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- 1 Mental fitness during transition to fatherhood

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Mental fitness during transition to fatherhood

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Abstract

Transition into fatherhood is often marked by a period of adjustment, uncertainty and psychological distress and challenges for many men, along with social isolation and relationship problems. Risk factors for paternal mental health issues are maternal depression, marital distress, parenting stress, gender role stress, mismatched expectations for pregnancy and after childbirth, poor physical health, inadequate self-care behaviours, avoiding seeking help for mental health issues, and having a child with sleeping, feeding and temperament problems. Paternal depression, anxiety and post-traumatic stress disorder can have negative impacts on the social and emotional wellbeing of fathers, their partners and their children. Nevertheless, these issues are not widely acknowledged, recognised or treated. Men's mental health illness is a silent crisis. They often fail to seek help due to their feeling of shame, stigma for a lack of emotional control, distress or anxiety related to utilising mental health support services, and underrating the severity of their symptoms. These necessitate the need for timely attention, psychological support and proper education to minimise their risk of mental health issues. Although research has indicated fathers' inclination toward being included in practices such as the mental health assessment, perinatal education and postnatal educational approaches need to be inclusive of fathers and encourage them to seek support for their paternal mental health issues and parenting difficulties.

Key Words: Childbirth, Father; Mental health; Parenting

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Core Tip: Transition to fatherhood can have both positive and negative effects on the social and emotional wellbeing of fathers, their partners and their children. The importance of appropriate timely support and education during pregnancy and after childbirth along with the gaps in practice highlight the need for high-quality educational approaches for fathers that will help enhance their mental health and increase their confidence and practical parenting skills.

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INTRODUCTION

Before the 20th century, pregnancy and birth were considered women's business and the birthing room was not a man's place. In the mid-1960s, a model of family-centred perinatal care emerged in western countries, aiming to enhance the emotional bond between parents and their children. This model emphasised parent education and preparation for pregnancy and childbirth and encouraged both parents to actively take part in caregiving and decision-making. As a result, fathers became more involved in pregnancy and childbirth-related activities[1].

A father's attendance at birth can offer benefits such as enhanced maternal satisfaction, improved father-child attachment and development of essential life skills [2]. Events in the birthing room, however, can be unpredictable and reactions to these events can sometimes be distressing to expectant fathers, diminishing any positive feelings[3]. According to a qualitative study in the United Kingdom[4], fathers reported being traumatised after attending labour and birth without adequate prior education and preparation. Another online qualitative study in the United Kingdom[5] showed that witnessing birth procedures and being inadequately prepared for possible complications were traumatising experiences for the fathers. A meta-ethnographic synthesis of fathers' experiences of complicated births from the United Kingdom, Sweden, New Zealand and Japan has shown that fathers are deeply affected by the childbirth experience, feel helpless and develop depression and post-traumatic stress disorder (PTSD), which in turn cause negative effects on the couple's mental health, relationships and the parent-baby bond. They feel vulnerable in the birthing room and express their need to receive more attention and recognition as part of a unit with the mother during the perinatal period[6].

Transition into fatherhood is often marked by a period of adjustment, uncertainty and psychological distress and challenges for many men, along with social isolation and relationship problems. A systematic review has shown that the prevalence of fathers' anxiety disorders range between 4.1%–16.0% during pregnancy and 2.4%–18.0% during the postnatal period[7]. After the birth of their child, 11.2% and 12.0% of fathers experience symptoms of depression at one and 6 months postpartum, respectively[8]. Another meta-analysis has shown that one in ten Australian fathers suffer postnatal depression or anxiety due to fatherhood challenges, establishing their new parenting identity and other related fears and concerns[9]. Uncertainty about their parental role in a shared parenthood style, a lack of sexual intimacy and emotional closeness, feeling lonely and isolated, and the demands of external requirements, such as work commitments, family financial status and childcare restrictions – especially due to the coronavirus disease 2019 (COVID-19) pandemic – can inject a significant amount of stress into their everyday lives and affect their mental health. Poor paternal mental health increases the risk of maternal depression and exacerbates its subsequent negative impacts on a child's behavioural, emotional, cognitive and physical development later in life. For example, the study by Paulson *et al*[10] showed that in the United States depressed fathers were more likely to put their infants to bed awake and were less likely to sing songs, engage in enrichment activities or play outside with their children[10]. Rominov showed that paternal depression among fathers in Australia was associated with a lack of confidence at parenting,

excessive infant crying and decreased physical contact and educational interactions between fathers and children[11]. The study by Davis *et al*[12] reported that the risk of American fathers spanking their one-year-old infants was four times greater in American fathers who were depressed[12]. In an Australian study, by following infants of fathers with symptoms of postnatal depression through to childhood, Fletcher *et al*[13] demonstrated that these children were 3 times more likely to show behavioural, development and wellbeing issues at 4-5 years of age[13].

RISK FACTORS OF MENTAL HEALTH ISSUES IN FATHERS

Risk factors for paternal mental health issues are maternal depression, marital distress, parenting stress, gender role stress, mismatched expectations for pregnancy and after childbirth[14], poor physical health, inadequate self-care behaviours, avoiding seeking help for mental health issues, and having a child with sleeping, feeding and temperament problems[15]. In addition to these, the recent impact of the COVID-19 pandemic has compounded the psychological burden of fatherhood on men, and compared to mothers, fathers report that this is a greater burden overall[16]. They have heightened anxiety and feel vulnerable due to the economic impact of COVID-19. Some men are stressed due to the inability to work from home, while others who have to work from home feel isolated and miss the social connections of their usual workplace. Physical distancing can make fathers feel emotionally disconnected, especially if they experience economic difficulties or disrupted work-family balance. A lack of emotional involvement can be followed by alcohol and drug abuse, antisocial and risky behaviours, interpersonal difficulties and domestic violence, and can also compromise children's safety, mental health, growth and development[17].

Over time, these progressively negative changes can diminish men's self-esteem and confidence, and under some circumstances may result in suicide. Suicide is the number one killer of men under 50 years of age and nearly 600000 men worldwide commit suicide every year[18]. Using initial modelling, the Brain and Mind Centre at the University of Sydney has suggested that the number of annual suicidal attempts following COVID-19 in Australia may increase by 750 additional cases in the next five years[19].

PERINATAL EDUCATION FOR FATHERS

A traumatic childbirth or a life-threatening complication during labour and birth can cause PTSD in couples, in particular fathers as the birth attendants[6,20]. According to a systematic review, men's mental health illness is a silent crisis. They often fail to seek help due to their feeling of shame, stigma for a lack of emotional control, distress or anxiety related to utilising mental health support services, and underrating the severity of their symptoms[21]. This necessitate the need for timely attention, psychological support and proper education to minimise their risk of mental health issues [22]. Supporting the mental health of fathers and including them in assessments, care pathways and care planning are activities/schemes that have been suggested to help them build realistic expectations and achieve far better outcomes for them and the whole family[17]. To this aim, preventative educational approaches have been recommended[19]. While the systematic review of literature shows the positive effects of social support and postnatal education on mothers' mental health[23], one out of three Australian fathers often miss this opportunity and do not receive proper social support and paternal education throughout the perinatal period[24]. According to Fletcher *et al*[25], many Australian fathers lack insight into the challenges that they are likely to face during pregnancy, in the birthing room and beyond, and mainly focus on acting as a support person for their partner. Some fathers feel challenged by the antenatal visits being focused on the expectant mothers, as well as the lack of attention shown to them during labour and birth. They also express their concerns of limited education and support due to a lack of understanding about what fathers can do and how they feel by healthcare professionals, or short visiting times during pregnancy and after birth. They report that their needs for early parenting skills are not met and feel excluded from targeted and accessible perinatal information, especially those who are from culturally and linguistically diverse backgrounds, socially disadvantaged groups, or those who live in areas where such education is not offered[26].

In some health settings, antenatal education and preparations are offered to both parents to address their needs and smooth this major transition. A qualitative study by Alio *et al*[27] in the United States has shown that African American fathers' attendance at antenatal educational classes and their involvement during pregnancy care decrease maternal stress levels and encourage positive maternal behaviours, which may in turn enhance the health of the newborn. Despite these benefits, evidence indicates that, with the main focus being on labour and birth preparation, mothers remain the target audience of the majority of parents childbirth education programs. Also, these programs generally fail to prepare the fathers for changes in their self-identity and relationship with their partner, their future role as a father and emotional and psychological aspects of parenthood, as reported in a qualitative study from Australia[28]. A survey of fathers attending antenatal classes at John Hunter Hospital, King George V Memorial Hospital and Royal Hospital for Women in New South Wales, Australia [29], has shown that although the classes better inform some fathers about the changes happening during pregnancy and increase their confidence about childbirth, they express their needs for education on more practical skills.

MOBILE TECHNOLOGY AND HEALTH EDUCATION: TARGETING NEW FATHERS

In Australia, 91% of adults older than 18 years use smartphones, and the majority of them prefer to access the internet from their smartphones than from a desktop computer[30]. Widespread access to mobile technology and the multifaceted and fast-expanding features of smartphones, along with their wide geographic and demographic coverage, have enabled health promotion professionals to use them for developing and providing evidence-based health information and interventions to individuals directly[31].

A growing number of parents use mobile apps and social media for health information and education. There are thousands of pregnancy and parenting apps on the two major app stores (Google Play Store and Apple App Store) that are used as the first source of information by many pregnant and postnatal women to fill their knowledge gaps, even before they visit a health professional for their condition[32]. Nevertheless, the evolution in perinatal educational mobile apps has not stretched proportionately. The majority of apps are designed to target mothers and, despite an expression of interest from fathers demanding more targeted education and support during the perinatal period, the mobile apps for fathers are scarce. A systematic review in 2018 showed that there are 1806 pregnancy-related apps for mothers, but only 13 are available for new or expecting fathers and just 9 offer general parenting advice to fathers[33].

The worldwide release of a number of father-focused apps in recent years, which have taken an idiomatic, peer-like approach, has shown that fathers are inclined to use online sources to communicate and connect with others and enhance their parenting experiences and skills[33]. Also, fathers who feel left out of traditional programs for antenatal education attempt to look for information elsewhere, often using mobile technology to overcome these barriers. For example, a social work app from the United States, mDad, has been used by fathers to learn about ways of engaging with their infants[34]. Milk Man[35] was the first Australian breastfeeding app for fathers that aimed to enhance the role of men as supportive breastfeeding partners and provided a conversation forum for them to engage with other fathers for support seeking and knowledge sharing. A later Australian text message-based mobile intervention by Fletcher *et al*[36], the SMS4dads, provided mental health support to the expecting or new fathers with infants younger than three months, addressing three areas: father-infant care, father-partner support and fathers' self-care. Findings from the studies on these father-focused apps have demonstrated that mobile technology can be highly effective in facilitating education and support for fathers, and can be successful in achieving health promotion goals. Nevertheless, there is a shortage of evidence-based apps for fathers and a real-life need for comprehensive, highly targeted paternal-focused educational apps. Although some commercial apps try to fill the gap, the quality and validity of the provided information are questionable and unknown. There is an enormous opportunity for public health organisations to build upon what is known about reaching fathers using mobile apps in order to impact positively on the health of all members of the community[35].

CONCLUSION

Gaps in clinical practice

Despite the negative impact of paternal depression, anxiety and PTSD on the social and emotional wellbeing of fathers, their partners and their children, these issues are not widely acknowledged, recognised or treated. Although fathers have inclination toward being included in practices such as the mental health assessment, perinatal education and postnatal educational approaches are not inclusive of fathers.

Even though there are some face-to-face educational classes for fathers in some countries and regions, there is usually an issue of access due to timing, location or socio-economic factors. According to one Australian study, pregnant women often have to reduce their work hours, take additional breaks or stop working altogether – some might even lose their job[37]. This requires the fathers to maximise their contribution to the family's income by working longer hours, resulting in limited availability for face-to-face perinatal educational classes. Furthermore, fathers are a population that is generally difficult to involve in public participation due to a variety of reasons, such as gender role expectations, attitudes on parenting practices, lack of paternity support from employers and their own expectations of men's involvement during the perinatal period[25,38]. These barriers can be surpassed by offering family-related approaches that take men's educational needs into account, such as after-hours educational classes that better match with men's availability, employing male educators, displaying posters that exhibit fathers' images and providing educational material to men when they are waiting in the clinic for antenatal appointments[39].

While in some cultures it is the mother's full responsibility to look after children[40-42], regardless of their geographical area fathers can still be better equipped for transition to parenthood by receiving information on fundamental matters such as managing their own distress and anxiety, learning practical skills in dealing with role and relationship changes, as well as understanding their newborn's crying, settling behaviours, growth and development[37]. They also need to be encouraged to seek support for their paternal mental health issues and experience a smooth transition to fatherhood.

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CASE REPORT

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Trihia HJ, Souka E, Galanopoulos G, Pavlakis K, Karelis L, Fotiou A, Provatas I

LETTER TO THE EDITOR

- 17 Self-monitoring of blood glucose in gestational diabetes mellitus patients during the COVID-19 pandemic in low- and middle-income countries
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Peer Reviewer of *World Journal of Obstetrics and Gynecology*, Roberta Granese, MD, PhD, Professor, Department of Obstetrics and Gynaecology, University Hospital of Messina, Messina 98125, Italy. robertagr74@gmail.com

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Microglandular hyperplasia-like mucinous adenocarcinoma of the endometrium: A rare case report

Helen J Trihia, Efthymia Souka, George Galanopoulos, Kitty Pavlakis, Loukas Karelis, Alexandros Fotiou, Ioannis Provatas

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Abstract

BACKGROUND

Microglandular hyperplasia (MGH) is a proliferation of endocervical glands, related to estrogen stimulation, mainly occurring in the reproductive age group. The differential diagnosis includes endometrial adenocarcinoma with MGH-like pattern (MGA), a distinction that may be particularly problematic in curettage specimen.

CASE SUMMARY

A 57-year-old, postmenopausal woman was admitted in our hospital for surgical treatment. She had been diagnosed with a uterine leiomyoma, after complaints of irregular vaginal bleeding. She underwent dilatation and curettage (D&C) and subsequent total abdominal hysterectomy with bilateral salpingo-oophorectomy. D&C were compatible with MGA. Histologically, a proliferation of small glands, without intervening stroma, with mucin production, accumulation of neutrophils in the gland lumen and stroma, mild nuclear atypia and rare mitoses, were seen. In the hysterectomy specimen, the endometrium was thickened, but without apparent tumor formation. On microscopic examination, a residual similar adenocarcinoma was seen in the isthmus and more conventional-of endometrioid and mucinous type, in the rest of the endometrium.

CONCLUSION

MGH-like proliferation with mild cytologic atypia, detected in the endometrial curettage specimen of a postmenopausal woman, should alert pathologists for MGA of the endometrium. VIM, p16, PAX-2, CD10 and CD34 may help in the differential diagnosis.

