care.

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REVIEW

Desmopressin for the treatment of female storage lower urinary tract symptoms

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Abstract

Female storage lower urinary tract symptoms are prevalent and bothersome. They are usually attributed to an overactive bladder and treated with antimuscarinics. Nevertheless, failure of conventional treatment to alleviate nocturia in particular and epidemiological data suggesting that nocturnal polyuria is the only or a contributing factor to nocturia, has attracted interest in decreasing nighttime urine production as a method of managing nocturia. A reduction in urine production could also, at least temporarily, delay daytime storage symptoms by delaying bladder filling. Therefore, desmopressin, the synthetic analogue or naturally occurring antidiuretic hormone, could have a role in the management of female frequency, urgency and urgency incontinence. This work aims to review data on the use of desmopressin in females with storage symptoms. Available evidence indicates that desmopressin is efficacious in reducing nighttime urine production and episodes of nocturia, resulting in fewer sleep interruptions. This translates into improved quality of life. Desmopressin is also effective in postponing micturition, urgency and incontinence for several hours after being taken on demand. The tolerability profile of desmopressin is good and significantly improved compared to historical figures due to the introduction of new oral formulations, tailoring the dose according to gender and age and adhering to instructions for fluid restriction before administration. The incidence of hyponatremia, desmopressin's most important side-effect, is less than 3% in recent trials. The efficacy of desmopressin, combined with its improved safety profile, makes it an interesting method for treating female storage lower urinary tract symptoms.

Key words: Lower urinary tract symptoms; Storage; Nocturia; Overactive bladder; Desmopressin; Female; Nocturnal polyuria

Core tip: Recent data suggest that desmopressin in its oral formulations offers significant improvements in nocturia as well as daytime storage symptoms in female patients. The treatment rationale for nocturia is that nocturnal polyuria due to inadequate antidiuresis is a major contributing factor to nocturia. In the case of daytime storage symptoms, desmopressin taken on demand can postpone their manifestation by delaying bladder filling. Desmopressin is well tolerated and the risk of hyponatremia is low with appropriate dosing, based on a lower minimum effective dose in females compared to males.

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INTRODUCTION

Arginine vasopressin (AVP), a hormone produced by the neurohypophysis, is an integral part of the complex

mechanism regulating water homeostasis. AVP decreases urine production and increases its concentration by promoting osmotic reabsorption of solute-free water in the collecting tubules of the kidney[1] through activation of V2 receptors. AVP secretion is principally determined under physiological conditions by the osmotic pressure of plasma and mediated by specialized osmoreceptor cells in the hypothalamus.

Inadequate antidiuresis caused by a deficiency in AVP secretion or resistance to its action at the kidney level may lead to the development of clinical syndromes such as diabetes insipidus, primary nocturnal enuresis or nocturnal polyuria. Deficiencies or defects in vasopressin secretion can often be corrected by using desmopressin, a synthetic analogue of the naturally occurring hormone.

Desmopressin has increased potency and prolonged duration of action compared to AVP. Unlike AVP, desmopressin is V2-receptor specific so it reduces urine production without inducing pressor activity. It is the only available antidiuretic drug and has been used for over 30 years. Three different formulations of desmopressin have been available: nasal spray, hard oral tablet (0.1 and 0.2 mg) and since 2005 the desmopressin melt oral lyophylizate (administered sublingually without water) formulation (60 and 120 μg).

According to the International Urogynecological Association (IUGA) and the International Continence Society (ICS), female lower urinary tract symptoms (LUTS) include increased daytime urinary frequency, nocturia, urgency and urinary incontinence[2]. The symptom complex of urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology is defined as the overactive bladder (OAB) syndrome. The prevalence of female storage lower urinary tract symptoms is 59.2%, as shown in the EPIC study[3]. Nocturia in particular is a very common complaint in women. 54.5% of the female survey population had to wake up to void once or more per night and 24.0% at least twice.

The pathophysiology of OAB is not completely elucidated but detrusor overactivity, the finding of involuntary detrusor contractions during the filling phase of the micturition cycle, is still considered to play an important role. The symptom of nocturia from a pathophysiological point of view is as complex as overactive bladder; even although it is traditionally attributed to a decreased bladder functional capacity in the context of OAB, the role of nocturnal polyuria is increasingly recognized[4]. Nocturnal polyuria is defined as a nocturnal urine output greater than 20% of the total daily in young people and 33% in the elderly, with the value for middle age falling between the two extremes[5]. Fifty-seven percent to sixty-four percent of patients with nocturia have confirmed nocturnal polyuria with the percentage increasing to as high as 89% in patients treated with a blockers or anticholinergics for benign prostatic hyperplasia (BPH) or OAB[4,6,7].

Based on the current knowledge of the physiology of lower urinary tract and the pathophysiology of lower urinary tract dysfunction, the amount of urine produced cannot be an etiological factor but may exacerbate underlying pathology. Therefore, the rationale for the use of desmopressin in the treatment of OAB patients is that through a decrease in urine production, it will increase the time taken to reach functional bladder capacity between micturitions, thereby reducing frequency and urgency and offering symptomatic improvement. This is very similar to the rationale for use of desmopressin in nocturia patients. An inadequate antidiuresis may have an etiological role in cases where nocturnal polyuria is present and then the rational of using desmopressin is most obvious.

This review aims to investigate the use of desmopressin for the treatment of female storage LUTS. Only papers in peer-reviewed journals that reported results on female populations were considered.

DESMOPRESSIN FOR NOCTURIA

Prospective studies investigating the efficacy and safety of desmopressin in women with storage LUTS are summarized in Table 1.

In a phase-Ⅲ, randomized, double blind study investigating the safety and efficacy of oral desmopressin in the treatment of nocturia[8], women with at least 2 episodes per night and a nocturia index score of more than 1 (defined as the mean nocturnal volume divided by largest voided volume) entered a dose-finding phase starting at 0.1 mg orally administered desmopressin, with weekly dose increments to 0.2 and 0.4 mg, if necessary. Patients who experienced a complete response to any of the doses or a greater than 80% response on the maximum tolerated dose followed a one week washout. Provided that their washout voiding diary values returned to at least 78% of their baseline ones, they were randomized to receive their optimal desmopressin dose or placebo in a double-blind fashion for another 3 wk. Eighty patients withdrew during the dose-finding and washout phases (adverse events 27.5%, failure of diuresis to return to baseline values 37.5%, lack of response 10%) and 144 were finally randomized.

After 3 wk of treatment, 46% of patients on desmopressin had a 50% or greater reduction in nocturnal voids compared with 7% on placebo ($P < 0.0001$). The mean number of nocturnal voids, duration of sleep until the first nocturnal void, nocturnal diuresis and ratios of nocturnal to 24 h and nocturnal to daytime urine volumes changed significantly in favor of desmopressin *vs* placebo ($P < 0.0001$).

As far as safety is concerned, headache and nausea were reported by 22% and 8% of patients during the dose titration. Clinically relevant hyponatremia was reported in 6% of the population but serum sodium levels were below the normal range during the study in 12%. All cases of hyponatremia occurred during the dose titration period. Two deaths occurred during the same period but neither could be directly associated with the study

Table 1 Summary of studies investigating desmopressin in female storage

Study	Indication	Design	Desmopressin dose/formulation	Comparator	*n*	Primary end-point	Result
Lose *et al*[8], 2003	Nocturia	RCT	0.1, 0.2, 0.4 mg oral, hard tablet	Placebo	144	Percent of patients with > 50% reduction in nocturia	Significant *vs* placebo
Weiss *et al*[9], 2012	Nocturia	RCT	10, 25, 50, 100 μg oral lyophylizate	Placebo	341	Reduction in no of voids, patients with > 33% reduction in nocturia	Significant *vs* placebo for both co-primary end-points
Yamaguchi *et al*[11], 2013	Nocturia	RCT	10, 25, 50, 100 μg oral lyophylizate	Placebo	58	Reduction in nocturia episodes	Significant *vs* placebo for 25 and 50 mg
Sand *et al*[13], 2013	Nocturia	RCT	25 μg oral lyophylizate	Placebo	261	Reduction in nocturia episodes, percent of responders (> 33% reduction)	Significant *vs* placebo
Hilton *et al*[14], 1983	Nocturia (MS)	RCT, crossover design	20 μg nasal	Placebo	16	Reduction in nocturia episodes	Significant *vs* placebo
Eckford *et a*[15], 1994	Nocturia (MS)	RCT	20 μg nasal	Placebo	22	Reduction in nocturia episodes	Significant *vs* placebo
Eckford *et al*[16], 1995	Nocturia (MS)	Open label, non-randomized, placebo controlled, incremental dose	20, 40 , 60 μg nasal	-	8	Nocturnal urinary volume and osmolarities	Significant *vs* placebo No significant for 40 and 60 *vs* 20 μg
Robinson *et al*[18], 2004	Daytime incontinence (any type)	RCT, crossover design	40 μg nasal	Placebo	60	4-h post-dose periods with no urine leakage	Significant *vs* placebo
Hashim *et al*[19], 2009	OAB	RCT, crossover design	0.2 mg oral, hard tablet	Placebo	41	Time to various OAB symptoms in 8 h post dose	Significant *vs* placebo
Han *et al*[20], 2011	OAB	Open label, randomized	Desmopressin 0.2 mg plus solifenacin 5 mg	Desmopressin 0.2 mg	68	Time to first frequency or urgency episode	Significant for combination *vs* desmopressin monotherapy

RCT: Randomized controlled trial; OAB: Overactive bladder.

drug. As was expected, adverse events associated with desmopressin treatment were usually mild and comparable with placebo in the selected population of women entering randomization for whom efficacy and safety were established during the uncontrolled dose titration. It is worth mentioning that overall, 50% of the patients were excluded during the study because of adverse events.

The authors of the study concluded that oral desmopressin is an effective and well-tolerated treatment for nocturia in women. Nine years later, in a 4 wk, randomized, double-blind study comparing 10, 25, 50 or 100 μg desmopressin orally disintegrating tablet (melt) *vs* placebo in adults with at least two episodes of nocturia per night but no formal requirement for documented nocturnal polyuria[9], 341 women were recruited. The study had two co-primary endpoints: change in mean number of nocturnal voids and proportion of subjects with > 33% reduction in mean number of nocturnal voids from baseline. The study also investigated the minimum effective dose (MED) of desmopressin.

A greater decrease in number of nocturnal voids and a greater increase in the proportion of subjects with > 33% reduction in nocturnal micturitions were observed with increasing doses of desmopressin. The effect was significant *vs* placebo for all desmopressin doses except the 10 μg for both the co-primary endpoints. Significant effects were also noted for the reduction of nocturnal urine volume and the increase in initial period of undisturbed sleep *vs* placebo. The improvements in quality of life outcomes, including self-rated sleep quality and the Nocturia Quality of Life questionnaire, were also significant.

The incidence of adverse events increased for increasing doses of desmopressin and was within the expected range. As far as hyponatremia is concerned, six women on active treatment had reductions in serum sodium to < 125 mmol/L, none in the 25 μg group. These drops all occurred within a week of treatment initiation.

The results of all analyses of voiding data in this study indicated that the MED for desmopressin orally disintegrating tablets is 25 μg in women and the 10 mg dose was sub-therapeutic. The MED for the 416 men also included in the study was 100 μg.

The influence of concurrent voiding dysfunction on the efficacy of desmopressin in the treatment of female nocturia was examined in a retrospective analysis of 84 women with more than 2 episodes of nocturia at initial evaluation[10]. Women were treated with 100 μg desmopressin for 1 mo and were escalated to 200 μg for another month in case of lack of effect of the initial dose. Among the 84 patients, 51 (60.7%) complained of concomitant OAB symptoms and were treated with anticholinergics. As far as nocturia etiology is concerned, 59 patients (70.2%) had nocturnal polyuria, 6 (7.1%) had reduced nocturnal bladder capacity, and 19 (22.6%) had both. A dose escalation in 39.3% women was required.

Overall, 73 women (86.9%) showed improvement of nocturia and the mean number of nocturia episodes (1.4 ± 1.5) was significantly reduced compared to baseline (3.7 ± 1.3) ($P < 0.05$). A ≥ 50% reduction in the number of nocturnal voids compared with baseline was observed in 41 of 84 women (48.8%). The 41 women with a ≥ 50% reduction in the number of nocturnal voids had a lower baseline urgency grade (according to the urinary sensation scale) compared to the 32 women who showed smaller improvements.

The authors concluded that lower urinary tract symptoms (other than nocturia) and urgency in particular may reduce the effect of desmopressin in the treatment of nocturia and should be adequately addressed in order to maximize the efficacy of antidiuresis.

In another randomized, double-blind study comparing 10, 25, 50 or 100 μg desmopressin orally disintegrating tablet (melt) *vs* placebo in Japanese patients[11], the dose-response relationship of pharmacodynamic variables measured after a single dose of desmopressin was investigated along with the mean reduction of nocturia episodes after 28 d of treatment. Among the 111 patients completing the protocol, 58 were female. More than 50% but not all patients had nocturnal polyuria.

In the female population of the trial, there was an increase in the duration of antidiuretic action (DOA) of desmopressin, defined as the time with urine osmolality > 200 MOsm/kg after dosing. The DOA for the 25, 50 and 100 mg doses was 3, 4.41 and 5.59 h respectively; all significant compared with placebo. As far as a reduction of nocturia episodes is concerned, a significant reduction was seen in the 25 and 50 μg groups (mean reduction 1.81 and 1.70 respectively) but not the 10 or 100 μg compared with placebo. Significant changes were also observed for desmopressin over placebo in the secondary study outcomes: prolongation of initial undisturbed sleep, reduction in nocturnal diuresis and the ratio of nocturnal to 24 h urine volume.

The incidence of adverse events was within the expected range. No patients on active treatment had serum sodium < 130 mEq/L during any treatment period. Only two patients had serum sodium levels below 135 mEq/L, both of whom were male and > 65 years of age.

After analyzing both the female and male subpopulations of the study, the authors concluded that male patients require approximately 58 mg of desmopressin to achieve the duration of antidiuretic action that females achieve with 25 mg.

Taking into consideration evidence from previous trials[9,11,12] indicating that the effective dose of desmopressin may be lower in females than in males, a 3 mo, randomized, double-blind, placebo controlled study was designed to assess the efficacy and safety of a 25 mg orally disintegrating tablet of desmopressin in the treatment of women with at least 2 episodes of nocturia per night without significant daytime symptoms[13]. In all, 261 women were randomized. Desmopressin achieved a statistically significant reduction from baseline in mean number of nocturnal voids compared to placebo (treatment effect -0.22 voids, $P = 0.028$). The other co-primary endpoint, the percentage of responders, defined as the patients with a decrease of at least 33% in the mean number of nocturnal voids at each study visit compared to baseline using a longitudinal analysis, was also met: the odds ratio of responding to desmopressin compared to placebo was 1.85 ($P = 0.006$). The treatment difference was similar for patients younger than 65 and 65 years old or older, was evident from 1 wk into the study and maintained throughout the 3 mo treatment period.

Desmopressin was also shown to significantly increase the mean time to first nocturnal void by 49 min compared to placebo and decrease nocturnal urine volume at 3 mo. Significant increases in health related quality of life and sleep quality were also observed. Nevertheless, the percentage of patients with a decrease of at least 33% in the mean number of nocturnal voids at the 3 mo visit compared to baseline was not significantly different between treatment arms.

Desmopressin was well tolerated overall. Adverse events with an incidence of 2% or more in either treatment group included dry mouth, headache, medication error, somnolence and rash, leading to a 3% discontinuation rate in the desmopressin arm compared to less than 1% for placebo. As far as hyponatremia is concerned, sodium levels remained greater than 125 mmol/L throughout the trial and 3 transient decreases to less than 130 mmol/L were recorded which recovered in 2-4 d without requiring discontinuation of treatment.

The authors concluded that at a dose of 25 μg, desmopressin orally disintegrating tablet is an effective and well tolerated treatment for women with nocturia and supported recommendations for gender specific desmopressin doses.

The efficacy of desmopressin in the treatment of nocturia in female patients with neurogenic bladder dysfunction due to multiple sclerosis has been assessed in a randomized, double-blind, placebo controlled, cross-over study of 16 women, published 30 years ago[14]. Twenty microgrammes of desmopressin were administered intranasally at bedtime. Desmopressin achieved significant changes in early morning urine osmolality and nocturia episodes.

Eleven years later, 22 women and 11 men, younger than 65 years of age with multiple sclerosis and nocturnal frequency, with or without enuresis, were recruited into a study assessing the efficacy and safety of desmopressin[15]. Following a two week placebo run-in to establish baseline values, patients entered a double-blind, placebo-controlled, cross-over study of 20 μg intranasal desmopressin at bedtime. Desmopressin achieved significant improvements in nocturia, reduced nocturnal urinary volume and the ratio nocturnal to 24 h urine volume. There were no cases of clinically significant hyponatremia and only two cases of asymptomatic hyponatremia were reported.

The same study team conducted an open-label, incre-

mental-dose safety and efficacy study of desmopressin in women with multiple sclerosis and nocturia[16]. Neither a significant decrease in nocturnal urinary volumes nor an increase in urinary osmolality was achieved by doses of desmopressin larger than 20 mg. A dose of 60 μg was associated with a decreased serum sodium level at the end of the 24 h period post administration. The authors concluded that as there were no benefits and a possibility of clinical hyponatremia with doses higher than 20 μg, these doses cannot be recommended.

A pooled analysis of data from three short-term, randomized, controlled efficacy studies of desmopressin orally disintegrating tablet or solid tablet, with treatment extension periods of 40-56 wk in patients with nocturia[17], indicated that efficacy was maintained and in some cases increased after long-term treatment compared with short-term for females as well as in males. This analysis also showed that long-term efficacy is not a result of early discontinuation of dissatisfied patients.

DESMOPRESSIN FOR DAYTIME STORAGE SYMPTOMS

The efficacy and safety of 40 μg doses of desmopressin nasal spray in managing daytime female urinary incontinence was explored in a multicenter, randomized, double-blind, placebo-controlled study with a cross-over design published in 2004[18]. Sixty women with mixed (32), predominantly urge (13), or predominantly stress (15) incontinence received study medication. The primary efficacy endpoint was the number of periods with no leakage for 4 h after dosing.

There was a significantly higher incidence of periods with no leakage in the first 4 h after dosing with desmopressin compared to placebo (62% *vs* 48%). There were no differences in outcome when analyzed according to type of incontinence. There was also a higher frequency of dry days on desmopressin than on placebo; 36% of patients had no leakage on virtually all treatment days for 4 h after dosing. The time from dosing to first incontinence episode was longer on desmopressin (6.3 *vs* 5.2 h), whilst the volume leaked per incontinence episode was lower on desmopressin than placebo. The total volume voided over the 24 h period after administration was consistently lower on desmopressin (1180 *vs* 1375 mL).

There were no serious or severe adverse events reported despite the relatively high dose used in the study and those most commonly reported on desmopressin were headache (36%) and nausea (10%). Three percent of women withdrew from the study because of mild adverse events.

A phase Ⅱb, double-blind, randomized, placebo-controlled study with cross-over design investigated the efficacy of 0.2 mg of oral desmopressin in patients with idiopathic OAB[19]. The rationale behind this "proof of concept" study was that desmopressin would postpone OAB symptoms by reducing the speed at which the bladder fills. Female and male patients were given 3 doses of 0.2 mg desmopressin on alternate days and 11 doses of placebo on all other days during the 2 wk double-blind phase. The primary endpoint was the time to the first OAB symptom episode (micturition, urgency, urge incontinence) during the first 8 h following treatment.

Forty-seven male and 41 female patients were randomized and results were not presented separately for each gender. There was an 8 min delay in the first post-dose micturition for desmopressin compared to placebo (92 min *vs* 84 min) which was not statistically significant. The delay in the second and third micturitions was statistically significant, resulting in one less micturition in the first 8 h post dosing for desmopressin compared to placebo. The time to the first and second urgency episodes was statistically significant on the drug compared to placebo. As far as urge incontinence was concerned, the majority of patients (78%) did not experience any leakage in the first 8 h following treatment, but no significant difference was found between drug and placebo days with regards to the number of UUI episodes in the first 8 h following dosing. However, if incontinence frequency was classified as severe (≥ 2 episodes/3 d) or mild (≤ 1 episodes/3 d), there was significantly less incontinence episodes with desmopressin in severe cases compared to placebo.

According to the authors, this proof-of-concept study showed that desmopressin reduces OAB symptoms by increasing the time to the first OAB episode, with an overall improvement in QoL and minimal and tolerable side-effects, and therefore it represents a feasible method for symptomatic relief at least in the short-term. Its use as a per-needed tablet for management of OAB merits further assessment.

The use of a combination of anticholinergics and desmopressin in the treatment of overactive bladder was investigated in an open-label, randomized study[20]. Female patients with OAB and at least four voids in the first 8 h of the day after waking-up, excluding the first morning void, were recruited. Patients were randomly assigned to receive 5 mg of solifenacin (anticholinergic group) or 5 mg of solifenacin and 0.2 mg of desmopressin (combination group) for 2 wk. Patients were instructed to take the tablets after the first morning void. The primary efficacy endpoint was the increase in time to each of the first frequency or urgency episode. Thirty-one women in the anticholinergic group and 37 in the combination group completed the study.

Time to first micturition was 12 min later for the combination group compared to anticholinergic group (117 *vs* 105 min). This difference was not statistically significant in contrast to the difference in times to the second and third voids and time to the first urgency episode which were significant for the combination treatment compared to anticholinergic monotherapy. Combination treatment was also significantly better in reducing the total number of urinary frequency and urgency episodes during the first 8 h of the day as well as in improving quality of life scores. Age > 65 years and voided volume > 150 mL were predictors of improvement with combination treatment.

The authors concluded that the combination of desmopressin and an anticholinergic could be considered a feasible method for relief of symptoms in female patients with OAB.

CONCLUSION

Our review of the literature has revealed a renewed interest in the use of desmopressin for the treatment of female LUTS. Indeed, the majority of relevant trials have been published during the past 3-5 years.

Desmopressin has been available for over thirty years in the intranasal formulation for most of this period. Multiple reports of hyponatremia in elderly patients as well as in children have led to an increased awareness of this particular risk associated with desmopressin and have restricted its further clinical development. Due to this safety issue, desmopressin nasal spray lost Food and Drug Administration approval in 2007, leading to its worldwide withdrawal for the indication of nocturnal enuresis in children. Despite this, newer formulations of desmopressin are a well-established treatment in the management of childhood enuresis[21]. Drug dosing, variable absorption and misuse were major problems with the intranasal spray[22].

The switch to desmopressin tablet and more recently to the orally disintegrating formulation has been associated with a decrease in the incidence of hyponatremia[23,24]. Indeed, in all the recently reviewed trials for the role of desmopressin in the management of female storage LUTS, the incidence of hyponatremia and more specifically of clinically relevant hyponatremia was low. The superior pharmacokinetic and pharmacodynamic properties of the orally administered formulations are only one of the reasons for this observation[25-27]. Another reason is the identification of age and low baseline plasma sodium concentration as important risk factors for hyponatremia[23]. Finally, the awareness of a lower minimum effective dose in female patients compared to males[12] has led to more appropriate dosing.

The incidence of hyponatremia is currently less than 3%[23]. Evidence in this review suggests that desmopressin is currently a well-tolerated and safe treatment for females with LUTS.

Apart from the improved safety of oral formulations of desmopressin, another factor leading to a recent increase in the number or trials conducted in female populations is increased awareness of the prevalence and pathophysiology of nocturia. Nocturia in women was for many years attributed to OAB and was treated mainly with anticholinergics. The association of age with a reduction in the sensitivity of the osmoregulatory system resulting in inadequate production of AVP and a disturbance in the circadian rhythm of urine production has brought focus on nocturnal polyuria as an etiological factor of nocturia. Indeed epidemiological studies have found nocturnal polyuria in the vast majority of females with nocturia.

In our review, desmopressin administration achieved significant reduction in nocturia episodes and nocturnal urine production, which in most trials was translated to improvements in sleep and quality of life.

Trials conducted in females with daytime symptoms have confirmed that desmopressin is effective in at least postponing the development of storage symptoms and may be a useful on-demand medication for the management of OAB symptoms, particularly in combination with other treatments that address them around the clock.

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Peritoneal carcinomatosis from advanced ovarian cancer: To treat or not to treat ethical issues suggested by a case study

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Abstract

This article provides a brief description of an epithelial ovarian cancer (EOC) case (stage Ⅳ) treated with the association of complete CytoReductive Surgery and hyperthermic intraPEritoneal chemotherapy (HIPEC). The use of HIPEC in EOC makes theoretic sense in view of the high rates of recurrence following standard treatment, but there are no randomized clinical trial to date and HIPEC for these patients still represents a radical treatment where the choice of no treatment may be acceptable since definitive cure is unlikely. We reviewed the entire decision making process considering the risk/benefit of the procedure in term of mortality/morbidity, the quality of life and the psychological profile of the patient 1 year after surgery. The platform World Health Organization-International Classification of Functioning, Disability and Health that permits evaluation of the person in relation to the psycho-social context is presented. A person-centred approach and assessment of health-related quality-of-life and disability in EOC survivors are of central importance for decision making.

Key words: Advanced epithelial ovarian cancer; Peritoneal carcinomatosis; Platform World Health Organization-International Classification of Functioning, Disability and health; Ethical issues; Hyperthemic intraperitoneal chemotherapy; Health related quality of life

Core tip: This paper addresses the topic of "treating the untreatable". Advanced epithelial ovarian cancer with peritoneal carcinomatosis is not susceptible of definitive treatment. Anyway we can gain time. To achieve this goal the patient undergoes extensive treatment that has a significant burden of morbidity and mortality with decrease in quality of life in the postoperative period. This manuscript is the report of the bioethical conference held in our institution between the multidisciplinary team that take care of these complex patients and the bioethical philosopher and the clinical psychologist. Aim of the conference was to seek for bioethical

counsel in this cohort of patients highlighting the relationship of medical counseling, terminal state, the patient's individual preferences, psychological evaluation and health related quality of life. The case is evaluated by a patient-centered approach through the platform World Health Organization-International Classification of Functioning, Disability and Health that is presented into the article text.

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INTRODUCTION

The standard treatment for patients with advanced epithelial ovarian cancer (EOC) (stage Ⅲ or Ⅳ) is surgical debulking followed by platinum/paclitaxel-based adjuvant therapy. Although high rates of patients respond well to this therapy, about half of the patients relapse within 5 years[1] and long-term survival is achieved in only 10%-20% of patients[2]. Intraperitoneal route with the intravenous administration in primary stage Ⅲ ovarian cancer has been consequently studied in large randomized trials[3] and demonstrated that bidirectional chemotherapy using intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel significantly improved survival in patients with optimally debulked stage Ⅲ disease[4]. Despite these convincing data, intraperitoneal chemotherapy with normothermia still presents several limits, basically consisting of the inability of this technique to penetrate into tumor nodules larger than 3 mm[5].

On the other hand a significantly higher rates of treatment-related toxicities, side effects, complications[6-20] and a temporary reduction in quality of life[21-23] have been observed. All these adverse events could moreover lead to a potentially higher resource use[24,25]. To overcome these problems, intraperitoneal chemotherapy can be supplied intraoperatively, improving the tumor response to cancer chemotherapy drugs through the combination of drugs with hyperthermia[26,27]. Hyperthermia added to intraperitoneal chemotherapy might enhance the antimitotic effect by several mechanisms as known since the second half of the 90s[28,29].

The association of complete cytoReductive surgery (CRS) and hypertermic intraperitoneal chemotherapy (HIPEC) has shown to improve survival in patients with pseudomyxoma peritonei, malignant peritoneal mesothelioma or peritoneal carcinosis from advanced abdominopelvic tumors with high level of evidence[30-33]. EOC has no definitive data upon the effectiveness of the association of CRS and HIPEC[34] but some ongoing randomized clinical trials are meant to assess the clinical efficacy of this therapeutic approach[35].

Two recently published systematic reviews, which analysed almost all the available international literature, concluded that this comprehensive treatment modality is a viable option in the management of patients with advanced EOC (stage Ⅲ e Ⅳ disease), with potential benefits comparable with the current standard of care (conventional secondary cytoreduction or systemic chemotherapy)[3,4].

Practical implications at the basis of CRS and HIPEC has been presented on previously published studies focused on the quality of life (QoL) post procedure[23,24,36-40]. All of these studies, however, are limited by the fact that disability was not measured according to the conceptualization of disability endorsed by World Health Organization (WHO)'s International Classification of Functioning, Disability, and Health (ICF)[41] which defines disability as the relationship between one's health condition and environmental factors expressed in activity limitations and/or participation restrictions.

No article was found regarding the use of an ethical advice for decision making in case of advanced EOC. Few physicians sought external ethical advice and decisions were entirely taken by the medical team. Direct involvement of family and treating physician was limited[42]. The main goal of this paper is to offer ethical consideration useful for decision making for advanced EOC, when HIPEC represents a radical treatment for patients where the choice of no treatment may be acceptable since definitive cure is unlikely.

RESEARCH

In this article we presented one case of advanced EOC (stage Ⅳ) treated with CRS and HIPEC with favourable outcome (grade 1) in term of Common Terminology Criteria for Adverse Events (CTAE)[43] classification after 1 year of follow-up. The patient gave written informed consent to this case presentation.

We discussed the case after 1 year with the main specialists involved in the care process: surgeon, oncologist, anaesthetist and intensivist.

We reviewed the entire decision making process taking into consideration the risk/benefit of the procedure in term of mortality/morbidity, quality of life and psychological profile of the patient 1 year after surgery.

A clinical psychologist and a bioethicist philosopher took part at the discussion.

CASE PRESENTATION

Clinical picture

The patient was a 64-year-old woman. Twenty-seven years ago she had a breast cancer, initially treated with quadrantectomy and chemotherapy and after a relapse treated with mastectomy and chemotherapy in 2001; consecutive follow-ups were negative.

In December 2011, an advanced EOC (FIGO stage Ⅳ) was diagnosed. She underwent total body computed

tomography-scan that showed a pelvic mass with massive ascites and pleural effusion positive for tumor cells. The diagnosis of an EOC serous type was made by transvaginal biopsy. Markers were elevated (CA125: 500 U/mL). She had 6 cycles of neoadjuvant chemotherapy with carboplatin (CDDP) and paclitaxel (PTX) with partial clinical response according with Response Evaluation Criteria In Solid Tumors criteria: the CA125 concentration was significantly diminished (75 U/mL); positron emission tomography scan was negative.

In June 2012, a month since chemotherapy, the patient underwent cytoreductive surgery with HIPEC: the Peritoneal Cancer -Index score was 5 and at the end of surgery no macroscopic residual disease was detected (Completeness of Cytoreduction 0[29]). She was discharged after 19 d: during the hospital stay she developed a severe thrombocytopenia (platelets < 20000). After two months from the surgery she underwent 3 cycles of adjuvant chemotherapy with CDDP and PTX. At the bioethical conference (12 mo since surgery) she was alive with no evidence of relapse.

Decision making: A surgical point of view

When the patient received the communication of the advanced EOC, she lived the diagnosis as a sentence that triggers the sense of the end.

Patient simplified a lot her condition. The main question was: "How much time remains and will I suffer from it?" She asked for a longer life and does not ask for quality of life. Surgeon spoke with her clearly. "Advanced EOC lead the patient to die with bowel occlusion without treatment. CRS and HIPEC allows a five years cancer-free in 15%-20% of the patients". He proposed this option as an experimental treatment conducted in a clinical trial. Patient and her family had two weeks to decide what to do. The crucial problem was the level of invasive treatment proposed. This consultation has the difficulty to balance the incidence of EOC recurrence and post-operative complications of CRS and HIPEC against the optimal front-line chemotherapy including a combination of platinum analogue and taxane.

Psychological profile one year after procedure

The patient accessed the interview willingly. Lucid and oriented over space and time, reality testing was intact. Attention, memory and concentration appeared to be adequate. Psychopathology history was negative. She constructs her history anchoring the events of illness that saw her, a 39-year-old woman with two young daughters, dealing with the cancer disease.

Her narration shows the presence of a lively temperament and determined character. When the disease and other tragic events, such as the loss of their first child at the end of pregnancy, have taken place in her life, she dealt with confidence in the doctors and her resources, but, at the same time, aware of the risks present.

She describes her husband as a person of few words, but with which she has a solid relationship characterised by the sharing of everyday life. Even the daughters, both married and with children, along with extended families, are a significant landmark and, even in the event of illness, were present and supportive.

When she dwells on the surgical procedure repeats several times: "if I had known that this recovery would have been so hard..." but then she concludes, "but my daughter says that I would have done the same".

In particular, she recalls the fear experienced in the post-intervention linked to the perception of a body that did not respond to commands and a shooting time that it seemed very long. Scar tissue are frequently emphasised in her speeches to husband that minimizes, and through some ironic joke, contributes to the acceptance the lady is building towards a change in her body.

She complains a strong weakness on the afternoon during which she stays in a chair for a long time. On the morning she perceives herself, in continuity with her whole life, as active and energetic; on the afternoon she seats throughout the rest of the day in an armchair because of fatigue. This situation forces her to a lifestyle in which she does not recognize. People do not always understand this fatigue, but the spur of the others makes her nervous.

ETHICAL CONSIDERATIONS

CRS is associated with morbidity and mortality and it is difficult to determine whether mortality and morbidity occurring after major CRS and HIPEC is caused by the surgery or the HIPEC or by the natural history of the EOC disease. Chua *et al*[4] reviewed 19 studies including CRS and HIPEC and found mortalities between 0% and 10% from any cause within 30 d of surgery. Postoperative events are common but mostly grade I (self-limiting) or grade Ⅱ, requiring only medical treatment for resolution[35]. Grade 1 events occurred in 22 of 30 (73%), including transient nausea and vomiting, diarrhea, thrombocytopenia, and pleural effusion. One or more grade 2 events occurred in 27 patients (90%), including nausea and vomiting, cardiac arrhythmia, hypertension, diarrhea, pleural effusion, line sepsis, and increased creatinine. Twelve patients (40%) experienced 1 or more grade Ⅲ complications that required invasive intervention, including anemia, pleural effusion, pneumothorax, fascial dehiscence, diarrhea, ileus, and pancreatic leakage.

The use of HIPEC in EOC is aimed at reduction of the high rates of recurrence following standard treatment. CRS and HIPEC allows a five years cancer-free in 15%-20% of the patients with EOC. Experience reported in the literature is increasing, but there are no randomized clinical trial to date[34] and HIPEC still represents a radical treatment for patients where the choice of no treatment may be acceptable since definitive cure is unlikely.

For this reason HIPEC in EOC should ideally be performed on a research protocol or their data prospectively collected in registries such as the Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer registry[35]. Every study should always be functional to the patient. It's important to ensure that the patient does not become sub-

ordinate to a research protocol because the feasibility of a treatment does not exhaust the question. Medical code of ethics states "Every treatments that affect the integrity and the mental and physical strength of the patient may be implemented, following an assessment of care needs, and only in order to obtain a real clinical benefit to the patient or alleviate their suffering. The doctor, also taking into account the patient's wishes if expressed, must refrain in diagnostic and therapeutic treatments from which we can't reasonably expect a benefit to the health of the patient and/or an improvement in quality of life"[44].

Even if the case presented had a good outcome (grade I as defined by CTAE classification), the patient has a strong weakness one year after CRS and HIPEC that forces her to a lifestyle in which she does not recognize herself. She says "if I had known that this recovery would have been so hard..."

In this complex situation the bioethical question is crucial.

Bioethics should be meant as the critical conscience of technological civilization that moves philosophical questions on the significance of the construction of human identity within the technological action. In this context the need to think of the technological process, involves the whole person and belongs to each person[45]. This "critical" enterprise should be participated by all those who, from different perspectives and with different cultural backgrounds, are interested in understanding the historical condition of contemporary human being. The field of bioethics is not derived solely from the fact that what is being discussed is theoretically and practically complex, but for the reason that the truth is an ethical judgment from the empirical data of other sciences. Bioethics loses its specificity if it does not examine the historical condition in which it addressed the question of life today: the binomial life-ethics placed inside the filter with which the experimental sciences think and govern the phenomena of life[45].

For this reasons the ethical data can never be an element that arises at the end of a process. We can't move the ethical question only when the evidence based medicine is uncompleted, as in EOC, because the wellness of the patient is not a clinical judgment. The ethical aspect can never be separated from the clinical practice because every human act has an ethical value and its lawfulness does not end in an appropriate technical gesture. It's necessary to make explicit the anthropological aspect that influences clinical decisions.

A help to the analysis of the situation of the patient can came from the platform World Health Organization-International Classification of Functioning, Disability and Health (WHO-ICF), that permits evaluation of the person in relation to the psycho-social context[41]; it also should help researchers and clinicians to reinterpret terminology or expressions they use daily, such as quality-of-life, proportionality, informed consent, rights, autonomy, vulnerability, discrimination, participation, from the perspective of ethics[46].

The ICF introduces a new conceptual and operational model that promotes a new vision of health and disability, and it is based on the definition of disability as a "difficulty in functioning at the body, person, or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors"[47]. Usually, physicians hypothesize the existence of a strict relationship between the patient's health related quality of life (HRQoL) and disability: the higher the disability is, the more impaired the HRQoL. All of these studies, however, are limited by the fact that disability was not measured according to the conceptualization of disability endorsed by WHO's ICF[41,48]. Therefore, changes in HRQoL or in disability profiles are again only explained by changes in a person's intrinsic health state. Patients reporting worse health status also reported higher levels of disability and lower quality-of-life. This finding shows that not only an objective, namely medically assessed, health status is related to quality-of-life and disability, but also health status perceived by patients is an important aspect to understand quality-of-life and disability[49]. A person-centered approach and assessment of health-related quality-of-life and disability in EOC survivors are of central importance. In fact, persons who experienced CRS and HIPEC, including those who are not severely affected anymore, report a substantial impact of the disease on some areas of participation[22,23,36-40]. For this reason, the identification of participation areas that are mostly affected by the disease can provide useful inputs to guide rehabilitation and care. For example, younger people not only have different rehabilitation needs and personal resources compared with older persons but also encounter different opportunities in tackling daily life difficulties in their workplace, community, and other settings. They experience the environment in different ways. In this sense, seeing the person in the interaction with the environment might explain why self-reported levels of health, disability, and HRQoL change among persons. Exploring the HRQoL in term of ICF's concept allows to evaluate the person in relation to the psycho-social context and to define the proportionality of the treatment. There is a strictly clinical judgment on the proportionality which defines the cost-benefit of the treatment, but also the patient point of view determines the proportionality. The tolerability of the condition takes part in the determination of proportionality, which has not to be confused with the expectations of the patient. Tolerability must be evaluated in term of pain but also in term of feeling of suffering. Treatment planning with the patient helps to assess the tolerability. The evaluation of feasibility of CRS and HIPEC considering the concept ICF "of disability and functioning" can help both doctor and patient to decide not only in term of survival, but also in term of HRQoL. The final decision must come from a doctor-patient negotiations (and not from a contractual process), in which the doctor has to be aware that the decision making is never equal.

The informed consent stays at the end of this com-

munication process and requires enough time to create an adequate relational context. The patient's informed decision not exhaust the relationship, but still remains a working progress where the patient should have the chance to change his decision, because the psico-social context may change.

Some data suggest that when patients fully understand their situation as a "terminal state" they are less likely to submit to extensive, life-threatening or QoL-threatening therapies[50,51].

It is likely that any treatment will impair QoL, at least in the short-term. However, like health, quality-of-life as well is the result of the interaction of many elements. Consequently, both the attribution of a complete subjective meaning to this concept and its transformation into a mere quantitative parameter should be avoided[46]. On the one hand, emphasizing the concept of the quality-of-life by drawing on people's subjective experience (desires, expectations, projects, *etc*.) involves the loss of the intersubjective perspective, which establishes the relationship between rights and duties. On the other hand, focusing on the quantitative parameters, that are more easily measured, may determine misunderstandings in the assessment of the relevance of the quality-of-life for the individual. All of that implies a new idea of well-being: the quality of life also derives from the quality of relationships[46].

The aim of the article was not to suggest an interventional protocol to guide the decision, but an EOC patient-centered ethical approach through the platform WHO-ICF that permits evaluation of the patient in relation to the psycho-social context. This approach may improve the decision making process of both patient and doctor without removing individual responsibility.

CONCLUSION

The need to raise the subject of disability as a relationship between environment and pathological condition derives from a single fact: the changes in the living conditions in Western societies resulting from scientific and technological progress made it possible for an ever increasing number of people to live with their disease, with their impairments. The recognition of this fact is useful in addressing, not only issues related to the disease (which can be only partially addressed), but also for environmental intervention planning and it is therefore crucial to think of the treatment relationship as a question of justice[52].

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CASE REPORT

Metastasis to a uterine leiomyoma originating from lung cancer: A case report

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Abstract

The uterus is an uncommon site of metastasis especially from a primary lung adenocarcinoma. More frequently, extragenital primary tumours, including lung cancer, metastasize to the ovaries. In the literature, lung cancer metastasizing to the uterus is rare and has been reported to involve the endometrium and uterine serosa. Here, we report an unusual case of a 58-year-old woman who had a history of lung adenocarcinoma with subsequent metastasis to a single uterine fibroid only. The patient was known to have a long history of asymptomatic fibroids. In 2008, she was diagnosed with lung adenocarcinoma which was treated with primary surgery and adjuvant chemotherapy. Four years later, a routine abdominal computerised tomography scan showed an enlargement of the fibroid and she underwent a hysterectomy and bilateral salpingo-oophorectomy. Pathology reported a lung adenocarcinoma metastatic to the uterine leiomyoma with a similar morphology to the original pulmonary malignancy and this was confirmed with immunohistochemical staining. She had no evidence of metastatic disease elsewhere. The final diagnosis was metastasis of a primary lung adenocarcinoma confined to a uterine leiomyoma. Our patient also fulfilled the criteria for a phenomenon called tumour-to-tumour metastasis in this case a primary malignancy having metastasized to a benign tumour. In conclusion, metastasis of a primary lung cancer to the female reproductive tract has been documented, but clinicians should also be aware that metastasis to benign gynaecological tumours such as fibroids can also occur, especially in the setting of tumour-to-tumour metastasis. In addition, the clinical history and use of immunohistochemistry are invaluable in reaching a diagnosis.

Key words: Uterine metastasis; Lung cancer; Metastasis to leiomyoma; Tumour-to-tumour metastasis; Lung adenocarcinoma metastasis; Metastasis to female genital tract

Core tip: Our paper describes a rare occurrence of metastasis from a lung cancer to a uterine leiomyoma only without involvement of the endometrium, serosa or adnexae. This has not been reported in recent literature. We also describe the utility of immunohistochemistry in reaching a diagnosis which was essential in our patient who was asymptomatic-unlike those previously reported. The phenomenon of "tumour-to-tumour" metastasis, which not many gynaecologists have heard of, is also described in our report. The importance of knowing that the formation of metastasis to the female genital tract, although uncommon, is highlighted.

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INTRODUCTION

Lung cancer metastasizes most frequently to the regional lymph nodes, the surrounding pulmonary structures, the liver, adrenal glands, bones and brain. Metastasis of this common malignancy to the female genital tract is unusual and specifically to the uterus, is rare. A review of the literature shows that the commonest site in the female genital tract to be affected by pulmonary metastasis is the ovary, with several cases documented so far[1-4]. Lung metastasis to the uterus is much rarer. To our knowledge, there have been only two cases of non-small cell lung cancer (NSCLC) with metastasis to the uterus reported in recent years - one to the uterine serosa and the other to the endometrium[5,6].

Here we report a rare case of an asymptomatic postmenopausal woman with lung cancer metastasis to a uterine leiomyoma.

CASE REPORT

In July 2008, a 54-year-old postmenopausal Chinese woman, para 3, was diagnosed to have a non-small cell lung cancer. She had presented only with a cough of a six weeks' duration and a computed tomography (CT) scan of the thorax, abdomen and pelvis showed a 22 mm × 20 mm upper lobe left lung lesion. An incidental 150 mm × 150 mm uterine fibroid was also noted (Figure 1A). After a left upper lobectomy and lymphadenectomy her recovery was uneventful. Histology confirmed a poorly differentiated adenocarcinoma with 2 out of 3 left hilar lymph nodes involved. The resection margins were free on tumour and the inferior pulmonary ligament lymph nodes were not involved. The tumour cells were positive for thyroid transcription factor-1 (TTF-1). She was staged as ⅡA NSCLC (T1N1M0). She received adjuvant chemotherapy with cisplatin and vinorelbine and remained disease free at subsequent follow-ups. The patient was a non-smoker whose only medical history was that of uterine fibroids which she had had since her first pregnancy, 23 years earlier. For her subsequent visits, a metastatic surveillance for the primary lung cancer was carried out with yearly CT scans of the thorax, abdomen and pelvis. No further imaging, *e.g.*, ultrasonography was performed for the uterine fibroid.

In September 2012, the patient was referred to our Department of Obstetrics and Gynaecology. The uterine fibroid had increased slightly in size (170 mm × 160 mm) causing bilateral hydronephrosis noted on the annual CT scan done for metastatic surveillance (Figure 1B). There was no evidence of disease recurrence and the patient remained completely asymptomatic. Clinically, she had a firm, regular, mobile 22-cm uterine mass palpable. Transabdominal and transvaginal ultrasonography revealed a cystic degenerative uterine mass (137 mm × 123 mm × 104 mm) with no increased vascularity demonstrated on Doppler studies suggesting a uterine leiomyoma (Figure 2). The ovaries were not visualised and endometrium was thin. Pap smear and renal function were normal. She underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy in October 2012. Intra-operatively, a 24-wk size uterus was found with atrophic tubes and ovaries, all of which were removed intact to avoid any disease dissemination. The specimen was then cut open intra-operatively to confirm the impression was that of a degenerated fibroid with a cystic cavity filled with brownish fluid and some calcifications (Figure 3). The patient recovered uneventfully. The final histology report showed a poorly differentiated carcinoma consistent with metastatic lung cancer showing similar morphology to the previous pulmonary malignancy. Immunohistochemical staining was strongly positive for TTF-1 and cytokeratin (CK) 7. The lesion was confined to the leiomyoma with no involvement of the endometrium, cervix or adnexae (Figure 4). The resection margins were free of tumour.

Subsequent metastatic survey with CT and bone scans was performed and did not show any disease. At her last follow-up in May 2013, she remained in remission with no evidence of recurrence and was clinically well.

DISCUSSION

The most common extragenital primary sites resulting in metastases to the uterine corpus are the breast (42.9%), colon (17.5%), stomach (11.1%) and pancreas (11.1%). The lung accounts for less than 5% of extragenital primary tumours and most of these are adenocarcinomas, the most frequent subtype of NSCLC[7].

In recent literature, there have been two reported cases of NSCLC with metastasis to the uterus. The first case involved a patient who presented with postmenopausal bleeding and a uterine lesion on surveillance positron emission tomography/CT imaging. She had had previous lung resection for NSCLC 3 years earlier. Sixteen months post-operatively, she developed suspicious mediastinal lymphadenopathy. An endometrial sampling showed uterine carcinosarcoma and subsequent hysterectomy and bilateral salpingo-oophorectomy revealed that besides the carcinosarcoma, there were other neoplastic foci in the uterine serosa, adenexae and cervix consistent with metastatic lung cancer[5]. The second case described a patient with advanced stage NSCLC treated with primary chemotherapy. Ten months after completing treatment, she complained of vaginal bleeding and ultrasonography showed an endometrial thickness of 10 mm. An endometrial biopsy confirmed endometrial metastasis from the primary lung cancer. A hysterectomy was not performed for this patient due to her clinical condition and advanced disease[6]. In both these cases, the patients had clinical symptoms (abnormal vaginal bleeding) and radiological abnormalities suggestive of a uterine malignancy. Differently from these reports, our patient was completely

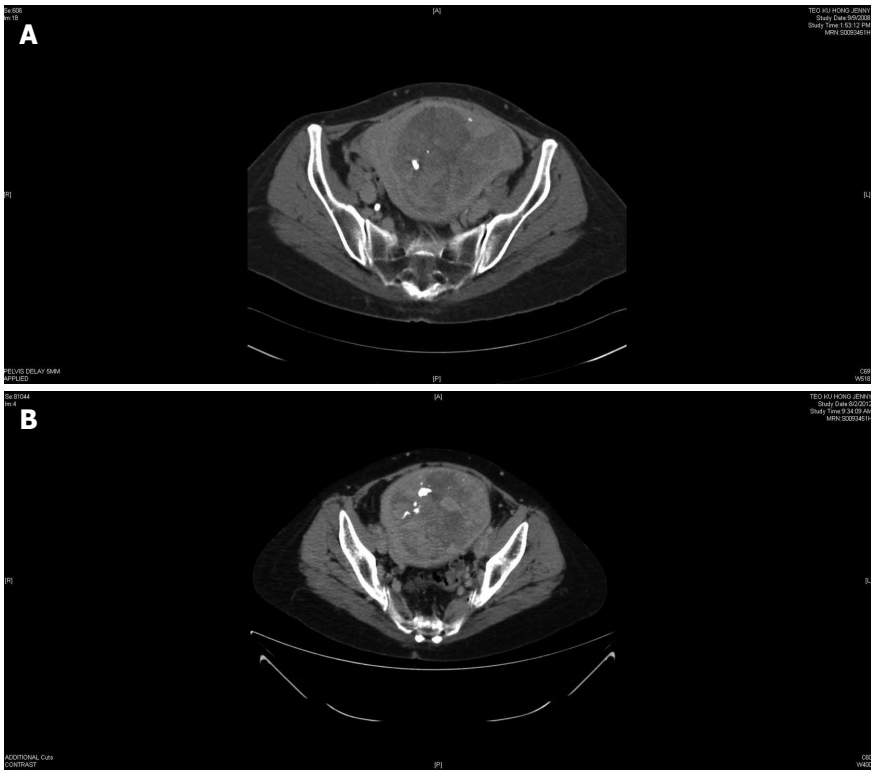

Figure 1 Computed tomography scan of the pelvis showing fibroid uterus. A: August 2008; B: September 2012.

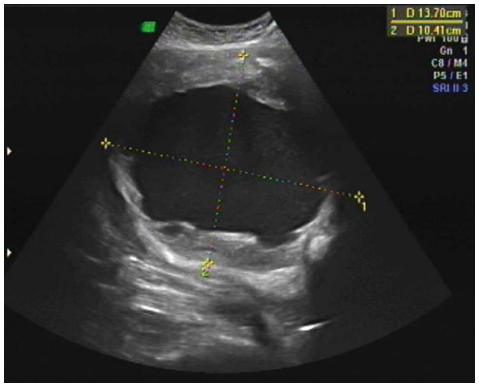

Figure 2 Transabdominal ultrasound showing fibroid with cystic degeneration.

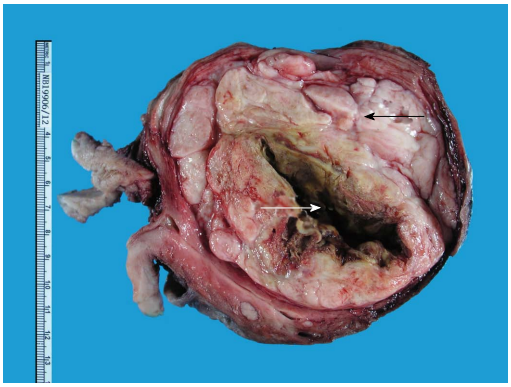

Figure 3 Hysterectomy specimen showing myometrial fibroid (black arrow) with cystic cavity (white arrow).

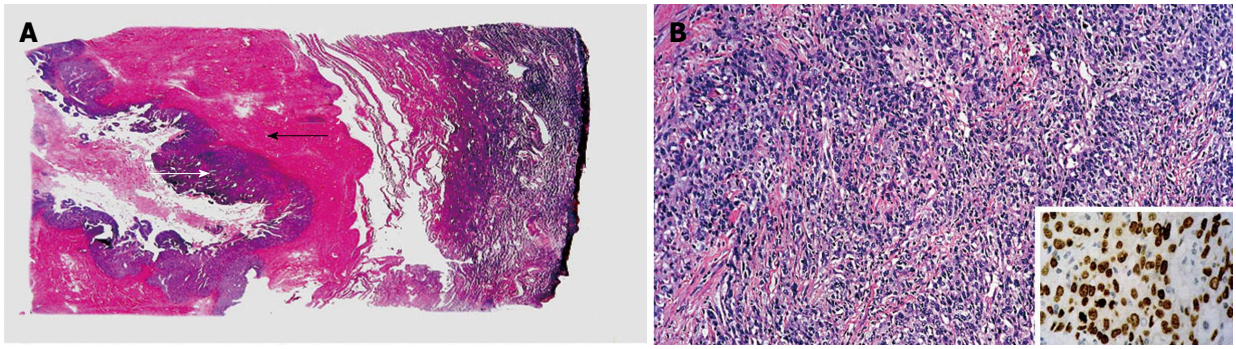

Figure 4 Histopathology. A: Tumour cells (white arrow) surrounding cystic cavity and the leiomyoma (black arrow); B: Sheets of malignant cells and those staining positive for thyroid transcription factor-1 (inset).

asymptomatic, had no evidence of disease progression or recurrence for 4 years since her initial diagnosis of lung cancer, had a long history of fibroids and there was no radiological suspicion of metastatic disease. She had not

experienced any abnormal vaginal bleeding and the endometrium was thin thus an outpatient endometrial sampling was not performed unlike the previous cases. As the overall pre- and intra-operative impressions were that of a leiomyoma only, we performed an extrafascial hysterectomy and salpingo-oophorectomy without surgical staging. The clinical picture here was neither consistent with a primary uterine malignancy nor with metastasis of a lung malignancy.

Although pathological examination did reveal leiomyoma, the final diagnosis was clinched by immunohistochemistry which is valuable in proving the primary origin of the malignant component. TTF-1 is a protein which stains positively in pulmonary adenocarcinomas and is sensitive and specific for respiratory and thyroid malignancies[8]. In this patient, her initial histology showed a lung cancer which stained for TTF-1 and the subsequent pathology report of the hysterectomy specimen also showed tumour cells similarly positive for TTF-1, ascertaining the pulmonary origin of the lesions in the leiomyoma. CK staining with CK7 and CK20 is also useful in distinguishing primary and metastatic lung adenocarcinomas from other malignancies, *e.g.*, colorectal tumours. Primary and metastatic pulmonary adenocarcinomas show a typical $CK7^{+}/CK20^{-}$ staining pattern which was comparable in our case, corroborating the diagnosis of lung cancer with metastasis and excluding a primary uterine malignancy[9].

Other metastatic sites in the female genital tract originating from the lung that have been reported include the cervix and vagina and these are rare too. In their analysis of 325 cases with metastasis to the female genital tract, Mazur *et al*[1] found that in 149 cases, the origin of the primary tumour was extragenital, the remainder being intragenital metastases. The ovaries and vagina were the most frequent sites of metastasis and most of these extragenital primaries were adenocarcinomas of the gastrointestinal tract.

Tumour-to-tumour metastasis was described by Campbell *et al*[10] by the following strict criteria: there must be > 1 primary tumour, the recipient tumour being either benign or malignant (a leiomyoma in our case); the donor tumour must be a proven malignancy (lung adenocarcinoma in our case) and this must metastasize with an established growth in the recipient tumour. Finally, a pre-existing lymphoma must be excluded should metastatic lymphadenopathy occur. Our patient fulfils all the criteria for this uncommon phenomenon and to date, about 60 cases of metastasis from a malignancy to a benign tumour have been reported[11].

In conclusion, metastasis from a lung adenocarcinoma to the female genital tract is uncommon and to a uterine leiomyoma only is rare. Even in an asymptomatic patient with a long-standing history of a benign condition like fibroids and with no clinical evidence of disease recurrence for a few years, one should be aware that the formation of metastases can occur. The history of the initial disease and the use of immunohistochemical markers like TTF-1 and CK7 are essential in distinguishing between a primary versus metastatic uterine adenocarcinoma and localizing the pulmonary origin. Although there are not enough data to quote a prognosis for this patient, it would seem optimistic at this point as the metastatic survey post-operatively was negative and the metastatic tumour was completely resected with clear margins.

COMMENTS

Clinical diagnosis

The clinical findings were that of a firm, regular, 22-cm uterine mass on abdominal and pelvic examination with a normal cervix and no adnexal masses.

Differential diagnosis

The possible differential diagnoses of the pelvi-abdominal mass were a uterine fibroid, which was the most likely given the long-standing history and lack of symptoms, a uterine sarcoma or an ovarian pathology, which were less likely in view of the history, lack of symptoms and clinical findings.

Laboratory diagnosis

Laboratory testing did not contribute greatly in this case and the main methods were a full blood count, renal function test and Pap smear cytology which were all normal.

Imaging diagnosis

A computed tomography scan of the thorax and abdomen was done which showed no recurrent lung disease but slight enlargement of the uterine fibroid causing upper urinary tract dilatation - this was confirmed on ultrasonography which was suggestive of degenerating uterine leiomyoma.

Pathological diagnosis

The gross pathological finding was that of a degenerated fibroid with a cystic cavity and the microscopic findings were that of metastasis of the original lung cancer to the uterine leiomyoma which was confirmed with immunohistochemical staining for thyroid transcription factor-1 (TTF-1) and cytokeratin (CK) 7.

Treatment

The treatment for the primary lung cancer was left upper lobectomy and lymphadenectomy with adjuvant chemotherapy and for the metastatic disease to the uterus, the treatment was total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Related reports

Other contents would include the pattern of metastasis of primary lung cancer, *i.e.*, mainly to the regional lymph nodes and liver/brain and the possibility of haematogenous spread to more distant organs like the uterus in this case.

Term explanation

TTF-1 is a protein nuclear transcription factor that is expressed in lung and thyroid tissue and is used in anatomic pathology as a marker to determine if a tumour arises from the lung or thyroid. CK7 is a protein found in the glandular epithelium of thyroid and breast tissue but not in others like the colon or prostate. It is commonly used in conjunction with CK20 to distinguish between colon cancer and other types *e.g.* ovarian.

Experiences and lessons

Large uterine masses in the presence of a known primary malignancy may be associated with secondary (metastatic) disease rather than the commonly assumed primary uterine pathology.

Peer review

The article reminds us that when clinicians encounter pelvic masses, it is important to think beyond the commoner gynaecological pathologies, especially in the setting of a known primary malignancy. The authors also aim to increase awareness of the phenomenon of "tumour-to-tumour" metastases and the value of immunohistochemistry in reaching a diagnosis to educate readers on these less commonly used but essential methods.

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GENERAL INFORMATION

World Journal of Obstetrics and Gynecology (*World J Obstet Gynecol*, *WJOG*, online ISSN 2218-6220, DOI: 10.5317) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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WJOG covers topics concerning pregnancy complications, obstetric surgical procedures, diagnostic imaging, endoscopy, reproductive endocrinology, tumors, pelvic diseases, evidence-based medicine, epidemiology and nursing.

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Acknowledgments

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic

programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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EDITORIAL

Infertility and gynaecological oncology

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Abstract

Infertility and gynaecological cancer are two major problems in the field of women's health, where both have serious implications on a woman's physical, social and emotional wellbeing. There are well established links between many aspects of infertility and different types of gynaecological malignancies, including etiology, pathogenesis and disease management. In this special issue there are valuable articles that highlight different aspects of the relationship between infertility and gynaecological oncology. The issue covers conditions that represent risk factors for both infertility and gynaecological neoplasia. There is emphasis on the role of the fallopian tube being a critical organ for both conditions. There is a review on the advances in cancer diagnosis and treatment with consideration of the preservation of patient fertility. The various technologies for fertility preservation are reviewed and their strengths and weaknesses discussed. One of the important fertility preservation techniques is cryopreservation of embryo oocytes or ovarian tissue. This special issue emphasises that fertility preservation is now an important consideration in oncology clinics, and the options available to patients are routinely offered. Future developments will offer women in this difficult situation more options for fertility preservation, with an individualised approach for each patient. Equally, for infertile patients it is important to assess the risk of malignancy so as to provide optimal and timely intervention.

Key words: Infertility; Gynaecological tract; Cancer; Malignant; Tumour

Core tip: Infertility and gynaecological cancer are two major problems in the field of women's health, where both have serious implications on a woman's physical, social and emotional wellbeing. In this special issue there are valuable articles that highlight different aspects of the relationship between infertility and gynaecological oncology. This special issue emphasises that fertility preservation is now an important consideration in oncology clinics, and the options available to patients are routinely offered.

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INFERTILITY AND GYNAECOLOGICAL ONCOLOGY

Infertility and gynaecological cancer are two major problems in the field of women's health, where both have serious implications on a woman's physical, social and emotional wellbeing. There are well established links between many aspects of infertility and different types of gynaecological malignancies, including etiology, pathogenesis and disease management. In this special issue there are valuable articles that highlight different aspects of the relationship between infertility and gynaecological oncology.

Some of the conditions contributing to female factor infertility are known risk factors of gynaecological neoplasia, and infertility may itself be a risk factor for the development of several types of gynaecological neoplasms.

Factors playing a role in both infertility and gynaecological tumours include hormonal factors and endometriosis[1]. Also factors that prolong exposure to ovulation as infertility increase the risk of ovarian cancer, due to the damaging effects of the liberated reactive oxygen species on the regional epithelium[2]. The review by El Sabaa[3] addresses the different conditions that play a role in both infertility and gynaecological oncology.

Magdy and El-Bahrawy[4] specifically review the role of the fallopian tube in infertility and gynaecological oncology. Tubal factor infertility is a leading cause of female factor infertility[1]. Tubal dysfunction may due to tubal occlusion, peritubal adhesion and fimbrial damage, all of which can lead to reproductive failure. Recently several studies suggested a role for the fallopian tube in the development of ovarian carcinoma[5].

With advances in cancer diagnosis and treatment, there is notable improvement in patient survival. The ability to have children is significant for the well-being in cancer survivors. The management of gynaecological malignancies involves surgery, pelvic radiotherapy and chemotherapy, for which infertility and subfertility are common sequelae. Hence fertility preservation is a particularly challenging area in this setting. Recently fertility sparing management of gynaecological cancers has been developed.

As the trend to delay childbearing continues a greater number of women are being diagnosed with endometrial cancer at a stage in life when they wish to conceive. In his review Farthing[6] presents the studies addressing the success and limitations of conservative medical treatment with progestagens in such situation as an alternative to hysterectomy and removal of both ovaries in suitable cases.

Due to improved cure rates from radical chemo-radiotherapy many young women treated for cervical cancer will wish to attempt to preserve their fertility[7]. Evidence of the impact of pelvic radiotherapy on the female reproductive organs, the currently available fertility sparing options, and possible future strategies are reviewed by Welsh and Taylor[8].

Different fertility preservation techniques may be performed prior to both surgery and chemotherapy, to enable subsequent pregnancy in the patient or a surrogate mother. One of these techniques is cryopreservation of embryo oocytes or ovarian tissue[9]. Similarly, evolving chemotherapy regimens with replacement of alkylating agents will reduce the incidence of infertility. In their review Sacco *et al*[10] discuss different scenarios of how infertility presents a clinical problem in gynaecological malignancies as a complication to the use of chemotherapy. The various technologies for fertility preservation are reviewed and their strengths and weaknesses discussed. Wahba and Al-Inany[11] in their article provide the details of the options for ovarian stimulation for fertility preservation in women with gynecological cancer. Their review also addresses the issue of increased levels of estradiol during ovulation induction in women with estrogen sensitive cancers, such as breast and endometrial cancer.

This special issue emphasises that fertility preservation is now an important consideration in oncology clinics, and the options available to patients are routinely offered. Future developments will offer women in this difficult situation more options for fertility preservation, with an individualised approach for each patient. Equally, for infertile patients it is important to assess the risk of malignancy so as to provide optimal and timely intervention.

