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Editorial

Compulsory Vaccination: The Limit between Public and Private

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The first vaccine was created by the British physician Edward Jenner in 1796 to prevent smallpox, demonstrating that inoculating material from a lesion could protect against a subsequent infection, thereby beginning a new era. A century later, new vaccines were developed with a relevant impact on the occurrence of a large number of infectious diseases, many of them eradicated, and the collective effect of achieving high vaccine coverage became evident. The United States Center for Disease Control (CDC) declared that vaccines represent one of the ten most valuable purchases of the 20th century, compared to drinking water.[1]

Brazil has one of the most complete population vaccination programs and, mainly, accessible. In recent years, the refusal to receive vaccination and the consequent decline in herd or population immunity have contributed to the return of infectious diseases already under control, through numerous outbreaks with harm to public health, causing polarized debates among groups in favor and against vaccines.[2] In the meantime, in order to protect the individual and the population and justify the continuation of the current vaccination program, the Brazilian Justice has been called several times. Currently, there is jurisprudence for the compulsory vaccination of children according to the vaccination schedule of the National Vaccination Program of the Ministry of Health.[3]

Nevertheless, with the globalization of access to information over the internet, there is a mismatch between knowledge and emotional vulnerability leading to the emergence of opportunists who make use of "fake news" to reverberate old and already defined situations that seem new for many people, leading to the start of some debates again. The current scientific, political and ethical challenges faced in dealing with refusal to vaccinate have been reported in previous decades. The issue raised is the balance of compulsory and coercive vaccination. Is it reasonable to impose compulsory vaccination?

In Brazil, the smallpox vaccination was declared mandatory for children in 1837 and for adults in 1846. However, this resolution was not enforced, also because the vaccine production on an industrial scale in Rio did not start until 1884. In June 1904, Oswaldo Cruz motivated the government to send a project to the Congress in which mandatory vaccination would be established throughout the national territory. Only individuals who proved they were vaccinated would be able to have employment contracts, travel authorization, enroll at school, etc. Even with the growing number of smallpox cases in Rio de Janeiro, part of the population rejected the vaccine, considered to be liquid from the pustules of sick cows, and there was a rumor that people who were vaccinated would develop bovine features.[4]

Then, the Anti-Vaccination League was created. It united the political agitation and the vaccine refusal in an episode known as the "Vaccine Uprising", in which several conflicts occurred, with the struggle between military and insurgent forces. After a total balance of 945 people arrested, 461 deported, 110 injured and 30 killed in less than two weeks of conflict, President Rodrigues Alves was forced to give up mandatory vaccination. Later, in 1908, when the city was hit by the most violent smallpox epidemic in its history, people rushed to be vaccinated, in a contrary direction to the episode of the Vaccine Uprising.[4]

The effectiveness of the measure was demonstrated with the disease eradication, showing that high vaccination rates lead to the protection of the entire community.

In December 2019, we began to hear about a new virus that presented itself as highly infectious, the SARS-CoV-2. In the following months, every day the scientific community woke up with new data on morbidity and mortality. From astonishment to the declaration of a pandemic by the World Health Organization (WHO), all researchers and large laboratories started looking for treatments and vaccines to fight the new disease.

In our current scenario, COVID-19, caused by the infection of the new coronavirus, is spreading on all continents and so far, there is still no vaccine with proven efficacy and safety to fight it, despite the advanced stage of clinical research.

With the promise that some formulations will be available in the first half of the year 2021, some questions emerge and touch the role of mandatory vaccination to protect the community, with the social interest conflicting with the individual interest.

Is it desirable to have a community free from an infectious and deadly disease as a result of a high vaccine coverage? The

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answer is “yes”, but again, the so-called anti-vaccine groups are beginning to move to disseminate fanciful versions through social networks, anticipating the debate between mandatory vaccination and the own conviction of each individual. A new plan of action against vaccines is now seeking to manipulate a larger proportion of the population by saying that once vaccinated, we will all be at risk of serious adverse events.

A secondary and also bad effect of the current pandemic was the significant drop in Brazilian vaccine coverage due to restrictive circulation measures that brought concern to health authorities about the upsurge of diseases that were already close to eradication by vaccination.

In view of the above, the two arguments - the obligation and the conviction of being immunized by a vaccine that proves effective and safe against COVID-19 - make this debate important and necessary. The balance between the two can be an important reinforcement to achieve high coverage and consequently, the immunization of the entire community.

A law determining mandatory vaccination, never with violence, might be necessary to guarantee vaccination and a safe social life. However, convincing the population by information and education must always be part of the essential instruments for a better understanding of the positive value of vaccination and thus, maintain the confidence of most Brazilians in vaccines and in the health professionals who recommend them.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Centers for Disease Control and Prevention (CDC) Ten great public health achievements–United States, 1900-1999. MMWR Morb Mortal Wkly Rep. 1999;48(12):241–243
2 Colgrove J. Vaccine refusal revisited - the limits of public health persuasion and coercion. N Engl J Med. 2016;375(14):1316–1317. Doi: 10.1056/NEJMp1608967
3 Ministério da Saúde. Imunização: SUS disponibiliza 18 vacinas para crianças e adolescentes [Internet]. 2020 [cited 2020 Nov 12]. Available from: https://www.gov.br/saude/pt-br/assuntos/noticias/sus-disponibiliza-18-vacinas-para-criancas-e-adolescentes
4 Fundação Oswaldo Cruz (FIOCRUZ) A revolta da vacina [Internet]. 2005 [cited 2020 Nov 7]. Available from: https://portal.fiocruz.br/noticia/revolta-da-vacina-2

Risk Factors for Urinary Incontinence in Pregnancy: A Case Control Study

Fatores de risco para incontinência urinária na gravidez: Um estudo de caso controle

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Abstract

Objective Urinay incontinence (UI) is a major public health problem that can harm women in any period of life, including during the gestational period. Urinary incontinence during pregnancy has been studied because this condition can reduce the quality of life and interfere in several aspects of the maternal-fetal binomial. The aim of this study was to determine the prevalence of UI in nullipara pregnant women and to identify risk factors associated with UI in this population.

Methods This is a case-control study in which we invited nullipara women between 12 and 20 weeks of pregnancy to participate in the research. They were asked to answer a specific questionnaire, write a 3-day bladder diary, and undergo a urogynecological evaluation including pelvic organ prolapse quantification (POP-Q), empty stress supine test (ESST), and pelvic floor muscle assessment.

Results A total of 70 out of 73 patients accepted to participate in the study, and the prevalence of UI in this population was 18.3%. Tobacco use was identified as an independent risk factor for UI in pregnant women (odds ratio 8.0). All other factors analyzed were not significantly associated to UI in pregnancy.

Conclusion Urinary incontinence can be a major problem in pregnancy. We identified the use of tobacco as a risk factor for developing UI in pregnancy, which provides an extra reason to encourage patients to quit smoking.

Keywords

- urinary incontinence
- pregnancy
- pelvic floor
- tobacco use

Resumo

Objetivo A incontinência urinária (IU) é um importante problema de saúde pública que pode trazer prejuízos às mulheres em qualquer período da vida, inclusive durante o período gestacional. A IU durante a gravidez tem sido estudada por ser capaz de reduzir a qualidade de vida e interferir em vários aspectos do binômio materno-fetal. O objetivo deste estudo foi determinar a prevalência de IU em gestantes nulíparas e identificar fatores de risco associados a essa população.

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Métodos Este é um estudo de caso-controle em que foram convidadas mulheres nulíparas entre 12 e 20 semanas de gravidez para participar do projeto. Elas foram submetidas a um questionário específico, diário miccional de 3 dias e avaliação uroginecológica, incluindo quantificação de prolapso de órgãos pélvicos (POP-Q), teste de esforço com volume residual e avaliação da musculatura do assoalho pélvico.

Resultados Um total de 70 das 73 pacientes aceitaram participar do estudo, e a prevalência de incontinência urinária nessa população foi de 18,3%. O uso de tabaco foi identificado como fator de risco independente para a IU em gestantes (OR 8,0). Todos os outros fatores analisados não foram significativamente associados à perda urinária nessa população.

Conclusão A incontinência urinária pode trazer prejuízos para pacientes durante o período da gestação. O tabagismo foi identificado como fator de risco para o desenvolvimento de IU em gestantes, o que denota mais um motivo para encorajar as pacientes a abandonarem o hábito.

Palavras-chave
- incontinência urinária
- gestação
- assoalho pélvico
- tabagismo

Introduction

Pregnancy is one of the main risk factors for the development of urinary incontinence (UI) in young women. Physiological changes during pregnancy, such as increasing pressure of the growing uterus and fetal weight on the pelvic floor muscle (PFM) throughout pregnancy, together with pregnancy-related hormonal changes such as increased progesterone, decreased relaxin, and decreased collagen levels, may lead to reduced strength and supportive and sphincteric function of the PFM. Pregnancy may associate with the reduction of the PFM strength, which can lead to stress urinary incontinence (SUI).[1]

The prevalence of UI among pregnant women has been found to be from 18 to 75%; it increases with gestational age and is typically worst in the third trimester followed by second and first trimesters, respectively.[2–4]

Studies in pregnant women with SUI have found significantly decreased PFM strength in incontinent pregnant women as compared with continent pregnant women.[5]

Although UI is non-life threatening, the effect on the women's quality of life can be substantial. Women with moderate-to-severe UI may suffer from emotional disorders, social embarrassment, loss of self-esteem, and have sexual relationship difficulties, since many present loss of urine during the sexual act.[6,7]

The symptoms could worse after the gestational period and are mainly related with delivery. A systematic review and metanalysis of women with UI, with a follow-up period longer than 1 year after delivery, showed that vaginal delivery was associated with a 2-fold risk of developing UI compared with cesarean section (CS) and a 3-fold risk compared with elective CS.[8]

This study has the objective to evaluate the prevalence and the main risk factors for developing UI in nulliparas women. This period is commonly very important and expected for these patients, and the loss of urine could be distressing, reducing quality of life and interfering in several aspects of the maternal–fetal binomial.

Methods

This is a case control study performed at Hospital São Lucas from the *Pontifícia Universidade Católica do Rio Grande do Sul* (PUCRS) between January and June 2017. We prospectively invited all pregnant patients who started antenatal follow-up and included those between 12 and 20 weeks of pregnancy, focusing on factors strictly related to their current pregnancy. We excluded those patients in the first trimester of pregnancy to avoid cases of miscarriage in the current pregnancy and those in the third trimester, because this is when the women have greater weight gain and physiological changes, which are confounders to urinary symptoms. Only single pregnancies were included. The exclusion criteria were previous delivery, neurological disease, previous surgery for pelvic floor dysfunction, UI prior to the current pregnancy, chronic diabetes, and previous pelvic radiotherapy. Institutional Review Board approval was obtained prior to the beginning of the study.

All subjects completed a specific questionnaire (International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form [ICIQ-UI SF]) and underwent physical exam including urogynecological evaluation (Pelvic organ prolapse - quantification, empty stress supine test, and PFM assessment).

The patients who were diagnosed with UI (ICIQ-UI SF score ≥ 3) were referred to physiotherapy treatment.

All data were anonymous and analyzed using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Univariate logistic regression analysis was performed with respect to UI and possible predictive factors. Descriptive analysis was performed using frequencies, means, and standard deviations. The Kolmogorov-Smirnov test was used to evaluate if the data had a normal distribution. For comparison between groups, we used the following tests: Chi-squared or Fisher

Table 1 Frequencies of demographic and clinical characteristics in our study group

Variable	Total ($n = 70$) %
White race	74.3
Diabetes	4.3
Arterial hypertension	10.1
Smoking	10.0
Previous abortion	18.6
Previous surgery to gestation	15.7

exact test for categorical variables, and Student *t*-test for independent samples to verify difference between averages. Associations were considered statistically significant if *p*-value < 0.05.

