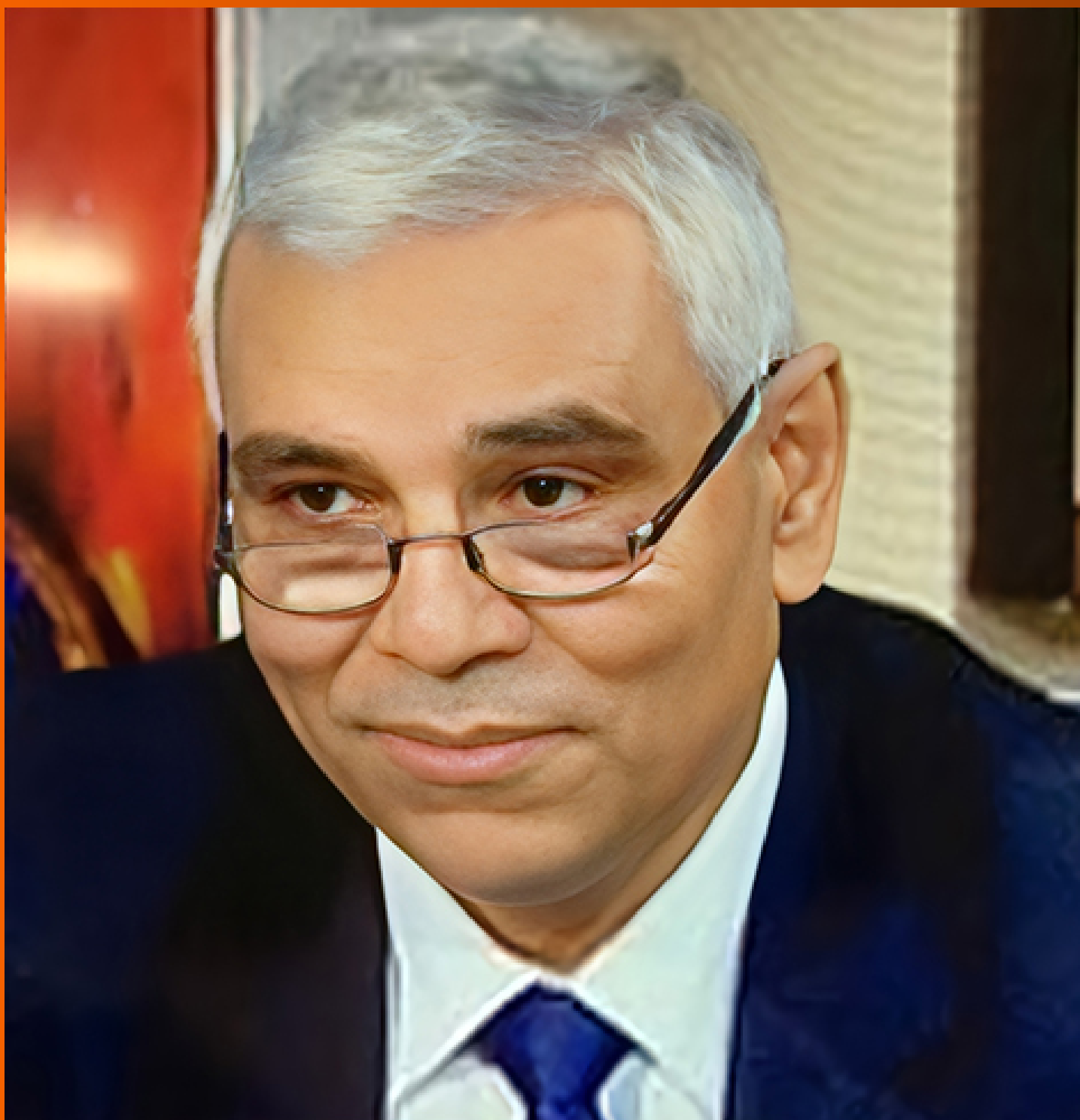


World Journal of *Obstetrics and Gynecology*

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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