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TOPIC HIGHLIGHT

Mona A El-Bahrawy, MBBCh, MSc, PhD, FRCPath, *Series Editor*

Pathological conditions predisposing to infertility and gynaecological neoplasia

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Abstract

Some of the conditions long blamed for female factor infertility are now acknowledged as well established risk factors of gynecological neoplasia. This realization has lead to the proposition that infertility might be a risk factor for the development of several types of gynecological neoplasms. This review addresses different conditions that play a role in both infertility and gynaecological neoplasia. An intricate interplay between growth factors and hormonal factors (estrogens and progestins, androgens and gonadotropins) is said to link the state of infertility to some gynecological tumors. The relation between endometriosis -as one of the well established causes of female infertility - and ovarian cancer is well known. Endometriosis has been particularly related to endometrioid and clear-cell ovarian carcinomas. Another evidence for this association is embodied in finding endometriotic lesions adjacent to ovarian cancers. The polycystic ovary syndrome (PCOS), one of the most prevalent endocrine disorders and a long studied cause of female infertility increases the risk of endometrial carcinoma. The link between PCOS and endometrial carcinoma seems to be endometrial hyperplasia. PCOS-associated endometrial carcinoma tends to present at a younger age and early stage, with lower grade and lower risk of metastasis. Turner's syndrome and other types of ovarian dysgenesis constitute a rare cause of infertility and are known to confer a definite risk of germ cell tumors. There seems to be a link between infertility and an increased risk of gynecological neoplasia. Hence, it is important to assess the risk of malignancy in each category of infertile patients so as to provide optimal and timely intervention.

Key words: Infertility-gynecological cancer; Endometriosis; Polycystic ovary syndrome; Ovarian dysgenesis; Endometrioid carcinoma; Clear cell carcinoma; Turner's syndrome; Gonadoblastoma; Hyperestrogenemia

Core tip: Female infertility is now acknowledged as a risk factor of gynecological neoplasia. In this mini-review we conduct a comprehensive literature review to verify this prospect. The principal pathogenetic mechanisms linking infertility to gynecological neoplasia are pointed out. The relationship between each of endometriosis and polycystic ovary syndrome and gynecological neoplasia is explored in depth. We discuss the relation of Turner's syndrome (the prototype of ovarian dysgenesis) to gynecological cancer. Is there a relation between increased risk of ovarian cancer and ovulation-stimulation drugs? We will attempt to answer this question.

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INTRODUCTION

In a World Health Organization 1992[1] study of 8500 infertile couples, the female factor was responsible for infertility in 37% of cases *vs* the male factor which was responsible in 8% of cases, while both factors were jointly

responsible for infertility in 35% of cases[1]. Ovulatory disorders, genetic factors, endometriosis, pelvic adhesions, tubal obstruction and hyperprolactinemia together constitute the principal causes of female factor infertility[1].

IS THERE A RELATION BETWEEN INFERTILITY AND GYNECOLOGICAL NEOPLASIA?

Some of the conditions responsible for female factor infertility are known risk factors of gynecological neoplasia. Ovarian and endometrial cancers are associated with several risk factors such as low parity, early age of menarche and late age of menopause[2].

It is a well known fact that infertile females are more at risk of endometrial cancer[2].

Compared with fertile ones, infertile women had an adjusted odds ratio for endometrial cancer of 1.7 (95%CI: 1.1-2.6). On the other hand, infertile women due to ovarian factors had an adjusted odds ratio of 4.2 (95%CI: 1.7-10.4) suggesting that much of the increased risk of endometrial carcinoma seen in some infertile women might be ascribed to anovulation[3]. In the same context, there is some evidence to suggest that infertility increases risk of ovarian cancer as well[4,5].

Numerous studies have endeavored to explain the observed increased risk of ovarian cancer in infertile females. Most have inferred that factors operative in that setting include the pathogenesis of infertility itself, the effects of ovulation inducing drugs, a "putative" shared genetic susceptibility to infertility and ovarian cancer, or an as yet unrecognized factor[6].

The etiology of ovarian cancer is poorly understood. Many hypotheses point to the cumulative insults of repeated ovulation "theory of incessant ovulation[7]" coupled with exposure of the ovary to high gonadotropin levels. These factors are believed to be the proximate players that can stimulate cell proliferation and malignant transformation of the ovarian surface epithelium. Factors interrupting ovulation and empowering progesterone stimulation or androgen reduction were found to decrease the risk of ovarian cancer. Such factors include pregnancy, breastfeeding and the use of oral contraceptives. On the other hand, factors that prolong exposure to ovulation as infertility were found to augment the risk[8-12] by as much as 36%-46%[4,5].

In fact the number of lifetime ovulatory cycles (LOC) relative to age was found to be a significant predictive factor for survival in ovarian cancer patients, where patients with higher LOC had worse overall survival (HR = 1.67; 95%CI: 1.20-2.33)[13]. Years before that research was conducted; the role of ovarian surface epithelium in ovulation had been demonstrated. Ovarian surface epithelial cells in the vicinity of the apical portion of preovulatory graafian follicles produce a urokinase which augments the production of tumour necrosis factor-α. The latter induces matrix metalloproteinase gene expression, apoptosis and inflammatory necrosis leading to follicle rupture. Afterwards, the disrupted ovarian epithelium is reconstituted by stem cell multiplication. The damaging effects of the liberated reactive oxygen species and the reparative/regenerative events that occur due to the repeated bouts of ovulation[14] have been linked to surface epithelial ovarian cancer. During the ovulatory process, DNA integrity of surface epithelial cells surrounding the rupture point is deranged. Replication of such cells will perpetuate the putative DNA error which might play a role in ovarian carcinogenesis[15].

In the same context, vitamin E and progesterone have been experimentally proven, recently, to confer protection against ovarian neoplastic transformation by abrogating ovulation associated oxidative bursts and by improving the repair capacity of surface epithelium[16].

Different phases of a woman's reproductive life display varying sensitivities of ovarian cells to hormone stimulation. Loss of ovarian function taking place during transition to menopause results in follicular depletion and hence fluctuation in estrogen and a corresponding surge in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. However, menopause is also associated with a remarkable attenuation of the negative feedback exerted by gonadal steroids on the hypothalamo-pituitary axis. Based on these facts, Tung *et al*[17] came to the conclusion that the risk reducing effects of anovulatory states as pregnancy and intake of oral contraceptives were more pronounced in pre-menopausal compared to postmenopausal women.

Evidence is now accumulating about the existence of stem cells in postnatal and adult mammalian (including human) ovaries. This has great potential for initiating major developments in understanding and managing ovarian infertility as well as ovarian carcinogenesis[18].

Pathogenetic link between infertility and gynecological "malignancy"

Abnormalities in growth factors and hormonal status seem to be the pivotal players in this link.

Growth factors: Adipose tissue and stromal cells of the ovary generate growth factors, *e.g.*, insulin-like growth factor 1 (IGF-1), transforming growth factor and tumor necrosis factor after hormonal stimulation. A complex interplay of growth factors in polycystic ovary syndrome (PCOS) patients is believed to be the main cause of subfertility/infertility in these patients[19,20]. One such example is the elevated serum IGF-I concentrations in obese PCOS patients[21-25]. On the other hand, growth factors can enhance cellular autonomy and are stimulatory to neoangiogenesis, which are key factors in tumor development and progression[26-28]. In the endometrium, estrogen exerts its trophic effect *via* driving the local expression of the *IGF-1* gene[24]. Genetic variation in strategic genes in the IGF pathway may have impact on the rate of endometrial cell proliferation/differentiation and hence on the risk of malignant transformation[25].

Steroid hormones have been implicated in the etiopathogenesis of epithelial ovarian cancer[26].

Androgens: Hyperandrogenemia during the reproductive years is known to interfere with the normal ovulatory cycle and may result in infertility[27-31]. Several lines of evidence point to a possible role for androgens in ovarian carcinogenesis. There is increased incidence of ovarian cancer after menopause when there is relative predominance of androgens over estrogens. Androgen receptor positivity is expressed in 90% of ovarian cancers with favorable outcomes and chemotherapy induced reduction in androgen elaboration by cancer cells[26].

Gonadotrophins: Pituitary gonadotrophins are considered indirect tumor promoters for ovarian cancer. Furthermore, there is increasing evidence that ovarian and uterine carcinomas express gonadotrophin receptors, indicating the possibility of a direct tumorigenic role for FSH and LH[29-32].

Estrogens: It is a well established fact since 1947, that prolonged endometrial stimulation by unopposed estrogen is a risk factor for the development of endometrial cancer[33]. Anovulatory females recorded higher serum levels of estrogen and higher incidence of endometrial carcinoma especially in PCOS[34].

ENDOMETRIOSIS AND CANCER

Multiple factors seem to be involved in the etio-pathogenesis of both endometriosis and ovarian cancer including hormonal, genetic and immunologic factors. Endometriosis confers a twofold increased risk of developing ovarian cancer rising to fourfold in high risk endometriosis patients with infertility[2].

Several studies confirm endometriosis as an independent risk factor for ovarian cancer[35]. In fact, these two conditions share common predisposing factors, comparable patterns of local invasion and distal spread, similar response to estrogen-induced growth signaling, resistance to apoptosis and genomic instability[35].

The incidence of endometriosis in epithelial ovarian cancer has been calculated to be 4.5%, 1.4%, 35.9% and 19% for serous, mucinous, clear-cell and endometrioid ovarian carcinoma, respectively[35]. It is common knowledge now that the latter two types (endometrioid[36] and clear-cell ovarian[37] carcinomas) are the types most frequently associated with endometriosis[37].

Another evidence for this association is finding endometriotic lesions adjacent to ovarian cancers. Common genetic alterations[38] as *PTEN, p53*[39-41], *HNF-1* activation[42], *K-ras*[42,43], and *bcl* gene mutations[39,44] present further evidence to a possible sequence of genetic changes resulting in transition from endometriosis to ovarian cancer[40]. Furthermore, analogous to neoplastic proliferations, endometriosis has been shown to be monoclonal with several studies documenting loss of heterozygosity[39,42,45,46].

Recently, mutation of *ARID1A*, a tumor-suppressor gene[39,47], and loss of BAF250a[48], both detected in tumor tissue and contiguous foci of atypical endometriosis (but not in distant endometriotic lesions)[48] have been considered important early events in the malignant transformation of endometriosis to endometrioid and clear cell carcinomas[39,48,49].

Another phenomenon linking endometriosis to ovarian cancer is the state of heme and iron induced oxidative stress and chronic inflammation[39,50,51] associated with endometriosis. This state entails cytokine release that through a series of complex steps can eventually culminate in unregulated mitosis, growth, apoptosis and migration; all of which represent key events in tumour development and progression[40,42].

Endometriosis-associated ovarian cancer has been shown to have a more favorable biological behavior as compared to non-endometriosis-associated ovarian cancer, with presentation at a lower stage and a better survival[35].

PCOS AND GYNECOLOGICAL NEOPLASIA

The PCOS is one of the most prevalent endocrine disorders, affecting around 5%-10%[52] of women in the reproductive age group. PCOS is characterized by signs of hyperandrogenism[53], obesity[54], hirsutism[55,56], anovulation, infertility, menstrual irregularities[57] and insulin resistance[58,59]. On sonographic examination the ovaries are usually enlarged with multiple small cysts (2-8 mm)[60,61].

PCOS patients have long-term, higher risk for endometrial hyperplasia and endometrial cancer[62-65], (three[34] to fourfold[66]) due to chronic anovulation which results in continuous estrogen stimulation of the endometrium, unopposed by progesterone[60,67].

Most of the factors known to increase the risk of developing endometrial cancer as obesity, long term unopposed hyperestrogenaemia, nulliparity, infertility and diabetes[68-70] are also known to be associated with PCOS.

The link between PCOS and endometrial carcinoma seems to be endometrial hyperplasia. Forty-eight point eight percent of PCOS cases have endometrial hyperplasia[34]. The estimated rate of progression from hyperplasia to carcinoma within 2 to 10 years seems to be 0.4% for simple hyperplasia[60] and approaches 18% for cases of atypical complex hyperplasia[60,71].

PCOS-associated endometrial carcinoma tends to present at a younger age and early stage, with lower grade and lower risk of metastasis. These factors have practically invited some authors[72,73] to advocate conservative management of carcinoma in these patients.

PCOS has also been reported to be associated with low-grade endometrial stromal sarcoma and uterine carcinosarcoma[74].

Other sex hormone dependent cancers as breast and ovarian cancers have also been linked to PCOS[61]. Recent evidence about association between PCOS and ovarian malignancy are still conflicting[71,74]. According to Danish

studies, the implied state of infertility *per se* increases the risk of borderline and malignant ovarian tumors[75]. High local steroid and growth factor concentrations - frequently observed in PCOS - are considered risk factors for ovarian carcinoma[61]. However, a large scale British study confirms that the standardized mortality rate for ovarian cancer in these patients does not exceed 0.39 (95%CI: 0.01-2.17)[76]. There is insufficient evidence to implicate PCOS in the development of vaginal, vulval and cervical cancers[34].

OVARIAN DYSGENESIS, GENETIC INFERTILITY AND CANCER

Sex chromosome abnormalities compose the largest category of chromosome aberrations and the most common genetic cause of infertility among humans[77-80]. Dysgenetic gonads are at risk for development of germ cell tumors[81-84] which may stem from genetic and/or hormonal factors[85,86].

Dysgenetic gonads are reported to progress to invasive germ cell neoplasms namely; dysgerminoma and less commonly embryonal carcinoma, teratoma, yolk sac tumor and choriocarcinoma[87]. Accordingly some authors[81,88] advocated prophylactic gonadectomy once the diagnosis of gonadal dysgenesis is established.

Turner syndrome is one of the most common conditions resulting from cytogenetic abnormalities where there is complete or partial monosomy of the X-chromosome. These patients have a significantly increased risk of ovarian gonadoblastoma[81,85], dysgerminoma[84] and cancer of the corpus uteri in addition to a constellation of somatic tumors including central nervous system, ocular and urinary bladder tumors[85,89,90]. Paradoxically, risk for breast cancer is decreased among patients with Turner syndrome[85,91,92].

FERTILITY DRUGS AND GYNECOLOGICAL CANCER

Generally, data concerning the possible association of exposure to ovulation induction medications and developing invasive ovarian cancer show no increased risk[6,93-95]. A group exploring the long-term (over 20 years) health effects of ovarian-stimulation drugs showed no relationship between ovarian cancer risk and ovulation-stimulation drugs[91]. However they stressed the importance of continuous monitoring to verify whether such risks were higher among particular user cohorts[96-98]. According to some studies, women who failed to conceive after infertility treatment were found to be at a higher risk for ovarian malignancy compared to women who responded successfully[6,91,99].

The relationship of these agents with risk of breast and endometrial cancer is still controversial[95,100].

CONCLUSION

Infertility seems to confer an increased risk of gynecological neoplasia. It is important to assess the risk of malignancy in each category of infertile patients so as to provide optimal timely intervention. To date, no solid relation has been declared between fertility drugs and causation of gynecological malignancy.

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TOPIC HIGHLIGHT

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Fallopian tube: Its role in infertility and gynecological oncology

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Abstract

Disorders of the fallopian tube play a very important role in both infertility and gynaecological oncology. Tubal factor infertility is considered among the leading causes of female factor infertility. Many tubal disorders are related to infertility including congenital anomalies, acute and chronic inflammatory diseases, endometriosis and other pathologies that result in partial or total fallopian tube obstruction. In the field of gynaecological oncology, ovarian surface epithelial tumors remain one of the most fatal malignancies in women worldwide carrying the worst prognosis among female genital malignancies. For decades, the cell of origin of epithelial tumors has remained controversial and was largely believed to be surface ovarian epithelium. Recently several studies suggested that there is a major role of the fallopian tube in the development of ovarian surface epithelial tumors, mainly high grade serous carcinoma and other tumour types. In this article we review the role of the fallopian tube in both infertility and gynaecological oncology.

Key words: Fallopian tube; Infertility; Endometriosis; Salpingitis; Serous carcinoma

Core tip: Disorders of the fallopian tube play a major role in infertility. These disorders include congenital anomalies, inflammation and different other causes of tubal obstruction. Recently several studies suggested a role for the fallopian tube in the development of ovarian carcinoma, mainly high grade serous carcinoma. This article reviews the role of the fallopian tube in infertility and gynaecological oncology.

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INTRODUCTION

The fallopian tube plays an important role in problems related to infertility[1] and is only recently recognized to play the leading role in the pathogenesis of pelvic (non-uterine) serous carcinomas[2].

THE FALLOPIAN TUBE AND INFERTILITY

Infertility is defined as couple's failure to conceive after 1 year of regular, unprotected intercourse[3]. Tubal factor infertility is among the leading causes of female factor infertility accounting for 7%-9.8% of all female factor infertilities. Tubal disease directly causes 36% and 85% of all cases of female factor infertility in developed and developing nations respectively[4].

The fallopian tubes must be patent with normal anatomic relation to the adjacent ovary to allow the capture

of an ovum, provide a suitable environment for fertilization, and transport the fertilized ovum to the endometrial cavity for implantation[3]. Transport of gametes and embryos is achieved by complex interaction between myosalpynx contractions, ciliary activity and the flow of tubal secretions[5]. This complex movement also aims at stirring of the tubal contents to ensure mixing of gametes and embryos with tubal secretions[6]. The fallopian tube itself acts as a sperm storage site as the endosalpinx provides a favorable environment for sperms. Sperm-endosalpingeal contact preserves the viability of sperms increasing the chance for successful fertilization[1].

Tubal factor infertility may result from complete blockage of the distal end of the fallopian tube (hydrosalpinx) as a sequelae of sexually transmitted disease (STD), surgical intervention or other intra-abdominal conditions, non-gynecological abdomino-pelvic infection, endometriosis, or a congenital anomaly. Proximal obstruction may result from salpingitis isthmica nodosa (SIN) or other inflammatory conditions, or it may be idiopathic. Peritubal adhesions or damage to the lining of the tube can impair tubal mobility, oocyte pickup, and/or sperm and embryo transport[7].

CONGENITAL ANOMALIES AND GENETIC DISORDERS

Congenital müllerian duct abnormalities are considered fairly common and have been estimated to be present in 1 in 500-700 women, yet complete absence of fallopian tube is a very rare condition that is usually unilateral and asymptomatic[8,9]. Absence or loss of patency of segments of the fallopian tube (atresia, hypoplasia, or interruption)[10], and ampullary atresia[11] were also described. These may be unilateral or bilateral, and can occur without or in conjunction with uterine anomalies, such as uni or bi-cornuate uterus[10].

The use of diethylstilbestrol (DES) during pregnancy was discontinued decades ago, but surgical specimens from patients who were born during the DES era may still be examined today, showing substantial developmental damage to the fallopian tubes. Fetal exposure to DES results in shortened, sacculated, and convoluted fallopian tubes. The fimbriae are constricted, and the os is pinpoint. The mucosa may be absent and if present, the plicae do not develop[1].

Tubal dysfunction may also be caused by the immotile cilia of Kartagener's syndrome[5], including about one half of the patients with primary ciliary dyskinesia (PCD). The latter is an autosomal recessive condition with estimated incidence of 0.5-1 in 30000 live births, causing dysfunctional motility of cilia and impaired mucociliary clearance, resulting in many clinical manifestations including recurrent sinopulmonary disease, laterality defects and infertility[12].

INFLAMMATORY DISEASES

Salpingitis causes tubal occlusion, peritubal adhesion and fimbrial damage, all of which can lead to reproductive failure[13,14]. Microorganisms and the host's immune response may result in scar tissue formation, altering the activity of tubal cilia, resulting in the partial or complete destruction of cilia with alteration of the composition and viscosity of the tubal secretions[15]. The inflammation in the tube may extend to adjacent tissues, including the ovary, forming a tubo-ovarian abscess[16].

Three major types of salpingitis are recognized: acute, chronic, and granulomatous/histiocytic[1].

Acute salpingitis (other than physiologic salpingitis, occurring at time of menses or puerperium)[1,16] is the pathologic correlate of the clinical entity, pelvic inflammatory disease (PID), which occurs in young, sexually active women in the reproductive age[1]. Acute salpingitis may be caused by an ascending infection, following invasive procedures (such as curettage or the insertion of intrauterine devices)[17], or secondary to STD by Chlamydia, N. gonorrhoeae or Mycoplasma[16]. Seminal fluid acts as a vehicle through which microbes are transferred to the upper genital tract. Some microorganisms have the ability to attach to the surface of spermatozoa, whilst others are obligate intracellular parasites within the spermatozoa[15]. Other non-sexually transmitted pathogens (*e.g.*, *E. coli*, *streptococci*, *staphylococci*, *coliform bacilli*, and *anaerobes*) may reach the tubes *via* the blood stream or lymphatics, especially after an abortion or pregnancy[16]. The response of the mucosa of the fallopian tube to microorganisms is not uniform. For example, *E. coli* cause swelling of the ciliary tips with adhesions between shortened and swollen cilia and cause shortened microvilli in non-ciliated cells. N. gonorrhoeae causes invagination in ciliated cells and loss of microvilli in non-ciliated cells[15].

Chlamydia trachomatis (a Gram-negative bacterium) is the most common organism of STDs worldwide[18], it can be isolated from a large portion of women with tubal factor infertility and elevated anti-C trachomatis antibodies can be detected in more than 70% of women with tubal occlusion. Yet, the exact pathogenesis of C trachomatis-induced tubal damage is still unknown with no available effective vaccines[19,20]. The primary site of chlamydial infections is the columnar endocervical epithelial cells[20]. It has been hypothesized that the host immune response by C trachomatis infection is responsible for the damage rather than the infection itself[21,22]. The protective host immune response is induced by production of antibodies against chlamydial major outer membrane protein (MOMP). This was supported by the recent findings that immunization with a native MOMP induces protection[22]. However, antibodies against chlamydial heat shock protein (HSP) 60 are associated with pathologies, which may provide an explanation for the observation that whole chlamydial organism-based vaccines is associated with exacerbated pathology. Chlamydial infection leads to tubal ciliated epithelial destruction with subsequent tubal infertility and ectopic pregnancy *via* production of cytokines, including interleukin (IL)-1, which has a toxic effect on ciliated tubal cells[15]. Chlamydia can enter a dormant, per-

sistent state, where, in the absence of a productive infection, there is still a low level of immune stimulation from antigen recognition. This low level stimulation is believed to cause chronic inflammatory cell infiltration[20].

In chronic salpingitis, the tubal fimbriae adhere to the ovary and adjacent tissues with subsequent obliteration of the ostium, leading to a hydrosalpinx or pyosalpinx. Hydrosalpinx is typically bilateral, but it may be unilateral. Late stages of chronic salpingitis may result in fibrous obliteration of the whole tubal lumen[16].

Granulomatous and histiocytic salpingitis may result from infection by different organisms (*e.g.*, Mycobacterium tuberculosis, Schistosoma, Oxyuris vermicularis, Actinomyces, Coccidioides immitis) or as part of a systemic granulomatous disease (*e.g.*, sarcoidosis and Crohn's disease)[17]. It may also be induced by local non-infectious causes, including foreign bodies introduced for diagnostic or therapeutic purposes (*e.g.,* lubricant jellies, mineral oil, powder or lipiodol)[1,16,17].

The commonest cause of granulomatous salpingitis is infection with Mycobacterium tuberculosis; predominantly affecting females below the age of 40 years, with peak age between 21-30 years. Tubal involvement occurs in 80%-90% of women with genital tuberculosis and is usually bilateral (90% of the cases)[23,24]. Tuberculous salpingitis is uncommon in the western world yet prevalent in developing countries[24], accounting for much less than 1% of cases in the United States, while representing nearly 40% of cases in India[1].

Female genital tuberculosis occurs secondary to primary disease elsewhere in the body. The spread is usually hematogenous or *via* the lymphatic route[24]. Sexual transmission of the disease is also documented but direct spread from other intraperitoneal foci is very rare[23]. Tuberculosis may cause minimal tubal damage and lead to ectopic pregnancy. However, extensive damage to the tubes can lead to tubal blockage in 60% of cases. Peritubal adhesions and tubo-ovarian masses have been found in 47.2% of cases[24]. As the tubercles enlarge and coalesce, they may erode through the mucosa and discharge their contents into the tubal lumen, leading to progressive scarring, with plica distortion and agglutination. Calcification can occur in areas of fibrosis[1,16,17].

Female genital schistosomiasis was described for the first time in a young Egyptian woman more than 100 years ago[25]. Tubal schistosomiasis may be one of the common causes of granulomatous salpingitis worldwide; yet it is rare in the United States[1,16]. More than 207 million people, representing 85% of those who live in Africa, are infected with schistosomiasis[26]. In Africa, the fallopian tube is involved by schistosomiasis in 22% of all infected women[1,2], with 7% presenting by infertility. The cervix, fallopian tubes and vagina are the most common gynecological sites to be affected. Blood vessel anastomoses between the pelvic organs are probably responsible for "spill-over" of eggs into the genital tract[27]. Gross findings appear to be related to fibrosis surrounding the eggs, producing a nodular or fibrotic tube[1,16].

Fungal infection rarely can cause tubo-ovarian abscesses or granulomatous salpingitis. Responsible organisms include Blastomyces dermatitidis, Coccidioides immitis, Candida, and Aspergillus reaching the fallopian tube by hematogenous spread or in the course of disseminated disease[1,16]. Pseudo-xanthomatous salpingitis (referred to as "pigmentosis tubae") is associated with endometriosis, yet it also might result from salpingitis with associated hemorrhage[1,16,17]. A granulomatous reaction may also be encountered in small to medium size arteries in patients with giant-cell arteritis[16].

ENDOMETRIOSIS

Endometriosis affects 5%-10% of the general female population of reproductive age[28], including 50%-60% of women and teenage girls with pelvic pain[29]. About 30%-50% of women with endometriosis are infertile[30]. Infertile women are 6-8 times more likely to have endometriosis than fertile women. Of infertile women 25%-50% have endometriosis[8,29]. Tubal endometriosis is identified in approximately 10% of fallopian tubes, most commonly involving the distal end[31]. Normally, endometrial tissue can be found within the mucosa of intramural and isthmic segments of the fallopian tube, referred to as endometrial colonization[1]. Endometriosis of the tube can be found within the lumen (focal replacement of tubal epithelium by uterine mucosa)[17]; or myosalpinx or on the serosa. Occasionally, tubal endometriosis may produce a mass simulating a tumor (polypoid endometriosis). Post-salpingectomy endometriosis is an apparently common form of endometriosis that occurs in the tip of the proximal stump of the fallopian tube years after tubal ligation[1].

Despite extensive research, several mechanisms have been proposed to explain endometriosis-related tubal factor infertility with no consensus reached to date[32]. The most popular hypothesis involves retrograde menstruation into the peritoneal cavity[33]. The retrograde menstruation of non-sterile menstrual blood into the peritoneal cavity provides a route for microbial transport. The menstrual debris may also promote continued survival and persistence of these microorganisms in the upper genital tract. These microorganisms may replicate causing tubal damage and the microflora stimulate chemotaxis of macrophages and the subsequent secretion of secondary inflammatory mediators identified in this condition[15].

Other mechanisms include: (1) associated pelvic inflammation causing adhesions and scar formation with subsequent impaired ovarian oocyte release or capture as well as impairment of tubal transport due to physical obstruction[15,30] in advanced stages of endometriosis[33]; (2) associated increased volume of peritoneal fluid[30], that contains increased numbers of macrophages and their secreted products (*e.g.*, growth factors, cytokines, and angiogenic factors) affecting various aspects of reproduction[33]. Also a macromolecular ovum capture inhibitor, causing formation of a membrane over the fimbrial cilia,

has been detected in the peritoneal fluid from women with endometriosis[15]; (3) Recently, endometriosis has been proposed to be an autoimmune disease because of the presence of a variety of autoantibodies against endometrium, ovary and sperm, these autoantibodies can be an important risk factor in endometriosis-associated infertility[34]; (4) Other theories are altered hormonal and cell-mediated function due to increased IgG and IgA antibodies and lymphocytes in the endometrium of women with endometriosis leading to alteration of endometrial receptivity and embryo implantation; and (5) associated endocrine and ovulatory disorders (*e.g.*, longer follicular phase with possibly lower serum estradiol levels and lower LH-dependent progesterone secretion during the luteal phase of the cycle)[30].

SIN or "adenomyosis" of the fallopian tube is a pseudo-infiltrative lesion consisting of diverticula of tubal epithelium in the isthmus. It occurs in women between the ages of 25 and 60 years (average, 30 years)[1]. The incidence of SIN in healthy, fertile women ranges from 0.6% to 11%[31]. It is bilateral in approximately 85% of cases[17]. It is accompanied by infertility in approximately one-half of patients[17] by interfering with upward sperm migration[31]. It may be difficult to distinguish SIN from tubal endometriosis in some cases[1].

ECTOPIC PREGNANCY

Ectopic pregnancy is defined as a pregnancy occurring outside the uterus or in an abnormal site within the uterus; 95%-99% arise in the fallopian tube[35]. The vast majority (80%) occur in the ampulla, with the isthmus (10%) and infundibulum (5%) being less common sites[31]. About 25% of tubal pregnancies have ruptured by the time of diagnosis[1]. This may impair/destroy tubal function with partial occlusion or luminal adhesions[36]. The usual treatment for tubal pregnancy is salpingectomy, yet segmental tubal resection may be appropriate in selected cases[17]. Retention of fertility after an ectopic pregnancy depends on how that pregnancy was managed and on the presence or absence of known risk factors[37]. Improvements in management of ectopic pregnancies have enhanced efforts towards preserving subsequent fertility; a principal goal of conservative treatment. However, conservative treatments are likely to increase the recurrence rate of ectopic pregnancy as the conserved tube is usually a damaged tube[38].

THE FALLOPIAN TUBE AND GYNECOLOGICAL ONCOLOGY

Primary fallopian tube adenocarcinoma is rare, accounting for less than 0.2% of cancer diagnoses among women annually[39]. Tubal carcinoma represents 0.7%-1.5% of gynecologic invasive malignancies[1] with an incidence of 0.41 per 100000 women in the United States[40]. In England and Wales, 40 cases of primary tubal adenocarcinoma are registered annually[41].

On the other hand, ovarian cancer is the 6th most common cancer in women worldwide and the 7th most common cause of cancer death[42] with an age-adjusted incidence rate 12.7 per 100000 women per year. This is based on cases diagnosed in 2005-2009 from 18 SEER geographic areas[43]. In Western countries, ovarian carcinoma is the 5th most common malignancy ranking 4th in cancer mortality, accounting for 4% of cancer in women and is the most frequent cause of death due to gynecological cancer. In United States women, ovarian cancer ranks 9th in incidence and 5th in mortality, accounting for 3% of cancers and 5% of cancer deaths. Serous carcinoma is the most common type of the ovarian epithelial malignancies, accounting for approximately 80% of cases[44].

Ovarian cancer has one of the highest death-to-incidence ratios[2,45] and is considered the most lethal of gynecologic malignancies[44]. The age-adjusted death rate is 8.2 per 100000 women per year in the United States[43].

A prerequisite for the success of early detection of any disease is the clear understanding of its natural history[46]. The high ovarian cancer related death rates have been attributed to the unavailability of effective screening tools, the absence of early symptoms in many patients, and the typical presentation at advanced stages when prognosis is poor[2,47]. One of the greatest obstacles to the detection of early-stage ovarian cancer was the poor understanding of its histogenesis and pathogenesis[2].

Until recently, the incessant ovulation theory has been the most accepted theory of ovarian carcinogenesis. According to this theory, constant ovulation-induced damage and repair of the ovarian surface epithelium (OSE) results in malignant transformation[48]. Ovarian carcinoma was also traditionally thought to originate from the OSE or ovarian epithelial inclusions (OEI)[2,49]. Hence, investigative efforts for early detection were centred on the ovary for decades. However, all have not been successful[2,50], as they failed to identify a convincing precursor in the ovary[49]. This was greatly reflected on the overall survival for women with ovarian cancer, which has not changed in any fundamental manner over the last 50 years[43].

Over the last several years, based on combined morphological and molecular data, a dualistic model for the pathogenesis of ovarian carcinoma has emerged[50,51]. The dualistic model divides ovarian epithelial tumors into two categories: Type Ⅰ and Type Ⅱ[1]. Type Ⅰ tumors are generally low-grade; including low grade serous carcinoma (LG-SC), low-grade endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma and malignant Brenner tumor. These tumors usually present at low stage and behave in a relatively indolent fashion[49]. In contrast, type Ⅱ tumors are high-grade, highly aggressive and present in advanced stage. They have been said to arise "*de novo*". They include high-grade serous carcinoma, high-grade endometrioid carcinoma, malignant mesodermal mixed tumour and undifferentiated carcinoma[1,49].

It is now believed that the fallopian tube may be the origin of ovarian carcinoma, rather than the ovarian surface epithelium, traditionally regarded as the origin of ovarian carcinoma[17].

ROLE OF THE FALLOPIAN TUBE IN TYPE Ⅰ OVARIAN SURFACE EPITHELIAL TUMORS

Low grade serous carcinoma is thought to evolve in a stepwise fashion from ovarian surface epithelial inclusions (OEIs)/serous cystadenomas to serous borderline tumors to invasive carcinoma[2,49,52], although they can be *de novo*[53].

The fallopian tube plays a central role in various components of this stepwise sequence[54] as it is proposed that the majority of OEIs are derived from the fallopian tube epithelial cells. These cells are capable of implanting on the ovarian surface[2] at the time of ovulation when the surface ovarian epithelium is ruptured[55].

This idea is supported by the following evidence: (1) Epithelial cells from tubal mucosa are easily shed after flushing the fallopian tube[55]; (2) Most (78%) of the OEIs and serous cystadenomas display morphological features and immunophenotype of tubal type epithelium (calretinin-/PAX8+/tubulin+)[2,50]; (3) Fallopian-derived OEIs may represent intra-ovarian endosalpingiosis; and (4) There is evidence against mesothelial origin of OEIs with müllerian metaplasia including, scarceness of hybrid or intermediate type of OEIs with both mesothelial and tubal phenotypes. In addition, studies show mesothelium-derived OEIs are not capable of growing into tumour masses with low cellular proliferative activity, compared to fallopian-derived OEIs that showed high proliferative activity and immuophenotype that are similar or almost identical to ovarian serous tumors[2,50].

ROLE OF THE FALLOPIAN TUBE IN TYPE Ⅱ OVARIAN SURFACE EPITHELIAL TUMORS

Accumulating evidence suggests that the fallopian tube epithelium, predominantly in the fimbrial region[1,49], is the source of a significant proportion of high-grade serous carcinomas[49]. This is based on identification of epithelial atypia, carcinoma *in situ*, and small high-grade serous tubal carcinomas in risk-reducing salpingo-oophorectomy (RRSO) specimens from women with BRCA mutations[1,56].

Mutation of TP53 is a hallmark of high-grade pelvic serous carcinoma[57]. The identification of TP53 mutations in Serous Tubal Intra-epithelial Carcinomas (STICs) provides support for the tubal origin of high-grade serous carcinomas[1,49]. More recently it has been found that that there are short stretches of morphologically normal tubal epithelium that are immunohistochemically positive for p53, and that have a Ki-67 proliferation index higher than normal tubal epithelium but lower than STICs. A minimum of 12 tubal secretory epithelial cells that are p53 positive has been proposed as a definition for a "p53 signature," which is a candidate for a STIC precursor. p53 signatures are also found in the general population. TP53 mutations have been found in a majority of p53 signatures[1,49].

Other molecular evidence strongly supporting the theory of fallopian tube origin of high-grade serous are: (1) lack of convincing definitive precursors of high-grade serous carcinoma in the ovary; (2) in RRSO specimens, occult carcinomas are more common in the fallopian tube than in the ovary; (3) STICs are associated, almost exclusively, with high-grade serous carcinoma, and not other histological types; (4) a high frequency of identical TP53 mutations in STICs/p53 signatures and synchronous ovarian/peritoneal high-grade serous carcinomas; (5) the finding of fallopian tube epithelial dysplasia in isolation exhibiting aneusomy for multiple chromosomes; (6) significant differences in telomere lengths between STICs and their paired concurrent ovarian/peritoneal high-grade serous carcinomas (if STICs merely represented metastases of ovarian/peritoneal carcinomas, they would be expected to have telomeres of similar lengths); (7) gene expression profiles of tubal and ovarian serous carcinomas are similar; and (8) gene expression patterns of ovarian serous carcinomas are more similar to those of normal tubal mucosa compared with normal ovarian epithelium[1].

Junctions between the different types of epithelia are often hot spots for carcinogenesis. Their role in neoplasia in certain locations, *e.g.,* cervical squamo-columnar, gastro-esophageal, and ano-rectal junctions is well recognized. Given the mounting evidence implicating the fimbria as the site of origin of ovarian serous carcinoma, the fallopian Tube-Peritoneal Junction (TPJ) is be considered a potential site of ovarian carcinogenesis. This junction is defined as the junction of the columnar epithelium of the fallopian tube and the mesothelium of the tubal serosa[1].

In are recent study TPJ was found to be highly tortuous with tongues of mesothelium extending from the infundibular peritoneal-fimbrial junction at the outer edges of the fimbriae, onto the fimbrial plicae to join the tubal epithelium at various points along and between fimbrial plicae and plica tips[58]. Transitional metaplasia occurs at the TPJ[59-61], and is reported in several studies[59,62]. It is likely that the transitional metaplasia is a normal event in the TPJ, analogous to squamous metaplasia in the cervical transformation zone[58], and may be analogously a site of tumour origin.

The origin of serous neoplasms at the TPJ could also explain the rare detection of stage I high-grade serous carcinoma. In addition, the extensive lymph-vascular system normally found at this junction with almost direct contact to the basement membrane of the tubal epithelium may explain the early spread of a minimally invasive tubal carcinoma throughout the abdominal cavity due to easy and rapid access into this system when the primary tumour is still of microscopic size[58].

Among ovarian surface epithelial tumors, the origin of intestinal-type mucinous ovarian and Brenner tumors is even more confusing than that of serous tumors as they lack a Mullerian phenotype. The recent suggestion that mucinous and Brenner tumors may arise from transitional metaplasia[61] indicates that the TPJ may be involved in carcinogenesis of a wide variety of ovarian neoplasms.

In view of the potential importance of the TPJ in ovarian, tubal, and pelvic neoplasia, a recent protocol for exami-

nation of the fallopian tubes has been proposed, designated the SEE-FIM protocol[63]. The goal of this protocol is to insure complete examination of the ovarian surface and tubal mucosa with maximum exposure of the fimbriae[63].

In summary, serous tumors develop from the fallopian tube, endometrioid, and clear cell tumors arise from fallopian tube endometriosis and mucinous, and Brenner tumors develop from transitional-type epithelium located at the TPJ[58].

Although the data suggesting that EOC arises in extraovarian sites and involves the ovaries secondarily is compelling, serous neoplasms (low- and high-grade) involve the ovaries and other pelvic and abdominal organs, much more extensively than the fallopian tubes. Similarly, although endometrioid and clear cell carcinomas develop from endometriosis that frequently occurs in multiple sites in the pelvis, these neoplasms are almost always confined to the ovaries. It is likely that the propensity for growth in the ovary is mulifactorial, but the precise reasons for this are unknown[58].

So the fallopian tube appears to be a strong player both in infertility and gynaecological neoplasia. This highlights the importance of thorough fallopian tube status investigation in the course of assessment of women presenting with either infertility or gynaecological tumors.

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TOPIC HIGHLIGHT

Mona A El-Bahrawy, MBBCh, MSc, PhD, *Series Editor*

Fertility sparing management of endometrial complex hyperplasia and endometrial carcinoma

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Abstract

The standard treatment of endometrial cancer or atypical hyperplasia is surgical removal of the uterus and ovaries. In early stage disease this has an excellent chance of cure but results in infertility. Although the majority of patients are postmenopausal an increasing number of patients with atypical hyperplasia or endometrial cancer are presenting with a desire to retain their fertile potential. In the last 8 years a number of studies have been published involving 403 patients with endometrial cancer and 151 patients with Atypical hyperplasia treated with high dose progestagens. The response rate is 76.2% and 85.6% respectively with endometrial cancer having a recurrence rate of 40.6%. There is a 26% recurrence rate in atypical hyperplasia. Overall 26.3% of those wishing to conceive had a live baby. Although concerns exist about the risks of medical treatment, those that fail this treatment do not appear to have a significantly poorer prognosis although 20 patients (3.6%) had either ovarian cancer or metastatic disease discovered during treatment or follow up.

Key words: Endometrial cancer; Fertility sparing

Core tip: Early endometrial cancer is successfully treated with hysterectomy in most cases but an increasing number of women develop the disease whilst still hoping to conceive. We are gathering an increasing amount of data to accurately describe the risk they are taking by undergoing medical treatment with progestagens as an alternative.

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INTRODUCTION

Endometrial cancer is the commonest gynaecological malignancy in the western world and usually affects post menopausal women. However up to 14% of these cancers are now diagnosed in the premenopausal with about 4% occurring in those under the age of 40 years in the United States[1]. As the trend to delay childbearing continues a greater number of women are being diagnosed with endometrial cancer at a stage in life when they wish to conceive. Therefore the standard management of hysterectomy with removal of ovaries needs to be fully justified and the possibility of managing patients medically whilst preserving their fertility should be considered. In the last decade a significant number of studies have been published allowing us to assess the success of this medical treatment so that we can advise our patients on the risks of fertility preservation in early stage endometrial cancer. However there are pitfalls of which every gynaecological oncologist should make themselves aware.

DIAGNOSIS

Irregular menstrual bleeding at any age needs to be in-

vestigated and the diagnosis of endometrial carcinoma is made by biopsy from the endometrial cavity either at hysteroscopy or outpatient endometrial sampling. The most accurate assessment is from biopsy obtained at hysteroscopy[2] but even then it can be difficult to make the distinction between atypical hyperplasia (AH) and invasive endometrial carcinoma (EC). As EC is actually found in the hysterectomy when the preoperative diagnosis was thought to be AH in approximately 30% of cases the treatment of both AH and early stage EC should be very similar[3,4].

STAGING

A number of studies have looked at the stage of disease in younger women with endometrial cancer and although the majority are stage 1a grade 1 disease, approximately 20% are found to have disease outside the uterus[5]. In addition up to 25% of women have either synchronous or metastatic ovarian tumours[6]. With standard management of hysterectomy and bilateral salpingo-oophorectomy the extent of disease can be assessed histopathologically and this is how the FIGO staging is determined. However if medical treatment is proposed the major initial disadvantage is the lack of histological confirmation of staging and the reliance on pre treatment imaging.

Ultrasound, computed tomography (CT) and contrast enhanced magnetic resonance imaging (MRI) have been used to stage early endometrial cancers and the MRI is the most accurate being able to predict myometrial invasion with a specificity of 96% and cervical invasion in 88%[7,8].

HORMONAL TREATMENTS

The majority of grade 1 endometrial cancers have progressed from hyperplasia and are thought to have arisen because of hormonal imbalances. Obesity where there is a higher level of circulating oestrogens from fat degradation, and polycystic ovaries where infrequent, anovulatory cycles are a feature suggest that a lack of balanced progesterone is responsible. Various types and doses of progesterones have been used to reverse the hyperplasia and EC. Initially Kinkel *et al*[9] described resolution of an endometrial malignancy in 25% of patients undergoing hysterectomy after treatment with progesterones. Although small doses of progesterone may be sufficient to balance the oestrogen in hormone replacement therapy a much higher does is required in AH and EC in these premenopausal women.

The majority of studies have used Medroxyprogesterone acetate in doses of 400-800 mg daily. This can, if necessary, be taken in divided doses. The next most common is megestrol but a recent study of 148 patients showed patients treated with megestrol had a higher chance of recurrence[10]. The levonorgestrol containing intrauterine device (IUS) has not been successfully when used in isolation. It may be useful for maintenance therapy after remission has been established and a randomised study has just opened in South Korea to evaluate this[11].

A meta analysis has been published involving 403 patients with endometrial cancer and 151 patients with Atypical hyperplasia treated with high dose progestagens[12]. The response rate is 76.2% and 85.6% respectively with endometrial cancer having a recurrence rate of 40.6%. There is a 26% recurrence rate in atypical hyperplasia. Overall 26.3% of those wishing to conceive had a live baby.

In comparison removal of the uterus and ovaries would be expected to give a disease free 5 year survival of 98.2%[13]. A recent review of 148 patients in eight hospitals in South Korea obtained similar response and recurrence free response rates (77.7% and 54% respectively). Of 33 patients who failed to respond to initial treatment, and had a hysterectomy, none of them recurred implying the risk of trying and failing medical treatment is low. Risk factors that increased the risk of recurrence were obesity (body mass index > 25) and a lack of pregnancy[10]. There were no reported deaths from disease in this study but in the meta analysis by Gallos *et al*[1] there were 2 deaths and 20 patients (3.6%) had disease in the ovaries either as a concommitent ovarian tumour or metastasis.

Therefore, despite the risk that more advanced or metastatic disease can be under diagnosed and despite the risk that the EC recurs in a large number of patients there do not appear to be significant long term risks to trying medical treatment.

FOLLOW UP

The various studies have given medical therapy for variable lengths of time and there is no single protocol that has been established. Most studies have sampled the endometrium 3 monthly, and continued medical management if there is a response for up to a year[14].

Similarly long term follow can be difficult. The risk factors that led to the original carcinogenesis are usually still present and with such a high recurrence risk patients need to be encouraged to either undergo immediate fertility treatment or continue with maintenance treatment. The frequency of future endometrial samples and whether office sampling or hysteroscopy is required has not been established. Hysterectomy at some stage following child birth would seem to be sensible as a way of preventing the disease recurring in the long term but when this should be performed and whether the risk of recurrence decreases with weight loss or the menopause is not known. Once recurrence has occurred a number of patients will respond to retreatment. However there are no established guidelines for how many times a patient should be retreated or for how long.

CONCLUSION

An increasing number of patients with either AH or EC will wish to preserve their fertility in the future. These patients need an accurate diagnosis and staging with con-

trast enhanced MRI to minimise their risk of unrecognised concomitant or metastatic disease.

Medical treatment with 400 mg to 800 mg daily of medroxyprogesterone acetate appears to be the best medical management with 3 monthly endometrial sampling to establish response. Treatment can be given for 6 mo to a year and approximately 75% will have a complete initial response with just over 50% having a response without subsequent recurrence. A failed response has theoretical disadvantages of finding more advanced disease but in published studies this is so small as to not be quantifiable.

All these factors need to be taken into consideration when advising a patient about her options but in addition she needs to consider the chances of conception once if treatment is successful. Many patients will be older and have presented with infertility. If the chances of a successful pregnancy are very low at the end of a year hormonal treatment with multiple endometrial samples and uncertainty about the future risk of recurrence then after careful consideration it is possible that the patient will decide to opt for the standard curative treatment of hysterectomy and removal of ovaries.

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TOPIC HIGHLIGHT

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Impact of pelvic radiotherapy on the female genital tract and fertility preservation measures

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Abstract

Radiotherapy to the pelvis can have a major and deleterious impact on the female genital tract. Despite significant advances in the technical delivery of radical pelvic radiotherapy there remains no way to avoid delivering substantial radiation doses to the ovaries and uterus for patients undergoing treatment for gynaecological cancers. Due to improved cure rates from radical chemo-radiotherapy and social trends toward delayed childbirth many women treated for cervical cancer with radical chemo-radiotherapy will wish to attempt to preserve their fertility. Whilst there are now established and emerging techniques for preserving ovarian function and ovarian tissue, there remains the difficulty of the irradiated uterus which, even if pregnancy can be achieved, results in an increased risk for pregnancy-related complications. Future developments may offer women in this difficult situation more and improved options for fertility preservation.

Key words: Radiotherapy; Cervical carcinoma; Premature menopause; Infertility; Fertility preservation

Core tip: Despite significant advances in the technical delivery of radical pelvic radiotherapy there remains no way to avoid delivering substantial radiation doses to the ovaries and uterus for patients undergoing treatment for gynaecological cancers. Due to improved cure rates from radical chemo-radiotherapy many women treated for cervical cancer will wish to attempt to preserve their fertility. This article reviews emerging techniques for preserving ovarian function and ovarian tissue, as well as the impact on the uterus and the risk for pregnancy-related complications. Future developments may offer women in this difficult situation more and improved options for fertility preservation.

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INTRODUCTION

Worldwide, cervical carcinoma is the third most common cancer in women, being responsible for nearly 10% of all cancers diagnosed in women in 2008[1]. However, there is major geographical variation in the incidence of cervical cancer across the globe, with a seven fold difference in the age-standardised incidence rate between East Africa, the region with the highest rate, and Western Asia, the region with the lowest rate[1]. Two peaks occur in the age-specific incidence rates of cervical carcinoma; the first peak occurs in women aged between 30-34 years and relates to women becoming sexually active in their late teens and early 1920s, resulting in an increase in the rate of infection with human papillomavirus[1,2]. In the United Kingdom between 2007 and 2009, the proportion

of cervical carcinoma cases occurring in women less than 45 years of age was 53%[1]. A continuous trend towards delayed childbearing has been observed in developed nations, resulting in an increase in the proportion of women diagnosed with a gynaecological cancer, typically cervical carcinoma, before their first pregnancy[3]. As a result of these epidemiological and social factors, a significant and perhaps increasing number of women of reproductive age who are diagnosed with a gynaecological cancer will wish to preserve their fertility[4-6].

The treatment of early-stage cervical carcinoma (International Federation of Gynecological Oncologists, FIGO stages Ⅰ and ⅡA cervical) is radical surgery, although radical radiotherapy is equally effective[7]. However, surgery for early-stage disease has the particular advantage of sparing fertility in cases that are suitable for radical trachelectomy[3]. For more advanced cases (FIGO stages ⅡB, Ⅲ and Ⅳ), standard treatment is with radical chemo-radiotherapy which combines external beam radiotherapy with weekly cisplatin followed by intra-uterine brachytherapy[8]. Radical radiotherapy for cervical carcinoma usually includes within the treatment volume: the pelvic lymph nodes, the uterus, the cervix and upper vagina, the fallopian tubes and ovaries, and the parametrial tissues. Modern radiotherapy techniques, utilising intensity-modulated external beam radiotherapy[9,10], and image-guided brachytherapy[11] can produce high rates of local control for cervical carcinoma. The prognosis for women with cervical carcinoma treated with radical chemo-radiotherapy varies according to FIGO stage, with the 5-year overall survival ranging from about 70% for stage ⅡB, to 50% for stages ⅢA and ⅢB, and 36% for stage ⅣA[12].

Given the favourable prognosis for many women treated for cervical carcinoma with radical chemo-radiotherapy, and given the demographic considerations discussed above, fertility preservation will often be an important issue for this cohort of women[4-6]. Unfortunately pelvic radiotherapy for pre-menopausal women, at radical treatment doses, results in complete ovarian failure and premature menopause. In addition, it causes direct damage to the uterus which in itself can result in an inability to conceive or carry a pregnancy to term[13,14]. The majority of the evidence for the effects of radiotherapy on female fertility derives from long-term follow-up studies of women treated with radiotherapy for cancer during childhood or adolescence[15-19]. Whilst this information from paediatric populations is of relevance to adult women receiving radiotherapy treatment, outcomes for patients treated in childhood are superior than for adults due to lower radiotherapy doses used for paediatric cancers and to the natural decline in fertility with age[20,21].

There are no completely satisfactory options for fertility preservation for women undergoing radical pelvic radiotherapy at present, yet there are interventions which should be offered for women to consider before they embark on treatment[4,22]. Evidence of the impact of pelvic radiotherapy on the female reproductive organs, the currently available fertility sparing options, and possible future strategies will be reviewed here.

IMPACT OF PELVIC RADIOTHERAPY ON THE FEMALE GENITAL TRACT

Pelvic radiotherapy by itself has significant consequences for female fertility. The degree of fertility impairment following radiotherapy is known to be dependent on the total radiation dose, the fractionation schedule, the radiation field, and age at the time of treatment[13,14]. It is now standard practice to give concurrent cisplatin chemotherapy as a radiosensitizer with radical radiotherapy for cervical carcinoma. It is reasonable to expect that this combination therapy will increase the impact of radiotherapy on fertility, on the basis of data on the long term effects of combined chemotherapy and radiotherapy in paediatric patients[23-25]. In addition, exposure to cisplatin in the context of single agent or multi-agent chemotherapy is known to cause ovarian failure, even in the absence of concomitant pelvic radiotherapy[13].

Aside from the impact of pelvic radiotherapy on the female reproductive organs, pelvic radiotherapy can also lead to damage to the vagina resulting in tissue fibrosis and vaginal stenosis. These late normal tissue changes can be severe and have a major impact on sexual function[26,27]. It is difficult to quantify these late effects of radiotherapy on vaginal tissues, and possibly as a result of such difficulties, the incidence of vaginal stenosis after radiotherapy reported in the literature ranges from 1.2% to 88%[26-29]. It is currently standard practice to attempt to minimise vaginal stenosis following pelvic radiotherapy by asking women to use vaginal dilators after radiotherapy[30-32]. A recent systematic review of evidence for the use of vaginal dilators following pelvic radiotherapy found that whilst vaginal dilation might help treat the late effects of radiotherapy, the use of vaginal dilation during treatment can cause increased tissue damage[29]. A Cochrane review by the same authors concluded that there is no reliable evidence to show that routine regular vaginal dilation during or after radiotherapy prevents the late effects of radiotherapy or improves quality of life[33].

Ovarian failure after radiotherapy

The human ovary contains a fixed number of primordial follicles, which is maximal during foetal life at 5 mo of gestation[5,18,20]. These are steadily lost through atresia, declining to about 500000 at the time of menarche[34]. After menarche, the number of viable primordial follicles continues to fall with increasing age, declining to about 1000 at the time of menopause at an average age of 50-51 years[20,35]. The rate of loss of ovarian follicles is not constant, and accelerated atresia of the primordial follicles occurs from approximately 35 years of age[35].

Oocytes are highly sensitive to radiation, and the LD50 (the radiation dose need to kill half the total number of oocytes) was estimated to be only 4 Gy[36], but more recently it has been reported to be less than 2 Gy[37]. Historically, complete ovarian failure has been known to occur after radiation doses in the region of 20 Gy in women under 40 years of age, and after only 6 Gy

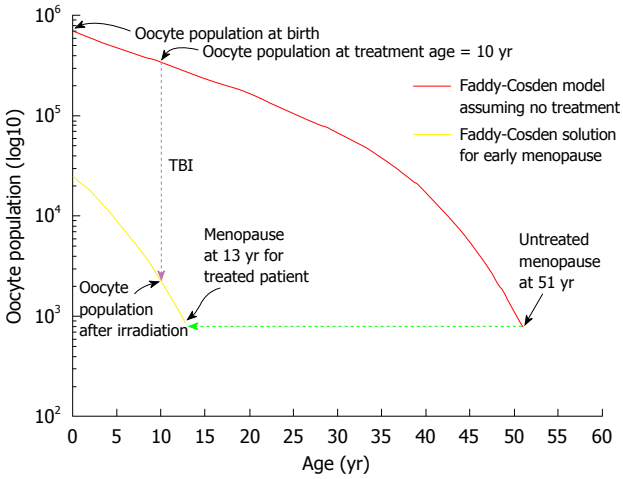

Figure 1 The effect of pelvic radiotherapy on oocyte population according to the Faddy-Gosden model. Faddy-Gosden model (Source[20], with permission) as extended by Wallace *et al*[21]. The graph illustrates the effect of total body irradiation with 14 Gy at 10 years, predicting ovarian failure at 13 years.

in older women[38]. Ovarian irradiation accelerates the natural process of follicular atresia, leading to premature menopause[20,21,37]. Due to the natural atresia of primordial follicles in the ovaries, for a given dose of radiation to the ovaries, the younger a woman is at the time of irradiation, the later will be the subsequent onset of premature menopause. This effect means that the sterilising dose of radiation falls with increasing age[20]. The Faddy-Gosden model of natural follicular atresia in healthy women has been extended by Wallace *et al*[20,21] to allow the prediction of the age of ovarian failure following treatment with a given dose of radiation (Figure 1). They have also calculated the effective sterilising radiotherapy doses (*i.e.*, the radiation dose causing ovarian failure in 97.5% of treated women) as a function of age: 20.3 Gy at birth, 18.4 Gy at 10 years, 16.5 Gy at 20 years, 14.3 Gy at 30 years and 9.5 Gy at 45 years[20].

Prediction of ovarian reserve prior to radiotherapy would be beneficial in order to avoid invasive procedures or unnecessary delays in treatment if fertility preserving measures are likely to be futile. Traditionally elevated follicle-stimulating hormone level has been used but various factors can cause a transient rise resulting in false prediction of menopause. Antimullerian hormone (AMH) is produced by growing follicles and may be a better indicator of ovarian function. The combination of serum AMH levels with ultrasound assessment of ovarian volume and total antral follicle count has been reported to more accurately predict the onset of ovarian failure[39,40].

Radiotherapy effects on the uterus

As well as the uterine dysfunction resulting from reduced ovarian hormone production, pelvic radiotherapy may also have a direct adverse effect on the uterus. Most of what is known about the long term effects of radiotherapy on the uterus comes from studies of women treated for childhood cancers[41,42]. However, these may be of limited relevance to adult women due to the significant changes that occur to the uterus during puberty[14,43,44]. Furthermore, the pre-pubertal uterus is thought to be more vulnerable to the effects of pelvic irradiation[14]. At puberty, as a result of rising ovarian oestrogen production, the uterus enlarges and changes shape from a tubular shaped organ to a pear shaped organ[43,44].

Radiotherapy doses between 14 and 30 Gy have been reported to result in adverse changes to the uterus including myometrial fibrosis, reduced uterine volume, reduced or undetectable blood supply and absent endometrium[41,42,45-47]. Critchley *et al*[41] assessed 10 women with premature ovarian failure due to whole abdominal irradiation in childhood. The uterine volume remained significantly lower in patients treated with pelvic radiotherapy compared with controls, and was correlated with age at the time of radiotherapy. Attempts to reverse these changes by means of cyclical hormone replacement therapy had limited success. Almost all treated women had loss of signal in one or both uterine arteries with Doppler ultrasound.

Holm *et al*[46] also used ultrasound to evaluate the impact of total body irradiation (TBI) with 8-14 Gy on internal genitalia and uterine blood flow. The median age was 12.7 years (range 6.1-17.6 years) at treatment and 21.5 years (range 11.6-25.6 years) at study entry. All participants had entered puberty but despite sufficient hormonal stimulus to achieve menarche in 11 out of 12 [eight with hormone replacement therapy (HRT) and 3 spontaneously], the median uterine volumes were still significantly reduced compared with normal controls. Uterine blood flow was impaired with systolic blood flow measurable in six of nine individuals, and diastolic blood flow visible in only one patient. These studies concluded that pre-pubertal irradiation may have an irreversible effect on uterine vasculature and development and that the endometrium may become unresponsive to hormonal stimuli due to a combination of effects on vasculature and to sex-steroid receptors[48].

The endometrial injury noted in the patients treated with TBI using a dose of 14.4 Gy was further studied by Bath *et al*[42] who propose this would prevent normal endometrial decidualisation (the post-ovulatory process of endometrial remodelling in preparation for pregnancy). This potentially leads to placental attachment disorders, including severe forms such as placenta accreta and placenta percreta[15,49,50]. In addition to these adverse endometrial changes it has also been suggested that pelvic radiotherapy can lead to thinning of the myometrium leading to an increased risk of uterine rupture during pregnancy[49,50].

There are few studies assessing the uterine changes after high dose pelvic radiotherapy in adults. Arrivé *et al*[51] undertook sequential magnetic resonance (MR) imaging imaging of 23 pre-menopausal women who received radiation for cervical cancer. A reduction in myometrial signal intensity on T2-weighted images was demonstrable by 1 mo after therapy and a decrease in uterine size was noted at 3 mo. A decrease in thickness and signal intensi-

ty of the endometrium was seen by 6 mo with earlier loss of uterine zonal anatomy. Four patients also had histopathological assessment which showed myometrial atrophy with fibrosis, inactive endometrium and reduction in vascular diameter. In postmenopausal women, irradiation did not significantly alter the MR imaging appearance of the uterus. The authors concluded that the early changes are due directly to radiotherapy but premature ovarian failure would have been contributory to the later atrophic changes.

Hormone replacement therapy is prescribed following radiotherapy to prevent menopausal symptoms. Combined cyclical therapy is indicated for patients previously treated for childhood cancers who still have a functional uterus. Following radiotherapy for cervical cancer, the very high doses delivered to the endometrial surface from brachytherapy is assumed to cause complete destruction of the basal layer of the endometrium. However, there have been several reports of persistent endometrial activity after treatment for cervical cancer. Habeshaw *et al*[52] reported 15 out of 63 patients treated for cervical cancer had breakthrough or cyclical vaginal bleeding when started on combined HRT several months to years after completing radiotherapy. Patients with an intact uterus following radiotherapy should therefore still be treated with oestrogen and a progestagen to avoid endometrial stimulation from unopposed oestrogen therapy.

Other than gestational surrogacy, there are no specific interventions available for uterine changes secondary to pelvic radiotherapy. Uterine dysfunction therefore represents a greater barrier to achieving viable pregnancy than does ovarian failure.

ADVERSE PREGNANCY OUTCOMES IN WOMEN TREATED WITH PELVIC RADIOTHERAPY

A number of long-term follow-up studies of pregnancy and neonatal outcomes in women treated in childhood for cancer with radiotherapy have now been published[17-19,53-57]. These studies have consistently found evidence of an increased risk of adverse pregnancy and neonatal outcomes for mothers with a prior history of irradiation in childhood, including: spontaneous miscarriages, pre-term labour, intrauterine growth retardation and low-birthweight infants[41,42,51,52]. While the risk increases with higher uterine dose, neonatal complications are noted with doses as low as 0.5 Gy.

There are no reports of a term pregnancy in patients who received more than 45 Gy to the whole uterus, which conventionally is the minimum dose delivered for gynaecological cancers. Hürmüz *et al*[58] have recently reported a patient with a full term pregnancy following pelvic chemoradiotherapy for anal cancer. Reviewing the radiotherapy fields, 30 Gy was delivered to the whole uterus while the lower segment and cervix received 50 Gy.

A fertility preserving approach using brachytherapy for cervical or vaginal clear cell adenocarcinoma was reviewed by Magné *et al*[59]. Seven of the 19 women treated for vaginal disease tried to become pregnant, with three delivering healthy term babies and one spontaneous abortion. In the 42 patients with cervical cancer, there were no successful pregnancies and two women reported spontaneous abortions.

A Canadian cohort study compared the risk of adverse pregnancy outcomes in female childhood cancer survivors who received abdominal-pelvic radiation and/or chemotherapy with alkylating agents with the risk among those who were treated by non-sterilising alkylating agents and those who were treated by non-sterilising surgery only[54]. There was no evidence of an increased risk of having a spontaneous abortion or an infant with a birth defect. Survivors receiving abdomino-pelvic radiotherapy were more likely to have a low birth weight infant (OR 3.64; 95%CI: 1.33-9.96), a premature low birth weight infant (OR 3.29; 95%CI: 0.97-11.1), or an infant who died in the perinatal period (OR 2.41; 95%CI: 0.50-11.5), compared with those receiving surgery. Risks of perinatal death and having a low birth weight infant increased with increasing dose of radiotherapy.

This association of children with low birth weight being born to mothers who had received pelvic radiotherapy has been confirmed in large studies from the United States that reviewed pregnancy outcomes among female participants in the Childhood Cancer Survivor Study (CCSS), a large multi-centre cohort of childhood cancer survivors[17,18,56]. The fertility of 5149 female survivors was compared to a cohort of 1441 randomly selected female siblings. The relative risk (RR) for survivors of ever being pregnant was 0.81 (95%CI: 0.73-0.90, $P < 0.001$) compared with siblings. In multivariate analysis, those who received an ovarian or uterine radiation dose greater than 5 Gy were less likely to have ever been pregnant with RR 0.56 for those receiving 5 to 10 Gy (95%CI: 0.37-0.85) and RR 0.18 for more than 10 Gy (95%CI: 0.13-0.26)[56].

Signorello *et al*[18] looked at singleton live births from female CCSS members from 1968 to 2002. This study included 2201 children of 1264 survivors and 1175 children of a comparison group of 601 female siblings. Survivors' children were more likely to be born pre-term than the siblings' children (21.1% *vs* 12.6%, $P < 0.001$). Compared with the children of survivors who did not receive radiotherapy, the children of survivors treated with a radiotherapy dose to the uterus of > 5 Gy had an increased risk of being born preterm (50.0% *vs* 19.6%, $P = 0.003$), low birth weight (36.2% *vs* 7.6%, $P = 0.001$), and small for gestational age (18.2% *vs* 7.8%, $P = 0.003$). Increased risks were also seen at lower uterine radiotherapy doses (starting at 0.5 Gy for preterm birth and at 2.5 Gy for low birth weight).

Similar findings were reported in a cohort review of 1688 female survivors of childhood cancer from the Danish Cancer Registry[57]. The outcomes of survivors, 2737 sisters, and 16700 comparison women in the population were identified from nationwide registries. More

than 34000 pregnancies were evaluated, 1479 of which were among cancer survivors. Survivors with any prior radiation had an increased excess risk of spontaneous abortion (OR 1.58; 95%CI: 1.2-2.2) which was greatest in those receiving higher doses to the ovaries and uterus (OR 2.8; 95%CI: 1.7-4.7).