Smoking was the only risk factor with statistical significance for UI in pregnancy, 57.1% of UI in smokers versus 14.3% in non-smokers OR 8.0. (►**Table 3**). Among the incontinent patients, 76.9% complained of SUI, and 53.8% complained of urgency. When we calculated the patients' body mass index (BMI), we found a higher mean BMI in incontinent patients (33.3 kg/m^2 incontinent vs 29.5 kg/m^2 in the continents), but the difference was not statistically significant in the sample. We invited 73 women to participate in the study according to our inclusion and exclusion criteria, 3 patients did not accept/ did not have time (estimated in 60 minutes plus the time required to write a bladder diary) available to complete the protocol. Our sample was 70 pregnant women between 12 and 20 weeks of pregnancy. The prevalence of incontinence in our study was 18.3%. In our group of 70 patients, 74.3% were white, 4.3% had diabetes, 10.1% had high blood pressure, and 10% were tobacco users. Regarding previous procedures, 18.6% of the patients revealed previous miscarriage, and 15.7% underwent previous surgery (exception for exclusion criteria) before pregnancy (►**Table 1**). During evaluation of the PFM strength, all patients recognized the PFM, 43.3% presented weak Kegel, 47.3% presented normal Kegel, and 9% strong Kegel. There was no difference in the PFM strength between continent and incontinent pregnant women. There was no difference in mean age and year of study between groups (25.9 years in incontinent group × 24.9 years in control). Regarding the number of years of study, the average in the incontinent group was 10.3 years, and 10.7 years in the continent group (►**Table 2**). The frequency of micturition per day in the incontinent group was 9.8 times, whereas among the continent group it was 8.4 times. Meanwhile, mean nocturia was 2.8 in the incontinent group and 2.1 in the control group. The length of the genital hiatus had a mean of 2.4 cm in both groups. The mean perineal length in the incontinent group was 3.8 cm, and 3.4 cm in the control group. In the incontinent group, the mean total vaginal length was 9.7 cm, while in the continent women it was 10.6 cm. There was no difference between bladder diary parameters and POP-Q measures between continent and incontinent pregnant women (►**Table 2**). Smoking was the only risk factor with statistical significance for UI in pregnancy, with 57.1% of UI in smokers versus 14.3% in non-smokers (odds ratio [OR] 8.0.) (►**Table 3**).

Table 2 Urinary incontinence in numeric variables according to univariate analysis (n = 70)

Variable	Urinary incontinence		*p**
	yes	No	
	(n = 13)	(n = 57)	
	x ± sd	x ± sd	
Age	25.9 ± 5.5	24.9 ± 6.6	0.624
Time with partner (in months)	56.3 ± 34.4	43.5 ± 37.9	0.271
Years of study	10.3 ± 3.1	10.7 ± 2.0	0.622
Number of previous pregnancies	1.2 ± 0.4	1.2 ± 0.5	0.986
Number of previous abortions	0.5 ± 0.8	1.1 ± 0.4	0.075
Daytime urinary frequency	9.8 ± 5.4	8.4 ± 3.4	0.377
Nocturia	2.8 ± 2.1	2.1 ± 1.9	0.233
Genital hiatus (cm)	2.4 ± 0.5	2.4 ± 0.6	0.906
Perineal body (cm)	3.8 ± 0.6	3.4 ± 0.8	0.212
Total vaginal length (cm)	9.7 1.7	10.6 ± 1.5	0.111
BMI (Kg/m2)	33.3 ± 8.8	29.5 ± 8.4	0.222

Abbreviations: BMI, body mass index; cm, centimeters; n, number; SD, standard deviation.
**P*-value calculated by Student *t*-test for independent samples.
x ± SD - mean ± standard deviation.

Table 3 Risk of urinary incontinence during pregnancy in all patients according to univariate analysis in categorical variables ($n = 70$)

Variable	Urinary incontinence %	OR	CI 95%	*p*-value
Tobacco Use	18.3**			
Yes	57.1	8.0	(1.52–41.86)	0.019***
No	14.3			
Diabetes	18.3			
Yes	33.3	2.2	(0.18–26.88)	0.512***
No	18.2			
HAS	18.3			
Yes	14.3	0.6	(0.07–6.32)	0.745***
No	19.4			
Abortion	18.3			
Yes	23.1	1.4	(0.32–6.06)	0.643*
No	17.5			
Previous surgery	18.3			
Yes	9.1	0.4	(0.04–3.36)	0.378*
No	20.3			

Abbreviations: CI, confidence interval; OR, odds ratio.
**PPP*-value calculated by the Chi-squared test of Pearson.
**Global risk of urinary incontinence (70 patients).
****P*-value calculated by Fisher exact test.

Results

We invited 73 women to participate in the period of study according to our inclusion and exclusion criteria, 3 patients do not accept - do not have time (estimated in 60 minutes more bladder diary) available to complete the protocol. Our sample was 70 pregnant women between 12 and 20 weeks of pregnancy. The prevalence of incontinence in our study was 18.3% (13 patients). In our group of 70 patients, 74.3% were white, 4.3% had gestational diabetes, 10.1% high blood pressure and 10% were tobacco users. In respect of previous procedures, 18.6% of the patients revealed previous miscarriage and 15.7% underwent any surgery (exception for exclusion criteria) before pregnancy (►**Table 1**).

During evaluation of pelvic floor muscle strength, all patients recognize pelvic floor muscle, 43.3% presented Kegel weak, 47.3% Kegel normal and 9% Kegel strong. There was no difference between pelvic floor muscle strength between continent and incontinent pregnant women. There was no difference in mean age and year of study among groups (25.9 years in incontinent group × 24.9 years in control). In years of study, the average in incontinent group was 10.3 years and 10.7 years in continent group (►**Table 2**).

The frequency of micturition per day among incontinent group was 9.8 times whereas among continent was 8.4 times. Meanwhile, mean nocturia was 2.8 for incontinent and 2.1 for control. The length of the genital hiatus had a mean of 2.4 cm in both groups. The mean perineal length between incontinent group was 3.8 cm and between control 3.4. Among the incontinent group, the mean total vaginal length was 9.7 cm, while among non-incontinent women it was 10.6 cm. There was no difference between bladder diary parameters and POP-Q measures between continent and incontinent pregnant women (►**Table 2**). Smoking was the only risk factor with statistical significance for UI in pregnancy, 57.1% of UI in smokers versus 14.3% in non-smokers OR 8.0 (►**Table 3**). Among the incontinent patients, 76.9% complained of SUI and 53.8% of urgency when we calculated the patients' body mass index (BMI), we found a higher mean BMI in incontinent patients (33.3 kg/m^2 incontinent vs 29.5 - kg/m^2 in the continents), but the difference was not statistically significant in the sample.

Smoking was the only risk factor with statistical significance for UI in pregnancy, 57.1% of UI in smokers versus 14.3% in non-smokers OR 8.0. (►**Table 3**).Among the incontinent patients, 76.9% complained of SUI and 53.8% of urgency When we calculated the patients' body mass index (BMI), we found a higher mean BMI in incontinent patients (33.3 kg/m^2 incontinent vs 29.5 kg/m^2 in the continents), but the difference was not statistically significant in the sample.

Discussion

The prevalence of UI depends on the population, habits, economic issues, and, in some studies, it could reach 75% of pregnant women.[2] The majority of studies are focused on Europe and North America, and only a few studies have shown the numbers in South America. In our sample, we identified an 18.3% of UI in nulliparous women. The inclusion of patients in the second trimester aimed to correlate other possible risk factors than those related to increased intra-abdominal pressure observed in the third trimester of pregnancy

The parity is an important factor for the development of UI, mainly for SUI. In a recent meta-analysis, Zhou et al.[9] found that the risk of UI is increased in women with two or more deliveries in comparison with nulliparous woman.

The occurrence of UI changes during different periods of pregnancy. In a questionnaire-based pilot study, Beksac et al.[10] demonstrated that the prevalence of any UI in nulliparous pregnant women was 4.9%, 9.8%, and 26.2% at 11–14, ~ 24, and ~ 37 gestational weeks, respectively. Stress urinary incontinence (3.3%, 6.6%, and 16.4% at 11–14, ~ 24 and ~ 37 gestational weeks, respectively) was found to be the main type of UI, as reported previously.[11,12] Regarding age at pregnancy, we have some discussions in the literature. Zhu et al.[13] reported SUI during pregnancy being associated with advanced maternal age. The risk of SUI incidence was increased with maternal age (OR = 1.041; 95% CI 1.027–1.055). This finding was supported by Hvidman et al.[14] who found out that pregnant women aged 30 years and older to be at significantly greater risk for SUI than younger women.

Contrary to the idea that younger women could have an additional protection in PFMs and ligaments, some works have shown that a pelvic floor injury sustained in young females may be more significant, and young age may not be protective. In a study that used ultrasound to investigate the extent of levator ani damage in low-risk primiparous women based on age found an inverse relationship between age and severity of levator ani damage.[15]

In our study, the only factor we could associate with risk to develop SUI was smoking. We found 53.1% of UI in the tobacco group versus 14.7% of UI in pregnant who did not smoke (OR 8.0, CI [1.52–41.86], $p = 0.019$), with statistical significance.

The carbon monoxide in cigarettes impairs oxygen transported to bodily tissues and results in muscle atrophy. The PFM is also affected. Smoking can cause coughing, chronic, and frequent coughing, thus increasing bladder pressure and exerting significant pressure on the PFM, which may lead to damaging the innervation to the PFM and aggravated SUI. Not only carbon monoxide but also nicotine has a stimulating effect on the detrusor muscle.[16]

The anatomy of the pelvic floor and physiology of the lower urinary tract play an important role in the background of the knowledge of the continence mechanism. Additionally, when we measured the genital hiatus, the perineal body and the total vaginal length, we did not see any difference between the groups.

Women with diabetes mellitus (DM) were at greater risk of incontinence than women without DM. In addition, the risk and severity of incontinence increased with the duration of the disease, with greater risk for developing symptoms in women with DM for 5 or more years.[17] In comparison with type 2 diabetes, gestational diabetes mellitus (GDM) was not correlated as a risk factor to develop UI. Some studies have

shown a small increase of risk in women with GDM, but the mechanism to this development remains unclear.[18] Most likely, this association is correlated with increased body mass index (BMI), obesity, and macrosomia of infants.

Obesity is a major risk factor for SUI in women. Obesity chronically strains and creates tension on the pelvic floor due to increased intra-abdominal pressure and may impair blood flow and nerve innervation to the bladder and urethra. Furthermore, obesity may increase pressure on the bladder, thereby affecting the neuromuscular function of the genital tract and contributing to pelvic floor and urethral dysfunction.[19–21]

In another study, Hvidman et al.[14] demonstrated that pregnant women with prepregnancy BMI of more than 30 - kg/m2 were associated with a high rate of SUI. Liang et al.[3] have shown women with a prepregnancy BMI of more than 30 kg/m2 to be at increased risk for developing SUI during pregnancy.

When analyzing the data in our study, the difference between the BMI of the groups was not shown to be statistically significant, but there was a trend toward significance, with a higher mean BMI in the patients presenting with incontinence. Obesity is a worldwide epidemic sickness. It is a risk factor for incontinence in patients of any age group, and this trend seems to be maintained during pregnancy and may even worsen due to the increase in intra-abdominal pressure caused by the gravid uterus.

In our study, the prevalence of UI was 18.3%, but, in contrast with most papers, we analyzed just nulliparous women in the second trimester of pregnancy.[22–24]

Urinary incontinence has a high prevalence in the general world population, especially in women.[25] Although the causes of UI are not fully understood, in most cases they are composed by habits and modifiable variables, like smoking and obesity. It is unfair for them to continue to suffer when evidence has clearly shown that pelvic floor exercises (PFEs) performed antenatally can reduce the risk of developing UI and also improve the symptoms of UI by strengthening the PFMs.[6,7]

Conclusion

Our sample was not sufficient for subgroup analysis, which is a limitation of our study, but the strength of the present study is that we selected only nulliparas in the early second trimester of pregnancy reducing the bias related to previous deliveries, current miscarriage, and confounding factors in the late pregnancy as weight gain an physiological changes related to urinary symptoms. In the evaluation of the possible risk factors associated with the onset of UI in nulliparous women, smoking was reported more frequently among those patients with UI complaints than in those without UI complaints. Obesity, although not representing statistical significance in this study, showed a trend toward significance. Other variables, such as hypertension, GDM, and previous surgical procedures did not correlate with the development of UI in our sample. Urinary incontinence is an important health issue in the gestational period and needs to be considered during the prenatal care.

Contributors
All of the authors participated in the concept and design of the present study; analysis and interpretation of data; drafting or revision of the manuscript, and they have approved the manuscript as submitted. All authors are responsible for the reported research.

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Conflict of interests
The authors have no conflict of interests to declare.