Key Words: Microglandular hyperplasia-like; Microglandular-like adenocarcinoma; Endometrium; Curettage; Pitfall

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Core Tip: When microglandular hyperplasia (MGH)-like proliferation is detected in the endometrial curettage of a postmenopausal woman, the pathologists must be vigilant for endometrial MGH-like endometrial adenocarcinoma type of carcinoma, as it may be misdiagnosed. The examination of scant biopsy specimens remains a challenge. Its recognition can avoid underdiagnosis and mistreatment of the patient.

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INTRODUCTION

Microglandular hyperplasia (MGH) is a characteristic proliferation of endocervical glands, often associated with estrogen and progesterone stimulation (oral contraceptives and pregnancy). It occurs in the reproductive age group and occasionally in postmenopausal women. The differential diagnosis is usually with endometrial adenocarcinomas resembling MGH, a distinction that can be very difficult in a biopsy or curettage (D&C). We report a case of a 57-year-old woman, with vaginal bleeding and a known uterine leiomyoma, diagnosed with MGH-like endometrial adenocarcinoma (MGA) in dilatation and curettage specimen. We address the difficulties of differential diagnosis and the hysterectomy findings.

CASE PRESENTATION**Chief complaints**

The patient suffered from uterine bleeding.

History of present illness

A 57-year-old, postmenopausal woman, was referred to our hospital for surgical treatment of a radiographically detected uterine leiomyoma, after irregular vaginal bleeding of seven days' duration.

History of past illness

None.

Personal and family history

The patient had undergone four *in vitro* fertilization attempts in the past, one of which resulted in a failed pregnancy. Last attempt took place eleven years before her clinical presentation with vaginal bleeding.

Physical examination

No clinical findings.

Laboratory examinations

No increase of tumour markers.

Imaging examinations

No mass forming findings.

Histological findings

Histological examination of D&C revealed a complex-microglandular proliferation of small back-to-back glands, without intervening stroma, with mucin production, accumulation of neutrophils in the gland lumen and stroma, mild nuclear atypia and rare mitotic figures (Figure 1). Alcian blue and PAS-D stains showed abundant luminal and occasional intracytoplasmic mucin. Invasion could not be assessed in the insufficient and fragmented curettage specimen. Our diagnosis was compatible with adenocarcinoma of the endometrium with extensive features mimicking microglandular hyperplasia of the cervix (microglandular hyperplasia-like mucinous adenocarcinoma of the endometrium- EAMGHP). The diagnosis was based mainly on the extent of the lesions, the finding of a very limited element of glands with complex back-to-back, cribriform and tubule-papillary architectural patterns, with focal pseudo-stratification and the presence of rare mitoses (Figure 1). Immunohistochemically, there was positivity for VIM (Figure 2), mCEA (Figure 1), ER, PR and p16 (Figure 2). The slides were reviewed by an eminent Gynecologic Pathologist (K.P), who agreed with our diagnosis of a low grade endometrial endometrioid carcinoma with features mimicking microglandular hyperplasia of the cervix. The patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH & BOOP). In the hysterectomy specimen, a pink polypoid lesion of 0.5cm was seen at the isthmus area. There were several Nabothian cysts seen in the cervix. Macroscopically, there was no obvious mass formation. The endometrial area was determined in a flat appearance macroscopically (Figure 3). On microscopic examination, a residual adenocarcinoma with partly similar features with those observed in the D&C specimen was seen in the isthmus area and more conventional carcinoma of mucinous (Figure 4) and endometrioid types with areas of ciliated cells and small non-villous papillae (Figure 4), in the rest of the endometrium. MGH-like areas were mostly replacing the surface areas of the more conventional carcinoma of the endometrium (Figure 4). The carcinoma was superficially infiltrative and was extending in adenomyosis areas. The final diagnosis was of a FIGO I, grade I-II, MGH-like endometrial adenocarcinoma.

In the cervix, apart from Naboth cysts, there was also a cystic structure, underneath the polyp, compatible with mesonephric remnant of ductal type, as well as a focus of reserve cell metaplasia in an endocervical crypt.

The postoperative recovery course was uneventful.

FINAL DIAGNOSIS

The patient was diagnosed with microglandular-like adenocarcinoma of the endometrium.

TREATMENT

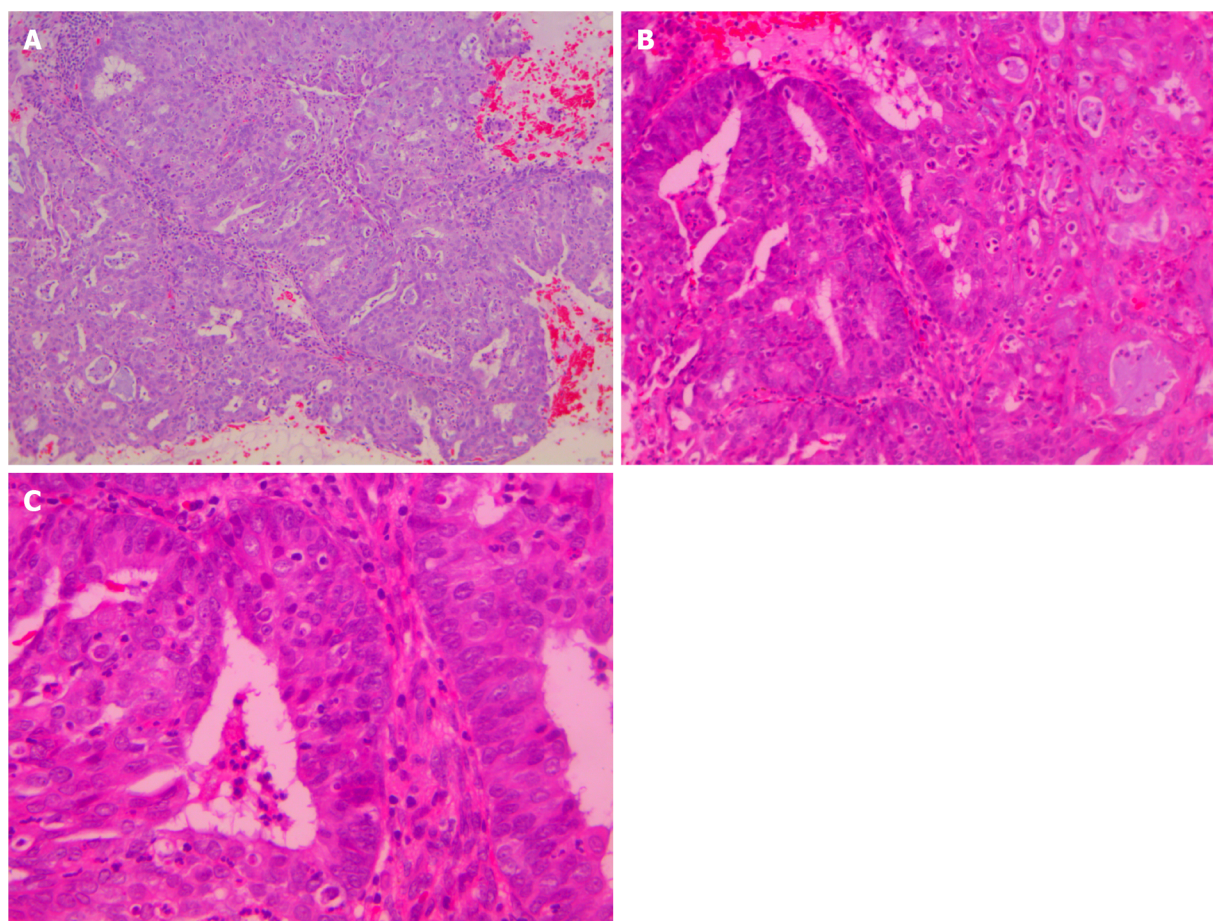
Then, this patient underwent TAH & BOOP (total abdominal hysterectomy and bilateral salpingo-oophorectomy).

OUTCOME AND FOLLOW-UP

The postoperative recovery course was uneventful. The patient is well 15 mo after surgical treatment.

DISCUSSION

MGH is a lesion, mostly seen in women of reproductive age, although it can be found in up to 6% of postmenopausal women[1]. It is a benign proliferation of endocervical glands and is often an incidental finding. It usually occurs in women who are either pregnant or are taking progesterone[2]. It was first described in a study of changes in the cervix of pregnant women[3]. The term MGH, was used for the first time, by Kyriakos *et al*[4] in 1968, for a group of patients on oral contraceptives. One year earlier, the resemblance of this lesion with endocervical adenocarcinoma, was thus far acknowledged[5]. Although, this is commonly associated with pregnancy and oral contraceptive use, it can occur in patients without this clinical history. Most cases are found incidentally, but gross abnormalities such as an erosion, polyp formation, or friable raised areas in the cervix can be seen. MGH can be focal or multifocal and can involve the surface epithelium and/or the endocervical glands. It is composed of closely packed glands of variable size and shape, with acute and chronic inflammatory cells and little

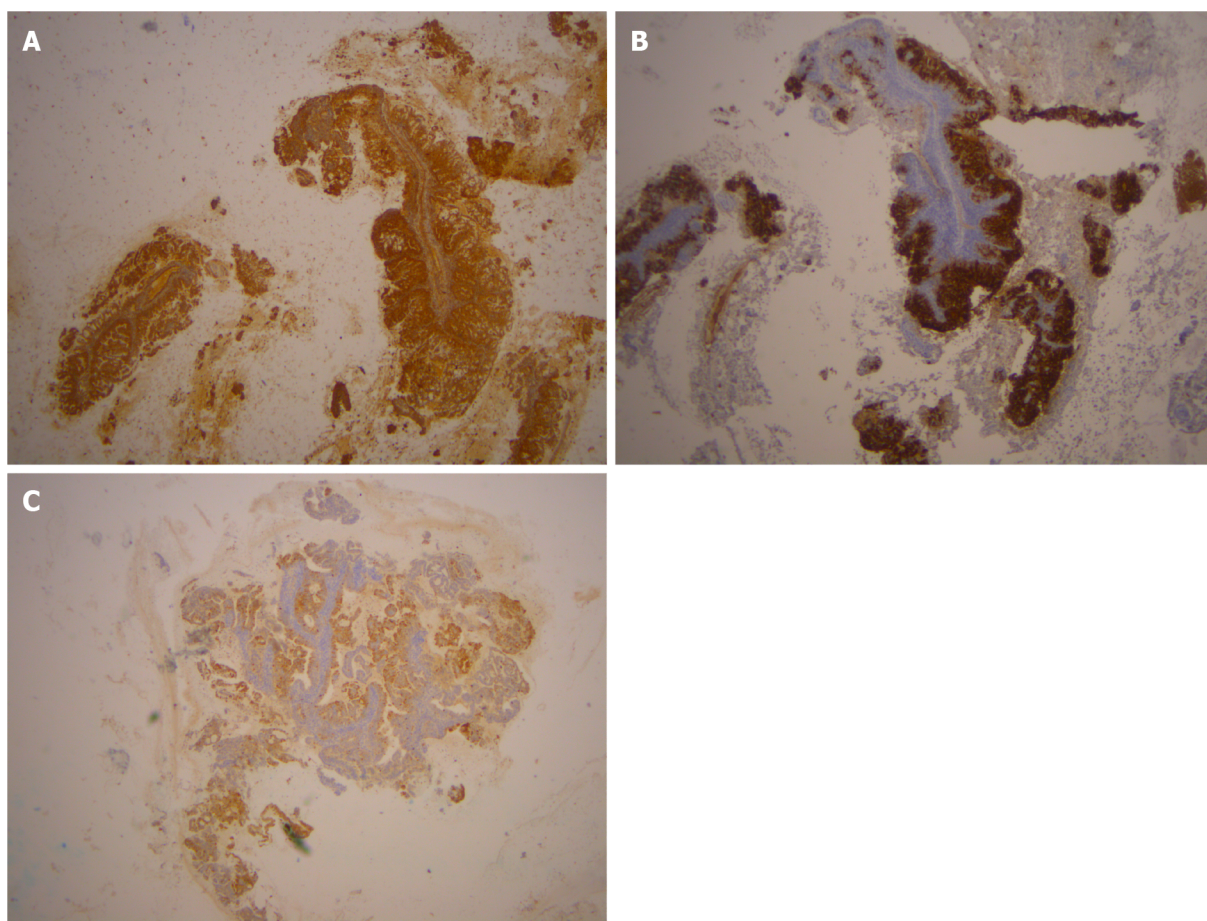


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Figure 1 Microglandular hyperplasia-like pattern in dilatation and curettage, hematoxylin-eosin staining. A: Complex microglandular proliferation of small back-to-back glands, without intervening stroma, with mucin production and accumulation of neutrophils in the gland lumen and stroma ($\times 10$); B: Rare area where Microglandular hyperplasia-like adenocarcinoma (on the right) is merging with more conventional endometrioid adenocarcinoma (on the left) ($\times 20$); C: Endometrioid adenocarcinoma area shows pseudostratification, mild atypia and rare mitoses ($\times 40$).

intervening stroma. The epithelium lining the glands is columnar or cuboidal and mucin producing and contains supra- or subnuclear vacuoles. The nuclei are usually uniform, but focal atypia can be encountered. Reserve cell hyperplasia and squamous metaplasia may be present. Mitotic figures are rare. Immunohistochemically, there is positivity of MGH for p63 in the reserve/immature squamous cells. It is therefore usually negative for p16; however, in rare cases can be strongly, but usually patchy-positive. Cases of MGH with p16 expression do not co-localize MIB-1 or cyclin E expression and are not associated with human papilloma virus infection. The differential diagnosis of the lesion includes endometrial adenocarcinoma with a microglandular pattern (EAMGP). Otherwise, typical endometrioid (or mixed endometrioid-mucinous or pure mucinous) carcinomas may have prominent microglandular pattern with eosinophilic secretions and acute inflammatory cells in the lumens and stroma. The differential diagnosis is with MGH, although this is invariably a purely endocervical lesion. The distinction rests on the merging of the microglandular pattern with that of a typical endometrioid carcinoma, with nuclear atypia and mitotic activity exceeding those in MGH. Positivity for p16 and vimentin and $> 10\%$ MIB-1 index, also favors microglandular adenocarcinoma. There is a great diagnostic challenge of differentiating between endocervical MGH and well differentiated endometrial adenocarcinoma with microglandular pattern, in biopsy and D&C. Therefore the above consist one of the most common reasons for consultation in gynecologic pathology. Both entities can be quite similar. Although, the presence of nuclear atypia and mitotic figures can be of help in the differential diagnosis-favoring endometrial adenocarcinoma- yet the latter may be deceptively underestimated.