The risk of radiotherapy induced germ line mutagenicity has also been assessed. In a United States cohort, 4214 children were born to cancer survivors with 157 (3.7%) having genetic diseases in contrast to 95 (4.1%) congenital conditions among 2339 children born to sibling controls. There was no increased risk of malformations, infant death, or altered sex ratio[55]. In the Danish series there were 82 (6.1%) birth defects among 1345 children of cancer survivors and 211 (5.0%) among 4225 children of sibling controls. These results provide reassurance that radiotherapy is very unlikely to cause inherited genetic disease in the children of cancer survivors[60].

These findings from large cohorts of women treated with abdomino-pelvic radiotherapy in childhood are all consistent with the complications of pregnancy that would be anticipated from the observations of reduced uterine volume, reduced elasticity of the myometrium and impaired uterine blood flow following pelvic radiotherapy described in section 2.2.

MEASURES TO PRESERVE FERTILITY PRIOR TO RADIOTHERAPY

Ovarian transposition

Whilst it may be practical to attempt to shield the ovaries from radiotherapy beams for some patients undergoing abdomino-pelvic radiotherapy, this will not be possible for women undergoing radical radiotherapy for gynaecological cancer due to proximity to the lymph node target volume. The ovaries are usually included in the radiation target volume for locally advanced cervical cancers due to the risk of ovarian metastases, with adenocarcinomas having a particular propensity for spread. However, for early stage disease and patients with pelvic sarcoma, lymphoma or receiving craniospinal irradiation there may be many benefits with ovarian preservation.

For these women, ovarian transposition, also known as oophoropexy, is a surgical procedure that attempts to move the ovaries outside of the radiation field. Although ovarian function can be preserved with this technique, it offers no protection to the uterus and so radiotherapy-induced uterine damage will continue to limit the chances of a successful pregnancy.

The procedure may be performed by open laparotomy and more recently with a laparoscopic technique[61-66]. The location selected for fixation of the transposed ovaries is dependent on the proposed pelvic radiotherapy field. For cervical carcinomas the transposed ovaries should be fixed well above the pelvic brim, since the standard superior border of the radiotherapy field is the L4/L5 or L3/4 vertebral space[66] (Figure 2). A high lateral position within the paracolic gutters is typically selected. Complications of ovarian transposition include benign ovarian cysts (23%), chronic pelvic pain (3%), and ovarian metastases (1%)[67]. Other reported complications include vascular injury, fallopian tube infarction, and ovarian migration[66-68].

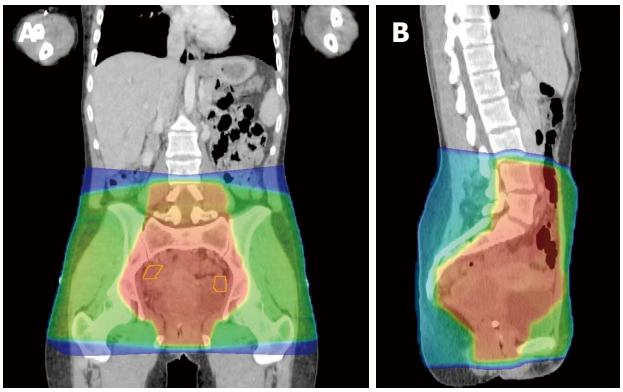

Figure 2 Typical radiotherapy dose distribution for cervical cancer. A: Coronal view; B: Sagittal view. The red area receives > 40 Gy, green > 10 Gy and blue < 10 Gy. Ovarian positions are contoured in yellow within the treated area, and transposition to the lateral para-colic region is required to be outside the low dose radiation region.

Covens *et al*[69] estimated the radiation exposure to each transposed ovary in three cervical cancer patients based on intra-uterine brachytherapy alone, and on external-beam pelvic radiotherapy (45 Gy), with and without para-aortic nodal irradiation (45 Gy). They estimated the mean radiation dose to each ovary following transposition for a course of intra-uterine brachytherapy as 1.3 Gy. The estimated doses for pelvic radiation without and with para-aortic lymph node irradiation were 1.4-1.9 Gy, and 2.3-3.1 Gy, respectively.

The reported success rates of ovarian transposition, in terms of preservation of ovarian function and fertility vary widely[15]. In a prospective study of 107 patients treated for cervical cancer, ovarian transposition to the paracolic gutters at the time of radical hysterectomy and lymphadenectomy was attempted[67]. Bilateral ovarian transposition was achieved in 104 of the 107 patients (98%). Of the 104 patients that underwent successful ovarian transposition, 59 were treated with vaginal brachytherapy alone to 60 Gy, and 25 other patients received external beam pelvic radiotherapy to 45 Gy with concurrent cisplatin, followed by vaginal brachytherapy to 15 Gy. Ovarian function was assessed by post-operative ultrasound and serial serum hormone levels. Preservation of ovarian function was achieved in 83% patients. After a median of 31 mo follow-up the rates of ovarian preservation were 100% for patients treated exclusively by surgery, 90% for patients treated by post-operative vaginal brachytherapy, and 60% for patients treated by post-operative external beam radiotherapy and vaginal brachytherapy.

Other methods of fertility preservation

The available methods for fertility preservation are summarised in Table 1. Aside from ovarian transposition, the

Table 1 Options for fertility preservation in women undergoing radical radiotherapy to the pelvis

Intervention	Procedure	Status	Time required	Pros	Cons
Ovarian transposition	Surgery to relocate ovaries within the abdomen outside of radiotherapy field	Established	Minimal (1 d)	Preserves oocytes and prevents premature menopause	Invasive surgical procedure; may require IVF; does nothing to protect uterus
Embryo cryopreservation	Mature oocyte aspiration, IVF, embryo freezing for later use	Established	2-3 wk	Established pregnancy rate of 20%-30% per transfer of 2 to 3 embryos	Requires 2 wk of ovarian stimulation; requires partner or donor sperm; requires functioning uterus or surrogacy
Donor oocytes and gestational surrogacy	IVF using donor oocytes and/or implantation of the embryo in a surrogate carrier	Established but infrequent	Not applicable	May be the only available option for some women with non-functioning uterus	Requires donor oocytes and gestational surrogate; ethical difficulties
Oocyte cryopreservation	Mature oocyte aspiration and freezing for later use	Experimental, live births reported, but only recommended as part of research	2-3 wk	Avoids need for partner or donor sperm at time of cryopreservation	Requires 2 wk of ovarian stimulation; requires functioning uterus or surrogacy
Ovarian tissue cryopreservation	Harvesting and freezing of ovarian tissue; re-implantation after radiotherapy or other gonadotoxic treatment	Experimental, but live births reported	Minimal (1 d)	Avoids need for partner or donor sperm at time of cryopreservation	Not appropriate if significant risk of ovarian involvement with malignancy

IVF: *In vitro* fertilisation.

only established method for women undergoing pelvic radiotherapy is embryo cryopreservation[5,6,70]. Mature oocytes are collected before treatment for *in-vitro* fertilisation and subsequent embryo cryopreservation. The Society for Assisted Reproductive Technology reported the live birth rate per transfer using frozen thawed embryos was 38.7% in United States women under 35 years old in 2010[71]. This technique requires a male partner or donor sperm for fertilisation. It may not suitable for many patients with cancer, because of the need for a period of ovarian stimulation that will delay the start of anti-cancer treatment.

Other fertility sparing interventions are available, but at the present time continue to be considered investigational. Oocyte cryopreservation requires ovarian stimulation and success depends on the number of mature oocytes retrieved. The oocyte survival rate (OR 2.46; 95%CI: 1.82-3.32) and high quality embryo rate (22% *vs* 8%) of oocyte cryopreservation with vitrification is significantly higher than with conventional slow freezing methods[72,73]. This improvement in technique and successful long term outcomes suggest this should now be considered an established treatment.

Ovarian tissue cryopreservation is the only option for prepubertal girls, patients who need treatment without delay or when ovarian stimulation is contraindicated due to hormone sensitive cancers[5,74-76]. Ovarian tissue is harvested laparoscopically and cryopreserved. With orthotopic transplantation, ovarian cortical fragments are reimplanted into the pelvic cavity once in remission[77,78]. However, following radiotherapy the vascular supply will be impaired and heterotopic transplantation to a remote site may be required. In 2001, Oktay *et al*[79] first reported successful transplantation to the forearm for a patient with cervical cancer, resulting in regular ovarian cycles for more than 1 year. There is the risk of introducing malignant cells preserved within the ovarian tissue. Since the first live birth was reported in 2004, orthotopic reimplantation has led to the birth of 17 healthy babies[80]. It also has the advantage of restoring endocrine function in young women after cancer treatment, with ovarian hormonal activity demonstrated within 3 to 6 mo after transplantation[81].

However, gestational surrogacy is the only option for women with preserved embryos, or preserved ovarian tissue but who have uterine compromise secondary to radiotherapy[76]. Similarly, women for whom other fertility sparing options are either inappropriate or fail have the option of oocyte donation with gestational surrogacy.

FUTURE PROSPECTS

Thankfully, fertility preservation is now an important consideration in oncology clinics, and the options available to patients are routinely offered. Despite the significant advances that have been made over the last three decades, and despite the availability of fertility sparing manoeuvres discussed above, there remain a significant number of women who will be rendered infertile as a result of life-saving cancer treatment. Techniques that do not require the preservation of embryos, or that do not require the delays associated with hormone stimulation, are the subject of ongoing intensive research efforts.

A particular problem remains for women whose uterus has been treated with radiotherapy. The first attempt at human uterus transplantation was undertaken in 2000. The transplanted uterus survived for 3 mo before failing due to thrombosis and necrosis[82]. This area has been the subject of ongoing active preclinical research efforts[83-86]. The first uterine transplant from a multi-organ donor was

undertaken in Turkey in 2011 and successfully achieved menstrual cycles after 20 d[87]. Recently two mother to daughter uterine transplants have been performed at the University of Gothenberg, Sweden and the results are awaited. Whilst there remain many technical obstacles to overcome, it may be possible to offer women who have received radiotherapy the option of uterus transplantation in the future.

CONCLUSION

Radiotherapy to the pelvis can have a major and deleterious impact on the female genital tract. Despite significant advances in the technical delivery of radical pelvic radiotherapy there remains no way to avoid delivering substantial radiation doses to the ovaries and uterus for patients undergoing treatment for gynaecological cancers. Due to improved cure rates from radical chemo-radiotherapy and social trends toward delayed childbirth many women treated for cervical cancer with radical chemo-radiotherapy will wish to attempt to preserve their fertility. Without specific interventions radical pelvic chemo-radiotherapy will always render women menopausal and infertile. Whilst there are now established and emerging techniques for preserving ovarian function and ovarian tissue, there remains the difficulty of the irradiated uterus which, even if pregnancy can be achieved, results in an increased risk for pregnancy-related complications, including spontaneous miscarriages, preterm labour, premature delivery, low birth weight, and placental abnormalities. Pre-menopausal women undergoing radical chemo-radiotherapy for gynaecological cancers need to be carefully counselled regarding the impact of this life-saving treatment on their fertility and sexual functioning, and offered support and access to such fertility sparing interventions as are currently available. Future developments may offer women in this difficult situation more and improved options for fertility preservation.

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TOPIC HIGHLIGHT

Mona A El-Bahrawy, MBBCh, MSc, PhD, FRCPath, *Series Editor*

Chemotherapy for gynaecological malignancies and fertility preservation

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Abstract

Infertility is an increasingly important issue for patients surviving cancer. Significant improvements in cancer management have led to greater numbers of patients living healthy and fulfilling lives for many years after a diagnosis of cancer, and the ability to bear children is a major component of well-being. Infertility is particularly challenging in gynaecological cancer, where multiple treatment modalities are often employed. Surgery may involve the removal of reproductive organs and subsequent chemotherapy may also lead to infertility. Mitigation of this through the use of cryopreservation of embryos, oocytes or ovarian tissue before chemotherapy may enable subsequent pregnancy in the patient or a surrogate mother. Suppression of ovarian function during chemotherapy is less well established, but promises a reduction in infertility without the risks associated with surgery. Similarly, evolving chemotherapy regimens with replacement of alkylating agents will reduce the incidence of infertility. With a combination of these techniques, an increasing proportion of patients may be able to conceive after completion of treatment, and there is no evidence of an increase in congenital abnormalities. This review discusses chemotherapy-induced infertility, interventions and success rates, and demonstrates that individualisation of management is required for optimum outcome.

Key words: Infertility; Chemotherapy; Gynaecological malignancies; Ovarian; Cryopreservation

Core tip: This paper summarises the main scenarios in which infertility presents a clinical problem in gynaecological malignancies subsequent to the use of chemotherapy. Many patients may have pre-existing infertility due to related medical conditions, and prior surgical interventions may be an important factor. Other factors to be considered include the associated prognosis and the potential need for rapid commencement of chemotherapy. The various technologies for fertility preservation are reviewed and their strengths and weaknesses discussed. The paper stresses that an individualised approach is necessary for each patient and that discussion of the issues at an early stage of management is important.

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INTRODUCTION

Infertility and subfertility are common sequelae of the management of gynaecological malignancies, and are a cause of psychological stress in cancer survivors. In one survey, three quarters of patients younger than 35 years who were childless at the time of diagnosis expressed

a desire to have children[1], while in a second study of adolescent females with cancer, over 80% of patients and their parents were interested in fertility preservation[2]. The ability to have children is also a determinant of well-being in cancer survivors[3,4]. Fertility issues in cancer patients have been made more prominent by an increase in survivorship across all cancers. By 2015, it has been estimated that 4% of all adults in the United Kingdom will be cancer survivors, and in some cancers, such as germ cell tumours and lymphomas, the proportion cured or surviving more than 10 years is much higher.

The management of gynaecological malignancies involves three treatment modalities which may contribute to a loss of fertility; surgery, pelvic radiotherapy and chemotherapy, resulting in fertility preservation being a particularly challenging area. A large proportion of patients will have surgery or radiotherapy that precludes a subsequent pregnancy, including the removal of both ovaries and/or uterus. However, fertility sparing surgery including unilateral oophorectomy or trachelectomy may be feasible[5,6]. While subsequent chemotherapy may cause infertility, this is by no means invariable. In addition, fertility preservation techniques such as embryo cryopreservation may be performed prior to both surgery and chemotherapy, thus allowing the option of surrogate pregnancy. In this paper we will specifically review the effects of chemotherapy on fertility, and techniques that may be employed to improve the chances of a successful pregnancy.

CHEMOTHERAPY INDUCED INFERTILITY

At birth females are believed to have their full lifetime quota of oocytes, and these are progressively lost from the menarche. These oocytes, enclosed within granulosa cells as primordial follicles, are immature, but following activation enter a growing phase and some of these will enter the pre-ovulatory phase. Many others will undergo atresia and not reach the ovulatory phase. Once the number of remaining oocytes falls below a critical number, menopause ensues. The rate at which primordial follicles are recruited into the activated growing state is controlled by feedback mechanisms including the release of anti-mullerian hormone[7].

There are several mechanisms by which chemotherapy can result in infertility. Chemotherapeutic drugs predominantly damage growing follicles as these are the active cell population. However some drugs may also damage the granulosa cells in the resting primordial follicles, leading to death of the immature oocyte. In addition to this direct damage, the loss of growing follicles will in turn disrupt chemical feedback loops and stimulate recruitment of more primordial follicles into this phase. With repeated cycles of chemotherapy, the result is an increase in primordial follicles leaving the resting pool and entering activation leading to a reduced pool at the end of chemotherapy[8].

The risk of infertility following chemotherapy depends on ovarian reserve. Age at chemotherapy has a big impact on the risk of infertility after treatment. In breast cancer regimens, for example, the commonly used adjuvant chemotherapy combinations (triplets including cyclophosphamide, fluorouracil, methotrexate and an anthracycline) are likely to cause permanent amenorrhoea in more than 80% of women over the age of 40 years but in less than 20% of women below the age of 30 years[9]. Anti-mullerian hormone levels have been shown to be useful as a marker of ovarian reserve[10] and levels fall more dramatically with increasingly gonadotoxic regimens in pre- and post-pubescent girls undergoing chemotherapy[11]. The risk varies with the type of chemotherapy, and alkylating agents such as cyclophos- phamide are now rarely used in the first line management of gynaecological malignancies.

Chemotherapy induced infertility in ovarian cancer patients

The main areas in which fertility-sparing surgery may be considered and combined with chemotherapy are early unilateral epithelial ovarian cancer (FIGO stages I a and I c), and in the treatment of malignant ovarian germ cell tumours. The latter are usually unilateral and even in advanced disease, surgery conserving the contralateral ovary and uterus is feasible. Germ cell tumours generally affect a young population, and fertility after chemotherapy has been frequently reported in this patient population, although reports generally rely on retrospectively collected data in this rare tumour group.

Several papers have demonstrated that return of a normal menstrual cycle is common after chemotherapy and normal childbearing is possible. Many of these papers include different chemotherapy regimens including cyclophosphamide, dactinomycin and vincristine, cisplatin, vincristine and bleomycin (PVB), forerunners to the now commonly used regimen of bleomycin, etoposide and cisplatin (BEP).

The MD Anderson Cancer Centre published a retrospective series of 26 patients treated with at least 3 cycles of BEP, 16 of whom underwent unilateral salpingo-oophrectomy. Questionnaires were completed surveying menstrual function and fertility. Of the 15 patients completing the questionnaire (only one did not but was known to be pregnant at her last follow up), 10 had maintained their normal menstrual function during treatment and 3 patients who had disrupted menstruation during chemotherapy had resumption of normal menses within 6 mo of completion of treatment. Three of these patients conceived without difficulty. Only one patient remained amenorrheic and this patient was subsequently diagnosed with dysgerminoma in the remaining ovary[12].

A further study of 52 women, who all underwent BEP chemotherapy with a median follow up period of 68 mo, included 41 patients who had had fertility-sparing surgery. Of these patients, one had high dose chemotherapy and stem cell transplant and was diagnosed with intermittent biological ovarian endocrine dysfunction.

Normal menstrual cycles were observed following treatment in 39 of the 40 patients who achieved complete remission having undergone fertility-sparing surgery. Of these patients 16 patients had attempted and 12 patients (75%) had successfully achieved conception. There were a total of 15 normal term pregnancies in this patient group. There was also one ongoing pregnancy, one miscarriage and one termination[13].

Another published study included 74 patients with malignant ovarian germ cell tumours with a mean age of 20.9 years. Of these, 47 patients received chemotherapy (30 BEP, 8 PVB, 3 VAC, 4 POMB/ACE, 2 other platinum based), 62% were amenorrhoeic during chemotherapy and 92% resumed normal menses after chemotherapy. Of these, 20 patients attempted conception and 19 were successful, including one after 12 mo. Fourteen live births were recorded in this group and four patients were pregnant at the time of writing the manuscript. No birth defects were reported in the offspring[14].

In early stage epithelial ovarian cancer, fertility data is limited, largely due to the relatively small proportion of patients for whom fertility remains an issue either due to age or surgery. Epithelial ovarian cancer, in contrast to germ cell tumours tends to affect women later in life and also frequently presents at an advanced stage where fertility-sparing surgery is not possible without compromising survival. For women with early stage ovarian cancer adjuvant platinum based chemotherapy is recommended for stage I C cancer and stage I A or B cancer in high-grade tumours only. A combination of platinum with paclitaxel is the standard of care but depending on individual characteristics, some patients will receive single agent platinum.

There are some retrospective studies of fertility following a conservative approach for early stage ovarian cancer, however numbers are small and the individual treatment characteristics are not always clear for the chemotherapy patients becoming pregnant. One multicentre retrospective study looked at 52 patients with stage I epithelial ovarian cancer who were treated with fertility sparing surgery between 1965 and 2000. Forty two had stage I A disease and 10 stage I C. Twenty patients had adjuvant chemotherapy with 11 receiving cisplatin or carboplatin with paclitaxel and one single agent cisplatin. The remainder had melphalan or cisplatin and cyclophosphamide. Twenty-four patients attempted pregnancy and 17 conceived (71%), leading to 26 term pregnancies and 5 spontaneous abortions. No congenital abnormalities were reported. The estimated survival was 98% at 5 years[15].

From these studies it is clear that there is a realistic expectation of pregnancy after chemotherapy for ovarian cancer where fertility sparing surgery is possible. However the numbers in such studies are small. Studies commonly document return of menses after chemotherapy but this should not be used as a surrogate endpoint for fertility. In other tumour groups it has been shown that even those who return to normal menstruation may have problems with infertility and not infrequently early menopause. A significant proportion of these women have a history of endometriosis which in itself is associated with infertility[16]. Therefore women must be carefully counselled taking into account age at treatment, risk of a somewhat increased chance of infertility compared to the population average and narrowed fertile window even if menstruation does resume[17]. The effects of targeted therapies which are entering clinical practice on fertility are unknown.

Chemotherapy induced infertility in other gynaecological cancers

Cervical cancer continues to be a problem in young women and a proportion of early stage cancers can be treated by fertility preserving surgery. When these cancers recur cytotoxic chemotherapy is increasingly used for the treatment of advanced disease. Following the publication of two randomised controlled trials demonstrating a survival gain from the use of cisplatin based combinations compared to single agent therapy, confidence has increased in their use[18,19]. The prognosis is often poor and of the order of 1-2 years but some type 1 tumours may remain controlled for several years with the use of chemotherapy and in selected cases hormone therapy.

Chemotherapy may also be used for the treatment of advanced or recurrent endometrial cancer, which is becoming an increasing problem in younger women in view of the epidemic of obesity affecting the western world. However, these women will not have an intact uterus and gestational surrogacy may be the only available option. Vulvar cancer is also increasing in younger women, in many cases associated with HPV. However, experience with chemotherapy is limited and remissions are generally of short duration.

PRESERVING FERTILITY

Fertility preservation in women undergoing chemotherapy may involve the choice of a chemotherapy regimen less likely to induce infertility as discussed above, the cryopreservation of embryos, oocytes or ovarian tissue, or the suppression of ovarian function during chemotherapy. Each of these techniques has potential advantages and disadvantages and the appropriate approach is dependent on clinical and social circumstances.

Embryo cryopreservation

Cryopreservation of embryos relies on *in vitro* fertilisation (IVF) techniques that have been in use for over 30 years, and have led to millions of conceptions and live births. In this procedure, eggs are harvested following ovarian stimulation, IVF is performed and embryos are then frozen and stored prior to thawing and implantation at a later date. Ovarian stimulation generally involves around 2 wk of daily injections of follicle-stimulating hormone (FSH), during which oestrogen levels and follicular growth are monitored. Final maturation of the oocyte is induced through injection of human chorionic gonadotrophin

and oocytes are aspirated under ultrasound guidance. Oocyte retrieval involves an outpatient surgical procedure, using a vaginal ultrasound probe to guide transvaginal aspiration of eggs. The procedure may be performed under sedation or general anaesthesia. Eggs are fertilised *in vitro* by sperm obtained from the patient's partner or donor sperm, and the zygote is then grown *in vitro* for up to 5 d prior to cryopreservation.

The first pregnancy following embryo cryopreservation was reported in 1983, with the first live birth reported the year after. Since then it is estimated that several hundred thousand babies have been born from cryopreserved embryos. Individual success rates are relatively high, with a pregnancy rate of around 60% following transfer in two reported series[20,21]. A recent review of the literature suggests that with modern techniques, cryopreserved embryos implant at comparable rates to fresh embryos[22]. The length of storage does not impact significantly on subsequent pregnancy outcome[23], and successful pregnancy has been reported following storage for over 10 years[24]. Embryo cryopreservation does not appear to be associated with an increased risk of congenital abnormalities[25,26].

In patients with oestrogen sensitive tumours such as endometrial or breast cancer increasing oestrogen levels may promote tumour growth. This has led to the investigation of alternative methods of ovarian stimulation in which low dose FSH is combined with tamoxifen or letrozole[27]. While this appears to be a feasible strategy, the utility in preventing cancer recurrence or progression is unproven.

While cryopreservation of embryos is well established, several potential disadvantages exist. As discussed above, ovarian stimulation must start within the first three days of the menstrual cycle, and this technique risks delaying the commencement of chemotherapy by up to 5 wk. In addition a small percentage of patients may need more than one cycle of ovarian stimulation in order to successfully obtain oocytes. This delay in commencement of therapy may cause anxiety in patients and their families, and be unacceptable to patients, leading to a decision to forgo fertility preservation.

Oocyte cryopreservation

Embryo cryopreservation may also be inappropriate for patients who are not currently in a stable relationship, and who do not wish to use donor sperm. Cryopreservation of oocytes may be preferable in these women. The procedure for egg cryopreservation is identical to that described above except that unfertilised eggs are harvested and stored. These oocytes are later thawed and fertilised, frequently using techniques such as intracytoplasmic sperm injection (ICSI), before implantation.

Cryopreservation of oocytes is less well developed than that of embryos, as oocytes are more vulnerable to damage during the freezing process, and it was initially feared that this technique would lead to increased birth defects. While the first reports of pregnancy following oocyte cryopreservation were made in the 1980's, these did not proceed to term and low success rates deterred further investigation. However, improved techniques led to increasing success in cryopreservation in the latter half of the 1990's and a live birth following oocyte cryopreservation and ICSI was reported in 1997[28], with several other reported successes following. A recent review of the literature has identified over 900 live births following oocyte cryopreservation; reassuringly this study showed no apparent increase in congenital abnormalities[29].

Cryopreservation of ovaries remains significantly less successful than that of embryos. In a meta-analysis published in 2006, live birth rates of around 2% were reported per oocyte thawed while the overall live birth rate per embryo transfer was 21%[30]. In a different study a rate of only one live birth per 65 embryo transfer cycles was achieved[31]. Recently, an alternative technique of cryopreservation has been developed which employs vitrification instead of slow-cooling. This technique involves the use of flash cooling and a higher concentration of cryoprotectants thus preventing the formation of ice crystals, and leading to the formation of an amorphous glass-like state instead. The use of vitrification and/or other technical advances have led to significantly increased oocyte survival following freeze-thawing, with rates of between 50% and 90% now reported[32].

The advantage with this technique is that there is no requirement for a partner or donor sperm. Additionally some people have religious or ethical beliefs which are opposed to embryo freezing. However the technique is less successful than embryo cryopreservation and is only available in certain centres. In addition, most funding agencies will not currently fund the technique due to its low success rate, and thus high cost per live birth.

Cryopreservation of ovarian tissue

This is very much an experimental technique in which ovarian tissue is surgically removed, frozen and then reimplanted after cancer treatment. At laparoscopy an ovarian wedge biopsy is performed, followed by dissection of the ovarian cortex into thin strips which contain immature follicles. These are then cryopreserved and reimplanted after completion of chemotherapy. The first success with this techniques was reported in 2000, with resumption of ovarian function after transplantation[33]. The first case of a live birth following ovarian transplantation was reported in 2004[34]. Subsequent debate has suggested it is not possible to convincingly prove that the pregnancy resulted from the transplant rather than from the in situ ovary[34,35]. However, over 10 live births have now been reported[36-39], supporting the validity of the technique.

Ovarian cryopreservation requires ovarian reserve in order to be successful and is therefore less likely to be a viable option in patients over 40 years of age. A disadvantage to the technique is the risk of implantation of cancer cells[40], which must be considered and discussed

with the patient prior to the procedure. It has been proposed as an option in preadolescent children[41]. Additionally, the procedure involves the use of general anaesthesia for both the ovarian biopsy and subsequent reimplantation, with attendant risks.

OVARIAN SUPPRESSION WITH GNRH ANALOGUES

Suppression of ovarian function through the use of GnRH analogues would be hypothesised to reduce the likelihood of subsequent ovarian failure, and such protection has been shown in animals[42]. It is thought they may act in several ways. By suppressing the ovaries, recruitment of primordial follicles into the maturation phase is prevented, leading to a reduction of the number of follicles in the vulnerable actively growing phase during exposure to cytotoxic drugs. The resultant low oestrogen state is thought to reduce circulation and therefore drug delivery to the ovaries and it has also been proposed that GnRH agonists upregulate anti-apoptotic factors in the ovary[43]. While early phase studies have been promising[44,45], there remains insufficient evidence to support the safety and effectiveness of gonadotropin-releasing hormone analogues and other means of ovarian suppression on fertility preservation. A Cochrane review published in 2011 identified four randomised controlled trials in this field, the combined results of which showed an increased chance of resumption of menses with co-treatment with intramuscular or subcutaneous GnRH agonists (RR = 1.90, 95%CI: 1.30-2.79) but no difference in pregnancy rates[46]. However, more recently published randomised trials have not shown significant differences in resumption of menses[47,48].

A large Italian randomised controlled trial did show a significant difference with use of GnRH analogues with a rate of early menopause following adjuvant chemotherapy for breast cancer of 25.9% in the control group compared to 8.9% in the group that received the GnRH analogue, triptorelin[49]. A limiting factor of the data is that it is nearly all from breast cancer populations who frequently will receive tamoxifen after chemotherapy which itself may interfere with menstruation. The follow up period is generally insufficient to allow evaluation of pregnancy rates and risk of premature menopause after resumption of menses. Results of ongoing trials such as the Southwest Oncology Group study, Prevention of Early Menopause Study are awaited along with mature data from some of the already published studies to be able to more conclusively evaluate this approach.

AVAILABILITY AND FUNDING

Fertility preservation techniques are not uniformly available, with techniques such as oocyte and ovarian cryopreservation limited to specialist centres, between which reported success rates vary. Funding availability also differs widely, both between and within countries. In the United Kingdom for example, the NHS may fund up to three cycles of IVF for any woman with infertility, but there is significant regional variation in the criteria applied, and the number of cycles funded. The cost of a self-funded cycle of IVF in the United Kingdom is approximately £5000 (approximately US $8000), and storage of embryos and oocytes may additionally incur costs of several hundred pounds per year. The costs for cryopreservation techniques are likely to be higher in the United States.

CONCLUSION

Infertility is a major concern in patients undergoing treatment for gynaecological malignancies, and can be overcome by a range of techniques, which have been outlined here. While fertility preservation will not be feasible in every patient, a discussion of the issue should be entered into early in the management of each patient, taking account of the local availability of services. A multidisciplinary approach will enable complex individualised interventions, which are necessary to maximise the chances of subsequent fertility and pregnancy. Counselling of patients is essential, and support should be available in the event of the procedure being unsuccessful.

While there are clearly ethical constraints on research, further progress with oocyte and ovarian cryopreservation is required to achieve comparable success rates to embryo implantation. Standardisation of techniques and cost reduction should make it feasible for funding agencies to provide more equitable availability of fertility preservation.

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TOPIC HIGHLIGHT

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Ovulation induction in the gynecological cancer patient

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Abstract

Malignancy is a serious disease that can lead to serious morbidity and mortality. However, the survival rates for women with cancers have increased significantly during the past decades, reflecting improved diagnosis and treatment. With the increased survival in young women with cancer, more attention is being paid to preservation of fertility, which is potentially jeopardized by chemotherapy and radiation therapy, aiming to limit the devastating sequelae of this serious illness by providing these young women with a hope for motherhood. *In vitro* fertilization with oocyte or embryo cryopreservation has emerged as an astounding method to preserve fertility. It entails induction of ovulation to produce oocytes, the number and quality of which are imperative factors predicting the potential efficacy of the fertility preservation procedure. The aim of this review is to discuss ovarian stimulation for fertility preservation in women with gynecological cancer.

Key words: Ovulation induction; Ovarian stimulation; Gynecological cancer

Core tip: Malignancy is a serious illness that is potentially life threatening. However, the survival rates for women with cancers have increased significantly during the past decade, reflecting improved diagnosis and treatment. The aim of this review is to discuss options for ovarian stimulation for fertility preservation in women with gynecological cancer.

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CANCERS IN REPRODUCTIVE AGE

Over the past two decades, cancer incidence rates have continued to increase[1], with approximately 10% of female cancer cases occurring under the age of 45 years[2]. Owing to the advancement in diagnosis and treatment of certain cancers at an earlier stage, improvement has been observed in the survival rates[2], raising more attention to improving the quality of life, particularly through the preservation of fertility, in these young women.

Candidates for fertility preservation are a rather heterogeneous group with a variety of underlying malignancies, the most common cancers being breast, melanoma, cervical, non Hodgkin's lymphoma and leukemia[3,4]. Gynecological cancers in this context include cancer of the breast and cancers arising from the reproductive organs (ovary, uterus, cervix and vulva). These cancers can affect patients in their reproductive years when their childbearing is not completed yet.

Approximately half of the demand for fertility preservation is from women with breast cancer[5] since it is the most common cancer in women in developed countries. In Europe, the incidence of breast cancer in premenopausal women over the past three decades was 30/100000[6]. Approximately 2% of cases occur in women aged 20-34 years and 11% in women aged 35-44 years[7]. Survival rates for breast cancer have risen in recent years, reaching 81%-87%.

Table 1 Risk of ovarian damage according to chemotherapy treatment used

High risk	Moderate risk	Low risk
Cyclophosphamide	Cisplatinum	Vincristine
Ifosfamide	Adriamycin	Vinblastine
Chlorambucil	Actinomycin	Methotrexate
Melphalan		Bleomycin
Busulfan		
Nitrogen mustard		
Procarbazine		

Endometrial cancer is considered the most common gynecological malignancy in the United States according to the American Cancer Society and the fourth most common cancer among women, behind only breast, lung and colorectal cancer[8]. However, it is rarely encountered for fertility preservation since more than 80% of cases occur in postmenopausal women and only less than 5% develop in patients younger than 40 years[9]. Ovarian cancer is primarily a disease of older women; however, it is estimated that 3% to 17% of ovarian tumors occur in women aged ≤ 40 years[10].

The oncological management of gynecological cancers used to bring the patient's fertility potential to an end due to the surgical removal of the reproductive organs harboring the malignancy. However, recently fertility sparing management of such cancers has been developed to safely remove or treat cancer without extirpating the reproductive organs. These include development of new surgical techniques, *e.g.*, radical trachelectomy for early stage cancer cervix (stage I AII)[11], unilateral adnexectomy with preservation of contralateral ovary and uterus for low malignant potential ovarian tumor[12] and early stage cancer ovary (stage I)[13], as well as novel treatment modalities, *e.g.*, high dose progestin therapy for early stage endometrial cancer (stage I A, grade 1)[14].

However, conservative surgery might entail the use of adjuvant chemotherapy or radiation therapy, both of which can still adversely affect the fertility potential. Ginsburg *et al*[15] reported decreased response in patients with cancer who had received chemotherapeutic agents before oocyte retrieval. The effect will depend on the patient's age as well as the type and dose of chemotherapeutic agent. According to their effect on ovarian reserve, chemotherapeutics are divided into three groups (high, moderate and low risk) (Table 1[16]). Alkylating agents seem to present the greatest risk of ovarian failure due to the profound loss of primordial follicles[17]. The effect of radiation therapy depends on the patient's age, site, type and dose of radiation[18].

Following fertility preserving management of gynecological cancer, the patient might conceive spontaneously. However, ovarian stimulation may be considered to cryopreserve oocytes and embryos before the adverse impact of chemotherapy/radiation therapy on ovarian reserve (as in breast cancer and cervical cancer). It might also be considered to increase the likelihood of pregnancy and decrease time interval to conception (as in endometrial cancer)[19] and in cases of associated infertility.

INDUCTION OF OVULATION IN GYNECOLOGICAL CANCER PATIENTS: THE CHALLENGES

Inducing ovulation in women with cancer should be considered cautiously and approached differently than inducing ovulation in women without cancer. Since these patients usually undergo only a single *in vitro* fertilisation (IVF) attempt before commencing chemotherapy or radiation therapy, it is crucial that as many cryopreserved embryos or oocytes as possible be obtained in this cycle for future use. Meanwhile, this should be attained with the absolute avoidance of ovarian hyperstimulation syndrome (OHSS), which can result in delay of chemotherapy and radiotherapy[20]. Unlike non-gynecological malignancies (*e.g.*, colon, hematological), gynecological cancers can be hormone responsive with resultant aggravation of the tumor due to the supraphysiological levels of estrogen released with ovarian stimulation. Thus, the fertility specialist encounters many challenges to attain this critical mission. Among these challenges are the following:

Decreased ovarian response

There are controversial reports on how cancer patients would respond to ovarian stimulation in IVF. Although some studies observed no significant change[21,22], the reproductive capacity of patients with cancers seems to be diminished and subjects with cancers are more likely to be poor responders[23]. Pal *et al*[24] reported an apparent adverse influence of malignant disease on the quality and performance of oocytes. Many explanations have been suggested. Among them, that cancer is associated with an increased catabolic state and malnutrition, resulting in weight loss which may affect the hypothalamic pituitary axis, resulting in hypothalamic dysfunction and a decrease in gonadotropin levels, thereby impairing the reproductive capacity[25]. Cancer is also associated with an increase in stress hormones which can lead to an increase in prolactin and endogenous opiate production, suppressing gonadotropin levels and further reducing fertility[26]. Moreover, recently Oktay *et al*[27] reported that women with breast and ovarian cancer, carriers of BRCA1 mutation, may respond poorly to ovarian stimulation. This may indicate a possible role of BRCA1 as an important factor responsible for the impairment in double stranded DNA break repair and a woman's infertility.

Time factor

Induction of ovulation has to be initiated before chemotherapy or radiation therapy since both therapies have deleterious effects on the ovarian reserve, resulting in premature ovarian failure and subsequent infertility[28]. Meanwhile, it is important to avoid prolonged deferral of chemotherapy or radiation therapy which can be det-

rimental to the success of cancer therapy. Typically, there is a gap of 4 to 6 wk between women undergoing breast cancer surgery and the commencement of chemotherapy, which is often sufficient to undergo ovarian stimulation. However, delayed referral of the patient to the fertility specialist results in time pressure. In this case, the best protocol that allows the quickest initiation of ovarian stimulation should be selected to shorten the deferral of chemotherapy/radiotherapy and allow early commencement of therapy. This can be ideally achieved with the use of the GnRH antagonist protocol[29]. In the conventional stimulation protocol, depending on the timing of the patient presentation, it takes up to 3 wk to reach the luteal phase when downregulation with a GnRH agonist can be started and continued for about 2 wk to prevent premature ovulation. Then, 9-14 more days are needed for ovarian stimulation with gonadotropins. On the contrary, GnRH antagonists immediately suppress the release of FSH and LH, preventing a premature LH surge. Administration is started when the size of the lead follicle reaches 12-14 mm at approximately day 6 of gonadotropin stimulation which begins on day 2, 3 of a menstrual cycle. Thus, GnRH antagonists significantly decrease the interval from patient presentation to oocyte retrieval compared to the conventional GnRH agonist protocol[30].

Instead of awaiting menses, further shortening of the interval to oocyte retrieval has been suggested by administering a GnRH antagonist during the preceding luteal phase to induce corpus luteum breakdown and synchronize the development of the next wave of follicles[31]. Menses will ensue a few days later with the ovarian stimulation initiated more quickly and the GnRH antagonist would then be restarted in the standard fashion[31]. Random-start stimulation protocol has been recently proposed as another alternative to avoid time wastage while awaiting the menses[32,33]. In this protocol, cancer patients in the luteal phase were started on GnRH antagonists to downregulate LH and initiate luteolysis. Simultaneously, follicular stimulation was initiated with recombinant FSH only to avoid exogenous LH activity which might prevent luteolysis. When this protocol was compared in a prospective multicenter trial with cancer patients stimulated during the follicular phase with either a short "flare up" protocol or an antagonist protocol, random start stimulation protocol yielded a similar number of aspirated oocytes, mature oocytes and fertilization rate[33]. However, more clinical studies are needed to assess the efficacy of this protocol, especially regarding the rates of clinical pregnancy and live-born infants originating from the use of cryopreserved embryos and oocytes[34]. It is important to stress that once a cancer diagnosis is established, early referral to a fertility specialist is highly encouraged to avoid unnecessary delay and facilitate prompt initiation of ovarian stimulation[35].

The associated increase in estradiol levels in hormonal dependent cancers

Induction of ovulation is typically associated with increased levels of estradiol. This can be serious in women with estrogen sensitive cancers, such as breast and endometrial cancer. Many strategies have been applied to minimize these estradiol peak levels. Among them are the following: (1) Tamoxifen. Tamoxifen can be used for controlled ovarian stimulation alone, starting on day 2-5 of the menstrual cycle in doses of 20-60 mg/d or in combination with gonadotropins**.** Not only does tamoxifen lower the peak estradiol levels compared to standard stimulation protocols[36], but also it has an antiestrogenic effect on breast tissue and is thus desirable to be used in estrogen receptor-positive breast cancer patients[37]; (2) Aromatase inhibitors. Aromatase inhibitors (including anastrozole and letrozole) are drugs of choice for the treatment of breast cancer in women with receptor-positive metastatic breast cancer. Their use has also been introduced as a new treatment option for ovulation induction[38]. It was reported that the peak estradiol level is lower in protocols that use aromatase inhibitors for ovarian stimulation[36]. Oktay *et al*[36] were the first to describe the use of letrozole in the GnRH-antagonist protocol in a study of 29 patients with breast cancer. The study included 33 ovarian stimulation cycles. In their study, letrozole in combination with FSH (letrozole-IVF) was compared to tamoxifen alone (Tam-IVF) and to tamoxifen in combination with FSH (TamFSH-IVF). They concluded that letrozole-IVF and TamFSH-IVF yielded more follicles, more mature oocytes and more embryos than Tam-IVF. Peak estradiol levels were lower with letrozole-IVF and Tam-IVF compared with TamFSH-IVF. Azim *et al*[39] described the use of letrozole in combination with gonadotropins in four patients with endometrial cancer. The estradiol levels in their study were lower compared with standard stimulation cycles. Data on the use of anastrozole for ovarian stimulation in anovulatory women, however, is more limited and studies so far do not support its use due to higher peak estradiol levels compared to letrozole[40]; (3) Using low doses of gonadotropins. The use of low dose gonadotropins (FSH 150 U/d) in the GnRH antagonist protocol in combination with letrozole was found to result in acceptable oocyte yield while maintaining low estradiol levels[36]. However, the use of higher doses of gonadotropins (FSH 150-375 U/d) in a GnRH antagonist protocol in combination with letrozole was recently studied by Ben-Haroush *et al*[41]. They reported a higher number of retrieved oocytes and frozen embryos than the lower dose schedule used in the study by Oktay *et al*[36], while similarly resulting in low levels of peak estradiol; (4) Using a GnRH antagonist protocol allows quick initiation of ovarian stimulation and pituitary suppression with a GnRH antagonist reduces the concentration of estradiol in patients with hormone dependent tumors[42]. Ben-Haroush *et al*[41] compared the use of high doses of FSH (150-375 U/d) in combination with letrozole in GnRH antagonist *vs* the long GnRH agonist protocol. Although the number of retrieved oocytes was higher in women in the long GnRH agonist protocol than the GnRH-antagonist protocol, the difference was not statistically significant; and (5) GnRH agonist trigger in the GnRH antagonist protocol has been shown to yield lower

estradiol concentrations compared to hCG trigger which potentiates the endogenous production of estrogen during the luteal phase owing to its longer half-life[43].

Avoidance of OHSS

OHSS is the most serious complication of ovarian stimulation since it is associated with significant morbidity which might necessitate hospitalization and intensive care. In cancer patients, the occurrence of this complication is critical since it may result in delaying or complicating planned life-saving cancer therapy. The risk of OHSS can be significantly lowered with the use of a GnRH antagonist protocol since it allows the use of a GnRH agonist trigger instead of the traditional hCG trigger if there is suspicion of overresponse to stimulation. Triggering the final oocyte maturation with hCG carries the risk of inducing OHSS[43], while using a GnRH agonist trigger in GnRH antagonist-based protocols dramatically reduces the risk of OHSS owing to the short half-life of GnRH agonist-induced endogenous LH surge which lasts for approximately 24-36 h compared to the longer half life of hCG which lasts for 7-10 d[44]. A recent Cochrane review comparing hCG to GnRH agonist trigger in antagonist cycles confirmed a 90% reduction in moderate to severe OHSS in the GnRH agonist group (OR = 0.10; 95%CI: 0.01-0.82 5 RCTs, 504 women)[45]. Meanwhile, the use of a GnRH agonist trigger was found to result in at least similar numbers of mature oocytes and cryopreserved embryos compared with hCG[46].

Therefore, in cases of estrogen sensitive cancers, the most recommendable protocol for induction of ovulation is the use of a GnRH antagonist in combination with letrozole (5 mg/d from the second day of menstrual cycle for 5-7 d) plus low dose gonadotropins[36]. This regimen allows an acceptable oocyte yield and keeps the circulating estradiol levels rather low compared with the standard ovarian stimulation protocols[47].

SAFETY OF OVARIAN STIMULATION IN CANCER PATIENTS

Safety is a major concern when considering induction of ovulation in cancer patients for the aim of fertility preservation, which may potentially decrease the chance of successful cancer treatment, increase the risk of maternal or perinatal complications, or compromise the health of offspring.

Risk of recurrence after ovarian stimulation

The risk of recurrence and the adverse impact on survival are real concerns for gynecological cancer survivors who desire to conceive after cancer therapy. Many studies have shown that pregnancy after breast cancer treatment does not appear to adversely affect recurrence or survival[48,49]. Oktay *et al*[36] followed their patients for a mean duration of 554 ± 31 d and they found that the cancer recurrence rate was similar in the IVF and control groups (3/29 *vs* 3/31 patients, respectively; HR = 1.5, 95%CI: 0.29-7.4). They noticed that the risk was not affected by cancer stage. In a larger follow-up report by Azim *et al*[50], the rate of cancer recurrence was compared among 79 women who elected to undergo ovarian stimulation with letrozole and gonadotropins for embryo or oocyte cryopreservation and 136 control patients (whom did not undergo fertility preservation procedures). The median follow-up after chemotherapy was 23.4 mo in the study group and 33.05 mo in the control group. They concluded that the recurrence and survival rates were similar in the two groups[50]. Thus, based on the above studies, induction of ovulation does not seem to increase the risk of recurrence compared to controls; however, more studies and longer follow up are needed.

Women who had undergone fertility sparing management for endometrial cancer did not have a higher incidence of cancer recurrence with the use of fertility drugs[51].

Several rare cases of ovarian stimulation have been reported in the literature after conservative treatment for borderline or invasive ovarian tumors[52-54]. Several pregnancies were achieved but in one case a uterine recurrence was observed and, most importantly, one woman died 7 mo after ovarian stimulation following extensive recurrence of an invasive lesion[52-54].

Newborn safety

Concerns about the safety of letrozole have been raised by the American Society for Reproductive Medicine through an abstract claiming possible teratogenic effects of letrozole[55], for which the use of letrozole for the purpose of induction of ovulation was discouraged. However, this concern was not supported by a large trial published in 2006 comparing newborn safety of letrozole with that of clomiphene citrate showing that congenital malformations were less frequent in the letrozole group[56]. It has been shown that the half-life of letrozole (approximately 30-60 h) is shorter than that of clomiphene citrate (5-7 d) and, thus, should be effectively cleared from the body by the time of embryo implantation, likely preventing a teratogenic effect when used in ovulation induction[57]. Another concern of cancer patients is whether offspring exposed to cytotoxic agents have an increased risk of birth defects. Several large studies that included more than 4000 offspring of cancer survivors showed no statistically significant increase in childhood malignancies or genetic malformations[58].

CONCLUSION

Fertility preservation through IVF technology is an evolving discipline that can minimize the devastating sequelae of cancer. Induction of ovulation is the critical step that determines the success of the fertility preservation. Gynecological cancers represent a real challenge to the fertility specialist due to possible hormonal responsiveness of the cancer, making induction of ovulation potentially detrimental. The use of GnRH antagonists, aromatase

inhibitors and triggering with GnRH agonists may provide reliable methods to minimize the unfavorable rise in estradiol levels. So far, reports on the safety of ovulation induction in these patients are reassuring and young women with cancer should be counseled about the option of fertility preservation as soon as the diagnosis of cancer is established.

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MINIREVIEWS

Cost effective evidence-based interventions to manage obesity in pregnancy

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Abstract

The rising tide of obesity has seen the prevalence of overweight and obese women presenting for antenatal care approach 50% in recent years. In addition, many pregnant women have gestational weight gain in excess of Institute of Medicine guidelines and develop obesity as a result of pregnancy. Both variables impact adversely upon pregnancy outcome. Individualised programs are not financially viable for cash strapped health systems. This review outlines an evidence-based, public health approach to the management of obesity in pregnancy. The interventions are affordable and in randomised and epidemiological trials, achieve benefits in pregnancy outcome.

Key words: Obesity; Pregnancy; Randomised trial; Evidence-based

Core tip: Public health approaches are feasible and effective to manage obesity in pregnancy. In primary care settings, women planning pregnancy should have their body mass index monitored in their medical record and receive nutrition advice, have comorbidities of depression and smoking addressed, receive influenza vaccination and education on gestational weight gain targets. Once pregnant, hospital management should focus on monitoring gestational weight gain to Institute of Medicine targets according to the patient's booking body mass index, combined with screening for diabetes, hypertensive and growth disorders. Following birth, care should handed back to primary care for ongoing weight interventions.

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INTRODUCTION

The rising tide of obesity has seen the prevalence of overweight and obese women presenting for antenatal care approach 50% in recent years[1]. Obesity at conception and gestational weight gain (GWG) in excess of Institute of Medicine guidelines both result in postnatal obesity, and each has an independent detrimental impact upon pregnancy outcome.

Obesity is a major risk factor for maternal and fetal complications, including maternal and fetal mortality, miscarriages, gestational diabetes mellitus (GDM), pregnancy-induced hypertensive disorders, infection, thromboembolic disease, obstructive sleep apnoea, fetal growth abnormalities, a need for induction of labour, difficulties with fetal monitoring and anaesthesia, birth trauma, caesarean section, post-partum haemorrhage, stillbirth and postpartum depression[1-17].

A pregnant woman of "normal" body mass index at

her booking antenatal visit who subsequently gains 20 kg in pregnancy will face similar complications to the mother who presents for antenatal care already obese but subsequently achieves an ideal GWG. Women who are obese at conception and then have excessive GWG experience the highest rate of complications.

In 2009, the Institute of Medicine revised its recommendations for GWG advising that overweight and obese women should restrict gains to 6.8-11.3 kg and 4.9-9.0 kg respectively[2]. Women of normal body mass index should restrict GWG to 11.5-16.0 kg. Whilst these levels remain subject to debate, and may be further refined as new studies are published, they remain the current goalposts for care.

The high prevalence of women who are overweight or obese at conception, and of women who have excessive GWG throughout pregnancy, means that every women presenting for antenatal care is at risk of obesity related complications. Expensive strategies to manage obesity in pregnancy are not logistically or financially feasible given the volume of caseload to manage. Instead, a public health approach is warranted. Universally applied cheaper interventions directed at the entire patient population are likely to have a greater clinical impact than expensive interventions directed at a motivated minority of extremely obese women.

How then, do we manage the obesity in pregnancy, and how do we assist all our antenatal patients achieve ideal GWG without sending our clinical services broke?

PREGNANCY PLANNING IN PRIMARY CARE

The start to this answer lies in primary care

All women attending primary care facilities should have their height, weight and body mass index recorded in their patient record. They should received feedback on their body mass index at every visit if it is greater than 25, and be informed of the increased pregnancy risks. The primary care provider should encourage each woman to engage with local opportunities for exercise and reinforce good dietary habits.

If a woman is specifically planning pregnancy, then folic acid and iodine supplements should be recommended. Obese women have an increased risk of neural tube defects that cannot be explain by non-use of a supplement alone, resulting in current recommendations that they take a higher dose 5 mg supplement rather than the lower 0.5 mg dose for prophylaxis[18]. Obese pregnant women also have lower levels of iodine and are at increased risk of iodine deficiency related complications[19]. Recommendation for supplementation conforms to a public health approach to obesity management in the women planning pregnancy.

An increasing number of reproductive age women have undergone bariatric surgery to manage their weight. Some of these women may still be overweight or obese, but others may have lost weight and be of normal body mass index. It is important to try and avoid pregnancy within 18 mo of bariatric surgery if possible as several studies have reported an increased risk of fetal growth and nutritional complications[20,21].

Depression is more common in obese women and is the major risk factor for postnatal depression. Addressing depression prior to conception can help influence the postnatal course and may lead to improved mother to child attachment[22,23].

Smoking cessation advice should be provided to women who smoke. Alcohol and other drug use should also be addressed. Although benefits are seen if women stop smoking at any stage of pregnancy, the earlier they stop, the greater the benefit.

Finally, influenza vaccination should be recommended. Influenza is more severe in obese pregnant women, but is a significant concern in all pregnancies[24]. Many women decide against vaccination as they have concerns over safety, and primary care providers need to address these concerns and reassure their patients[25].

The cost of these primary care interventions is minimal. Women will meet the cost of their recommended supplements and vaccination programs for influenza are already often nationally funded. Other measures should not add more than a few minutes to an existing scheduled consultation.

ANTENATAL CARE AND THE HOSPITAL RESPONSIBILITY

The first component of care is planning at the hospital-booking visit. Women who are excessively obese will need to be referred to centres able to manage their weight. However, the majority of antenatal care may be able to be safety provided closer to home.

It is important that the body mass index is recorded in the notes at booking. This enables maternity care staff to advise women of their Institute of Medicine recommended GWG for their body mass index (BMI) category and set a target for weight gain or restriction.

In reviewing the various meta analyses of randomised trials for interventions in pregnancy for overweight and obese pregnant women, dietary interventions are effective whereas physical exercise and mixed interventions are less so[26-29]. Furthermore, dietary interventions are cheaper and have greater acceptability to pregnant women.

For example, in the LIP trial, half the eligible women approached to enter the trial declined (n = 317). Of the 360 women randomised, a further 56 dropped out. Therefore, one could assume that the group of women completing the trial were a subgroup of motivated obese pregnant women. It was therefore disappointing that so few of this apparently motivated subgroup took advantage of the free exercise interventions offered. Dietary interventions were associated with excellent compliance with 92% of intervention women completing all sessions. In contrast, only 56% of intervention women attended the aerobic classes for at least half of the lessons[28].

If motivated pregnant obese women will not attend aerobic classes despite free gym membership, physical testing and personal coaching, and given the cost of the intervention to the public health budget, then meaningful changes in health status at a population level are unlikely to be achieved. Of course, this doesn't preclude staff from recommending women seek their own strategies to increase their levels of exercise through walking and making healthy choices in their daily life (*e.g.*, walking up the stairs and not taking a lift).

This swings the public health focus back to dietary interventions. In a recent meta-analysis, four dietary interventions were reviewed[26,30-33]. Three were effective. The common elements to the effective interventions were that they measured BMI at booking, weighed at each visit, and provided repeated feedback on GWG. The interventions had varying costs. One was expensive and involved ten sessions with qualified dieticians. Whilst effective as an intervention, it is not feasible to implement broadly as a public health strategy. The second effective dietary intervention provided brief feedback at each routinely scheduled antenatal visit on GWG and diet. It also included a session with a clinical psychologist to address psychological factors involved in weight management. However, the most effective strategy was also the cheapest. This involved the simple use of a diary with patient feedback at each visit on GWG.

This strategy can be easily implemented into routine obstetric practice. By placing scales in the clinic and recording weight at each visit into a hand held maternity card, and offering feedback during routinely scheduled consultations, we can imitate the strategy of the effective randomised trial for the minimal cost of some staff education and a set of scales.

The other public health interventions to be implemented in antenatal care are to advise all women to take Folic Acid and Iodine supplements. The role of Vitamin D supplements is less clear although Vitamin D deficiency is more common in obese pregnant women and their offspring and some authorities are now recommending routine supplementation[17,34].

The increased risk of gestational diabetes warrants routine screening with a full 75 g glucose tolerance test at 28 wk. Some centres also advocate an early test at 20 wk but the cost benefit of such a policy has not yet been fully evaluated[17]. In accordance with local hospital policies, consideration should also be made for formal anaesthetic review, and for surveillance of fetal growth and hypertensive complications given these risks are increased in obese pregnant women.

POSTNATAL CARE AND LINKING BACK INTO THE COMMUNITY

Following childbirth, overweight and obese women have an increased risk for thromboembolism. If delivery has been by caesarean section, then discussion about thromboprophylaxis is warranted. Some agencies recommend that all obese women should be offered thromboprophylaxis[1,17].

Overweight and obese pregnant women face increased difficulties with breastfeeding. This is often due to their large nipple and breast size. Midwifery staff may need to assist mothers with early feeding sessions to ensure correct attachment to avoid nipple trauma.

The final step in management is to ensure adequate transmission of information from the maternity hospital to the primary care provider. This is vital to continue monitoring and encouragement of any dietary strategies adopted in the antenatal period, to promote exercise and monitor for depression and breastfeeding difficulties. It is important that hospitals acknowledge obesity or excessive GWG are complications that impacted upon the pregnancy and note them in the discharge summary to draw attention to their ongoing management in primary care.

CONCLUSION

It is likely that increasing novel and effective strategies to manage obesity in pregnancy will emerge in the next few years. However, it will be important that these new strategies are compared to the current gold standard outlined in this review.

Healthcare is consuming increasing proportions of national expenditure and this situation cannot continue forever. We have to become more effective with the resources we have and implement those strategies with an evidence base we can afford.

Pregnancy is a time of idealization over reality; a time when interventions are accepted and women look to establish life changes. We cannot afford to miss this opportunity for intervention.

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RESEARCH REPORT

Effect of gynecologic oncologist availability on ovarian cancer mortality

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Abstract

AIM: To determine the association between the distribution of gynecologic oncologist (GO) and population-based ovarian cancer death rates.

METHODS: Data on ovarian cancer incidence and mortality in the United States was supplemented with United States census data, and analyzed in relation to practicing GOs. GO locations were geocoded to link association between county variables and GO availability. Logistic regression was used to measure areas of high and low ovarian cancer mortality, adjusting for contextual variables.

RESULTS: Practicing GOs were unevenly distributed in the United States, with the greatest numbers in metropolitan areas. Ovarian cancer incidence and death rates increased as distance to a practicing GO increased. A relatively small number (153) of counties within 24 miles of a GO had high ovarian cancer death rates compared to 577 counties located 50 or more miles away with high ovarian cancer death rates. Counties located 50 or more miles away from a GO practice had an almost 60% greater odds of high ovarian cancer mortality compared to those with closer practicing GOs (OR = 1.59, 95%CI: 1.18-2.15).

CONCLUSION: The distribution of GOs across the United States appears to be significantly associated with ovarian cancer mortality. Efforts that facilitate outreach of GOs to certain populations may increase geographic access.

Key words: Ovarian cancer; Gynecologic oncologists; Mortality; Access to care

Core tip: Ovarian cancer death rates increase with increasing distance to practicing gynecologic oncologists in the United States. Lower ovarian cancer mortality is significantly associated with geographic proximity to gynecologic oncologists. A more even geographic distribution of gynecologic oncologists may help in decreasing some barriers to appropriate, guidelines-based ovarian cancer care, which could result in reduced ovarian cancer deaths in the United States.

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INTRODUCTION

Ovarian cancer (OC) is the deadliest gynecologic malignancy and the fifth leading cause of cancer death among women in the United States[1]. Each year, more than 22000 women are diagnosed with and almost 16000 women die from the disease[1]. The majority of diagnoses (61%) are at late stages, when the disease is present in both ovaries and has spread throughout the peritoneal cavity[2]. Treatment for late-stage OC requires both surgery and chemotherapy, the costs of which confer a substantial burden on the United States healthcare system. The annual cost of managing OC patients in the United States is estimated to be approximately $612 million[3].

While treatment protocols for epithelial OC (accounting for 90% of all malignant cases) have improved, five-year survival for late-stage OC is just 27%[2]. The poor survival rate associated with OC is often attributed to the absence of gynecologic-specific signs and symptoms, and the lack of an effective screening test that can detect the disease at early stages. Currently, optimal surgery and delivery of chemotherapy are the only methods available to reduce OC mortality[4]. Several studies have suggested that optimal treatment (from staging through receipt of chemotherapy) resulting in better outcomes is more often achieved through subspecialist gynecologic oncologist (GO) care[5-9], leading several organizations to recommend OC patients receive treatment from GOs[4].

Despite the evidence and recommendations, many OC patients (about 30%-60%) are not treated by a GO[7,8]. Several barriers exist to receipt of guidelines-based care, including socioeconomic factors such as insurance status. In this study, we examined a potential geographic barrier to receipt of GO care. Our objective was to examine the geographic relationship between GO providers and OC mortality, in order to determine the effect that geographic availability of specialized care has on mortality, and add further evidence to the association between receipt of GO care and OC outcomes.

MATERIALS AND METHODS

Data sources and inclusion criteria

County level OC mortality data (2002-2006) were obtained from the Centers for Disease Control and Prevention (CDC) National Vital Statistics System (NVSS) through a public-use data file http://www.cdc.gov/nchs/ accessed on 2/17/2011. County-level contextual data were from several additional sources including: (1) Area Resource File (ARF 2008); (2) 2000 United States Census Summary File; and (3) United States Census Bureau's 2005 Small Area Health Insurance Estimates (SAHIE). OC incidence data (2002-2006) were obtained from CDC' s National Program of Cancer Registries (NPCR) and the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) for registries that met data high-quality criteria for publication[1]. Mortality data and incidence data covered 100% and 97% of the United States population, respectively. A list of practicing GOs in 2009, along with their practice address was obtained from the Foundation for Women's Cancer website (http://www.foundationforwomenscancer.org/find-a-gynecologic-oncologist. This list is populated by the Society of Gynecologic Oncologists and is estimated to cover 95% of practicing GOs (personal communication-SGO).

This study only includes data from the 48 contiguous United States states and the District of Columbia as the geography of Hawaii and Alaska results in transportation networks that are substantially different from other parts of the country. Of the 3141 counties that compose the United States, 32 counties and boroughs in Hawaii (5) and Alaska (27) were excluded from all analyses. Data from the remaining 3109 counties were used to examine the distribution of GOs (Figure 1). Data from 731 counties were suppressed due to less than four OC incident or death cases and patient confidentiality concerns; data from 198 counties were suppressed due to a death rate of zero and female population of 10000 or less; data from 112 counties in Kansas (45) and Minnesota (65) were excluded due to county-level incidence data release restrictions for these states. Data from the remaining 2068 counties were used to analyze the association between GO availability and county-level death rates (Tables 1-3, Figure 2).