References

1 Sangsawang B. Risk factors for the development of stress urinary incontinence during pregnancy in primigravidae: a review of the literature. Eur J Obstet Gynecol Reprod Biol. 2014;178:27–34. Doi: 10.1016/j.ejogrb.2014.04.010
2 Sangsawang B, Sangsawang N. Stress urinary incontinence in pregnant women: a review of prevalence, pathophysiology, and treatment. Int Urogynecol J Pelvic Floor Dysfunct. 2013;24(06): 901–912. Doi: 10.1007/s00192-013-2061-7
3 Liang CC, Chang SD, Lin SJ, Lin YJ. Lower urinary tract symptoms in primiparous women before and during pregnancy. Arch Gynecol Obstet. 2012;285(05):1205–1210. Doi: 10.1007/s00404-011-2124-2
4 Fritel X, Fauconnier A, Bader G, Cosson M, Debodinance P, Deffieux X, et al; French College of Gynaecologists and Obstetricians. Diagnosis and management of adult female stress urinary incontinence: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians. Eur J Obstet Gynecol Reprod Biol. 2010;151(01):14–19. Doi: 10.1016/j.ejogrb.2010.02.041
5 Mørkved S, Salvesen KA, Bø K, Eik-Nes S. Pelvic floor muscle strength and thickness in continent and incontinent nulliparous pregnant women. Int Urogynecol J Pelvic Floor Dysfunct. 2004;15 (06):384–389, discussion 390. Doi: 10.1007/s00192-004-1194-0
6 Stafne SN, Salvesen KA, Romundstad PR, Torjusen IH, Mørkved S. Does regular exercise including pelvic floor muscle training prevent urinary and anal incontinence during pregnancy? A randomised controlled trial. BJOG. 2012;119(10):1270–1280. Doi: 10.1111/j.1471-0528.2012.03426.x
7 Pelaez M, Gonzalez-Cerron S, Montejo R, Barakat R. Pelvic floor muscle training included in a pregnancy exercise program is effective in primary prevention of urinary incontinence: a randomized controlled trial. Neurourol Urodyn. 2014;33(01):67–71. Doi: 10.1002/nau.22381
8 Tähtinen RM, Cartwright R, Tsui JF, Aaltonen RL, Aoki Y, Cárdenas JL, et al. Long-term impact of mode of delivery on stress urinary incontinence and urgency urinary incontinence: a systematic review and meta-analysis. Eur Urol. 2016;70(01):148–158. Doi: 10.1016/j.eururo.2016.01.037
9 Zhou HH, Shu B, Liu TZ, Wang XH, Yang ZH, Guo YL. Association between parity and the risk for urinary incontinence in women: A meta-analysis of case-control and cohort studies. Medicine (Baltimore). 2018;97(28):e11443. Doi: 10.1097/MD.0000000000011443

10 Beksac AT, Aydin E, Orhan C, Karaagaoglu E, Akbayrak T. Gestational urinary incontinence in nulliparous pregnancy - a pilot study. J Clin Diagn Res. 2017;11(08):QC01–QC03. Doi: 10.7860/JCDR/2017/25572.10333
11 Mason L, Glenn S, Walton I, Appleton C. The prevalence of stress incontinence during pregnancy and following delivery. Midwifery. 1999;15(02):120–128. Doi: 10.1016/s0266-6138(99)90008-6
12 Sharma JB, Aggarwal S, Singhal S, Kumar S, Roy KK. Prevalence of urinary incontinence and other urological problems during pregnancy: a questionnaire based study. Arch Gynecol Obstet. 2009;279(06):845–851. Doi: 10.1007/s00404-008-0831-0
13 Zhu L, Li L, Lang JH, Xu T. Prevalence and risk factors for peri- and postpartum urinary incontinence in primiparous women in China: a prospective longitudinal study. Int Urogynecol J Pelvic Floor Dysfunct. 2012;23(05):563–572. Doi: 10.1007/s00192-011-1640-8
14 Hvidman L, Hvidman L, Foldspang A, Mommsen S, Bugge Nielsen J. Correlates of urinary incontinence in pregnancy. Int Urogynecol J Pelvic Floor Dysfunct. 2002;13(05):278–283. Doi: 10.1007/s001920200061
15 Quiroz L, Rostaminia G, Pickett SD, Peck J, Stone DE, Shobeiri S. The association between risk of levator ani damage and age in primiparous women. Female Pelvic Med Reconstr Surg. 2016;22(05):S13
16 Hannestad YS, Rortveit G, Daltveit AK, Hunskaar S. Are smoking and other lifestyle factors associated with female urinary incontinence? The Norwegian EPINCONT Study. BJOG. 2003;110(03):247–254. Doi: 10.1046/j.1471-0528.2003.02327.x
17 Lifford KL, Curhan GC, Hu FB, Barbieri RL, Grodstein F. Type 2 diabetes mellitus and risk of developing urinary incontinence. J Am Geriatr Soc. 2005;53(11):1851–1857. Doi: 10.1111/j.1532-5415.2005.53565.x
18 Saydah SH, Chandra A, Eberhardt MS. Pregnancy experience among women with and without gestational diabetes in the U.S., 1995 National Survey Of Family Growth. Diabetes Care. 2005;28(05):1035–1040. Doi: 10.2337/diacare.28.5.1035
19 Jain P, Parsons M. The effects of obesity on the pelvic floor. Obstet Gynaecol. 2011;13(03):133–142. Doi: 10.1576/toag.13.3.133.27664
20 Bump RC, Sugerman HJ, Fantl JA, McClish DK. Obesity and lower urinary tract function in women: effect of surgically induced weight loss. Am J Obstet Gynecol. 1992;167(02):392–397, discussion 397–399. Doi: 10.1016/s0002-9378(11)91418-5
21 Eltatawy HH, Elhawary TM, Soliman MG, Taha MR. The link between female obesity and urinary stress incontinence. UroToday Int J.. 2011;4(05):63. Doi: 10.3834/uij.1944-5784.2011.10.05
22 Ozerdoğan N, Beji NK, Yalçin O. Urinary incontinence: its prevalence, risk factors and effects on the quality of life of women living in a region of Turkey. Gynecol Obstet Invest. 2004;58(03):145–150. Doi: 10.1159/000079422
23 Tingthong W, Buppasiri P, Chongsomchai C, Temtanakitpaisan T, Sangkomkamhang U. Prevalence of urinary incontinence in pregnant women at 37 Tertiary Care Hospitals in KhonKaen Province. Thai J Obstet Gynaecol.. 2014;22(01):37–43
24 Hansen BB, Svare J, Viktrup L, Jørgensen T, Lose G. Urinary incontinence during pregnancy and 1 year after delivery in primiparous women compared with a control group of nulliparous women. Neurourol Urodyn. 2012;31(04):475–480. Doi: 10.1002/nau.21221
25 Botlero R, Urquhart DM, Davis SR, Bell RJ. Prevalence and incidence of urinary incontinence in women: review of the literature and investigation of methodological issues. Int J Urol. 2008;15(03):230–234. Doi: 10.1111/j.1442-2042.2007.01976.x

Advantages and Disadvantages of Medical Abortion, According to Brazilian Residents in Obstetrics and Gynaecology

Vantagens e desvantagens do aborto medicamentoso, segundo os residentes brasileiros em ginecologia e obstetrícia

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Abstract

Objective To find out which was the opinion of residents in obstetrics and gynecology about the advantages and disadvantages of medical abortion as compared with surgical procedures.

Method Cross-sectional multicenter study among residents in obstetrics and gynecology from 21 maternity hospitals located in 4 different geographical regions of Brazil, using a self-responded questionnaire with 31 questions related to their opinion and experience on providing abortion services.

Results Most residents agreed that "being less invasive" (94.7%), "does not require anesthesia" (89.7%), "can be accompanied during the process" (89.1%), "prevents physical trauma" (84.4%) were the main advantages of medical abortion.

Conclusion Residents perceived both clinical and personal issues as advantages of medical abortion.

Keywords
- abortion
- legal abortion
- hospital medical staff
- brazil

Resumo

Objetivo Descobrir qual foi a opinião dos residentes em ginecologia e obstetrícia sobre as vantagens e desvantagens do aborto medicamentoso em relação aos procedimentos cirúrgicos.

Métodos Estudo multicêntrico transversal entre residentes de ginecologia e obstetrícia de 21 maternidades localizadas em 4 diferentes regiões geográficas do Brasil, utilizando um questionário autorrespondido com 31 questões relacionadas à sua opinião e experiência na prestação de serviços de aborto.

Resultados A maioria dos residentes concordou que "ser menos invasivo" (94,7%), "não necessitar de anestesia" (89,7%), "poder ser acompanhado durante o processo" (89,1%), "prevenir trauma físico" (84,4%) foram as principais vantagens do aborto medicamentoso.

Conclusão Os residentes perceberam tanto questões clínicas como pessoais como sendo vantagens do aborto medicamentoso.

Palavras-chave
- aborto
- aborto legal
- corpo clínico hospitalar
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Introduction

Brazil has one of the most punitive abortion laws, similar as most of the countries in the Latin American region.[1] In spite of such legal restriction, it has one of the highest estimated incidence of abortions in the world[2,3] with ~ 500,000 illegal abortions per year among women aged between 18 and 39 years old.[4] It is estimated that > 200 women die every year in Brazil as a consequence of unsafe abortions.[5,6]

That situation has changed more recently, however, without any intervention of health authorities. Abortion related maternal mortality has been reduced in Brazil as in another Latin American countries, simply by the increasing utilization of misoprostol for pregnancy termination, by women themselves, instead of the more dangerous methods used earlier.[7,8]

In parallel to those changes in the practice of illegal abortions, an effort to improve access to legal abortion was being carried out. Although the Brazilian penal code permits abortion to protect women's lives and in case the pregnancy is the result of rape, the practice of legal abortion in public hospitals was almost inexistent until very recently. It was almost 25 years ago that an initiative to facilitate access to abortion after rape was taken, calling to what was called Interprofessional Forum Sexual Violence and Abortion emitted by law, with participation of leading obstetricians and gynecologists from all over the country, as well as Ministry of Health authorities.[9]

That initiative succeeded in stimulating the Ministry of Health to produce the norms for the care of women and adolescents who suffer sexual violence, including pregnancy termination when required. The first version was released in 1998, but it has been updated periodically, at least until 2010.[10] The Interprofessional Forum on Sexual Violence and Abortion permitted by the law was repeated for several years, stimulating the increase in the number of teaching hospitals that provide legal abortion services around the country.[11]

In spite of the norms and holding of repeated forums, the knowledge about the abortion laws and the requirements to provide safe, legal abortion services still remain poor.[12] It appears that the subject of abortion does not receive the same attention as other subjects, providing more technological information, which can serve for the improvements of the immediate care being provided to the patients, and consequently, the details of the law and on how to apply it remain practically ignored by a majority of Brazilian gynecologists.

In order to change that situation, it is fundamental to improve the training of the future specialists who are currently in their residency years. A key element that should be part of their training is about the procedures currently recommended for legal termination of pregnancy.

By now, there is general agreement that the emergence of drugs capable of inducing termination of pregnancy without any surgical intervention has led to improved access to safe legal abortion[13] or even to a less unsafe abortion when used by the women themselves.[14–16]

The recommended medical method for pregnancy termination is the combination of an antiprogesterone originally called RU 486 and currently known as mifepristone, with a prostaglandin administered 24 to 48 hours later.[17,18]

Recent very large studies strongly suggest that both surgical and medical methods are almost equally effective and safe.[19] The only important disadvantage of medical abortion is that it is not possible to administer a long acting contraceptive, such as an intrauterine device (IUD), immediately after the uterine evacuation,[20] as it occurs at home and the exact moment is unpredictable.

While misoprostol is available practically everywhere, in many countries mifepristone is not yet registered and not available, as it is the case of Brazil. Thus, the only form of medical abortion available in Brazil is misoprostol, which is registered only to be used by the vaginal route, and as such is recommended by the Ministry of Health itself for legal termination of pregnancy after rape.[21]

Accordingly, it is supposed that Brazilian departments of obstetrics and gynecology in medical schools should be using misoprostol with that purpose in their teaching hospitals and should be teaching the subject in undergraduate and postgraduate training, more so to their residents in obstetrics and gynecology.

It was surprising, however, that in the same study on which the present article is based, we found that 20% said that they had not received any information on the use of misoprostol during residency, and almost 30% of those who received information judged that the information received on misoprostol was not sufficient for their needs.[22]

This omission in the training of residents is an evident weakness in the teaching of the medical schools, but also suggest a lack of demand from the part of the residents.