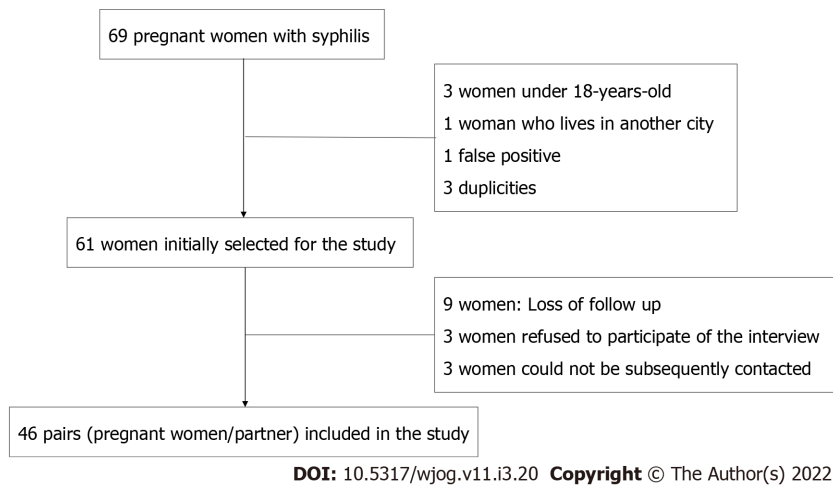


Figure 1 Forty-six pairs of pregnant women/partners were included in the study.

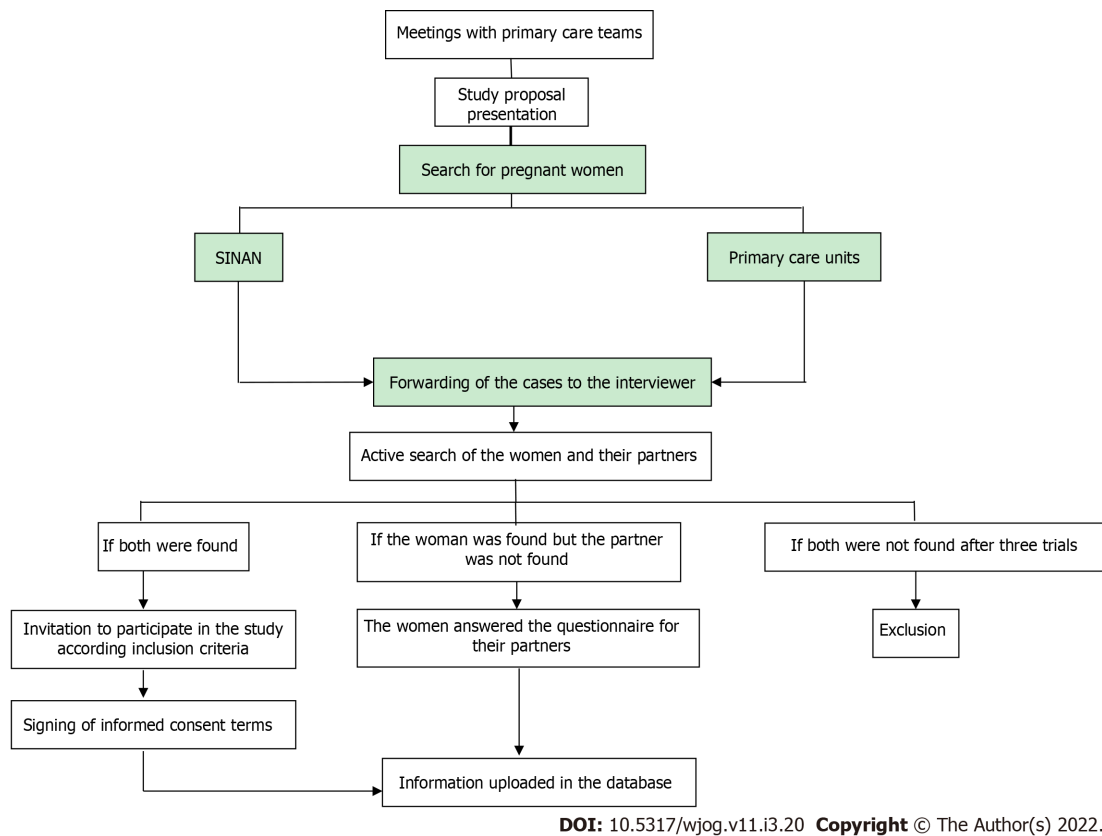


Figure 2 Steps of data collection.

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.