The WHO Classification of endometrial carcinomas (2014) is mostly based on morphologic features[6] and according to that they are classified in two broad categories, endometrioid non-serous carcinomas, or Bokham type 1 tumors and type 2, non-endometrioid, serous carcinomas. Type 1 includes endometrioid and mucinous carcinoma. Type 2 includes serous, clear cell, undifferentiated carcinoma and carcinosarcoma. Mucinous carcinomas, are classified as non-endometrioid carcinomas, with more than 50% of tumor cells containing intracytoplasmic mucin. A subset of mucinous carcinomas, designated MGA, due to its similarity to MGH of the endocervical glands (MGH), is acknowledged by

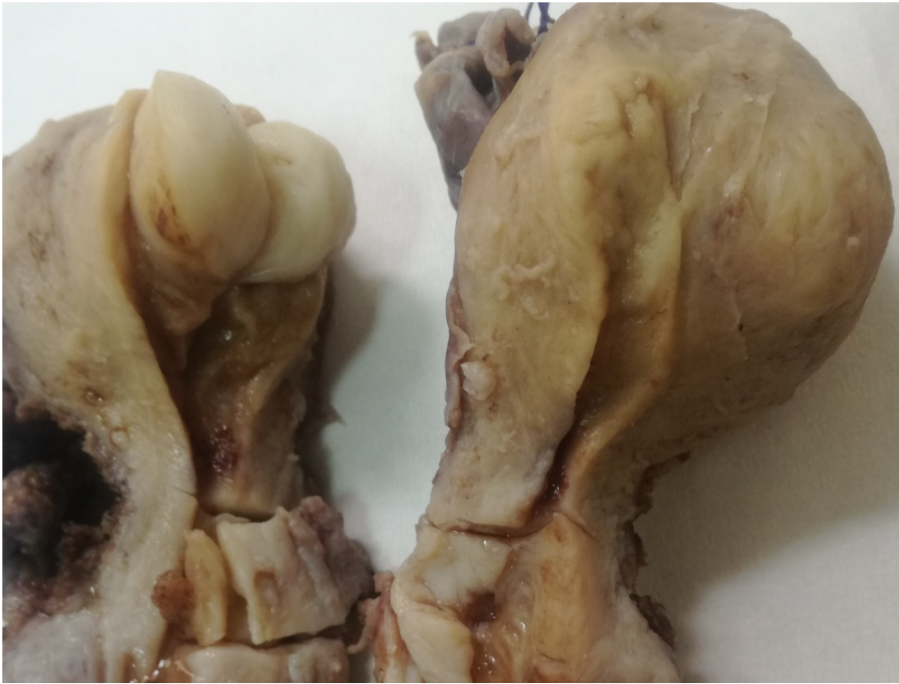


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Figure 2 Immunohistochemical staining. A: Immunohistochemical stain for VIM shows positive stain in the microglandular hyperplasia-like adenocarcinoma (MGA) in the curettage specimen ($\times 10$); B: Immunohistochemical stain for CEA shows positive stain in the MGA in the curettage specimen ($\times 10$); C: Immunohistochemical stain shows positive expression for p16 in the MGA in the curettage specimen ($\times 10$).

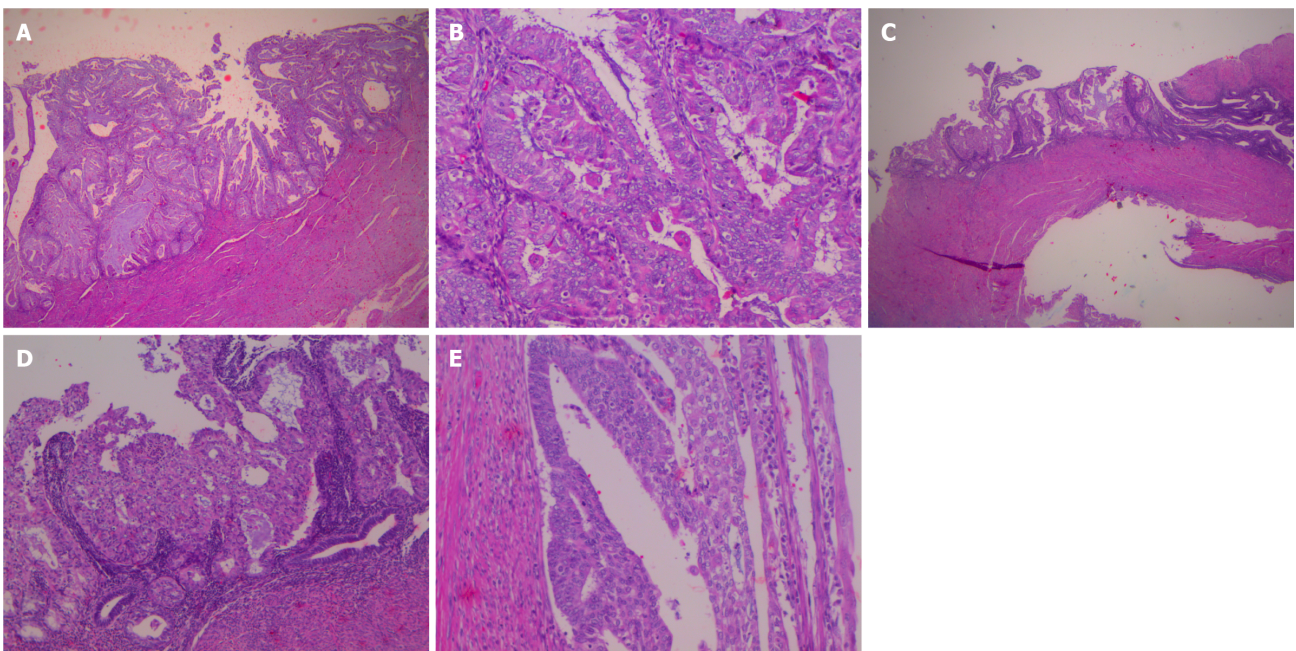
the WHO 2014. According to the revised 5th edition of WHO Classification of Female Genital Tumours, mucinous carcinoma is not included as a separate type 1 carcinoma type, but has been incorporated in the endometrioid type, as endometrioid carcinoma with mucinous differentiation[7]. Unusual histological patterns that may be seen in endometrioid carcinoma which are not associated with different prognosis, include among others the microglandular pattern. Tumors with notable microglandular pattern are characterized by small-to medium-sized, closely packed glands with eosinophilic secretions and numerous acute inflammatory cells. There is mild cytologic atypia and low mitotic rate. Mucinous pattern may be present in varying degrees and may predominate.

Mucinous differentiation of the endometrium can occur in a spectrum of lesions ranging from benign, like metaplasia to malignant, like adenocarcinomas with mucinous differentiation. It is very difficult to make a diagnosis of carcinoma in endometrial biopsies and curettings that show proliferative mucinous lesions, because the deceptively bland appearance of invasive mucinous adenocarcinoma at this site. Only limited information is available regarding criteria for distinguishing mucinous carcinoma from atypical mucinous proliferations and mucinous metaplasia of the endometrium. The threshold for diagnosing mucinous carcinoma in endometrial biopsies/curettings may be possibly lower than that of endometrioid carcinoma. There are three categories of mucinous proliferations of the endometrium (A, B or C), based on increasing degree of architectural complexity and cytologic atypia[8]. Type A, is characterized only by mucin-containing epithelial cells, single or in small tufts, within architecturally benign glands or in the endometrial surface. Type B, lesions are by definition more complex, and are characterized by mucin-containing epithelial cells forming pseudoglands with rigid punched out spaces with no supporting stroma. Type C alterations, are characterized by conspicuous cytologic atypia and architectural complexity, such as filliform growth. A high percentage of type B lesions are known to be associated with well differentiated endometrial adenocarcinoma, with no or minimal invasion. Mucinous lesions with complex (cribriform or prominent villous) architecture and absence of cytologic atypia are also characterized by low concurrent risk for deeply invasive cancer. The fact that type B microglandular lesions, are presented predominantly on the endometrial surface, without co-existing atypical hyperplasia, implies that a subset of well-differentiated adenocarcinomas arise *via* neoplastic



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Figure 3 Macroscopic appearance of the uterus. There are obvious the leiomyoma, the cervical polyp and the flat appearance of the endometrial area.



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Figure 4 Hysterectomy specimen. A: Residual carcinoma of conventional mucinous type in the hysterectomy specimen (× 20); B: Areas of ciliated and small non-villous papillae in the residual adenocarcinoma of the endometrium in the hysterectomy specimen (× 20); C: Adenocarcinoma with microglandular hyperplasia (MGH)-like pattern occurs on the tumor surface of conventional adenocarcinoma in a plaque-like fashion (× 10); D: Higher magnification of C (× 20); E: Adenocarcinoma with MGH-like pattern occurs on the tumor surface of conventional adenocarcinoma (another area) (× 40).

alterations in the surface epithelium.

MGA is by definition a rare type of endometrial mucinous carcinoma with microglandular architecture and mucinous and squamous features, which can mimic lesions of the endometrium and the cervix, both benign and malignant. MGA, was described for the first time by Young and Scully, in 1992[9]. The D&C in six cases was reported as “suspicious for malignancy that might be compatible with MGA of the endometrium or MGH of the cervix”. The patients were 37-84 years old and all women were postmenopausal, except of one case of cervical adenocarcinoma, which was premenopausal[8-13].

The clinical complaints were of vaginal spotting, discharge or bleeding. Six women were on exogenous hormones. From the clinical point of view, MGH is mostly presented in young women under hormone therapy. On the contrary, MGA mostly occurs in women of postmenopausal age. It is therefore known that the age of the patient and whether pre- or postmenopausal can be major clues for the correct diagnosis. Histologically, MGH and MGA share similar histological features. In MGH there is mild nuclear atypia and scarce mitotic activity. On the contrary, when nuclear atypia and mitotic figures are more pronounced, are in favor of MGA. In addition, subnuclear vacuolization can be present in MGH, which is not a feature in MGA. Staining for vimentin can help in the differential diagnosis, as it is positive in MGA and negative in MGH[14]. Both MGA and MGH have variable expression of estrogen and progesterone receptors[14]. Carcinoembryonic antigen (CEA) is often expressed in endometrial and endocervical adenocarcinomas, but is negative in endometrial mucinous adenocarcinoma and cervical MGH[11,12]. Qiu *et al*[14], describes absence of CEA staining in all cases of MGA and MGH. Immunostaining for CEA, ER, PR or p53 does not aid the differential diagnosis. Chekmareva *et al*[15] suggested that p16, CD10 and CD34 immunostaining could help in the differential diagnosis between MUC-AD and MGA of the endometrium on the one hand and benign endocervical lesions on the other. As reported, MUC-AD and MGA cases were positive for p16, whereas none of the cases with benign endocervical epithelial lesions and MGH showed p16 positivity, except from the reserve cells, typically located on the outer aspect of the endocervical glands. Also Baroetta *et al*[16] showed that 'CD34-dominant phenotype' of stromal cells was in favor of the cervical origin of the lesion and 'CD10-dominant phenotype' of stromal cells was compatible with the endometrial origin of the lesion. Overall, the immunohistochemical profile of endometrioid carcinomas, including mucinous carcinoma, overlaps with that of MGH (ER positive, p16 negative or patchy, variable Ki-67).

Loss of PAX2 expression in the epithelium, would favor the diagnosis of MGA[17]. Although, there are no antibodies completely sensitive and specific, a p16-positive/PAX2-negative phenotype, favors MGA (Table 1). Additionally, pathologists should be aware that MGA, are commonly p16-positive, as primary endocervical neoplasms.

Apart from MGH, MGH-like carcinoma should be differentiated from benign mucinous endometrial proliferations. Benign mucinous proliferation is supported by simple glandular architecture with mucin containing cells, absence of nuclear atypia and epithelial stratification[8].

In cases with no clues, a descriptive diagnosis is advised, such as 'atypical mucinous glandular proliferation' with a discussion of the differential diagnosis of under-sampled adenocarcinoma *vs* endocervical MGH. These patients should undergo further clinical and radiologic evaluation, including thorough endometrial curettage. The likelihood of finding adenocarcinoma on subsequent hysterectomy is partly related to the degree of architectural complexity. Nevertheless, this can be challenging in actual practice[18]. The presence of MGH-like glands in an endometrial sampling in peri- or postmenopausal women, regardless of the degree of complexity, should be mentioned and discussed.

Mutational analysis for KRAS has been suggested to be of aid in cases of small and fragmented biopsies[19], as complex mucinous proliferations largely harbor KRAS mutations.

Features that mimic endocervical MGH may be seen on the surface or at the periphery of some endometrioid adenocarcinomas. Often, these are grade I tumors[10] with mucinous differentiation, with predilection for post-menopausal women.

In all similar with ours presented cases in the literature, residual carcinomas were seen in the hysterectomy specimen, consisting of conventional carcinomas of mucinous or endometrioid type, in association with MGH-like carcinoma. These findings support the idea that the microglandular pattern represents 'a line of differentiation that is more mature and less aggressive in comparison with conventional carcinoma and this microglandular pattern usually occurs on the tumor surface, where an area permits a proliferation of non-invasive cells'[7]. Plaque-like microglandular differentiation is found on the surface of conventional adenocarcinoma[10]. The studies of Jacques *et al*[20] and Fukunaga[12] supported this argument but Zaloudek *et al*[11] and McCluggage and Perenyi[21] found MGH-like patterns in invasive areas of the tumor. In our case we found MGH-like carcinoma on the surface of the conventional endometrioid carcinoma in the hysterectomy specimen (ph 10). The conventional carcinoma was of mucinous or endometrioid type. There was no atypical hyperplasia present.

There is no clinical significance to MGH-like features in an endometrioid adenocarcinoma. The significance is purely to pathologists concerning the differential diagnosis in biopsy or curettage specimens, because under-sampling of this type of tumor may lead to hypo-diagnosis of MGA. The latter can present a true diagnostic challenge that many times may not be solved upon review of a limited sampling. The biopsy may only contain fragments of mucinous glandular proliferation with no nuclear atypia or mitotic activity and with no features of either hyperplasia or carcinoma. The only clue may be the patient's age and in some cases the clinical history of an endometrial tumor, endometrial thickening or uterine bleeding. If no other clues present, there is an important diagnostic rule of thumb, to consider the patient's age when considering a diagnosis of endocervical MGH in an endometrial sampling: if peri- or postmenopausal age, then the possibility of under-sampled adenocarcinoma with MGH-like features should be considered. The diagnosis of MGH in endometrial samples of postmenopausal women should not be made unless thorough examined[8]. Furthermore, features that favor EAMGP are a large amount of tissue in a biopsy, a lack of subnuclear vacuoles, transition to other patterns of endometrial adenocarcinoma, connection with endometrial stroma, an association with

Table 1 Morphological and immunohistochemical differences

	MGH	MGA
Subnuclear Vacuoles	+	-
Foamy stromal cells	-	+
VIM	-	+
p16	- (positivity in reserve cells)	+
PAX2	+	-
CD10-dominant phenotype of stromal cells	-	+ (endometrial origin)
CD34-dominant phenotype of stromal cells	+ (cervical origin)	-
Menopausal age	Reproductive (mostly)	Peri-or postmenopausal

MGH: Microglandular hyperplasia; MGA: MGH-like endometrial adenocarcinoma.

foamy stromal cells and the presence of complex endometrial hyperplasia or mucinous metaplasia in the background of endometrium. A descriptive diagnosis should be reserved for cases where the distinction is not possible, such as 'glandular proliferation with a microglandular-like pattern'. Additionally, the report should include a comment, suggesting either acquirement of additional tissue (*i.e.*, fractional curettage) or clinical correlation, to reach a definitive diagnosis.