In order to understand the reason for such lack of demand, we decided to evaluate which was the knowledge the residents had about the advantages and disadvantages of medical abortion with misoprostol, as compared with the use of surgical procedures.

Methods

This was a cross-sectional multicenter study in which residents from 21 maternity hospitals with residency programs in obstetrics and gynecology, located in 4 different geographical regions of Brazil, responded a questionnaire with 31 questions related to their opinion and experience on providing abortion services.

The hospitals selected are part of the Brazilian Network for Studies in Reproductive and Perinatal Health. All these hospitals are obliged to provide safe abortion services to women who meet the conditions determined under the current legislation, and the residents are expected to participate in providing these services. Residents are able to participate in the care of women requesting legal abortion, including their admission, physical examination, etc., but they may not necessarily take part in performing the abortion. The involvement of the residents in providing safe

abortion services was not necessarily the same in the different hospitals participating in the present study. A local supervisor was appointed at each of the participating hospitals. Each resident received a 31-item questionnaire to complete, although they were free to respond or not the full questionnaire or selected questions without being identified, as the completed (or not) questionnaire should be deposited in sealed boxes, which were opened only at the site and time of the analysis and there was no way to identify from which institution the box came or who had filled in each questionnaire.[22]

The purpose of this procedure was to ensure the privacy of the participants by reassuring them that the supervisor would not know whether they had decided to participate or not in the study. The data collection process continued until all the residents had had the opportunity to participate in the study.

The questionnaire included items regarding sociodemographic characteristics of the participants, their knowledge regarding medical abortion, their personal and professional experiences related to abortion, their opinion on the advantages and disadvantages of medical abortion in comparison with surgical abortion, among several other items which are not part of this analysis. In the data analysis, the association between the personal experience of the residents in providing legal abortion services and their opinion related to advantages or disadvantages of medical abortion was evaluated using the chi-squared test.

To do so, the residents were divided into two groups according to their experience of being involved in the care of women requesting legal termination of pregnancy: those who had such experience and those who did not have been involved in providing legal abortion services. We performed the entire analysis using the R software package (R Foundation, Vienna, Austria).[23]

The Institutional Review Board of the School of Medical Sciences of the Universidade Estadual de Campinas (UNICAMP, in the Portuguese acronym) approved the study protocol (CAAE: 21177013.3.0000.5404), as did the institutional review boards of each of the participating hospitals. The need for signed informed consent was waived considering the nature of the study and to ensure complete confidentiality.

Results

Characteristics of the Sample

At the time of the interview, there were 530 residents in obstetrics and gynecology in the 21 institutions included in the study, but only 83% were invited to participate in the survey and 77% returned the questionnaires (404 completed and 3 blanks). Seventy-one percent of the residents had been involved in providing legal abortion care to women. Most of them (327 or 81.1%) were female and 18.9% (76) were male. The majority did not have a stable partner at the moment of the interview (282; 70%), was < 27 years old (227; 56.3%) and referred that religion was very important (121; 36.8%) or important (176; 53.7%) in their lives (►**Table 1**).

Table 1 Sociodemographic characteristics of the respondents (n = 404)

Characteristics	n	%
Age (years old)	403	
≤ 27	227	56.3
≥ 28	176	43.7
Gender	403	
Female	327	81.1
Male	76	18.9
Marital Status	403	
Without a stable partner	282	70.0
With a stable partner	121	30.0
Year of residency	402	
1st or 2nd	274	68.2
3rd–5th	128	31.8
Region of birth		
Southeast	207	51.2
Northeast	117	29.0
North	35	8.7
South	28	6.9
Midwest	10	2.5
Another country	7	1.7
Declared religion *	403	
Catholic	235	58.3
Other	92	22.7
None	76	19.0
Importance of religion in their life	402	
Very important	121	36.8
Important	176	53.7
Of little or no importance	31	9.5

Advantages and Disadvantages of Medical Abortion

There were five conditions which were considered advantages by between 84 and 95% of the respondents: "being less invasive" (94.7%), "does not require anesthesia" (89.7%), "can be accompanied during the process" (89.1%), "prevents physical trauma" (85.6%) and "is less expensive"(84.4%). In the other extreme, there were 4 conditions that were considered disadvantages by between 70 and 76% of the respondents: "it has a higher failure rate" (76.2%), "it has more side-effects" (75.3%) and "bleeding may be greater" and "pain may be greater" (70.7% and 70.6%) respectively (►**Table 2**).

The only two advantages with a significantly higher percentage of agreement among the residents who had participated in legal abortion care were "feeling in control" and "being less invasive". "Feeling in control" was considered an advantage by almost two thirds of the residents

Table 2 General opinion of residents in obstetrics and gynecology on possible advantages and disadvantages of medical abortion compared with surgical abortion

Possible advantages/ disadvantages of medical abortion	Advantage %	Disadvantage %	Don't know %
Does not requires anesthesia (n= 398)	**89.7**	3.3	7.0
Women can see what is happening	51.3	29.7	19.0
More "natural", like a miscarriage	79.4	6.6	14.1
Prevents physical trauma	**85.6**	4.0	10.3
Feeling in control of the process	60.0	10.3	29.8
It is less invasive	**94.7**	1.5	3.5
More private, can be done at home	40.8	34.7	24.6
Can be accompanied	**89.1**	3.0	7.8
Less expensive	84.4	4.5	11.1
Pain may be greater	13.8	**70.6**	15.6
Bleeding may be greater	10.4	**70.7**	18.8
Requires more visits	32.6	47.0	20.4
Higher failure rate	6.6	**76.2**	17.1
Women may have chills	6.8	68.2	24.9
It has more side effects	5.0	**75.3**	19.6

with experience in caring for women having legal abortions and by just less than half of the residents without such experience. The difference in the case of "being less invasive" was much smaller, although statistically significant. The difference in the proportion who agreed that "can be accompanied during the process" is an advantage was close to significance (0.058), with eight percentual points difference between those with and those without the experience of caring for women having a legal abortion (►**Table 3**).

Table 3 Advantages and disadvantages of medical abortion as compared with surgical abortion according to the resident's experience of being involved in providing legal abortion services

Possible advantages and disadvantages of medical abortion	Evaluation of residents	Involved in providing legal abortion services		
		Yes %	Not %	*p-value*
Did not require anesthesia (n= 398)	Advantage Disadvantage Don't know	91.3 0.9 7.8	89.1 4.2 6.7	0.219
Women can see what is happening	Advantage Disadvantage Don't know	52.8 28.5 18.7	47.4 32.8 19.8	0.599
More "natural", like a miscarriage	Advantage Disadvantage Don't know	80.6 6.3 13.1	76.3 7.0 16.9	0.612
Prevent physical trauma	Advantage Disadvantage Don't know	97.2 3.6 9.2	81.7 5.2 13.1	0.366
Feeling in control of the process	Advantage Disadvantage Don't know	64.1 7.8 28.1	49.6 16.5 33.9	**0.008**
It is less invasive	Advantage Disadvantage Don't know	96.5 1.4 2.1	91.2 1.8 7.0	**0.043**

Table 3 (*Continued*)

Possible advantages and disadvantages of medical abortion	Evaluation of residents	Involved in providing legal abortion services		
		Yes %	Not %	*p-value*
More private, can be done at home	Advantage	40.6	41.2	0.868
	Disadvantage	34.1	36.0	
	Don't know	25.3	22.8	
Can be accompanied during the process	Advantage	91.5	83.3	0.058
	Disadvantage	2.5	4.4	
	Don't know	6.0	12.3	
Less expensive	Advantage	85.4	81.7	0.525
	Disadvantage	4.6	4.4	
	Don't know	10.0	13.9	
Pain may be greater	Advantage	14.3	12.4	0.243
	Disadvantage	72.1	67.3	
	Don't know	13.6	20.3	
Bleeding may be greater	Advantage	11.1	8.8	0.524
	Disadvantage	71.3	69.3	
	Don't know	17.6	21.9	
Requires more visits	Advantage	31.0	36.5	0.563
	Disadvantage	48.0	44.4	
	Don't know	21.0	19.1	
Higher failure rate	Advantage	6.8	6.1	0.304
	Disadvantage	77.9	72.2	
	Don't know	15.3	21.7	
Women may have chills	Advantage	7.1	6.1	0.302
	Disadvantage	69.9	64.3	
	Don't know	23.0	29.6	
It has more side effects	Advantage	5.3	4.4	0.920
	Disadvantage	74.9	76.3	
	Don't know	19.8	19.3	

Discussion

It was to be expected that the advantages on which a larger percentage of residents agreed were related to their clinical practice, such as "being less invasive", "does not require anesthesia" and "prevents physical trauma". These results agreed with an extensive review on women's perception of medical abortion in many different countries,[24] indicating that residents had a good evaluation of how women felt during this process.

It was interesting that a large percentage of residents also gave relevance to advantages for the women, such as "can be accompanied during the process" and "is more natural", which were also perceived as advantage by women, as indicated by the review mentioned above.[24]

Similarly, the disadvantages with higher percentage of agreement were also of very practical clinical relevance such as "it has higher failure rate" and "it has more side-effects". The relevance given to the risk of greater incidence of bleeding and pain reflects that they are the most common complaint of women treated with medical abortion.[25]

The only two advantages with higher percentage of agreement among the residents who had participated in legal abortion care reflects their better understanding of the feelings of the women who go through the process of having a pregnancy termination by the use of medications: "feeling in control", and "being less invasive" are clearly advantages for the women involved and not for the providers.[24] These results seems to be a reflection of the closer proximity to the women under the care of the residents involved in providing such care. This is another example of how the clinical practice is important in creating a better client-provider interaction, which is a key element of good health care.

Another important discussion that can be raised by the results is regarding the use on an outpatient clinic basis. Although women with pregnancies up to 12 weeks of gestation can receive outpatient care for medical abortion, a scheme proven to be feasible and safe through outpatient health-care facilities,[26,27] in Brazil, misoprotol is only approved for hospital use, which requires the hospitalization of women for medical abortion, a more invasive and expensive treatment option. Brazilian medical residents consider some important characteristics for outpatient use as advantages: "does not requires anesthesia", "it is less invasive", "can be accompanied", is "less expensive". They also do not consider the need of more visits to be a problem.

These opinions favor implementing such outpatient treatment choice.

The results of the present study may provide valuable information to those responsible for the orientation of women requesting legal termination of pregnancy and who should decide if they prefer a surgical or a medical procedure, as our results inform which are the most important advantages and disadvantages of medical abortion in the judgment of residents, a very valuable information for the women who will experience this procedure.

Conclusion

Residents perceived both clinical and personal issues as advantages of medical abortion.

Contributions

Faúndes A. and Pacagnella R. C. led the study from its conceptualization, organizing the data collection and data analysis and writing the paper. Duarte G. A. and Osis M. J. D. contributed to the conceptualization and planning of the study and participated in the critical review of the manuscript at all stages up to its final approval. Bento S. F., Fernandes K. G. and Pádua K. S. contributed to the analysis and interpretation of the data and participated in the preparation of the manuscript and its critical review at all stages until its final approval.

Conflict of Interests

The authors have no conflict of interests to declare.