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REFERENCES

- 1 **Milanez H**, Amaral E. Why are we still unable to control the problem of syphilis in pregnant women and their newborns? *Rev Bras Ginecol Obstet* 2008; **30**: 325-327 [PMID: 19142511 DOI: 10.1590/s0100-72032008000700001]
- 2 **World Health Organization**. World Elimination of Congenital Syphilis: Logical Statement and strategy for action. [cited 20 January 2022]. Available from: http://apps.who.int/iris/bitstream/10665/43782/4/9789248595851_por.pdf
- 3 **Campos AL**, Araújo MA, Melo SP, Gonçalves ML. Epidemiology of gestational syphilis in Fortaleza, Ceará State, Brazil: an uncontrolled disease. *Cad Saude Publica* 2010; **26**: 1747-1755 [PMID: 20877935 DOI: 10.1590/s0102-311x2010000900008]
- 4 **Souza BSO**, Rodrigues RM, Gomes RML. Análise epidemiológica de casos notificados de sífilis. *Revista da sociedade brasileira de clínica médica* 2018; **22**: 94-98 [DOI: 10.25248/reas.e6848.2021]
- 5 **Plagens-Rotman K**, Jarzabek-Bielecka G, Merks P, Kędzia W, Czarnecka-Operacz M. Syphilis: then and now. *Postepy Dermatol Alergol* 2021; **38**: 550-554 [PMID: 34658692 DOI: 10.5114/ada.2021.108930]
- 6 **Plagens-Rotman K**, Przybylska R, Gerke K, et al Syphilis and a pregnant woman: a real danger for the woman and the child. *Postepy Dermatol Alergol* 2019; **36**: 119-124 [DOI: 10.5114/ada.2019.82833]
- 7 **Dias APSL**, Wanzeller RCM, Vital RSS, Silveira APS. A sífilis no atual cenário brasileiro : Uma análise de literatura. *Scientific Journal* 2018; **1**: 1-21 [DOI: 10.32336/2595-4970/v1n2a1]
- 8 **Brazil**. Ministry of Health. Secretaria de vigilância a saúde. *Boletim epidemiológico-Sífilis* 2017; **48**: 44
- 9 **Campos AL**, Araújo MA, Melo SP, Andrade RF, Gonçalves ML. [Syphilis in parturients: aspects related to the sex partner]. *Rev Bras Ginecol Obstet* 2012; **34**: 397-402 [PMID: 23197277 DOI: 10.1590/s0100-72032012000900002]
- 10 **Hildebrand VLPC**. Sífilis congênita: Fatores associados ao tratamento de parceiros. Dissertação apresentada com vistas a obtenção do título de Mestre modalidade profissional em saúde pública. *Rio de Janeiro* 2010; **1**: 85 [DOI: 10.1590/0102-311x00082415]
- 11 **Secretaria de Estado da Saúde Coordenadoria de Controle de Doenças**. CCD/SES-SP Centro de Referência e Treinamento DST/Aids-Programa Estadual de DST/Aids-CRT/DST/Aids-SP/CCD/SES-SP Área Técnica de Saúde da Criança-CRS/SES-SP Sociedade de Pediatria de São Paulo-SPSP Sociedade Brasileira de Infectologia-SBI. Nota Técnica Conjunta N° 001/2016/SPSP/SBI/ATSM/ATSC/CRT-PE-DST/AIDS/SES-SP-São Paulo, 2016 [DOI: 10.1590/1413-812320182411.00392019]
- 12 **Toldo MKS**, Menegazzo LS, Souto AS. A recrudescência da sífilis congênita. *Arquivo Catarinense Medicina* 2018; **47**: 2-10 [DOI: 10.1016/j.bjid.2018.10.204]
- 13 **Souza MHT**, Beck EQ. Compreendendo a sífilis congênita a partir do olhar materno. *Revista Enfermagem da UFSM* 2019; **9**: 1-13 [DOI: 10.5902/2179769232072]
- 14 **Delaunay M**, Cadranel J, Lusque A, Meyer N, Gounant V, Moro-Sibilot D, Michot JM, Raimbourg J, Girard N, Guisier F, Planchard D, Metivier AC, Tomasini P, Dansin E, Pérol M, Campana M, Gautschi O, Früh M, Fumet JD, Audigier-Valette C, Couraud S, Dalle S, Leccia MT, Jaffro M, Collot S, Prévot G, Milia J, Mazieres J. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. *Eur Respir J* 2017; **50** [PMID: 28798088 DOI: 10.1183/13993003.00050-2017]
- 15 **Holztrattner JS**, Linch GFC, Paz PAA, Gouveia HG, Coelho DF. Sífilis congênita: realização do pré-natal e tratamento da gestante e de seu parceiro. *Cogitare enfermagem*, 2019 [DOI: 10.5380/ce.v24i0.59316]
- 16 **Magalhães DM**, Kawaguchi IA, Dias A, Calderon Ide M. Maternal and congenital syphilis: a persistent challenge. *Cad*