CONCLUSION

When MGH-like proliferation is detected in the D&C of a postmenopausal woman, endometrial MGA type of carcinoma, should be excluded. The examination of scant biopsy specimens remains a challenge. Look for areas of typical endometrioid adenocarcinoma. Look for subnuclear vacuolation. Staining for vimentin, p16, PAX2, CD10 and CD34 can be of help in the differential diagnosis with MGH.

FOOTNOTES

Author contributions: Trihia HJ diagnosed the case and authored the paper; Pavlakis K confirmed diagnosis (second opinion); Fotiou A supported surgical management; Galanopoulos G took macroscopic photos; Rest co-authors helped in the review of the manuscript.

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Self-monitoring of blood glucose in gestational diabetes mellitus patients during the COVID-19 pandemic in low- and middle-income countries

Sumanta Saha

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Abstract

Self-monitoring of blood glucose (SMBG) is critical for gestational diabetes mellitus (GDM) care. However, there are several hurdles to its practice during the coronavirus disease 2019 (COVID-19) pandemic in GDM patients in low- and middle-income countries when GDM care recommendations emphasize telemedicine-based care. Based on available knowledge, this letter proposes the following barriers to SMBG in these GDM patients during the ongoing COVID-19 pandemic: Poor internet connectivity, affordability of SMBG and digital applications to connect with healthcare providers, government-imposed social mobility restriction, psychological stress, and mental health conditions. Nevertheless, definitive evidence will only be acquired from rigorous research.

Key Words: COVID-19; Gestational diabetes; Blood glucose monitoring; Self-monitoring; Developing countries; Patient compliance

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Core tip: The barriers to self-monitoring of blood glucose (SMBG), one of the main treatment components in gestational diabetes mellitus (GDM), remain underexplored among women in low and middle-income countries during the ongoing coronavirus disease 2019 (COVID-19) pandemic when the emphasis is on telemedicine-based care. Based on the facts known in this context, plausible barriers to SMBG in GDM patients include: Poor internet connectivity, affordability of SMBG and digital applications to connect with healthcare providers, government-imposed lockdowns to decrease COVID-19 transmission, psychological stress, and mental health conditions. However, only definitive research will provide the correct answers.

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TO THE EDITOR

Self-monitoring of blood glucose (SMBG) is one of the chief components of gestational diabetes mellitus (GDM) management to curb gestational hyperglycemia and perinatal complications[1]. Therefore, it is imperative to evaluate the SMBG practice among GDM patients living in low- and middle-income countries during the ongoing coronavirus disease 2019 (COVID-19) pandemic. In these women, pregnancy is often challenging due to poverty, lack of information, poor and inadequate quality services, teenage pregnancies, and cultural beliefs[2,3]. The COVID-19 pandemic has further compounded their GDM care. Presently, our knowledge on the barriers to SMBG practice in GDM patients during the COVID-19 pandemic remains sparse. I discuss here the possible barriers and intricacies of SMBG practice in GDM patients during this pandemic in the light of what is known; however, only definitive research will produce the answers.

The mobile-based technologies' role in ensuring SMBG compliance in GDM patients has become crucial in the COVID-19 pandemic[4]. The interim recommendation during the pandemic emphasizes sending SMBG reports electronically to healthcare providers (HCP) 2-3 wk after the first diabetes evaluation[5]. Then, the HCP determines the subsequent SMBG frequency based on glycemic control[5]. However, universal access to such telemedicine-based healthcare services is questionable in low- and middle-income countries, primarily due to the lack of uniform internet access[6,7].

Performing SMBG and sending the results to HCPs digitally incur costs for items like lancets, glucose reading meters, and featured smartphones. It might be expensive for GDM mothers in low- and middle-income nations, relying on out-of-pocket expenses[8]. This situation might have worsened due to the pandemic-led job losses and financial crisis[9].

There are challenges due to COVID-19-lockdown-led social immobility. Telemedicine-based GDM care is not accessible to every woman in the developing world, and many GDM patients have to rely on direct HCP-guided SMBG practice. Data from two Indian studies on nongestational diabetes patients suggest poor SMBG compliance during the COVID-19 lockdown period (28%-65%)[10,11]. Therefore, such government-imposed lockdowns are likely to be barriers for GDM patients, and studies are required to investigate it. Moreover, research is essential to determine if complying with COVID-19-related safety mandates (such as frequent handwashing, wearing a face mask, and social distancing) have complicated SMBG adherence in GDM patients.

For many GDM patients, additional pandemic-associated hurdles might include minimal or no direct family or peer support at home due to COVID-19-related quarantine requirements (of themselves or family members). Family support is crucial for the mental health of pregnant women during the COVID-19 pandemic[12].

Finally, psychological stress and mental health conditions due to the pandemic such as the death of close relatives, COVID-19-related mobility restrictions, and financial crisis also require scrutiny. According to an online survey, a substantial proportion of pregnant women presented with some mental disorder (about 37%) and increased stress levels (about 46%) during the COVID-19 pandemic [13]. Therefore, it is crucial to review the possibility of integrating mental health screening with antenatal care during the COVID-19 pandemic. The HCPs providing prenatal services may require additional training to perform such screening.

Altogether, given these scenarios, the COVID-19 vaccination drive is crucial to decrease social immobility restrictions, ensure women's economic empowerment, and establish easy direct contact with their HCPs so that SMBG practice among GDM patients remains uninterrupted in developing nations. Simultaneously, efforts to establish better telemedicine services and foster psychological counseling to overcome pandemic-associated stress are also desirable.

FOOTNOTES

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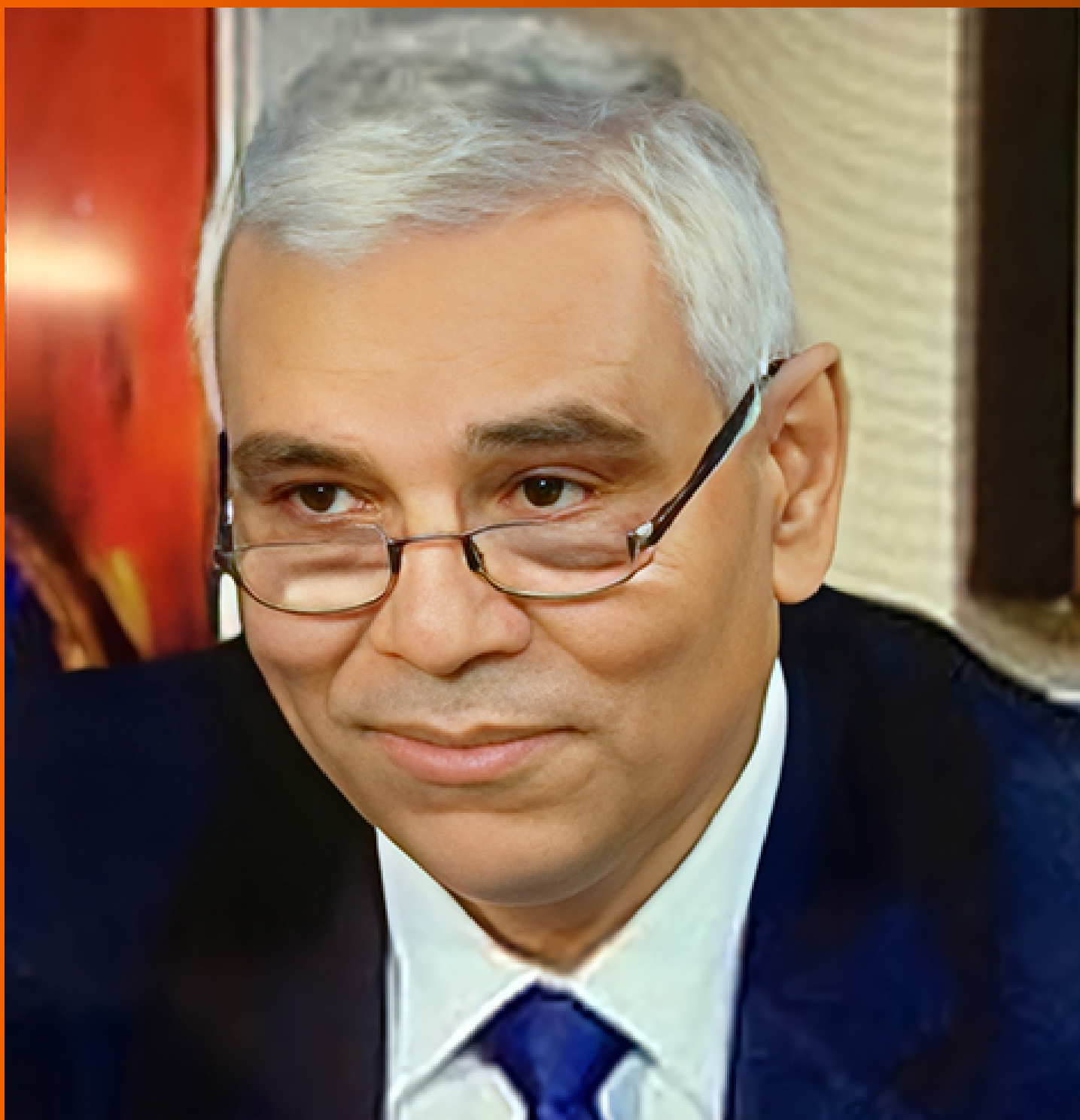
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- 20 Prevalence and factors associated with non-adherence to therapy among partners of pregnant women with syphilis in a city of northeastern Brazil

Fernandes LPMR, Oliveira CNT, de Brito BB, Freire de Melo F, Souza CL, Oliveira MV

CASE REPORT

- 33 Therapeutic challenges in metastatic follicular thyroid cancer occurring in pregnancy: A case report

Spinelli C, Sanna B, Ghionzoli M, Micelli E

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Observational Study

Prevalence and factors associated with non-adherence to therapy among partners of pregnant women with syphilis in a city of northeastern Brazil

Lilian Pinto Mota Rodrigues Fernandes, Caline Novais Teixeira Oliveira, Breno Bittencourt de Brito, Fabrício Freire de Melo, Cláudio Lima Souza, Márcio Vasconcelos Oliveira

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Abstract

BACKGROUND

One of the main difficulties faced in the prevention of the vertical transmission of syphilis is the inadequate treatment of pregnant women and their partners. The disease causes serious repercussions in infected newborns.

AIM

To evaluate the prevalence and factors associated with the therapeutic adhesion among partners of pregnant women with syphilis in a county in Northeastern Brazil.

METHODS

This is a descriptive, analytic, quantitative, cross-sectional study that was carried out through interviews with 46 pregnant women diagnosed with syphilis between 2017 and 2018 as well as with their partners. The interviews aimed at collecting data regarding sociodemographic characteristics, obstetric variables and information about syphilis, and partners' related variables.

RESULTS

Our results showed that 73.91% of the partners did not undergo appropriate treatments, and obtaining negative results in syphilis tests was the main reason for the absence of therapies. The following factors were significantly associated with the lack of treatment among partners: Being a partner that is not the current mate of the pregnant woman, having a level of schooling inferior to 8 years [odds

ratio (OR) = 10.28], and the pregnant woman undergoing up to two syphilis tests during the prenatal care (OR = 8.6). The study found a higher odds of absent treatment among partners if the pregnant woman is not white (OR = 13.88) or if the partner has less than 8 years of schooling (OR = 21.00) or has a monthly income of less than half the minimum wage (OR = 13.93).

CONCLUSION

The findings of this study show a high prevalence of partners that are not adequately treated for syphilis, a phenomenon that is strongly associated with socioeconomic factors.

Key Words: Partners; Syphilis; Syphilis in pregnancy; Treatment; Pregnant women; Prevalence

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Core Tip: Treating infected pregnant women and their partners is a challenging step in the prevention of syphilis vertical transmission. This study evaluated the prevalence and factors associated with the therapeutic adhesion among partners of pregnant women with syphilis in a county of northeastern Brazil. Here we demonstrated an important lack of treatment among the study partners, which was associated with various socioeconomic factors.

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INTRODUCTION

Syphilis is a systemic infectious disease with chronic evolution, having the *Treponema pallidum* as a causative agent. The disease can be transmitted through multiple routes, and the contagion mostly occurs through sexual contact and vertical transmission, from the mother to the fetus[1]. Although it is considered an easily diagnosed and treated disease, syphilis is still an important health issue worldwide [2,3]. The “acquired syphilis” is the form of the disease that can affect the sexually active adult population. When pregnant women are infected, the disease is classified as “syphilis in pregnancy” and, if not treated or inadequately treated, the infection is transmitted to the fetus, after the 16th week of pregnancy, leading to “congenital syphilis” (CS)[2,4,5]. Symptoms related to CS include early syphilis snuffles due to nasal ulceration, vesicular eruption, skeletal abnormalities, and hepatosplenomegaly[6].

The World Health Organization estimates that syphilis affects one million pregnant women each year around the world, leading to more than 300 thousand fetal and neonatal deaths, besides increasing the risk of premature death in more than 200 thousand children. In addition, it is considered a reemerging disease with a growing incidence even in developed countries[7,8]. Among the main difficulties faced in the prevention of the vertical transmission of syphilis, the inadequate treatment of pregnant women and their partners stands out. Even after appropriate treatment during prenatal care, pregnant women often experience reinfections by their partners, which can lead to the transmission of the disease to their children[9,10].

Therefore, the men's health is a crucial factor to be taken into account when considering the prevention of CS; however, sociocultural factors and institutional barriers seem to impair the achievement of satisfactory rates of adhesion to healthcare measures targeting the male population. Throughout the last few years, the number of non-treated partners has overcome the number of treated partners in Brazil[10-14]. From 2012 to 2017, 62% of the partners of pregnant women with syphilis were not treated in this country[15].

The impacts caused by syphilis go far beyond the health aspects. Important financial losses to the health economy have been associated with that disease. The expenditures demanded by a CS-affected newborn (NB) are three-fold higher than those required for the healthcare of NBs without syphilis, besides the permanent costs to individuals with neurological damage who require specialized and continuous attention from the health systems[16]. In 2018, the Brazilian Unified Health System spent approximately 2.8 million dollars on hospital procedures directly related to syphilis[17].