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References

1 Boland R, Katzive L. Developments in laws on induced abortion: 1998-2007. Int Fam Plan Perspect. 2008;34(03):110–120. Doi: 10.1363/ifpp.34.110.08
2 Diniz D, Medeiros M, Madeiro A. National abortion survey 2016. Cien Saude Colet. 2017;22(02):653–660. Doi: 10.1590/1413-81232017222.23812016
3 Sedgh G, Bearak J, Singh S, Bankole A, Popinchalk A, Ganatra B, et al. Abortion incidence between 1990 and 2014: global, regional, and subregional levels and trends. Lancet. 2016;388 (10041):258–267. Doi: 10.1016/S0140-6736(16)30380-4
4 Diniz D, Brito L, Ambrogi I, Tavares AB, Ali M. Understanding the sexual and reproductive health needs in Brazil's Zika-affected region: placing women at the center of the discussion. Int J Gynaecol Obstet. 2019;147(02):268–270. Doi: 10.1002/ijgo.12924
5 Malta M, Wells S, LeGrand S, Seixas M, Baptista A, Silva CMFP, et al. Abortion in Brazil: the case for women's rights, lives, and choices. Lancet Public Health. 2019;4(11):e552. Doi: 10.1016/S2468-2667 (19)30204-X
6 Grimes DA, Benson J, Singh S, Romero M, Ganatra B, Okonofua FE, Shah IHl. Unsafe abortion: the preventable pandemic. Lancet. 2006; 368(9550):1908–1919. Doi: 10.1016/S0140-6736(06)69481-6
7 Faúndes A. Misoprostol: life-saving. Eur J Contracept Reprod Health Care. 2011;16(02):57–60. Doi: 10.3109/13625187.2011.561940
8 Silva DFO, Bedone AJ, Faúndes A, Fernandes AMS, Lima e Moura VGA. Aborto provocado: redução da frequência e gravidade das complicações. Consequência do uso de misoprostol? Rev Bras Saúde Mater Infant. 2010;10(04):441–447. Doi: 10.1590/S1519-38292010000400004
9 Faúndes A, Bedone A, Silva JLP. I Fórum interprofissional para implementação do atendimento ao aborto previsto por lei: relatório final. Femina. 1997;25(01):69–78
10 Ministério da Saúde Secretaria de Atenção à Saúde Departamento de Ações Programáticas Estratégicas. Norma técnica: prevenção e tratamento dos agravos resultantes da violência sexual contra mulheres e adolescentes. Brasília (DF): Ministério da Saúde; 2010
11 Faúndes A, Araújo MJO, Andalaft Neto J, Ferreira MFO. Relatório final: X Fórum interprofissional sobre violência contra a mulher e implementação do aborto previsto na lei. Femina. 2007;35(01):55–58
12 Faúndes A, Duarte GA, Osis MJD, Andalaft Neto J. [Knowledge and opinion variations of Brazilian obstetricians and gynecologists face to legal abortion, between 2003 and 2005]. Rev Bras Ginecol Obstet. 2007;29(04):192–199. Doi: 10.1590/S0100-72032007000400005
13 Fiol V, Rieppi L, Aguirre R, Nozar M, Gorgoroso M, Coppola F, Briozzo L. The role of medical abortion in the implementation of the law on voluntary termination of pregnancy in Uruguay. Int J Gynaecol Obstet. 2016;134(Suppl 1):S12–S15. Doi: 10.1016/j.ijgo.2016.06.006
14 Ganatra B, Tunçalp Ö, Johnston HB, Johnson BR Jr, Gülmezoglu AM, Temmerman M. From concept to measurement: operationalizing WHO's definition of unsafe abortion. Bull World Health Organ. 2014;92(03):155. Doi: 10.2471/BLT.14.136333
15 Palma Manríquez I, Moreno Standen C, Álvarez Carimoney A, Richards A. Experience of clandestine use of medical abortion among university students in Chile: a qualitative study. Contraception. 2018;97(02): 100–107. Doi: 10.1016/j.contraception.2017.09.008
16 World Health Organization. Preventing unsafe abortion. Geneva: WHO; 2018
17 Kulier R, Kapp N, Gülmezoglu AM, Hofmeyr GJ, Cheng L, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2011;(11):CD002855. Doi: 10.1002/14651858.CD002855.pub4
18 World Health Organization. Safe abortion: technical and policy guidance for health systems. 2nd ed. Geneva: WHO; 2012
19 Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. Obstet Gynecol. 2015;126(01):22–28. Doi: 10.1097/AOG.0000000000000910
20 Laursen L, Stumbras K, Lewnard I, Haider S. Contraceptive provision after medication and surgical abortion. Womens Health Issues. 2017;27(05):546–550. Doi: 10.1016/j.whi.2017.03.012
21 Ministério da Saúde Secretaria de Atenção à Saúde Departamento de Ações Programáticas Estratégicas. Prevenção e tratamento dos agravos resultantes da violência sexual contra mulheres e adolescentes: norma técnica. 3a ed. Brasília (DF): Ministério da Saúde; 2012
22 Pacagnella RC, Bento SF, Fernandes KG, Araújo DM, Fahl ID, Fanton TF, et al; Grupo de Estudos sobre Aborto no Brasil. Knowledge on medical abortion among Brazilian medical residents in Gynecology and Obstetrics. Cad Saude Publica. 2020;36(36, Suppl 1): e00187918. Doi: 10.1590/0102-311x00187918
23 R Core Team. R: a language and environment for statistical computing [Internet]. ViennaR Foundation for Statistical Computing2017 [cited 2017 Mar 6]. Available from: http://www.www.R-project.org/
24 Ho PC. Women's perceptions on medical abortion. Contraception. 2006;74(01):11–15. Doi: 10.1016/j.contraception.2006.02.012

25 Saurel-Cubizolles MJ, Opatowski M, David P, Bardy F, Dunbavand A. Pain during medical abortion: a multicenter study in France. Eur J Obstet Gynecol Reprod Biol. 2015;194:212–217. Doi: 10.1016/j.ejogrb.2015.09.025

26 Platais I, Tsereteli T, Grebennikova G, Lotarevich T, Winikoff B. Prospective study of home use of mifepristone and misoprostol for medical abortion up to 10weeks of pregnancy in Kazakhstan. Int J Gynaecol Obstet. 2016;134(03):268–271. Doi: 10.1016/j.ijgo.2016.02.018

27 Winikoff B, Dzuba IG, Chong E, Goldberg AB, Lichtenberg ES, Ball C, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol. 2012;120(05):1070–1076. Doi: 10.1097/aog.0b013e31826c315f

Retrospective Evaluation of Patients Treated for Ectopic Pregnancy: Experience of a Tertiary Center

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Abstract

Objective In recent years, there has been an increase in the incidence of ectopic pregnancies; therefore, it is important for tertiary centers to report their approaches and outcomes to expand and improve treatment modalities. The aim of the present study was to evaluate the general characteristics, treatment and outcomes of cases diagnosed with ectopic pregnancy.

Methods In total, 432 patients treated for ectopic pregnancy between February 2016 and June 2019 were retrospectively evaluated.

Results Overall, 370 patients had tubal pregnancy, 32 had cesarean scar pregnancy, 18 had pregnancy of unknown location, 6 had cervical pregnancy, and 6 had interstitial pregnancy. The most important risk factors were advanced age ($>$ 35 years; prevalence: 31.2%) and smoking (prevalence: 27.1%). Thirty patients who did not have any symptoms of rupture and whose human chorionic gonadotropin (β-hCG) levels were $\leq$ 200 mIU/ml were followed-up with expectant management, while 316 patients whose β-hCG levels were between 1,500 mIU/ml and 5,000 mIU/ml did not have an intrauterine gestational sac on the transvaginal or abdominal ultrasound, did not demonstrate findings of rupture, and were treated with a systemic multi-dose methotrexate treatment protocol. In total, 24 patients who did not respond to the medical treatment, 20 patients whose β-hCG levels were $>$ 5,000 mIU/ml, 16 patients who had shown symptoms of rupture at the initial presentation, and 6 patients diagnosed with interstitial pregnancy underwent surgery. Patients with cervical and scar pregnancies underwent ultrasound-guided curettage, and no additional treatment was needed.

Conclusion The fertility status of the patients, the clinical and laboratory findings, and the levels of β-hCG are the factors that must be considered in planning the appropriate treatment.

Keywords
- ectopic pregnancy
- treatment
- methotrexate
- surgery
- expectant management

Introduction

Ectopic pregnancy is implantation of the fertilized ovum outside the endometrial cavity. According to various publications[1–4] its incidence in all pregnancies varies between 1/150 and 1/1,000.[1] In recent years, there has been an increase in the incidence of ectopic pregnancies due to a rise in sexually-transmitted diseases, and accordingly, in pelvic infections.[2] In spite of this increase in its incidence in the last decade, a decrease was achieved in the mortality rates associated with ectopic pregnancy due to the ability to routinely test for β-hCG and the increasingly widespread use of transvaginal ultrasonography.[3] The ability to establish a diagnosis before rupture enables patients to benefit from medical and conservative surgical treatments.[4] The present study aims to investigate the general

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characteristics, the treatment approaches and the outcomes of cases diagnosed with ectopic pregnancy at our clinic over a three-year period.

Methods

Study Design

In total, 432 patients diagnosed with ectopic pregnancy and treated in the Gynecology and Obstetrics Service at Gaziantep University Faculty of Medicine between February 2016 and June 2019 were retrospectively evaluated. The study was approved by the Gaziantep University Ethical Committee under number: 05/2011–16. Age, parity, previous deliveries and spontaneous/interventional abortions, methods of contraception, smoking status, history of previous ectopic pregnancy, tubal sterilization and pelvic surgery, β-hCG levels, ultrasound results, and treatment methods were retrospectively studied.

Data Collection

Maternal and obstetrical data were collected from the medical record software of the Obstetrics & Gynecology Clinic of the Faculty of Medicine of Gaziantep University.

Statistical Analysis

Descriptive data were presented as means ± standard deviations, medians, and percentages. The mean data were compared using the non-parametric Mann-Whitney U test. Values of $p < 0.05$ were considered statistically significant. The data were evaluated using the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, US) software, version 22.0.

Results

Out of 432 patients, 370 had tubal pregnancy, 32 had caesarean scar pregnancy,18 had pregnancy of unknown location, 6 had cervical pregnancy, and 6 had interstitial pregnancy. The mean age of the sample was 32,1 ± 6,3 years (range: 19 to 46 years). Of these patients, 15.3% had a history of 1 or multiple abortions, 13.9% had a history of previous ectopic pregnancy, 13,1% had a history of pelvic inflammatory disease, and 12.5% had a history of previous tubal surgery. In total, 27.1% of the patients smoked, and 31.2% were older than 35 years of age. Regarding the contraception method, 55.5% of the patients did not use any, 16.7% had intrauterine devices, 11.1% used the withdrawal method, 2.8% had tubal ligation, 4.2% used the male condom, 5.5% used oral contraceptives, and 2.8% used the calendar method. A total of 1.4% of the sample were breastfeeding. The results of the endometrial curettage indicated Arias-Stella reaction in 71%, and decidual reaction in 92% of the cases.

Ectopic pregnancies were diagnosed according to the diagnostic criteria adopted by our clinic.[5] In total, 18 patients who had an adnexial mass on ultrasound and who did not have any symptoms of rupture, and whose human chorionic gonadotropin (β-hCG) level was ≤ 200 mIU/ml were followed-up with expectant management; the β- hCG levels continued to demonstrate a gradual decrease during the follow-up. A total of 316 patients with tubal ectopic pregnancy whose β-hCG levels were between 1,500 and 5,000 mIU/ml, who did not have an intrauterine gestational sac on the transvaginal or abdominal ultrasound, and did not demonstrate findings of rupture were treated with a systemic multi-dose methotrexate treatment protocol. The endometrial curettage was performed as a tool

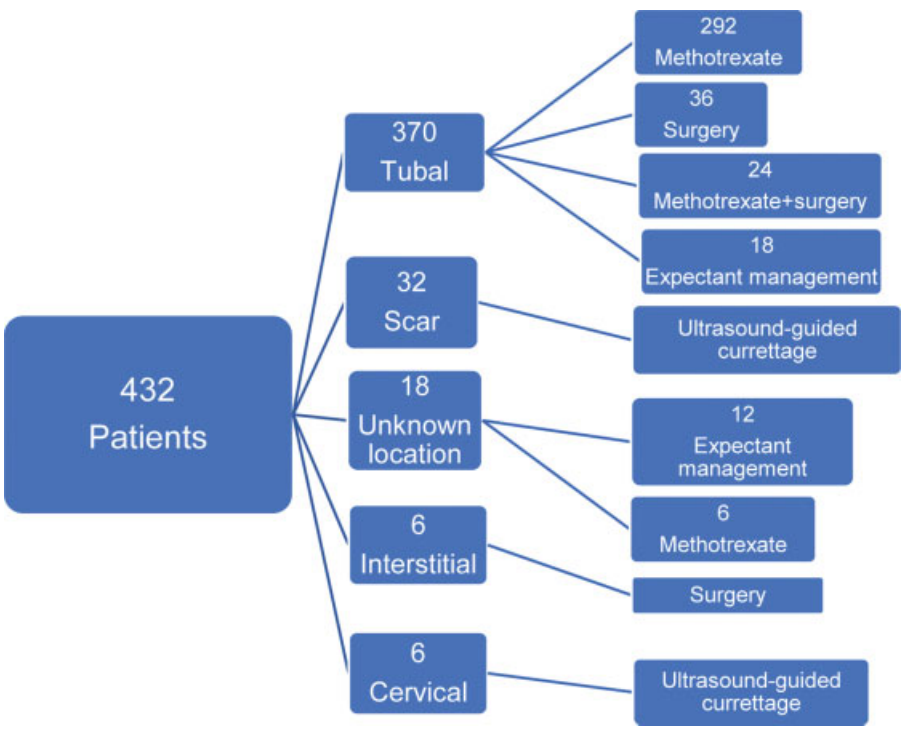

Fig. 1 Flowchart of the treatments.