Coding and variable definitions

County of residence (the geographic unit of analysis for this study) for each OC death was determined by using county Federal Information Processing Standards (FIPS) codes. FIPS codes were used to aggregate data at the county level, and to calculate five-year average OC incidence and death rates. FIPS codes were also used to categorize counties as metropolitan, non-metropolitan or rural based on 2003 USDA rural urban continuum (RUCA) codes. The following variables were included as measures of county socioeconomic status: (1) county household income inequality ratio; (2) the percent of county population living below the federal poverty line; and (3) the percent of county population without health insurance. The county household income inequality ratio is defined as the ratio of the number of households with incomes above the population's top 22% household income to the number of houses with incomes below the population's bottom 22% household income. To assess availability of physicians other than GOs for OC treatment, the average number of general surgeons, primary care physicians (PCPs) and obstetrician/gynecologists (OB/GYNs) per 100000 women in the county were derived using female population estimates from 2002-2006. Primary care physicians were defined as general practitioners, family medicine and internal medicine practitioners. Socioeconomic status and physician variables were categorized into equal tertiles (high, moderate and low) based on all counties included in the analysis. The 2002-2006 female population estimates were also used to calculate the county composition percentages for age, race, and ethnicity. Age was modeled as the percent of county population in the following age categories: 0 to 44 years, 45 to 54 years, 55 to

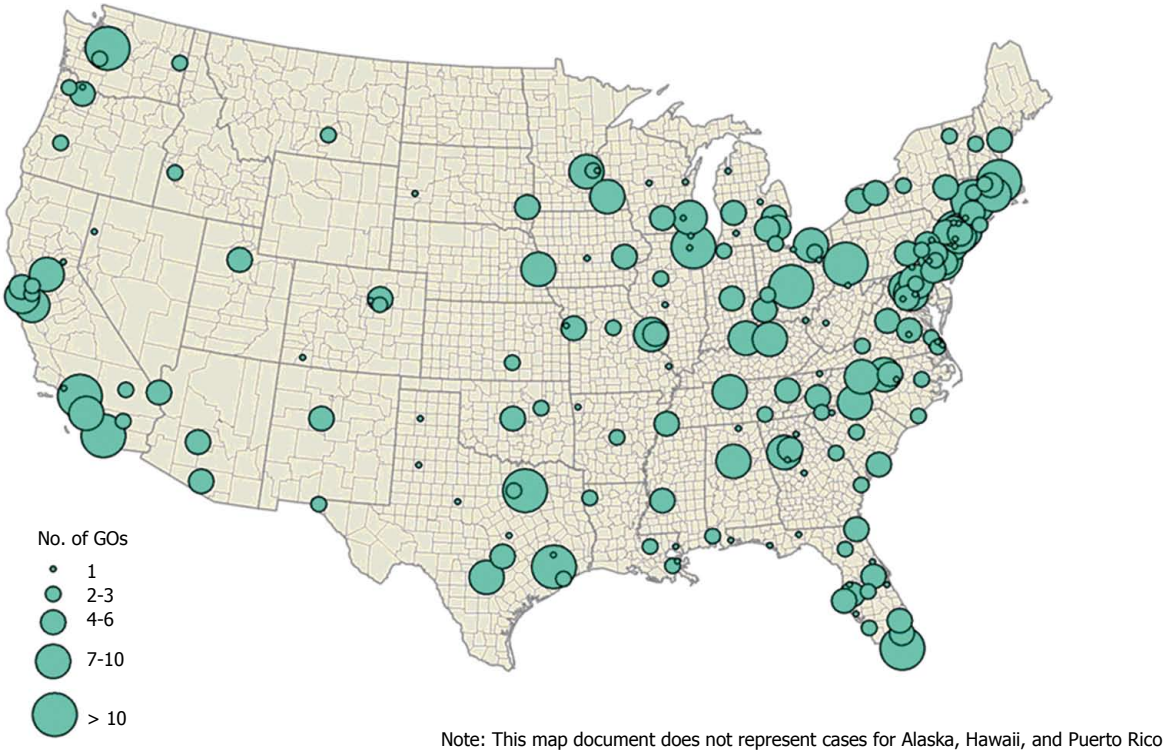

Figure 1 Location and number of gynecologic oncologist practices in the United States. GO: Gynecologic oncologist.

64 years, 65 to 74 years, and 75 years or older. Race/ethnicity was defined as the percent of county population in the following groups: non-Hispanic white, non-Hispanic black, non-Hispanic Asian-Pacific Islander, non-Hispanic other (which including non-Hispanic American Indian/Alaska Native), and Hispanic.

Statistical analysis

Mapping and statistical analyses were used to assess the relationship between the county-level death rate and distance to the nearest GO. County centroids were defined as the geographic center for a county and GOs were geocoded to latitude-longitude coordinate locations within the continental United States using ArcGIS (version 9, ESRI). Geographic access to specialized care was measured as the linear distance, ignoring roads, from county geographic centroid to nearest GO. This distance was then split into tertiles of 0-24 miles, 25-49 miles, and greater than 50 miles. Geographic availability to other less specialized care (PCPs, general surgeons and OB/GYN) was defined as the average number of each of these physicians per average female population (per 100000) for a county from 2002-2006 (data are from the Area Resource file). Death rates were dichotomized as low or high [less than or greater than the median death rate (11.6 per 100100)]. A logistic regression model was fit to the data to determine the association between distance to a GO and high county death rate, after adjusting for other county-level variables. Both forward and backward selection were examined, built with the criteria of a $P < 0.05$ value for model entry or inclusion, and both methods led to the same conclusions. The inclusion of OB/GYNs in the model caused a lack of stability due to collinearity with other variables; therefore even though it was found initially to be significant, this covariate was removed to improve the model stability. All statistical analyses were performed using SAS (version 9.2; Cary, North Carolina).

RESULTS

GO practice characteristics in the United States

The location and number of practicing GOs in the United States are shown in Figure 1. Of the 3109 United States counties, 2906 do not have a practicing GO and only 143 counties have more than one practicing GO. GO density is highest in the Northeast region of the United States. Within individual states, practicing GO locations are unevenly distributed, and practices tend to cluster in particular counties or regions. Florida appears to have a relatively even distribution of GOs across the state, while North Dakota and Wyoming have no practicing GOs within the state.

Table 1 shows GO practice location in relation to United States county characteristics. A total of 536 United States counties were within 24 miles of a practicing GO, 890 counties were located between 25 and 49 miles of a GO, and 1683 counties were located over 50 miles from a GO. The vast majority of counties within 24 miles of a GO practice (90.7%) were classified as metropolitan, whereas only 38.8% and 15.2% of counties within 25 to 49 miles and over 50 miles from a GO were classified as metropolitan, respectively. Most counties within 24 miles of a GO (81.9%) had a large difference in income among the highest and lowest earning households, while

Table 1 United States county characteristics by distance to gynecologic oncologist practice location

	Distance to closest gynecologic oncologist		
	0 to < 25 miles	> 25 to < 50 miles	> 50 miles
No. of US counties	**536**	**890**	**1683**
County designation	*n* (%)	*n* (%)	*n* (%)
Metropolitan	486 (90.7)	345 (38.8)	255 (15.2)
Non-metropolitan	42 (7.8)	424 (47.6)	901 (53.5)
Rural	8 (1.5)	121 (13.6)	527 (31.3)
Socioeconomic characteristics	***n* (%)**	***n* (%)**	***n* (%)**
Income inequality ratio[1]			
Low (< 3.84)	26 (4.9)	226 (25.4)	773 (45.9)
Moderate (> 3.84 to < 6.71)	71 (13.3)	323 (36.3)	664 (39.4)
High (> 6.71)	438 (81.9)	341 (38.3)	246 (14.6)
Percent of county below poverty level			
Low (< 11%)	295 (55.0)	292 (32.8)	452 (26.9)
Moderate (> 11% to < 15.2%)	163 (30.4)	307 (34.5)	577 (34.4)
High (> 15.2%)	78 (14.6)	291 (32.7)	654 (38.9)
Percent of county uninsured			
Low (< 13.3%)	257 (47.9)	333 (37.4)	437 (26.0)
Moderate (> 13.3% to < 18.5%)	181 (33.8)	321 (36.1)	563 (33.4)
High (> 18.5%)	98 (18.3)	236 (25.5)	683 (40.6)
Physician characteristics (per 100000 women)	***n* (%)**	***n* (%)**	***n* (%)**
Primary care physicians			
0	1 (0.2)	15 (1.7)	115 (6.8)
Low (< 105.79)	120 (22.4)	347 (39.0)	515 (30.6)
Moderate (> 105.79 to 169.97)	182 (34.0)	327 (36.7)	505 (30.0)
High (> 169.97)	233 (43.5)	201 (22.6)	548 (32.6)
General surgeons			
0	51 (9.5)	223 (25.1)	666 (39.6)
Low (< 11.72)	135 (25.2)	273 (30.7)	307 (18.2)
Moderate (> 11.72 to < 20.47)	138 (25.7)	249 (28.0)	352 (20.9)
High (> 20.47)	212 (39.6)	145 (16.3)	358 (21.3)
OB/GYNs			
0	65 (12.1)	327 (37.7)	936 (55.6)
Low (< 11.27)	94 (17.5)	235 (26.4)	259 (15.4)
Moderate (> 11.27 to < 20.53)	139 (25.9)	199 (22.4)	268 (15.9)
High (> 20.53)	238 (44.4)	129 (14.5)	220 (13.1)
Population Characteristics	**% (SE)**	**% (SE)**	**% (SE)**
Non-Hispanic white	77.6 (17.7)	82.5 (16.9)	81.4 (20.1)
Non-Hispanic black	12.1 (14.1)	10.0 (14.8)	7.0 (14.6)
Non-Hispanic Asian/Pacific Islander	2.4 (3.5)	0.8 (1.3)	0.6 (0.8)
Non-Hispanic other[2]	1.6 (1.2)	2.0 (4.8)	3.2 (8.1)
Hispanic	6.3 (8.8)	4.7 (8.7)	7.7 (14.6)
Ages 0 to 44	60.8 (5.2)	58.0 (5.3)	55.7 (6.6)
Ages 45 to 54	14.7 (1.3)	14.4 (1.5)	14.4 (1.6)
Ages 55 to 64	10.5 (1.6)	11.3 (1.8)	11.5 (2.0)
Ages 65 to 74	6.8 (1.7)	7.9 (1.6)	8.7 (1.9)
Ages 75+	7.3 (2.2)	8.4 (2.3)	9.8 (3.1)

[1]Defined as the ratio of the number of households with incomes above the population's top 22% household income to the number of houses with incomes below the population's bottom 22% household income; [2]Includes Non-Hispanic American Indian/Alaska Native.

Table 2 Ovarian cancer incidence and mortality by distance to gynecologic oncologist practice location

	Distance to closest gynecologic oncologist		
	0 to < 25 miles	⩾ 25 to < 50 miles	⩾ 50 miles
Mortality			
N	499	707	974
Rate (SE)	10.09 (3.14)	12.02 (4.73)	13.57 (6.43)
Incidence			
N	519	855	1418
Rate (SE)	14.21 (4.23)	15.11 (6.54)	16.31 (8.51)

Table 3 Adjusted odds of high ovarian cancer mortality by gynecologic oncologist practice location

County level variable	Odds ratio	Odds ratio 95%CI	*P*-value
Distance to GO			
⩾ 25 to < 50 miles *vs* < 25 miles	1.40	(1.04, 1.89)	0.029
⩾ 50 miles *vs* < 25 miles	1.59	(1.18, 2.15)	0.003
General surgeon per avg. pop.			
1st Tertile: (< 11.72) *vs* 0	0.35	(0.24, 0.50)	< 0.001
2nd Tertile: (> 11.72 to < 20.47) *vs* 0	0.35	(0.24, 0.51)	< 0.001
3rd Tertile: (> 20.47) *vs* 0	0.32	(0.22, 0.48)	< 0.001
Incidence Rate	1.15	(1.12, 1.18)	< 0.001
% Population Age 45 to 54	1.25	(1.15, 1.37)	< 0.001
% Population Age 75+	1.39	(1.31, 1.48)	< 0.001
% Population non-Hispanic Asian/Pacific Islander	0.88	(0.80, 0.96)	0.004
% Population Hispanic	0.99	(0.97, 1.00)	0.027

The model is adjusted for all the covariates shown in the county level variable column. GO: Gynecologic oncologist.

relatively few counties over 50 miles from a GO (14.6%) had a large difference in income among high and low earning households. Poverty levels were relatively low in counties within 24 miles of a GO (55.0% of counties had less than 11% of the population in poverty), and were higher in counties greater than 50 miles from a GO (38.9% of counties had 15.2% or more of population in poverty). Counties within 24 miles of a GO also had high densities of PCPs (43.5% had greater than 169 per 100000 women), general surgeons (39.6% had greater than 20 per 100000 women), and OB/GYNs (44.4% had greater than 20 per 100000 women). These physicians were less prevalent in counties 50 miles or greater from a GO practice compared to those within 24 miles of a GO practice. A substantial proportion of counties 50 miles or greater from a GO practice did not have any general surgeons (39.6%), and most did not have any OB/GYNs (55.6%). The majority of women in each distance category were non-Hispanic white, although the percentage was slightly lower in counties within 24 miles of a GO (range 77.6%-82.5%). Overall, higher percentages of women aged 65 and older were found in counties farther away from GO practice locations compared to those within 24 miles of a GO practice location.

OC burden in relation to GO practice

Table 2 displays OC incidence and mortality in relation to GO practice locations. Both OC incidence and death

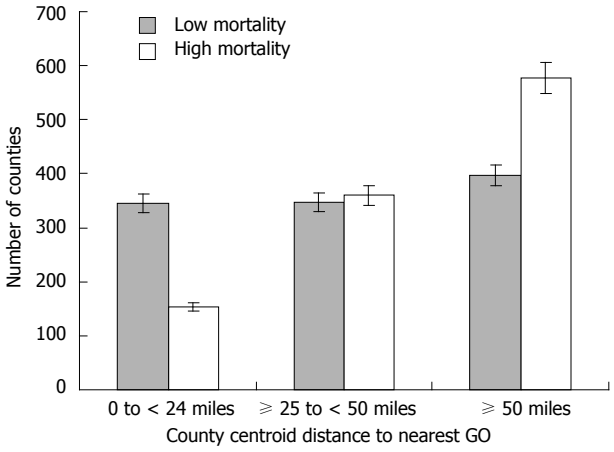

Figure 2 Dichotomized ovarian cancer mortality (high/low) by distance to gynecologic oncologist practice location. GO: Gynecologic oncologist.

rates increase as distance to GO practice increases. Counties within 24 miles of a GO practice location had the lowest incidence (14.21) and death (10.09) rates. Counties located 50 miles or greater from a GO practice had the highest OC incidence (16.31) and death (13.57) rates.

Figure 2 shows dichotomized county-level OC death rates in relation to GO practice location. The number of counties with a high death rate increased as distance from practicing GOs increased. A total of 153 counties within 24 miles of a GO had high death rates compared to 577 counties 50 miles or greater from a GO.

The adjusted results of the association between high OC mortality and GO practice location are shown in Table 3. High OC mortality was significantly associated with increased distance from GOs. Counties with GO practices 25-49 miles from the county centroid had a 40% greater odds of high OC mortality compared to those counties with practices within 24 miles (OR = 1.40, 95%CI: 1.04-1.89). Counties with practices greater than 50 miles to a GO had an almost 60% greater odds of high OC mortality (OR = 1.59, 95%CI: 1.18-2.15). The presence of a general surgeon was associated with a decreased chance of high OC mortality compared to counties without a general surgeon; however, this effect was relatively constant and the OR did not vary substantially in relation to increasing density of general surgeons per average population of women (ORs: 0.32-0.35). Other factors associated with an increased odds of high OC mortality include counties with high OC incidence rates (OR = 1.15, 95%CI: 1.12-1.18), counties with higher proportions of women aged 45-54 years (OR = 1.25, 95%CI: 1.15-1.37), and higher proportions of women 75 years or older (OR = 1.39, 95%CI: 1.31-1.48). Conversely, counties with higher proportions of non-Hispanic Asian/Pacific Islander and Hispanic women had a reduced odds of high OC mortality (OR = 0.88, 95%CI: 0.80-0.96, OR=0.99, 95%CI: 0.97-1.00, respectively).

DISCUSSION

Our findings indicate that there is an uneven distribution of GOs in the United States, with higher concentrations of GOs in metropolitan counties. While there are lower numbers of GOs overall compared to other potential OC practitioners, GO availability tends to be geographically similar to the availability of these other practitioners. Importantly, we have established that increasing distance from a GO has a significant association with increased likelihood of higher OC death rates.

Previous studies with other cancers have demonstrated similar results. In addition to uneven distribution of specialists, Odisho *et al*[10] noted significant prostate, bladder and kidney cancer mortality reductions in counties with urologists compared to those without. Similar results have been reported with regard to dermatologists and melanoma[11]. A lung cancer study also reported uneven distribution of specialist providers, but found no difference in mortality based on the density of thoracic surgeons or oncology services[12]. Further, this study reported that a higher proportion of PCPs (as opposed to specialists) was associated with a lung cancer mortality reduction in some populations[12]. This PCP finding is somewhat consistent with our study in that we also observed decreased OC mortality in relation to the density of general surgeons; however, the mortality reduction in our study was similar regardless of increasing density of PCPs.

Current and projected shortages in the availability of cancer care providers have been well-documented. In a recent workshop sponsored by the United States Institute of Medicine, it was noted that almost all oncology professions are experiencing workforce shortages, including physicians, nurses, allied health care professionals, public health workers, social workers, and pharmacists[13]. A 2007 study commissioned by the American Society of Clinical Oncology found that the demand for oncologists is likely to increase dramatically by the year 2020, driven by the aging and growth of the population as well as improvements in cancer survival rates[14]. The supply of oncologists is only projected to increase 14% during the same timeframe, creating a shortage of 2500 to 4080 oncologists[14]. A similar situation exists for gynecologic oncologists. A 2010 study projected that at constant training rates, the annual number of new cancer cases per practicing GOs will rise 19%, with an expected increased caseload of almost 20% over the next 40 years[15]. In New Zealand, which also has an uneven distribution of GOs, a reorganization of gynecologic cancer care has been suggested in order to ensure that all patients have access to subspecialists in the face of GO shortages[16]. This model is based on one adopted in the United Kingdom, and establishes a connection between major comprehensive cancer centers that have GOs and smaller satellite hospitals without GOs. This connection may help to facilitate multidisciplinary care for patients in the smaller centers. Additionally, a national gynecologic cancer steering group with representation from the comprehensive cancer centers, and key medical and nursing disciplines would oversee care coordination, including development of a standardized protocol for treatment

and referral guidelines[16]. A similar coordinated approach may assist with alleviating the negative outcomes (higher OC mortality) that geographic barriers to GO care has in the United States. However, it should be noted that several other factors in addition to geographic availability may impact receipt of quality care for OC in the United States. These factors are numerous and include lack of insurance or other socioeconomic limitations, language and cultural differences, psychosocial, lifestyle and behavioral factors[17-19].

Given the lack of geographic availability of GOs in many areas in the United States, an emphasis on OC prevention may be suggested. However, OC is difficult to prevent and no evidence-based early detection methods are currently available[4]. Several studies investigating serum CA-125 levels in combination with transvaginal ultrasound as a potential early detection method resulted in more harms than benefits to patients[20,21], and did not reduce overall OC mortality[20]. A comprehensive evidence review assessing oral contraceptive use for OC prevention also found the potential for more harms than benefits, particularly with regard to effects on quality of life from increases in breast cancer and vascular events caused by oral contraceptive use[22]. The identification of patients who are at an increased risk for OC due to genetic mutations in the *BRCA* gene currently offers the greatest potential for prevention of OC[23]. Stressing the importance of family history knowledge, and appropriate genetic counseling and testing to determine BRCA status among women may ultimately reduce ovarian cancer risk and mortality in some women[24].

This study has several strengths. To our knowledge, it is the first to relate geographic proximity to GOs with lower OC mortality in the United States. Additionally, the use of population-based OC data from a large portion of the United States likely improved the accuracy of the results. Limitations to this study include the ecologic study design which impedes the ability to apply the results at the individual level. Also while our data sources were current at the beginning of the study, they are now slightly dated and the years of OC incidence and mortality vary from that of the practicing GOs. However, since OC incidence and death rates changed little over the last decade, and any changes in GO numbers and distribution by state are relatively minor, this likely has little impact on the results. Finally, although our data sources are comprehensive in coverage, a small percentage of GO providers and OC incident cases remain missing from our analysis. It is unlikely that the results would be different based on these small percentages; however, we are unable to make any conclusions with regard to the areas where data are missing.

The uneven distribution of GOs across the United States appears to be significantly associated with OC mortality, with death rates increasing as distance to GO increases. These findings may have important implications for the oncology workforce and cancer control planning. Appropriate genetic counseling and testing for the prevention of OC, as well as facilitated outreach to GOs in order to provide a coordinated approach to quality OC care, may be promoted through the efforts of cancer control planners in the United States National Comprehensive Cancer Control Program. Future studies examining the effects of GO distribution on OC mortality at the individual level may assist with further defining barriers to quality OC care in the United States.

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COMMENTS

Background

Ovarian cancer (OC) is the deadliest gynecologic malignancy and the fifth leading cause of cancer death among women in the United States. Several studies have suggested that optimal treatment and better outcomes for OC are more often achieved through subspecialist gynecologic oncologist (GO) care. Despite this evidence many patients (about 30%-60%) are not treated by a GO.

Research frontiers

OC is a deadly disease, with no known effective prevention. Studies in areas that improve treatment and outcomes from the disease, such as receipt of care from a GO, is a research hotspot in OC mortality reduction.

Related publications

http://www.ncbi.nlm.nih.gov/pubmed/17540806; http://www.ncbi.nlm.nih.gov/pubmed/21256581; http://www.ncbi.nlm.nih.gov/pubmed/16449677

Innovations and breakthroughs

Research into factors related to limited access to GO (such as patient socioeconomic factors) is an important and timely topic. This study examines whether geography may be a potential barrier to GO access.

Applications

OC mortality increases significantly as distance to GO increases. These findings have important implications for the oncology workforce and cancer control planning. Facilitated outreach to GO and a more coordinated and quality approach to OC care is suggested.

Terminology

Gynecologic oncologist: A physician who has completed an obstetrics and gynecology residency and then pursued subspecialty training through a gynecologic oncology fellowship (which includes intensive surgical, chemotherapeutic, radiation, and research training). Geographic Information System: integrates data for analyzing and displaying all forms of geographically referenced information which allows for viewing, understanding, and interpreting data to reveal relationships, patterns, and trends.

Peer review

In this study, the authors examined a potential geographic barrier to receipt of GO care. The objective of the study was to examine the geographic relationship between GO providers and OC patient mortality, in order to determine the effect that geographic availability of specialized care has on mortality. The experimental design is appropriate, and the data seem high quality. This is an interesting article.

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RESEARCH REPORT

Fetal lung surfactant and development alterations in intrahepatic cholestasis of pregnancy

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Abstract

AIM: To investigate the association between total bile acid (TBA) level during intrahepatic cholestasis of pregnancy (ICP) and fetal lung surfactant alteration.

METHODS: We recruited 42 ICP and 32 normal pregnancy women in this study. The maternal blood, fetal blood and amniotic fluid TBA level were detected using a circulating enzymatic method. Umbilical blood pulmonary surfactant protein A (SP-A) was evaluated with enzyme-linked immunosorbent assay. High performance liquid chromatography was used for the determination of phosphatidyl choline (PC), phosphatidyl inositol (PI), lysolecithin (LPC) and sphingomyelin (SM). Amniotic fluid lamellar body was counted with a fully automatic blood cell counter. Fetal lung area and fetal body weight were calculated from data obtained with an iu22 color supersonic diagnostic set. Clinical information of a nonstress test, amniotic fluid properties and neonatal Apgar score, and birth weight were recorded for review.

RESULTS: The TBA level in maternal blood, fetal blood and amniotic fluid in the ICP group were significantly higher than that in the control group (maternal blood: 34.11 ± 6.75 mmol/L *vs* 4.55 ± 1.72 mmol/L, $P < 0.05$; fetal blood: 11.9 ± 2.23 mmol/L *vs* 3.52 ± 1.56 mmol/L, $P < 0.05$; amniotic fluid: 3.89 ± 1.99 mmol/L *vs* 1.43 ± 1.14 mmol/L, $P < 0.05$). Amniotic fluid PC and PI in the ICP group were significantly lower than that in the control group (PC: 65.71 ± 7.23 μg/mL *vs* 69.70 ± 6.68 μg/mL, $P < 0.05$; PI: 3.87 ± 0.65 μg/mL *vs* 4.28 ± 0.74 μg/mL, $P < 0.05$). PC/LPC ratio of the ICP group was lower than that of the control group (14.40 ± 3.14 *vs* 16.90 ± 2.52, $P < 0.05$). Amniotic LB in the ICP group was significantly lower than that of the control group ((74.13 ± 4.37) × 10^9/L *vs* (103.0 ± 26.82) × 10^9/L, $P < 0.05$). Fetal umbilical blood SP-A level in the ICP group was significantly higher than that of the control group (30.26 ± 7.01 ng/mL *vs* 22.63 ± 7.42 ng/mL, $P < 0.05$). Fetal lung area/body weight ratio of the ICP group was significantly lower than that of the control group (5.76 ± 0.63 cm^2/kg *vs* 6.89 ± 0.48 cm^2/kg, $P < 0.05$). In the ICP group, umbilical cord blood TBA concentration was positively correlated to the maternal blood TBA concentration ($r = 0.746$, $P < 0.05$) and umbilical blood SP-A ($r = 0.422$, $P < 0.05$), but it was negatively correlated to the amniotic fluid lamellar corpuscle ($r = 0.810$, $P < 0.05$) and fetal lung area/body weight ratio ($r = 0.769$, $P < 0.05$). Furthermore, umbilical blood TBA showed a negative correlation to PC, SM and PI ($r_{pc} = 0.536$, $r_{sm} = 0.438$, $r_{pi} = 0.387$ respectively, $P < 0.05$). The neonatal asphyxia, neonatal respiratory distress syndrome, fetal distress and perinatal death rates in the ICP group are higher than that of the

control group.

CONCLUSION: ICP has higher TBA in maternal and fetal blood and amniotic fluid. The high concentration of TBA may affect fetal pulmonary surfactant production and fetal lung maturation.

Key words: Intrahepatic cholestasis of pregnancy; Total bile acid; Pulmonary surfactant; Surfactant protein; Phospholipids; Amniotic fluid lamellar body

Core tip: We studied total bile acid (TBA) concentration in maternal, fetal and amniotic fluid and its relationship with fetal surfactant, surfactant protein A, amniotic lamellar body and fetal lung development. Results demonstrated that intrahepatic cholestasis of pregnancy (ICP) has higher TBA in maternal and fetal blood and amniotic fluid. The high concentration of TBA may affect fetal pulmonary surfactant production and fetal lung maturation. It calls attention to delayed maturation of fetal lungs in ICP patients and to take steps to carefully check and improve fetal pulmonary maturity.

Ding YL, Zhang LJ, Wang X, Zhou QC, Li N, Wang CX, Zhang XQ. Fetal lung surfactant and development alterations in intrahepatic cholestasis of pregnancy. *World J Obstet Gynecol* 2014; 3(2): 78-84 Available from: URL: http://www.wjgnet.com/2218-6220/full/v3/i2/78.htm DOI: http://dx.doi.org/10.5317/wjog.v3.i2.78

INTRODUCTION

Intrahepatic cholestasis of pregnancy is a maternal metabolic disease affecting up to 5% of pregnancies[1]. It is characterized by rising maternal serum bile acids and can be complicated by fetal distress, neonatal asphyxia and neonatal respiratory distress syndrome[2-4]. The etiology of intrahepatic cholestasis of pregnancy (ICP) is poorly understood but the perinatal complications are closely correlated with maternal total bile acid (TBA) level[5,6]. Savonius found that high TBA can cause neonatal lung injury but its mechanism is not clear[7]. In order to explore fetal lung alteration during ICP and its possible mechanisms, we investigated maternal and fetal TBA, fetal surfactant production and fetal lung development.

MATERIALS AND METHODS

Protocols were approved by Central South University Xiangya Second Hospital Scientific Research Department. Informed consents were obtained from all patients involved in this study.

Clinical information

A total of 72 cases were recruited in this study during 2010 and 2011. It includes 40 ICP patients and 32 normal pregnant women with singleton pregnancy delivered using cesarean section. In the ICP group, the patients' ages were from 18 to 40 years old and the average age was 27.7 ± 1.37 years. The gestational ages were from 33 wk to 41 wk + 5 d and the average gestational age was 37.25 ± 2.34 wk. In the normal pregnancy group, the patients' ages were from 19 to 36 years old and the average age was 27.2 ± 4.67. The gestational ages were from 33 ± 2 to 40 ± 6 wk and the average gestational age was 37.5 ± 2.67 wk. There were no statistical differences between the ICP group and control group for maternal age, gestational age or pregnancy times. ICP was diagnosed with the diagnostic criteria referenced in the eighth edition of the national text book of obstetrics and gynecology[8]. Patients with liver disease, gall bladder disease, chronic vascular disease, gestational hypertension, gestational diabetes, anemia, kidney disease, heart disease or other pregnancy complications were excluded.

Sample collections

Maternal blood was collected at a fasting state before cesarean section. Fetal blood was collected through the umbilical artery immediately after delivery of the fetus during cesarean section. Amniotic fluid was collected with a syringe through the amniotic membrane just after cutting and separating the myometrium during cesarean section, with careful attention to avoid blood pollution.

Blood specimens were injected into a test tube dedicated with heparin immediately after being collected. After centrifuge (3000 r/min, 15 min), the supernatant was collected and stored at -20 ℃ for future experiments. For amniotic fluid, the upper solution was collected after centrifuge (3000 r/min, 15 min), then mixed 1:1 volume with methanol/chloroform. After centrifuge again (2500 r/min, 10 min), the lower liquid was extracted and mixed with a methanol-water extractor (1:1, v/v). The supernatant and interface impurities were discarded after centrifuge (2500 r/min, 10 min), 10 mL lower fluid was taken and sealed into a test tube, then stored for future tests at -20 ℃. Before testing, a mobile phase containing chloroform was used to dissolve the samples.

Amniotic fluid assay for TBA, SPA, phospholipids

TBA was detected using the automatic biochemical analyzer (Hitachi 7060, Japan) with the TBA detection kit (Sigma, Shanghai Trading Co. Ltd.), following the instruction of the assay kit. The calibration was made each time using the standard calibrator. Surfactant protein A (SP-A) was detected with the SP-A detection kit using an enzyme-linked immunosorbent assay (Wuhan technology co., China and United States)[9]. Phospholipids phosphatidylcholine (PC), phosphatidylinositol (PI), lysolecithin (LPC) and sphingomyelin (SM) were detected with high-performance liquid chromatography (HPLC, Shanghai National Medicine Chemical Reagent Co. Ltd.) with the standard phospholipids (Sigma, Shanghai Trading Co. Ltd.). uPrasil column (300 mm × 4 mm, 5 μm)

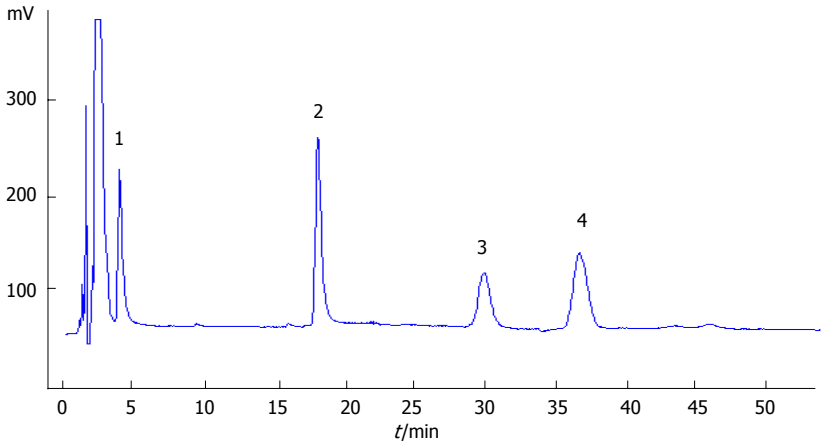

Figure 1 Chromatogram of phospholipids. High-performance liquid chromatography was used for phospholipids measurement. Peaks represent the phospholipids extracted from amniotic fluids. Peaks refer to the following components: 1: Phosphatidylinositol; 2: Phosphatidylcholine; 3: Lysolecithin; 4: Sphingomyelin.

was used with a HW2000 chromatographic data station for data analysis. The procedures and steps were carried out accurately following the instructions of the agent kit and instrument. The phospholipid concentration results are shown in Figure 1. Amniotic fluid lamellar body was counted using a hematology analyzer (ABX-Pentra120, Diamond Diagnostics, United States).

Ultrasonography

Color ultrasonic diagnostic system (Philips iu22, United States, probe frequency 2.5-6.0 OMHZ) was used for fetal lung area and fetal body weight within 3 days of delivery. Fetal body weights were assessed and calculated by checking the fetal biparietal diameter, head circumference, abdominal circumference and femoral length. Fetal lung areas were calculated by measuring the fetal left and right lung area by freezing an image shot when the fetal heart was at the diastolic phase while the probe was parallel to the longitudinal line of the fetus. The area was digitally analyzed by the computerized system automatically. Data was taken by one professional individual using a mean of 3 measurements. Total lung area and lung area/body weight were digitally calculated[10].

Fetal heart rate patterns, amniotic fluid characteristics and neonatal Apgar score were recorded for evaluation. The situation of the neonates was also recorded for three days to evaluate the fetus and neonates.

Statistical analysis

Software SPSS13.0 was used for statistics. Student *t*-test was used for measurement data and χ^2 test was used for numerous data. Correlation was analyzed using Pearson and Spearman correlation analysis.

RESULTS

Total bile acid level

The TBA concentration in maternal peripheral vein blood, fetal umbilical artery blood and amniotic fluid in the ICP group was 34.11 ± 6.76, 11.9 ± 2.23, and 3.89 ± 1.99 mmol/L respectively. They were significantly higher than that of the control group which were maternal: 4.55 ± 1.72 mmol/L, fetal: 3.52 ± 1.56 mmol/L, and amniotic fluid: 1.43 ± 1.14 mmol/L ($P < 0.05$ respectively). In addition, the TBA level in maternal serum was higher than that in fetal serum or amniotic fluid in both the ICP group and control group (Table 1).

Amniotic phospholipid components and lamellar body

The PC and PI concentrations in amniotic fluid in ICP group were 65.71 ± 7.23 μg/mL and 3.87 ± 0.65 μg/mL respectively. They were evidently lower than that in the normal control group (69.70 ± 3.68, 4.28 ± 0.74 μg/mL respectively, $P < 0.05$). In the ICP group, LPC content in amniotic fluid was 4.72 ± 0.86 μg/mL, which was much higher than that in control group (4.21 ± 0.64 μg/mL, $P < 0.05$); the SM content in both groups had no statistical difference. The ratio of PC/LPC in the ICP group (14.40 ± 3.14) was much lower than that of the control group (16.90 ± 2.52, $P < 0.05$). The lamellar body in the ICP group was evidently lower than that of the control group ($P < 0.05$) (Table 1).

Fetal SP-A and fetal lung area/body weight

In the ICP group, fetal SP-A concentration was 30.26 ± 7.01 ng/mL, which is significantly higher than that of the control group, 22.63 ± 7.42 ng/mL ($P < 0.05$). The fetal lung area/body weight ratio of the ICP group was 5.76 ± 0.63 cm^2/kg, while the control group was 6.89 ± 0.48 cm^2/kg, which is a significant difference ($P < 0.05$) (Figure 2).

Correlation analysis

The maternal TBA concentration and fetal TBA level are positively correlated ($r = 0.746$, $P < 0.05$). Fetal TBA is positively correlated with fetal SP-A concentrations ($r = 0.422$, $P < 0.05$), but negatively correlated with amniotic fluid lamellar small mass ($r = 0.810$, $P < 0.05$) or fetal lung area/body weight ratio ($r = 0.769$, $P < 0.05$). Furthermore, fetal TBA is negatively correlated with am-

Table 1 Variable characteristics between intrahepatic cholestasis of pregnancy and the control group

	Control (n = 32)	Intrahepatic cholestasis of pregnancy (n = 40)
Total bile acid (mmol/L)		
Maternal serum	4.55 ± 1.72	34.11 ± 6.75[a]
Umbilical artery serum	3.52 ± 1.56	11.9 ± 2.23[a]
Amniotic fluid	1.43 ± 1.14	3.89 ± 1.99[a]
Amniotic fluid phospholipids		
PC (μg/mL)	69.70 ± 6.68	65.71 ± 7.23[a]
PI (μg/mL)	4.28 ± 0.74	3.87 ± 0.65[a]
LPC (μg/mL)	4.21 ± 0.64	4.72 ± 0.86[a]
SM (μg/mL)	3.95 ± 0.53	3.63 ± 0.66
PC/LPC (μg/mL)	6.90 ± 2.52	14.40 ± 3.14[a]
Lamellar body (× 10^9/L)	103.0 ± 26.82	74.13 ± 4.37[a]
Perinatal outcomes		
Fetal distress	4 (12.4)	13 (32.5)
Neonatal asphyxia	1 (3.13)	2 (5)
NRDS	2 (6.25)	6 (15)
Perinatal death	0	1 (2.5)

Data are expressed as absolute mean ± SD or numbers (percentage). PC: Phosphatidylcholine; PI: Phosphatidylinositol; LPC: Lysolecithin; SM: Sphingomyelin; NRDS: Neonatal respiratory distress syndrome. [a]P < 0.05 *vs* control group.

niotic fluid PC, SM and PI (r_{pc} = 0.536, r_{sm} = 0.438, r_{pi} = 0.387, P < 0.05). In addition, amniotic fluid lamellar body are positively correlated with fetal lung area/body weight ratio (r = 0.929, P < 0.05).

Perinatal outcomes

The fetal distress, neonatal asphyxia, neonatal respiratory distress syndrome and perinatal death rates in the ICP and control group are shown in Table 1.

DISCUSSION

Intrahepatic cholestasis of pregnancy is a peculiar disease in middle-late pregnancy, with the pathological characteristics of hepatic capillary bile duct silts, causing increasing clinical bile components in peripheral blood and liver function damage[11,12]. High TBA has toxic cellular effects to many organs and mainly affects the fetus[13], leading to perinatal complications such as fetal distress, meconium inhaled syndrome and neonatal asphyxia[3,4]. The mechanism of ICP causing poor perinatal outcome has not yet been elucidated. Current studies suggest that maternal TBA level is the most sensitive index to diagnose ICP and predict the perinatal outcomes[4,14,15].

Fetal serum bile acid is synthesized from fetal liver, which increases with the gestational weeks. During late normal pregnancy, fetal blood bile acid concentration is higher than the maternal level[16,17]. Bile acid as fat soluble small molecules, diffuses through the placenta, then to maternal blood circulation and the normal liver system removes them from the body. During ICP, under the action of various factors, maternal bile acid levels increase, which damages the placenta, causing insufficiency of placental transferring, leading to fetal bile acid deposition in the body, and finally the fetal blood and the amniotic

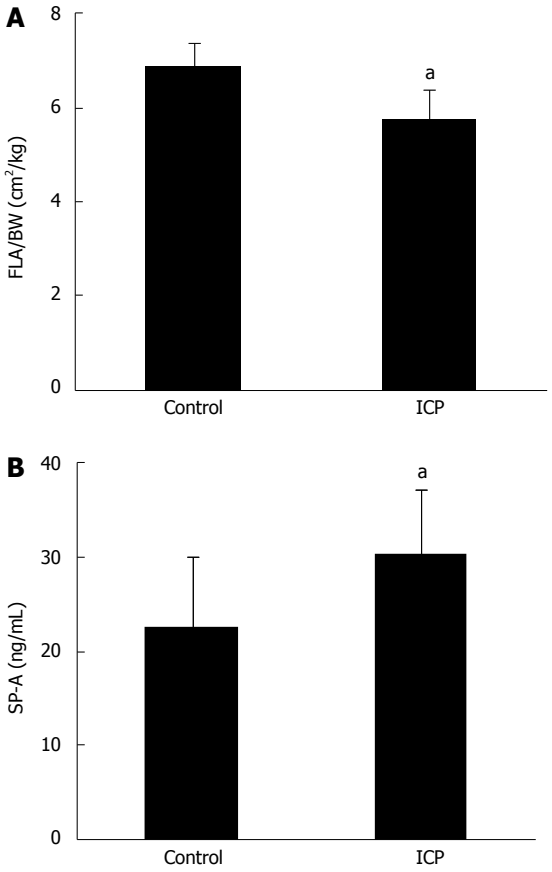

Figure 2 Fetal lung area/body weight ratio and fetal surfactant protein A. A: Ratio between fetal lung area (FLA) and fetal body weight (BW). [a]P < 0.05 *vs* control; B: Fetal surfactant protein A (SP-A) concentration. Intrahepatic cholestasis of pregnancy (ICP) has a higher SP-A than that in the control group, [a]P < 0.05 *vs* control.

fluid bile acid levels become higher[18]. With the rise of maternal bile acid concentration, fetal blood bile acid increases and causes delay of fetal lung development[15].

Animal experiments and clinical studies have demonstrated that ICP leads to fetal and neonatal acute lung injury and causes bile acid pneumonia[19]. The cause of poor perinatal outcomes due to ICP is not very clear. Injection of cholic acids into the rabbit trachea induces dyspnea and respiratory failure[20]. The morphological changes are consistent with neonatal pulmonary hyaline membrane disease, decreasing of light transmittance, swelling, atelectasis and pulmonary hyaline membrane disease[6,14,21]. After giving pulmonary surfactant treatment, the symptoms and pathological changes reduce or disappear[22,23]. In a bronchoalveolar fluid study (BALF), it was found that the more bile acid content in BALF, the less production of the pulmonary surfactant A and D. It was demonstrated that the lung injury induced by bile acid is associated with pulmonary surfactant insufficiency[6]. Zecca *et al*[19] found that bile acids exist in all newborns in the BALF study on ICP.

Cholic acid can cause a dysfunction of surface active substances synthesis in the lung and induces an inflammatory reaction and chemical pneumonia. With bronchoalveolar lavage, Hills *et al*[24] found that the pulmonary

phospholipid content is lower in sudden infant death syndrome than in normal cases, and bile acid content increased. It prompted the idea that bile acid may achieve the role of pulmonary surfactant to the lungs through acting on phospholipase[24]. In this study, umbilical cord blood SP-A in the ICP group is higher than that of the normal group and the umbilical cord blood total bile acid concentration is also higher. SP-A is the lung protein component of pulmonary surfactant, which is a hydrophilic multifunctional glycoprotein. Under normal circumstances, the alveolar capillary barrier is intact, which can prevent SP-A serum from entering the blood circulation. When the lungs are injured, the alveolar capillary permeability increases, then SP-A leaks from the alveolar cavity to the alveolar capillaries, which induces an increasing blood SP-A concentration[25]. We speculated that high amniotic bile acid concentrations can destroy the continuity of the pulmonary vascular endothelium, causing the fetus alveolar capillary damage and increasing alveolar capillary permeability. SP-A can damage the alveolar capillary membrane barrier, then get into the blood circulation, leading a SP-A rise in serum[26,27].

Pulmonary surfactant is synthesized in alveolar type Ⅱ epithelial cells. When lung injury happens, the AT Ⅱ cell synthesis ability decreases, which leads to the alveolar capillary permeability increasing and pulmonary surfactant decreasing[28,29]. Cholic acid can promote the secretion of phospholipase A2 and restrain and reduce the secretion of pulmonary surface active substance[20]. So, even although the amniotic fluid lecithin/sphingomyelin ratio (L/S) indicates mature lung, unusually high levels of cholic acid can still reverse the activity of phospholipase A2, causing a relative lack of lung surface. When using pulmonary surfactant to treat newborns diagnosed with bile acid pneumonia, Zecca found that clinical symptoms and signs obviously improved[19]. In our study, PC and PI levels in ICP amniotic fluid are lower than that in normal pregnancy. We speculate that there may be high concentrations of bile acids in the amniotic fluid and fetal circulation which work together in the respiratory tract and lungs of the fetus. A high level of bile acid has a cytotoxic effect in the lungs, destroying the AT-Ⅱ cells and decreasing PS, PC and PI synthesis. Our results showed that the ICP's LPC in amniotic fluid levels are higher than that of the normal group, which might be caused by the degradation in the amniotic fluid. As to what causes the degradation of the PC, further studies are needed. LPC has a direct toxic effect which may damage AT Ⅱ cells, then affect the synthesis of PS. It can increase the damaging effect to the alveolar capillary system caused by TBA in fetal blood and amniotic fluid. This change may result in increasing cell membrane permeability and alveolar infiltrates.

The lamellar body is the special structure of lung surface active material stored in alveolar type Ⅱ cellular cytoplasm which has a typical structure like an onion[30]. LB can be found in normal middle pregnancy and increases obviously at 34 to 36 gestational weeks. It is discharged by alveolar type Ⅱ cells and attached to the alveolar surface, then contacts with amniotic fluid. Amniotic fluid LB increases gradually with the progress of pregnancy and fetal maturity. So, the LB measurement can predict fetal lung maturity[31]. Reports shows high bile acid can induce fetal rat alveolar type Ⅱ epithelial cells to degenerate through necrosis, the cell surface microvilli structure disappears, the nucleus and mitochondria swells, the balloon sample changes and ridge cavitations disappear[25]. It can also result in the decrease of lamellar corpuscle numbers and the disappearing of the board layer structure.

In conclusion, our study demonstrated that maternal bile acid concentration is associated with fetal and amniotic fluid bile acid level. A maternal high blood bile acid level results in an increased fetal and amniotic bile acid level, which leads to a reduced synthesis of fetal pulmonary surfactant and delayed fetal lung development. High bile acid concentration has an increased perinatal morbidity and mortality. This study may help us to predict perinatal outcomes, to develop strategies improving the prenatal outcome, and to further study the mechanism of how fetal pulmonary AT-Ⅱ cells are affected. It calls attention to delayed maturation of fetal lungs in ICP patients and to take steps to carefully check and improve fetal pulmonary maturity.

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COMMENTS

Background

Intrahepatic cholestasis of pregnancy (ICP) can be complicated by fetal distress, neonatal asphyxia and neonatal respiratory distress syndrome. The etiology of ICP is poorly understood but the perinatal complications are closely correlated with maternal total bile acid (TBA) level. It is necessary to explore fetal lung alteration and development during ICP and its possible mechanisms affecting fetal pulmonary maturation.

Research frontiers

Lung development in ICP is a research hotspot since neonatal respiratory distress syndrome is a serious complication which is usually related to the immaturity of fetal lungs. Finding out the relationship of TBA concentration in maternal, fetal and amniotic fluid and its association with fetal surfactant, surfactant protein A, amniotic lamellar body and fetal lung development will help us to predict and improve perinatal outcomes. It calls clinical attention to delayed maturation of fetal lungs in ICP and to improve fetal pulmonary maturity.

Innovations and breakthroughs

Previous studies have found that high TBA can cause neonatal lung injury but its mechanism is not clear. In order to explore fetal lung alteration during ICP and its possible mechanisms, the authors investigated maternal and fetal TBA, fetal surfactant production, fetal surfactant protein level and fetal lung development. The study demonstrated that a maternal high blood bile acid level results in an increased fetal and amniotic bile acid level, which leads to a reduced synthesis of fetal pulmonary surfactant and delayed fetal lung development.

Applications

This study may help to predict perinatal outcomes, to develop strategies im-

proving the perinatal outcome, and to further study the mechanism of how fetal pulmonary AT-Ⅱ cells are affected. It calls attention to delayed maturation of fetal lungs in ICP patients and to take steps to carefully check and improve fetal pulmonary maturity.

Terminology

ICP: It is also called obstetric cholestasis, jaundice of pregnancy, or pruritus of pregnancy. It is a medical condition during pregnancy in which hepatic capillary bile duct silt. It typically presents with itching and can lead to complications for both mother and fetus. Pulmonary surfactant: It is a surface-active lipoprotein complex formed by type Ⅱ alveolar cells which reduces surface tension. Mature surfactant in the fetus is very important for neonates to start normal breathing after birth.

Peer review

The manuscript has new information on lung volume and levels of surfactant phospholipid and surfactant protein A in ICP. This information advances to understanding fetal lung injury in ICP.

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OBSERVATIONAL STUDY

Simulation training in contemporary obstetrics education

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Abstract

AIM: To investigate the use of the Gaumard's Noelle S550.100 Maternal and Neonatal Simulators for teaching forceps delivery.

METHODS: Twenty two (n = 22) resident physicians were enrolled in a simulation course on operative forceps deliveries. The physicians enrolled in the course were all part of an accredited Obstetrics and Gynecology residency program and ranged in their training from post graduate year (PGY) 1-4. Each participant received simulation based teaching on the indications, contraindications, proper application, delivery and removal of forceps by a single teacher. The Gaumard's simulator and Simpson forceps were used for this course. Statistical analysis using SPSS statistical software was performed after the completion of the simulation training program. A paired student t-test was performed to compare the cohort's mean pretest and post simulation training scores. Follow up skills assessment scores at one month, 3 mo and 6 mo were compared to the baseline pretest score using a paired student t-test.

RESULTS: There was statistically significant improvement in the post simulation training performance evaluations compared to the pretest, 13.7 (SD = 3.14) *vs* 7.9 (SD = 4.92), $P < 0.05$. Scores at 1 mo, 3 mo, and 6 mo were compared to the pretest score and showed retention of skills: 4.6 (SD = 5.5, 95%CI: 2.21-7.07), 4.4 (SD = 5.2, 95%CI: 2.13-6.70), and 5.6 (SD = 4.8, 95%CI: 3.53-7.75) points, respectively. There were statistically significant differences between residents by post graduate training year on pretest scores, however these differences were not present after simulation training. Pretest scores for PGY 1, 2, 3, 4 were 3.5 (SD = 2.27, 95%CI: 2.13-5.00), 7.25 (SD = 6.70, 95%CI: 1.50-13.00), 10.75 (SD = 1.5, 95%CI: 9.50-12.00), 12.17 (SD = 2.57, 95%CI: 10.33-14.00). After simulation training PGY 1 residents did as well as well as the upper level residents. Posttest mean test scores for PGY 1, 2, 3, 4 were 13.75 (SD = 1.49, 95%CI: 12.75-14.63), 10.25 (SD = 0.24, 95%CI: 4.25-14.00), 15.00 (SD = 1.16, 95%CI: 14.00-16.00), 15.17 (SD = 0.75, 95%CI: 14.67-15.67).

CONCLUSION: Our simulation based training program not only produced short term gains, but participants were able to retain the skills learned and demonstrate their knowledge months later.

Key words: Simulation; Education; Forceps; Delivery; Labor

Core tip: In this article the authors investigated the use of the Gaumard's Noelle S550.100 Maternal and Neonatal Simulators for teaching forceps delivery. They describe the process of developing a simulation program, application, and evaluation at Banner Good Samaritan Medical Center. The intervention was successful in teaching resident physicians the steps of application, delivery and removal in forceps operative delivery. The authors hope is that their method may be applied in

development of a variety of simulation based programs to improved education in obstetrics.

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INTRODUCTION

As rapid technologic growth expands the skills set of graduating residents in obstetrics and gynecology (ob/gyn) in the areas of minimally invasive surgery, there is a profound loss of basic skills in operative delivery. The current average number forceps deliveries for graduating ob/gyn residents are below what is necessary to be proficient in this invaluable skill. The average ob/gyn resident has performed 6 forceps assisted operative vaginal deliveries, compared to 120 laparoscopic surgeries[1]. As the use of forceps decline, cesarean sections and the associated complications are more prevalent than ever. Cesarean sections account for over one third of deliveries performed each year and outnumber operative vaginal deliveries by three to one. In 2007, cesarean sections were at an all-time high at 32%[2,3]. Cesarean delivery involves major abdominal surgery, and is associated with higher rates of maternal and neonatal complications compared with vaginal birth[4,5]. The rates of cesarean sections vary widely depending on geographic region, and some authors argue this is due to a regional lack of skilled providers in operative vaginal delivery[6].

The residency program at Banner Good Samaritan Medical Center was keenly aware of this trend as their own residents experienced decreasing numbers of real life forceps deliveries. Simulation training was presented as a viable solution to providing graduate medical training in forceps delivery without effecting patient safety.

Other surgical specialties have harnessed the power of simulation to provide residents with a foundation of skills prior to performing procedures on live patients[7]. This is particularly important for emergency situations and high stress surgical scenarios[7,8]. General surgeons have developed simulation courses based on proven techniques for teaching fundamental laparoscopic skills. The strength of these courses is in providing residents experience performing skills in the safety of the simulation lab where failures of efficiency can be overcome without effecting patient care. Furthermore, simulation training provides equality in resident training as it is not dependent on the chance of exposure to surgical emergencies.

The existence of the Simulation Education and Training Center at Banner Good Samaritan Medical Center was a critical factor in the creation of this program. Opened in 2006, this 6000 square foot, two million dollar facility has trained 5000 health care professional. The aim of this program was to evaluate the use of the Gaumard's Noelle S550.100 Maternal and Neonatal Simulators in the development of a forceps simulation program for training residents in obstetrics and gynecology.

MATERIALS AND METHODS

Study design

Resident physicians in obstetrics and gynecology from a single center participated in simulation training as part of their education in operative delivery techniques. Their performance before and after training was recorded to evaluate and improve forceps training for resident physicians. Initially, 25 residents chose to participate, with only 3 unable to complete the course. The residents were divided into five groups. Participants were first able to perform a simulated forceps delivery and given a pretest score on their performance based on a specific checklist (Figure 1). Each group then received simulation based teaching on the indications, contraindications, proper application, delivery and removal of forceps by a single teacher. A posttest was then administered using the same assessment checklist to evaluate their forceps delivery skills. Video recordings of the 22 residents were obtained at their 1 mo, 3 mo, and 6 mo follow up assessments.

Sixteen steps were identified as critical aspects for forceps application and delivery based on Dennen's Forceps Deliveries, 3rd Ed[9]. The steps were reviewed by six independent board certified physicians in obstetrics and gynecology from the Department of Obstetrics and Gynecology at Banner Good Samaritan Medical Center. The steps were rated in terms of importance and weighted averages calculated to gauge if any steps should be excluded from the assessment or tutorial.

The same checklist was used for each of the evaluations. A blinded scorer was used to grade each anonymous video recording. The physician scoring each video was unaware of the resident's identity, as well as their year of post graduate training to limit bias. Residents were gowned and gloved in the video to hide their identity. A second evaluator reviewed all of the follow up videos to establish reliability of the score assessment tool. Both evaluators were board certified in obstetrics and gynecology for over 10 years and routinely performed forceps deliveries at a large tertiary care center. Both evaluators had performed over 100 forceps deliveries and had experience evaluating resident performance in operative deliveries for over 10 years.

Simulation training

The decision was made to teach the following steps for placement of the first blade: identifying fetal position, orientation of the forceps, choice of first blade, application of the first blade in the vertical position, use of the vaginal hand to guide placement of the first blade, advancement of the blade into the horizontal position along the opposite thigh.

Steps for placing the second blade included: starting

Name_____
Date _____
Date _____
Date _____

	Pre	Post	1 mo	3 mo	6 mo
Chose appropriate type of forceps					
Correctly identified position of vtx					
Chose correct first blade for placement					
Started vertically					
Proper vaginal hand placement					
Proper upper hand placement					
Brought forcep out along thigh					
Started vertically with second blade					
Proper vaginal hand placement-second					
Proper upper hand placement					
Brought forcep out along thigh-second					
Verified correct placement-post fontanelle					
Verified correct placement-sagital suture					
Verified correct placement-blades					
Correct hand positioning for traction					
Appropriate traction direction					
Appropriate removal of forceps					

Figure 1 Checklist for pretest and posttest.

in the vertical position, placement of vaginal hand to guide blade, and advancing blade from vertical to horizontal along the opposite thigh.

Additional steps included, checking the placement of the forceps on the neonatal head by feeling for the posterior fontanel and sagittal suture. Finally, steps for delivery included correct hand position for traction and appropriate removal.

Examples of the steps in forceps application and desired hand positions are illustrated in Figure 2.

Statistical analysis

Statistical analysis using SPSS statistical software was performed after the completion of the simulation training program. A paired student *t*-test was performed to compare the cohort's mean pretest and post simulation scores. Follow up skills assessment scores at 1 mo, 3 mo and 6 mo were compared to the baseline pretest score using a paired student *t*-test.

RESULTS

Inter-rater reliability was investigated by calculating the Pearson correlation coefficient. This provided evidence on the reliability of the testing instrument itself. Pearson correlation between evaluator one and two was 0.7 ($P < 0.001$).

The pretests were compared to posttest scores for the 22 participants who complete the simulation curriculum. There was statistically significant improvement in the post simulation training performance evaluations compared to the pretest, 13.7 (SD = 3.14) *vs* 7.9 (SD = 4.92), $P < 0.05$. Scores at one month, three months, and six months were compared to the pretest score and showed retention of skills (Figure 3). The difference between pretest and follow up scores at one month, three month and six month were: 4.6 (SD = 5.5, 95%CI: 2.21-7.07), 4.4 (SD = 5.2, 95%CI: 2.13-6.70), and 5.6 (SD = 4.8, 95%CI: 3.53-7.75) points, respectively (Table 1).

There were statistically significant differences between residents by post graduate training year on pretest scores, however these differences were not present after simulation training. Pretest scores for PGY 1, 2, 3, 4 were 3.5 (SD = 2.27, 95%CI: 2.13-5.00), 7.25 (SD = 6.70, 95%CI: 1.50-13.00), 10.75 (SD = 1.5, 95%CI: 9.50-12.00), 12.17 (SD = 2.57, 95%CI: 10.33-14.00). PGY 1 residents as a group scored lower compared with PGY 2, 3, and 4. After simulation training PGY 1 residents did as well as well as the upper level residents. Posttest mean test scores for PGY 1, 2, 3, 4 were 13.75 (SD = 1.49, 95%CI: 12.75-14.63), 10.25 (SD = 0.24, 95%CI: 4.25-14.00), 15.00 (SD = 1.16, 95%CI: 14.00-16.00), 15.17 (SD = 0.75, 95%CI: 14.67-15.67).

Increased year of resident training had a statistically significant association with higher pretest skills assessment scores, (Pearson correlation = 0.637, $P = 0.001$). However, after simulation training there was no difference in skills assessment scores among resident based on year of training with forceps delivery.

DISCUSSION

Simulation training offers a solution to the problem of declining resident exposure to forceps operative deliveries nationally. Our simulation based training program not only produced short term gains, but residents were able to retain the skills learned and demonstrate their knowledge months later. Analysis of pretest scores showed an association between forceps skills and year of training, with improved scores with increased year of post graduate year. However, after simulation training this association no longer exists. Considering, clinical experience

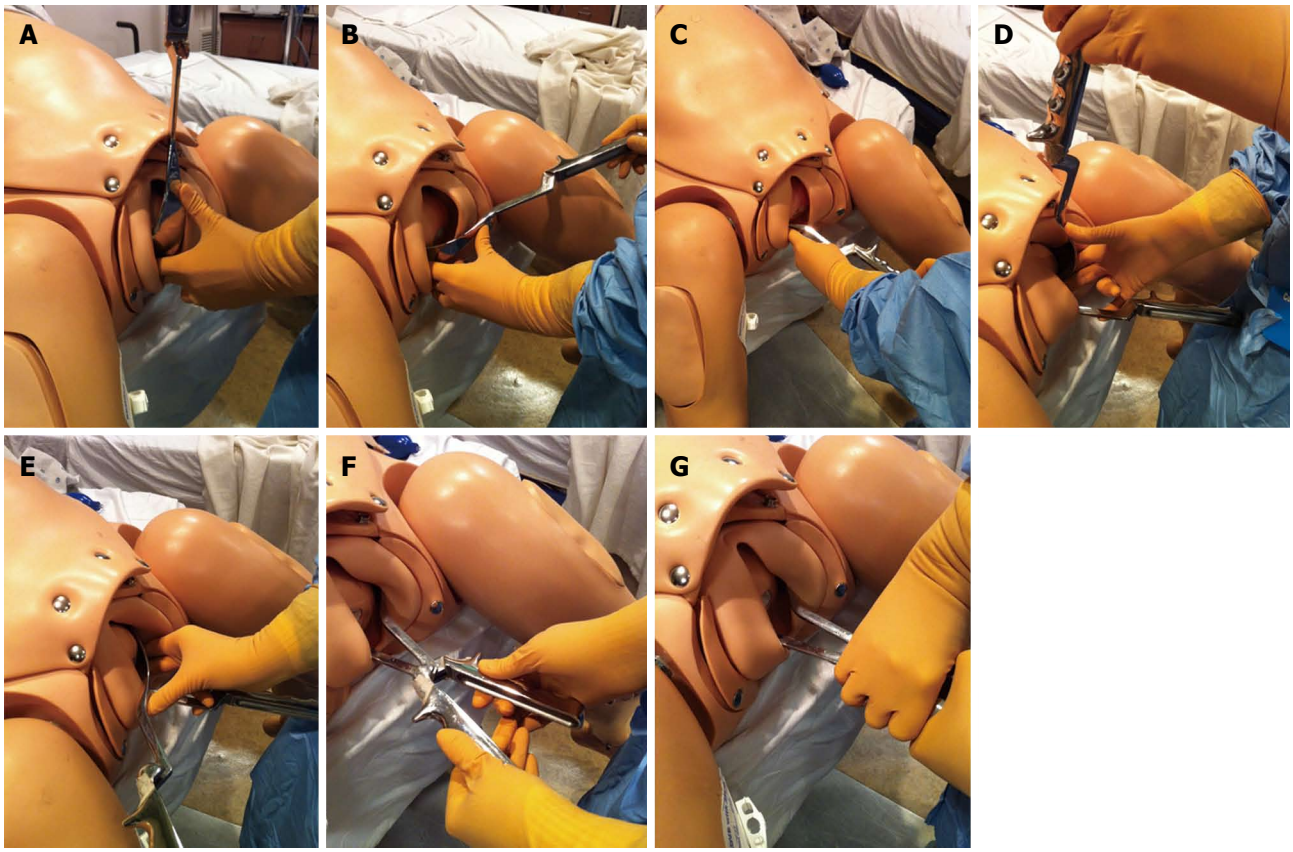

Figure 2 Examples of the steps in forceps application and desired. A: The vertical application of the first blade of closed Simpson forceps; B: Position of the vaginal hand used to guide the first blade; C: Rotation of the handle of the blade to the horizontal position along the opposite thigh; D: Application of the second blade starting in the vertical position; E: Position of the vaginal hand in order to direct the placement of the second blade; F: Lock forceps in the correct orientation; G: Placement of hands and direction of traction.

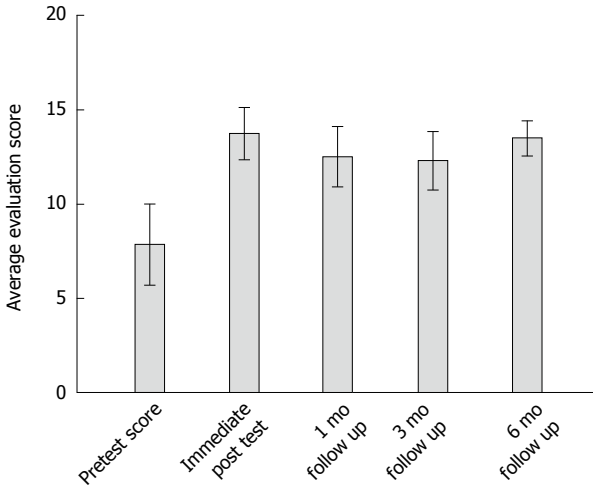

Figure 3 Average residency scores on forceps application skills before and after simulation training. Error bars: 95%CI.

with forceps generally increases by year of training, our study suggests that these differences in real life experience may be overcome by simulation training. Simulation training has the potential for providing the necessary experience resident physicians need in adjunct with real life experience to produce qualified obstetricians with the necessary skills to perform operative deliveries independently.

The Gaumard's Noelle S550.100 Maternal and Neonatal Simulators was limited in its ability to replicate a forceps delivery. The anatomy of a real fetal skull, specifically the contours if the maxillary bone, provide the points of articulation for the forceps instrument. The Noelle S550.100 Neonatal Simulator did not have the same cranial bone structure and thus the forceps frequently slipped or became misplaced during the delivery. Therefore, the trainees in this study were only expected to apply the forceps correctly and demonstrate the correct plane of traction. The residents were not expected to complete the delivery due to the limitations of the simulator. The maternal simulator in contrast had very realistic anatomy; fetal station could correctly be identified by palpation of the ischial spines just as in a live patient.

Another limitation of this program is the lack of data collected on the effect of simulation training on resident performance in real life settings. An opportunity for further program evaluation includes follow up surveys to assess if simulation training increased resident confidence and likeliness to perform forceps deliveries when in practice. Twenty percent of the residents who took part in this program are now in practice and their feedback on whether or not they routinely perform forceps deliveries would provide important follow up data to support con-

Table 1 Comparison of the difference between pretest, posttest and follow up assessments

	Paired differences					*t*	*df*	Sig. (2-tailed)
	Mean	SD	SEM	95%CI of the difference				
				Lower	Upper			
Pretest-immediate posttest	-5.864	4.357	0.929	-7.795	-3.932	-6.313	21	0.000
Pretest-one month follow up	-4.636	5.482	1.169	-7.067	-2.206	-3.967	21	0.001
Pretest-post 3 mo	-4.409	5.152	1.098	-6.693	-2.125	-4.014	21	0.001
Pretest-post 6 mo	-5.636	4.756	1.014	-7.745	-3.527	-5.558	21	0.000

tinued simulation education.

Additionally, research opportunities to further investigate the effect of simulation training on resident performance in real life settings would include a prospective study with assessment of real life operative delivery skills assessments before and after simulation training.

COMMENTS

Background

The current average number forceps deliveries for graduating ob/gyn residents are below what is necessary to be proficient in this invaluable skill. Cesarean sections account for over one third of deliveries performed each year. Cesarean delivery involves major abdominal surgery, and is associated with higher rates of maternal and neonatal complications compared with vaginal birth. The rates of cesarean sections vary widely depending on geographic region, and some authors argue this is due to a regional lack of skilled providers in operative vaginal delivery. Simulation training is a viable solution to providing graduate medical training in forceps delivery without effecting patient safety.