- Saude Publica* 2013; **29**: 1109-1120 [PMID: [23778543](#)]
- 17 **Brazil.** Ministry of Health. DATASUS. [cited 20 January 2022]. Available from: <http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sih/cn>
- 18 **Araújo SR**, Farias AL, Alcântara DS, Marroni SN, Buges NM, Magalhães CCCRGN, et al Mother's experience against congenital syphilis occurrence in their children. *Electronic J Collect Heal* 2020; **42**: 1-8 [DOI: [10.25248/reas.e2760.2020](#)]
- 19 **Bassani F**, Smianotto M, Wink DR. Sífilis congênita. Anuário Pesquisa e Extensão Unoesc Videira. Santa Catarina, 2017 [DOI: [10.5433/1679-0359.2020v41n5p1739](#)]
- 20 **Godói LN**, Gomes LM, Rocha HMS. Epidemiologia da sífilis gestacional e congênita no estado de Goiás no período de 2013 a 2018. *Revista Brasileira Mil Ciências* 2019; **5**: 8 [DOI: [10.36414/rbmc.v5i13.19](#)]
- 21 **Brazil.** Ministry of Health. Secretaria de Vigilância em Saúde. Departamento de doenças de condição crônica e Infecções Sexualmente Transmissíveis. Protocolo clínico e diretrizes terapêuticas para atenção integral às pessoas com infecções sexualmente transmissíveis (IST). Brasília-DF, 2019: 248
- 22 **Silva MJN**, Barreto FR, Costa MCN, Carvalho MSI, Teixeira MG. Distribuição da sífilis congênita no estado do Tocantins, 2007-2015. *Epidemiol Serv Saude* 2020; **29**: e2018477 [DOI: [10.5123/s1679-49742020000200017](#)]
- 23 **Santos RRE**, Cunha BO, Silva CVC, Silva EB, Parente FS, Campos RALS, et al Análise da ocorrência da sífilis gestacional no estado do Pará em dez anos. Atena editor, 2020: 12 [DOI: [10.22533/at.ed.0182016044](#)]
- 24 **Morais MB**, Costa EG, Dutra, Silva JS. Análise dos casos de sífilis congênita no município de Manhuaçu/MG. *Pensar Acadêmico* 2019; **17**: 50-59 [DOI: [10.14295/jmphc.v7i1.454](#)]
- 25 **Lafetá KRG**, Martelli Júnior H, Silveira MF, Paranaíba LMR. Maternal and congenital syphilis, underreported and difficult to control Sífilis. *Rev Bras Epidemiol* 2016; **19**: 63-74 [DOI: [10.1590/1980-5497201600010006](#)]
- 26 **Figueiredo MSN**, Cavalcante EGR, Oliveira CJ, Monteiro MDFV, Quirino GDS, Oliveira DR. Perception of nurses on the adhesion of partners of pregnant women with syphilis to the treatment. *Revista da Rede Enfermagem do Nordeste* 2015; **16**: 345-354 [DOI: [10.15253/2175-6783.2015000300007](#)]
- 27 **Favero MLDC**, Ribas KAW, Costa MCD, Bonafé SM. Sífilis congênita e gestacional : notificação e assistência pré-natal. *Arch Heal Sci* 2019; **26**: 2-8 [DOI: [10.17696/2318-3691.26.1.2019.1137](#)]
- 28 **Felix ICG**, Oliveira TF, Souza CDF, Machado MF. Análise de tendência da sífilis congênita no estado da Bahia de 2008 a 2017. *Revista Ciência e Saúde*, 2020 [DOI: [10.21876/rcshci.v10i1.873](#)]
- 29 **Brazil.** Brazilian Institute of Geography and Statistics. [cited 20 January 2022]. Available from: <https://cidades.ibge.gov.br/brasil/ba/itapetinga/panorama.acesso> em 24 de julho de 2020. 2010
- 30 **Araújo EC**, Monte PCB, Haber ANCA. Evaluation of prenatal care for syphilis and HIV detection in pregnant women attended in a rural area of Pará State, Brazil. *Revista Pan-Amazônica Saúde* 2018; **9**: 33-39 [DOI: [10.5123/s2176-62232018000100005](#)]
- 31 **Saab, F.** Prevalência de sífilis em gestantes que abortaram atendidas pelo programa de proteção à gestante-PPG do estado de Sergipe, de 2005 à 2007-Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Ciências da Saúde. Brasília-DF, 2009 [DOI: [10.7322/abcs.v34i3.602](#)]
- 32 **Silva DAM**, Bois F, Duro E. Factores asociados con falla en el diagnostico y tratamiento de sífilis materna. *Medicina Infantil* [DOI: [10.1016/s0025-7753\(00\)71414-x](#)]
- 33 **Brazilian Federal Council of Nursery.** Nota Técnica-Nº 03-2017. Brasília-DF, 2017: 4 [DOI: [10.21475/ajcs.18.12.10.pne1341](#)]
- 34 **Cardoso ARP**, Araújo MAL, Cavalcante MS, Frota MA, Melo SP. Análise dos casos de sífilis gestacional e congênita nos anos de 2008 a 2010 em Fortaleza-Ceará, Brasil. *Ciência e Saúde Coletiva* 2018; **23**: 563-574 [DOI: [10.1590/1413-81232018232.01772016](#)]
- 35 **Levorato CD**, de Mello LM, da Silva AS, Nunes AA. Factors associated with the demand for health services from a gender-relational perspective. *Cien Saude Colet* 2014; **19**: 1263-1274 [PMID: [24820609](#) DOI: [10.1590/1413-81232014194.01242013](#)]
- 36 **Siepierski SF**, Rosa CCN, Nascimento BA. Incidência de sífilis em gestantes atendidas nas unidades de saúde no município de Teixeira de Freitas, Bahia. *Revista Mosaicum* 2018; **180**-196 [DOI: [10.26893/rm.v14n27.181-196](#)]
- 37 **Heringer ALDS**, Kawa H, Fonseca SC, Brignol SMS, Zarpellon LA, Reis AC. [Inequalities in congenital syphilis trends in the city of Niterói, Brazil, 2007-2016]Desigualdades en la tendencia de sífilis congénita en la ciudad de Niterói, Brasil, 2007-2016]. *Rev Panam Salud Publica* 2020; **44**: e3 [PMID: [32038724](#) DOI: [10.26633/RPSP.2020.8](#)]
- 38 **Brazil.** Ministry of Health. Secretaria de vigilância em Saúde. Departamento de Vigilância epidemiológica. Nota Informativa No 2-sei/2017-DIAHV/SVS/MS. Brasília-DF, 2017