for diagnosis in 67 suspected cases, and the diagnosis was confirmed. The size of the ectopic mass and the fetal cardiac activity did not change the treatment approach for tubal ectopic pregnancies, since it is a relative contraindication.[6] According to this protocol, 1 mg/kg of methotrexate was administered on days 1, 3, 5, and 7, and 0.1 mg/kg of leucovorin was administered on days 2, 4, 6, and 8 intramuscularly, until success was achieved (15% minimum decrease in β-hCG levels based on the tests performed on methotrexate days).[7] The patients were treated surgically if their β-hCG levels on the 9th day did not decrease, or if they showed sypmtoms of rupture during the methotrexate treatment. The success rate of the multi-dose methotrexate treatment was determined as 92.4%. In total, 24 patients underwent surgery after or during the methotrexate treatment. The β-hCG levels of 18 of these patients did not decrease after the medical treatment, and 6 patients showed symptoms of rupture. These 24 patients who did not respond to the medical treatment (all cases of tubal ectopic pregnancies), 20 patients whose β-hCG levels were $\geq$ 5,000 mIU/ml, 16 patients who had shown symptoms of rupture at the initial presentation, and 6 patients diagnosed with interstitial pregnancy underwent surgery (36 laparoscopic and 30 laparotomic surgeries). Out of the 66 patients who underwent surgery, 48 underwent salpingectomy. A total of 12 patients had tubal abortion, and their abdomens were closed after a lavage of the abdominal cavity, without any additional intervention; 6 interstitial pregnancies underwent wedge resection. Ultrasound-guided curettage was performed in 6 cervical and 32 caesarean scar pregnancies. Following the curettage, these 38 patients showed a progressive fall in their β-hCG levels, and required no additional treatment. In total, 18 patients with pregnancy of unknown location on ultrasound were followed-up with expectant management; 12 of these patients did not need any intervention, and 6 were treated with systemic methotrexate because of an irregular increase in the β-hCG levels. Finally, 68.9% of the patients were submitted to a systemic multi-dose methotrexate treatment, 9.7% underwent surgery, 8.8% were submitted to ultrasound-guided curettage, 6.9% underwent expectant management, and 5.5% were submitted to surgery after the methotrexate treatment. A flowchart of the treatments is shown in ►**Fig. 1**.

Table 1 Delivery, spontaneous and interventional abortion rates of the patients

		Number of patients	%
Parity	Nullipara	66	15.3
	Primipara	168	38.9
	Multipara	198	45.8
Spontaneous abortion	None	366	84.7
	1	36	8.3
	2	18	4.2
	3	12	2.8
Surgical abortion	None	378	87.5
	1	30	6.9
	2	24	5.5

Table 2 Number of previous ectopic pregnancies, cesarean sections, and tubal surgeries

	Number of operations	Number of patients	%
Ectopic pregnancy	0	372	86.1
	1	48	11.1
	2	12	2.8
Cesarean section	0	192	44.4
	1	72	16.7
	2	84	19.4
	3	54	12.5
	4	30	6.9
Tubal surgery	0	378	87.5
	1	42	9.7
	2	12	2.8

Table 3 Levels of human chorionic gonadotropin (β-hCG) among the treatment groups

	Number of patients	β-hCG (mIU/ml)	*p*-value
Methotrexate	298	2457 ± 1642	0.123
Surgery	42	5189 ± 4555^{B}	0.041*
Ultrasound-guided curettage	38	1996 ± 2107	0.813
Expectant management	30	126 ± 78^{A}	0.021*
Methotrexate + surgery	24	2989 ± 2623	0.442

Note: *Significant at 0.05 level; [A]significantly lower than the others; [B]significantly higher than the others).

The distribution of the cases with regard to the gestational age based on the date of the last menstruation was as follows: weeks 5 to 7 in 52.4% (226); and weeks 8 to 10 in 47.6% (206). At the initial presentation, 16 cases (3.7%) had shown symptoms of rupture. Stable vital signs were observed in 416 cases (91.7%). The delivery and the rates of spontaneous and surgical abortions are summarized in ►**Table 1**; the number of previous ectopic pregnancies, cesarean sections and pelvic surgeries are summarized in ►**Table 2**; and the levels of β-hCG among the treatment groups are described in ►**Table 3**.

Discussion

Although the mortality rate in cases of ectopic pregnancy has decreased due to the advances in diagnosis and treatment, its incidence has increased in parallel to the increase in the prevalence of pelvic inflammatory diseases, increasing maternal age, and the increasing use of infertility treatments.[7] The aim of the treatment for ectopic pregnancy has shifted from ensuring survival to preserving fertility, and the conservative surgical techniques were developed to maintain

fertility. The treatment options for ectopic pregnancies include expectant management, methotrexate treatment, ultrasound-guided currettage and surgery. The treatment modality should be selected based on the overall condition of the patient, the laboratory findings, and the fertility status.[8] In the present study, we evaluated the approaches we adopted in the treatment of ectopic pregnancy, and discussed our treatment spectrum along with the literature.

In the present study, ectopic pregnancies were most common in the no-contraception group (55.5% | $n = 240$), while intrauterine devices were used by 36 (16.7%) patients. A history of tubal surgery was present in 18 patients (8.3%), and a history of previous ectopic pregnancy, in 30 patients (13.9%). The most important risk factors were advanced age (> 35) and smoking (respectively; 135 (31.2%), 117 (27.1%)). The generally known risk factors for ectopic pregnancy were encountered at moderate rates among the patients included in the present study.[9,10]

Studies about expectant management have reported success rates varying between 54% and 92.3%; however, expectant management has the highest success rates in patient groups with low β-hCG levels ($\leq$ 200 mIU/ml).[11,12] In total, 30 patients followed-up with expectant management had significantly lower β-hCG levels compared with the other groups, and our success rate was of 100%. Thus, selecting appropriate patients in the determination of the treatment modality can significantly increase the success rate.

Methotrexate is a folic-acid antagonist, and it inhibits the production of tetrahydrofolate, which is required for the synthesis of DNA, RNA, and ATP. The treatment with methotrexate can be administered locally or systemically. Previous studies determined lower success rates with a single-dose protocol than with a multi-dose protocol, particularly when the β-hCG levels are high. The multi-dose methotrexate treatment appears to be as effective as laparoscopic salpingostomy in the treatment of ectopic pregnancies (the comparison of multi-dose methotrexate with surgery: 82% to 71%; relative risk (RR): 1.15%; 95% confidence interval (95% CI): 0.93–1.43 respectively).[12] A systematic review of randomized studies[13] revealed that single-dose methotrexate (50 mg/m^2, or 1 mg/kg) had a lower success rate than the multi-dose treatment (the comparison of single dose-multi-dose methotrexate in four studies[14]: 71% to 88%; RR: 0.82%; 95%CI: 0.72–0.94 respectively). Meanwhile, administering an additional dose when a single-dose fails was found to have an effectiveness comparable to that of salpingostomy and the multi-dose treatment (RR: 1.01; 95%CI: 0.92–1.12).[13,14] We have been administering the multi-dose treatment regimen for years, with high success rates; and although the systemic treatment was reported to have side effects such as pneumonia, stomatitis, and alopecia, our patients did not show any side effects, which can be explained by the controlled use of the medication at appropriate doses and on appropriate patients.

The serum β-hCG levels are closely related to the success rates obtained with the medical treatment. A previous study[15] revealed that the initial β-hCG level was the most useful prognostic data to predict the success of the methotrexate treatment. In another study,[16] methotrexate was found to have a success rate of 94% when the initial β-hCG level was lower than 10,000 mIU/ml, and a success rate of 75% when it was higher than 10,000 mIU/ml. More recent publications have shown that a cut-off level between 2,000 mIU/ml 5,000 mIU/ml is more appropriate for high success rates. Similarly, in the present study, we determined higher success rates with an initial β-hCG level below 5,000 mIU/ml.

In the management of cervical and cesarean scar pregnancies, aspiration curettage can be combined with cervical tamponade using a Foley catheter for hemostasis. Besides these procedures, local prostaglandin can be used following the curettage. In case of uncontrollable bleeding, the ligation of the cervical branches of the uterine artery and the ligation of the bilateral hypogastric arteries can be considered. As a last resort, hysterectomy can be performed.[17] In the present study, 6 patients with cervical pregnancies and 32 patients with cesarean scar pregnancies were treated with ultrasound-guided curettage, without any additional interventions. The β-hCG levels of the patients gradually decreased to zero after the curretage. Based on this result, one can state that a successful ultrasound-guided curettage procedure is quite effective as a standalone treatment in patients diagnosed with scar and cervical pregnancies.

Endometrial sampling in the diagnosis of ectopic pregnancy is still controversial.[18] The presence of decidual and typical Arias-Stella reactions in endometrial curettage material without fetal tissue and placental components is an important finding for ectopic pregnancy. Although Arias-Stella reactions were reported to be present at a rate of 40% to 70% in ectopic pregnancies, the presence of a decidual reaction without an Arias-Stella reaction was also reported to corroborate the diagnosis.[19] In line with the literature, the Arias-Stella reaction was determined at a rate of 71% in the cases who underwent endometrial curettage in the present study, and the decidual reaction was determined in 92% of the patients. We must remember that all phases of the endometrium can be found in an ectopic pregnancy, and none are pathognomonic.[20] Nevertheless, examining an endometrial sample can be helpful in patients with unclear differential diagnosis.

The gold standard in the surgical treatment of ectopic pregnancy is laparoscopic surgery, because it is associated with shorter operations and hospitalization, lower blood loss and lower need for analgesics, and a lower total cost. Intra-abdominal adhesion is also less frequent after laparoscopy compared with laparotomy.[21] Meanwhile, laparoscopy may not be the primary choice for patients who are hemodynamically unstable and patients with severe intra-abdominal bleeding. Surgical procedures have a greater impact on future fertility compared with the medical treatment, and the probability of natural conception significantly decreases, particularly after a salpingectomy. On the other hand, the treatment with salpingostomy is typically not preferred by clinicians because of persistent trophoblastic activity and the risk of tubal bleeding.[22] Among the ectopic pregnancies treated at our clinic, those with hemodynamic instability, β-hCG levels higher than 5,000 mIU/ml, and those not

responding to the methotrexate treatment were treated with surgical methods. Of such patients, 60% underwent laparoscopy, and 40% underwent laparotomy. Of the 30 patients who underwent surgery, 24 underwent salpingectomy, while 6 had tubal abortions, and the abdominal cavity was irrigated and lavaged without any additional treatment.

Conclusion

In conclusion, the early and correct diagnosis of ectopic pregnancy is important to prevent mortality and morbidity. It must be taken into consideration that conventional risk factors are not always present, and patients in low-risk groups should be examined thoroughly. In the treatment of ectopic pregnancy, methotrexate therapy, surgical intervention, and expectant approaches have high success rates without complications when administered to the correct patients. Determining the most appropriate treatment approach is of vital importance. The fertility of the patients, the clinical and laboratory findings, and the serum β-hCG levels are factors that must be considered in planning an appropriate treatment.