Research frontiers

There are increasing demands on the health care system to adhere to the highest standards of safety and cost efficiency. Additionally, new changes to the Accreditation Council for Graduate Medical Education restrictions on resident work hours creates further challenges to garnering the necessary skills in operative delivery. The power of simulation has been harnessed by varies surgical specialties to provide residents with a foundation of skills prior to performing procedures on live patients.

Innovations and breakthroughs

Simulation training is particularly important for emergency situations and high stress surgical scenarios. General surgeons have developed simulation courses based on proven techniques for teaching fundamental laparoscopic skills. The strength of these courses is in providing residents experience performing skills in the safety of the simulation lab where failures of efficiency can be overcome without effecting patient care. Furthermore, simulation training provides equality in resident training as it is not dependent on the chance of exposure to surgical emergencies.

Applications

This study suggests that simulation training may provide the needed training in forceps deliveries that are required for residents in obstetrics and gynecology to be proficient in these skills.

Terminology

Forceps are tools used to assist in the second stage of labor for a variety of indications, such as: arrest of descent, prolonged second stage, maternal exhaustion, pr concerning fetal heart tracings. The second stage of labor is defined as the periods of labor after complete cervical dilation during which time the fetus passes through the pelvis, but prior to expulsion.

Peer review

This is a well-designed observational study in which resident physicians participated in a simulation course on operative forceps deliveries, before and after assessment were performed. The findings demonstrate the potential utility of simulation training to provide experience and technical skills that are not readily available in real life settings. These methods may be beneficial for teaching a variety of obstetrical skills that may in the future improve the health of mothers and children.

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REVIEW

Acceptability of self-collected human papillomavirus specimens in cervical cancer screening: A review

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Abstract

Cervical cancer morbidity and mortality is an important public health problem around the world. Some of the barriers to cervical cancer screening include the embarrassment, discomfort, lack of privacy and time and cost associated with clinician-collected, clinic-based screening with cytology or human papillomavirus tests. Self-collection of a human papillomavirus (HPV) test has been found to be generally more acceptable, less embarrassing, more comfortable, more private and easy to do and preferred to pelvic examination for cervical cytology by many women worldwide. The most commonly reported limitation to self-collection is a woman's lack of confidence in her ability to perform it correctly. Self-collected human papillomavirus tests have been shown to be as or more sensitive than cytology or clinician-collected HPV tests. With confidence-building education about self-collection, it is likely a viable method to extend the reach of screening in high and low-resource areas around the world.

Key words: Cervical cancer; Self-collected; Human papillomavirus; Acceptability

Core tip: Self-collected human papillomavirus specimens using swabs, brushes or lavage devices have been found to be as accurate as clinician-collected specimens. With appropriate education to increase self-efficacy and confid ence in the quality of the collection and the results, self-collected HPV tests may improve cervical cancer detection among unscreened and underscreened women in high and low resource areas.

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INTRODUCTION

Though it is largely preventable, cervical cancer is an important cause of morbidity and mortality throughout the world. The age-adjusted incidence of cervical cancer is 14 cases per 100000 women worldwide. It is as high as 15.7 per 100000 in less developed areas of the world and 9.9 per 100000 in more developed areas. The age-standardized mortality rate for cervical cancer is 8.3 per 100000 for women in less developed regions, with a much lower rate of 3.3 per 100000 women in more developed areas[1]. The much lower rates in more developed areas underscore the importance of effective screening programs. In lesser developed regions with fewer healthcare resources, the lack of a reliable screening test and inadequate screening coverage result in more new cervical cancer cases and ultimately in more cervical cancer deaths[2].

Human papillomavirus (HPV) infection is now known to be a necessary cause of cervical cancer and as a result, testing women for high-risk subtypes of HPV is proving to be an effective method of screening. As the

relative value of HPV testing in cervical cancer screening became more apparent, a variety of self-collection options were developed. Self-sampling options tend to be more acceptable to women because they overcome the previously identified barriers to cervical cancer screening. As a result, self-collection of HPV specimens will extend the reach of cervical cancer screening programs even in low-resource areas.

BARRIERS TO CERVICAL CANCER SCREENING

While every woman is an individual in terms of how personal characteristics and life circumstances affect her health care behaviors, women who are underscreened or unscreened for cervical cancer often experience one or more of a number of common barriers to participation. In a group of primarily urban minority women, the reluctant tended to possess a fatalistic attitude, believing that they are better off not knowing about their cancer or that cancer occurs in those who have bad luck. Additionally they reported a lack of family support and lack of understanding of the risk of cervical cancer[3]. Among 300 women in Botswana who answered questions about their perceptions of barriers to Papanicolau (Pap) testing, 32% found it embarrassing and 52% believed that getting a screen suggested a woman is sexually active. Many (63.3%) of the women who had never been screened and 51.7% of those who had been screened thought lack of information was a barrier for screening for cervical cancer. However, none of the barriers identified by the women was significantly associated with their screening behaviors[4]. In a study of 493 women in Brazil, 36.7% of women had adequate knowledge of cervical cancer, 67.2% had an appropriate attitude (recognized the importance of screening) and 69.6% reported having had a Pap in the past 3 years. The barriers to undergoing Pap testing with the highest scores were a lack of symptoms of cervical cancer and the embarrassment associated with the exam[5]. In a study 345 Appalachian women aged 40-64, questions regarding barriers were grouped according to the PRECEDE-PROCEED model as predisposing factor barriers, enabling factor barriers and reinforcing factor barriers. Barriers that were found among more than half of the women included: (1) worry (78%); (2) fear of cancer (67%); (3) embarrassment (56%); (4) the belief that cervical cancer (52%) and polyps (50%) would have symptoms; (5) unavailability of public transportation (71%); (6) preference for home screen (66%); (7) insurance coverage (65%); and (8) lack of choice of a male or female provider (62%)[6]. Among 21-65 year-old Malaysian women, 70% reported that cervical cancer screening is too embarrassing and almost half found the attitude of clinic staff, the lack of female healthcare providers, the worry associated with the outcome and the fear that she would no longer be a virgin after the test were important barriers[7]. In a review of the literature on cervical cancer screening in Asian women, barriers to screening could be grouped as cognitive, emotional, economic, logistic or social. Barriers to screening identified in each of these categories included a lack of understanding of the reason for or benefits of testing, fear, time away from work, lack of insurance, transportation and childcare issues, wait times in the clinic, and lack of support from family and healthcare clinic staff[8]. Lastly, a study of women with cervical abnormalities who were enrolled in a research program to help them navigate the healthcare system in multiple cities in the United States found that nearly half of the women experienced at least one barrier to care and some experienced as many as seven. Barriers that significantly delayed time to diagnosis included the presence of comorbidities, health insurance issues, minimization of the importance of treatment, out of town travel, and employment demands or healthcare system problems. Interestingly, the time from detection of the cervical abnormality to definitive diagnosis was not affected by fear, attitudes toward providers, perceptions about tests and treatments, quality of communication, ability to read and write, or language[9].

SELF-COLLECTED HUMAN PAPILLOMAVIRUS TEST

Self-collection of cervicovaginal HPV specimens is purported to be a viable alternative to Pap testing or clinician-collected HPV specimens that will overcome some of these barriers and extend the reach of screening in low-resource or underscreened populations. A variety of self-collection methods have been developed and tested around the world to determine their diagnostic accuracy (Figure 1). The available devices today include swabs, brushes, and lavage devices. In addition to the polyester (Dacron) tipped swab, flocked swabs are now available. The flocked swab is a variation on the polyester swab that comprises a solid plastic applicator with short nylon fibers attached perpendicularly to the tip. It is designed to allow the specimen to remain near the surface of the swab for ease of retrieval relative to the traditional cotton or Dacron swab. An additional variation on the swab includes the Fournier device. Its swab is wrapped in a sheath much like a tampon applicator. Upon insertion, the woman pushes the end of it to deploy the swab and after collection the swab retreats back into the sheath to prevent absorption of vaginal secretions when the device is removed. There are also a variety of brushes available including the cervical sampler brush and broom-shaped devices commonly used for clinician-collection of cervical cytology specimens. The Evalyn brush also offers an applicator to ease deployment of the brush. Following collection, the pink cap is snapped back onto the transparent applicator and the specimen is transported dry to the lab. Cervical lavage devices have also been developed. For the lavage, the woman inserts the device as she would a tampon and then pushes and holds a button for three seconds. During that time, a small amount of sterile fluid is released from the end near the proximal vagina and

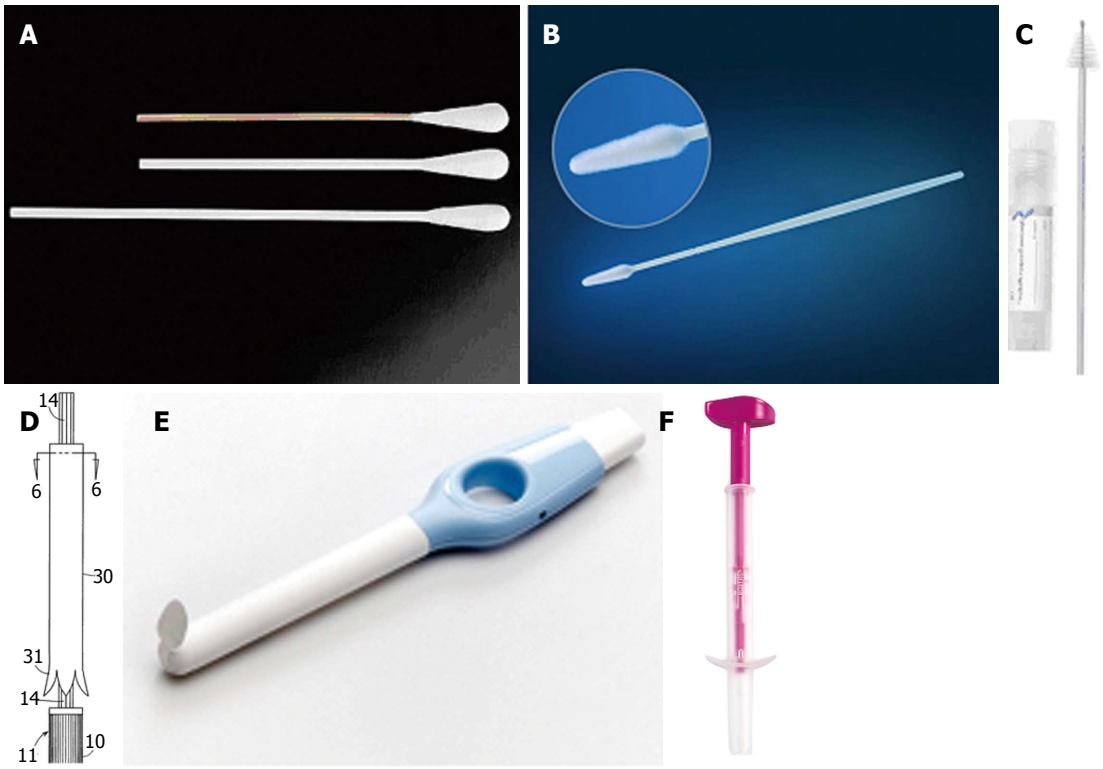

Figure 1 Self-collection device. A: Dacron swab (http://www.danlab.fi/WebRoot/GPL/Shops/16092008-100026/4B75/27BB/C58D/08D9/5A21/0A28/1011/F968/300234.jpg); B: Flocked swab (http://img.bosscdn.com/photo/product/82cda9df62bc1a6f25394c652966adb6/cervical-specimen-collection-flocked-swabs.jpg); C: Cervical sampler brush (http://www.mysynergylab.com/uploads/images//DigeneCervicalBrush.JPG); D: Fournier device (http://patentimages.storage.googleapis.com/US6387058B1/US06387058-20020514-D00000.png); E: Delphi screener (http://www.medicaldevice-network.com/contractor_images/10440/images/140283/large/4-delphi-screener.jpg); F: Evalyn brush (http://www.roversmedicaldevices.com/images/new_images/02_EVALYN%20INGESCHOVEN.jpg).

cervix. When she releases the button, the fluid flows back into the device along with cervical and vaginal cells.

The agreement of HPV self-collected specimens with clinician-collected specimens has been demonstrated to be strong in several studies[10-13]. The sensitivity of the self-collected studies has been consistently as high or higher than that of cervical cytology specimens for the detection of high-grade cervical intraepithelial neoplasia[10]. Self-collected HPV tests are emerging as an alternative to cervical cytology or even clinician-collected HPV tests because their diagnostic accuracy has been favorable and the self-collection kit can be distributed in person or by mail with the collection occurring almost anywhere. If HPV self-collection methods are acceptable to women and they are willing to collect, self-collection has the potential to extend the reach of screening to under- or unscreened women in high or low resource regions.

ACCEPTABILITY OF SELF-COLLECTION

The acceptability of self-collected HPV samples has been examined in a number of different ways. It is usually measured by an interview or a written questionnaire and compared with clinician-collected HPV or Pap test with acceptability parameters determined by the previously reported barriers to cervical cancer screening. Pain, discomfort, degree of embarrassment, level of privacy, ease of use, trust or confidence in the results are commonly measured parameters for acceptability. Other studies focused on women's preferences for self-collection or clinician-collection and the reasons for their preferences.

Swabs

The acceptability of self-collection of HPV samples using some type of soft swab has been examined in various locations internationally. In Ontario, women's responses to self-sampling were stratified by age and in both the younger (< 50 years old) and the older (> 50 years old) groups more than 45% of women preferred self-sampling to a clinician examination or had no preference[14]. A predominantly unscreened sample of women in India was invited to self-collect a HPV test either in the clinic or in their homes. Younger women (< 45 years old) and those invited for home collection were more likely to agree to participate. Among those who lived in remote areas where screening may only be possible once or twice in a lifetime, 71.5% said they would be willing to self-collect at home and 53.8% said they would be willing to go to a clinic to self-collect[15]. The response to self-collection in Uganda was very positive with 93.66% willing to self-collect a sample with no more than 5% of the sample concerned that the self-collection would be embarrassing or painful or too difficult to perform correctly. Most women were willing to either have the swab kit dropped off and picked up by a community health worker or to return the swab to the clinic themselves[16].

In a comparison of self-collection with a clinician collected Pap test, Mexican women reported the overall acceptability of the self-collection to be significantly greater than the Pap. They also reported less pain, less discomfort, less embarrassment and more privacy with self-collection than with the Pap. A majority (68%) preferred self-collection, citing greater comfort and less embarrassment as the primary reasons. Those who did prefer the Pap noted greater confidence in the results as the primary reason[17,18]. Similarly, in Puerto Rico[19] and Nicaragua[20], the overall acceptability of the self-collection was significantly higher. The individual acceptability parameters all scored higher for the self-collection with the exception of "comfort" in Nicaragua, seemingly because the women interpreted the question as comfort with the accuracy of the results rather than a measure of physical comfort. Nonetheless, in both studies more women preferred clinician-collection because they had more confidence in the accuracy of the results. The acceptability of self-collected swabs was also high in Ontario, London and in a predominantly Hispanic sample from New York City. In Ontario, two thirds of the sample found the swab easy and comfortable to self-collect and 87.7% were willing to perform self-collection again in the future[21]. In London the characteristics of the self-collected swab that appealed to most women were the lower levels of embarrassment, discomfort, anxiety and unpleasantness associated with it. Clinician-collection was preferred by some women because they had greater confidence in the results. There were some demographic differences in attitudes toward self-collection in that married women were more positive than single women and Asian women were more negative than women of other ethnicities[22]. One third of women in a New York City study preferred self-collection because they found it easy to use, less painful and more private than clinician collection. Almost two thirds could identify nothing unfavorable about self-collection. Once again, those who preferred the clinician collection did so because they had more confidence in the physician's ability to do it properly. There were statistically significant differences in preference for ethnicity and education with non-Hispanic and more educated women preferring self-collection most[23]. A Cincinnati-based study asked adolescent women about their preferences before and after they performed self-collection. Their impressions of self-collection improved after they tried it themselves but even then more women preferred clinician-collection because they thought the results were more trustworthy[24]. A comparison of a polyester swab (dry transport) to a flocked swab (transported in liquid medium) in Switzerland found no difference between the two in overall acceptability though a few more women thought the wet transport system was slightly more complex[25]. In the northeastern United States, the acceptability of a self-collected swab was compared with that of a tampon with 90% of the respondents reporting they would be willing to self-collect in the future with either device. In a series of open-ended questions, respondents reported concern that the swab may break and that they would still want to have their annual physicals with a provider even if they self-collected their cervical cancer screen. There was a potential for bias in this study in that only 67 of 103 participants completed the questionnaire[26]. A Canadian study (n = 200) compared the acceptability of screening for HPV with vulvar and vaginal swabs as well as a urine specimen. In terms of overall acceptability, 88.2% of participants found a vaginal swab acceptable compared with 79% for the physician exam. In general they ranked the acceptability in order from furthest away to closest to the cervix. Of note the rank order of the sensitivities of the tests was the inverse[27]. In the Cameroon, all subjects agreed to self collect and self-collection scored more favorably than clinician collection for all parameters (embarrassment, pain, anxiety and ease of use) except confidence in the quality of collection, which scored much higher for the clinician collection. Women with a greater understanding of HPV and those who had been screened for cervical cancer in the past were significantly more likely to prefer self-collection[28]. Finally a qualitative study of African American women living in the Mississippi delta comprised focus groups with a total of 87 women exploring their HPV and cervical cancer knowledge as well as their attitudes toward self-collection. Of the 87 participants, 9 returned for a second phase to perform self-collection. Participants were willing to self-collect but had some concerns about accuracy, cost and the possibility of the specimen getting lost in the mail. They liked the privacy associated with home collection and avoiding the wait time associated with clinic appointments. Positive feedback from the nine who self collected included having female study personnel explain the collection and getting to handle a sample device during the explanation[29].

Brushes

The overall acceptability of self-collection with a cervical sampler brush was quite high (mean score 4.33 on 5-point scale) in a study in rural China, though 74% of women preferred clinician collection to self-collection. The primary reason was because they had greater confidence in the accuracy of the results. Among those who did prefer self-collection, there was substantial variation in the primary reason for their preferences including greater convenience, less embarrassment, less cost and greater comfort. There was no association of demographics with preferences[30]. Self-collection with a cytobrush was reviewed positively by a group (n = 435) of women in Munich. Nearly all of them said they were willing to self collect at home in the future and very few of them found the collection difficult to perform. When asked about their preference of self-collection or clinician-collection, 63% preferred them equally and 23% preferred self-collection[31]. Among 134 women in the Netherlands who self-collected with the Evalyn brush, 95% reported the experience, the instructions and the convenience as good, very good or excellent. Nearly all (95%) preferred self-sampling with the primary reasons that is simpler to use and less painful than clinician collection. Reliability of the result was the main reason for 6 of the 7 who preferred

clinician collection[32]. A randomized trial in Holland demonstrated a significantly higher response rate to an invitation to self-collect with the brush kit mailed to their homes (30.8%) than to an invitation to come to the clinic for cytology (6.5%) among a group of Dutch women who had not responded to a reminder for their regular cervical cancer screen. The 29-33 years old age group had the lowest response rate in the self-sampling group[33]. Self-collection with a sampler brush was also reviewed favorably in the Netherlands with 70% of the 135 participants preferring self-collection to clinician-collection for their next exam and 91% reporting that the brush was easy to use[34].

Lavage devices

Lavage devices for self-collection have also been found to be highly acceptable to women. In Italy, 2480 women who had not previously responded to screening invitations were randomized to receive a letter of invitation for a Pap test, a letter of invitation for a clinic-based HPV test, a letter of invitation to request by phone a home HPV kit or a self-collection kit. The self-collection kit had the best response rate and the only rate that was significantly higher than the standard of care (letter of invitation for a Pap). Among the women who completed the questionnaires, 78.4% preferred the self-collection and the most commonly reported reasons were that they could do it themselves and it was more private[35]. A large Dutch study of nonresponders found that though adjusted response rate to an invitation to self collect with a lavage device was only 27.5%, it was significantly higher than the rate (16.6%) in the group receiving the standard Pap reminder letter[36]. In addition, in a pooled analysis of the Dutch brush and lavage studies, ethnicity, age and screening history predicted response rate with native Dutch, older age and previously screened women responding more often than immigrant, younger and underscreened or never-screened women[37]. In a similar study, 31.5% of Finnish nonresponders opted to participate in self-collection either by return-mailing a sample in the kit or presenting to clinic to self-collect a sample. The comparison group, sent a reminder card for clinician collection had a significantly lower response rate (25.9%)[38]. A group of 197 low-income women from New York City successfully self-lavaged a short time after their routine Pap test. A significantly higher percentage (96%) found the self-collection comfortable compared with the Pap (47%). Seventy-nine percent indicated they would prefer the self-collection with the lavage device for their next screening, largely because of the greater level of comfort and the convenience of the self-collection[39]. Among 354 Thai women who self-collected a cervicovaginal sample for cytology with the Kato device, more than 80% found it more convenient and less painful and 78.6% said they prefer it for their next cervical cancer screen. Though 94.3% of women were either satisfied or very satisfied with self-collection with this device, 57.6% thought the clinician collection was likely to produce more accurate results[40]. Though the Kato device was used to collect a cytology specimen, the process and likely the level of acceptability would be the same if the sample had been used to test for HPV. A London-based study involving focus groups (n = 28 total) explored Muslim women's attitudes toward the thought of self-collection with a swab or a lavage device. The women were somewhat reluctant to endorse self-sampling though they all preferred the swab because it was smaller and seemed less messy to use[41]. In a group of 205 Italian women, 111 self-collected with a cervical sampler kit and the others used the self-lavage device. The entire group also underwent a pelvic exam with clinician-collected sample. Both self-collection methods were well accepted in terms of increased comfort and decreased embarrassment compared with clinician collection. However, the scores for overall acceptability and embarrassment were significantly better for the lavage device than for the cervical sampler. Among those in the lavage group, 77.6% preferred self-sampling to clinician-collection and in the cervical sampler group, 60.4% preferred self-sampling[42].

Other sampling devices

The acceptability of the Fournier device was examined in home collection in the Little Haiti section of Miami, Florida. More than 90% of women found it easy to use, were comfortable using it at home and said they would recommend it to a friend. Self-collection was preferred by 86.8% of the women who also had a Pap. As is common, the women who did not prefer self-collection expressed concern about having performed the collection correctly[43].

Intent to self sample

In addition to evidence generated through randomized trials and observational studies of self-collection compared with clinician-collection, women who have been educated about cervical cancer screening and HPV, and then surveyed regarding their preference for self-sampling as an alternative to a pelvic examination have responded in favor of self-collection. A large proportion of Kenyan women have stated they would be comfortable with self-collection (82%) and would prefer to collect at home rather than going to a clinic for an examination (84%)[44]. In a similar survey of willingness to self-collect, 80% of Ugandan women responded that they would be willing. An examination of the characteristics that predict a woman's willingness to self-collect revealed that older age and a feeling of embarrassment with home-collection were negative predictors while a willingness to have a health worker deliver the swab to her home and go to a clinic for a pelvic examination if the HPV results were abnormal were positive predictors[45]. A study of personality characteristics predictive of willingness to self collect in college students found that women whose personality profiles ranked highly in extraversion, openness and conscientiousness were less likely to be deterred by the common barriers to self-collection[46].

CONCLUSION

Cervical cancer prevention is an important health priority

around the world. Historically, cytology based screening programs have been effective in reducing morbidity and mortality but there are still significant numbers of unscreened or underscreened women in more developed as well as less developed countries. Barriers to cervical cancer screening range from personal issues such as the embarrassment and discomfort associated with the speculum exam and issues with being examined by a male provider to logistical concerns such as transportation to a clinic, childcare during the visit and the extended clinic wait times keeping women away from a job or family. Human papillomavirus testing, including self-sampling for HPV has been demonstrated to be as or more sensitive than cytology in the detection of high-grade cervical neoplasia. A number of different self-collection instruments including various brushes, swabs and lavage devices have been developed and found to be highly acceptable to women. The number of acceptability studies, conducted on at least five continents, continues to grow and the preponderance of the evidence indicates that women find the various types of self-collection instruments highly acceptable. Most women have indicated a preference for self-collection and willingness to self collect in the future. The most commonly occurring limiting factor to self-collection has been the woman's confidence that she is collecting the specimen correctly. Another reason offered by women who preferred the clinician exam to self-collection despite a higher acceptability for self-collection was their concern that they would lose contact with their physicians. They preferred the clinician-collection because it provided an opportunity for somewhat regular interaction with the provider. These are important concerns that need to be considered in the development and implementation of large scale screening projects designed to draw unscreened or underscreened women by offering self-collection. Simple diagrams and written instructions for literate populations or clear oral instructions by culturally similar women who have used the device are likely to help overcome this barrier. As with any screening program, the systems-related barriers will need to be minimized for the extended reach of the screening program to have a meaningful impact on mortality and quality of life. With these caveats, self-collection of human papillomavirus specimens as a primary screen for cervical cancer seems to be highly acceptable to women and has the potential to extend the reach of screening programs, particularly in previously unscreened or underscreened women.

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REVIEW

Preeclampsia: Definitions, screening tools and diagnostic criteria in the supersonic era

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Abstract

Preeclampsia is still a major risk factor for maternal-fetal health. Therefore, early identification of pregnant women at risk for preeclampsia is a big priority in obstetrics in order to decrease the mortality and morbidity associated with this disease. On the basis of well known and new pathophysiological mechanisms of preeclampsia, different biochemical and ultrasonographic parameters have been investigated in the literature, without finding an ideal marker for early screening. In this brief review, we present the best studied ultrasonographic markers and the most recent genetic factors and promising emerging biomarkers of preeclampsia, to date. We hope that in the future the combination of these tests will allow us to predict which women are at risk of preeclampsia.

Key words: Preeclampsia; Diagnosis of preeclampsia; Screening of preeclampsia; Ultrasonographic markers of preeclampsia

Core tip: Preeclampsia is a very important disease in pregnancy but substandard care has been found in its management. The core content of this paper is the review of the literature to evaluate possible markers for early diagnosis of preeclampsia.

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INTRODUCTION

Preeclampsia is still an important cause of maternal and fetal death. The 8th report of the Confidential Enquiries into Maternal Deaths in the United Kingdom reported that in the triennium 2006-2008, 261 women died from complications directly or indirectly related to pregnancy. Among these, 22 deaths were related to preeclampsia and 20 of 22 cases demonstrated substandard care[1].

Moreover, preeclampsia is an important risk for the health of the baby. The Perinatal Mortality Report of the United Kingdom[2] reports that 5% of stillbirths without congenital abnormality occurred in women with preeclampsia and that half of the women with severe preeclampsia gave birth preterm.

Then a question arises. Is the real problem to find a univocal definition of this complex disease or to find markers for the screening of preeclampsia? Or is the problem in the inadequate treatment?

In this review, we focus our attention on the possibility of screening for preeclampsia based on the data available in the literature.

However, the present report needs to include the definition of preeclampsia.

There has been confusion about the definition of hypertensive disorders in pregnancy for a long time.

In 2001, the International Society for the Study of Hypertension in Pregnancy[3] provided a consensus on classification, adopting the statement of the Australasian

Society for the Study of Hypertension in Pregnancy (ASSHP)[4] and the report of the National High Blood Pressure Education Program (NHBEP)[5].

The definition and classification is the following: hypertension in pregnancy, systolic blood pressure (SBP) ⩾ 140 mmHg and/or diastolic blood pressure (DBP) ⩾ 90 mmHg.

Four categories are identified: (1) preeclampsia: *de novo* hypertension after 20 wk gestation associated with proteinuria. Proteinuria is defined as appearance of urinary protein greater than 300 mg/d or a spot urine protein/creatinine ratio ⩾ 30 mg/mmol; (2) gestational hypertension: de novo hypertension alone after 20 gestational weeks; (3) chronic hypertension: hypertension diagnosed before 20 wk gestation or preconception hypertension; and (4) preeclampsia superimposed on chronic hypertension: in a woman with chronic hypertension, development of proteinuria and/or symptoms associated with preeclampsia after 20 gestational weeks.

In the definition of hypertension, both ASSHP and NHBPEP consider values below 140/90 mmHg as absolute values and do not provide an increase in blood pressure of 15 mmHg and 30 mmHg, respectively, for diastolic and systolic levels.

The ASSHP and NHBPEP agree on the definition and classification of hypertensive disorders during pregnancy with an important difference: the NHBPEP considers only hypertension associated with proteinuria as diagnostic criteria, whereas the ASSHP uses a clinical classification based on the pathophysiology of the disorder[4]. In fact, the definition of preeclampsia includes renal insufficiency, liver disease, neurological problems, hematological disturbances and fetal growth restriction (FGR), along with hypertension and proteinuria.

In 2009, the American Society of Hypertension (ASH) published a position paper that summarized the definitions and clinical features regarding the different forms of hypertension during pregnancy[6] and included the guidelines of the American College of Obstetricians and Gynecologists.

Like other opinions, the ASH position paper considers hypertension as a SBP ⩾ 140 mmHg and/or DBP ⩾ 90 mmHg, avoiding the dated concept of an increase in DBP of 15 mmHg or more and an increase in SBP of 30 mmHg or more. In the definition of preeclampsia, proteinuria is defined by the appearance of urinary protein greater than 300 mg/d, a spot urine protein/creatinine ratio ⩾ 30 mg/mmol or a qualitative dipstick +1. The protein/creatinine ratio is recommended in the ASH position paper because dipsticks have many false-positives and negatives and urine collection may be difficult in pregnancy.

The terminology used is that recommended by NHBPEP: preeclampsia/eclampsia, gestational hypertension, chronic hypertension and preeclampsia superimposed on chronic hypertension.

However, the ASH position paper also introduces new entities: (1) late postpartum hypertension: usually the blood pressure returns to normal in the immediate postpartum in preeclamptic women or in women with hypertensive disorders in pregnancy. However, there is a little known entity in which the hypertension appears after delivery in women with normotensive gestation and regresses within the first post-partum year; (2) late postpartum eclampsia: the eclamptic convulsions occur from 48 h to several weeks after delivery; and (3) early gestational hypertension: a very rare entity in which patients have excessive sensitivity to progesterone due to activating mineralocorticoid reception mutations. These women develop early hypertension concomitantly with the progesterone rise in the first trimester.

Preeclampsia in the ASH position paper is usually defined by hypertension associated with proteinuria, but the American Society of Hypertension suggests the distinction between "Less Severe" and "More Severe" preeclampsia (defined by the American College of Obstetrics and Gynecology as mild and severe preeclampsia) on the basis of symptoms, hypertension level and clinical data. The "more severe preeclampsia" is defined as the presence of severe hypertension (⩾ 110 mmHg diastolic and ⩾ 160 mmHg systolic), nephrotic range proteinuria, oliguria, neurological symptoms, thrombocytopenia (< 100000/μL), hemolysis and abnormal liver function.

Despite this distinction, the American Society of Hypertension recommends that even just a suspicion of preeclampsia is a sufficient reason for hospitalization because all preeclampsia is potentially explosive.

In 2010, the National Institute for Health and Clinical Excellence (NICE)[7] published a guideline, including a classification. The definition and classifications are as follows: (1) chronic hypertension: hypertension that is present at the booking visit or before 20 wk gestation. It can be primary or secondary in etiology; (2) gestational hypertension: a new hypertension presenting after 20 wk gestation without significant proteinuria; (3) preeclampsia: a new hypertension presenting after 20 wk gestation with significant proteinuria. Significant proteinuria is defined as +1 or more in an automated reagent strip or urinary protein/creatinine ratio greater that 30 mg/mmol or greater that 300 mg protein in 24 h urine collections; (4) eclampsia: a convulsive condition associated with preeclampsia; (5) HELLP syndrome: hemolysis, elevated liver enzymes and low platelet count; (6) severe preeclampsia: preeclampsia with severe hypertension and/or with symptoms and/or biochemical and/or hematological impairment. In addition, the Guideline Development Group has defined three different levels of hypertension: mild, moderate and severe; (7) mild hypertension: diastolic BP 90-99 mmHg, systolic blood presure (BP) 140-149 mmHg; (8) moderate hypertension: diastolic BP 100-109 mmHg, systolic BP 150-159 mmHg; and (9) severe hypertension: diastolic BP 110 mmHg or greater, systolic BP 160 mmHg or greater.

In agreement with the ASH position paper, the NICE guidelines recommend hospitalization of preeclamptic women with all degrees of hypertension.

The 2010 guidelines of the Royal College of Obstetrics and Gynecologists (RCOG)[8] regarding the Manage-

Table 1 Uterine artery doppler studies for the prediction of preeclampsia

Ref.	Weeks of evaluation (wk)	Sensitivity	Specificity
Campbell *et al*[10]	16-18	68%	69%
Valensise *et al*[11]	22	74%	97.5%
Jacobson *et al*[12]	24	44%	73%
Arduini *et al*[13]	18-20	64%	94%
Ziemmermann *et al*[14]	21-24	56%	83%
Bower *et al*[15]	18-22	75%	86%
Chan *et al*[16]	20	27%	97%
North *et al*[17]	19-24	27%	90%

ment of Severe Preeclampsia substantially agree with the other definitions of preeclampsia, but there are still differences about the definition of severe preeclampsia compared to the NICE guidelines. The RCOG considers severe preeclampsia as the presence of a DBP ⩾ 110 mmHg on two occasions or a SBP ⩾ 170 mmHg on two measurements with significant proteinuria (at least 1 g/L).

In agreement with the ASH position paper, the RCOG guidelines report the evidence level I b and II b regarding the measurement of blood pressure, referred to below.

The woman should be rested and sitting at a 45 degree angle. The cuff should be an appropriate size and be placed at the level of heart. The diastolic pressure is taken at the 5th Korotkoff phase, therefore the older concept that gravid women show large differences between the 4th and the 5th Korotkoff phase has been abandoned and the 5th Korotkoff has been established as the sound of true diastolic pressure.

SCREENING FOR PREECLAMPSIA

Ultrasounds

Uterine artery Doppler: The increase of impedance to flow in the uterine artery is evidence of impaired trophoblastic invasion of the maternal spiral arteries, a well known mechanism of the pathophysiology of preeclampsia. In fact, several studies have shown a reduction in the maternal uterine resistance index with advancing gestational age in normal pregnancy[9], while the presence of an increased resistance in maternal flow or the presence of a notch as evidence of abnormal uterine flow has been associated with the development of preeclampsia. For many years, the Doppler ultrasound evaluation of uterine arteries has been used to predict an unfavorable pregnancy outcome. However, discrepant results are described among studies in the literature (Table 1) which could be due to the different gestational age at which the women were evaluated, the different populations included, the single or two steps examination, the different cut-off of abnormal resistance index and finally the differences in ultrasound (US) Doppler technique.

In an unselected population, Bower *et al*[15] reported a sensitivity of 75% and specificity of 86% for preeclampsia in women at 18-22 wk gestation with an abnormal resistance index (above the 95th percentile and/or with the presence of a notch within the uterine artery Doppler waveform), with a better prediction for severe conditions. Valensise *et al*[11] found a sensitivity of 74% and specificity of 97.5% for the development of gestational hypertension in primigravidas at 22 wk gestation with increased impedance (resistance index more than 0.58).

Other authors report less favorable results. Chan *et al*[16] found that sensitivity of the test for preeclampsia was 27% and specificity was 97% in women at 20 wk gestation. Similar results from North *et al*[17] found a sensitivity of 27% and specificity of 90% at 19-24 wk gestation.

With the aim of reducing the number of false-positives, Steel *et al*[18] proposed a two step trial for uterine Doppler US with the first evaluation at 18 wk gestation and in the presence of increased impedance (resistance index greater that 0.58), a second Doppler evaluation at 24 wk gestation. The authors reported a sensitivity for preeclampsia of 63%. Also, Bower *et al*[19] reported an increase of positive predictive value (PPV) for preeclampsia from 12% to 28%, reanalyzing women at 24 wk with abnormal Doppler US at 20 wk gestation.

Several studies regarding the application of Doppler uterine evaluation as a screening tool have been conducted in selected populations at risk for preeclampsia. Arduini *et al*[13] evaluated women with previous gestational hypertensive disorders or essential chronic hypertension at 18-20 wk and reported a sensitivity of 64% and a specificity of 94%, but the true value of those data are still questionable. In fact, several biases and criticisms have been levelled at data from this research group. Jacobson *et al*[12] found a sensitivity of 44% and specificity of 73% for preeclampsia in women with chronic hypertension or a history of preeclampsia. Caruso *et al*[20] examined women with chronic hypertension in order to assess the predictivity power of Doppler uterine US and found a sensitivity of 78% and specificity of 45%.

Valensise *et al*[11] observed that the value of Doppler uterine evaluation as a screening test strictly depends on the studied population in his Paramount study. The PPV for hypertension is acceptable for screening in the high risk population, while in low risk pregnant women the correlation seems to be weaker. More recently, Elena Parretti from Florence[21] conducted a cross-sectional (at 24 wk gestation) and a longitudinal (at 16, 20 and 24 wk gestation) study of uterine artery Doppler in normotensive women with risk factors for preeclampsia. In agreement with other investigators, the value of 0.58 as the normal resistance index and a PPV of 44% were confirmed, still inadequate for a screening test. Instead, with a longitudinal approach, the PPV seemed to improve to 72.2% by reducing a number of false-positive results.

To improve the possibility of using the Doppler velocimetry of the uterine arteries as a screening for preeclampsia, several studies have proposed other parameters likely to be integrated with the Doppler evaluation.

Valensise *et al*[22] proposed the combination of Doppler and 24 h automated maternal blood pressure evaluation. This study stated that in the presence of abnormal Doppler and asymptomatic raised blood pressure, pa-

tients had a higher incidence of pregnancy complications with a PPV of 76% for preeclampsia.

With the aim of reducing the number of false-positive patients, other authors have proposed the use of Doppler velocimetry associated with biochemical parameters.

Elevated levels of second trimester β-human chorionic gonadotropin have been found in plasma of patients at risk for hypertensive disorders in pregnancy[23]. A study by Elsandabesee *et al*[24] demonstrated that in the presence of a diastolic notch, the association of serum screening with alpha-fetoprotein and β-human chorionic gonadotropin improves sensitivity and PPV to 91% and 41% respectively.

Initial studies showed a significant decrease in placental protein-13 (PP-13) levels in preeclamptic women[25,26], while recently Stamatopoulou *et al*[27] did not show a relationship between PP-13 levels and preeclampsia. Akolekar *et al*[28] studied PP-13 associated with PAPP-A (pregnancy-associated plasma protein A) and uterine artery Doppler US in the first trimester in 208 preeclamptic patients and in 416 normal pregnancies; a significant reduction of PP-13 level was shown in early preeclampsia but not in late preeclampsia, with a PPV for early preeclampsia of 79% and 49% for late preeclampsia. Although PAPP-A was reduced and uterine velocimetry Doppler was increased in preeclampsia, the combination of these parameters with PP-13 does not appear to improve the sensitivity of PP-13[28].

A systematic review in 2010[29] studied the role of biochemical markers associated with ultrasonographic markers to improve the possibility of prediction for early preeclampsia. The authors included 37 articles within their review in which the most frequently studied biochemical markers were hCG (human chorionic gonadotropin), inhibin A, α-fetoprotein, sFlt-1 (soluble fms-like tyrosine kinase 1), PAPP-A, activin A, placental growth factor (PlGF) and PP-13. In some cases, markers were evaluated in the second trimester as well as the ultrasound velocimetry, in other cases the markers were assessed during the first trimester before ultrasonographic evaluation. The analysis of these papers elucidates that the addition of biochemical markers to uterine artery Doppler ultrasound scan in the second trimester or the combination of first trimester biochemical and second trimester uterine velocimetry improves the predictive performance of ultrasound alone and of markers alone. This review also suggests that the addition of maternal characteristics does improve their predictive power.

Despite these promising results, the heterogeneity between studies regarding gestational age at the study time or the selected populations (high *vs* low risk) led to uncertainty about the combination of ultrasonographic and biochemical markers as a screening procedure for preeclampsia.

Maternal echocardiography: It is well known that important changes occur in pregnancy in the hemodynamic and cardiovascular system, with initial vasodilatation adaptation of the maternal cardiovascular tree that begins in the first trimester as a consequence of invasion of the spiral arteries by trophoblasts. Indeed, the remodeling of the spiral arteries contributes 20% to 26% to the total reduction of systemic vascular resistance in the second trimester[30]. Another important change is the increase in blood volume. A study based on the multifrequency bioelectrical impedance documented that total body, extracellular and intracellular water increased significantly and progressively from the first to the second trimester[31].

Cardiovascular and hemodynamic modifications consist of an increased preload, a decreased afterload, an increased compliance of the vascular tree and a ventricular remodeling at the level of the heart. Therefore, there is an enlargement of the vascular bed and an increase in blood volume to fill the enlarged vascular bed. Conversely, an inadequate placentation and the failure of the hemodynamic adaptation were identified as the basis of the pathological process leading to pregnancy complications. In 1988, Nisell *et al*[32] showed that in preeclamptic women, independently of the cardiac output, a high peripheral resistance can be observed and in those with a low cardiac output generally, a low birth weight could occur. Duvekot *et al*[33] observed that patients with FGR had a smaller left atrial diameter and a failure of cardiac output in early pregnancy.

On this basis, Valensise *et al*[30] designed a different study to evaluate the predictive value of some echocardiographic parameters for maternal and fetal complications, alone or associated with uterine Doppler velocimetry[30,34].

The same author[30], in his first study on this topic, evaluated the relationship between cardiac systolic and diastolic function and uteroplacental resistance in a longitudinal observation of 248 patients with a normal pregnancy. He reported a significant reduction in resistance index between first and second trimester in the uterine Doppler velocimetry. The echocardiographic evaluation showed a significant increase in left atrial diameter, stroke volume and cardiac output in normal pregnant women throughout gestation, mainly from the first to the second trimester, according to the fall of the uterine resistance index that contributes to a decrease of the afterload.

Conversely, in a study[35] performed on 21 pregnancies complicated by gestational hypertension, the analysis of systolic and diastolic function associated with morphological left ventricular modifications showed that hypertensive women have an altered geometric pattern with concentric hypertrophy. Functionally, this finding is associated with higher blood pressure, higher total vascular resistance (TVR) and higher uterine resistance index compared to normotensive patients. Therefore, the use of maternal cardiac function evaluation in women presenting with an abnormal uterine Doppler resistance index in the second trimester is recommended to increase the prediction of hypertensive disorders of pregnancy. With the scope to increase the predictive values for gestational hypertension of ultrasound evaluation, Valensise *et al*[36] carried out echocardiography in 36 women with uterine Doppler abnormalities (bilateral notch and RI > 0.58)

at 24 wk gestation, showing a normal ventricular left isovolumic relaxation time (IVRT) in the normotensive women group, evidence of adequate diastolic function; while in patients with pathological outcomes, an elevated IVRT, meaning cardiac diastolic dysfunction and an altered ventricular geometric pattern was found, evidence of abnormal cardiac adaptation to pregnancy. Therefore, he proposed the association of data from maternal cardiovascular adaptation with uterine artery screening to reduce the number of false-positive diagnoses of pathological pregnancy.

In a subsequent study[37], the same research group evaluated the predictive value for maternal and fetal complications of TVR and left ventricular morphology in normotensive high risk primigravidas with a bilateral notch of uterine artery at 24 wk. They reported that the increase of TVR above the cut-off had a sensitivity at 89%, specificity at 94%, PPV at 77% and negative predictive value at 97%. Considering the importance of the assessment of the cardiac function in pregnancy, another study[34] was conducted to evaluate the significance of myocardial function associated with abnormal uterine Doppler velocimetry in women with hypertensive complications and in normal pregnancy. The results showed that in pregnancy with abnormal uterine artery Doppler and complicated outcomes, the myocardial function is impaired prior to the development of complications and remains depressed 6 mo postpartum; in women with normal uterine artery and normal pregnancy, the myocardial function was unchanged compared to the postpartum; in patients with bilateral notching and a normal outcome of pregnancy, an enhanced myocardial function is reported and the authors hypothesize that it is a crucial mechanism to maintain normal hemodynamic parameters.

Echocardiographic parameters of cardiac performance during pregnancy could be an important predictor of pregnancy complications and a predisposition to cardiovascular disease in normotensive women.

Genetic assessment

Preeclampsia is a complex multisystem and multifactorial disorder with an unclear genetic component. However, it can be hypothesized that well known etiological factors may have a genetic implication[38]. In the past, it has been suggested that Mendelian or mitochondrial gene transmission could be a cause of preeclampsia; however, studies conducted on monozygotic twins did not confirm this hypothesis. Fetal genotype was also investigated without demonstrating a clear role in determining an increased risk of preeclampsia[38].

Not only the genotype but also the m-RNA expression of specific genes seems to be associated with the development of preeclampsia[38]. Indeed, Rajakumar *et al*[39] identified 368 genes differentially expressed in preeclamptic women and normotensive patients in a recent study analyzing leukocyte gene expression. Particularly, he observed that this different expression concerns genes that play a central role in functions, such as cell proliferation, inflammation, apoptosis, immune function and angiogenesis that are involved in the pathogenesis of preeclampsia.

Therefore, it appears that preeclampsia is a complex multifactorial and multigenic disease.

In a systematic review, Mütze *et al*[38] reported more than 50 candidate genes as predisposing factors for preeclampsia but only a few genes account for about 70% of research.

Evaluating the current state of the literature regarding the role of gene polymorphisms in preeclampsia, we distinguish different genes on the basis of their pathophysiological role in this disease: endothelial dysfunction, oxidative stress and placental thrombosis.

Genes involved in endothelial dysfunction: Different genes were identified in endothelial remodeling and their polymorphisms have been associated with endothelial dysfunction, although with controversial results.

For example, it is well known that endothelin-1 (ET-1) is an important vasoconstrictor produced by endothelial and smooth muscle cells and that endothelial-1 converting enzyme (ECE-1) is connected with ET-1 concentration. However, one study examined the role of polymorphism Lys198As in the ET-1 in preeclamptic women but found no significant association[40]. Another recent study[41] evaluated the polymorphism Lys198Asn of ET-1 and Thr34IIe of ECE-1 and no statistically significant differences in polymorphic frequencies between hypertensive pregnant women and the control group were found. Moreover, the gene encoding for endothelin-1 receptor was investigated but the polymorphism considered (231G>A) was not found to be related to the risk of preeclampsia[42].

Genes encoding for information regarding blood pressure, hemodynamic changes and vascular remodelling as gene components of the renin-angiotensin systems have been investigated to evaluate the presence of polymorphism candidates for involvement in preeclampsia.

The polymorphism in intron 16 (insertion/deletion) of angiotensin converting-enzyme (*ACE* gene) is associated with changes in ACE activity. A large study by Serrano *et al*[43] in 665 preeclamptic women and 1046 controls did not find a significant association of a deletion form with preeclampsia. Li *et al*[44] investigated polymorphism of the *ACE* gene and the polymorphism A1166C of angiotensin Ⅱ receptor type 1 gene (*AT1R*) in a Chinese population. He found no significant differences in the frequency of genotypes of the *ACE* gene and *AT1R* gene in preeclampsia and normal pregnancy; however, preeclamptic women carrying the deletion form are more susceptible to developing renal dysfunction.

Another recent study investigated the association of both polymorphisms with the risk of preeclampsia[45] and showed that the polymorphisms of the renin angiotensin system could be associated with elevated oxidative stress involved in preeclampsia development. Although is well known that the renin angiotensin system contributes to fetoplacental blood flow regulation, there are still no conclusive studies regarding the association of genetic polymorphisms of this system and preeclampsia.

Nitric oxide is an important regulator of vasodilatation and vascular remodeling and its production by nitric oxide synthase (eNOS) is known to be decreased in preeclampsia.

Häkli *et al*[46] evaluated the polymorphism Glu298Asp of *eNOS* gene in 132 preeclamptic women and 113 controls and found a similar distribution in both populations. A systematic review[38] on genes and preeclampsia regarding the eNOS E298D polymorphism concludes that this polymorphism does not seem to be related to a significantly increased risk of preeclampsia.

The production of vasoactive substances regulating the vascular tone is mediated by estrogen receptors α and β (ER α/β). Polymorphisms for these receptors have been reported to be associated with vascular disorders and the pathogenesis of hypertension[47]. Maruyama *et al*[47] found a similar distribution of polymorphisms in preeclamptic women and the control group when considering the relationship between four SNPs (single nucleotide polymorphisms) in ER β and preeclampsia. Another study[48] investigated two polymorphisms of the *ER α* gene (c.454 -397T>C and c.454 -351A>G) in 119 women with severe preeclampsia and 103 normotensive women and found no association between severe preeclampsia and single gene polymorphism; however, the presence of both polymorphisms (TT/AA genotypes) was significantly more frequent in severe preeclamptic patients than in the normotensive population. However, Zhang[49] did not confirm these data in a study in a Chinese population conducted on 204 preeclamptic subjects and 236 normal women, reporting a similar distribution of combined polymorphisms of *ER α* gene in both groups.

In recent years, the attention has been focused on binding of vascular endothelial growth factor (VEGF) and PlGF and their receptor Fms-like tyrosine kinase-1 receptor (sFlt-1) that stimulates placental vasculogenesis and angiogenesis; this interaction leads to decreased circulating levels of PlGF and in preeclamptic women an increase in sFtl-1 and a corresponding decrease in PlGF is observed. A recent meta-analysis[50] of 11 case-control studies analyzing 1069 preeclamptic women and 1315 normal pregnancies concluded that VEGF polymorphisms +936C/T and -634G/C were associated with preeclampsia and there was no evidence of the association between them. Only one study, to the best of our knowledge, has been published regarding the polymorphisms in Flt-1 receptor, based on the observation that a misregulation of Flt-1 results in over-expression of sFlt-1, and could contribute to pathophysiology of preeclampsia. Kim *et al*[51] did not find a significant difference in frequencies of the dinucleotide repeat polymorphism in preeclamptic women and the normotensive group.

Genes implicated in oxidative stress: It has been reported that oxidative stress plays an important role in the etiology of preeclampsia. Indeed, in an imbalance between reactive oxygen species (ROS) production and antioxidant defence, placental oxidative stress may stimulate syncytiotrophoblast apoptosis resulting in impaired placental function characteristic of preeclampsia[52].

In recent years, the expression of *OLR1* gene encoding for LOX-1 receptor (low-density lipoprotein oxidized) has been investigated in preeclamptic women. Indeed, LOX-1, extensively studied for its role in myocardial ischemia, is a powerful mediator of endothelial dysfunction through generation of superoxide, induction of chemokine expression and inhibition of nitric oxide production leading to cell apoptosis[53]. An immunohistochemical study in preeclamptic placentas showed LOX-1 positive specimens in syncytiotrophoblasts significantly upregulated compared with normal placentas, confirming the elevated apoptotic activity of syncytiotrophoblasts in preeclampsia[53].

The Western blot examination of OLR-1 expression in syncytiotrophoblasts had a higher expression in cases of preeclampsia and other pregnancy diseases[54]. OLR1 is the main scavenger receptor responsible for up-take of LDL-ox within placental cells. The high level of OLR1 expression is evidence of enhanced oxidative stress in preeclamptic placentas, in agreement with previous observations of elevated levels of serum lipid peroxides in preeclampsia[55,56].

Polymorphisms in genes involved in the production of ROS or in the metabolism of these reactive species can also lead to placental dysfunction.

Among anti-oxidant systems, an important role is played by placental glutathione S-transferase (GST) which contributes to placental detoxification. Zusterzeel *et al*[57] reported that homozygous genotype GST 1b/1b was significantly more represented in preeclamptic women than in normotensive controls (OR = 3.4), which could result in a lower detoxification capacity.

Conversely, Kim *et al*[58] showed that *GST* gene polymorphisms, as well as polymorphisms in the oxidative stress related genes, do not seem to be factors of susceptibility to preeclampsia in their study of 214 normotensive pregnant women and 121 preeclamptic patients.

Cytochrome P4501A1 (CYP1A1) was also related to preeclampsia; however, no study demonstrated the association between the single CYP4501A1 and preeclampsia[58].

Although single polymorphism does not seem to increase susceptibility to gestational hypertensive disorders, Zusterzeel *et al*[59] described a significant association between higher ROS production or a lower detoxification pattern and preeclampsia development when studying the simultaneous occurrence of severe genetic polymorphisms (GST, epoxide hydrolase and CYP1A1) in women developing preeclampsia.

Polymorphisms of the gene encoding for superoxide dismutase (SOD) were also investigated, with SOD acting as a cell protector from superoxide radicals. Kim *et al*[58] reported no association between gene polymorphisms and susceptibility for preeclampsia. More recently, two missense polymorphisms of extracellular SOD (Arg-213Gly and Ala40Thr) were investigated in 114 normotensive women and 159 preeclamptic patients and no significant differences were found, but it has been demonstrated that women carrying these polymorphisms do

Table 2 Biochemical markers predicting preeclampsia

Markers	Ref.	Age of testing	Sensitivity	Specificity
hCG	Jauniaux *et al*[73]	2nd trimester	72.7%	90%
	Merviel *et al*[74]	2nd trimester	54.5%	93.5%
Inhibin A	Spencer *et al*[75]	1st or 2nd trimester	68%	95%
	Florio *et al*[76]	2nd trimester	38.9%	92.5%
PP-13	Nicholaides *et al*[77]	1st trimester	90%	90%
AFP	Jauniaux *et al*[73]	2nd trimester	72.7%	70%
	Kuo *et al*[78]	2nd trimester	61.5%	47.3%
Activin A	Florio *et al*[76]	2nd trimester	61.1%	77.5%
	Spencer *et al*[75]	2nd trimester	63%	95%
PAPP-A	Poon *et al*[79]	1st trimester	20.5%	95%
	Spencer *et al*[80]	1st trimester	62.1%	95%

hCG: Human chorionic gonadotrophin; PP-13: Placental protein-13; AFP: α-fetoprotein; PAPP-A: Pregnancy-associated plasma protein A.

present with a higher risk of severe preeclampsia complicated by FGR[60]. Another recent study[61] in Romanian women described that the genotype Val/Val was significantly associated with preeclampsia and a more clinically severe disease.

Inherited thrombophilias: The observation that women developing preeclampsia subsequently have a higher risk of thromboembolism has often suggested the existence of a correlation between inherited thrombophilias and preeclampsia[62,63]. The occurrence of villous thrombosis is also considered an important mechanism in the pathogenesis of preeclampsia. The condition of inherited thrombophilias is generated by specific polymorphisms in genes encoding for specific coagulation factors. These polymorphisms include factor V Leiden mutation (G1691G>A mutation Factor V), methylenetetrahydrofolate reductase (MTHFR) (MTHFR 677C>T), the prothrombin mutation (G20210G>A) and the plasminogen activator inhibitor-1 mutant genotype (PAI-1 4G/4G>5G/5G).

In 1995, Dekker *et al*[64] described an association between inherited thrombophilias and severe preeclampsia. Since then, many studies have followed on the role of thrombophilic mutations in gestational hypertensive disorders, with contradictory results. In a 2005 review, Calderwood *et al*[65] report inconclusive results due to the absence of large scale, randomised controlled studies. However, he did underline a feasible association between placental troubles and factor V Leiden. A large meta-analysis by Kosmas *et al*[66] with almost 3000 women focused on factor V Leiden reports an odds ratio of 2.3, showing the important role of this polymorphism as a risk factor for preeclampsia. The same author reports[67] a moderately increased risk of preeclampsia in carriers of heterozygous and homozygous mutation of MTHFR 667 (OR = 1.3). However, a subsequent review by Pabinger[68] of several interesting studies reports no association between factor V Leiden and prothrombin mutation (G20210G>A) compared to hypertensive gestational disorders.

Our study group analyzed a link between inherited thrombophilias and preeclampsia with preeclamptic and normal pregnant women and no evidence of an association between preeclampsia and factor V Leiden or prothrombin gene mutation[69] was found. Given the low PPV of a single thrombophilia in the detection of preeclamptic risk, we conducted another study considering the association of double inherited thrombophilias and risk of adverse pregnancy outcomes. We found a slight but significant association between the combination of MTHFR C677T with Factor Ⅷ and the combination of factor Ⅱ and factor V mutations and the occurrence of abruptio placentae; however, we did not find an increased incidence of adverse pregnancy outcomes in subjects with a combination of MTHFR C677T and factor V Leiden or in patients with the simultaneous presence of factor Ⅱ mutation and PAI-1 (G5/G5)[70].

A recent review[71] of preeclampsia and inherited thrombophilias reports that mild preeclampsia is unlikely to be associated with thrombophilias, but severe and early onset preeclampsia seems to be significantly related to inherited thrombophilias, and preeclamptic patients carrying gene mutations are at greater risk of developing more severe forms and sequelae.

In agreement with these findings, our study group highlighted that in preeclamptic patients with inherited thrombophilias, a more severe involvement of kidneys and a more severe damage in the course of hypertensive gestational disease might occur[72].

It is therefore clear that there are contradictory results regarding the association between thrombophilic gene mutations and preeclampsia and there are no consistent data to suggest mandatory thrombophilic screening as predictive of preeclampsia.

New biochemical markers

In obstetrical practice, a long-term objective is to identify ideal maternal biomarkers for preeclampsia but it is very difficult because the "ideal marker" requires the coexistence of different characteristics: noninvasiveness, high sensitivity and specificity and a high PPV to predict disease prognosis. We currently have a plethora of studies intended to identify an ideal biomarker; however, differences in the studied populations, the methodologies and the interpretation of results make it difficult to perform a systematic analysis of all the markers (Table 2). Therefore, in this review we only consider markers that have been proposed more recently as potential new biomarkers.

Research of these new emerging biomarkers arises from the new model of pathogenesis of preeclampsia which focuses on the angiogenesis process rather than the vasoconstrictive phenomenon[81].

VEGF and PlGF are among the proangiogenic factors, soluble endoglin (sEng) and soluble fms-like tyrosine kinase 1 receptor(sFlt-1) are among the antiangiogenic factors.

Cells expressing VEGF are located near fenestrated endothelia and the inhibition of VEGF leads to pathological conditions in many organs with fenestrated endothelia (*e.g.*, liver, kidney, choroid plexus, *etc.*), as observed in se-

vere preeclampsia. PlGF is expressed mainly by placental cells and its levels increase from the second to third trimester. Both VEGF and PlGF bind to the VEGF receptor family, named Flt-1 and kinase insert domain receptor (KDR). PlGF binds more actively to Flt-1, while VEGF binds to KDR. It has been suggested that sFlt-1 acts to modulate VEGF availability[82].

This evidence confirms the antiangiogenic role of soluble form of VEGF-PlGF receptor sFlt-1.

sFlt-1 binds these angiogenic factors and inhibits their vasodilatory effect. The other antiangiogenic factor is sEng. In animal studies, it allows the formation of the endothelial tube, increases capillary permeability and could be responsible for hypertension, nephrotic syndrome and liver dysfunction during preeclampsia[83].

A recent review reported significant changes in the levels of sFlt-1, PlGF and sEng in preeclamptic patients with a different time course, the earliest in the first trimester for PlGF and later for sFlt-1 and sEng.

Levine *et al*[84,85], in two studies from 2004 and 2006, demonstrated that levels of sFlt-1 increased 5 wk before the onset of clinical disease and parallel levels of PlGF and VEGF decreased due to the binding by sFlt-1, while the levels of sEng increased 2-3 mo before clinical disease.

More recently, the level of PIGF has been evaluated in pregnancy complicated by hypertension disease[86] and it has been found that a positive PIGF test can predict delivery before 37 wk in over 90% of pregnant women with hypertensive disease. Therefore, a low level of PIGF could be used before 35 wk in hypertensive women to evaluate the risk of pregnancy complications. sEng level also seems to be prognostic and its level appears to be correlated with severe preeclampsia or eclampsia[87]. Despite this evidence, there are no conclusive data yet on their diagnostic capability, the cut-off of normality and the time or strategy to measure these markers.

Regarding diagnostic capability, a recent extensive study conducted on 2200 patients with PlGF and sFlt-1 in the first trimester found a sensitivity of 55% and 57% respectively and a specificity of 43% and 40% respectively[88]; this result does not improve later in pregnancy. It is evident that the predictive positive value is too low to use this marker in the first trimester for screening for preeclampsia. Other strategies in measuring angiogenic factors have been proposed: a longitudinal evaluation and a ratio between two factors.

Indeed, an increase from first to second trimester of sFlt-1, sEng and PlGF[89] has been demonstrated in preeclamptic women. On the other hand, several studies have proposed a ratio between sFlt-1 and PlGF (sFlt-1: PlGF)[90] and between PlGF and sEng (PlGF:sEng)[91] based on the observation that levels of PlGF and sFlt-1 are altered together in preeclampsia, reporting an important improvement in sensitivity (88.5% and 100% respectively) and specificity (88.5% and 98% respectively). Despite these promising results, larger studies are needed to confirm these finding.

Our brief review of the possibility of early screening for preeclampsia analyzed the most recent literature and highlighted the lack of a single certified method able to predict the risk. However, despite the complexity of clinical and pathophysiological behavior of preeclampsia, it is possible that in the future the combination of several tests will allow us to predict women at risk of preeclampsia.

One point needs to be underlined: we started from ultrasonic evaluations (uterine arteries Doppler US) and in a relatively short period we arrived at a supersonic era in which more promising and accurate tests seem to come from the laboratory.

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REVIEW

Role of minimally invasive surgery in complex adnexal tumours and ovarian cancer

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Abstract

Ovarian cancer is one of the most common causes of cancer-related death in women. Adnexal masses are frequently diagnosed during reproductive age and often require surgical removal. The risk of malignancy when dealing with a complex adnexal mass should be defined prior to surgery and several scoring systems may be useful for this purpose. Laparoscopic management of ovarian tumours allows a minimally invasive approach with respect to several oncological assumptions. In the last decade concerns have been raised regarding the risk of cyst rupture and tumour spillage as a consequence of the laparoscopic technique itself both in early and advanced stages of ovarian cancer. Although limited data have been reported in the literature on the use of minimally invasive techniques in ovarian cancer, the clear benefits of this approach must be balanced with the potential hazards in different clinical situations. Laparoscopic staging in borderline tumours and presumed early-stage ovarian cancer performed by a laparoscopic oncologist seems to be safe and effective when compared to laparotomy. The precise role of laparoscopy in patients with more advanced cancer is still to be defined, and the risk of suboptimal surgery should never outweigh the potential benefits of minimally invasive surgery. Thus, a tailored prediction of optimal laparoscopic debulking is mandatory in these patients.

Key words: Ovarian cancer; Laparoscopy; Borderline tumour; Adnexal masses

Core tip: The systematization of laparoscopic techniques and the improvement in technology have provided the basis for the increased use of laparoscopy in oncology in the last decade. Preoperative evaluation of complex adnexal masses and surgical planning are key factors in defining the most appropriate tailored therapy for each patient. Herein, we address the limitations and concerns regarding the use of minimally invasive techniques in the treatment of complex adnexal masses and ovarian cancer, including the clinical scenarios of borderline tumours, and both early and more advanced stages of the disease.

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INTRODUCTION

In the last two decades there has been increasing interest in the use of minimally invasive techniques in the field of gynaecological oncology. The role of laparoscopy

has been widely used in cervical and endometrial cancer due to its known clinical benefits such as magnification of the operative field, reduced intraoperative and postoperative complications, less intraoperative blood loss, and a shorter postoperative recovery. Nevertheless, the laparoscopic approach for the staging of ovarian cancer and management of suspicious adnexal masses has raised several concerns among gynaecological oncologists such as a possible reduction in radical surgical excision, an increased risk of port-site metastases or a higher recurrence rate related to more frequent intra-operative tumour cyst rupture.

Ovarian cancer is the sixth most common cause of cancer-related death among women in Europe[1] . Women have a 1 in 70 lifetime risk of developing ovarian cancer and more than 200000 women worldwide are diagnosed each year with ovarian cancer. Unfortunately, more than 65% of cases are diagnosed at advanced stages, and the five-year overall survival rate is 46%[2]. Of note, ovarian cancer is identified incidentally in up to 13% of cases after oophorectomy for a presumed benign adnexal mass[3]. Early ovarian cancer (EOC) includes cases in which the tumour is limited to the pelvis [Federation of Obstetrics and Gynecology (FIGO) stages Ⅰ-Ⅱb], whilst the term advanced ovarian cancer (AOC) is used for cases with extrapelvic disease or metastasis (FIGO stages Ⅱc or more). The five-year survival of EOC is noted to be over 90%. This figure is in sharp contrast to that of patients affected with more advanced disease, where the 5-year survival rate is poor at approximately 25%.