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).

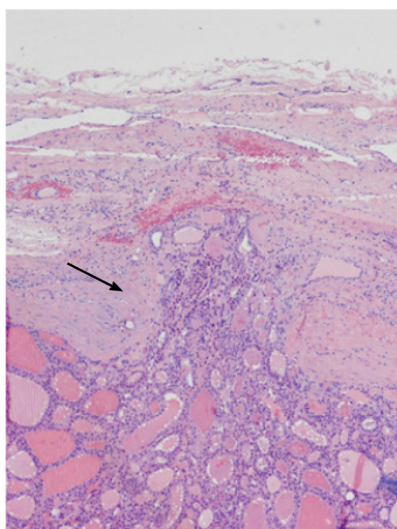
Because of the complex nature of the disease, 2 mo after the last surgery the patient underwent oral RAI. The first cycle (131-iodine, 3700 MBq dose) did not show the expected improvement. Therefore, it was decided to perform a second round of radioiodine treatment (131-iodine, 5550 MBq dose). Due to 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

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REFERENCES

- 1 Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. *Am J Obstet Gynecol* 2003; **189**: 1128-1135 [PMID: 14586366 DOI: 10.1067/s0002-9378(03)00537-4]
- 2 Budak A, Gulhan I, Aldemir OS, Ileri A, Tekin E, Ozeren M. Lack of influence of pregnancy on the prognosis of survivors of thyroid cancer. *Asian Pac J Cancer Prev* 2013; **14**: 6941-6943 [PMID: 24377629 DOI: 10.7314/apjcp.2013.14.11.6941]
- 3 Schlumberger M, Tubiana M, De Vathaire F, Hill C, Gardet P, Travagli JP, Fragu P, Lombroso J, Caillou B, Parmentier C. Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 1986; **63**: 960-967 [PMID: 3745409 DOI: 10.1210/jcem-63-4-960]
- 4 Shaha AR, Shah JP, Loree TR. Differentiated thyroid cancer presenting initially with distant metastasis. *Am J Surg* 1997;