Contributions

All authors participated in the conception and design of the present study; in the analysis and interpretation of data; in the draft or revision of the manuscript; and they have approved the manuscript as submitted. All authors are responsible for the reported research.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Demirdag E, Guler I, Abay S, Oguz Y, Erdem M, Erdem A. The impact of expectant management, systemic methotrexate and surgery on subsequent pregnancy outcomes in tubal ectopic pregnancy. Ir J Med Sci. 2017;186(02):387–392. Doi: 10.1007/s11845-016-1419-5

2 Tsevat DG, Wiesenfeld HC, Parks C, Peipert JF. Sexually transmitted diseases and infertility. Am J Obstet Gynecol. 2017;216(01):1–9. Doi: 10.1016/j.ajog.2016.08.008

3 Gaskins AJ, Missmer SA, Rich-Edwards JW, Williams PL, Souter I, Chavarro JE. Demographic, lifestyle, and reproductive risk factors for ectopic pregnancy. Fertil Steril. 2018;110(07):1328–1337. Doi: 10.1016/j.fertnstert.2018.08.022

4 Jauniaux E, Jurkovic D. Ectopic pregnancy: 130 years of medical diagnostic challenges. BJOG. 2018;125(13):1672. Doi: 10.1111/1471-0528.15454

5 Tulandi T. Ectopic pregnancy: choosing a treatment [Internet]. 2020 [cited 2010 Feb 10]. Available from: https://www.uptodate.com/contents/ectopic-pregnancy-choosing-a-treatment

6 Paull C, Robson SJ. Hospital admission and surgical approach to tubal ectopic pregnancy in Australia 2000 to 2014: A population-based study. Aust N Z J Obstet Gynaecol. 2018;58(02):234–238. Doi: 10.1111/ajo.12727

7 Lipscomb GH. Medical therapy for ectopic pregnancy. Semin Reprod Med. 2007;25(02):93–98. Doi: 10.1055/s-2007-970048

8 Hsu JY, Chen L, Gumer AR, Tergas AI, Hou JY, Burke WM, et al. Disparities in the management of ectopic pregnancy. Am J Obstet Gynecol. 2017;217(01):49.e1–49.e10

9 Mashiach R, Kislev I, Gilboa D, Mazaki-Tovi S, Seidman DS, Goldenberg M, Bouaziz J. Significant increase in serum hCG levels following methotrexate therapy is associated with lower treatment success rates in ectopic pregnancy patients. Eur J Obstet Gynecol Reprod Biol. 2018;231:188–191. Doi: 10.1016/j.ejogrb.2018.10.046

10 Craig LB, Khan S. Expectant management of ectopic pregnancy. Clin Obstet Gynecol. 2012;55(02):461–470. Doi: 10.1097/GRF.0b013e3182510aba

11 Moawad N, Baker S, Hergert S, Shuster J, Robinson M. Trends in the surgical management of ectopic pregnancy with the addition of MIS faculty. J Minim Invasive Gynecol. 2017;24(7, Supplement) S81. Doi: 10.1016/j.jmig.2017.08.216

12 Mavrelos D, Memtsa M, Helmy S, Derdelis G, Jauniaux E, Jurkovic D. β-hCG resolution times during expectant management of tubal ectopic pregnancies. BMC Womens Health. 2015;15:43. Doi: 10.1186/s12905-015-0200-7

13 Mol F, Mol BW, Ankum WM, van der Veen F, Hajenius PJ. Current evidence on surgery, systemic methotrexate and expectant management in the treatment of tubal ectopic pregnancy: a systematic review and meta-analysis. Hum Reprod Update. 2008;14(04):309–319. Doi: 10.1093/humupd/dmn012

14 Nieuwkerk PT, Hajenius PJ, Ankum WM, Van der Veen F, Wijker W, Bossuyt PM. Systemic methotrexate therapy versus laparoscopic salpingostomy in patients with tubal pregnancy. Part I. Impact on patients' health-related quality of life. Fertil Steril. 1998;70(03):511–517. Doi: 10.1016/s0015-0282(98)00212-x

15 Lipscomb GH, Givens VA, Meyer NL, Bran D. Previous ectopic pregnancy as a predictor of failure of systemic methotrexate therapy. Fertil Steril. 2004;81(05):1221–1224. Doi: 10.1016/j.fertnstert.2003.09.070

16 Alur-Gupta S, Cooney LG, Senapati S, Sammel MD, Barnhart KT. Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis. Am J Obstet Gynecol. 2019;221(02):95–108.e2. Doi: 10.1016/j.ajog.2019.01.002

17 Guzowski G, Sieroszewski P. Invasive ultrasound in the management of cervical ectopic pregnancy. Eur J Obstet Gynecol Reprod Biol. 2014;172:7–9. Doi: 10.1016/j.ejogrb.2013.10.016

18 Brady PC. New evidence to guide ectopic pregnancy diagnosis and management. Obstet Gynecol Surv. 2017;72(10):618–625. Doi: 10.1097/OGX.0000000000000492

19 Bestel M, Karaaslan O, Bestel A, Salman S. Therapeutic curettage on follow up human chorionic gonadotropin levels in ectopic pregnancy. East J Med. 2019;24(02):200–203. Doi: 10.5505/ejm.2019.26818

20 de Haan J, Vandecaveye V, Han SN, Van de Vijver KK, Amant F. Difficulties with diagnosis of malignancies in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2016;33:19–32. Doi: 10.1016/j.bpobgyn.2015.10.005

21 Ades A, Parghi S. Laparoscopic resection of cesarean scar ectopic pregnancy. J Minim Invasive Gynecol. 2017;24(04):533–535. Doi: 10.1016/j.jmig.2016.11.006

22 Laganà AS, Vitale SG, De Dominici R, Padula F, Rapisarda AMC, Biondi A, et al. Fertility outcome after laparoscopic salpingostomy or salpingectomy for tubal ectopic pregnancy A 12-years retrospective cohort study. Ann Ital Chir. 2016;87:461–465

Fetal Echocardiography Indications and Lack of Association between Abnormal Exams and Advanced Maternal Age: A Cross-Sectional Study - Fetal Abnormal Echocardiography

Indicações para realização de ecocardiografia fetal e ausência de associação entre exames alterados e idade materna avançada: Um estudo transversal - Ecocardiografia fetal anormal

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Abstract

Objective To analyze the most frequent referrals for fetal echocardiography, including advanced maternal age and its association with abnormal results.

Methods We included all pregnant women referred to perform fetal echocardiography (gestational age 22–32 weeks) in 2 health centers in Rio de Janeiro, from June 2015 to June 2016. Advanced maternal age was considered when age was $>$ 35 years at the time of delivery). Referral reasons and results were recorded, according to the Brazilian Fetal Cardiology Statement. Crude and adjusted prevalence ratios were calculated (Poisson regression). We considered $p < 0.05$ as significant.

Results A total of 1,221 tests were analyzed. Abnormal fetal echocardiography was observed in 14.82% of the cases. The most frequent abnormalities were interventricular septal defect (6.39%), septal hypertrophy (3.35%) and atrioventricular septal defect (1.14%). Routine exams were performed in 559 women, 289 were referred for advanced maternal age and 373 were referred according to the Brazilian Fetal Cardiology Statement criteria. An obstetric ultrasound suggesting fetal cardiac abnormality, maternal diabetes, increased nuchal translucency, and obstetric ultrasound suggesting a noncardiac abnormality were strongly associated with an abnormal fetal echocardiography. Abnormal results were not more frequent in women with advanced maternal age when compared with the rest of the study group.

Conclusions It was observed that routine exams and advanced maternal age referrals were very frequent. Those exams were not associated to fetal echocardiography abnormalities. In this scenario, when the obstetric ultrasound suggests a fetal cardiac

Keywords

- congenital heart disease
- prenatal diagnosis
- fetal heart
- fetal ultrasonography

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abnormality, the fetal echocardiography probably is abnormal. Therefore, obstetric ultrasound is a good screening method.

Resumo

Objetivo Analisar as indicações mais frequentes para realização de ecocardiografia fetal, incluindo idade materna avançada, e a associação destas com exames alterados.
Métodos Foram incluídas todas as gestantes que realizaram ecocardiografia fetal na idade gestacional entre 22 e 32 semanas, em 2 centros de referência no Rio de Janeiro, no período de junho de 2015 a junho de 2016. Foi considerada idade materna avançada se no momento do parto a idade materna fosse > 35 anos. As indicações e os resultados dos exames foram registrados, segundo a Diretriz Brasileira de Cardiologia Fetal. Foram calculadas as razões de prevalência brutas e ajustadas através da regressão de Poisson, considerando-se $p < 0,05$.
Resultados Um total de 1.221 exames foram analisados. A frequência de exame ecocardiográfico alterado foi 14,82%. As alterações mais frequentes foram defeito do septo interventricular (6,39%), hipertrofia septal (3,35%) e defeito do septo atrioventricular (1,14%). Quinhentos e cinquenta e nove exames foram realizados com indicação de rotina, 289 por idade materna avançada e 373 preenchiam critério de acordo com a Diretriz Brasileira de Cardiologia Fetal. O exame ecocardiográfico alterado foi associado ao ultrassom obstétrico sugerindo cardiopatia fetal, ao diabetes materno, à translucência nucal aumentada e ao ultrassom obstétrico sugerindo alteração extracardíaca. Não foi observada maior frequência de exame ecocardiográfico alterado nas gestantes com idade materna avançada, comparado ao restante da amostra.
Conclusão Constatou-se elevada frequência de indicações de rotina, e por idade materna avançada isoladamente, que não foram associados a alterações da ecocardiografia fetal. Em nosso meio, quando o ultrassom obstétrico sugere cardiopatia fetal, é muito provável que a ecocardiografia fetal também seja anormal. Portanto, o ultrassom obstétrico é um bom método de rastreio pré-natal.

Palavras-chave
- cardiopatias
- cuidado pré-natal
- coração fetal
- ultrassonografia pré-natal

Introduction

Congenital cardiac anomalies occur in ~ 8 to 18 per 1,000 live births. Research shows that 3 to 4 % of live births have major heart defects that require intervention during the 1st year of life.[1] The frequency of congenital heart defects is six times higher than chromosomal defects and four times higher than neural tube defects.[2,3] These anomalies are responsible for up to 10% of deaths in children.[1,4] Fetal diagnosis of cardiac anomalies can improve the prognosis and contribute to the reduction of infant morbidity and mortality, directing expectant mothers to specialized centers.[1,5]

There is still no criterion based on scientific evidence to indicate a fetal echocardiography scan for all pregnant women.[6] The American Heart Association published a protocol in 2014 with recommendations for screening of pregnant women considered at high risk. According to this, when the risk of cardiac alteration exceeds 3%, fetal echocardiography should be performed; when the risk is > 2 to 3%, the test should be considered.[7]

More recently, the Brazilian Society of Cardiology has published the Brazilian Guideline of Fetal Cardiology, highlighting the clinical conditions that increase the risk of fetal heart alteration and the indications for a fetal echocardiography scan.[8]

Although advanced maternal age (> 35 years at the time of delivery) is an important maternal-fetal risk, associated with maternal hypertension, c-section delivery, prematurity, and low birth weight, such factor alone does not constitute risk of fetal heart alteration and, therefore, is not an indication for fetal echocardiography in the two aforementioned guidelines.[7–9]

The sensitivity of 88.5% and 100% specificity of fetal echocardiography in detecting congenital heart abnormalities should be emphasized, which makes this test an important diagnostic tool.[10]

The objective of this study was to analyze the most frequent indications for fetal echocardiography, the alterations found, and if there was an association of advanced maternal age and other factors with abnormal results in two reference centers in Rio de Janeiro.

Methods

Cross-sectional, analytical study approved by the Research Ethics Committee of Federal Fluminense University, under

number CAAE: 51113115.1.0000.5243. Informed consent was waived by the ethics board.

Pregnant women with gestational age between 22 and 32 weeks who underwent fetal echocardiography at Hospital Federal de Bonsucesso or at the Clínica Carlos Bittencourt in Rio de Janeiro from June 2015 to June 2016 were included. Cases of fetal heart poorly visualized were excluded.

Fetal echocardiography was performed by the same pediatric cardiologist, using PHILIPS ENVISOR (Philips, Andover MA, USA) and GE VOLUSON E (GE, Milwaukee WI, USA), with transducers sized 5 to 3.3 Mhz. All tests showed good visualization of the fetal heart, with apical sections of four and five chambers, short and long axis visualization and visualization of the aortic arch and ductus arteriosus. When necessary, color Doppler evaluation was performed. The assessed outcome was an abnormal fetal echocardiography examination (yes/no), suggesting structural or non-structural/functional cardiac alteration. Advanced maternal age was considered if >35 years at the expected delivery date. The indications for the screening were recorded, and all pregnant women with indications in accordance with the Brazilian Fetal Cardiology Guidelines were considered a risk group.