Given the scenario of growing cases of acquired syphilis, syphilis in pregnancy, and CS, and considering the existence of difficulties in the implementation of healthcare measures for male populations, this study aimed to describe the prevalence of syphilis among pregnant women in the city of Itapetinga in northeastern Brazil, as well as to identify factors associated with the therapeutic

adhesion of partners whose women tested positive for the disease during pregnancy.

MATERIALS AND METHODS

This descriptive, analytic, quantitative, cross-sectional study was carried out with pregnant women diagnosed with syphilis between 2017 and 2018 as well as with their partners. The data collection occurred between January and June 2019.

The initial projection of the study was to analyze 56 couples (pregnant women with syphilis/partners) based on the mean number of syphilis cases that occur in the study city according to the Brazilian System of Information for Notifiable Diseases (SINAN). However, the notification of cases overcame the aforementioned mean in 2018, reaching 69 cases and showing an increase in the occurrence of syphilis in pregnant women in the study city.

Cases of syphilis in pregnancy were defined as pregnant women who had at least one positive syphilis test, in accordance with the classification of the Brazilian Ministry of Health. Three pregnant women under 18 years old, one who lives in another city, one with a negative confirmatory test (false positive), and three duplicities in SINAN were excluded from the study. Loss to follow-up occurred with nine pregnant women who moved to another city, three who refused to participate in the interview, and three who could not be subsequently contacted. Finally, 46 pairs (pregnant women/partners) were included in the study (Figure 1).

In order to contact the patients, epidemiological surveillance professionals and contributors of this study performed an active search. Informed consent was obtained from the pregnant women who accepted to participate in the study and, then, the interviews were conducted in their homes. If their partners lived in the same residence, they were immediately invited to participate in the study as well and, if they accepted, signed informed consent was also obtained. Otherwise, partners who did not live with the correspondent pregnant women were searched according to the addresses informed by the pregnant women. Finally, if the partners could not be contacted, the pregnant women provided the partners' information required in the study. The steps of data collection are described in Figure 2.

The data collection tool was adapted from the questionnaire used in the Born in Brazil Program (2003) and National Health Survey (2017), epidemiological surveillance research performed by Brazilian governmental health agencies. The questionnaire was organized into four sections (A, B, C, and D). Sections A (sociodemographic characteristics) and B (obstetric variables and information about syphilis) were conducted with pregnant women, whereas C (partner's identification variables) and D (variables regarding treatment and complementary information) were used to obtain information from partners. In order to adapt the questionnaire language, a pilot study was performed with pregnant women without a syphilis diagnosis. In this stage, a number of participants corresponding to 20% of the study sample were included and the data collection occurred in a single moment, in an individual and presential way, with pregnant women who were waiting for their prenatal consultation in a basic health unit in the study city. The questionnaire showed to be suitable, and it was well accepted by the participants in this pilot study.

The information regarding the number of prenatal consultations, results of syphilis tests, and drugs used in pregnancy, as well as their doses, were collected from the Brazilian pregnant women card or from the medical records from primary care units.

A database was elaborated in Microsoft Office Excel and analyzed through the EPI-INFO statistical pack (version 7.1.5.2). The Pearson's chi-square test was performed with a 5% significance level and 95% confidence interval to compare frequencies. The association measures were done through the odds ratio (OR) calculation in the univariate analysis. Subsequently, a multivariate analysis using the Statistical Package for the Social Sciences (SPSS, Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. IBM Corp.) was performed through logistic regression with all the variables for which a *P*-value was inferior to 0.20 was obtained in the univariate analysis. For the final model, the variables with *P* < 0.05 were taken into consideration in the block with the best adjustment through the Homer-Lemeshow method.

The study was put into practice after the approval by the Research Ethics Committee of the Multidisciplinary Institute of Health of the Federal University of Bahia, under protocol number 2.995.408 and the certificate of presentation of ethical appreciation number 97664818.3.0000.5556.

RESULTS

Tables 1 and 2 show the descriptive analysis performed on the pregnant women included in the study and their partners. With regard to the pregnant women's socioeconomic profile, 63% (*n* = 29) were aged between 18 and 24 years, and most of them did not have mates, were not white, and had less than 8 years of schooling, and a monthly income higher than half the minimum wage. Regarding obstetric antecedents, half of the women did not use any contraceptive method, 30% have had at least one spontaneous abortion, and most of them had their prenatal care started up to the third month of

Table 1 Descriptive analysis of data regarding pregnant women with syphilis (*n* = 46)

Variable	<i>n</i>	%
Pregnant women		
Age (yr)		
25 or older	17	36.96
18 to 24	29	63.04
Marital status		
With a mate	21	45.65
Without a mate	25	54.35
Ethnicity		
White	10	21.74
Not white	36	78.26
Schooling level		
8 yr or more	20	43.48
Less than 8 yr	26	56.52
Monthly income		
Higher than half a MW	30	65.22
Less than half a MW	16	34.78
Contraceptive use		
No	23	50.00
Yes	23	50.00
Number of syphilis tests		
Up to 2 tests	16	34.78
3 or more tests	30	65.22
Beginning of the prenatal care		
Until the 3 rd month of gestation	32	71.11
After the 3 rd month of gestation	13	28.26
Number of prenatal consultations		
At least 6 consultations	27	58.70
Less than 6 consultations	19	41.30

MW: Mean minimum wage for the years 2017 and 2018, equivalent to 945.50 Brazil Reals.

gestation, attending to more than six consultations before the delivery.

Concerning the syphilis-related variables, most individuals were diagnosed by a nurse, had no previous information about syphilis, and received information about the disease from the health professionals. Moreover, 80% of the participants had Venereal Disease Research Laboratory (VDRL) test titers higher than 1:4, and no information about the titers observed in the second VDRL test was found for 48% of the pregnant women. In 99% of the pregnant women, benzathine penicillin was the drug of choice for the treatment of syphilis, and 56.5% of the doses were administered in a hospital or in an emergency care unit.

In this study, ten pregnant women (22%) had syphilis in previous pregnancies and most women (percentage) have already undergone at least one previous treatment for the disease, which suggests the occurrence of reinfections. A pregnant woman was diagnosed with syphilis only during the delivery and five NBs had congenital syphilis, from which one died due to this condition.

With respect to the partners, most of them were 25 years or older, were not white, had less than 8 years of schooling and a monthly income higher than half the minimum wage, and had no formal work. In addition, 26% of them were unemployed. Regarding their health condition, most partners qualified their health status as good, did not attend a medical consultation in the last year, and consumed

Table 2 Descriptive analysis of data regarding partners of pregnant women with syphilis (*n* = 46)

Variable	<i>n</i>	%
Partners		
Age (yr)		
18 to 24	21	45.65
25 or older	25	54.35
Ethnicity		
White	14	30.43
Not White	32	69.57
Schooling level		
8 yr or more	16	37.21
Less than 8 yr	27	62.79
Monthly income		
More than half a MW	26	56.52
Up to half a MW	20	43.48
Occupation		
Commerce, industry, or freelance	34	73.91
Not working	12	26.09
Formal work		
Yes	15	32.61
No	31	67.39
Last attendance to a medical consultation		
Less than 1 yr ago	18	41.86
More than 1 yr ago	25	58.14
Health status		
Regular	13	28.26
Good/Very good	33	71.74
Appropriate treatment		
Yes	12	26.09
No	34	73.91
Reasons for absent treatment		
Negative syphilis tests	13	38.23
The partner was communicated but refused treatment or did not attend the primary care unit	09	26.47
The partner was not communicated	06	17.65
Others	06	17.65

Three data were ignored by the responding pregnant women. MW: Mean minimum wage for the years 2017 and 2018 in Brazil, equivalent to 945.50 Brazil Reals.

alcoholic beverages more than once a month. Complementarily, 23% of them reported the use of other drugs. Among the illicit drugs mentioned, marijuana was the most prevalent (82%), followed by cocaine (8%).

Appropriate treatment was not performed in 73.91% (*n* = 34) of the partners. Among the individuals who did not undergo treatment, 38.23% (*n* = 13) were informed that the therapy would not be necessary since they had negative syphilis tests. On the other hand, 26.47% (*n* = 9) of them told that they were communicated about the need for treatment, but refused to go to the health unit. Moreover, 23.52% (*n* = 8) told that they were not informed about the need for treatment or did not have further contact with the

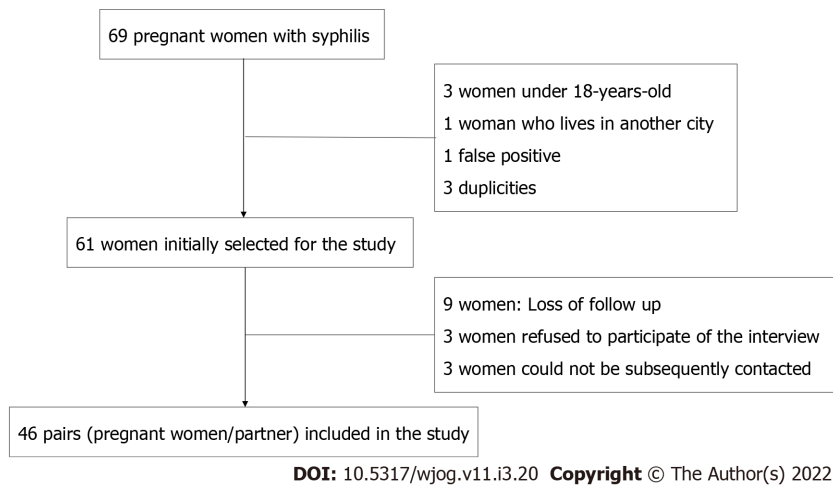


Figure 1 Forty-six pairs of pregnant women/partners were included in the study.

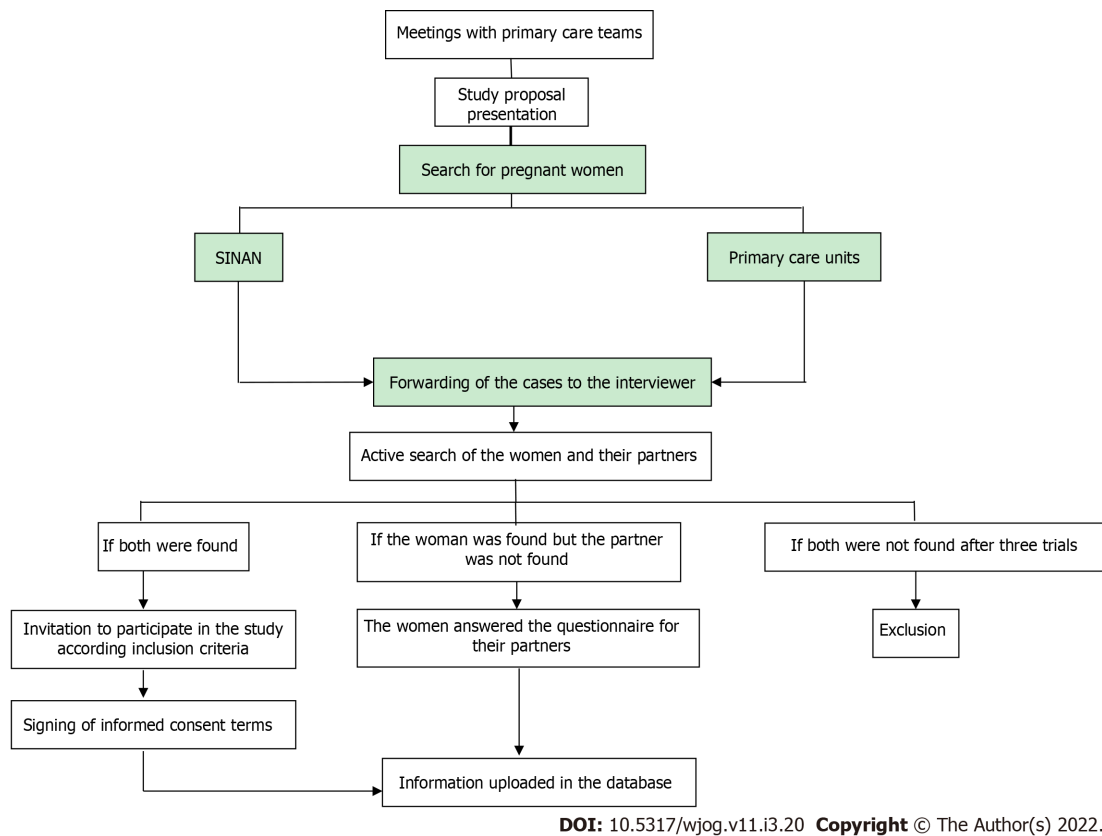


Figure 2 Steps of data collection.

women. Some untreated individuals told that they did not have available time for the therapy, were afraid of injections, or had a work schedule incompatible with the health unit opening time.

The univariate analysis evidenced that the absence of treatment among partners was significantly associated with some women-related factors, namely, not having a current mate (OR = 5.50), having less than 8 years of schooling (OR = 6.27), and undergoing up to two syphilis tests during pregnancy (OR = 8.6). The analysis with partner-related variables showed that not treating for syphilis was associated with having less than 8 years of schooling (OR = 10.28) and a monthly income of up to half the minimum wage (OR = 13.93).

Multivariate analysis (Table 3) of pregnant women-related variables showed that identifying themselves with an ethnicity other than white is an important characteristic for the occurrence of non-treated partners (OR = 13.88). Among partners, such analysis revealed that having less than 8 years of schooling (OR = 21.00) and a monthly income lower than half the minimum wage (OR = 12.23) were correlated with the absence of syphilis treatment.

Table 3 Final logistic regression model according to groups of variables selected for absence of treatment among partners

Variable	OR (95%CI)	P value
Pregnant women		
Ethnicity other than white	13.88 (1.38-14.1)	0.02
Partners		
Less than 8 yr of schooling	21.00 (2.70-177.47)	0.00
Monthly income of less than a half MW	12.23 (1.39-107.44)	0.02

MW: Mean minimum wage for the years 2017 and 2018 in Brazil, equivalent to 945.50 Brazil Reals. OR: Odds ratio.

DISCUSSION

Some studies show a high prevalence of non-treated partners of pregnant women with syphilis in multiple regions of Brazil[9,14,15]. However, studies on syphilis in pregnancy including direct interviews with partners are rare, since most published data on this issue only contain information provided by pregnant women. Of note, the importance of the concomitant treatment of pregnant women and partners is well established in the scientific field and recommended by governmental agencies, which is the most suitable approach in order to reduce the risk of recontamination as well as the prevalence of the disease and the occurrence of CS[18-21].

The characteristics of pregnant women observed in this study corroborate the findings of other Brazilian studies showing a higher prevalence of the disease among women between 18 and 24 years old, which represents a higher rate of infection among young women of reproductive age, mainly teenagers[22-24]. This study showed that when pregnant women do not have a current mate, the odds of the absence of treatment among partners is higher than if the pregnant woman is married, corroborating the findings by Lafetá and colleagues[25]. According to Figueiredo *et al*[26], the type of relationship of a couple (a stable relationship or not) should be carefully taken into consideration by health professionals since it will determine the most suitable strategy to reach a higher therapeutic adherence among partners.