- 174: 474-476 [PMID: [9374217](#) DOI: [10.1016/s0002-9610\(97\)00158-x](#)]
- 5 **Kim H**, Kim HI, Kim SW, Jung J, Jeon MJ, Kim WG, Kim TY, Kim HK, Kang HC, Han JM, Cho YY, Kim TH, Chung JH. Prognosis of Differentiated Thyroid Carcinoma with Initial Distant Metastasis: A Multicenter Study in Korea. *Endocrinol Metab (Seoul)* 2018; **33**: 287-295 [PMID: [29947184](#) DOI: [10.3803/EnM.2018.33.2.287](#)]
- 6 **Ozdemir N**, Senoğlu M, Acar UD, Canda MS. Skull metastasis of follicular thyroid carcinoma. *Acta Neurochir (Wien)* 2004; **146**: 1155-8; discussion 1158 [PMID: [15744853](#) DOI: [10.1007/s00701-004-0290-8](#)]
- 7 **Anil S**, Lal PM, Gill DS, Beena VT. Metastasis of thyroid carcinoma to the mandible. Case report. *Aust Dent J* 1999; **44**: 56-57 [PMID: [10217022](#) DOI: [10.1111/j.1834-7819.1999.tb00537.x](#)]
- 8 **Hefer T**, Manor R, Zvi Joachims H, Groisman GM, Peled M, Gov-Ari E, Laufer D. Metastatic follicular thyroid carcinoma to the maxilla. *J Laryngol Otol* 1998; **112**: 69-72 [PMID: [9538450](#) DOI: [10.1017/s0022215100139921](#)]
- 9 **Scarrow AM**, Colina JL, Levy EI, Welch WC. Thyroid carcinoma with isolated spinal metastasis: case history and review of the literature. *Clin Neurol Neurosurg* 1999; **101**: 245-248 [PMID: [10622453](#) DOI: [10.1016/s0303-8467\(99\)00040-2](#)]
- 10 **Daumerie C**, De Potter P, Godfraind C, Rahier J, Jamar F, Squifflet JP. Orbital metastasis as primary manifestation of thyroid carcinoma. *Thyroid* 2000; **10**: 189-192 [PMID: [10718558](#) DOI: [10.1089/thy.2000.10.189](#)]
- 11 **Mazzaferri EL**. Approach to the pregnant patient with thyroid cancer. *J Clin Endocrinol Metab* 2011; **96**: 265-272 [PMID: [21296990](#) DOI: [10.1210/jc.2010-1624](#)]
- 12 **Galofré JC**, Riesco-Eizaguirre G, Alvarez-Escolá C; Grupo de Trabajo de Cáncer de Tiroides de la Sociedad Española de Endocrinología y Nutrición. Clinical guidelines for management of thyroid nodule and cancer during pregnancy. *Endocrinol Nutr* 2014; **61**: 130-138 [PMID: [24176541](#) DOI: [10.1016/j.endonu.2013.08.003](#)]
- 13 **Khaled H**, Al Lahloubi N, Rashad N. A review on thyroid cancer during pregnancy: Multitasking is required. *J Adv Res* 2016; **7**: 565-570 [PMID: [27408758](#) DOI: [10.1016/j.jare.2016.02.007](#)]
- 14 **Gibelli B**, Zamperini P, Proh M, Giugliano G. Management and follow-up of thyroid cancer in pregnant women. *Acta Otorhinolaryngol Ital* 2011; **31**: 358-365 [PMID: [22323846](#)]
- 15 **Yu SS**, Bischoff LA. Thyroid Cancer in Pregnancy. *Semin Reprod Med* 2016; **34**: 351-355 [PMID: [27741551](#) DOI: [10.1055/s-0036-1593484](#)]
- 16 **Turner HE**, Harris AL, Melmed S, Wass JA. Angiogenesis in endocrine tumors. *Endocr Rev* 2003; **24**: 600-632 [PMID: [14570746](#) DOI: [10.1210/er.2002-0008](#)]
- 17 **Kung AW**, Chau MT, Lao TT, Tam SC, Low LC. The effect of pregnancy on thyroid nodule formation. *J Clin Endocrinol Metab* 2002; **87**: 1010-1014 [PMID: [11889153](#) DOI: [10.1210/jcem.87.3.8285](#)]
- 18 **Sahin SB**, Ogullar S, Ural UM, Ilkkilic K, Metin Y, Ayaz T. Alterations of thyroid volume and nodular size during and after pregnancy in a severe iodine-deficient area. *Clin Endocrinol (Oxf)* 2014; **81**: 762-768 [PMID: [24811142](#) DOI: [10.1111/cen.12490](#)]
- 19 **Alves GV**, Santin AP, Furlanetto TW. Prognosis of thyroid cancer related to pregnancy: a systematic review. *J Thyroid Res* 2011; **2011**: 691719 [PMID: [21811666](#) DOI: [10.4061/2011/691719](#)]