The laparoscopic approach for surgical staging or restaging of ovarian cancer was first reported in the mid 1990s[4]. When considering a minimally invasive approach it is of utmost importance to perform an accurate preoperative evaluation and to define the rules for surgical management of adnexal masses. As patients with EOC confined to the ovary have a good 5-year survival rate, important considerations including quality of life and fertility preservation should also be taken into account. Finally, the specific clinical features of borderline tumours raise important considerations in the laparoscopic management of these neoplasms.

In this review, we will address the limitations and concerns of the use of minimally invasive techniques in the treatment of complex adnexal masses and ovarian cancer.

EVALUATION AND MANAGEMENT OF COMPLEX ADNEXAL MASSES

Adnexal masses are a worrisome issue for gynaecologists worldwide. They may be symptomatic or incidentally discovered and can be found in females of all ages, even in fetuses. The prevalence of adnexal masses in the premenopausal asymptomatic population is about 8%, and decreases to 2.5% in postmenopausal women. The diagnostic evaluation of the mass is guided by the anatomic location, symptoms, age and reproductive status of the patient. The expertise of the multidisciplinary team in charge of the patient is essential in women with adnexal masses at high risk of malignancy, and therefore, they should be referred to specialized centres, whereas patients at low-risk can be managed at general hospitals[5]. The American College of Obstetricians and Gynecologists has proposed guidelines for the management of adnexal masses and the detection of EOC[6].

Serum markers, such as CA125 or CA 19.9 have been widely used in the diagnostic evaluation of adnexal masses. Unfortunately, the positive predictive value (PPV) for malignancy of these glycoproteins has been shown to be lower than 20% in the best scenarios of postmenopausal asymptomatic women[7]. Another emerging tumour marker that deserves special mention is the human epididymis secretory protein 4 (HE4)[8,9], a protein overexpressed in ovarian and endometrial cancers. That was the rationale for including HE4 in addition to CA125 in the Risk of Ovarian Malignancy Algorithm (ROMA), which has been used over the last five years yielding an improved PPV for the detection of high-risk patients when compared with previous decision-making strategies[10,11]. Another model widely used over the past two decades is the Risk of Malignancy Index (RMI), which is calculated using several ultrasound variables, the menopausal status and the CA125 level. Its relative simplicity makes it easy to use[12,13]. Recently, Van Gorp *et al*[14] compared the diagnostic accuracy of ROMA with the RMI and subjective assessment by ultrasound in 432 women with a pelvic mass who were scheduled to undergo surgery in a single-centre prospective cohort study. Surprisingly, the subjective assessment proved to be more accurate than the other two methods, suggesting that the addition of plasma biomarkers did not only further improve the usefulness of ultrasonography, but in contrast, worsened the diagnostic value.

Laparotomy is still the most widely used approach, particularly in patients with complex masses at ultrasound. In order to increase the rate of the minimally invasive approach in these patients, Canis *et al*[15,16] suggested a reasonable approach for managing adnexal masses under suspicion in specialized centres. Laparoscopy should be the first indication in both premenopausal and postmenopausal patients, excluding tumours exceeding 12 cm or in the presence of obvious advanced disease. In cases in which malignancy is histologically diagnosed intraoperatively, a complete surgical staging should be performed either by laparotomy or laparoscopy, according to the extent of the disease and the surgeon's experience. Under these conditions the need for laparotomy to treat benign neoplasms could be reduced from 42% to 14%. Ghezzi *et al*[17], showed that the availability of a precise diagnosis from a frozen section might favour a laparoscopic approach independently of clinical or ultrasound characteristics or level of tumour markers. They demonstrated that frozen section analysis was 100% sensitive enabling optimal staging in 16.9% of postmenopausal women with a diagnosis of ovarian cancer.

The laparoscopic approach to complex adnexal masses must always maintain the principle that the specimen

Table 1 Operative evaluation of macroscopic characteristics predicting the potential of malignancy in adnexal masses

Multiloculation
Aberrant neovascularization at ovarian surface
Thick cystic wall
Papillary excrescences
Firm adhesions
Ascites
Bilaterallity
Infiltration of surrounding structures

could be malignant. Therefore, special care should be taken while establishing the pneumoperitoneum, in order to avoid rupture of the cystic wall. Systematic examination of the abdominal cavity should be performed and reported after surgery. Peritoneal washings and biopsies of any suspicious areas are also mandatory.

Laparoscopic examination is essential to identify adnexal masses at high-risk of malignancy. Several macroscopic findings must be borne in mind and included in the operative report (Table 1). In the presence of a high-risk suspicious mass at the preoperative evaluation the mass should be mobilized bluntly with gentle traction of the ligamentary structures that support it, therefore, avoiding the possibility that the small and sharp laparoscopic instruments could damage the mass. Laparoscopic trocars should be secured to the abdominal wall to avoid any leakage of CO_2 and gas evacuation must be carried out at the end of the procedure through the trocar sheave and never directly through the wall incision. Under these conditions, the only limitation for the laparoscopic management of adnexal masses is the size of the endoscopic bag, as the whole mass should be contained in this device to permit its safe extraction through the abdominal wall without risk of contamination (Figure 1). To facilitate the manoeuvre of exteriorization, the fascia and the skin incision may be increased to 2-3 cm. As the tumour is being removed, morcellation of large specimens is allowed always inside the bag. Once the extraction has been successfully completed, the trocar can be replaced in its orifice and easily secured using a fascial closure instrument, thus permitting continuation of the procedure if necessary.

BORDERLINE OVARIAN TUMOURS

Borderline ovarian tumours (BOTs) form a separate entity within the group of epithelial ovarian tumours recognized by the World Health Organization (WHO). Three terms are used to clasify these tumours: borderline tumour, tumour of low malignant potential, and atypical proliferative tumour. They represent about 15%-20% of all epithelial ovarian malignancies and have a worldwide incidence of 1.8-4.8 per 100000 women per year. In comparison with ovarian carcinomas, BOTs are diagnosed at a lower FIGO stage, tend to appear in younger women (average 10 years younger), have a higher infertility rate and they are not usually associated with other neoplasms. Although prognosis for patients with BOTs is, in general,

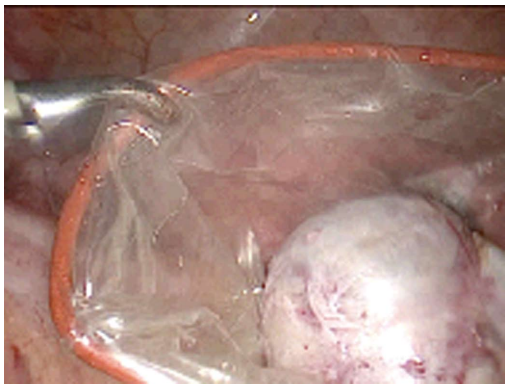

Figure 1 Specimen retrieval.

excellent, a minority will have a more aggressive form and may have long-term recurrence with a global 10-year recurrence rate of 10%-20%[18]. Therefore, the correct management and follow up is essential in these patients.

BOTs are characterized by increased epithelial proliferation accompanied by nuclear atypia (usually mild to moderate) and mildly increased mitotic activity with no stromal invasion. In typical serous BOTs, approximately 35% of patients have implants, which are either invasive (25%) or non-invasive (75%), and an invasive peritoneal implant is an adverse prognostic factor. When a BOT is identified at surgery by intraoperative histology, the recommended treatment is laparoscopic salpingo-oophorectomy (Figure 2). The correct staging surgery includes exploration of the entire abdominal cavity, peritoneal washings, omentectomy, multiple peritoneal biopsies, and complete resection of all macroscopic suspected lesions. For resection of the primary tumour, bilateral salpingo-oophorectomy in combination with hysterectomy is recommended, although some authors suggest that hysterectomy may cause more morbidity without a clear role in overall prognosis. Lymphadenectomy is not indicated. If a mucinous tumour is suspected or intraoperative histologic consultation leads to this diagnosis, appendectomy should be performed.

BOTs are usually diagnosed in women during reproductive age, which implies that therapeutic decisions regarding fertility-sparing surgery, treatment of infertility or premature hormonal deprivation, intra and postoperative morbidity, and adjuvant chemotherapeutic treatments are particularly pertinent. Nevertheless, the risk of recurrence and the risk of progression to invasive disease, which accounts for up to 2%-4% should be taken into consideration. The fertility-sparing options can range from cystectomy to adnexectomy, however, patients who undergo a conservative ovarian cystectomy should be informed that there is a substantial risk of relapse, and recurrence can even develop many years later, therefore, a long-term follow up must be agreed[19].

Laparoscopy is an attractive approach for BOTs supported by lower morbidity and fewer adhesions than laparotomy (both important for fertility). However, in many studies, laparoscopic management of BOTs was

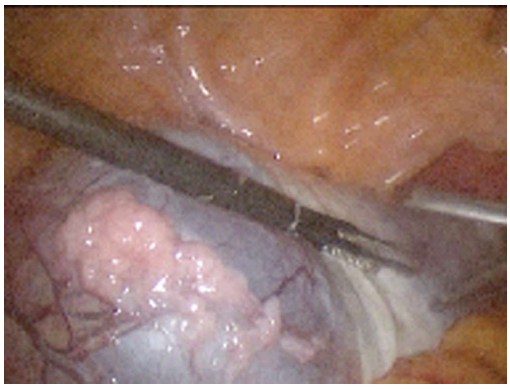

Figure 2 Macroscopic findings in borderline tumour.

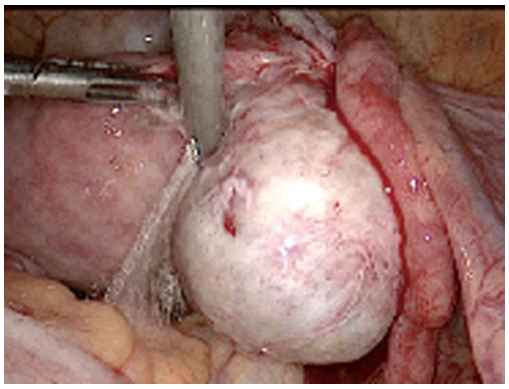

Figure 3 Laparoscopic cystectomy technique.

associated with a higher rate of cyst rupture and incomplete staging, probably due to low experienced surgeons[18,19]. Therefore, a laparoscopic approach for BOTs should always be performed by oncologic surgeons with expertise in extensive laparoscopic procedures in order to obtain both an optimal surgical staging and an optimal prognosis (Figure 3). In each patient affected by a suspicious adnexal mass it is essential to perform a careful and systematic examination of the abdominal cavity in order to detect possible peritoneal invasive implants. Ghezzi *et al*[17] reported a statistically significant difference in the rate of minor postoperative complications, with 6.7% of patients in the laparoscopy group experiencing such an event compared to 42.1% of patients in the laparotomy group. Fanfani *et al*[20] tested the accuracy of narrow band imaging in BOTs in order to increase the sensitivity of laparoscopy in the detection of peritoneal implants. This technology processes the spectral characteristics of the narrow-bind light aiming to enhance visualisation of the subperitoneal vessels. This allows significant improvements in the detection of tumoral implants in the peritoneum, as well as occult lesions, by revealing their characteristic surface staining or vascular pattern. This method has introduced the concept of "optical biopsy", and this principle of precise detection of malignancy has more recently been used in the laparoscopic management of recurrent platinum sensitive ovarian cancer[21] (Figure 4).

Intraoperative rupture is one of the main concerns

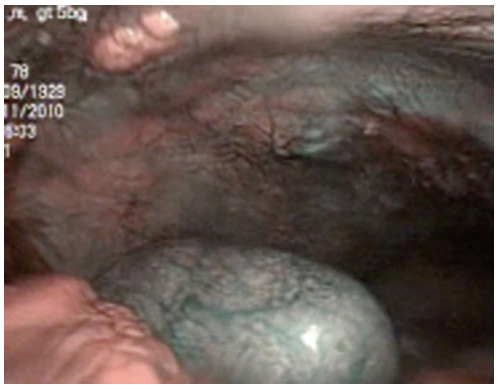

Figure 4 Narrow binding imaging in advanced ovarian cancer.

during the laparoscopic management of adnexal masses. Although the rupture rate is regarded to be higher for laparoscopy than for laparotomy in several studies, it did not affect the recurrence risk of BOTs[22-24]. Moreover, ovarian cyst rupture was not related to the surgical route, but to the implementation of cystectomy instead of adnexectomy[22]. Since the recurrence rate after cystectomy is high, it has been suggested that laparoscopic cystectomy should be considered only in women with one ovary or with bilateral tumours who wish to preserve their childbearing potential[22,23]. Nowadays, there is no evidence that adjuvant treatments improve prognosis or survival, as these tumours have poor response rates to traditional cytotoxic agents[24]. Some studies have shown that treatment with adjuvant platinum-based chemotherapy for invasive serous BOTs improves the prognosis with a relapse rate of less than 22%[25].

Fertility-preserving treatments are often desirable for women of reproductive age who are diagnosed with BOTs. When conservative surgery is indicated, the uterus and at least part of an ovary are preserved. Although data suggest that the rate of recurrence is higher after conservative surgery, this possibility could be offered to those women who wish fertility-sparing surgery due to their personal interests. It should be noted that conservative management should be limited to selected patients with complete resection in the absence of invasive peritoneal implants. Cystectomy should be considered only in bilateral tumours or in patients with one ovary, as oophorectomy has resulted in a lower recurrence rate in the contralateral ovary in comparison to cystectomy. If a relapse in the remaining ovary occurs conservative management may be offered, but this should be reserved for patients without invasive implants who are young (age < 40 years), desire fertility preservation, and engage in long-term follow-up (Figure 5). Cystectomy is not safe in patients undergoing conservative management for mucinous borderline tumours due to an increased risk of recurrence as invasive carcinoma. If the relapse occurs as invasive disease, complete debulking should be performed. If no relapse occurs after childbearing, there is no need to perform restaging surgery as long as the patient accepts a long-term follow up[26-29].

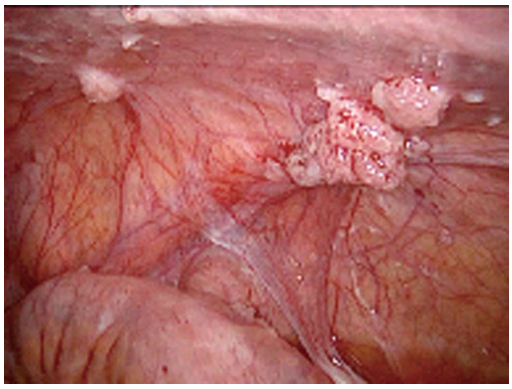

Figure 5 Peritoneal invasive implants in mucinous borderline tumours.

The impact of conservative fertility-sparing surgeries has been compared with more extensive surgical approaches. Yinon *et al*[30] studied the recurrence rate in 40 patients who underwent unilateral salpingo-oophorectomy *vs* 22 patients who were managed conservatively with ovarian cystectomy. Recurrence rates were found to be similar between the two groups (27.5% *vs* 22.7%, respectively, $P = 0.8$). Park *et al*[31] confirmed these results in a group of 360 women with BOT. A radical approach was associated with a similar recurrence rate (5.1%) to conservative management (4.2%), with no differences in disease-free survival rates. Patterns of recurrence also seem to differ between the fertility-sparing and the radical surgery group, where isolated recurrence in the remaining ovary was the most frequent form of relapse in the former and recurrence in the contralateral ovary in the latter. Therefore, a systematic follow-up should be planned in order to detect recurrences and complementary surgery after fulfilling childbearing desires can be agreed with the patient.

EARLY-STAGE OVARIAN CANCER

The extended approach for surgical staging of EOC is usually performed by exploratory laparotomy including hysterectomy and salpingo-oophorectomy, pelvic and paraaortic lymph node dissections, omentectomy, peritoneal washings, and peritoneal biopsies following the recommendations of the International FIGO[32]. Reich published the first report on laparoscopic staging in EOC in the early 1990s[33]. Two decades ago Querleu *et al*[4] published the first report on laparoscopic complete restaging of nine patients with EOC. After these initial reports there has been a progressive improvement in the instrumentation and imaging quality, which has led to more groups considering this approach in selected patients.

The Cochrane Collaboration recently performed a systematic review to evaluate the benefits and risks of laparoscopy compared with laparotomy for the surgical treatment of FIGO stage I ovarian cancer[34]. This meta-analysis did not find any publications that met the inclusion criteria to address this subject. Even with the lack of well-established evidence and the low quality of available survival data, several studies address important issues concerning the role of laparoscopy in this type of tumour. Three different studies[35-37] have analysed the differences in survival rates between patients undergoing laparoscopy *vs* laparotomy for EOC. No statistical difference was observed in survival rates or other oncological parameters. Laparoscopy showed less blood loss and better recovery with a significantly higher operative time, which could be explained by the learning curve in this type of procedure. Other authors[38] found, in short series, that the laparoscopic approach in EOC resulted in significantly worse overall survival in comparison to laparotomy. However, these results are questionable as comprehensive staging was not the purpose of laparoscopy in most of these women. A shorter interval to chemotherapy was demonstrated by Park and colleagues in patients staged by laparoscopy than in patients staged by laparotomy (12.8 ± 4.9 d *vs* 17.6 ± 8.3 d), confirming that a minimally invasive approach does not delay important adjuvant treatment, and may avoid delays due to surgical complications more frequently associated with laparotomy[39].

Laparoscopy also seems to have more advantages when fertility-sparing treatment is indicated in well-differentiated FIGO I a stages in women wishing to conceive. In these cases, laparoscopic staging should include a complete pelvic and paraaortic lymph node dissection, omentectomy, and unilateral salpingo-oophorectomy with preservation of the uterus as well as the contralateral ovary and tube after careful checking for the absence of suspicious areas, and if detected, directed biopsies should be performed. Patients should be advised that several studies have reported an increased recurrence rate with fertility-sparing techniques[40,41]. Therefore, it is advisable to proceed with a strict follow-up and complete restaging, which can be performed also by laparoscopy after delivery. Muzii *et al*[42] reported two pregnancies with term deliveries and two miscarriages out of 27 unexpected ovarian cancer patients who underwent fertility-saving laparoscopy and a follow up of 20 mo.

Port-site metastasis is one of the main concerns among gynaecological oncologists while managing ovarian cancer in either early or advanced stages. The positive CO_2 pressure with changes in peritoneal ambient pressure and the possible facilitation of tumoral cell implantation at the trocar sites due to gas leakage are considered to be the possible mechanisms of this complication. Initial reports showed a very high rate up to 20% in patients with ascites, affected by recurrent or advanced disease or undergoing multiple laparoscopic procedures. More recent series have shown a prevalence of port-site metastasis lower than 2%, which is similar to traditional laparotomy[43,44]. There are several manoeuvres that can be adopted in order to prevent this complication, although none have been clearly demonstrated to be effective in well-designed trials[45,46] (Table 2). The laparoscopic surgeon has to take into account this possible complication in cancer managed by laparoscopy irrespective of the dis-

Table 2 Surgical manoeuvres in order to decrease port-site metastasis in the laparoscopic management of complex adnexal masses

Using wound protectors
Minimizing tumour manipulation
Anchoring ports to prevent dislodgment
Avoiding carbon dioxide leakage and sudden desufflations
Using gasless laparoscopy
Irrigating and suctioning the abdomen, instruments and ports before removal
Using heparin or 0.25%-1% povidone-iodine solution to irrigate wounds and the abdomen
Excising trocar sites and deliberate closure of all abdominal layers including the peritoneum after laparoscopy; or postoperative port-site radiation
Resuming definitive surgery or chemotherapy early
Using 5-fluorouracil, topical taurolidine or intraperitoneal endotoxin

ease stage.

Another concern with the laparoscopic approach is the feared possibility of an increase in the risk of rupture of malignant masses in comparison to laparotomy. However, various studies have shown that this risk is similar to that observed following laparotomy, which ranges from 11.4%-30.3%[47-51]. Vergote *et al*[48] performed a review of a large series of 1545 patients with different stages of ovarian cancer in which reduced progression-free survival was associated with increased cystic rupture. In contrast, Sjövall and colleagues[52] showed that tumour rupture during surgery did not have an impact on survival in 394 patients.

Finally, a recent systematic review of 11 observational studies[53] showed that the laparoscopic approach for EOC had less blood loss with an overall conversion to laparotomy of 3.7%. The overall rate of recurrence in studies with a median follow-up period of 19 mo was 9.9% concluding that the operative outcomes of the laparoscopic approach in patients with EOC was comparable with those of laparotomy.

Taking into consideration the lack of high-grade evidence, the laparoscopic approach in the early stages of ovarian cancer seems safe and effective in terms of oncologic outcomes. In addition, early recovery and initiation of adjuvant therapy may be beneficial for patient outcome, however, oncological manoeuvres adopted during surgery should be similar to those performed during laparotomy.

ADVANCED-STAGE OVARIAN CANCER

The standard treatment of AOC includes upfront surgery with intent to accurately diagnose and stage the disease and to perform maximal cytoreduction, followed by chemotherapy in most cases. Rosenoff *et al*[54] reported the use peritoneoscopy for pretreatment evaluation in ovarian cancer four decades ago. In the early 1990s, pioneers in laparoscopic surgery used minimally invasive techniques to treat gynaecologic cancers, including laparoscopic staging of EOC and primary and secondary cytoreduction in advanced and recurrent disease in selected cases[55,56]. The potential role of minimally invasive surgery in the treatment of AOC is warranted for the following: (1) laparoscopic assessment of the feasibility of upfront surgical cytoreduction by laparotomy in patients with advanced ovarian cancer; (2) laparoscopic debulking of advanced disease; (3) laparoscopic reassessment in patients with complete remission after primary treatment; and (4) laparoscopic assessment and cytoreduction of recurrent disease[55].

Different indications for the laparoscopic approach in advanced ovarian cancer have been described including triage for resectability, second-look assessment, and in select cases, primary or secondary cytoreduction (Figures 6 and 7). Laparoscopy offers multiple advantages over traditional laparotomy including smaller incisions, improved visualization, less blood loss, reduction in the need for analgesics, decreased morbidity and a more rapid recovery. An additional advantage for patients with ovarian cancer requiring adjuvant therapy includes a shorter interval before initiation of adjuvant therapy[56].

Gallotta *et al*[57] reported the outcome of laparoscopic secondary cytoreduction in patients with localized recurrence of ovarian cancer. Twenty-nine patients with localized recurrent ovarian cancer were selected for laparoscopic cytoreduction. A complete debulking was achieved in 96.2% of cases with a median disease-free survival time of 14 mo. The median operating time was 188 min with a median estimated blood loss of 150 mL and a median hospital stay of 4 d. No intraoperative complications occurred and two conversions to laparotomy occurred due to technical difficulties.

Fagotti *et al*[58] retrospectively evaluated ovarian cancer patients with isolated platinum sensitive relapse, defined as the presence of a single nodule in a single anatomic site. In every case the presence of isolated relapse was assessed at preoperative positron emission tomography-computed tomography (PET/CT) scan and confirmed by cytoreductive laparoscopy followed by Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Out of 84 women with platinum sensitive relapse, 10 cases showed isolated relapse and were treated with laparoscopic/robotic cytoreduction and HIPEC. In all cases, a complete debulking was achieved. The median operative time was 122 min (95-140 min), with an estimated blood loss of 50 cm^3 (50-100 cm^3) and a median length of hospital stay of 4 d (3-7 d). The interval from surgery to adjuvant chemotherapy was 21 d (19-32 d). No grade 3/4 surgical, metabolic, or haematologic complications occurred. In all cases, postoperative PET/CT scan was negative and no recurrence was observed after a median time of 10 mo.

More recently, another report[59] evaluated the prognostic impact of routine use of staging laparoscopy (S-LPS) in patients with AOC. All women were submitted to S-LPS before primary debulking surgery (PDS) or neoadjuvant treatment (NACT) and interval debulking surgery (IDS). The surgical and survival outcomes were evaluated in 300 consecutive patients submitted to S-LPS. One hundred forty-eight (49.3%) women were considered suitable for PDS and the remaining 152 (50.7%)

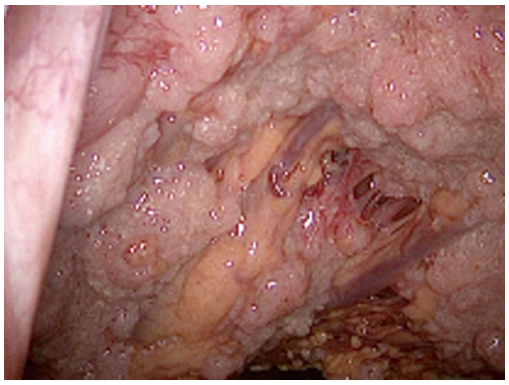

Figure 6 Extensive bowel infiltration in advanced-stage ovarian cancer.

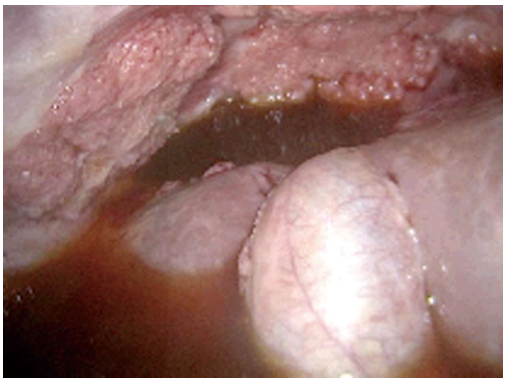

Figure 7 Liver and diaphragmatic infiltration in stage III ovarian cancer.

received NACT. The percentages of complete (residual tumour, RT = 0) and optimal (RT < 1 cm) cytoreduction following PDS and IDS were 62.1% and 57.5%, 22.5% and 27.7%, respectively. The number of post-operative complications in the NACT/IDS group were lower than that in the PDS group with a median disease-free survival interval in women with RT = 0 at PDS of 25 mo (95%CI: 15.1-34.8), which was longer than that in all other patients, irrespective of the type of treatment they received. At multivariate analysis, residual disease and performance status maintained an independent association with PFS (60).

Nezhat *et al*[60] described their preliminary experience with laparoscopic total primary or interval cytoreduction in 32 women with presumed advanced (FIGO stage ⅡC or greater) ovarian, fallopian tube, or primary peritoneal cancers. Seventeen patients underwent total laparoscopic primary or interval cytoreduction, and 88.2% had optimal cytoreduction. Eleven underwent diagnostic laparoscopy and conversion to laparotomy for cytoreduction, and 72.7% had optimal cytoreduction. Four patients had biopsies, limited cytoreduction or both. In the laparoscopy group, 9 patients have no evidence of disease (NED), 6 are alive with disease (AWD), and 2 have died of disease (DOD), with a mean follow-up time of 19.7 mo. In the laparotomy group, 3 patients have NED, 5 are AWD, and 3 have DOD, with a mean follow-up of 25.8 mo. Estimated blood loss and length of hospital stay were less for the laparoscopy group, while operating time and complication rates were not different. Median time to recurrence was 31.7 mo in the laparoscopy group and 21.5 mo in the laparotomy group. The authors concluded that laparoscopy is an effective tool in advanced ovarian cancer in order to predict optimal debulking.

Interestingly, a prospective study[61] reported the accuracy of laparoscopy performed to describe intraabdominal extent of the disease in AOC. One hundred sixty-eight cases were considered eligible for the study. A per-protocol analysis was performed on 120 cases. The worst laparoscopic assessable feature was mesenteric retraction, whereas the remaining variables ranged from 99.2% (peritoneal carcinomatosis) to 90% (bowel infiltration). The accuracy rate was over 80% for both single parameters and overall score. The parameters used to predict the resectability of the tumour by laparoscopy should be chosen according to the experience of the surgical team in order to minimize the rate of suboptimal surgery (Table 2).

There is still controversy in defining the exact role of laparoscopy in advanced disease. Prediction of resectability is one of the most valuable tools in patient management and might facilitate a better selection of patient candidates for neoadjuvant chemotherapy.

CONCLUSION

In conclusion, although limited data has been reported on the use of minimally invasive techniques in ovarian cancer, the clear benefits of this approach must be balanced with the potential hazards in different situations. Laparoscopic staging in borderline tumours and presumed early-stage ovarian cancer should be performed by a trained laparoscopic oncologist and seems to be safe and effective in comparison to laparotomy. Early recovery and reduced intraoperative complications and blood loss leads to a short period before initiation of adjuvant therapy. In addition, fertility-sparing management in well selected patients managed by laparoscopy could have additional benefits in terms of pregnancy rates. There is still insufficient data supporting the role of laparoscopy for advanced ovarian cancer, but the minimally invasive approach permits selection of candidates for primary optimal cytoreduction resulting in a lower rate of suboptimal surgeries.

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REVIEW

Unwanted pregnancies, unwanted births, consequences and unmet needs

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Abstract

Worldwide women have to cope up with heavy burden of unwanted pregnancies, mistimed, unplanned, with risk to their health. Their children and families also suffer. Such pregnancies are root cause of induced abortions (safe/unsafe) and grave consequences. Women, their partners can, for most part, prevent unwanted pregnancies by using contraceptives. However many women either do not use any contraceptive or use methods, with high failure rates. These women account for 82% of pregnancies that are not desired. Remaining unintended pregnancies occur among women who use modern contraceptive, either because they had difficulty using method consistently or because of failure. Helping women, their partner use modern contraceptives effectively is essential in achieving Millennium Development Goals for improving women's health, reducing poverty. If all women in developing countries use modern contraceptives, there would be 22 million less unplanned births, 25 million fewer induced, 15 million fewer unsafe abortions, 90000 less maternal deaths and 390000 less children losing their mothers. Also making abortion services broadly legal, by understanding size, type of unmet needs, most important by creating awareness in communities can surely help tackle this problem to a large extent.

Key words: Contraception; Induced abortion; Pregnancy; Unmet need; Unsafe abortion

Core tip: Unintended pregnancies are the root cause of induced abortions, both safe and unsafe, and their grave consequences all over the world. The high rates of unintended pregnancies all over the world are due to many reasons, including unmet needs of modern contraceptives. This article throws light on issues of unmet needs of contraception, unintended births their consequences and rates of unsafe abortions and their reasons all over the world.

Chhabra S, Kumar N. Unwanted pregnancies, unwanted births, consequences and unmet needs. *World J Obstet Gynecol* 2014; 3(3): 118-123 Available from: URL: http://www.wjgnet.com/2218-6220/full/v3/i3/118.htm DOI: http://dx.doi.org/10.5317/wjog.v3.i3.118

INTRODUCTION

In 2008, two hundred and eight million pregnancies occurred worldwide, out of which 102 million resulted in intended births (49%), 42 in induced abortions (20%) (22 legal and 20 unsafe)[1], 33 (16%) in unintended births and 31 (15%) in miscarriages[2]. Singh[3] reports, around 86 million unintended pregnancies occurring each year with grave consequences, unsafe abortions which lead to disabilities and deaths, stillbirths, neonatal deaths[4,5] affecting families, nations, particularly in low/middle income countries[1,6]. Such pregnancies slow the progress towards socioeconomic development, lead to population growth, difficulties in providing education for all and eradication

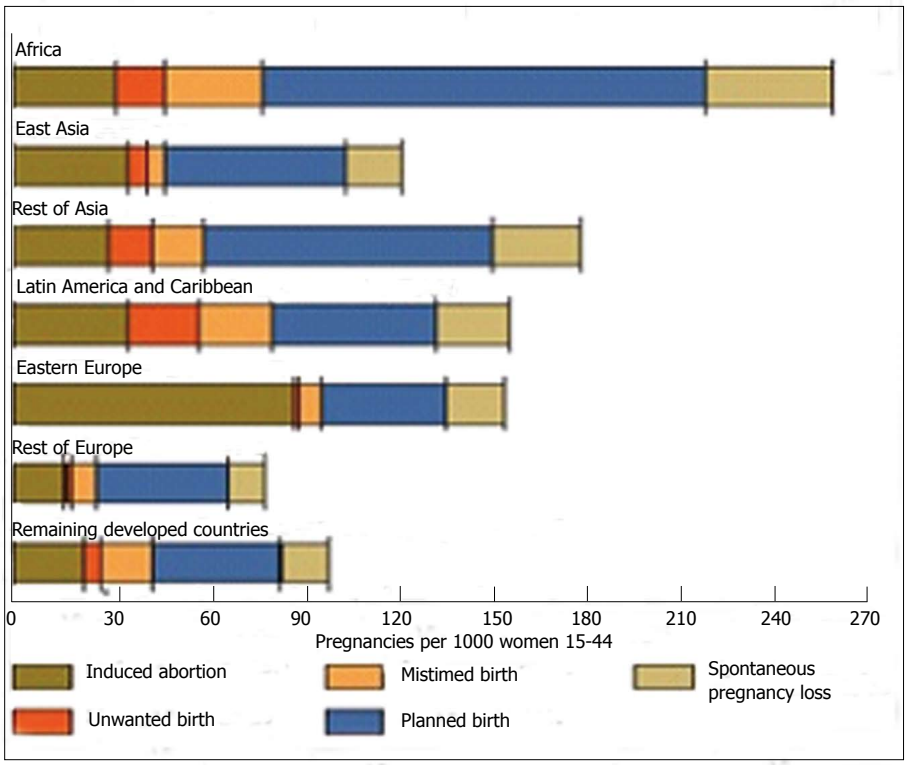

Figure 1 The regional pregnancy levels worldwide.

of extreme poverty and hunger.

GLOBAL STATUS

Of developed countries, the United States has the highest unintended pregnancy rates, including in teens[7]. Worldwide 40% of pregnancies among white women, 67% blacks, 53% Hispanics[8] and 48% among Southeast Asian are unintended[9]. Each year, 2.7 million unintended pregnancies occur in young women in Southeast Asia[9]. Worldwide between 1995-2003, the overall abortion rate dropped from 35 to 29, but remained virtually unchanged at 28, in 2008[1]. Overall, pregnancy rates are higher in developing world than in developed countries[3,10] (Figure 1). In India annually 78% conceptions are unplanned and 25 % unwanted. The abortion rates are strikingly similar for developed and developing countries, however close to half of abortions are unsafe, (98% from developing countries)[11]. Indian Council of Medical Research, reported 13.5 illegal abortions per 1000 pregnancies[12]. Given that abortions taking place at registered facilities are grossly under-reported in India[13-17], figures represent only tip of the iceberg. Many studies reveal 3.4-14.0 induced abortions per 100 live births[14,18]. According to NFHS-3, India has 13.2% unmet need for contraception, 50 % for spacing methods[19].

Worldwide, 60% of women of reproductive age (15-44) live in countries where abortion is broadly legal[20] and remaining 40%, almost entirely in the developing world where abortion is highly restricted[21]. Globally, laws are varied based on grounds for which abortion is permitted, range from no grounds or to save a woman's life, to preserve physical health or mental health or rape or incest, in cases with fetal impairment or even for economic or social reasons, and without restriction. In 32 countries, abortion is not legally permitted on any grounds and in 36 countries, it is permitted when a woman's life is threatened. A further 59 countries allow abortion to save a woman's life, to preserve her physical health, and to protect her mental health. Fourteen countries, including India, permit on all the above and also socioeconomic grounds. A total of 56 countries and territories allow it without restriction[22] (Figure 2). There has been effect of issues like Global Gag, under which agencies receiving USAID funds are prohibited from performing or campaigning for abortion. Contrary to its stated intentions, the global gag rule resulted in more unwanted pregnancies, unsafe abortions, and female deaths[23]. Moreover, some laws seek to protect or otherwise recognize the fetus as human. The American Convention on Human Rights, a treaty signed by 24 Latin American countries states that from the moment of conception, human beings have rights[24].

REASONS FOR SEEKING ABORTION

The reasons cited for choosing abortion are broadly similar globally. Although official records in India show

Figure 2 World abortion map, 2013. Source: www.eorldabortion.com.

Table 1 Contraceptive failure rates and unintended pregnancies, 2007

Contraceptive method	Number of contraceptive users 000 s	Estimated failure rate (typical use) %	Number of women with accidental pregnancies (typical use) 000 s
Female sterilization	232564	0.50	1163
Male sterilization	32078	0.15	48
Injectables	42389	0.30	127
IUD	162680	0.80	1301
Pill	100816	5.00	5041
Male condom	69884	14.00	9784
Vaginal barrier	2291	20.00	458
Periodic abstinence	37806	25.00	9452
Withdrawal	32078	19.00	6095
Total	712586	4.70	3369

Available from[31]. IUD: Intra-uterine device.

contraceptive failure and risk to mother's health as leading reasons[25], reliability of these records, for obvious reasons can be questioned. Where effective contraceptive methods are available and widely used, the rates decline sharply, but nowhere to zero[26].

CONTRACEPTION AND ABORTION

Many women and men either do not have access to appropriate contraceptive methods, or lack adequate information and support to use them effectively. Studies have examined the reasons why some women do not use contraception, though they do not want to become pregnant, referred to as unmet need for family planning[27-29]. Study by Alan Guttmacher Institute[30] reveals that 54% women who had abortion had used contraception during the month they became pregnant, however 76% pill users, 49% condom users reported having used methods improperly, 13% pill users, 14% condom users reported correct use, 46% of women had not used any contraceptive during the months they became pregnant. Of these, 33% had perceived themselves to be at low risk for pregnancy, 32% had concerns about methods, 26% had unexpected sex and 1% had been forced to have sex. Trussell and United Nations Population Division have also reported contraceptive failure rates with estimated unintended pregnancies (Table 1)[31].

Studies reveal that unwanted pregnancies and induced abortions due to contraceptive failure were 48% and 54% in United States[32] and 65% unwanted pregnancies in France respectively[33]. Proportions are more in countries with higher levels of contraceptive use.

COMPLICATIONS OF UNSAFE ABORTIONS AND CARE

About one third of women who undergo abortion, experience serious complications, but less than half receive appropriate medical care. Currently, about 8.5 million women globally suffer from complications of unsafe abortions annually and 3 million remain without treatment[3]. World Health Organization[21] reports that 47000 women died worldwide in 2008 and around 13% pregnancy related deaths were due to unsafe abortions[34]. Annually in Asia, 12% maternal deaths are due to unsafe abortions[21]. Mortality represents only a fraction of abortion related complications, as many more experience life threatening and other morbidities[35,36]. An estimated 7.4 million disability-adjusted life years are lost annually as a result of unsafe abortion[6]. Each year 1.6 million women have secondary infertility and 3-5 million suffer from chron-

Table 2 Demographic and health survey 2000-2009 for unmet need and demand for family planning

Region/Country	Unmet need for spacing A	Unmet need for limiting B	Unmet need Total C = (A + B)	Met need (CPR) D	Total demand for family planning E = (C + D)	Percentage of demand satisfied F = (D/E)
East Asia and Pacific	6	8	14	57	71	79
Europe and Central Asia	4	9	13	60	73	83
Latin America and Caribbean	7	10	17	63	80	77
Middle East and North Africa	4	7	11	57	68	84
South Asia	8	12	20	47	67	70
Sub-Saharan Africa	17	9	26	25	51	45

Available from[28]. CRP: Contraceptive prevalence rate.

ic reproductive tract infections. Rarely bowel injuries can also occur. Agarwal *et al*[37] has reported an unusual case of bowel injury 52 d after induced abortion.

Though most of morbidity and mortality are preventable, yet millions of women suffer due to unavailability of treatment in health care system. So the concept of Post Abortion Care has become visible, a global approach for prevention. The essential elements include: emergency treatment of potentially life-threatening complications, contraceptive counseling services and linkage to other emergency services[38].

UNMET NEEDS

Unmet needs are global, which look at issues related to the family planning needs of reproductive population in a quantifiable mode for prevention of pregnancy or birth or consequences, in currently married women who do not want any more children or who want to postpone their next birth, but are not using any form of family planning[28]. Conventional estimates of unmet need include only married women, but sexually active unmarried, especially teenagers, those with postpartum amenorrhea, using a less effective contraceptive method or using an effective method incorrectly, or dissatisfied, or with contraindications to its use, with unwanted births without access to safe and affordable abortion services; and those with related reproductive health problems, also need to be included.

A recent study revealed that in 2010 worldwide, 146 million (130-166 million) women aged 15-49 years who were married or in a union had an unmet need for family planning. The absolute number is projected to grow from 900 million (876-922 million) in 2010 to 962 million (927-992 million) in 2015, and will increase in most developing countries[39]. The uptake of modern contraceptive methods worldwide has slowed in recent years, from an increase of 0.6% points per year in 1990-1999 to an increase of only 0.1% points per year in 2000-2009. In Africa, the annual increase in modern contraceptive use fell from 0.8% points in 1990-1999 to 0.2% points in 2000-2009[40]. Demographic Health survey (2000-2009) has revealed unmet need, met need and total demand for family planning (Table 2).

CAUSES

The causes of unmet needs are complex. Surveys and other indepth research from 1990s[41,42] reveal a range of obstacles and constraints that can undermine a woman's ability to act on her childbearing preferences. In the developing world, her reasons for not using contraceptives most commonly include concerns about possible side-effects, the belief that they are not at risk of getting pregnant, poor access to family planning, their partner's opposition to contraception or their own opposition because of religious or personal reasons. Other less common reasons are lack of knowledge about contraceptive methods or health concerns. Thirteen surveys completed in 1999 and 2000 by DHS revealed similar findings[43].

WOMEN'S EDUCATION

Education is an important determinant of unmet need for contraception. Both husband's and wife's education affect unmet need for spacing. As per a study in Ethopia[44] about one in five women (18.9% in 2000 and, 20.5% in 2005) with no education had unmet need for spacing, while 11.6% in 2000 and 14.8% in 2005 had unmet need for limiting. Unmet need progressively declined with higher levels of women's education.

RELIGION, CONTRACEPTION AND ABORTION

Religion has a strong influence on sexuality and abortion practices. A study revealed that most Buddists believe that conception occurs when the egg is fertilized, emergency contraception could prevent a fertilized egg from implantation. It therefore is against religion as they see abortion as an act of killing[45]. Catholics believe in using natural methods of contraception rather than modern and are strictly against abortion. According to them "Human life must be respected and protected absolutely from the moment of conception….. Abortion is gravely contrary to the moral law…."[46]. In Hinduism contraception and abortion are not strictly prohibited, there are varying views. In Islam all forms of contraception are acceptable in special circumstances and abortion is permitted if mother's life is at risk. Jewish law prohibits use of contraceptives in males, but there is no mention of females. In Sikhism there are no hard and fast rules for use of contraceptives and abortion. They can have it as and when required.

THE WAY FORWARD

In each country, broader education and communication programs can help address social, cultural barriers and misconceptions. From a policy perspective, reducing unmet need is important for achieving both demographic goals and enhancing individual rights.

It is essential for nations to adopt a continuum of care, access to family planning, emergency contraception, and other reproductive-health services. It is essential to know why women choose abortion and how to reduce morbidity and mortality. Making abortion legal is an essential prerequisite in making it safe. Under the current scenario of high mortality and morbidity, medical means offer great potential for improving access and safety as it does not require extensive infrastructure and is non-invasive.

Not only treatment of complications of unsafe abortion should be extended throughout the health care system, family planning advice and assistance should be offered after treatment of complications; designed with women's preferences in mind. Those wanting to prevent or postpone conception, using an ineffective method, those using an effective method incorrectly and those using an unsafe or unsuitable method[13,47]. Reducing unmet need is an effective way to prevent unintended pregnancies, abortions and births.

A key argument is that meeting unmet needs, saves lives, but to what extent does society value women's lives?

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MINIREVIEWS

Retained placenta: Do we have any option?

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Abstract

Retained placenta is a known cause of post-partum haemorrhage and maternal mortality. A recent systemic review has confirmed that the incidence of retained placenta had increased all over the world, which is more common in developed countries. Failure of retroplacental myometrium contraction is the main cause of retained placenta. Maternal age greater than 35 years, grandmultipara, preterm labor, history of previous retained placenta, and caesarean section were the risk factors for retained placenta. Manual removal of the placenta has been the treatment of choice. Attempts had been made by clinician and researchers to find a safe, effective and reliable method to avoid the need for surgical intervention. The efficacy and safety of prostaglandin, nitroglycerin or acupuncture in the management of retained placenta are yet to be further evaluated. Nonetheless, till date only intra-umbilical vein oxytocin has been studied extensively but with varied success. More randomized clinical trials are needed to address this issue. However, if immediate manual placenta removal service is unavailable, a trial of intra-umbilical vein oxytocin 100 IU at a total volume of at least 40 mL while preparing for transfer to a tertiary center or theatre may result in spontaneous expulsion of the placenta.

Key words: Retained placenta; Manual removal of the placenta; Intra-umbilical vein; Oxytocin; Prostaglandin; Misoprostol; Carboprost; Acupuncture

Core tip: Retained placenta is a known cause of post-partum haemorrhage and maternal mortality. The incidence of retained placenta had increased all over the world, which is more common in developed countries. Manual removal of the placenta has been the treatment of choice. However, it is a surgical intervention requiring anaesthesia with potential risk and complication. This manuscript reviews various methods that had been reported in the management of retained placenta.

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INCIDENCE OF RETAINED PLACENTA

Retained placenta (RP) is a known cause of post-partum haemorrhage (PPH) and maternal mortality. Although this is such an important event, it is often under-reported as the after-event consequences are much more focused and attract a more appealing report. In veterinary reports RP appears more in the dairy farms where cows are reported with this problem[1]. However, RP in women varies between regions of the world and also according to

how it is defined. The reported data may not truly give the exact number of events especially from those countries with lower resources and also as a result of its retrospective reporting. All types of previous uterine surgeries had been shown in early days to increase the incidence rate of RP. In fact it was three times higher with induced labour[2]. Although it was reported that RP was significantly higher in United Kingdom compared to Uganda[3], it is unclear whether or not this is a result of under-reporting. A recent systemic review[4] has confirmed that the incidence of RP had increased all over the world, which is more common in developed countries. In India, Chhabra[5] reported that RP occurred in 0.008% of childbearing women. Titiz *et al*[6] reported an incidence of 3.0% in Australia while Belachew *et al*[7] reported an incidence of 2.1% in Sweden. The median rate of RP at 30 min (2.67% *vs* 1.46%, $P < 0.02$) and median manual removal rate (2.24% *vs* 0.45%, $P < 0.001$) were found to be higher in developed countries. It was also found that the overall rate of manual removal in the United Kingdom has risen (mean of 0.66% in 1920s *vs* 2.34% in 1980s, $P < 0.0001$).

DEFINITION

To date, there is no consensus as to the duration of the third stage of labour, *i.e.*, when placenta should be delivered. Traditionally, interventions are advised if the placenta remains undelivered between 20 to 60 min at the third stage[8]. Studies[9,10] showed that the risk of PPH increased after 30 min elapsed of the third stage of labour, although any delay in active intervention would increase the chance of spontaneous placenta delivery. Hence, the placenta being labeled as "retained" largely depends on balance between the risk of PPH and likelihood of spontaneous placenta delivery. Availability of local facilities such as operating theater, blood bank, and trained medical personnel should be taken into consideration. Hence, National Institue for Health and Clinical Excellence guidelines suggested 30 min, while WHO recommended 60 min elapsed of the third stage to be defined as RP[11].

PATHOPHYSIOLOGY

Back in 1933, Brandt[12] had described the physiology of uterine contraction for placenta detachment from decidual bed in the third stage of labour. He divided the third stage into four phases: latent, contraction, detachment and expulsion phase. The latent phase is immediately after delivery of fetus, where all parts of the myometrium contract except the myometrium behind the placenta that remains relaxed. The retro-placental myometrium contracts during contraction phase, leading to placental detachment. Further contractions of the myometrium expel the placenta from the uterus.

Failure of retro-placental myometrium contraction is the main cause of RP. An observational study also revealed that retro-placental myometrium contraction in dysfunctional labour was lesser than in normal labour[13]. Hence, it is likely that retro-placental contractility fails to occur throughout the process of labour as RP and dysfunctional labour were found to be closely related[9]. A recent study using ultrasonography had confirmed this theory and further improved the understanding of normal and abnormal third stage of labour[14].

RISK FACTORS

Maternal age greater than 35 years and grandmultipara are associated with a seven-fold increase in risk of RP[15]. Fibrous tissue in the uterus of grandmultipara women results in a reduction of contractility power, which is more pronounced in women at an advanced maternal age. Increased abnormality of placenta implantation in grandmultipara also plays a major factor in the pathogenesis of RP.

A history of previous RP increases 2.4-fold the risk of recurrence in subsequent pregnancy[16]. This risk can be as high as 29-fold as demonstrated by another study conducted in Saudi Arabia[2], while a recent study also showed an OR of 12.6 to have recurrent RP[17]. Uterine surgeries such as Caesarean section (OR = 12) and dilatation curettage (OR = 4.4) are significantly associated with RP[18]. These procedures inadvertently cause injury to the endometrium, thus facilitating abnormal placenta implantation and further leading to morbidly adherent placenta.

RP is found strongly in association with preterm labour, particularly less than 27 wk of gestational age with a relative risk of 6 to 13[9,19]. It is believed that risk factors such as infarction or fibrinoid degeneration of decidual arterioles that frequently cause preterm labour lead to abnormal adherence of the placenta[20].

Uterine abnormalities are also associated with a certain degree of RP. Golan *et al*[21] found incomplete uterine septum at hysteroscopic examination in 15% of women who underwent manual removal of the placenta (MRP). Other documented risk factors include induction of labour (3-fold rise) and analgesia such as pethidine (3.5-fold rise)[2].

VARIOUS TREATMENT MODALITIES

Surgical intervention

Traditionally MRP is the treatment of choice for RP. MRP requires insertion of the operator's hand into the uterus through the vagina[22]. The operator's hand follows the umbilical cord to identify the interface between the uterus and maternal surface of the placenta. Dissection of the uterine-myometrium plane is achieved by using fingers in a side-to-side motion. The other hand should be placed at the uterine fundus over the abdomen to minimise risk of uterine perforation[23].

Regional anaesthesia such as spinal anaesthesia is recommended for MRP if epidural anaesthesia is not in place earlier during labour. Use of regional anaesthesia is preferred in obstetric cases to avoid the risk of general anaesthesia such as failed intubation and Mendelsons Syndrome from gastric content aspiration[24]. In the presence of rapid blood loss or haemodynamic instability, general

Table 1 Comparison of various trials[33].

Study	Number of patients	Oxytocin dose (IU)	Total volume infused (mL)	Manual removal of placenta rate (%)
Makkonen *et al*[31]	109	50	20	72.1
Frappell *et al*[40]	41	10	20	63.0
Weeks *et al*[23]	577	50	30	61.3
Selinger *et al*[36]	30	10	20	60.0
Caroli *et al*[37]	286	20	40	58.2
Gazvani *et al*[38]	81	20	20	53.8
Kristiansen *et al*[34]	51	10	10	52.6
Sivalingam *et al*[35]	35	30	30	47.0
Huber *et al*[39]	200	10	20	38.0
Wilken-Jensen *et al*[32]	37	100	30	27.8
Lim *et al*[33]	61	100	40	30.0

anaesthesia is required[25]. The availability of anaesthetist during the procedure would facilitate the performance of further interventions in the occurrence of complications associated with MRP such as haemorrhage, uterine perforation and occasionally morbidly adherent placenta.

An aseptic technique is essential to minimize the risk of haemorrhage and endometritis[23]. The time elapse "accepted" by many obstetricians to removal of the placenta varies between 30-60 min in the absence of haemorrhage[26]. As MRP is also associated with endometritis, the use of prophylactic broad-spectrum antibiotics is recommended[27]. Administration of glyceryl trinitrate (intravenous or sublingual) to relax the uterus in the presence of a tightly closed cervix and avoidance of using sharp curette reduce the risk of uterine perforation[28,29].

Pharmacological interventions

Intra-umbilical vein oxytocin injection: The use of oxytocin in the management of the third stage and RP had been reported in various studies. It is based on the finding of failure of retro-placental contraction, which resulted in RP. However, intra-umbilical vein oxytocin injection in the management of RP had been shown to have various degrees of success mainly due to different techniques, doses of oxytocin, volumes of fluid and timings of injection.

According to the injection method proposed by Pipingas *et al*[30], using size-10 infant feeding tube directly into the umbilical vein 5 cm before the insertion of cord into the placenta, delivery of oxytocin into the retro-placental myometrium has improved.

The dosage of oxytocin used ranges from 10 IU to 100 IU with a greater chance of success found at a higher dosage (Table 1). As reported by Makkonen *et al*[31], there was no significant change in the MRP rate when 50 IU oxytocin was used. This is consistent with a larger double-blind, randomized controlled trial (Release Study) using 50 IU oxytocin, which demonstrates no statistical difference in the MRP rate between oxytocin and placebo groups[3]. Nonetheless, two studies by Wilken-Jensen *et al*[32] and Lim *et al*[33] had achieved the lowest rate of MRP (< 30%) by advocating dosage 100 IU of oxytocin.

The total volume of fluid being injected into the umbilical vein also differs between trials[34-36]. Most of the studies used 10 to 30 mL except two studies by Caroli *et al*[37] and Lim *et al*[33] which used 40 mL. The reported MRP rate by Caroli *et al*[37] was higher than that by Lim *et al*[33] (58.2% *vs* 30.0%), but the disparity may be due to difference in the dosage of oxytocin used (20 IU *vs* 100 IU).

The interval from oxytocin administration to decision for MRP varies from 15 to 45 min or depending on clinical judgment of the obstetrician[31,34-40]. There is always a concern of the increasing risk of PPH with increment of this interval, especially more than 30 min, which had been shown in several studies[9,10].

A Cochrane review including 15 trials with 1704 women that compared the use of intra-umbilical vein oxytocin injection with saline solution had shown a reduction in MRP rate although there was no statistical difference (OR = 0.9). The authors concluded that the use of oxytocin *via* umbilical vein injection is simple and inexpensive but further research is required to ascertain the optimal timing for MRP[41].

Prostaglandin: Prostaglandin is an effective uterotonic agent and has a role in the management of PPH. It has a combination of pharmacodynamic properties with myometrial stimulation, vasoactive mechanism and reduction in platelet function. The use of prostaglandin in management of RP is based on the mechanism that retro-placental myometrium contracts during the contraction phase and leads to placental detachment[14].

The study to evaluate the efficacy of prostaglandin is limited. Prostaglandin resulted in a statistically significant reduction in MRP when compared with oxytocin (RR = 0.43; 95%CI: 0.25-0.75), with a shorter time interval from drug administration to delivery of the placenta (mean difference -6.00; 95%CI: -8.78--3.22)[39]. However, the meta-analysis only analysed two small trials[41], thus intra-umbilical vein injection of prostaglandin needs further evaluation.

Misoprostol: Van Stralen *et al*[42] review the usage of sublingual misoprostol 800 μg among 95 patients with RP in a low resource setting. The trial failed to show any benefit of using misoprostol in the management of RP. MRP was required in 40% of the treatment group patients compared to 33% in the placebo group.

Carboprost: Carboprost tromethamine, a methylated analogue of PGF2-α, is a uterotonic agent which is more potent and has a longer duration of action.

Lately, the use of carboprost has been extended for RP. According to Habek, intra-umbilical vein injection of 0.5 mg carboprost suspended in 20 mL of 0.9% saline yielded the highest therapeutic success rate of 85.7% as compared to two other groups of oxytocin (76.9%) and methylergometrine (64.2%)[43].

Nitroglycerine: Studies with regards to the use of nitroglycerine (NTG) in management of RP has been described and reported in several clinical trials using dif-

ferent dosages, routes of administration, alone or in combination with other agents. Various degrees of success were reported. However, most were observational studies with a small number of patients.

Chedraui and Insuasti[44] in 2003 reported successful deliveries of all RPs in 30 patients, which was in contrary to a 15% success rate in a study by Visalyaputra *et al*[45]. They were given intravenous NTG 50 μg, which was increased by 50 μg every 2 min until a maximum dose of 200 μg[44]. There were five patients who complained of short-duration headaches but no other significant clinical adverse events. The mean duration to achieve delivery of the placenta was 5.3 ± 1.1 min.

Bullarbo *et al*[46] in a small study of 24 patients demonstrated a success rate of 100% by administering subcutaneous NTG 1 mg after intravenous oxytocin compared to only 8.3% in the placebo group. Similarly, Ekerhovd *et al*[47] successfully delivered 21 out of total 24 RPs without significant side effects.

This is consistent with a Cochrane review[48], which then concluded that subcutaneous NTG appeared to be effective and safe but its routine use is not yet recommended due to small sample size.

Acupuncture

The use of acupuncture in the management of RP involves stimulation of certain acupoints to promote uterine contractions. Chauhan *et al*[49] in their retrospective review of 45 patients who required MRP found that 30 of them had acupuncture to expel the placenta. Twenty-five out of 30 patients who had acupuncture delivered the placenta within 20 min. Four of the remainder required MRP for placenta accreta. There were significantly fewer patients in the acupuncture group experiencing PPH (13% *vs* 47%).

UNDIAGNOSED MORBIDLY ADHERENT PLACENTA

Morbidly adherent placenta implies abnormal invasion of the placenta tissue into the inner or outer myometrium or through the serosa of the uterus (termed accrete, increta or percreta, respectively)[50]. It could be one of the reasons for RP, which is also associated with significant maternal morbidity and mortality. Over the last decades, there has been a steady rise in the incidence of morbidly adherent placenta as reflected by the rising number of caesarean deliveries. It is estimated the incidence of morbidly adherent placenta to be 1.7 per 10000 women[50]. In most cases, there were always established risk factors whereby at least one risk factor was identified in 94% of cases[51]. The risk of having morbidly adherent placenta increased in women with previous caesarean scar, previous uterine surgeries, *in vitro* fertilization pregnancy and placenta praevia[52]. Advanced maternal age, even without any previous caesarean delivery, has been found to be associated with morbidly adherent placenta[50].

A high index of clinical suspicion should be exercised in women who are at risk. The use of ultrasonography with Doppler studies and magnetic resonance imaging (MRI) may be of use in reaching the diagnosis antenatally, thus assisting in the delivery care[53]. Till date, there is difficulty in identifying cases of morbidly adherent placenta in those without any risk factor. In such cases, diagnosis is only made after unsuccessful removal of the placenta at delivery.

Traditionally, hysterectomy has been advocated for such cases. However, it is associated with various morbidities such as PPH, massive blood transfusion, intensive care unit admission, ureteric/bladder injury, infection and prolonged hospitalisation. Alternatively other conservative strategies have been implemented to minimise these complications and preserve fertility. Uterine devascularisation *via* embolisation, uterine compression sutures, uterine tamponade and administration of methotrexate during the post-partum period have all been used to manage morbidly adherent placenta conservatively[54]. However, these conservative approaches are very much dependent on the amount of bleeding, haemodynamic status, surgical expertise, facilities available and the desire for fertility preservation.

CONCLUSION

MRP remains the mainstay of treatment for RP. Clinicians and researchers had been trying hard to find a safe, effective, simple and reliable method to manage RP without the need for surgical intervention. The efficacy and safety of prostaglandin, NTG or acupuncture in the management of RP are yet to be further evaluated. Till date, only intra-umbilical vein oxytocin has been studied extensively but with varied success. More randomized clinical trials are needed to address this issue. However, if immediate MRP service is unavailable, a trial of intra-umbilical vein oxytocin 100 IU at a total volume of at least 40 mL while preparing for transfer to a tertiary center or theatre may result in spontaneous expulsion of the placenta.

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CLINICAL TRIALS STUDY

Utility of a hemoglobin A1C obtained at the first prenatal visit

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Abstract

AIM: To evaluate the utility of the hemoglobin A1C (HbA1C) at the first prenatal visit as a triaging tool in patients at high risk for gestational diabetes (GDM).

METHODS: The HbA1C was obtained at the first prenatal visit prior to 20 wk. Women with a HbA1C ⩾ 6.5% (group one) were instructed on diet and daily self-monitoring of blood glucose. Women with a HbA1C between 5.7%-6.4% (group two) were offered testing or daily self-monitoring of blood glucose. Women with a HbA1C < 5.7% (group three) were tested at 24-28 wk. Patients were tested for GDM using the two step testing and Carpenter and Coustan values as cutoffs. Medication was started if patients failed to meet glycemic goals of fasting ⩽ 95 mg/dL (5.3 mmol/L) and 2 h postprandial ⩽ 120 mg/dL (6.7 mmol/L).

RESULTS: In group one (n = 16), 15/16 (95%) required medication to achieve euglycemia. The mean gestational age at which medication was required was early at 14 ± 6 wk. Postpartum, 14/16 patients (87%) remained diabetic. Group two contained 82 patients. Sixty-sixpatients (80%) were given a diagnosis of GDM and 52 patients (64%) required medication. The mean gestational age at which medication was started in group two was 20 ± 7.8 wk. There were 205 patients in group three, 18 patients (8.7%) were diagnosed with GDM and 13 patients (6%) required medication. In comparison to group three, patients in group one were 220 times more likely to require medication (95%CI: 26.9- > 999, P < 0.0001). Patients in group two were 26 times more likely to require medication (95%CI: 12.5-54.3, P < 0.0001).

CONCLUSION: A HbA1C obtained at the first prenatal visit can be used to triage patients based on the level of glucose intolerance found.

Key words: Gestational diabetes; Pregnancy; Hemoglobin A1C; Glycosylated hemoglobin

Core tip: Hemoglobin A1C (HbA1C) has been endorsed by the World Health Organization for use in diagnosing diabetes and also for identifying degrees of glucose intolerance. This has not been validated in pregnancy. This study looks at a cohort of patients who received a HbA1C at the begining of pregnancy to see if the HbA1C can be used as a triaging tool for identifying patients with undiagnosed diabetes and for identifying a degree of glucose intolerance that would benefit from early intervention. HbA1C ⩾ 6.5% is consistent with preexisting diabetes. HbA1C between 5.7% and 6.4% demonstrates a level of glucose intolerance associated with risk of Gestational Diabetes which may benefit from early intervention.

Moore LE, Clokey D. Utility of a hemoglobin A1C obtained at the first prenatal visit. *World J Obstet Gynecol* 2014; 3(3): 130-133 Available from: URL: http://www.wjgnet.com/2218-6220/full/v3/i3/130.htm DOI: http://dx.doi.org/10.5317/wjog.v3.i3.130

INTRODUCTION

Gestational diabetes (GDM) is carbohydrate intolerance with onset or first recognition during pregnancy. A major limitation of this definition is the inclusion of women with undiagnosed preexisting diabetes who are at risk for complications different from women with diabetes occurring only during pregnancy.

Treatment of gestational diabetes is geared towards reducing glucose concentrations in order to reduce the risks to mothers and infants. The Hyperglycemia and Pregnancy Outcome (HAPO) study demonstrated that maternal hyperglycemia at levels lower than those diagnostic of diabetes were associated with increased birth weight and cord-blood serum C-peptide levels[1]. Other studies have shown that the offspring of diabetic mothers may be programmed to develop obesity and type 2 diabetes by the intrauterine environment[2,3].

Measurement of Hemoglobin A1C (HbA1C) has been endorsed by the American Diabetes Association (ADA) as a diagnostic and screening tool for diabetes but not for GDM[4]. The World Health Organization (WHO) has concluded that HbA1C can be used as a diagnostic test for diabetes if standardized assays are used[5].

Advantages of HbA1C are that it does not require fasting and is less prone to day to day variations. Disadvantages are possible racial differences and interference by anemia, hemoglobinopathies, and some medications. HbA1C reflects the average glucose over 2 to 3 mo.

The ADA and WHO recommend using HbA1C $\geqslant$ 6.5% as a cut point for the diagnosis of diabetes. Using the ADA guidelines, patients with HbA1C between 5.7%-6.4% are at an increased risk for diabetes and microvascular complications and are designated as having impaired glucose tolerance[4]. The WHO expert group made no formal recommendations on the interpretation of HbA1C levels below 6.5%[5]. However, as the HbA1C rises, the risk of diabetes increases disproportionately in a curvilinear fashion.

It is not known whether HbA1C between 5.7% and 6.4% confers an increased risk of GDM as it does for type 2 diabetes. The use of HbA1C $\geqslant$ 6.5% for the diagnosis of diabetes has not been validated during pregnancy.

We sought to determine if a HbA1C at the first prenatal visit, in women at high risk for GDM, was useful in identifying women with undiagnosed diabetes or impaired glucose tolerance who may benefit from early testing and intervention for gestational diabetes.