In this study, most pregnant women and partners had less than 8 years of schooling. In addition, partners with that level of schooling had a 21-fold higher odds of not being treated than individuals with more years of schooling. The association between the occurrence of syphilis and low educational level was described by previous studies as well[23,27,28]. Of note, the schooling level is often used as an indicator of the socio-economic conditions of a population, since low-educated people who have a limited understanding of the importance of healthcare and preventive measures are considered more vulnerable individuals[28].

The odds of lacking treatment among partners was 13.88-fold higher if the pregnant women and partners identified themselves with an ethnicity other than white. According to the Brazilian Institute of Geography and Statistics, 64.35% of the population of the study city is not white, which matches the ethnical profile of the patients included in this study[29]. A study including 110 pregnant women from another Brazilian city observed that being a white woman was significantly associated with carrying out the appropriate treatment for syphilis in partners[10]. Complementarily, other reports show a higher prevalence of syphilis in pregnancy and CS among women who identify themselves with a race other than white[7,20,22].

It has to be emphasized that there was a high proportion of pregnant women who reported previous spontaneous abortions in this study (30.4%), and a possible relationship between this data and the presence of syphilis. According to the Brazilian Ministry of Health, 40% of the pregnancies in women with non-treated syphilis results in spontaneous abortion[21,30]. Another Brazilian study identified a rate of 18% of abortions and high syphilis rates among pregnant women, suggesting that the infection may be a factor associated with that outcome. Although the present study was not designed to verify this association, these data attract attention and should be further investigated in future studies.

The data regarding the beginning of prenatal care and the number of consultations observed in this study corroborate previous investigations in which a higher prevalence of partners' treatment was associated with starting prenatal care before the third month of pregnancy and attending to at least six consultations before delivery[12,30]. These results reinforce the need for a higher adhesion to prenatal care. However, the assurance of access to prenatal care and diagnostic tests alone is not enough to ensure a meaningful improvement in health assistance since strategical and educative actions to qualify professionals for the management of syphilis as well as well-organized health services aiming to control that disease may be lacking[13,15,31].

Moreover, there was a significant association in the univariate analysis between performing not more than two syphilis tests in pregnant women and the lack of treatment among partners, which corroborates the study by Silva and colleagues[32]. The authors identified that women who underwent less

than five diagnostic tests during prenatal care experienced a higher number of failures in the syphilis-related diagnosis and treatment, and it was supposed to be due to the low access to consultations and diagnostic tests as well as to the lack of knowledge about the outcomes associated with the disease. In addition, the necessity for constant monitoring of syphilis cases by health professionals including the performance of diagnostic tests has to be considered in order to reduce the occurrence of failures in the prevention of the disease[13].

Nurses diagnosed most of the pregnant women in this study and 89% of the patients reported that they received explanations about the disease. Nonetheless, 73.91% of the partners were not adequately treated. However, Campos and colleagues verified an increase in the partners' therapeutic adhesion when information about syphilis was provided to pregnant women after the diagnosis, highlighting the importance of the quality of the counseling[9]. Our study points towards the necessity of evaluating the quality of the explanations provided by the health professionals to patients as well as the frailties of the health service when calling up the partners to undergo the treatment[13]. Therefore, it is important to promote a permanent education of the professionals involved in prenatal care, which may allow the magnification of the capturing and reception of sexual partners of pregnant women in order to perform an appropriate treatment and to improve the quality of the prenatal assistance[15,27].

With regard to the environment in which the benzathine penicillin was administered, more than half of the pregnant women and partners were referred to a hospital or an emergency care unit, probably because of the fear of potential penicillin-related side effects by health professionals from the primary care units in which these patients were accompanied. However, the reference of pregnant women and partners to tertiary care units may be followed by a delay in attendance, impossibility to confirm if the patient underwent the treatment, and loss of continuity of the patients' care in primary care units[26]. Health agencies have highlighted the importance of administering penicillin in the primary care units, mainly in pregnant women and partners, due to the risk of vertical transmission. Moreover, the prevalence of allergic reactions among patients treated with penicillin ranges from 0.01% and 0.05% [33]. Finally, it has to be emphasized that the need to move to hospitals or emergency care units may influence the therapy adhesion of the partners since their transport depends on financial sources, which can be unavailable.

Of note, most partners of pregnant women diagnosed with syphilis were 25 years or older, and the rate of absent treatment was higher in the group of individuals aged 18 to 24 years. However, no statistical significance was observed with that association, which was probably due to the small sample (Tables 4 and 5). Previous studies point toward a higher syphilis prevalence among partners aged 21 to 30 years[9] and a higher odds to undergo treatment among those aged between 20 and 29 years[10].

In both univariate and multivariate analyzes, statistically significant associations were verified between the lack of syphilis treatment for the partner and a monthly income of less than half the minimum wage. This data corroborates other studies that attribute the absence of syphilis treatment for pregnant women and partners to unfavorable socioeconomic factors[10,28,34]. Although it does not occur only in people from lower social classes, syphilis is often associated with low income, a variable that hinders the appropriate diagnosis and treatment of diseases since it is considered an important predictor of limited access to health services[16]. Complementarily, 67% of the partners did not have formal work, another data that highlights the vulnerabilities of the population studied.

With respect to the consumption of alcoholic beverages, 54% of the partners told that they drink more than once a month and 23% reported the use of other illicit drugs, with marijuana being the most prevalent, followed by cocaine. No statistically significant association was observed between the use of drugs and the lack of treatment of the partners. However, it has to be emphasized that such associations have been verified by previous studies[9,10,16].

Among the partners of this study, 71.7% considered themselves as having a "good" or "very good" health status, and most of them did not attend a medical consultation in the last year. Levorato *et al*[35] observed that men who say that they have no disease have a 2.89-fold higher odds of not seeking health services for preventive care. In the present study, that association was not verified probably due to the limited statistical power of the sample.

The image of the man built through history is an omnipotent identity that does not get sick, and male individuals tend not to take health care seriously. In that context, women seek health services 1.9 times more than men[36]. Associated with that, if health policies do not include special strategies targeting men's health, such a population is not attracted to health services[9]. The carelessness of healthcare services regarding men's health becomes evident with the high number of partners that do not undergo syphilis treatment and with the lack of inclusion of partners in prenatal care, which should be a priority in aiming for an effective cure for pregnant women and reduction of the incidence of syphilis[36].

In this study, 73.91% of the partners were not adequately treated, and similar results were reported in other papers[12,18,32,37]. The lack of treatment among partners has been considered the main fault in the treatment of pregnant women. Worryingly, the rate observed here is higher than the prevalence observed in Brazil in 2018 (53%)[21].

The main reasons for the absence of treatment were getting negative results in syphilis tests (38.23%) and refusal of the call-up by the primary care units (26.47%). A similar result was observed in the study by Hildebrand *et al*[10]. Of note, the treatment of partners of pregnant women with syphilis with a dose of benzathine penicillin (2.4 million international units) is recommended even if the serological results

Table 4 Univariate analysis of characteristics related to pregnant women with syphilis and absence of treatment of their partners (n = 46)

Variable	OR (95%CI)	χ^2	P value
Pregnant Women			
Age (yr)			
25 or older	1		
18 to 24	3.36 (0.85-13.14)	3.18	0.07
Marital status			
With a mate	1		
Without a mate	5.50 (1.24-24.25)	5.63	0.02
Ethnicity			
White	1		
Not white	4.14 (0.9-18.36)	3.78	0.06
Schooling level			
8 yr or more	1		
Less than 8 yr	6.27 (1.41-27.86)	6.56	0.01
Monthly income			
More than half a MW	1		
Up to half a MW	3.50 (0.66-18.49)	2.34	0.11
Contraceptive use			
No	1		
Yes	1.57 (0.41-5.95)	0.45	0.36
Spontaneous abortion			
No	1		
Yes	2.72 (0.51-14.53)	1.45	0.20
Beginning of the prenatal care			
Until the 3 rd month of gestation	1		
After the 3 rd month of gestation	1.30 (0.29-5.86)	0.12	0.52
Number of prenatal consultations			
At least 6 consultations	1		
Less than 6 consultations	1.77 (0.45-6.91)	0.69	0.31
Number of syphilis tests			
At least 3 tests	1		
Up to 2 tests	8.68 (1.00-75.01)	5.00	0.02

Oral and non-oral contraceptives. MW: Mean minimum wage for the years 2017 and 2018 in Brazil, equivalent to 945.50 Brazil Reals. OR: Odds ratio.

are negative[38].

Performing an active search to contact patients was a limiting factor of this research. Sometimes, it was necessary to do more than one visit to a single residence, mainly to find the partners. Among 46 women, 22 (47.8%) responded with the information about the partners, which resulted in the ignoring of some information and in a possible information bias. Among the reasons for the women who respond to their partners are: Some pregnant women did not allow the study contributors to interview their partners, other women did not live with their partners anymore, some partners refused to provide informed consent, some potential participants moved to another city, five women did not communicate their partners about the syphilis diagnosis, and one partner was arrested due to drug traffic.

Table 5 Univariate analysis of characteristics related to partners of pregnant women with syphilis and absence of treatment among them (n = 46)

Variable	OR (95%CI)	χ^2	P value
Partners			
Age (yr)			
25 or older	1		
18 to 24	2.00 (0.50-7.91)	0.99	0.25
Ethnicity			
White	1		
Not white	1.20 (0.29-4.9)	0.06	0.53
Schooling			
8 or more years	1		
Less than 8 years	10.28 (2.17-48.67)	10.17	0.00 ^a
Monthly income			
More than half a MW	1		
Up to half a MW	13.93(1.61-120.35)	8.16	0.00 ^a
Occupation			
Commerce, industry, or freelance	1		
Not working	5.26 (0.60-46.05)	2.65	0.10
Formal work			
Yes	1		
No	2.77 (0.71-10.86)	2.23	0.12
Last attendance to a medical consultation			
Less than 1 yr ago	1		
More than 1 yr ago	2.54 (0.65-9.94)	1.85	0.15
Health status			
Regular	1		
Good/Very good	1.38 (0.33-5.75)	0.20	0.45

^aStatistically significant association ($P < 0.05$). Three data were ignored by the responding pregnant women. MW: Mean minimum wage for the years 2017 and 2018 in Brazil, equivalent to 945.50 Brazil Reals. OR: Odds ratio.

The analyses performed here have never been evaluated in the study region before. The results obtained by this study provided a view on an important aspect of fighting syphilis-the treatment of sexual partners-and contribute to the knowledge about the theme. This study also reveals important information that may potentially aid in the improvement of the strategies of therapeutic follow-up for the disease and stimulate the conduction of studies with a bigger sample on this theme, since the low availability of financial sources limited the extension of the study region.

CONCLUSION

Factors associated with the treatment of the partners of pregnant women with syphilis represent a challenge to be overcome by the public health agencies. This study faced various difficulties given the nature of the investigation, and the important obstacles found when working in such a vulnerable social context. The research allowed the identification of factors related to the treatment of partners of pregnant women with syphilis, which was associated with socioeconomic variables and prenatal assistance, evidencing frailties in care practices that hinder the interruption of the disease's transmission chain. The findings highlight the need for greater attention from health managers and other professionals to populations with unfavorable socioeconomic conditions, low schooling level, low income,

single women, and women who underwent not more than two syphilis tests during prenatal care. In that context, it is necessary for the inclusion of partners in prenatal assistance as well as investments in educative and strategic actions for the qualification of health professionals for the management of syphilis. Finally, further studies are needed for a better understanding of the factors associated with the inappropriate management of syphilis.

ARTICLE HIGHLIGHTS

Research background

It is not new that syphilis is a major health concern worldwide. The disease can be transmitted through multiple routes, and the contagion mostly occurs through sexual contact and vertical transmission, from the mother to the fetus. Although it is considered an easily diagnosed and treated disease, syphilis is still an important health issue worldwide.

Research motivation

Worryingly, the congenital form of the *Treponema pallidum* infection is still a big concern, mainly in underdeveloped countries, although it is an avoidable condition. The prevention is mainly based on the proper diagnosis of the disease during pregnancy and the subsequent treatment of the pregnant women and their partners. In this sense, the adherence of partners to the treatment has to be highlighted as a key step in the prevention of such a devastating disease.

Research objectives

To evaluate the prevalence and factors associated with the therapeutic adhesion among partners of pregnant women with syphilis in a county of northeastern Brazil.

Research methods

This is a descriptive, analytic, quantitative, cross-sectional study that was carried out through interviews with 46 pregnant women diagnosed with syphilis between 2017 and 2018 as well as with their partners. The interviews aimed at collecting data regarding sociodemographic characteristics, obstetric variables and information about syphilis, and partners' related variables.

Research results

Our results showed that 73.91% of the partners did not undergo appropriate treatments, and obtaining negative results in syphilis tests was the main reason for the absence of therapies. The following factors were significantly associated with the lack of treatment among partners: Being a partner that is not the current mate of the pregnant woman, having a level of schooling inferior to 8 years (odds ratio [OR] = 10.28), and the pregnant woman undergoing up to two syphilis tests during the prenatal care (OR = 8.6). The study found a higher odds of absent treatment among partners if the pregnant woman is not white (OR = 13.88) or if the partner has less than 8 years of schooling (OR = 21.00) or has a monthly income of less than half the minimum wage (OR = 13.93).

Research conclusions

The findings of this study show a high prevalence of partners that are not adequately treated for syphilis, a phenomenon that is strongly associated with socioeconomic factors.

Research perspectives

We expect that this study may aid public health managers in the identification of factors associated with the non-adhesion to syphilis treatment by pregnant women's partners, which can help in the elaboration of effective health campaigns aiming at reducing the prevalence of the disease. Moreover, further research should be performed in order to better understand the persistence of congenital syphilis, mainly in underdeveloped countries.

FOOTNOTES

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, manuscript drafting, critical revision, and editing, and approval of the final version.

Institutional review board statement: This study was reviewed and approved by the Ethical Committee of Research in Human Beings of the Multidisciplinary Institute of Health-Campus Anísio Teixeira from the Federal University of Bahia (IMS-CAT/UFBA) under the protocol number 97664818.3.0000.5556 and committee opinion number 2.995.408.

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Therapeutic challenges in metastatic follicular thyroid cancer occurring in pregnancy: A case report

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Abstract

BACKGROUND

Hormones could play a role in the evolution of follicular thyroid cancer (FTC) for which we discuss an unusual presentation of FTC occurring during pregnancy.

CASE SUMMARY

A pregnant woman was admitted with FTC metastasis resulting in a gluteal mass. Preoperative abdominal computed tomography revealed liver metastasis for which the patient underwent total thyroidectomy and liver resection, oral radioiodine therapy and radiotherapy, followed by embolization of the pelvic mass. The patient died of cerebral hemorrhage 16 mo after the initial diagnosis.