- 20 **Longo DA**, Anthony S. Fauci AS. Harrison's Principles of Internal Medicine. New York: McGraw-Hill, 2012
- 21 **Huang TC**, Cheng YK, Chen TW, Hsu YC, Liu EW, Chen HH. A 'silent' skull metastatic follicular thyroid carcinoma mimicking as a benign scalp tumor in a pregnant woman. *Endocrinol Diabetes Metab Case Rep* 2017; **2017** [PMID: [28203373](#) DOI: [10.1530/EDM-16-0100](#)]
- 22 **Yoshimura M**, Hershman JM. Thyrotropic action of human chorionic gonadotropin. *Thyroid* 1995; **5**: 425-434 [PMID: [8563483](#) DOI: [10.1089/thy.1995.5.425](#)]
- 23 ACOG Practice Bulletin No. 144: Multifetal gestations: twin, triplet, and higher-order multifetal pregnancies. *Obstet Gynecol* 2014; **123**: 1118-1132 [PMID: [24785876](#) DOI: [10.1097/01.AOG.0000446856.51061.3e](#)]
- 24 **Dean DS**, Hay ID. Prognostic indicators in differentiated thyroid carcinoma. *Cancer Control* 2000; **7**: 229-239 [PMID: [10832109](#) DOI: [10.1177/107327480000700302](#)]
- 25 **Walkington L**, Webster J, Hancock BW, Everard J, Coleman RE. Hyperthyroidism and human chorionic gonadotrophin production in gestational trophoblastic disease. *Br J Cancer* 2011; **104**: 1665-1669 [PMID: [21522146](#) DOI: [10.1038/bjc.2011.139](#)]
- 26 **Tafari M**, De Santis E, Coppola L, Perrone GA, Carnevale I, Russo A, Pucci B, Carpi A, Bizzari M, Russo MA. Bridging hypoxia, inflammation and estrogen receptors in thyroid cancer progression. *Biomed Pharmacother* 2014; **68**: 1-5 [PMID: [24286852](#) DOI: [10.1016/j.biopha.2013.10.013](#)]
- 27 **Coelho RG**, Fortunato RS, Carvalho DP. Metabolic Reprogramming in Thyroid Carcinoma. *Front Oncol* 2018; **8**: 82 [PMID: [29629339](#) DOI: [10.3389/fonc.2018.00082](#)]
- 28 **Gabriela V**, Arciuch A, Di Cristofano A. Estrogen signaling and thyrocyte proliferation. In: Ward L. Thyroid and parathyroid diseases-new insights into some old and some new issues. London: IntechOpen, 2012
- 29 **Huang Y**, Dong W, Li J, Zhang H, Shan Z, Teng W. Differential expression patterns and clinical significance of estrogen receptor- α and β in papillary thyroid carcinoma. *BMC Cancer* 2014; **14**: 383 [PMID: [24884830](#) DOI: [10.1186/1471-2407-14-383](#)]
- 30 **Gharib H**, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P; AACE/ACE/AME Task Force on Thyroid Nodules. American Association Of Clinical Endocrinologists, American College Of Endocrinology, And Associazione Medici Endocrinologi Medical Guidelines For Clinical Practice For The Diagnosis And Management Of Thyroid Nodules--2016 Update. *Endocr Pract* 2016; **22**: 622-639 [PMID: [27167915](#) DOI: [10.4158/EP161208.GL](#)]
- 31 **Zahid M**, Goldner W, Beseler CL, Rogan EG, Cavalieri EL. Unbalanced estrogen metabolism in thyroid cancer. *Int J Cancer* 2013; **133**: 2642-2649 [PMID: [23686454](#) DOI: [10.1002/ijc.28275](#)]
- 32 **Mizoshiri N**, Shirai T, Terauchi R, Tsuchida S, Mori Y, Saito M, Ueshima K, Kubo T. Metastasis of differentiated thyroid cancer in the subchondral bone of the femoral head: a case report. *BMC Musculoskelet Disord* 2015; **16**: 286 [PMID: [26452365](#) DOI: [10.1186/s12891-015-0748-2](#)]
- 33 **Spinelli C**, Rallo L, Morganti R, Mazzotti V, Inserra A, Cecchetto G, Massimino M, Collini P, Strambi S. Surgical management of follicular thyroid carcinoma in children and adolescents: A study of 30 cases. *J Pediatr Surg* 2019; **54**: 521-