MATERIALS AND METHODS

All patients received a HbA1C as part of routine prenatal labs at the first prenatal visit. Patients with a HbA1C $\geqslant$ 6.5% were counseled on diet, exercise and daily self-monitoring of blood glucose and were referred to the diabetes in pregnancy clinic. Patients with HbA1C between 5.7%-6.4% were given the choice of immediate testing for GDM or to begin daily self-monitoring of blood glucose. Additionally, they were counseled on diet and exercise and tested for GDM at 24-28 wk if necessary. Patients with a HbA1C < 5.7% were tested for gestational diabetes at 24-28 wk. Testing for GDM was performed using the standard two step testing and Carpenter and Coustan values were used as cutoffs. Patients with GDM performed self-monitoring of blood glucose four times a day: fasting and two hours after each meal. Glycemic goals were fasting $\leqslant$ 95mg/dL (5.3 mmol/L) and two hour postprandials $\leqslant$ 120 mg/dL (6.7 mmol/L). Medication was started if 20% of values over a two week period exceeded these goals. Medications used included insulin and oral antidiabetic agents. All patients with the first prenatal visit prior to 20 wk were eligible for inclusion. Determination of HbA1C values was done using the TOSOH G8 AutoHPLC (High Performance Liquid Chromatograph). This method is approved by the National Glycohemoglobin Standardization Program (NGSP) and is not affected by the presence of hemoglobinopathies or anemia. This method is subject to interference from the presence of haemoglobin E (HbE). HbE is a hemoglobin variant most common in persons of Thai, Cambodian, Vietnamese or Laotian descent. The enrollment period was from October 2011 to March 2012. Patients with known diabetes were excluded. Data was collected by chart review after delivery. This study was approved by the Institutional Review Board at the University of New Mexico as a retrospective cohort study.

Statistical analysis

Statistical analysis was performed using the SAS package version 9.3. Sample size was chosen assuming that the incidence of GDM in patients with HbA1C $\geqslant$ 5.7 was 15%. In patients with HbA1C < 5.7% the incidence of GDM was assumed to be 5%. A 2:1 ratio of patients with HbA1C < 5.7% to patients with HbA1C $\geqslant$ 5.7% was used to compensate for the comparatively low incidence of GDM in the former group. Desired enrollment numbers were 98 patients with HbA1C $\geqslant$ 5.7 % and 196 patients with HbA1C < 5.7%. The study was powered to have an 80% probability of detecting a difference in the incidence of GDM between patients with HbA1C < 5.7% compared to patients with HbA1C $\geqslant$ 5.7% at a significance level of 0.05. Logistic Regression was used to calculate odds ratios and ANOVA was used to determine the effect of group on the use of medication and the week medication was started.

RESULTS

Three-hundred-three patients had sufficient data for analysis. This included 98 patients with HbA1C $\geqslant$ 5.7% and 205 patients with HbA1C < 5.7% Ethnicity was determined by patient self-reporting; 78% were Hispanic of Mexican descent, 15% Caucasian, 3% Native American, 1% Asian, 1% African American and 0.68% other. Patient demographics including age, parity, BMI and ethnicity are shown in Table 1.

Patients were assigned to groups based on HbA1C.

Table 1 Patient demographics

	A1C ⩾ 6.5% (*n* = 16)	A1C = 5.7%-6.4% (*n* = 82)	A1C < 5 .7% (*n* = 205)
Age	32 ± 6.6 yr	28 ± 4.7 yr	25 ± 4.4 yr
Parity	2.9 ± 1.7	1.7±1.1	0.86 ±. 0.78
BMI	37.3 ± 6.9	32.1 ± 7.7	28.8 ± 6.1
Ethnicity	Hispanic = 14	Hispanic = 61	Hispanic = 162
	Caucasian = 0	Caucasian = 8	Caucasian = 38
	Native Am. = 2	Native Am. = 6	Native Am. = 2
	African Am. = 0	African Am. = 4	African Am. = 0
	Asian = 0	Asian = 3	Asian = 1
	Other = 0	Other = 0	Other = 2

All values are ± SD.

Table 2 Diagnosis of gestational diabetes and medication use by group

	GDM diagnosis *n*%	Required meds *n*%[1] %[2]	Mean gestation at initiation of medication
Group 1[3] (*n* = 16)	16 (100)	15 (95) (95)	14 ± 6 wk
Group 2[4] (*n* = 82)	66 (80)	52 (64) (80)	20 ± 7.8 wk
Group 3[5] (*n* = 205)	18 (8.7)	13 (6) (72)	31 ± 4.3 wk

[3]HbA1C ⩾ 6.5%; [4]HbA1C: 5.7%-6.4%; [5]HbA1C < 5.7%; [1]Percentage of the group that required medication; [2]Percentage of patients in the group with a diagnosis of gestational diabetes (GDM) that required medication. HbA1C: Hemoglobin A1C.

Group one (n = 16) had a HbA1C ⩾ 6.5%. Group two (n = 82) had a HbA1C between 5.7% and 6.4%. Group three (n = 205) had a HbA1C < 5.7%.

We identified 16/303 patients (5.4%) who met criteria for overt diabetes diagnosed during pregnancy. Ninety-five percent or 15/16 patients with a HbA1C ⩾ 6.5% (group one) required medication to achieve euglycemia during pregnancy. Postpartum, 14/16 patients in group one (87%) were diagnosed with type 2 diabetes based on a 75 g two hour challenge test.

Fifty-one patients in group two were diagnosed based on testing. An additional 15 patients in group two were given the diagnosis of GDM because daily self-monitoring of glucose demonstrated a need for medication to achieve glycemic goals.

All patients in group one, 66 patients (80%) in group two, and 18 patients (8.7%) in group three were given a diagnosis of GDM. To achieve glycemic goals, 94% of patients in group one, 64% of the patients in group two and 6% of the patients in group three required medication. Within each group, of the patients who required medication, the mean gestational age at which medication was started was 14 ± 6.0 wk in group one (range 6-28 wk), 20 ± 7.8 wk in group two (range 8-35 wk) and 31 ± 4.3 wk in group three (range 19-36 wk) as shown in Table 2.

Based on group alone, the odds of requiring medication to control blood glucose in comparison to group thee patients who had normal HbA1C values, was 220 times higher in group one (95%CI: 26.9- >999, P < 0.0001) and 26 times higher in group two (95%CI: 12.5-54.3, P < 0.0001).

DISCUSSION

An A1C drawn at the first prenatal visit is convenient for the both the patient and provider. The test can be done as part of routine prenatal labs and does not require the time commitment of the standard two step testing and does not require fasting. Our data indicates that the HbA1C performed at this time will also provide useful information for the management of the patient who is at high risk for gestational diabetes.

In patients with overt diabetes, HbA1C has been correlated with average glucose concentration as measured by daily evaluation of capillary blood glucose levels. However, during pregnancy HbA1C levels have not been used to manage patients because HbA1C levels perform poorly in differentiating women with normal pregnancies from those with GDM. A secondary analysis of the HAPO data was undertaken to determine if HbA1C measurement could provide an alternative to the oral glucose tolerance test in pregnant women[6]. HbA1C measurements were taken at the time of the oral glucose tolerance test (OGTT). Birthweight > 90th percentile, primary cesarean section and clinical neonatal hypoglycemia, preterm delivery, preeclampsia and cord C-peptide > 90th percentile were evaluated. The authors concluded that HbA1C was not a useful alternative to the OGTT because it was not predictive of these adverse outcomes. Our data suggests that the HbA1C at the first prenatal visit, if prior to 20 wk, rather than at the time of the OGTT, can be used to identify women with a level of glucose intolerance that will benefit from early modification of diet and exercise and early testing or self-monitoring of blood glucose. In support of the previous statement, the mean gestational age of medication initiation in groups one and two of our study, was lower than the gestational age at which routine testing for GDM is performed.

In our study we divided patients into three groups based on the recommendations of the ADA for diagnosis: patients with overt diabetes of pregnancy (HbA1C > 6.5%); patients with impaired glucose tolerance (HbA1C between 5.7%-6.4%) and normal glucose tolerance (HbA1C < 5.7%). Our study appears to support the clinical relevance of these categories in pregnancy. Ninety-five percent of patients with HbA1C of 6.5% or greater and 64% of patients with a HbA1C between 5.7 and 6.4 required medication to achieve euglycemia. This is consistent with a study by Balaji looking at 255 Asian women at risk for GDM reported that high (> 6.1%) and intermediate (5.3%-6%) HbA1C in the first trimester was associated with an elevated risk of GDM[7]. In that study 100% of patients with HbA1C > 6% and 23% of the patients with intermediate range HbA1C developed GDM. González-Quintero *et al*[8] found that HbA1C of 6% at the time of diagnosis of GDM was associated with a 61% increase in the odds of insulin use.

One limitation of the study is its retrospective design.

Retrospective studies in general are subject to selection bias. We attempted to ameliorate this effect by including all patients who met inclusion criteria and for whom there was sufficient data for analysis. A second limitation is that 15 patients in group 2, who were labeled as gestational diabetic, did not receive an oral glucose tolerance test. These patients performed daily monitoring of blood glucose and despite counseling on diet and exercise failed to meet glycemic goals and required medication indicating a degree of glucose intolerance consistent with the diagnosis.

The HbA1C $\geqslant$ 6.5% identifies women with a degree of hyperglycemia consistent with preexisting diabetes who have a high risk of requiring medication to achieve euglycemia and who may benefit from dietary counseling and daily monitoring of blood glucose. HbA1C between 5.7%-6.4% identifies women with a degree of glucose intolerance who may benefit from early testing. These women are also at high risk of requiring medication to achieve euglycemia if diagnosed with GDM. HbA1C < 5.7% is associated with minimal risk of GDM.

COMMENTS

Background

Gestational Diabetes and preexisting diabetes in pregnancy are becoming increasingly more common. Early identification allows intervention with resultant improved outcomes.

Research frontiers

There is current controversy on the best method of screening for and diagnosing gestational diabetes and preexisting diabetes in pregnancy. In this study the authors evaluate a hemoglobin A1C (HbA1C) obtained at the first prenatal visit as a tool for identification of patients who may benefit from early intervention for glucose intolerance.

Innovations and breakthroughs

This is the first study to look at the use of the HbA1C specifically in pregnant patients and to use the HbA1C to determine a course of management.

Applications

Data from this study can be used to create protocols for the management of patients based on the value of the HbA1C obtained at the first prenatal visit.

Terminology

Gestational diabetes: Glucose intolerance with onset or first recognition during pregnancy. HbA1C: a measure of the amount of glycated hemoglobin. HbA1C gives a picture of glycemic control over the preceeding 3 mo.

Peer review

The manuscript studied the utility of HbA1C at the first prenatal visit to detect the gestational diabetes (GDM) in local population. The study used the ADA and WHO cutoff to divide over 300 subjects based on HbA1C levels and determine the risk of GDM and subsequent management. The study identified significant high detection rate of GDM with high Hb1AC group with over 200 time more likely to require medication. The results are interesting.

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RANDOMIZED CONTROLLED TRIAL

Effect of vaginal speculum lubrication on cervical cytology and discomfort during smear examination

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Abstract

AIM: To evaluate the role of lubricant gel in the cytology of a Pap smear and whether it results in an improvement in the discomfort experienced by women while undergoing Pap smear screening.

METHODS: A total of 151 women were analyzed in the study. After screening for inclusion criteria, a Pap smear was taken with no lubricant in all the women and the discomfort experienced was rated on a visual analogue scale. The women underwent a second Pap smear on the next visit using a lubricant gel and were again rated on a visual analogue scale for the discomfort felt. The pathologist was blinded to the fact of whether the lubricating gel was used.

RESULTS: The number of unsatisfactory smears in the no gel group was 3 *vs* 5 in the gel group, $P < 0.05$. However, a significant difference ($P = 0.00$) was observed in the visual analogue pain score in both groups, suggesting that application of lubricant gel over the speculum improves the pain experienced by women.

CONCLUSION: Using a small amount of lubricant over the speculum does not impair cervical cytology but significantly improves the discomfort experienced by women while undergoing a Pap smear.

Key words: Lubrication; Cytology; Pain scoring; Pap smear; Discomfort

Core tip: Vaginal speculum lubrication has no effect on cervical cytology and improves the discomfort experienced in Pap smear screening.

Madaan M, Singh A, Puri M, Kaur H, Trivedi SS. Effect of vaginal speculum lubrication on cervical cytology and discomfort during smear examination. *World J Obstet Gynecol* 2014; 3(3): 134-137 Available from: URL: http://www.wjgnet.com/2218-6220/full/v3/i3/134.htm DOI: http://dx.doi.org/10.5317/wjog.v3.i3.134

INTRODUCTION

Worldwide, cervical cancer is the third most common cancer in women. In 2008, there were an estimated 529000 new cases of cervical cancer, of which over 85% occurred in developing countries[1]. Although these numbers are staggering, there has been a marked improvement in early detection of cervical carcinoma with the advent of Pap smears as a screening test. Despite this, there are many women who do not get regular screening with Pap smears. The reasons could be lack of health education, lack of health insurance, cultural barriers, discomfort[2] or anxiety regarding the procedure. Health care providers can address this issue by minimizing the patient's discomfort while performing a Pap smear. Lubricating the speculum can reduce the patient's discomfort and improve the woman's compliance with a Pap smear examination.

The routine teaching in gynecology over the years has

discouraged the use of gel lubricant because of concerns that the lubricant might interfere with the cytology results[3]. A few studies in the literature have addressed this issue and others have also raised some concerns.

We designed this study to formally investigate whether gel interferes with cervical cytology and whether it has any effect on the pain perception of the woman.

MATERIALS AND METHODS

The study was conducted at Lady Hardinge Medical College and Smt Sucheta Kriplani Hospital, New Delhi from November 2010 to July 2011. The study was approved by the Institutional Review Board of the hospital. Women aged 18 to 50 years attending the gynecology outpatient clinic were enrolled in the study. Women presenting with infectious gynecological complaints, genital bleeding or with history of cervical cancer, chronic pelvic pain, hysterectomy or allergy to gel lubricant were excluded from the study. Prior informed consent was taken from the participants. Information regarding age, parity, duration of married life, contraceptive use and history of abnormal Pap smears was obtained from all the women.

All women recruited for the study underwent a Pap smear twice using an appropriate size metal Cusco's speculum. In the first visit, the Pap smear was taken using a dry speculum, with no water or gel, as per the usual practice. The second smear was taken 3-4 d later after applying xylocaine jelly over the outer surfaces of the superior and inferior blades of the Cusco's speculum. The xylocaine jelly contained lignocaine hydrochloride 20 milligram as the active ingredient, hypromellose, methyl hydroxybenzoate, propyl hydroxybenzoate, sodium hydroxide, purified water and hydrochloric acid for pH adjustment.

The smear was taken using an Ayre's spatula and endocervical brush, spread on a glass slide and fixed in 95% isopropyl alcohol for 10 min. The glass slides from the no gel and the gel group were kept in separate containers to prevent contamination of the slides. After drying, the slides were sent to the cytopathologists who were blinded to the group assignments of the smear. The Pap smears were analyzed and classified according to the revised Bethesda scoring 2001. The smear was considered unsatisfactory if 75% of the epithelial cells were covered by blood, inflammation or artifacts.

After each Pap smear, the women were asked to rate their discomfort on a visual analogue scale (VAS) ranging from 0 (no discomfort) to 10 (most discomfort).

In the present study, each woman served as her own control. The Pap smears were collected by one of the three gynecologists at the level of consultant. It was a double blinded trial as both the patients and the cytopathologists were unaware of the method used in collecting the Pap smear.

Statistical analysis

Past studies have indicated the incidence of unsatisfactory smears to be 1.5%-4%. So taking the average incidence as 2.5% and the margin of error as 2.5%, the minimum sample size was calculated to be 150. A χ^2 test and unpaired *t*-test were used for different statistical calculations.

RESULTS

A total of 210 women were enrolled in the present study. The first Pap smear without gel was taken in 180 women who met the inclusion criteria. Out of these 180 women, 29 were lost to follow up. A repeat Pap smear with gel was taken in 151 women who reported for the second visit as per the protocol. Thus, our final sample size was 151. Figure 1 shows the consort flow diagram of the study.

The mean age of women in the study population was 34.6 ± 8.6 years. The mean duration of married life was 12.8 ± 8.1 years and mean parity was 2.0 ± 1.3 (Table 1).

There was no significant difference in the percentage of unsatisfactory smears, low grade squamous intraepithelial lesions or high grade squamous intraepithelial lesions in the gel versus no gel group (Table 2). There were no cases of invasive cancer in the study population.

However, a significant difference (P = 0.0) was observed in the visual analogue pain score between the gel group (mean VAS: 1.2 ± 1.5) and no gel group (mean VAS: 2.1 ± 1.8), as shown in Figure 2.

DISCUSSION

Our study showed that using a small amount of lubricant on the outer side of superior and inferior blades of speculum does not affect the cytology of Pap smears. Thus, speculum lubrication may be performed as a routine practice during Pap smear collection to minimize discomfort to the woman. This is in accordance with earlier studies[4-7] where the same observation was made. In the majority of these studies, subjects were randomized into two groups, while in our study the same woman served as her own control.

A study by Charoenkwan *et al*[8] found a higher incidence of unsatisfactory smears (12.1% *vs* 1.7%) in gel contaminated smears. It should be noted that in their study they applied gel directly over the external cervical os in contrast to our study where we applied the gel over the outer aspects of speculum to facilitate the entry of the speculum. Köşüş *et al*[9] also reported significantly increased rates of unsatisfactory smears in the gel applied group.

The present study also showed that applying gel over the speculum significantly improves the pain score of the women, thus reflecting a reduction in the discomfort associated with undergoing a Pap smear. The majority of studies found in the literature comment on the effect of gel on cervical cytology and only a few studies have evaluated the effect on minimizing the pain for the woman. Gilson *et al*[7] found no significant alteration in patient discomfort with speculum gel lubrication in their study on 40 patients. In a study by Hill *et al*[10], lower pain scores were observed in the gel group compared to speculum

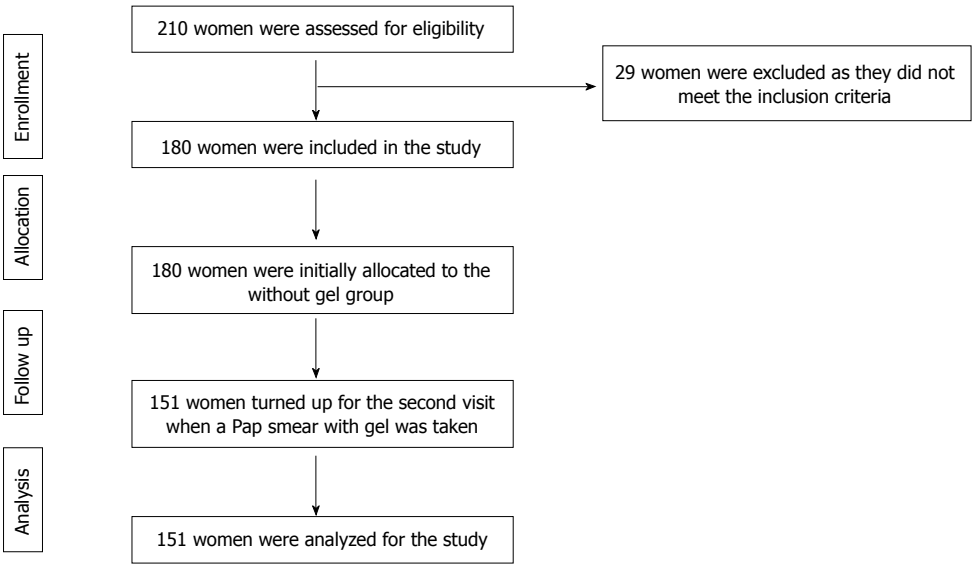

Figure 1 Consort flow diagram.

Table 1 Age distribution of study population *n* (%)

Age interval (yr)	Frequency
< 30	63 (41.7)
30-40	48 (31.8)
40-50	35 (23.2)
50-60	5 (3.3)
Total	151

Table 2 Comparison of Pap cytology results in both groups *n* (%)

Cytology results	Without gel	With gel	*P* value
Unsatisfactory	3 (1.9)	5 (3.3)	0.2
NILM	146 (96.7)	142 (94.0)	0.1
Granulomatous cervicitis	0 (0)	1 (0.7)	0.2
LSIL	0 (0)	1 (0.7)	0.2
HSIL	2 (1.3)	2 (1.3)	0.5

NILM: Negative for intraepithelial lesion or malignancy; LSIL: Low grade squamous intraepithelial lesion; HSIL: High grade squamous intraepithelial lesion.

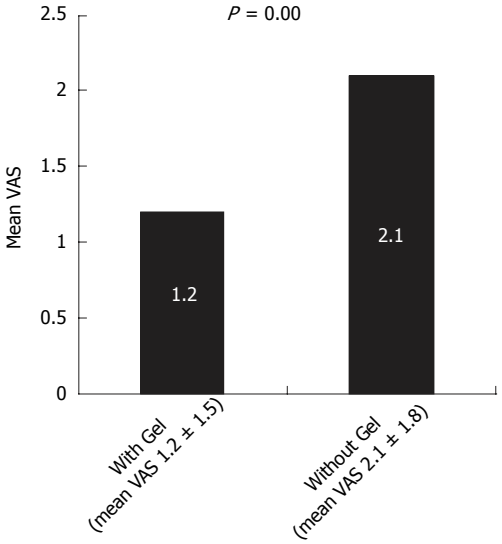

Figure 2 Comparison of mean visual analogue score in both groups. VAS: Visual analogue score.

lubrication with water ($P < 0.01$).

The strength of our study lies in the fact that we evaluated both the parameters simultaneously, *i.e.*, the effect of gel on cervical cytology and pain scoring. The low overall pain scores observed in both groups could be due to experienced gynecologists performing the test.

However, our study is not without limitations. We repeated the procedure with gel on the same woman and this could have resulted in less anxiety due to preexisting increased awareness of the procedure and lower pain scores. However, this protocol was planned so that all women underwent their first smear without gel as per routine protocol so that the diagnoses was not missed in case gel obscured smear cytology or if the woman did not return for repeat testing. Postmenopausal women and women with infective etiology were intentionally excluded from the study as the discomfort caused by a speculum is more in these women. Women with epithelial cell abnormalities were too few in the study to be able to evaluate whether there is an increase in false negative rates with gel. We would recommend doing the same study on larger subset of population using liquid cytology.

The use of gel for vaginal speculum lubrication in the collection of Pap smears had no adverse effect on cervical cytology results and it significantly decreased the level of discomfort in women undergoing Pap smear screening.

COMMENTS

Background

Cervical cancer is still one of the most common cancers in females despite the

application of widespread screening. The common reason cited for noncompliance among women for cervical cancer screening is the discomfort associated with speculum insertion.

Research frontiers

This study was conducted to evaluate whether lubrication of the vaginal speculum improves the discomfort for women as well as its effect on cervical cytology.

Innovations and breakthroughs

Contrary to the old dictum that no speculum lubrication should be used while taking a Pap smear, a few studies have been conducted in the recent past that show that speculum lubrication improves the discomfort during smear examination. However, the effect of speculum lubrication on cervical cytology is conflicting.

Applications

The study shows that speculum lubrication improves the discomfort for women and that it does not affect cervical cytology. However, there is further scope to do a larger study using liquid cytology.

Terminology

A visual analogue score is an objective means of assessing pain felt by a person who marks the intensity of pain experienced on a scale ranging from 0 to 10.

Peer review

This article evaluated the effect of vaginal speculum lubrication with xylocaine gel on cervical cytology and pain scoring in Pap smear screening and concluded that vaginal speculum lubrication with xylocaine gel did not influence the Pap smear screening.

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CASE REPORT

Leiomyoma of the umbilical cord artery: A case report

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Key words: Umbilical cord; Leiomyoma; Non-trophoblastic tumor; Pregnancy

Core tip: Leiomyoma is a benign tumor originating from non-striated muscle that is rare in tissues outside of the uterus. This article presents an extremely rare case of umbilical cord artery subendothelial leiomyoma.

Rovas L, Dauksas R, Simavicius A. Leiomyoma of the umbilical cord artery: A case report. *World J Obstet Gynecol* 2014; 3(3): 138-140 Available from: URL: http://www.wjgnet.com/2218-6220/full/v3/i3/138.htm DOI: http://dx.doi.org/10.5317/wjog.v3.i3.138

Abstract

A leiomyoma is a benign tumor originating from non-striated muscle that is typically found in the uterus. Intravenous leiomyomatosis is a rare form found within the veins, usually associated with uterine fibroids, and tends to recur. These masses can spread from the uterus throughout the venous system. A rare case involving a subendothelial leiomyoma found in an umbilical cord artery is presented in this article. A 21-year-old patient presented with symptoms of preterm labor, which resulted in the premature birth of a female below the 10th percentile for 24-wk gestational age. The newborn died three days later, and microscopic analysis of the umbilical cord revealed occlusion of the artery by nodular structures. The antepartum diagnosis of intravascular leiomyoma was identified by immunohistochemistry showing that approximately 70% of all tumor cells were diffusely positive for smooth muscle markers, including desmin and smooth muscle actin. These findings indicate the possibility of a pathologic association between the umbilical cord leiomyoma, restriction of fetal growth and preterm delivery due to impaired circulation of blood in the umbilical cord.

INTRODUCTION

Intravenous leiomyomatosis (IVL) is a rare smooth muscle tumor found within the veins of the uterus. The masses are benign-appearing but can exit the uterus and spread throughout the venous system[1]. This condition is related to benign metastasizing leiomyoma, in which the masses appear in distant locations such as the lung, heart and kidneys.

Tumors of the umbilical cord are rare, and cases of subendothelial leiomyoma are even more infrequent. To our knowledge, there are no published reports concerning umbilical cord leiomyomas. However, we recently encountered a case of an unusual non-trophoblastic tumor in an umbilical cord that was diagnosed during histochemical examination after childbirth.

CASE REPORT

A healthy, 21-year-old multiparous pregnant woman presented at Siauliai Hospital at 24 wk of gestation because of bleeding and uterine contractions. The patient had no significant medical history except for a miscarriage at 13 gestational weeks one year before. The current pregnancy was spontaneous without any problems to date.

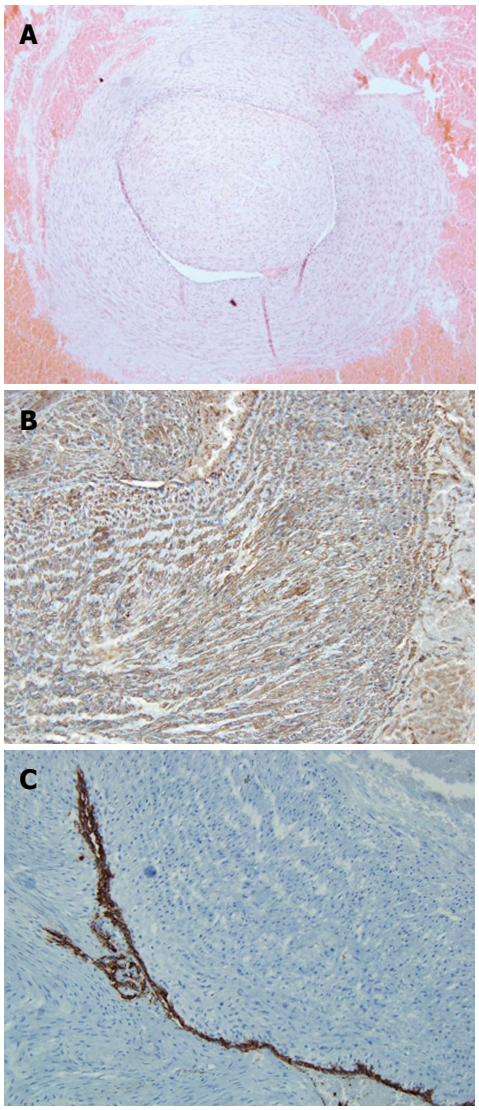

Figure 1 Photographs. A: Circumscribed intravascular tumor. Micrograph showing the intravascular tumor lined with endothelium (hematoxylin-eosin staining, magnification × 20); B: Smooth muscle actin immunohistochemistry. Micrograph showing tumor cells immunoreactive for smooth muscle actin (magnification × 20); C: $CD34^+$ immunoreactivity in tumor cells. Immunohistochemistry revealed the presence of $CD34^+$ tumor cells beneath the endothelium (magnification × 20).

Transvaginal and transabdominal ultrasound did not detect any lesions within the fetus, placenta or umbilical cord. The estimated weight of the fetus was less than the 10^{th} percentile. A blood analysis did not indicate the presence of any inflammatory processes. Regular contractions were detected during cardiotocography. Despite treatment with nifedipine, a selective calcium channel inhibitor used to stop premature uterine contractions, a spontaneous preterm birth occurred. The extremely premature newborn died after three days, and no anomalies were found at autopsy. The maternal surface and membranes of the placenta were unremarkable.

The umbilical cord measured 50 cm in length and was inserted centrally. Microscopic examination of an umbilical cord specimen revealed that arteries were occluded by polyploid nodular structures consisting of oblong, mitotic non-active cells, which formed patches in some places. Further analysis revealed a lesion lined with endothelium (Figure 1A). A diagnosis of intravascular leiomyoma was confirmed by immunohistochemistry that showed that the tumor cells were diffusely positive for smooth muscle markers, including desmin and smooth muscle actin (Figure 1B). Approximately 70% of the tumor cells showed cytoplasmic actin immunoreactivity. Tumor cells were also immunoreactive for antibodies against CD34 (Figure 1C).

DISCUSSION

The histogenesis of primary neoplastic alterations of placenta and umbilical cord are divided into two main groups[2]. They can be of a trophoblastic origin, including placental trophoblastic tumors, choriocarcinomas and hydatidiform moles, or non-trophoblastic, such as in chorioangioma and teratomas. Leiomyomas are of the second group of non-trophoblastic origin, which are extremely rare in the umbilical cord[3]. However, non-trophoblastic tumors are asymptomatic, and can remain undetected during examination of secundines, only being detected incidentally[2].

IVL is a nonmalignant tumor usually confined to the pelvic venous system and histologically characterized as a smooth muscle tumor mass growing within the uterus[4,5]. The cardinal microscopic feature is the protrusion of a smooth muscle endothelium-covered tumor into the vessels. Vascular leiomyomas may be difficult to distinguish from hemangiomas, which are more commonly found in the umbilical cord, and are cavernous[6]. Although IVL are typically confined to the uterine veins, they can progress along the veins into the inferior vena cava, and have been described within intracaval, intracardiac, intrarenal and pulmonary arteries[7,8]. Of the reported cases of IVL[4], none were detected in umbilical cord.

The case described in this article is the first known report of IVL in an umbilical cord artery. There were no suspicions concerning an umbilical cord tumor before delivery, and the leiomyoma was detected only during microscopic examination after birth. It is not clear how the leiomyoma extended in to umbilical cord artery. The umbilical cord forms within the body stalk of the developing embryo from the omphalomesenteric duct, yolk sac and the allantoic duct at around 6 wk into the gestational period[9]. IVL grows in the uterine vascular tree and can presumably metastasize into the fetal-maternal circulation. Although the cause of the fetal growth restriction and preterm delivery in this case is unknown, it is possible that the umbilical cord artery pathology and impaired blood circulation resulting from the leiomyoma contributed.

COMMENTS

Case characteristics

A healthy 21-year-old pregnant women presented with symptoms of preterm labor.

Clinical diagnosis

Premature labor, intrauterine growth restriction.

Differential diagnosis

Premature labor, abruptio placenta.

Laboratory diagnosis

Blood analysis did not reveal any sign of inflammatory processes.

Imaging diagnosis

Pregnancy: 24 wk gestation with normal anatomic development of the fetus. Cervix: 3 cm; normal placenta and umbilical cord. Intrauterine growth restriction.

Pathological diagnosis

Leiomyoma.

Treatment

The patient was treated with nifedipine (calcium channel blocker).

Term explanation

The CD34 protein is a member of a family of single-pass transmembrane proteins expressed in early hematopoietic and vascular-associated tissue.

Experiences and lessons

This case report not only describes the extremely rare intravenous locations of leiomyomas, but also suggests that all available methods should be used to ascertain causes of poor pregnancy outcomes.

Peer review

This article presents the first known report of an intravenous leiomyoma within the umbilical cord. The tumor was diagnosed after immunohistochemical analysis to confirm the origin.

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REVIEW

Association between gamete source, exposure and preeclampsia: A review of literature

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Abstract

Preeclampsia complicates 3%-5% of pregnancies and is one of the major causes of maternal morbidity and mortality. The pathologic mechanisms are well described but despite decades of research, the exact etiology of preeclampsia remains poorly understood. For years it was believed that the etiology of preeclampsia was the result of maternal factors, but recent evidence suggests that preeclampsia may be a couple specific disease where the interplay between both female and male factors plays an important role. Recent studies have suggested a complex etiologic mechanism that includes genetic imprinting, immune maladaptation, placental ischemia and generalized endothelial dysfunction. The immunological hypothesis suggests exaggerated maternal response against fetal antigens. While the role of maternal exposure to new paternal antigens in the development of preeclampsia was the initial focus of research in this area, studies examining pregnancy outcomes in pregnancies from donor oocytes provide intriguingly similar findings. The pregnancies that resulted from male or female donor gametes or donor embryos bring new insight into the role of immune response to new antigens in pathogenesis of preeclampsia. The primary goal of the current review is the role of exposure to new gametes on the development of preeclampsia. The objective was therefore to provide a review of current literature on the role of cohabitation length, semen exposure and gamete source in development of preeclampsia.

Key words: Preeclampsia; Donor embryos; Donor oocytes; Donor sperm; Primipaternity

Core tip: Preeclampsia is a potentially life threatening complication of pregnancy, etiology remains unresolved. For decades it was believed to be a disease of mainly maternal origin with many pathologic mechanisms being described, however evidence suggests that an interplay between maternal and paternal factors may play an important role in pathogenesis. The aim on this publication therefore was to provide review of current literature on association of gamete source, exposure and the risk of preeclampsia.

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INTRODUCTION

Preeclampsia complicates 3%-5% of pregnancies and is one of the major causes of maternal morbidity and mortality in both developed and low income countries[1]. While the physical manifestations of preeclampsia have been well characterized and may include hypertension, proteinuria and intrauterine growth restriction, the primary etiology remains unknown[1-3]. The pathologic

mechanisms described include impaired cytotrophoblast invasion of spiral arteries, exaggerated inflammatory response and endothelial cell damage with subsequent impairment of multiple organs[3,4].

Despite decades of research, the exact etiology of preeclampsia remains unclear with several proposed hypotheses that include genetic imprinting, immune maladaptation, placental ischemia and generalized endothelial dysfunction[5]. The immunological hypothesis suggests that an exaggerated maternal response against fetal antigens precipitates the pathological findings[6]. Evidence for this hypothesis stems in part from studies examining duration exposure to paternal antigens and a correspondingly lower incidence of preeclampsia in subsequent pregnancies[7,8].

Studies focused on the outcomes of pregnancies from donor oocytes confirmed the observations of initial research examining the role of maternal exposure to new fetal antigens in the development of preeclampsia. The studies on pregnancies that resulted from donor gametes (or either male or female origin) or donor embryos bring new insight into the role of immune response to new antigens in pathogenesis of preeclampsia[9-12]. The immunologic hypothesis explaining the etiology of preeclampsia is complex and beyond the scope of this article. Experimental studies shown presence of major and minor histocompatibility antigens in human semen, it is therefore seminal priming prior to pregnancy can induce maternal tolerance to paternal alloantigens and thus protect from preeclampsia[13]. These experiments focus on the expression of transplantation antigens [human leukocyte antigen (HLA)] by human trophoblast and their potential to induce maternal immunologic responses where regulatory T cells and cellular signals indolamine 2,3-dioxygenase, and transforming growth factor-β play important roles. Autoimmune mechanisms have also been with emphasis on the role of maternal antiphospholipid antibodies and anti-angiotensin Ⅱ type I receptors[14-17]. For interested readers we recommend the more comprehensive reviews of immunology and preeclampsia[17,18].

The objective of this paper is to provide a review of current literature on the role of cohabitation length, semen exposure and gamete source in development of preeclampsia.

PRIMIPATERNITY AND NULLIPARITY

The risk of preeclampsia among nulligravid women is three times higher then for multiparous women and a history of prior normal pregnancy has long been considered "protective" for the risk of preeclampsia[3,19]. The incidence of preeclampsia was higher for nulliparas in their first pregnancy, than it was subsequent pregnancies in the same women with a subsequent pregnancy, provided that it was fathered by the same partner (OR = 2.96, 95%CI: 1.80-4.88)[8].

It was thought that, in contrast to multiparas whose subsequent pregnancy is fathered by the same man, the risk of recurrence remains as high for woman with interval partner change as it is for nulliparas. These findings prompted researchers to investigate the role of a new father (or "primipaternity" a term first introduced by Robillard *et al*[20] in 1993) rather then nulliparity in the development of preeclampsia[21-23]. Subsequent investigations by Robillard *et al*[20], reviewing cases in a Caribbean population showed increased risks of preeclampsia in multiparous women after changes in paternity. Similarly, Tubbergen *et al*[24] showed prevalence of having severe preeclampsia or HELLP syndrome to be significantly higher among multiparous women who conceived with new partner. Li *et al*[25] in a large retrospective cohort study showed that change in paternity increased the risk of hypertensive disorders of pregnancy for women who were normotensive during their previous pregnancy. The results presented by Trupin *et al*[26] also support immunological hypothesis of preeclampsia. They showed that 29% of preeclampsia cases in multiparous women with an interval partner change were attributable to primipaternity, however the risk of preeclampsia remained lower in these women comparing to nulliparae. These findings imply that any previous pregnancy, even after change of partner may provide some protection. The association between preeclampsia and primipaternity was further confirmed by Bandoli *et al*[27] in the study on risk factors for preeclampsia and small for gestational age fetuses. The investigators evaluated the number of potential confounding factors, including maternal diseases, alcohol and tobacco use, history of preeclampsia and race and found that primipaternity remained a significant risk factor for preeclampsia (Table 1).

Some of the discrepancies in studies looking at new male partners may also relate to the duration of sexual cohabitation with a new partner, or duration of antigenic exposure preceding a pregnancy. Verwoerd *et al*[28] found that primipaternity was not a significant risk factor for preeclampsia. However, analysis of their results in the light of duration of sexual cohabitation, suggested that a duration of sexual cohabitation of 6 mo or fewer months was associated with increased risk of preeclampsia in multigravid group (OR = 3.9, 95%CI: 1.2-13.4). A recent prospective study by Chigbu *et al*[29] in southern Nigeria population also showed that woman who changed their partners before next pregnancy did not have increased risk for preeclampsia. In contrast to the first study investigators did not find any difference in duration of sexual cohabitation (7.9 ± 1.3 mo *vs* 7.5 ± 2.1 mo, $P = 0.531$) between women with preeclamptic and uncomplicated pregnancies. This latter study is limited by the fact that there were only 11 patients with change in paternity, which may explain the conflicting findings (Table 1).

Further evidence to support a hypotheses of immune tolerance and the documented protective effects of pregnancy, stems from the observation that women with history of miscarriage like multiparas have reduced risk of preeclampsia. Saftlas *et al*[30] evaluated 4589 nulliparous woman enrolled in Calcium for Preeclampsia Prevention

Table 1 Studies reporting preeclampsia and pregnancy-induced hypertension in relation to change of paternity

Ref.	Design	Sample size	Main outcome measures	Findings
Robillard *et al*[20]	Case control	74 hypertensive cases 60 controls	Change of paternity	Change of paternity was 61.7%, 10% and 16.6% inn PIH group, chronic hypertension group and controls respectively ($P < 0.0001$)
Feeney *et al*[21]	Matched case control	47 cases with preeclampsia 47 normotensive controls	Change of paternity	13 cases with paternity change *vs* 3 controls with paternity change ($P < 0.01$)
Ikedife[22]	Case series	46 eclamptic multiparous patients	74% of subjects had paternity change	
Chng[23]	Case report	Case of severe preeclampsia in the patient with prior history of uneventful first pregnancy after change of paternity		
Tubbergen *et al*[24]	Retrospective case control study	333 multiparous subjects with hypertensive disorder 182 multiparous normotensive subjects	Change of paternity	22.6%-preeclamptic multiparas with change of paternity; 27.0%-HELLP multiparas with change of paternity; 3.3%-change of paternity among normotensive multiparas OR for preeclampsia among subjects with new partner was 8.6 (95%CI: 3.1-23.5) and for HELLP 10.9 (95%CI: 3.7-32.3) comparing to normotensive subjects
Li *et al*[25]	Retrospective cohort	140147 pregnancies	Incidence of preeclampsia/eclampsia	OR for preeclampsia among women with previous normal pregnancy and change of paternity was 1.3 (95%CI: 1.1-1.6)
Trupin *et al*[26]	Prospective cohort	5800 pregnancies	Incidence of preeclampsia	Adjusted OR for preeclampsia among multiparas with change of paternity 1.4 (95%CI: 0.8-2.4)
Bandoli *et al*[27]	Prospective cohort	1396 pregnancies	Incidence of preeclampsia	OR for preeclampsia 2.75 (95%CI: 1.33-5.68) among women with change paternity
Verwoerd *et al*[28]	Case control	60 multigravidae with preeclampsia 60 normotensive multigravidae	Change of paternity	Change of paternity was 38.3% *vs* 21.7% (cases *vs* controls) Uncorrected OR for preeclampsia with primipaternity 2.3 (95%CI: 0.9-5.5)
Chigbu *et al*[29]	Prospective cohort	732 pregnancies	Incidence of preeclampsia	Preeclampsia in 3.5% of cases *vs* 3.1% controls (NS)
Saftlas *et al*[30]	Retrospective cohort	4589 pregnancies	Incidence of PIH and preeclampsia	Adjusted OR for preeclampsia among women with history of abortion who conceived again with same partner 0.55 (95%CI: 0.21-0.97)
Olayemi *et al*[31]	Prospective cohort	2630	Incidence of hypertension in pregnancy	History of same paternity abortion was protective against preeclampsia (HR = 0.46, 95%CI: 0.22-0.96)

PIH: Pregnancy induced hypertension; NS: Non significant.

trial and found that prior abortion fathered by the same partner reduced the risk of preeclampsia by 50%. These results were replicated by Olayemi *et al*[31] as well as Eras *et al*[32] who evaluated the risk associated with preeclampsia and found that women with an aborted pregnancy of the same paternity experienced the same protective effect against preeclampsia (Table 1).

DONATED GAMETES

Pregnancies that result from donor gametes provide another controlled opportunity to study immunologic aspects of preeclampsia. Need *et al*[33] in 1983 were the first to suggest a higher incidence of preeclampsia in pregnancies resulting from insemination with donor sperm. Although their study was an uncontrolled descriptive case series, further studies demonstrated a similarly increased risk of preeclampsia in the pregnancies that result from donor inseminations[34-36]. A retrospective study by Hall *et al*[37] however, failed to demonstrate increased risk of preeclampsia in donor sperm recipients. Although no differences were observed, the control group in this study had a higher baseline incidence of preeclampsia (11.5%) than is typically reported in the general population, perhaps accounting for the inability to detect an increased risk in the donor sperm cohort (Table 2).

Given the increased risk seen with donor sperm, one would similarly expect that pregnancies in donor oocyte or donor embryo recipients would be associated with similar risk of preeclampsia. Initial studies using an assisted reproductive technology model looking at women receiving embryos derived from donor oocytes would have similarly increased risks of preeclampsia. Studies demonstrated an increased risk to that seen in some donor sperm and primipaternity cases[10,11,38]. Although these findings were intriguing, the patients using donor oocytes were older than their controls. Klatsky *et al*[9] provided the largest in a retrospective cohort study of 158 pregnancies including aged matched controls and found an increased risk of both preeclampsia and pregnancy induced hypertension in donor oocyte recipients (OR = 4.0, 95%CI: 1.5-13.8; OR = 4.2, 95%CI: 1.5-11.9 respectively). These findings were recently confirmed again by Tranquilli *et al*[12] (Table 2).

Of note a small study of 26 donor embryo recipients failed to detect a difference, but was likely underpow-

Table 2 Studies reporting preeclampsia and pregnancy-induced hypertension in donor oocytes, donor sperm and donor embryos pregnancies

Ref.	Design	Sample size	Main outcome measures	Findings
Donor oocytes				
Söderström-Anttila *et al*[11]	Retrospective cohort	51 oocyte donation pregnancies 97 IVF age matched controls	The incidence of PIH and preeclampsia	The incidence of PIH in primiparae was 30% in oocyte donor recipients and 13% in IVF controls ($P < 0.05$), no difference in preeclampsia incidence between two groups
Salha *et al*[10]	Retrospective cohort	27 donor oocytes pregnancies 27 age-and parity matched controls	The incidence of preeclampsia	Preeclampsia incidence 16% *vs* 3.7% (cases *vs* controls), $P < 0.05$
Keegan *et al*[38]	Retrospective anonymous questionnaire study	199 oocyte donor recipients 488 autologous IVF controls	The incidence of PIH	Rate of pregnancy induced hypertension in < 35 years old was 42% *vs* 12%, $P < 0.001$ (cases *vs* controls) and > 40 years old 26% *vs* 14%, $P = 0.003$ (cases *vs* controls)
Klatsky *et al*[9]	Retrospective matched cohort	77 donor oocytes recipients 81 autologous IVF controls	The incidence of PIH and preeclampsia	16.9% of cases with preeclampsia *vs* 4.9% controls 24.7% of cases with PIH *vs* 7.4 % controls Adjusted OR for preeclampsia with donor oocytes OR = 4.0 (95%CI: 1.2-13.8) and for gestational hypertension OR = 4.2 (95%CI: 1.5-11.9)
Tranquilli *et al*[12]	Retrospective matched cohort	26 donor oocytes recipients 52 autologous ICSI pregnancies 52 AMA controls	Prevalence of preeclampsia	Prevalence of preeclampsia 19.2% in donor oocyte recipients *vs* 0% in autologous ICSI and AMA controls ($P < 0.001$)
Donor sperm				
Need *et al*[33]	Case series	584 AID pregnancies	The incidence of preeclampsia	Preeclampsia incidence 9.3%
Smith *et al*[35]	Retrospective cohort	37 donor insemination pregnancies 44 controls	The incidence of preeclampsia	24.3% of cases with preeclampsia *vs* 6.8% controls RR for preeclampsia with donor insemination RR = 1.85 (95%CI: 1.20-2.85)
Hoy *et al*[34]	Retrospective cohort	1552 donor insemination pregnancies 7717 controls	The incidence of preeclampsia	8.4% of cases with preeclampsia *vs* 5.2 % controls Adjusted OR for preeclampsia with donor insemination OR = 1.4 (95%CI: 1.2-1.8)
Salha *et al*[10]	Retrospective cohort	33 donor sperm pregnancies 33 age-and parity matched controls	The incidence of preeclampsia	Preeclampsia incidence 18.2% *vs* 0% (cases *vs* controls), $P < 0.05$
Hall *et al*[37]	Retrospective cohort	45 donor insemination pregnancies 173 controls	The incidence of proteinuric hypertension	No difference in incidence of proteinuric hypertension between cases and controls (13.3% *vs* 11.0%)
Kyrou *et al*[36]	Retrospective cohort	438 donor insemination pregnancies 275 partner sperm	The incidence of preeclampsia	Preeclampsia incidence 10.9% *vs* 7.2% (cases *vs* controls), difference 3.7%; 95%CI: -0.8 to 7.8
Donor embryos				
Porreco *et al*[39]	Retrospective cohort	23 donor embryos pregnancies 24 age matched IVF controls	The incidence of preeclampsia	26% of cases with preeclampsia *vs* 29% controls OR for preeclampsia with donor embryos OR = 0.86 (95%CI: 0.24-3.09)
Salha *et al*[10]	Retrospective cohort	12 donor embryos pregnancies 12 age-and parity matched controls	The incidence of preeclampsia	Preeclampsia incidence 25% *vs* 0% (cases *vs* controls), NS

AMA: Advanced maternal age; AID: Artificial donor insemination; IVF: *In vitro* fertilization; ICSI: Intracytoplasmic sperm injection; PIH: Pregnancy induced hypertension; NS: Non significant.

ered[39]. Pregnancies that result from surgically obtained sperm for *in vitro* fertilization (IVF) are similar, immunologically to donor sperm pregnancies, as their partners have not had sufficient antigenic exposure to their husband's sperm. In these cases maternal exposure to paternal sperm antigens prior to embryo transfer is limited, a situation that could be of a key importance if the sperm antigens, not semen antigens were responsible for mounting immunologic tolerance. Wang *et al*[40] evaluated the outcomes of pregnancies that resulted from regular IVF or intracytoplasmic sperm injection (ICSI) cycles with ICSI pregnancies were surgically obtained sperm was used. They observed that risk for pregnancy induced hypertension was doubled (OR = 2.1, 95%CI: 1.30-3.62) and risk for preeclampsia tripled (OR = 3.10, 95%CI: 1.59-6.73) in the latter group (Table 2).

LENGTH OF SEXUAL COHABITATION

Marti *et al*[41] observed that woman with preeclampsia had

Table 3 Studies reporting preeclampsia and pregnancy-induced hypertension in relation to length of sexual cohabitation and use of barrier contraception

Ref.	Design	Sample size	Main outcome measures	Results
Robillard *et al*[7]	Retrospective cohort	1011 pregnancies	Incidence of PIH	Incidence of PIH was 10.6% (entire cohort) and 5.1% among women with > 12 mo of sexual cohabitation (11.9% and 3.3% for primigravidae, respectively)
Verwoerd *et al*[28]	Case control	60 cases with preeclampsia 60 normotensive controls	Length of sexual cohabitation	Unprotected sexual cohabitation of > 6 mo was a negative predictor for preeclampsia (coefficient -0.57, SE 0.62, $P = 0.03$)
Olayemi *et al*[31]	Prospective cohort	2630 pregnancies	Incidence of hypertension in pregnancy	Length of sexual cohabitation before pregnancy was protective against hypertension in pregnancy (HR = 0.96, 95%CI: 0.93-0.99) but not preeclampsia (HR = 1.07, 95%CI: 0.00-1.15)
Kho *et al*[42]	Prospective cohort	2507 pregnancies	Incidence of preeclampsia	OR for preeclampsia were 2.32 (95%CI: 1.03-5.25) and 1.88 (95%CI: 1.05-3.36) for short sexual relationship of less then 3 mo and less then 6 mo respectively
Klonoff-Cohen *et al*[43] 1989	Case control	110 preeclamptic cases 115 normotensive controls	Contraceptive and reproductive history of subjects	OR for preeclampsia for barrier contraceptive users was 2.37 (95%CI: 1.01-5.58)
Mills *et al*[44]	Merge data from two prospective cohort studies	13914 pregnancies (total)	Incidence of preeclampsia	OR for preeclampsia in barrier contraceptive users were 0.85 (95%CI: 0.71-1.12) (one study) and 0.85 (95%CI: 0.49-1.45) (second study)
Saftlas *et al*[46]	Case control	258 cases 182 controls	Length of sexual cohabitation	OR for preeclampsia among women with long (> 90%) sexual relation-OR = 0.3 (95%CI: 0.1-0.9)

PIH: Pregnancy induced hypertension.

three times shorter length of sexual cohabitation with their partners than did women with normal pregnancies and thus proposed that spermatozoal HLA can either induce maternal tolerance to conceptus or cause maternal immunologic enhancement. The inverse relationship between length of sexual cohabitation and pregnancy induced hypertension was later demonstrated by Robillard *et al*[7]. They interviewed 1011 woman regarding paternity and length of cohabitation and found that a duration of sexual cohabitation of greater that 12 mo prior to pregnancy decreased the incidence of pregnancy induced hypertension from 10.6% to 5.1%, and that difference was even more pronounced in the primigravidae subgroup (11.9% to 3.3%). Another study documented a protective effect after only 6 mo[28] (Table 3).

Two large prospective cohort studies showed that women diagnosed with preeclampsia and gestational hypertension were more likely to have history of recent initiation of sexual relations with their partners than woman with uncomplicated pregnancies[31,42]. The short duration of sperm exposure prior to pregnancy has been postulated to be a factor responsible for higher prevalence of preeclampsia in younger populations (Table 3).

Other studies have shown that the use of barrier contraception and thereby limiting the exposure to paternal sperm antigens was associated with an increased risk of preeclampsia. Such a association was first documented by Klonoff-Cohen *et al*[43] in a case control study. Authors showed that women who used barrier contraception were over twice as likely to develop preeclampsia. These results however could not be reproduced in later study by Mills *et al*[44] in 1991 (Table 3).

The role of semen exposure and its effect on development of preeclampsia has been subject of many studies. It seems that not only duration of sperm exposure plays role. It has been hypothesized that vaginal and oral sperm exposure prior to pregnancy may exert different effects.

Vaginal exposure is not the only posited mechanism for immunologic exposure. Koelman *et al*[45] showed in a small study (41 preeclamptic patient, 44 controls) that women with preeclampsia were less likely to have been engaged in oral sex with their partners prior to index pregnancy. In their study preeclamptic women were also less likely to swallow sperm during oral sex with the father of their pregnancy. Using enzyme-linked immunosorbent assay they were able to detect soluble HLA in seminal plasma and showed that its levels were not different between men that fathered normal and preeclamptic pregnancy. The investigators postulated that oral exposure in particular, through exposure of maternal gastrointestinal tract mucous membranes to paternal soluble HLA induced a tolerance to future pregnancies with the same partner. The Koleman study, however, did not control for length of sexual relation before pregnancy. A similar case-control study of 440 pregnancies, examined the association between seminal fluid exposures and the development of preeclampsia, using detailed questionnaires about sexual practices, failed to find an association with reduced rates of preeclampsia. Increasing vaginal exposure to paternal semen, however, was significantly associated with a lower incidence of preeclampsia, with 70% reduction rate for women with the highest 10th percentile exposure[46].

CONCLUSION

Preeclampsia is a syndrome that involves both multiple organs and is associated with many risk factors. Currently,

both experimental and clinical studies support a role for immune dysfunction in the etiology of preeclampsia. We reviewed the evidence that gamete source and prior exposure may be associated with the risk of preeclampsia. Non-autologous gametes, both donor oocytes and donor sperm, as well as exposure to new paternaly derived antigens appear to play an important role in development of the disease. Most studies support the hypothesis that maternal exposure to male antigens either in sperm or through prior pregnancies has some protective effect. Available data support hypothesis that incidence of preeclampsia and pregnancy induced hypertension decrease with increasing length of sexual cohabitation. Examination of the pregnancy outcomes resulting from assisted reproduction using donor gametes contribute clinical evidence to evaluate the hypothesis that preeclampsia may be causally related to novel antigenic exposure in the conceptus.

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REVIEW

Prevention of shoulder dystocia related birth injuries: Myths and facts

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Abstract

Traditionally, brachial plexus damage was attributed to excessive traction applied on the fetal head at delivery. Recently, it was proposed that most injuries occur spontaneously *in utero*. The author has studied the mechanism of neurological birth injuries based on 338 actual cases with special attention to (1) fetal macrosomia; (2) maternal diabetes; and (3) methods of delivery. There was a high coincidence between use of traction and brachial plexus injuries. Instrumental extractions increased the risk exponentially. Erb's palsy following cesarean section was exceedingly rare. These facts imply that spontaneous neurological injury *in utero* is extremely rare phenomenon. Literary reports show that shoulder dystocia and its associated injuries increased in the United States several-fold since the introduction of active management of delivery in the 1970's. Such a dramatic change in a stable population is unlikely to be caused by incidental spontaneous events unrelated to external factors. The cited investigations indicate that brachial plexus damage typically is traction related. The traditional technique which precludes traction is the optimal method for avoiding arrest of the shoulders and its associated neurological birth injuries. Effective prevention also requires meticulous prenatal care and elective abdominal delivery of macrosomic fetuses in carefully selected cases.

Key words: Shoulder dystocia; Erb's palsy; Fetal macrosomia; Brachial plexus injury; Two-step delivery; Birth injury

Core tip: Traditionally, brachial plexus injury at birth has been considered traction related. Recently, several authors proposed that one-half or more of these injuries occur spontaneously "*in utero*" resulting from myometrial activity. Study of 338 birth injuries found close association with deliveries that had involved manual and instrumental extractions. Only one Erb's palsy occurred following cesarean section. These findings indicate that spontaneous intrauterine brachial plexus damage is extremely rare. Meticulous antenatal care, elective abdominal delivery of grossly macrosomic fetuses and non-interference with the natural birthing process are recommended for preventing shoulder dystocia and its dire consequences.

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INTRODUCTION

Since the 19th century double blind, controlled, prospective investigation has been the hallmark of scientific pedantry. However, not all medical puzzles yield themselves for evaluation by this important but costly and time consuming research approach. Injuries associated with arrest of the shoulders of the fetus at birth are eminent examples. Untold numbers of neonates are left with neurological damage following this complication every year, yet in any single service its incidence is low. Many newborn babies would need to be sacrificed at the altar

of pure science if investigators insisted on resolving this problem through this revered gold standard of research. Not since the Aztecs had offered the hearts of forty-thousand slaves to their gods have human lives been considered freely expendable for causes that contemporary society found noble and worthwhile.

Medical history shows that sophisticated methodology, whatever valuable is no substitute for intuition and deductive logic. The latter qualities made it possible for open minded scientists, such as Jenner, Lind, Holmes, Semmelweis, Pasteur, Koch, Sanger, M and P Curie, Fleming, Gregg, McBride, Friedman, Clarke and others to promote the progress of medicine. Rigid demand for experimental evidence delayed for four decades clinical implementation of "asepsis" for the prevention of childbed fever at the cost of tens if not hundreds of thousands of lives.

Not unlike in ancient Egypt, physicians face court action in the United States if their treatment entails bad outcome. Mercifully, monetary compensation has replaced death penalty that had been favored in the valley of the Nile 3000 years ago. As a result, medical documentation of incidents of birth injuries that are scattered in hundreds of hospitals can be found in abundance in the files of malpractice attorneys and insurance companies. The author's group gained access to these sources and collected 338 medical records which described shoulder dystocia related fetal injuries or deaths in detail. As explained in previous publications[1,2], in many cases the attorney's preliminary review was not followed by litigation. In those instances when court action ensued the records were only attached to the data base after the legal proceedings had been concluded. Eventually, cases were collected on the ground of the following criteria: (1) Neonatal brachial plexus damage that persisted for at least 6 mo with or without clinical diagnosis of shoulder dystocia; (2) Damage-other than brachial plexus palsy-that persisted at least six months with clinical diagnosis of arrest of the shoulders at birth; and (3) Perinatal death against the background of documented shoulder dystocia at birth.

The diagnosis of shoulder dystocia was mentioned in over 90% of the records. The remaining ones only referred to brachial plexus injury. Absence of documented diagnosis is considered by some investigators evidence to indicate that the brachial plexus palsy occurred without arrest of the shoulders[3]. This distinction is only relevant in the medico-legal context, since the injury has never been attributed to the arrest of the shoulders but to traction used by the physician or midwife in charge. Therefore, for the purpose of their studies the participants of this research included those cases in their material where brachial plexus injury occurred but the diagnosis of shoulder dystocia was not documented.

DEFINITION OF SHOULDER DYSTOCIA

Paradoxically, this important clinical complication has no generally accepted criteria. According to current American interpretation the diagnosis is applicable when in the absence of spontaneous expulsion of the fetus the "standard delivery procedure of gentle downward traction" of the fetal head fails to accomplish delivery. This definition ignores the fact that routine use of traction is disapproved in some European countries[4,5] and was discouraged in the United States also until the mid-1970's[6-9]. Non-interference with the birthing process is still practiced by British obstetricians[4,10], whose proverbial "cold blooded" detachment much impressed this writer during the years of his training in England. It has also been favored in the Perinatal Center of the UMDNJ in Newark throughout the last 40 years[11] in spite of the contrary advice of standard textbooks and of the American College of Obstetricians and Gynecologists (ACOG). By traditional interpretation interruption of the delivery process following expulsion of the fetal head is a physiological phenomenon which does not warrant intervention. It occurs at least in one-half of the deliveries of primiparous women and in about one-fourth of all multiparas. The next uterine contraction which seldom is delayed more than 2-3 min expels the body of the child spontaneously. The time interval can be shortened by administering slow intravenous infusion of oxytocin in low concentration.

Conservative interpretation of normal birthing process affects the criteria of shoulder dystocia since only when the next contraction fails to expel the body becomes this definition applicable. Therefore, with this technique the diagnosis is objective and does not depend on the judgment of the accoucheur. It is a matter of note that in the practices of physicians who embrace this approach the incidence of shoulder dystocia tends to be low[12,13].

Interpretation of the so called "turtle sign" differs for those who accept the conservative concept of shoulder dystocia from that of others. Retraction of the head from the perineum following relaxation of the uterus is considered a physiological phenomenon which requires no intervention. The fetal body is likely to be delivered spontaneously with the next contraction. It is true however, that "real" shoulder dystocia relatively often is preceded by turtle sign. It should be regarded therefore a warning about possible forthcoming arrest of the shoulders rather than a diagnostic sign of it. Most importantly, its occurrence should be considered a relative contraindication for any attempt at delivery before the next uterine contraction.

There has been some dispute about the question of whether even a short waiting for the spontaneous expulsion the fetal body is warranted before the use of traction[14]. For reason to be discussed later, the idea of prompt traction reflects unawareness of the normal mechanism of the birthing process. Because the author considers any interference at this stage of the delivery ill-advised, this subject is outside the scope of discussion at this point.

FETAL EFFECTS OF ARREST OF THE SHOULDERS

In the absence of consensus about the diagnostic criteria

Table 1 Predisposing factors for shoulder dystocia

Preconceptional	Prenatal	Intrapartum
Small maternal stature	Low glucose tolerance	Protracted latent phase
Obesity	Preeclampsia	Protracted labor (1st stage)
Diabetes (or family history)	Gestational diabetes	Protracted labor (2nd stage)
High maternal birth weight	Large for gestational age fetus	Conduction anesthesia
Past birth of LGA child	Excessive weight gain (> 18 kg)	Use of oxytocin
Narrow pelvis	Postdatism	Arrest of labor
Past incidence of shoulder dystocia	Postmaturity	Vacuum extraction
"Elderly" primigravida	Induction of labor	Forceps delivery

LGA: Large for gestational age.

of arrest of the shoulders the rate of fetal damage associated with it cannot be determined. In the Perinatal Center in Newark head and body have been delivered during separate uterine contractions in about 1 out of 3 instances. Such cases were described in the records as normal spontaneous vaginal births. Obviously, some of these deliveries would have been labeled as shoulder dystocia elsewhere. Thus, the statistics of those doctors who "pull" routinely differ from those who "do not pull". Like apples and oranges, the results of these groups cannot be compared. Therefore, the impression deriving from the literature, namely that about 1 out of 10 cases of shoulder dystocia entails lasting fetal damage is an educated guess at best.

The characteristic damages associated with arrest of the shoulders are Erb's and-less often-Klumpke's palsies. Neurologists generally endorse the opinion that these are traction related injuries[15]. Rarely, the lesion may be bilateral. Fractures of the scull, clavicle and humerus are relatively frequent and so are intracranial hemorrhage and hypoxic brain damage[16]. The latter ones can be life threatening and may occur with or without brachial plexus affliction. Injuries of the spinal cord and the phrenic nerve are rare. Minor brachial plexus lesions that are apparent at birth usually disappear after a few weeks or months. These are probably pressure rather than traction related injuries. Afflictions that persevere for more than six months are likely to remain permanent.

PREDISPOSING FACTORS FOR ARREST OF THE SHOULDERS

Factors listed in Table 1 have been found conducive to arrest of the shoulders at delivery. Because their significance varies on a broad range, only those considered of major clinical importance require discussion in some detail.

Pelvic contraction

The importance of feto-pelvic relations is obvious even for the uninitiated. The expediency that a large head cannot pass through a small opening was already taken into account by medieval architects when they built the dungeons of Castel Sant' Angelo in Rome, the Bastille in Paris and the Tower of London. Manufacturers of kings' crowns and men's hats used this knowledge even earlier. Unfortunately, physicians failed to take notice of this information until the 17th century. Consequently, "midwifery" practiced by granny midwives only turned into "obstetrics" after Mauriceau[17] had recognized the importance of the relationship between the size of the fetal head and the capacity of the mother's pelvis. Considering this background and the information that even a low for gestational age infant may encounter severe shoulder dystocia in case the pelvis is inadequate[18], the fact that some current texts describe not only antepartum but even intrapartum pelvic assessment unnecessary represents a romantic and adventurous but ill-conceived return to the Middle Ages. Also surprising is the fact that in spite of the well-recognized role of diabetes in the causation of fetal macrosomia, shoulder dystocia and other serious complications, antenatal diabetic screening in the absence of predisposing factors was still labeled unnecessary relatively recently[19].