CONCLUSION

Human chorionic gonadotropin and estrogen stimulation might have a role in cancer growth, especially during pregnancy. FTC management aims to stop disease progression and overcome hormonal imbalances after thyroidectomy thus reducing fetal complications. It is still under debate whether it is possible to combine optimal timing for treatment to ensure the best possible outcome with reduction of fetal complications and risk of cancer growth.

Key Words: Gluteal pain; Follicular thyroid cancer; Metastases; Pregnancy; Unusual presentation; Case report

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Core Tip: We discuss an uncommon presentation of follicular thyroid cancer occurring during pregnancy. Beta human chorionic gonadotropin and estrogens could take part in the progression of thyroid tumors.

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INTRODUCTION

Thyroid cancer is reported as the second most common type of cancer diagnosed during pregnancy, followed by breast cancer[1]. Although the effects of pregnancy on the behavior of this tumor have already been widely discussed, the number of reported cases is too small to draw any conclusions. We assume that beta human chorionic gonadotropin (β -hCG) and estrogens could play a role in the progression and prognosis of the tumor. To date, few reports of follicular thyroid cancer (FTC) causing bone metastases[2-5] (skull[6], mandible[7], maxilla[8], spine[9] and orbit[10]) are described, whereas no cases of gluteus metastases have been reported.

Its management during pregnancy remains challenging. It is crucial to stop the disease progression as well as to overcome the hormonal imbalances after thyroidectomy to avoid fetal complications as a consequence of maternal hypothyroidism[11,12]. The actual standard of care for patients diagnosed with thyroid cancer is a total or near-total thyroidectomy either in the second trimester or after delivery. This treatment is followed by radioactive iodine administration (RAI), contraindicated during pregnancy, as an additional treatment for differentiated thyroid cancer (DTC)[13]. The RAI treatment, with the subsequent total loss of thyroid function and follow-up scintigraphy, is usually postponed to the neonatal period in order to avoid fetal congenital hypothyroidism. A deferred postpartum treatment does not seem to alter the prognosis of thyroid cancer. To our knowledge, patients who undergo postponed surgery should receive thyroid hormone suppression treatment (L-thyroxine) until the definitive surgical treatment[14,15]. It remains controversial to establish whether it is beneficial to postpone the treatment schedule in order to avoid early delivery or if a timely treatment should be mandatory.

CASE PRESENTATION

Chief complaints

Herein we report on an otherwise healthy pregnant woman who came to our attention with hip pain associated with a mass resulting as an FTC metastasis.

History of present illness

A 43-year-old pregnant woman, with no other comorbidities, was admitted at her 30th wk of gestation at our Institution for progressive pain in the right gluteal/iliac region.

History of past illness

Past history showed no smoking or alcohol consumption habits, neither allergies nor history of hypertension, diabetes mellitus, bronchial asthma, tuberculosis or neck swelling.

Personal and family history

No hormonal fertility treatment had ever been performed on the patient who conceived naturally, carrying her first healthy pregnancy.

Physical examination

Physical examination showed a palpable lump of the right gluteus.

Laboratory examinations

Blood tests revealed: thyroglobulin ≥ 10000 (normal value: 3-40 ng/mL), α -FP = 93.4 (normal value: < 6.0 ng/mL), β -hCG = 896 (post-partum) and calcitonin = 15.2 pg/mL (normal value: < 16 pg/mL).

Imaging examinations

The abdominal and pelvic computed tomography (CT) scan and magnetic resonance imaging (Figure 1)



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Figure 1 Magnetic resonance imaging of the lower abdomen and pelvis. Solid formation with osteolytic involvement of the right sacrum, of the sacroiliac synchondrosis and of the contiguous iliac bone was observed.

revealed a solid polylobate mass of 7.3 cm × 7.9 cm × 11 cm with osteolytic involvement of the right portion of the sacrum, of the sacroiliac synchondrosis and of the contiguous iliac bone, extending to the soft tissues of the gluteus. The fetus was delivered *via* cesarean section at 35 wk of gestation without any issue reported concerning his wellbeing. After delivery, a total hysterectomy with bilateral adnexectomy and biopsies of the gluteal mass were performed.

Preoperative ultrasonography and CT scan showed a right thyroid lobe nodule with maximum axial diameter of 12 mm. No enlarged laterocervical, mediastinal, hilar and axillary lymph nodes were found whilst a 5.5 cm solid mass was detected within the liver parenchyma (4th and 8th segments).

FINAL DIAGNOSIS

The histopathological examination confirmed differentiated epithelial follicular neoplasm by morphology and immunohistochemistry (CK+, TTF1+, thyroglobulin +) compatible with FTC metastasis (stage IV). To our knowledge, there have been no previous case reports of FTC in young pregnant patients presenting with gluteal and liver metastasis with no sign of thyroid symptoms.

TREATMENT

Given these findings and the age of the patient, we opted for a total thyroidectomy and liver resection with cholecystectomy (Figure 2).

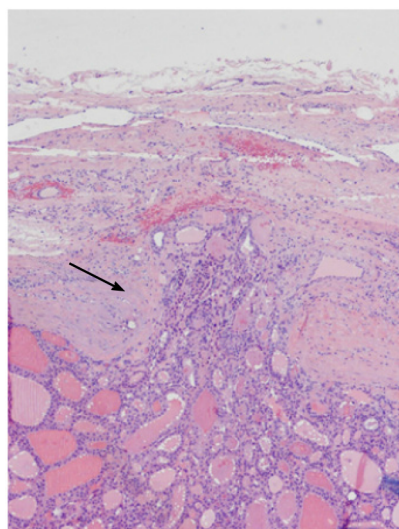
Because of the complex nature of the disease, 2 mo after the last surgery the patient underwent oral RAI. The first cycle (131-iodine, 3700 MBq dose) did not show the expected improvement. Therefore, it was decided to perform a second round of radioiodine treatment (131-iodine, 5550 MBq dose). Due to the non-resectability of the pelvic mass, 20 d after the RAI treatment, the patient underwent palliative radiotherapy with an external beam on D10 with a total dose of 2000 cGy in 5 fractions. Following radiotherapy, the right gluteal mass displayed an initial reduction with pain relief although after a few months relapsed. Therefore, it was considered to perform a vascular embolization leading to subtotal devascularization of the tumor.

OUTCOME AND FOLLOW-UP

A positron emission tomography (PET)/CT scan performed about 2 mo later showed the failure of this last procedure. Eventually, the patient died of cerebral hemorrhage 16 mo after the initial diagnosis.

DISCUSSION

Amongst all DTCs detected in women during their fertile age, about 10% are diagnosed during pregnancy or shortly after[16]. Female prevalence and increasingly age-specific incidence in women



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Figure 2 Follicular thyroid carcinoma. Fibrous capsule invasion (black arrow). The growth pattern is typically micro and/or macrofollicular. No cytonuclear atypia were present. Original magnification for the panel, $\times 40$.

during the child-bearing period suggests a possible role of sexual hormones in the development of thyroid cancer, especially in cases of DTCs (papillary thyroid carcinoma and FTC). However, there is an ongoing debate about the role of pregnancy hormones with regard to the prognosis of DTC[17,18]. The pathophysiological framework of an increased risk of developing thyroid cancer and its progression in pregnant patients is still under debate. β -hCG and estrogen stimulation, increased vascularization and the absence of immune surveillance against cancer may be involved[19]. Hormonal stimulation during pregnancy might escalate the progression of thyroid cancer, suggesting that a more aggressive approach might be required in affected women[20-22]. Thyroid gland size normally increases by 30% during the first and third trimesters of pregnancy, and thyrotropin (TSH) levels fluctuate during pregnancy as they decrease during the first trimester to return to normal range during the following months[23].

β -hCG belongs to the subfamily of glycoprotein hormones, displaying a structural accordance both with TSH and its receptors. This similarity suggests the basis for β -hCG cross-reactivity with the TSH receptor[24]. β -hCG has a stimulating effect on the thyroid gland as it can be noted in gestational trophoblastic diseases that present with high levels of β -hCG and hyperthyroidism. Furthermore, β -hCG is the strongest stimulator of thyroid growth during the first trimester of pregnancy[25]. Therefore, in susceptible thyroid follicular cells (*e.g.*, when *BRAF* and *RAS* mutations or *RET/PTC* and *PAX8-PPAR- γ* rearrangements occur), an excessive β -hCG stimulation may lead to rapid cancer progression[26].

Estrogen levels exert their effects through more complicated mechanisms. They have an indirect effect through increasing the serum thyroxine that binds globulin. A manifestation of their direct effect is estrogen receptor (ER) presentation on thyroid gland cells[27]. ER α and ER β are intracellular nuclear receptors that exist in normal and neoplastic thyroid cells. When estradiol binds to ER α it enhances cell proliferation. On the contrary, ER β inhibits these effects and leads to apoptosis[28,29]. Recent studies compared expression of ER α and ER β in normal thyroid cells and malignant thyroid cells, revealing different levels of expression of ER α and a decreased ER β activity in the latter[30,31].

The musculoskeletal system represents the most common localization for FTC metastases, which can develop in areas of high blood flow, like the red marrow of the axial skeleton, including the vertebrae (42%-52%), femur (9%-20%), skull (2%-16%) and pelvis (5%-13%)[32]. FTC usually presents itself as a single nodule, which can be either well defined or extensively infiltrating. Lymph node involvement is extremely rare[33]. Magnetic resonance imaging, CT, PET and scintigraphy could complete the diagnostic work-up to reveal metastases[34].

Surgery is the gold standard treatment for FTC. In all patients it is mandatory to balance risks against advantages of thyroid lobectomy with subsequent completion *vs* initial total thyroidectomy[33,35]. Thyroid cancer during pregnancy poses many challenges due to the need to carefully focus on both optimal timing for recommended treatments and the risks of cancer growth. The Endocrine Society recommends thyroidectomy following delivery for pregnancy-related DTC in patients showing no evidence of advanced disease or rapid progression. Meanwhile it is advisable to perform thyroidectomy during the second trimester of pregnancy in complicated cases. Lymph node dissection is not indicated in the absence of palpable lymph nodes[35-39]. Suppressive treatment with levothyroxine therapy is required after surgical treatment. Its aim is to keep TSH levels below 0.1-1 mU/L, with monthly monitoring of TSH and T4 levels.

However, if surgery is performed during pregnancy, levothyroxine therapy should promptly begin after surgery[39,40]. The post-surgical radio-ablation of the residual thyroid tissue facilitates the use of thyroglobulin detection and radioiodine scanning for long-term follow-up. Consequently, for patients at risk of recurrence and for those with known distant metastatic disease, 131I ablation may represent a valid therapeutic strategy[20]. Not all patients benefit from radioiodine therapy, and this treatment is contraindicated in pregnant and in breastfeeding women[30].

The presence of molecular pathway alterations in different DTC (*RET/PTC* rearrangements, *RET* mutations, *BRAF* mutations, *RAS* mutations and *VEGFR-2* expression) has allowed the development of new selective drugs. Tyrosine kinase inhibitors are small organic compounds inhibiting tyrosine kinase autophosphorylation and activation; most of them are multikinase inhibitors. Tyrosine kinase inhibitors act on the aforementioned molecular pathways involved in growth, angiogenesis and local and distant spread of DTC and are emerging as a new approach for aggressive thyroid cancer[41].

CONCLUSION

β-hCG and estrogen stimulation might have a role in cancer growth, especially during pregnancy. FTC management aims to stop disease progression and overcome hormonal imbalances after thyroidectomy thus reducing fetal complications. It is still under debate whether it is possible to combine optimal timing for treatment to ensure the best possible outcome with reduction of fetal complications and risk of cancer growth.

FOOTNOTES

Author contributions: Spinelli C, Sanna B and Micelli E participated in conception and design, drafting the article and acquisition of data; Sanna B and Ghionzoli M participated in acquisition of data and analysis and interpretation of data; All of the co-authors interpreted the data, participated in the completion of the article, and approved the final version of the article.

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CASE REPORT

- 40 Primary peritoneal hemangioendothelioma simulating an ovarian cyst: A case report and review of literature

Spinelli C, Ghionzoli M, Strambi S

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Primary peritoneal hemangioendothelioma simulating an ovarian cyst: A case report and review of literature

Claudio Spinelli, Marco Ghionzoli, Silvia Strambi

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Abstract

BACKGROUND

Epithelioid hemangioendothelioma (EHE) is an extremely rare tumor with a prevalence of one in a million and a very heterogeneous spectrum of disease that varies from an indolent to a metastasizing aggressive disease, with the liver, lung and bone being the primarily involved organs. Peritoneal forms of EHE are even rare, and only 12 cases have been reported to date in the literature.

CASE SUMMARY

A 66-year-old female came to our attention complaining low abdominal and perineal pain. Magnetic resonance imaging examination showed a 52 mm × 58 mm × 32 mm cystic mass with some smooth septa, simulating an ovarian cyst. Explorative laparoscopy demonstrated the presence of a peritoneal mass of augmented consistency connected with a sigmoid epiploic appendix in the right side of the Pouch of Douglas, that was surgically removed. Histological examination revealed a primitive peritoneal hemangioendothelioma. The patient easily recovered from surgery with no residual pain or discomfort. She is regularly attending a 3-years follow-up that is negative for local recurrence of disease or distant metastases.

CONCLUSION

Peritoneal form of EHE often simulates masses of other nature, as in our case. Given its unspecific clinical and radiological presentation, patients are often forced to a large series of tests and examinations before reaching a definitive diagnosis, that can only histologically made. The possibility of EHE should always be considered in case of unexplained chronic abdominal pain associated to a non-specific mass.

Key Words: Epithelioid hemangioendothelioma; Peritoneal hemangioendothelioma; Peritoneal tumor; Hemangioendothelioma; Unusual presentation; Case report

Core Tip: In this article we describe the case of a woman of middle age who came to our observation for chronic abdominal pain. Diagnostic examinations showed a mass of undefined nature which simulated an ovarian cyst due to its pelvic position and its morphological features. Histological examination revealed a primary peritoneal hemangioendothelioma, which is an extremely rare form of epithelioid hemangioendothelioma, with only 12 cases reported in the literature to date. Epithelioid hemangioendothelioma has a very heterogenous spectrum of disease that varies from an indolent to a metastasizing aggressive disease, with the liver, lung and bone being the primarily involved organs.

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INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is an extremely rare neoplasm with a prevalence of 1:1000000 [1], and as such, the current reported cases are limited to single reports and series aimed to better describe the clinical, pathologic, and molecular characteristics, as well as the best treatment approaches [2].