- 526 [PMID: 29935896 DOI: 10.1016/j.jpedsurg.2018.05.017]
- 34 **Schlumberger MJ.** Papillary and follicular thyroid carcinoma. *N Engl J Med* 1998; **338**: 297-306 [PMID: 9445411 DOI: 10.1056/NEJM199801293380506]
 - 35 **Haugen BR,** Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016; **26**: 1-133 [PMID: 26462967 DOI: 10.1089/thy.2015.0020]
 - 36 **Moosa M,** Mazzaferri EL. Outcome of differentiated thyroid cancer diagnosed in pregnant women. *J Clin Endocrinol Metab* 1997; **82**: 2862-2866 [PMID: 9284711 DOI: 10.1210/jcem.82.9.4247]
 - 37 **Modesti C,** Aceto P, Masini L, Lombardi CP, Bellantone R, Sollazzi L. Approach to thyroid carcinoma in pregnancy. *Updates Surg* 2017; **69**: 261-265 [PMID: 28639240 DOI: 10.1007/s13304-017-0476-2]
 - 38 **Vannucchi G,** Perrino M, Rossi S, Colombo C, Vicentini L, Dazzi D, Beck-Peccoz P, Fugazzola L. Clinical and molecular features of differentiated thyroid cancer diagnosed during pregnancy. *Eur J Endocrinol* 2010; **162**: 145-151 [PMID: 19828692 DOI: 10.1530/EJE-09-0761]
 - 39 **Papini E,** Negro R, Pinchera A, Guglielmi R, Baroli A, Beck-Peccoz P, Garofalo P, Pisoni MP, Zini M, Elisei R, Chiovato L; Italian Association of Clinical Endocrinologists; Italian Thyroid Association. Thyroid nodule and differentiated thyroid cancer management in pregnancy. An Italian Association of Clinical Endocrinologists (AME) and Italian Thyroid Association (AIT) Joint Statement for Clinical Practice. *J Endocrinol Invest* 2010; **33**: 579-586 [PMID: 20634642 DOI: 10.1007/BF03346652]
 - 40 **Messuti I,** Corvisieri S, Bardesono F, Rapa I, Giorcelli J, Pellerito R, Volante M, Orlandi F. Impact of pregnancy on prognosis of differentiated thyroid cancer: clinical and molecular features. *Eur J Endocrinol* 2014; **170**: 659-666 [PMID: 24510913 DOI: 10.1530/EJE-13-0903]
 - 41 **Ferrari SM,** Fallahi P, Politti U, Materazzi G, Baldini E, Ulisse S, Miccoli P, Antonelli A. Molecular Targeted Therapies of Aggressive Thyroid Cancer. *Front Endocrinol (Lausanne)* 2015; **6**: 176 [PMID: 26635725 DOI: 10.3389/fendo.2015.00176]



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