Obesity

It is a widespread misconception that danger of postoperative complications makes abdominal delivery in morbidly obese women undesirable. Since their risks increase when cesarean section is performed after protracted labor and also because arrest of the shoulders may be as much as 10-times more frequent in this group than in the general population, gross obesity frequently makes cesarean delivery the preferable choice[20]. While reviewing cases of arrest of the shoulders at delivery it became apparent that far too often little attention had been paid to maternal weight increase during pregnancy. Insofar as obesity is conducive to diabetes and thus to excessive fetal size, the importance of preventing undue maternal weight gain by restricting its gestational increase to 10-12 kg with appropriate diet is readily apparent.

Past history of shoulder dystocia

Previous shoulder dystocia is widely considered an indication for cesarean section. While a desirable choice in most instances, trial of labor may be a reasonable alternative when predisposing factors that prevailed in the preceding pregnancy (such as gestational diabetes, fetal macrosomia, protracted labor and difficult forceps extraction)

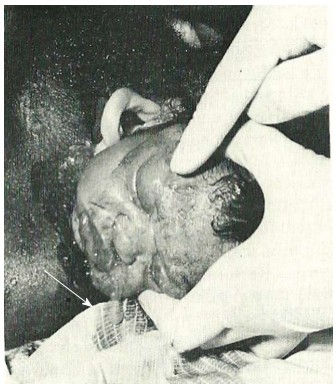

Figure 1 The picture illustrates a "2-step delivery" complicated by umbilical cord around the fetal neck. External rotation occurred shortly after the expulsion of the head and the delivery process stopped at that point. The cord was loosened but no attempt was made to extract the body. The picture taken at the onset of the next uterine contraction depicts its effect, namely expulsion of amniotic fluid from the respiratory tract (arrow). Since external electronic monitoring had demonstrated variable fetal heart rate decelerations at the end of the 2nd stage of labor, the cord complication was anticipated. Courtesy of Dr. Vivic Johnson.

are not present or appear avoidable.

Conduct of delivery

Interference with the physiological birthing process has been so widespread in recent decades that probably few obstetricians have witnessed a normal spontaneous labor and delivery during their career. In the course of its passage through the pelvic inlet the sagittal suture of the skull is in or close to the transverse diameter. As the head enters the mid-pelvis the caput rotates 90 degrees. In 96% of the instances the small fontanel moves anteriorly. It is under the symphysis when the caput reaches the outlet. These turns and the descent itself are brought about by uterine contractions and represent passive accommodation to the available space. After the emergence of the head expulsion of the fetal body is preceded by another 90 degree rotation around its axis, since the chest cannot pass between the sciatic spines unless the shoulders occupy the antero-posterior diameter of the pelvis. This process brings about "external rotation of the head" on the maternal perineum. In a considerable minority of deliveries the contraction stops after the emergence of the head but before its external rotation. It only occurs 2-3 min later. This process called "2-step delivery"[11] is a physiological phenomenon and carries no inherent risk[4-13,21-23]. Evidence of fetal compromise on electronic monitoring rarely justifies extraction of the body since the associated stress exacerbates preexisting hypoxia and may lead to meconium aspiration. Use of traction before external rotation of the head is futile and stressful for the fetus because the shoulders cannot traverse the pelvis in transverse rotation. It follows therefore that traction immediately after the delivery of the head invites arrest of the shoulders and may lead to Erb's palsy. For this reason, apart from major degree of abruption of the placenta or uterine rupture almost no situation calls for manual traction within the 3-4 min time frame of spontaneous vaginal delivery.

Tight umbilical cord around the fetal neck should be slackened but the temptation to extract the fetus must be resisted. While delivering the body the uterus compresses the chest and expels amniotic fluid and meconium from the respiratory tree (Figure 1). Cutting the nuchal umbilical cord prior to delivery of the shoulders is a dangerous polypragmasy which has no place in obstetrical practice[22,24].

In medicine as much as in everyday life to prevent a mishap one must know what brings it about. With regard to prevention of brachial plexus injuries, for reasons that go beyond the boundaries of medical science this question has become a battle ground of conflicting opinions: (1) Almost one-half of obstetrical malpractice claims relate to shoulder dystocia in America; (2) Skyrocketing malpractice premiums have forced capable doctors into early retirement; (3) Prodigious expenses of legal procedures have augmented the costs of maternity care; (4) The high costs of malpractice actions hindered the introduction of a national health care system; (5) Escalating brachial palsy cases required opening of neurosurgical units specializing in Erb's palsies; (6) Contradictory opinions have left doctors without guidance about the conduct of labor and delivery; (7) Obstetricians' obvious confusion has undercut patients' confidence in their knowledge and integrity; (8) The prevailing state of affairs turns capable medical students away from the specialty of obstetrics; and (9) Search for quick remedy obscures the fact that preventing birth injuries is the only long-term solution. Although contradictory views in medical publications dealing with this subject tend to confuse the picture, the basic issues are not particularly complex.

According to traditional thinking Erb's and Klumpke's palsies are physical injuries caused by use of excessive force during the extraction of the child from the birth canal. This concept is still favored by obstetricians in some foreign countries and probably everywhere by neurologists[15,21]. In contrast, among American obstetricians the idea that most injuries develop "*in utero*" spontaneously has gained wide acceptance[25-29]. It is understandable, that it struck a favorable cord in the hearts of practitioners. If Erb's palsies are spontaneous "*in utero*" injuries then there is no cause for self-doubt or self-reproach. Besides, this idea offers a firm ground for defending malpractice claims. If most injuries occur spontaneously, physicians are immune against litigations because it can never be alleged that "more likely than not" the damage derived from medical error. Formal acceptance of this concept would promptly end many obstetrical malpractice claims and could reduce insurance premiums by 40% or more. It is hardly surprising therefore that the arguments about the merits of the respective points of view have gone beyond the limits of disciplined academic dispute. Therefore, it amounted to an impressive example of professional integrity that a prominent protagonist of the "*in utero*" injury concept withdrew his initial claim when he recognized that the results of his animal experiments

Table 2 Birthweight distribution in 316 cases of fetal damage associated with shoulder dystocia[1]

Birth weights	Number of cases	Percentage of total
2500-2999 g	6	2%
3000-3499 g	20	6.0%
3500-3999 g	68	21.5%
=	=	=
4000-4499 g	107	34%
-	-	-
4500-4999 g	72	22%
5000-5499 g	32	10.5%
5500-5999 g	9	3%
⩾ 6000 g	2	0.5%

=: Traditional borderline for macrosomia; -: New American borderline for macrosomia. Based on traditional standards, less than 10% of all fetuses qualify for the definition of macrosomia. In this material 70% of all birth injuries were sustained by neonates belonging to this group. [1]Tables 2-4 show the results of mathematical calculations presented in previous publications. Copies of original articles containing details of the data analysis by the group's biostatistician can be obtained from the author.

Table 3 Birth weight associated risk of shoulder dystocia related fetal injury at delivery

Birth weight	National average	Sample	Estimated risk of damage
Under 3000 g	24%	2%	1:12000
3000-3249 g	17%	2%	1:8500
3250-3499 g	20%	4.5%	1:4444
3500-3749 g	16%	12%	1:3333
3750-3999 g	13%	9.5%	1:3368
4000-4249 g	5.5%	20%	1:275
4250-4499 g	3%	14%	1:214
4500-4749 g	0.8%	14%	1:57
4750-4999 g	0.3%	8%	1:37
5000-5249 g	0.2%	8%	1:25
⩾ 5250 g	0.2%	6%	1:33

In previous publications the author arbitrarily defined "acceptable" risk for fetal injury as 1% noting that the maternal risk of permanent injury in case of cesarean section is much lower. The table shows that the limit of acceptable risk is already exceeded at the 4500 g level and increases to 3%-4% when the fetal weight is 5000 g or more.

had been misinterpreted[27].

Conduction anesthesia during labor

Since it was recognized during the early days of spinal and epidural anesthesia that it had significant side effects, concern was expressed about the desirability of its routine use[30]. The untoward effects of conduction anesthesia fall into four major categories[31]: (1) Cardiovascular toxicity; (2) Maternal and fetal central nervous system toxicity; (3) Reduced uterine blood flow; and (4) Decreased uterine contractility.

Clinically, these effects manifest in convulsions, hypotensive episodes, cardiac arrhythmias leading to cardiac arrest and lasting neurological damage by injection into the spinal canal rather than into the epidural space. Eventually, in the absence of medical consensus it was women's demand that turned epidural anesthesia into a routine procedure[32].

Fetal macrosomia

Large fetal size plays a major role in arrest of the shoulders at birth[16,33-38]. However, it has been problematic to quantitate the magnitude of the risk[39]. Therefore, concern about increasing cesarean section rates induced professional organizations to encourage practitioners to deliver markedly large for gestational age (LGA) fetuses vaginally[40]. Apparently reassured by the claim that 50% or more of all brachial plexus injuries are spontaneous "*in utero*" events, as recently as 2002 and 2005 the ACOG[41] and the Royal College of Obstetricians and Gynaecologists (RCOG)[42] advised physicians to deliver fetuses of diabetic mothers weighing as much as 4500 g and those of non-diabetic women up to 5000 g vaginally and to use traction if the body does not soon follow the head.

In the course of a review of cases of shoulder dystocia related birth injuries that had occurred between 1960 and 2007 the author's group evaluated the distribution of birth weights of affected neonates[16]. The findings summarized in Table 2 show that a relatively small group of macrosomic babies suffered the overwhelming majority of injuries. The weight related increase of permanent damage showed a logarithmic curve rather than a geometric line. This finding implies that danger of underestimating fetal weight exceeds that deriving from overestimation.

Based on the above mentioned evidence the risks of damage for individual fetuses belonging to various weight groups were evaluated next. The calculation took into account the birth weight distribution in the United States[43] along with the information that about 1 out of 100 deliveries involve shoulder dystocia[44] and 1 out of 10 such newborn babies sustain permanent injury[45]. The results of this calculation are indicated in Table 3.

The investigated cases derived from 40 states or districts of the Union. The mothers' parity ranged from zero (112 cases) to more than six (4 cases). Maternal ages ranged from 13 to 45 years with the majority of them falling into the middle range. The ratio of male *vs* female neonates was 51:49.

Birth injures included 259 incidents of brachial plexus damage, 32 cerebral palsies, 6 cases of mental retardations, 16 developmental delays, 12 traumatic cerebral bleedings, one spinal cord dissection, and 8 perinatal deaths. The method of delivery was spontaneous on 200 occasions. Forceps were used for delivery 61-times, vacuum extraction on 41 occasions and both instruments (ventouse followed by forceps) 14-times. Several babies suffered multiple injuries. Three childbirths concluded by the Zavanelli maneuver[11] and cesarean section were included in the spontaneous vaginal delivery group.

According to reliable statistics[19], "in all series there is a two or threefold increase in the rate of cesarean delivery with high birthweight". This being the case, the gradually increasing frequency of fetal injuries in the LGA and macrosomic categories derived from a gradually diminishing number of vaginal deliveries of large fetuses. Obviously this circumstance biased the above presented results. When based on this knowledge the calculation

Table 4 Risks of shoulder dystocia related fetal damage in spontaneous and instrument assisted deliveries

Birth weights	Spontaneous deliveries	Instrumental extractions
Under 3500 g	1:5660	1:900
3500-3999 g	1:1740	1:110
4000-4499 g	1:204	1:24
4500-4999 g	1:41	1:6
⩾ 5000 g	1:25	1:3

Birth weight related fetal risks for damage in cases of spontaneous *vs* instrument assisted deliveries. Note that use of extraction instruments increases the chance for fetal damage almost 10-fold.

was adjusted, it transpired that the actual risks for lasting damage in these groups were more than 2.5% when the weight exceeded 4500 g and 5% when the child weighed more than 5000 g. Evaluation of these findings even on the ground of high school mathematics permitted the conclusion that widely quoted and relied on statistics[39,40] had grossly overestimated the number of cesarean sections needed for preventing of one fetal injury.

Arguments against elective abdominal delivery on the basis of estimated fetal weight have often included the warning that sonography was likely to overestimate the fetal size. Review of the literature clarified however, that in the 5000 g danger zone ultrasound examinations underestimated the fetal weight in 80% of the instances[46-48]. This fact indicates that the real danger associated with reliance on sonography is failure of identifying some excessively large fetuses rather than overestimating those who are not unduly large.

Because maternal risks associated with abdominal delivery are substantially less, in the writer's opinion a chance of 1% for permanent fetal damage is the acceptable maximum in contemporary practice. Even this liberal view incorporates obstetricians' traditional prejudice, namely that the mother's life is more precious than that of her unborn child. Consequently, the final arbiter of any relevant decision has to be the pregnant woman whose tolerance concerning maternal and fetal risks may differ from that of her obstetrician or of the consensus of medical opinion.

Instrumental deliveries

Observant obstetricians drew attention to the fact several years ago that mid-forceps extractions had markedly increased the incidence of shoulder dystocia[49]. By the same token, in the authors' material shoulder dystocia related fetal injuries had often been preceded by forceps or ventouse extractions. Between 1973 and 2006 not less than 117 records referred to instrumental deliveries[50]. When the material was distributed into weight groups (less than 3750 g/3750-4499 g/4500 g or more), it was learned that extraction instruments were frequently used in each of them (37%/40%/27%).

Comparison between the various technical procedures was hindered by two circumstances: (1) The ACOG elected to change the criteria of mid and low forceps operations in the 1980's. Since some physicians continued adhering to the old definitions, the documentations with regard to the actual types of the operations were often inconclusive; and (2) Whereas a statement pertaining to the nature of forceps operations usually appeared in the records, the majority of ventouse users provided no explanation.

Among those forceps procedures where the nature of the operation was stated 2 were performed at the outlet, 27 were low forceps and 29 mid-pelvic operations. Three forceps, one ventouse and one ventouse-forceps procedures were marked as "high".

Although in the entire material about two-thirds of the deliveries were spontaneous, the incidents of central nervous system (CNS) damage in the spontaneous and instrumental delivery groups were close to equal (37 *vs* 33). Thus, the use of instrument almost doubled the risk of CNS damage.

The data permitted a comparison between spontaneous deliveries on the one hand and extractions by instrument on the other. The result of this calculation is shown in Table 4. The tabulation indicates that in most categories the risk of major injury was more than 10-times higher when forceps or vacuum extractor was used than when unassisted delivery of the child was allowed.

This study does not support the claim that ventouse is more accident prone than forceps[51]. In fact the opposite was the case in this material. It transpires however, that both instruments augment the risks and that gradually increasing fetal weight increases them exponentially. The findings imply that one percent chance for fetal injury already prevails when extraction instrument is used for the delivery of a 4000 g fetus. Therefore, the author considers such a fetal weight the uppermost limit for a relatively safe extraction procedure in virtually any clinical situation. Undoubtedly, mid-cavity operations carry even higher danger.

Impaired glucose tolerance and diabetes

Routine glucose screening was not a requirement during those years while the medical records utilized for the here cited study were generated[52]. On this account evaluation of the predisposing effect for shoulder dystocia of maternal glucose intolerance was hindered. Only about two-thirds of all records contained reference to diabetic screening and some of these were not standard tests. Therefore, the information they provided was often equivocal. This circumstance limits the validity of the investigators' calculation, namely that whereas only 10% of all neonates weigh more than 4000 g in the general population, the rate is about 50% for diabetic mothers and 20% for those women with "predisposition" for diabetes[53]. Typically, positive screening test followed by negative 3 h glucose tolerance test was considered indicative of predisposition. In the > 4000 g weight group the risk of birth damage was 5-times increased for infants of diabetic mothers and twice for those of pre-diabetics as compared to others. Birth weights exceeding 4500 g seem to be 10-times more likely to occur among babies of dia-

betic women than among those of non-diabetic ones[16].

In light of the data reviewed routine diabetic screening of all pregnant women and attentive treatment of the disease are considered absolutely necessary. Although good management must take into account many relevant factors, including pelvic dimensions, previous births, maternal diet and others, in most instances an estimated fetal weight of 4000-4200 g represents for the author the uppermost limit for vaginal delivery in case of confirmed maternal diabetes. Assessment of fetal weight and size by ultrasound should be considered an obligatory routine in case of suspicion of LGA fetal status.

EFFECTS OF PRACTICE PATTERNS

During the 50 years covered by the studies of the author's group, routine management of labor has changed in many respects. It is necessary therefore to consider the potential effects of new developments upon the birthing process and its complications.

Oxytocin

When the drug entered the market it often caused uterine hyper-stimulation. Later it was only administered in intravenous drip under electronic fetal monitoring. Therefore this side effect became substantially reduced. This being the case, although it is suspected to increase the chance for shoulder dystocia, the drug is unlikely to be a major predisposing factor for arrest of the shoulders since it did not affect its rate during its relatively liberal use in clinical practice between the 1950's and 1970's.

Electronic fetal heart rate monitoring

Dysfunctional labor predisposes for shoulder dystocia. Designed to register uterine activity and evaluate fetal condition, external monitoring combined with tokography is useful and innocuous. By allowing the obstetrician to eliminate abnormal labor patterns and thus avoid difficult deliveries, electronic monitoring substantially reduced the number of factors conducive to brachial plexus injuries.

Fetal scalp blood pH determination

The technique is difficult, costly, labor intensive, in untrained hands inaccurate and carries the risk of causing fetal infection. It enjoyed popularity initially and was used with relative frequency for three decades. The technique largely disappeared from clinical practice by the early 2000's. It is unlikely that it influenced the rate of shoulder dystocia.

The "labor curve"

During the first half of the 20th century dysfunctional labor was tolerated for long periods of time because a cesarean section rate of 5% was considered the acceptable maximum. Friedman's[54] research pointing out the dangers of protracted labor changed physicians' thinking. Introduction of fetal heart rate monitoring that allowed recognition of "fetal distress" had similar effect. As a result, by the 1970's cesarean section rates rose to 10%-15%. The bush fire no longer could be stopped. At the turn of the century the rate of abdominal deliveries reached 30% and then increased even further. While it's other effects are disputable, this development was bound to reduce the incidence of shoulder dystocia and the related fetal injuries for more than one reason: (1) The fact alone, that the number of vaginal deliveries decreased by almost one-third allowed the expectation that shoulder dystocia would be reduced by the same rate; and (2) Many abdominal deliveries are done for protracted labor predominantly due to large fetal size[19]. Thus a high proportion of difficult vaginal deliveries that were conducive to shoulder dystocia became replaced by cesarean sections. In effect, changes that turned "obstetrics" into "perinatology" were such in nature that they were bound to cut the prevailing rates of shoulder dystocia and its related fetal injuries markedly. Obviously, any theory addressing the subject of causation must explain why Erb's palsies have continued to increase in America despite a marked reduction of its predisposing factors.

MISCELLANEOUS FACTORS AFFECTING INCIDENCE OF SHOULDER DYSTOCIA

The above mentioned change in the management of the birthing process that had escaped critical evaluation for several decades diverted the investigations of the author's group to new directions.

Geographic variations

The rates of shoulder dystocia differ in various geographic areas and at various time periods. Examples are its increasing rate in the United States[55,56], a high proportion of brachial plexus injuries deriving from a moderate number of shoulder dystocia incidents in Sweden[57,58] and its infrequent occurrence in the British Islands[42,59,60], Hong Kong[61] and Israel[62,63]. High birth weights of Swedish babies and relatively low weights of Chinese ones probably played a role in the quoted trends. This circumstance underlines the rule that conclusions based on one particular racial group do not always apply to others.

Chronologic fluctuations in the rates of shoulder dystocia

Disputes in America about the causes of shoulder dystocia have involved the contention that its incidence had not changed for decades[64]. The data presented in support of this claim included statistics from foreign countries where this complication had been rare. This arbitrarily mixed material did not reflect the state of affairs in the United States. Therefore, a computer search was undertaken. It yielded 20 reports that included 26 separate studies for the years of 1949-2005. The periods of observation ranged in the various studies from 1 to 10 years. The results deriving from these statistics are shown in Table 5.

Table 5 Incidence of shoulder dystocia in the United States between 1949 and 2005

Time periods (yr)	Number of reports	Ref. numbers of reports[1]	Average incidence per 100 births[2]
1949-1974	5	[55,65-68]	0.26%
1975-1990	10	[49,55,56,69,70-74]	1.22%
1991-2005	11	[56,74-81]	1.65%

[1]Two authors presented multiple reports; [2]Some reports referred to number of cases per 100 vaginal births. These were adjusted under the premise that the rate of cesarean section was 20%. Note that the rate of shoulder dystocia increased almost 5-fold by the 2nd and more than 6-fold by the 3rd time period as compared to the 1949 to 1974 average.

The data reveal that arrest of the shoulders occurred rarely (about 2-3 out of 1000 births) prior to the mid-1970's. Its rates rose rapidly thereafter until and including the first decade of the current century. In some services the increase was as high as 10 to 15-fold. Thus, rather than having remained stable cases of arrest of the shoulders and its neonatal consequences increased exponentially in the United States since the 1970's. This development appeared mysterious for a variety of reasons: (1) Changes in practice patterns eliminated or markedly reduced the number of predisposing factors for shoulder dystocia since the 1950's; (2) While the incidence of arrest of the shoulders increased in America its rate remained stable in the British Islands; (3) Circulars from medical organizations inundated practitioners with instructions about the prevention and management of arrest of the shoulders in recent years; and (4) Few issues of obstetrical journals appeared without studies discussing shoulder dystocia related problems.

Because the turnaround happened in the 1970's, the author elected to study those changes that had taken place in the practice of obstetrics around that time. This inquiry brought into focus two articles published by Wood *at al*[82,83] in the leading British specialty journal in 1973. Utilizing the at that time novel scalp blood pH technic during normal deliveries, these investigators found that after the emergence of the head the pH of the capillary blood fell at a rate of 0.04 to 0.14 units per minute although the neonates had excellent Apgar scores. Presumably because the technique was as yet unreliable at that time, these papers generated little interest in Great Britain. In contrast, they caused concern in the United States. Without explaining why, new editions of textbooks announced that the fetus must be extracted from the birth canal following the expulsion of the head without delay[84,85].

Wood *at al*[82,83] inconclusive research certainly deserved rechecking in order to assess its clinical relevance. However, things went the opposite way. Practice patterns were modified overnight but only quarter of a century later were scalp capillary pH levels studied during the head-to-body delivery interval in well-equipped laboratories by investigators who had experience with the technique. Aware of the clinical implications of their research their attention focused on babies who encountered shoulder dystocia. They found that delayed delivery of the body did not alter capillary pH significantly[80,86,87]. Investigations by Gurewitsch[88] based on more than 200 cases revealed that delayed delivery of the body caused no clinically significant change in the fetal metabolic equilibrium for up to 8 min.

Perhaps the most persuasive contribution to this subject was the investigation of Locatelli *et al*[23]. These research workers undertook a prospective study involving 789 patients who gave birth by the conservative method. It was found that the mean head-to-body interval was 88 s and the decline of the umbilical artery pH was only 0.0078 units per minute. They concluded that spontaneous birth did not significantly increase the risk on neonatal acidemia. Obviously, Wood *et al*[82,83] grossly overrated the decline of the fetal scalp blood pH during the delivery process. Thus, the reason for the still ongoing effort directed at shortening the head-to-body delivery time is difficult to understand.

In the opinion of the writer of this review the abrupt change in the management of the delivery process introduced into practice in the mid-1970's has been and remains the most important single factor responsible for the rapid increase of arrests of the shoulders at birth and the associated fetal neurological injuries in the United States.

It should be a matter of great concern that a group of investigators who had attempted in earnest to reduce the head-to-body interval to a minimum ended up with unprecedented 13.8% and 10.8% rates of arrest of the shoulders[89,90]. News of this "shoulder dystocia tsunami" raised no eyebrows among "fetal rescue" advocates. They reiterated a few years later: "Shoulder dystocia is an unpreventable obstetric emergency"[64].

Indeed, arrest of the shoulders is unpreventable if one prefers to believe that brachial plexus palsy has little to do with the method of delivery. Investigators who refrained from using traction during the birthing process, reduced the rate of this dangerous complication to the range of 0.2% without even trying[12,13].

On account of its adverse effect upon the practice of medicine, the fact that in the long run prevention of catastrophic birth injuries is the most effective approach to avoiding costly malpractice litigations deserves a brief mention in the context of the ongoing controversy[91].

Methods of delivery and shoulder dystocia

In order to evaluate the fetal effect of delayed delivery of the body after arrest of the shoulders, the writer's group reviewed in their medico-legal material those births that had occurred after 1974. Only 103 records documented the head-to-body intervals. Table 6 shows the relevant findings.

Table 6 Head-to-body delivery times in 103 cases of shoulder dystocia related neonatal neurological damage

Head-to-body interval	Number of cases
0-1 min	32
1-2 min	38
2-3 min	12
3-4 min	5
4-5 min	8
5-6 min	2
6-7 min	2
7-8 min	2
8-9 min	0
9-10 min	2

Note that in 82 instances (80%) delivery involving neurological injury of the child was accomplished within 3 min. Before 1973 these cases would not have been classified as shoulder dystocia. Because delay of the next contraction by 5 min does not endanger the fetus, the use of traction was unnecessary in the majority of these cases.

In a high proportion of the cases (42%) the 5 min Apgar score was less than five. Clinical experience shows that babies who are born spontaneously are in good condition even if the body is expelled with 5 min delay[11,88]. Thus, the low scores in this group most likely derived from stress caused by the extraction efforts.

Although the United Kingdom remained unaffected by the American shoulder dystocia crisis, the RCOG in 2005 endorsed the idea that the fetus must be extracted from the birth canal after the delivery of the head[42]. The "Guidelines" of the College cited the so called CESDI report in support of this advice stating that the investigation had found that 47% of babies who perished following deliveries complicated with shoulder dystocia "died within 5 min of the head having been delivered". Actually, members of the CESDI Committee emphasized that the adverse outcomes were unrelated to the head-to-body delivery intervals. They explained that the neonatal deaths had resulted from substandard management of the labor and inadequate skills on the part of doctors in charge[92]. The misleading misinterpretation of the official report by the RCOG Guidelines was duly pointed out by this writer's group in a recent review article sponsored by the Royal Society of Medicine in London[93].

Research performed one century ago utilizing fetal cadavers showed that typical brachial plexus lesions could be induced by applying strong traction upon the fetal head against resistance[94]. More recent experimentation conducted by French neurologists confirmed the earlier findings[95]. Utilizing sophisticated methodology Allen produced evidence that supported a relationship between aggressive management of the birthing process and neurological birth injuries[96]. He concluded based on his experiments that brachial plexus lesions sustained at birth were traction injuries and demonstrated that when encountering strong resistance, physicians subconsciously double the effort that the extraction of a child under normal circumstances requires.

Based on an extensive review Gurewitsch *et al*[97] concluded that "the single greatest correlate with neonatal brachial plexus injury after shoulder dystocia is (the) degree of clinician-applied traction".

Brachial plexus injury and cesarean section

Disregarding the fact that the observed cases of brachial plexus "paresis" had been only transitory, it has been proposed that babies born without any traction suffered brachial plexus damage (*i.e.*, "paralysis"). It has also been claimed that Erb's palsies are frequent among babies born by cesarean sections.

In the material that included 338 fetal injuries typically related to shoulder dystocia, only one child sustained Erb's palsy during abdominal birth. The case in question was a term delivery by elective repeat cesarean section. During the operation the surgeon found extensive adhesions at the area of the previous lower segment transverse incision. He could not create adequate opening and it was with great difficulty that the child was extracted eventually through a small incision. This incident was rare enough to deserve publication. Based on the stated details the article presented the opinion that most likely this child sustained typical traction injury[98].

Ubachs *et al*[99] analyzed 130 brachial plexus injuries of which 28 were associated with breech extractions. The authors noted that all vertex deliveries involved extensive manipulation and concluded that none of the cases could be attributed to "intrauterine maladaptation". They emphatically pointed out that no injury in their material had been associated with cesarean delivery.

Most obstetricians have encountered cases where delivery of the shoulders across a small incision cut through an uneffaced cervix caused as much difficulty as arrest of the shoulders during a vaginal birth does. This being the case it seems likely that most of those extremely rare brachial plexus palsies that are associated with abdominal deliveries are traction related.

PREVENTION OF SHOULDER DYSTOCIA AND BRACHIAL PLEXUS INJURIES: CONTROVERSIAL ISSUES

Because education pertaining to its management has little if any effect upon the rate of fetal injuries associated with arrest of the shoulders[100], this complication needs to be avoided as far as possible. Since prevention requires understanding of the cause of the problem[101], any prevailing theory has to be consistent with established facts in order to prove its validity. Therefore, advocates of the respective concepts must be able to answer several relevant questions: (1) Why did the rate of shoulder dystocia increase exponentially in the United States during the last 40 years in spite of the fact that changing practice patterns eliminated many of its predisposing factors? (2) Why did the rate of shoulder dystocia remain stable in Great Britain while it escalated in America? (3) Why do instrumental extractions increase the rate of brachial plexus palsies exponentially? (4) Why is brachial plexus injury literary rarity among neonates delivered by cesarean section? (5) Why is

maternal diabetes a strong predisposing factor for neurological birth injuries? (6) Why do most Erb's palsies occur in association with documented diagnosis of shoulder dystocia? (7) What experimental model supports the validity of the respective etiological theories? and (8) Does lack of diagnosis of shoulder dystocia indicate that Erb's was sustained spontaneously "*in utero*"?

The following are the answers of the author to these questions:

Question 1: The population of, and the living conditions in the United States have been stable during the 20th century. No new circumstance has emerged that could conceivably have caused fetuses to suffer Erb's or Klumpke's palsies *in utero* six-times more often than 50 years ago. The cause of the damage has to be therefore extrinsic.

Question 2: Up to 2005 the method of delivery remained conservative in the British Islands whereas it has been changed to "active" management in the United States. As a result, up to recently the rate of shoulder dystocia had been low in the United Kingdom[59,60,102].

Question 3: Should neurological injuries occur spontaneously *in utero* the use of ventouse or forceps could not affect their incidence. The documented relationship underlines the role of traction in the causation of injuries. Following instrumental extraction of the caput the uterus seldom expels the body within 30 or even 60 s. As a result, doctors adhering to active management are compelled to apply manual traction after the instrumental delivery of the head virtually invariably.

Question 4: Because 15% to 35% of all births involved the abdominal route in recent decades, the extreme rarity of Erb's palsy among cesarean babies is noteworthy. Obstructed labor accompanied by strenuous uterine activity is a frequent indication for abdominal deliveries. If the activity of the uterus had caused a significant proportion of brachial plexus injuries, Erb's palsies should be frequent among babies delivered by cesarean section on account of obstructed labor. However, this is not the case.

Question 5: Diabetes causes fetal macrosomia and broadens the shoulders out of proportion to the diameters of the head[33]. These effects predispose for arrest of the shoulders at birth and explain why big fetuses of diabetic mothers are particularly prone to suffering damage[50,53].

Question 6: The records reviewed by the authors were unselected and had been generated by many doctors and nurses in almost as many hospitals. Their references to shoulder dystocia were not influenced therefore by policies, interpretations or biases that may have been prevalent in some institutions or certain geographical areas. Had a high proportion of injuries been spontaneous "*in utero*" accidents there would have been no reason for them to coincide in > 90% of all instances with a complication (*i.e.*, shoulder dystocia) which only occurs once out of 100 deliveries.

Question 7: Experimental evidence supports the role of traction in the causation of Erb's and Klumpke's palsies[94,95]. No comparable evidence has been presented on behalf of the spontaneous "*in utero*" injury mechanism.

Question 8: This question is irrelevant to the pathological mechanism for several reasons: (1) The cause of brachial plexus injury is traction. Whether excessive pulling is done during or in the absence of arrest of the shoulders does not influence the mechanism of the injury; (2) With traditional delivery the criteria of shoulder dystocia are unequivocal. With active management the diagnosis is subject to the judgment of the accoucheur. It has therefore no objective validity; and (3) If one believes that the absence of shoulder dystocia proves that brachial plexus injury has occurred spontaneously "*in utero*", his or her judgment may become biased, even if subconsciously against acknowledging this diagnosis. Uninfluenced by such specious interpretation, more than 90% of the records in the author's data base that came from hundreds of different geographic locations, indicated that shoulder dystocia and brachial plexus palsies had occurred coincidentally.

Predicting shoulder dystocia

Reflecting unawareness of medical history, the dictum: "arrest of the shoulders cannot be predicted" has been repeated incessantly in recent years. Advocates of this truism must have overlooked that Jenner had not proposed only to vaccinate those unidentifiable children who had been singled out by Fate to contract smallpox. By the same token, Lind did not try to find out which ones of the embarking sailors for a voyage overseas would need a supply of fresh fruits in order to avoid scurvy. Similarly, Semmelweis did not restrict his aseptic measures to women whose destiny had been to roll in fever within a few days. Had these scientists wasted their time trying to "predict" the next victims of smallpox, scurvy or childbed fever, the secrets of these diseases would have remained unresolved for many more decades. In the same spirit, brachial plexus palsies must be avoided by general precautionary measures rather than by trying to determine who may need such protection next time.

Considering the present state of knowledge one must accept the probability that shoulder dystocia even in the best hands will continue to complicate two or three out of 1000 births for some time unless gifted soothsayers figure it out how to predict the victims. Until then, American obstetricians must live with the thought that only 80%-90% of currently prevailing brachial plexus palsies are preventable even if the urge of rescuing healthy babies from the womb is successfully resisted.

The causes of shoulder dystocia and the mechanisms of brachial plexus injuries are well understood. This problem is no different from many others that medical research has already resolved.

Basic principles concerning use of traction for delivery

It is a strange aspect of the shoulder dystocia controversy that the management of delivery is usually discussed as if long established concepts of modern obstetrics were fairy tales. Ever since the vacuum extractor had been

introduced into clinical practice it has been a rule that traction should only be applied at the time of uterine contraction[103]. This requirement ensures that expulsive uterine force supplements traction, thus eliminating the need for using undue effort. In violation of this concept, instructions governing the management of normal delivery encourage doctors to apply traction 30 or 60 s after the emergence of the head; the time when the contraction has just ended. As a result, the physician is forced to use more effort than would be needed if he waited for the next uterine systole. Although the latter would expel the fetus without intervention anyway, the risk of stretch injury could be already reduced if the obstetrician waited for a contraction and used traction in synchrony with it. That the condition of the fetus does not deteriorate between the contractions has been proven beyond any doubt[12,13,28,80,88]. Therefore, it defies elementary logic that an obstetrician who may have to wait several minutes for a contraction before delivering a severely compromised fetus with the ventouse, must extract a perfectly normal child by sheer force right after the expulsion of the head.

Medical errors leading to shoulder dystocia

Because the subject had been disregarded in the past, the role of the method of delivery in the causation of birth injuries has been stressed in this review. However, the records used for this research also revealed numerous departures from good obstetrical practice (not necessarily in conflict with minimum contemporary requirements) that were common denominators of the described accidents: (1) Assessment of the pelvic dimensions was often omitted or not documented in any detail; (2) Small maternal stature was ignored even if the mother was primigravida or had diabetes; (3) Frequently diabetic screening was either not done or equivocal test results were disregarded; (4) Confirmed diabetes seldom was treated effectively and only rarely with the involvement of an expert; (5) Excessive maternal weight gain seldom received attention and dietary instruction was rarely offered; (6) Frequently, not even by manual palpation was fetal weight assessed at or near term gestation; (7) Suspected LGA fetal status was not always evaluated with ultrasound; (8) Even if fetal macrosomia was suspected preparation for a difficult delivery was seldom made; (9) Some instrumental extractions of LGA fetuses were done without clear indication; and (10) Often only McRoberts maneuver, suprapubic pressure and manual traction were used for the management of shoulder dystocia.

It was a thought provoking feature of these unfortunate accidents that with relatively few exceptions not one single misjudgment but a combination of errors had led to neonatal injury. Correction of any one of them could have avoided the bad outcome on many occasions.

EPILOGUE

For physicians who due to indoctrination, habituation or temperament are addicted to rescuing babies from the birth canal the above shown list offers "Ten Commandments of Avoiding Shoulder Dystocia". With just a little luck they will find them helpful. For others who can be persuaded to allow mothers give birth naturally, the 11th Commandment: "Use two-step delivery!" may be the compass that guides them to the Promised Land where the rate of arrest of the shoulders is only 2-3 out of 1000 births. The return voyage there should not take another forty years. Some clever doctors from the United Kingdom, Israel, Ireland and Hong Kong have already found their ways there. Yet, it may be a worrisome journey for one who decides to sail across the Ocean of Misgivings with doubts in his mind, not unlike the sailors of Santa Maria did in the 15th century when they were still not quite convinced that the earth was round.

Having been accepted by too many obstetricians in the New World, belief in the ritual of reducing head-to-body delivery time and in the myth of "*in utero*" acquired Erb's palsies has become a matter of faith. "Faith can move mountains". Actually, it has already moved one when the ancient fortress of sound obstetric practice in London opened its gate and invited the trans-Atlantic Trojan horse inside its walls.

Lack of supporting evidence does not automatically sink attractive new ideas back into oblivion. More comforting is to think that the missing evidence is hidden somewhere nearby. The alternative would be to admit that well-meaning doctors have deceived themselves when they announced the discovery of a magic formula, capable of solving a distressing medical problem and putting the evil jinn of malpractice claims back into the bottle from where he had escaped. Alas, facts do not always prevail over wishful thinking. It is difficult for doctors who have done what they considered best for their patients to acknowledge that some of their activities were counterproductive. Ignatz Semmelweis was tormented by this thought throughout his life. Some others found easier ways out.

Almost two centuries ago Oliver Wendell Holmes presented a thesis which was important enough to be remembered thousand years from now. He eloquently, logically and correctly explained the cause and patterns of spread of puerperal fever[104]. His lecture included the unwelcome news that doctors who provided care for women in labor unwittingly transferred a deadly disease from one mother to the next. Having given due consideration to his already famous colleague's discovery, Professor Meigs one of the foremost authorities in obstetrics at that time, declared his own opinion. With one single sentence he may have sealed the fate of more women than the number of those whom all obstetricians in America saved from death during his professional lifetime. He also demonstrated that men incapable of seeing the difference between "belief" and "knowledge" could achieve distinguished reputation in medicine: "I prefer to believe"-he said-"that childbed fever is brought about by the will of Providence, which I understand, than that it is caused by an unknown contagion, which I don't"[105].

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MINIREVIEWS

Gynecological malignancies and hormonal therapies: Clinical management and recommendations

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Abstract

Every year in the world a large number of women receive a diagnosis of gynecological cancer and undergo a therapy such as surgery, chemotherapy and radiotherapy to the pelvic region. A large portion of these patients are already in menopause, but for younger patients therapies are responsible of early menopause. The physical and psychological symptoms due to iatrogenic menopause significantly reduce the quality of life; however hormone replacement therapy (HRT) has a high efficacy in reducing menopausal symptoms. The prescription of HRT in patients with story of gynecological cancer is debated because its safety has not been completely proven. The main criticism is based on the theory that the hormone replacement could stimulate growth of residual cancer cells increasing the risk of recurrence.

Key words: Iatrogenic menopause; Gynecological cancer; Hormone replacement therapy; Risk of recurrence; Climateric symptoms; Cardiovascular benefits; Clinical practice

Core tip: In this paper we analyze the role of hormone replacement therapy (HRT) in patients affected by gynecological neoplasms with iatrogenic menopause symptoms. We have analysed more than 70 articles with the aim to evaluate the possibility of using HRT in different gynaecological malignancies related to stage and grade of the neoplasm. The literature shows that the use of HRT is controversial in type I of endometrial cancer, endometrioid type of ovarian cancer, uterine cervix adenocarcinoma and endometrial stroma and leiomyosarcoma.

Perrone AM, Pozzati F, Santini D, Rossi M, Procaccini M, Casalini L, Santi E, Tesei M, Zamagni C, De Iaco P. Gynecological malignancies and hormonal therapies: Clinical management and recommendations. *World J Obstet Gynecol* 2014; 3(4): 162-170 Available from: URL: http://www.wjgnet.com/2218-6220/full/v3/i4/162.htm DOI: http://dx.doi.org/10.5317/wjog.v3.i4.162

INTRODUCTION

Hormone replacement therapy (HRT) consists in the administration of synthetic or natural female hormones to compensate the diminution or deprivation of natural hormones. Estrogenic therapy is useful in reducing menopausal symptoms like night sweats, insomnia, hot flushes, sexual disorder and dyspareunia[1-7]. Moreover Estrogens are effective in preventing the acceleration of bone turnover and the bone loss associated with menopause, and in reducing cardiovascular accident a diabetes insurence. HRT is the use of Estrogen alone (ERT) or, in women with an intact uterus Estrogen combined with a Progestin (EPT) to prevent endometrial proliferation

that can exacerbate an endometrial cancer. In fact, Estrogen brings an endometrial proliferation by increasing estrogen/progesterone receptors and cellular mitosis in the endometrial glandular epithelium. The association of Progestin creates a down-regulation of these receptors and moreover an induction of the activity of the 17 β-estradiol dehydrogenase which transforms Estradiol into Estrone that has an inferior activity. The association of Progestin thereby reduces the estrogenic stimulus on the endometrium[8]. Under the progestin influence, the histology of the endometrium changes from proliferative to secretive, and this reduces the risk of insurance of hyperplasia[9]. In the past 10 years much confusion has been generated regarding the use of HRT in the general population[10]. In fact HRT led to some important risk like breast cancer, venous thromboembolic events, stroke and coronary artery events[11]. After the publication of "Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health"[11] a general consensus on HRT has been agreed. However in oncological environment the use of HRT remains subject of debate. Women treated for gynecological cancer invariably incur the consequences of Estrogen deficiency due to the surgical resection of the ovaries, irradiation and chemotherapy[12]. Because of the underlying fear of cancer survivors, the insecurity of the clinicians, the lack of national or societal guidelines and the possibility of litigation should the woman develop a recurrence whilst taking oestrogen therapy, most clinicians do not prescribe HRT to these patients[12] regardless of tumour type and disease stage[13]. This has led to many women being denied the use of HRT thereby increasing the number of young patients who experience the effects of iatrogenic menopause. This is severely more intense than the natural onset both because of the sudden decline in estrogen/androgen levels and because of the younger age of the patients[14-16]. In particular severe hot flushes, vaginal dryness, sexual dysfunction, sleep disturbances, and cognitive changes may significantly affect quality of life[17]. The purpose of this review is to analyze the possibility of using ERT or EPT in patients who have been treated for gynecological malignancies with the aim of establishing recommendations for clinical practice.

RESEARCH

We reviewed the literature using the terms: HRT, ovarian cancer, cervical cancer, uterine sarcoma, endometrial cancer, borderline ovarian tumor. We analyzed more than 70 articles for the present study.

OVARIAN CANCER

Epithelial ovarian cancer

Epithelial ovarian cancer (EOC) is the most common type of ovarian cancer and the leading cause of gynaecological cancer related mortality[18,19]. It typically develops as an insidious disease[18,20,21], with few distinct symptoms until the tumour has become large or disseminated[19]. Currently, cytoreductive surgery combined with platinum-based chemotherapy is the standard treatment also for patients of child-bearing age. Cytoreductive surgery for a malignant ovarian tumour frequently results in the loss of ovarian function and menopausal symptoms[22]. HRT use for these patients is controversial because of the potential stimulation of residual cancer cells and the induction of new hormone-dependent disease[23]. Epidemiological investigations have suggested that malignancies of the genital tract may be associated with hormonal stimuli and with the ingestion of long-term oral estrogen[24,25]. *In vitro* experiments have yielded inconsistent results regarding the estrogen stimulation of cancer cell proliferation. Certain *in vitro* experiments have shown that estrogen is capable of stimulating the proliferation of malignant cells[26,27]. While some results of these studies showed tumour cell growth inhibition by estrogen[28], other authors found no effect of estrogen on malignant cell growth[29,30]. There are 4 different histological types of epitelian ovarian cancer: serous, endometrioid, clear cell and mucinous carcinoma. The 70% of EOC are serous type and probably derive from the ovary epithelium or the fallopian tube[23]. Endometrioid and clear cell tumours normally occur in patients that have ovarian inclusion cyst or foci of endometriosis. Endometrioid type of adenocarcinoma is similar to histological type of endometrioid adenocarcinoma of endometrium[31,32]. Endometrioid EOC express estrogen receptors and for this reason it is retained that HRT can stimulate post-surgical residual cancer. Even so, there are no studies that have shown a real association between HRT and the development of EOC after treatment[33]. Studies about HRT use after treatment of endometrioid cancer shows that HRT can be used in patients affected by early stage of endometrioid EOC. Although in patients with Stage 3 endometrioid adenocarcinomas because of the high possibility of residual disease after surgery the use of HRT is not secure in clinical practice[23]. Two meta-analyses with contrasting data about the impact of HRT on EOC follow up have been published, the first demonstrating no increase in relative risk of EOC in patients having HRT and the second demonstrating a little but significant raise in risk after long use (10 years plus)[34,35]. Different studies have investigated the possible adverse effects of HRT in patients who have undergone surgery and chemotherapy for EOC. Guidozzi *et al*[12] realized a prospective randomized study of 130 patients diagnosed with advanced stage, high grade serous ovarian cancer to analyze the effects of HRT on survival. That women who had earlier taken estrogens or had ovarian low malignant cancer were excluded. All of these patients underwent cytoreductive surgery and after cisplatin-based chemotherapy were randomized to have either oral Premarin *vs* placebo. After a follow up of 48 mo no considerable divergence in survival was noted between the two groups and the study establishing that HRT can be somministrated with the purpose of

Table 1 Epithelial ovarian cancer

Ref.	Study design	HRT *vs* control	Stage	Type of HRT	Months HRT	Months follow up	Recurrence HRT *vs* controls	Study conclusions
Eeles *et al*[37]	Retrospective case-control	78/295	1-2: 55% 3-4: 45%	Oral Estrogen Estrogen + Progestogen Estrogen + Tibolone	Median 28	Median 42	-	No effects of HRT on prognosis
Guidozzi *et al*[12]	Randomized controlled trial	59/66	1-2: 27% 3-4: 73%	Conjugate Estrogen	28	Mean 42	32 *vs* 41	No effect of HRT on DFS and OFS
Bebar *et al*[36]	Retrospective cohort study	31/0	NS	Non-conjugated-Estrogen + Progestogen	Mean 25	Mean 55	3	No effect of HRT on progression of EOC
Ursic-Vrscaj *et al*[38]	Retrospective case-control	24/48	1-2: 54% 3-4: 46%	Non-conjugated-Estrogen Estrogen + Progestogen Estrogen + Tibolone	Mean 24	Mean 49	5 *vs* 15	No effect of HRT on survival
Mascarenhas *et al*[33]	Prospective cohort study	649 EOC 150 BOT	1-2: 60% 3-4: 40%	Estrogen Estrogen + Progestogen	Up to 24	60	-	Better survival in HRT users *vs* non users
Li *et al*[39]	Prospective cohort study	31/45	1-2: 28% 3-4: 72%	Conjugated-Estrogen + Progestogen	Mean 28.7	Mean 31.4	-	No effect of HRT on cumulative survival HRT improve quality of life

HRT: Hormone replacement therapy; EOC: Epithelial ovarian cancer; NS: Not specified; BOT: Borderline ovarian tumor; DFS: Disease free survival; OFS: Overall free survival.

improving quality of life in young EOC survivors without increasing risk of recurrence[12].

A prospective cohort study by Mascarenhas *et al*[33] considered 649 women with EOC and 150 women with borderline ovarian tumours who were clustered according to pre and post cancer utilization of HRT using self-questionnaires. The work analyzed the effects of HRT before and after the diagnosis of both tumors on 5-year survival. There were found no significant divergence in EOC survival between the group of women who had HRT before cancer diagnosis and that who did not have it. Some data indicated a better survival for patients who had HRT before the arising of EOC, but there is not a clear explanation according to period or recent time of use. There are analogous data and no proof of an association between HRT use before diagnosis of endometrioid EOC was found. Better survival was reported for serous type women but a better survival after endometrioid tumours was suggested too[33]. A retrospective cohort by Bebar *et al*[36] describe 31 women with ovarian cancer treated with surgery and following chemotherapy who had non-conjugate estrogens for a mean period of 25 mo. Median follow up was 35 mo. Progression of disease occurred in only three patients, and one patient developed early stage breast cancer[36]. A retrospective study by Eeles *et al*[37] illustrated 373 women with endometrial cancer (EC) who had primary surgery after that, 78 of these patients had HRT in different formulations and 259 did not. In the group who had HRT there was a higher number of younger women most between the ages of 30 and 40 years, with earlier and well differentiated cancers. There was no considerable dissimilarity in disease free survival between those who had HRT and those who had not after checking for age, disease stage, tumor grade and interval to recurrence[37]. Ursic-Vrscaj *et al*[38] compared every patient with EOC at Stage I -Ⅲ treated with estrogen, with two non treated patients at the same stage of disease. They found similar disease free and overall survival in the two groups. Li *et al*[39] carried out a study aimed at assessing the impact of post-surgical HRT on life quality and prognosis in women with ovarian malignancies. HRT was administrated in 31 patients, 44 patients did not receive HRT. A long-rank test revealed no difference in survival between patients with and without HRT. HRT administered following surgery exhibited no apparent negative effects on prognosis in EOC, while post-surgical HRT aided in the stabilization of serum calcitonin levels and improved quality of life in these patients[39].

Current literature does not support the view that HRT facilitates the development and recurrence of ovarian cancer[36,38]. Thus, ovarian malignancy after clinical management of cytoreduction and adequate chemotherapy is not a contraindication for HRT. HRT may be a good option for patients with serious symptoms of menopause and osteoporosis. Nevertheless, the use of HRT still lacks the support of large-scale multi-center prospective double-blind randomized studies, particularly regarding its effect on tumour growth in patients with gross residual tumours. Therefore, care should be taken to limit the use of HRT as much as possible to patients with satisfactorily controlled ovarian malignancy. The suitable duration of HRT is currently under debate with no definite conclusions based on large-scale studies. Consideration should be given to an individual's specific clinical circumstances as well as the severity of menopausal symptoms. The results of the studies we have analyzed are listed in Table 1.

Borderline ovarian tumour

Borderline ovarian tumors (BOTs) comprise approximately 15%-20% of all epithelial ovarian malignancies[40,41]. They are known for their low malignant potential and for unclear associated risk factors. Patients with BOTs are, in general, younger than women with EOC: their average age at diagnosis is between 45 years old[42], and 30% of patients are less than 40 years old. BOTs can be unilateral or bilateral. Similarly to carcinoma, they can spread to the peritoneum and, eventually, to the lymphonodes[43]. Standard surgical treatment is based on bilateral salpingo-oophorectomy with or without hysterectomy. After comprehensive surgical staging, cystectomy or unilateral annessiectomy can be offered to patients who want to preserve their fertility[44]. However, young patients fot whom fertility-sparing surgery is not feasible (because of BOTs diffusion or recurrent disease) will suffer from iatrogenic menopause. For these patients HRT is an important issue. In 2006 Mascarenhas *et al*[33] showed that out of 150 patients with BOTs, 93% survived at least five years and out of these, 51% had used HRT after diagnosis. In 2012, Fischerova *et al*[45] concluded that HRT should be offered to these patients.

In literature, no prospective randomized study on HRT after BOTs was found, but we agree with the idea that HRT should be proposed in patients with bothersome symptoms for the same reasons that HRT is offered to patients with ovarian cancer.

Germ cell ovarian tumour

Ovarian germ cell tumors (OGCT) includes benign or maligna. Dysgerminoma, yolk sac tumour, embryonal carcinoma, polyembryoma, non-gestational choriocarcinoma, mixed germ cell tumours, and teratomas (immature, mature, and monodermal types)[46] are all OGCTs. The age of insurance is between 10 and 30 years of age[47]. Fertility sparing surgery is possible but most patients are submitted to adjuvant chemotherapy (*e.g.*, bleomycin + etoposide + cisplatin)[48] and radiotherapy. This results in a gonadal dysfunction leading to transient or permanent ovarian failure[49]. There is no evidence that hormones increase recurrence or decrease overall survival of ovarian cancer survivors and, although the research has been almost exclusively in epithelial ovarian cancer survivors, there seems to be no reason why HRT should not be given to survivors of OGCT[50]. On this basis, in 2009 Singh *et al*[23] concluded that these patients can benefit from the use of HRT.

Sex cord ovarian tumour

Sex cord-stromal tumours include granulosa cell tumours (GCTs), thecomas, Sertoli-Leydig cell tumours, gynandroblastoma. The most malign and the most common sex cord stromal neoplasms is GCT[51] which are also the most common. They secrete steroid hormones and diagnosis in frequently secondary to hypoestrogenism symptoms onset. Fertility preserving surgery can be offered in Stage 1 patients; a total abdominal hysterectomy with bilateral salpingo-oophorectomy is mandatory for all other patients[23]. Regarding the possible use of hormonal treatment to restore patients from menopausal symptoms, although no studies have been published, the general consensus is that HRT should not be used because of their hormone-dependent nature. In fact about 30% of GCTs are Estrogenic Receptor Positive and 100% are Progesteron Receptor positive[52]. In 2013, Guidozzi[50] confirmed that it may be prudent to avoid estrogen therapy in women who are survivors of ovarian stromal tumours, in particular if the tumour was a GCT.

EC

EC is the most frequent gynaecological cancer. We can divide EC into 2 different types: Type I is the endometrioid histotype, which express estrogen and progesterone receptor and normally has a low grade. Major risk factors are prolonged use of estrogen, obesity and physiological hyperestrogenism. Type Ⅱ EC normally has a serous-papillary or clear cell histotype, it doesn't express Estrogen and Progesterone receptors and habitually it has a high histological grade and for this reason it is more offensive than type I [53]. This malignancy principally affects post-menopausal women, although about 20%-25% of women with EC are pre-menopal and about 5% have less than 40 years of age[54]. This cancer is normally diagnosed at an early stage (85% of patients in Stage I or Ⅱ) because of abnormal uterine bleeding as a prevalent symptom of the neoplasm[55]. Surgery represents the principal treatment: the typical surgical intervention is total hysterectomy and bilateral salpingo-oophorectomy to leave out the risk of ovarian metastasis or ovarian cancer. In advanced stages or precarious clinical conditions of the patient the primary treatment is radiotherapy. Because of the important role played by estrogens in the onset of the most common endometrial cancer, HRT may stimulate the growth of occulti tumour cells remaining after surgical treatment. For this reason replacement of this hormones after disease treatment seems to be contraindicated. However there is no evidence that HRT may adversely affect disease free survival and the recurrence rate in women treated for endometrial cancer[56,57]. Several studies have analyzed patients affected by endometrial cancer treated with HRT to reduce iatrogenic menopausal symptoms. Creasman *et al*[58] and Lee *et al*[59] in 1986 and in 1990 respectively, published case control studies on HRT in endometrial cancer Stage 1 patients finding a lower recurrence rate, longer disease-free and overall survival in users against non-users. In fact in the Lee series no recurrences occurred in estrogen users while HRT had been prescribed only in patients with low risk of recurrence (Stage 1A or 1B and low grade). The control group had a higher recurrence rate because of the higher-risk disease (Stage 1C grade 3). When only low-risk patients were compared Lee found no difference in recurrence rate. In 1990 two separate retrospective studies published by Bryant[60] and Baker[61], examined

Table 2 Endometrial cancer

Ref.	Study design	HRT *vs* control	Stage	Type of HRT	Months HRT	Months follow up	Recurrence HRT *vs* controls	Study conclusions
Creasman *et al*[58]	Retrospective case-control	47/174	1	Oral/Vaginal/Oral + Vaginal Estrogen	Mean 32	25-150	2 *vs* 15	Estrogen has a good effect on DFS an OS
Lee *et al*[59]	Case-control	44/99	1	Oral Estrogen	Median 64	24-84	0 *vs* 8	Estrogen are safe in low risk patients
Bryant[60]	Retrospective cohort	20	1-2	Conjugated Estrogen ± Depo Provera	12-132	42-168	NS	No recurrences in patients treated with HRT
Baker[61]	Retrospective cohort	31	NS	Oral/Vaginal/transdermal Estrogen		192	NS	No increase of recurrence or mortality in HRT users
Chapman *et al*[62]	Retrospective case-control	62/61	1-2	Oral/Vaginal Estrogen ± MPA 2.5 mg	Mean 49.1	Median 57.1	2 *vs* 8	No decreased DFI or increased recurrence in users *vs* non users in early stage
Suriano *et al*[63]	Retrospective cohort with matched controls	75/75	1-3	Oral Estrogen ± MPA 2.5 mg	Mean 83	Mean 83	2 *vs* 11	HRT ± Progestogen do not increate recurrence rate
Barakat *et al*[64]	Randomised double blind trial	618 *vs* 618	1-2	Oral Estrogen	Planned 36	Median 35.7	14 *vs* 12	Not completed. Low recurrence rate
Ayhan *et al*[65]	Prospective case-control	50/52	1-2	Conjugated Estrogen + Progesteron	Mean 49.1	Mean 49.1	0 *vs* 1	Postoperative HRT did not increase recurrence or death rate

HRT: Hormone replacement therapy; MPA: Medroxyprogesterone acetate; DFS: Disease free survival; OS: Overall survival; DFI: Disease free interval; NS: Not specified.

cancer survivors who received estrogen therapy after treatment and were followed up for 4-16 years. The stage of neoplasm was I - II in the Bryant study and was not specified in the Baker study. No recurrence of endometrial cancer was noted in either the studies. Chapman *et al*[62] examined women with stage 1 or 2 EC. There was no significant difference in recurrence rate between HRT users and non-users, however the groups were not homogeneous because patients in the non-users group had often a greater frequency of high grade and stage, and were older than patients submitted to HRT. In the year 2001 Suriano *et al*[63] studied women affected by stage I - II - III of EC and described a longer disease-free interval in HRT users *vs* non-users with a significant difference ($P = 0.006$). The study concludes that HRT with or without progestins does not seem to increase the risk of recurrence or death in patients treated for EC. The only randomized study was carried out by Barakat *et al*[64] in 2006. It started in 1997 and stopped in 2003 after the publication of the Women's Health Initiative results that made accrual impossible. For this reason they did not reach their goal of 2108 patients but they randomized 1236 patients who received either estrogen or non-estrogen therapy after undergoing surgery. The authors concluded that, although the study could not clearly define the safety of estrogen therapy in endometrial cancer survivors, there is a low recurrence rate (2.1%) and minimal incidence of new neoplasm. Ayhan *et al*[65] published in 2006 the first prospective case control study which showed that HRT administered immediately after surgical intervention did not amplify the recurrence or the mortality rate in Stage 1 and 2 EC survivors. The main limitation of this study was the small sample size and lack of randomization. These results were shown in a 2010 review by Singh *et al*[23]; however the author underlined that in endometrioid cancer of the endometrium the reason why HRT did not showed adverse effects may be due to the radical tumor excision because of early stage. In fact in advanced stage Type I of endometrial cancer there may be some residual cells after surgical treatment that can be stimulated by HRT and subsequently change the prognosis of the patient. The use of estrogen-progestogen HRT would probably suppress estrogen stimulated cell growth because of the progestogen combination, but there are no clear evidence data about this theory[23]. The studies listed above are resumed in Table 2.

UTERINE SARCOMA

Uterine sarcomas constitute a disparate category of malignancies which includes leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), undifferentiated endometrial sarcoma and carcinosarcoma. The data available in literature on the role of estrogen therapy after surgical treatment for uterine sarcomas are limited because they are uncommon tumors (3%-8% of all uterine malignancies in women). Most ESSs express steroidal receptors and are considered to be hormone-sensitive. Many studies have shown a regression or stabilization of recurrent low-grade ESS with endocrine therapy based on medroxyprogesterone acetate and Letrozolo (aromatase inhibitor)[66]. Patients with a history of ESS should not be treated with estrogen therapy or tamoxifen and, if present, withdrawal of estrogen therapy is strongly recommended[67]. LMSs are the most common

Table 3 Recommendations

Site	Tumour type	HRT
Ovary	EOC	
	Endometrioid	No[1]
	Others	Yes
	Germ cell ovarian tumour	Yes
	Sex cord ovarian tumour	No
Uterus	Endometrial cancer	
	Type 1	No[1]
	Type 2	No[1]
	Uterine sarcoma	
	Endometrial stroma sarcoma	No
	Leiomyosarcoma	No
Cervix	Adenocarcinoma	No
	Squamous	Yes

[1]To evaluate in a multidisciplinary team. HRT: Hormone replacement therapy; EOC: Epithelial ovarian cancer.

of uterine pure sarcomas (42%-60%) and some express estrogen and progesterone receptors at different levels. Avoidance of estrogen therapy is generally recommended in surgically treated women with LMS because of their potential hormone sensitiveness[68].

CERVICAL CANCER

Cervical cancer is the second most common gynaecological cancer with an important mortality and morbidity. Due to pap-test screening early diagnosis and therapies are increasing leading to a larger population of young women facing collateral gynaecological symptoms. Although fertility sparing treatment is possible in early stages, in advanced stages treatment consists of either radical surgery or primary chemo-radiotherapy. In squamous carcinoma, almost 80% of cervical cancers, ovary preservation is usually feasible and safe due to the low metastasis rate however for adenocarcinomas oophorectomy is usually recommended. Women with cervical cancer often undergo external radiotherapy or brachytherapy causing significant toxicity to the vagina. In addition to symptoms caused by iatrogenic menopausal status this may result in vaginal stenosis, dyspareunia and major sexual problems. Generally HRT is not refused in patients who complain of menopausal symptoms after treatment for squamous cervical cancer (SCC)[69]. SCC is not considered an estrogen responsive tumour even though estrogen receptors have been described in this tissue too. A study by Ploch[70] on 120 women showed no change in the survival rate or Disease Free Survival at five years in patients receiving HRT after treatment for cervical cancer Stage Ⅰ/Ⅱ. A higher risk seems to exist for cervical adenocarcinoma. It has been suggested that it should be treated in the same way as endometrial cancer because of the dependence of this histotype on oestrogen stimulation[71]. The adverse effect of radiotherapy like vaginal stenosis can be treated with local oestrogen subministration but there is no clear evidence about a linkage between hormonal therapy and a worse prognosis of cervical cancer[23].

BRCA MUTATION CARRIERS AFTER SALPINGO-OOPHORECTOMY

Women with germ line BReast CAncer type 1 (*BRCA1*) or *BRCA2* mutations have higher life time risk of ovarian (15%-56%) and breast (45%-80%) cancers than the general population (ovarian cancer 1.4%; breast cancer 12%)[72]. In women between 35 and 40 years old profilactic annessiectomy is recommended to reduce the risk of insurance of ovarian malignancies, causing the insurance of iathrogenic menopause with deterioration of quality of life. Two observational studies in women with *BRCA* mutation treated with prophylactic salpingo-oophorectomy showed no increase of breast cancer incidence in HRT users[73,74]. On the contrary, Million Women Study compared HRT users with non users receiving placebo and it demonstrate an increased risk of breast cancer in the first group of patients[75]. Current studies of women carring *BRCA2* mutation are non randomized and there is little data about the increased risk of breast cancer in this group of patients.

Because of the increased risk of osteoporosis, cardiovascular event, cognitive problems and vasomotor symptoms related to hyatrogenic menopause, we agree with the idea that short-term HRT should be propose[76].

CONCLUSION

HRT with Estrogen or Estrogen and Progestogen is the therapy with the highest efficacy in the treatment of physical and psychological symptoms of iatrogenic menopause. HRT can be administered in women with story of squamous cells carcinoma of the uterine cervix; conversely should not be prescripted in patients with endometrioid ovarian carcinoma, atypical histologies endometrial carcinoma, borderline ovarian tumour, germ cell ovarian tumours and *BRCA1-2* mutation carrier patients. The use of HRT in endometrioid EOC and endometrial cancer is debated because there are no studies that come to an agreement on this topic. We can speculate that the use could be stage-dependent, but in any case HRT should be discussed in a multidisciplinary team. HRT use is not safe endometrioid endometrial cancer, endometrioid ovarian cancer adenocarcinoma of the uterine cervix, endometrial stroma sarcoma and leiomyosarcoma. In these groups of patients non hormonal therapies are rational alternative to HRT to reduce vasomotor symptoms. These recommendations are resumed in Table 3. HRT should start after six months from the last treatment (chemotherapy or radiation therapy) to reduce thrombotic risk due to cancer, chemotherapy and hormone therapy.

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