The spectrum of disease is very heterogenous and varies greatly between an indolent disease and a metastasizing aggressive disease, with the liver, lung and bone being the primarily involved organs [2]. However, EHE can occur in various anatomical sites such as retroperitoneum, ovary, pleura, lymph nodes and subcutaneous fat [1], making the clinical presentation very unspecific and the diagnosis often challenging. Given its heterogeneity, also the prognosis differs from one patient to another. Traditionally, risk factors for worse outcomes have comprised anemia and weight loss, as well as pulmonary symptoms such as pleurisy [3,4]. An increased mitotic activity and size have also been seen to be correlated with a worse prognosis [5]. Peritoneal forms of EHE are seldom described: To date only 12 other cases have been reported (Table 1) [6-12].

In this article we describe the case of a woman of middle age who came to our observation for abdominal pain, which was then discovered to be caused by a primary peritoneal hemangioendothelioma simulating an ovarian cyst.

CASE PRESENTATION

Chief complaints

A 66-year-old female with history of right mammalian quadrantectomy followed by radiotherapy for breast cancer came to our attention complaining low abdominal and perineal pain.

History of present illness

A recent routinely gynecological examination showed the presence at ultrasound of a small fluid collection in the Douglas pouch, with normal genital organs.

History of past illness

There is no history of past illness.

Personal and family history

There is no personal and family history.

Physical examination

The physical examination and the laboratory blood tests including tumor markers levels (CEA, Ca 19.9, Ca 125, aFP) were all normal.

Laboratory examinations

Does not involve laboratory examination.

Table 1 Cases of peritoneal epithelioid hemangioendothelioma reported in the literature

Ref.	Journal	Number of cases	Average age	Sex	Treatment
Kalisher <i>et al</i> [6], 1968	<i>Cancer</i>	1	30	F	Surgery
Shih <i>et al</i> [7], 1995	<i>J Pediatr Surg</i>	1	13	F	Surgery
Lin <i>et al</i> [8], 1996	<i>Am J Surg Pathol</i>	3	52	2 F; 1 M	Surgery
Attanoos <i>et al</i> [9], 1997	<i>Histopathology</i>	1	51	M	Surgery
Ratan <i>et al</i> [10], 1999	<i>Surg Today</i>	1	11	F	Surgery
Melzack <i>et al</i> [11], 2004	<i>Virchows Arch</i>	2	28.5	2 M	Surgery
Posligua <i>et al</i> [12], 2006	<i>Int J Surg Pathol</i>	3	45.6	2 M; 1 F	Surgery
Total		12	19.2	6 F; 6 M	

F: Female; M: Male.

Imaging examinations

Colonoscopy was completely negative while abdominal contrast-enhancement computed tomography (CT) examination confirmed the presence of a 76 mm × 52 mm fluid collection with some incomplete septa located in the right paramedian region of the Douglas pouch with mild delayed enhancement. The patient was then submitted to an abdominal magnetic resonance imaging which detected the presence of a 52 mm × 58 mm × 32 mm cystic mass with some smooth septa, simulating an ovarian cyst (Figure 1).

FINAL DIAGNOSIS

Considering the impossibility to discriminate the nature of the mass, we decided to perform a diagnostic abdominal explorative laparoscopy.

TREATMENT

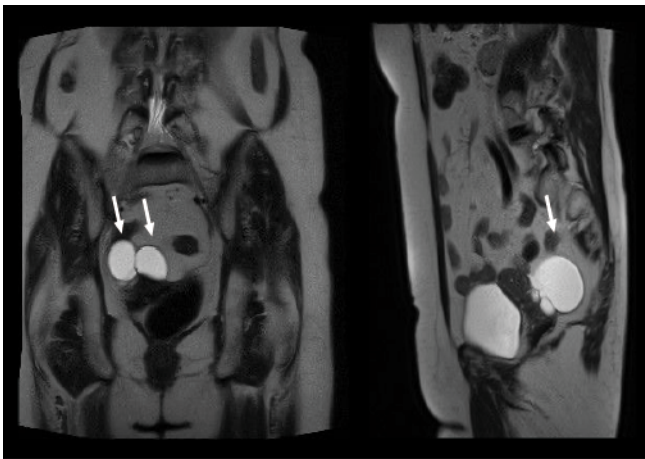
During surgery, a peritoneal mass of augmented consistency strictly connected with a sigmoid epiploic appendix was found in the right side of the Pouch of Douglas and surgically removed. Extemporaneous histological examination revealed the presence of a focal central area of necrosis and blood vessels of various dimension, intense chronic inflammation consisting of lympho-monocytoid cells, plasma-cells and histiocytes filled with hemosiderin, without atypic cells. No further surgical resection was therefore performed. Post-operative course was deemed uneventful, and the patient was discharged on 3rd post-operative day.

OUTCOME AND FOLLOW-UP

Definitive histological and immunohistochemistry examination demonstrated a primitive peritoneal hemangioendothelioma which consisted of a vascularized proliferation of blood vessels associated with involutive aspects and necrosis (Figure 2). A regular 3-years scheduled ultrasound and abdominal CT scan follow-up has shown neither local recurrence of the disease nor distant metastases. Currently, the patient is in good clinical condition without any residual pain or discomfort. Written informed consent was obtained from the patient for the anonymous publication of the case.

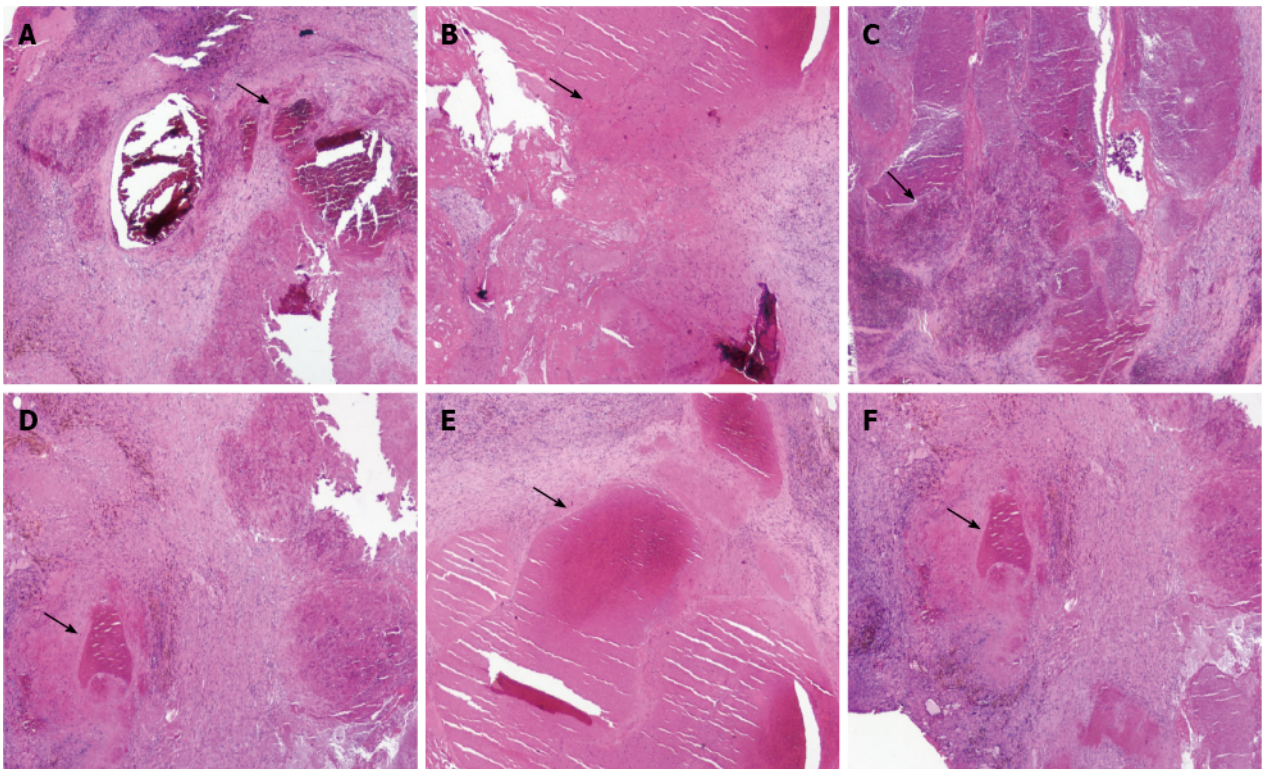
DISCUSSION

EHE is defined as a localized intrusive vascular tumor which originates from endothelial cells. It may originate from any anatomical site and can metastasize to soft tissues, bones and viscera[13]. The first description of EHE comes from Dail and Liebow in 1975: They defined it as an intravascular bronchoalveolar tumor involving the lungs[14]. The term “epithelioid hemangioendothelioma” was then coined by Weiss and Enzinger in 1982[15], to highlight a neoplasm made of “rounded or slightly spindled eosinophilic endothelial cells that grows in small nests or cords”. Nowadays, the World Health



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Figure 1 Magnetic resonance imaging scan showing the mass simulating an ovarian cyst (arrows).



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Figure 2 Histopathological analysis and immunohistochemical examination of the resected specimen. A-F: Vascular lesion composed of circumscribed proliferation of blood vessels with different size and caliber. The thin of the wall is different in the different vassells. Necrosis and degenerative aspects are associated with lympho-monocitoid and plasmacell infiltration. The presence of macrophages with hemosiderin is evident (black arrow) (magnification 2×).

Organization (WHO) and the International Society for the Study of Vascular Anomalies (ISSVA) classify EHE as a localized, intrusive and potentially metastasizing vascular tumor[16,17].

Mean age at presentation is 43 years, with the female sex having a slightly higher preponderance than the male sex (1.6 female patients to 1 male patient)[1,13]. In the pediatric population, only 24 cases have been described, with a mean age of 12 years[18]. Liver (21%), bone (14%), and lung (12%) are the most frequent sites of involvement of EHE, but this neoplasm can affect many other sites throughout the body, such as the neck region, the abdominal organs, the genitourinary tract, and also lymph nodes and breast[13].

Exact causes of EHE are still unknown. Tanas *et al*[19] identified WWTR1 (3q25) and CAMTA1 (1p36) as a couple of genes involved in the t(1;3)(p36;q25) chromosomal translocation that is seen in almost every EHE. However, Antonescu *et al*[20] depicted a different group of EHE, which is seen more

frequently in younger patients and without sex predilection, that shows a YAP1-TFE3 gene fusion. In addition, another study[21] has proposed the role of chronic Bartonella infection in the pathogenesis of EHE: in fact, the intraerythrocytic and intraendothelial infections, that this microorganism induces, could be linked to the rise of vascular tumors like EHE.

As to the peritoneal form of EHE, the main symptoms are abdominal pain and enlargement, with or without ascites, sometimes associated to nausea, vomiting and weight loss. Our patient reported an intermitting chronic abdominal pain, localized in the lower abdominal quadrants. The recurrent nature of this pain can be explained by the fact that the mass, simulating an ovarian cyst, underwent periodical episodes of bleeding, also causing fluid collects. Shiba *et al*[22], in a multicenter retrospective study on 42 Japanese patients, interestingly reported that the presence of symptoms at diagnosis, along with a tumor size greater than 3 cm, were significantly correlated with poor outcomes.

Imaging diagnostic in case of peritoneal EHE usually points out an unclear soft-tissue mass displaying reduced enhancement[23]. It can be associated with signs of invasion of the neighboring structures[13]. Comparison with previous imaging may demonstrate the slow growth rate commonly seen with EHE and less likely to be caused by any other tumor[1]. An omental mass, potentially presenting with tiny implants or wider nodules, is the most typical finding at surgery[12]. In our case, the surgical exploration showed the presence of a peritoneal mass, of augmented consistency, located in the Douglas pouch. Peritoneal carcinomatosis and malignant mesothelioma can easily simulate the aspect of EHE, and because of its rare prevalence, this can lead surgeons to not primarily consider EHE in the differential diagnosis. On the frozen section, the amount of the characteristic round cells with prominent cytoplasmic vacuoles containing erythrocytes is not always significant, but the myxohyaline feature in the stroma can be helpful; the presence of eosinophils is suggestive of EHE, as well[24,25]. Despite the widely infiltrative nature of peritoneal EHE, the single tumor cells generally show only minimal atypia, and the mitotic activity is generally low[12]. Some studies showed that histologic findings of spindle tumor cells and enhanced mitosis (above three mitotic figures per 50 HPF) are associated with worse outcome[1,5,26,27]. The mass of our patient also consisted of a central area of necrosis, vessels of various dimension, intense chronic inflammation with lympho-monocytoid cells, plasma-cells, histiocytes filled with hemosiderin; no atypic cells were found. Posligua *et al*[12] also suggest the use of electron microscopy in the diagnosis of EHE, because it allows to demonstrate the presence of Weibel-Palade bodies, that have been seen to be more specific for peritoneal EHE, compared to other visceral and soft tissues forms[28].

Immunohistochemistry is an essential part of the diagnostic algorithm, that allows to differentiate primary peritoneal EHE from morphologic pretenders, including carcinoma, mesothelioma of the epithelioid or deciduoid types, peritoneal deciduosis, epithelioid leiomyosarcoma, and malignant gastrointestinal stromal tumor with epithelioid features. In this regard, studies demonstrate that the vascular markers of factor VIII-antigen, CD31, CD34 and thrombomodulin, are very helpful to differentiate EHE from the other tumor types[12].

Because of the variable presentation, course, and outcome of EHE, there is not a standard treatment plan, and the type of therapy must be tailored for every patient[13]. For asymptomatic patients or those with comorbidities precluding treatment, an initial period of observation with repeated clinical and imaging evaluation is recommended to assess the possible progression of the disease[29]. To date, surgical resection represents the most practiced therapeutic option[30] even if few studies[29,31] have shown a reduced response of EHE tumors to the association of conventional chemotherapy and antiangiogenic therapy, which targets vascular endothelial growth factor receptors that are expressed in EHE. In this regard, molecules such as carboplatin, paclitaxel and bevacizumab have been used. Other studies have demonstrated clinical benefits obtained among patients (56%) treated with sirolimus as a single agent[32]. Immune inhibitors are being tested for the treatment of sarcomas and could potentially have a role in the future treatment plan of EHE[33,34]. Therapeutic strategies may be developed aiming to WWTR1-CAMTA1 or YAP1-TFE3 mutations, which are common in EHE[19,20].

CONCLUSION

EHE is a rare form of sarcoma that can present in any part of the body, and the peritoneal form of EHE often simulates masses of other nature, as in our case. Given its unspecific clinical and radiological presentation, patients are often forced to a large series of tests and examinations before reaching a definitive diagnosis, that can be made only histologically. The possibility of EHE should always be considered in case of slowly growing tumors that invade adjacent organs in the classic sites, as well as in case of unexplained chronic abdominal pain associated to a non-specific neoformation.

FOOTNOTES

Author contributions: Spinelli C conceived and designed the analysis; Strambi S collected the data and performed the analysis; Spinelli C, Ghionzoli M, Strambi S, contributed data or analysis tools and wrote the paper.

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