The data were collected retrospectively from medical records and stored in an Excel spreadsheet (Microsoft Corp., Redmond, WA, USA). Statistical analysis was performed using the Stata version 13.0 program (Stata Corp, LLC, College Station, TX, USA). The sample calculation was performed considering power of 80%, α of 0.05 and 2% difference in proportion between two groups (high and low risk), resulting in 1,044 subjects. The normality of the variable age was tested by the Shapiro Wilk test. The results are presented in medians and interquartile range (IQR). The frequency of indications for the scan, the altered echocardiography, and the alterations detected were calculated, with their respective 95% confidence intervals (95% CIs). Routine indications (regular exams without a specific indication) were analyzed. Differences between proportions were calculated by the chi-squared test. A bivariate analysis was performed with the outcome of the abnormal echocardiographic scan and possible associated variables. Poisson analysis (robust estimation and log-linking function) was performed to estimate crude and adjusted prevalence ratios (CPr and APr). Variables with p-value <0.20 were included to calculate the adjusted prevalence ratios. For final analyses, $p<0.05$ was considered significant.

Results

A total of 1,340 scans were performed; 119 were excluded due to poor visualization of the fetal heart. Thus, 1,221 results were analyzed. The average maternal age was 32 years old (IIQ 27–36). The frequency of altered echocardiography was 14.82% (181/1,221). Considering the Brazilian Fetal Cardiology Guidelines, 373 tests (30.54%) fulfilled the indication criteria, and, of these, 142 (38.06%) were abnormal. On the other hand, 848 exams (69.45%) did not meet risk criteria, and, of these, 39 (4.59%) were abnormal ($p<0.001$). Advanced maternal age was the isolated indication for 289 tests (23.67%). Of these, 31 results (10.72%) were altered. Routine indication was registered in 559 exams.

Among the group of pregnant women who met the criteria according to the Guidelines ($n=373$), the most frequent indications were an obstetric US suggesting extracardiac alteration (26.2%), maternal diabetes (18.5%), and monochorionic twinning (12.6%). Abnormal results were found more frequently when obstetric US suggested fetal heart disease in 82.35% of the cases. The most frequent indications and frequency of abnormal results are found in ►**Table 1**.

The most frequent changes were interventricular septal defect, in 6.39% (78/1,221), septal hypertrophy, in 3.35% (41/1,221), and atrioventricular septal defect, in 1.14% (14/1,221). The prevalence and crude prevalence ratio of fetal echocardiographic alterations were calculated according to risk factors (►**Table 2**).

In the multivariate analysis, the factors associated with higher frequency of altered fetal echocardiography (►**Table 3**) were maternal diabetes, fetal US suggesting cardiac or extracardiac alteration, and altered nuchal translucency. Advanced maternal age was not maintained in the model (p-value 0.072).

Table 1 More frequent indications for fetal echocardiography and frequency of abnormal results, according to the Brazilian Guideline of Fetal Cardiology

Indication	n	Abnormal results	%	95% CI
Obstetric US suggesting fetal cardiopathy	34	28	82.35	65.46–93.23
Chromosomal defects	20	14	70	45.72–88.10
Maternal Diabetes	69	22	31.88	21.17–44.20
Obstetric US suggesting extracardiac alteration	98	31	31.63	22.60–41.80
Increased Nuchal translucency	27	8	29.62	13.75–50.18
Cardiac rhythm disorders	12	3	25	5.48–57.18
Monochorionic twinning	47	4	8.51	2.36–20.37
Others	66	32	48.48	35.99–61.11

Table 2 Prevalence and crude prevalence ratio (CPr) of fetal echocardiographic alterations according to risk factors

Risk factor	n	%	Abnormal result (%)	CPr	*p*-value
Obstetric US suggesting fetal cardiopathy					
Yes	34	2.78	82.35	7,004	< 0.001
No	1,187	97.22	12.88	1	
Chromosomal defects					
Yes	20	1.64	70.00	5,034	< 0.001
No	1,201	98.36	13.40	1	
Maternal Diabetes					
Yes	69	5.65	31.88	2,310	< 0.001
No	1,152	94.35	13.80	1	
Obstetric US suggesting extracardiac abnormality					
Yes	98	8.02	31.63	3,092	< 0.001
No	1,123	91.98	13.35	1	
Increased nuchal translucency					
Yes	27	2.21	29.62	2,044	0.019
No	1,194	97.78	14.48	1	
Cardiac rhythm disorders					
Yes	12	0.98	25.00	1,696	0.295
No	1,209	99.01	14.72	1	
Monochorionic twinning					
Yes	47	3.84	8.51	0.922	0.823
No	1,174	96.15	15.07	1	
Maternal age alone					
Yes	289	23.66	10.72	0.666	0.029
No	932	76.33	16.09	1	

Table 3 Adjusted prevalence ratio (Apr) of abnormalities in fetal echocardiography and associated risk factors

Risk factor	APr	95% CI	*p*-value
Obstetric US suggesting fetal cardiopathy	6,144	4,548–8,302	< 0.001
Maternal Diabetes	3,508	2,378–5,176	< 0.001
Increased nuchal translucency	3,260	1,774–5,992	< 0.001
Obstetric US suggesting extracardiac abnormality	2,190	1,555–3,085	< 0.001

Discussion

The present study points to the excess of fetal echocardiography tests performed in pregnant women with advanced age without other comorbidities (23.87%). Although this factor constitutes a maternal-fetal risk, it does not constitute risk of fetal heart alteration. This screening was performed without recommendations supporting it. In the present study, as an isolated factor, a lower prevalence of echocardiographic alterations (CPr 0.66) was observed, not justifying its indication for screening; this recommendation was also published in other articles.[9–11]

The frequency of abnormal results was 14.82%, comparable to the result of Stümpflen et al.,[12] who reported 14.9% frequency of altered results. The authors studied pregnant women between 18 and 28 weeks who agreed to have the scan performed.[12] Persico et al.[13] studied risk pregnancies referred for chorionic villus biopsy and observed 11.6% of altered results. A national study in pregnant women without risk detected a frequency of 2.5% of altered tests.[14] The occurrence of altered results may vary depending on the indications and gestational age when the scan was performed. It is noteworthy that the present study was cross-sectional, and the patients were not followed up in the

postnatal period; all scans were performed during pregnancy.

Considering the altered results in the high-risk group, according to the Brazilian Fetal Cardiology Guidelines, the frequency was 38.06%, while in other indications it was 4.59%, a significant difference that highlights the importance of the adequate indication for fetal echocardiography. On the other hand, Nayak et al. found a high frequency of abnormal results in the group considered low risk, but no difference between high and low risk groups according to the Pediatrics Council of the American Society of Echocardiography. Of interest, the authors reported 26 exams who failed to detect fetal abnormalities on level-2 ultrasound (for poor window, operator error and other reasons). Those exams in other centers probably should have been considered "obstetric ultrasound suggesting a fetal cardiac abnormality." This particular result limits the recommendation that fetal echocardiography should be done in all pregnant women, irrespective of risk factors.[15] Other studies have found a high frequency of abnormalities in low-risk groups, which raises the need for detailed methodological assessment for proper comparisons.[16,17] We emphasize the need to follow recommended guidelines to optimize available resources.

In the risk group, the most frequent indication was obstetric US suggesting extracardiac alteration followed by maternal diabetes and monochorionic twinning. Meyer-Wittkopf et al.,[18] in 2001, reported the history of congenital heart disease in the family as the most frequent indication (44.5%). Friedberg et al.[19] also reported history of congenital heart disease in the family as the most frequent indication (22%), followed by maternal diabetes (18%) and obstetric US suggesting heart disease (13%). The authors mention that indications for fetal echocardiography have changed over the years as obstetric US has been more accurate, and the high availability of fetal echocardiography may induce indications.

The most frequent echocardiographic change was the interventricular septal defect (6.39%), followed by septal hypertrophy (3.35%) and atrioventricular septal defect (1.14%). Ozkutlu et al.[17] and Sainz et al.[20] found similar results. In Porto Alegre, a population-based study with low-risk pregnant women showed interventricular communication as the most frequent alteration, followed by heart rhythm disorders and fetal hypertrophic heart disease.[14] In our study, it is worth noting that maternal diabetes was the second most frequent indication in pregnant women at risk; septal hypertrophy, a functional change, is associated with this condition. Maternal diabetes is a risk factor for increased left ventricular mass, difficulty in left ventricular relaxation and systolic dysfunction.[21,22]

Factors associated with fetal echocardiographic alterations were obstetric US suggesting fetal heart disease (APr = 6,144), followed by maternal diabetes (APr = 3,508), altered nuchal translucency (APr = 3,260), and obstetric US suggesting extracardiac alterations (APr = 2,190). This result is in accordance with the literature.[17,23] It is important to stress that we analyzed the most frequent factors to obtain association estimates in our environment. Due to the study design, no direct risk estimates were obtained. Due to the frequency of the altered factors and scans, we opted for CPr and APr estimates. It is known that in this circumstance, the association estimation by odds ratio may overestimate the association.[24]

This study has limitations. The sample was obtained in two centers where fetal echocardiography was performed, and the study results may not reflect the reality of the city of Rio de Janeiro. In the period studied (2015 and 2016), according to the Superintendence of Health Surveillance, 90,539 and 83,057 live births were recorded, respectively (mean 86,798); thus, the present sample represented 1.4% of live births in the period.[25] Also, as a cross-sectional research, no further information on neonatal echocardiography examinations were collected.

Conclusion

From the results, it was found a high number of scans that did not meet the indication criteria of the Brazilian Fetal Cardiology Guidelines. Special attention should be given to the advanced maternal age, which alone does not constitute fetal risk for cardiac alteration and should not be considered an indication for fetal echocardiography. In our environment, when obstetric US suggests fetal heart disease, it is likely that the fetal echocardiography examination does the same, which reveals the high quality of obstetric US screenings.

Contributions

All authors participated in the concept and design of the present study; analysis and interpretation of data; draft or revision of the manuscript; and they have approved the manuscript as submitted. All authors are responsible for the reported research.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Cha S, Kim GB, Kwon BS, Bae EJ, Noh CI, Lim HG, et al. Recent trends in indications of fetal echocardiography and postnatal outcomes in fetuses diagnosed as congenital heart disease. Korean Circ J. 2012;42(12):839–844. Doi: 10.4070/kcj.2012.42.12.839
2 Alves Rocha L, Araujo Júnior E, Rolo LC, Barros FSB, Silva KP, Martinez LH, et al. Screening of congenital heart disease in the second trimester of pregnancy: current knowledge and new perspectives to the clinical practice. Cardiol Young. 2014;24(03): 388–396. Doi: 10.1017/S1047951113001558
3 Hunter LE, Simpson JM. Prenatal screening for structural congenital heart disease. Nat Rev Cardiol. 2014;11(06):323–334. Doi: 10.1038/nrcardio.2014.34
4 Allan LD. Echocardiographic detection of congenital heart disease in the fetus: present and future. Br Heart J. 1995;74(02):103–106. Doi: 10.1136/hrt.74.2.103
5 Słodki M, Respondek-Liberska M, Pruetz JD, Donofrio MT. Fetal cardiology: changing the definition of critical heart disease in the newborn. J Perinatol. 2016;36(08):575–580. Doi: 10.1038/jp.2016.20
6 Wright L, Stauffer N, Samai C, Oster M. Who should be referred? An evaluation of referral indications for fetal echocardiography in the detection of structural congenital heart disease. Pediatr Cardiol. 2014;35(06):928–933. Doi: 10.1007/s00246-014-0877-7

7 Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A, et al; American Heart Association Adults With Congenital Heart Disease Joint Committee of the Council on Cardiovascular Disease in the Young and Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Council on Cardiovascular and Stroke Nursing. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation. 2014;129(21): 2183–2242. Doi: 10.1161/01.cir.0000437597.44550.5d

8 Pedra SRFF, Zielinsky P, Binotto CN, Martins CN, Fonseca ESVB, Guimarães ICB, et al. Diretriz Brasileira de Cardiologia Fetal. Arq Bras Cardiol. 2019;112(05):600–648. Doi: 10.5935/abc.20190075

9 Mehari MA, Maeruf H, Robles CC, Woldemariam S, Adhena T, Mulugeta M, et al. Advanced maternal age pregnancy and its adverse obstetrical and perinatal outcomes in Ayder comprehensive specialized hospital, Northern Ethiopia, 2017: a comparative cross-sectional study. BMC Pregnancy Childbirth. 2020;20(01): 60. Doi: 10.1186/s12884-020-2740-6

10 Best KE, Rankin J. Is advanced maternal age a risk factor for congenital heart disease? Birth Defects Res A Clin Mol Teratol. 2016;106(06):461–467. Doi: 10.1002/bdra.23507

11 Rocha LA, Araujo Júnior E, Rolo LC, Barros FSB, Silva KP, Leslie ATFS, et al. Prenatal detection of congenital heart diseases: one-year survey performing a screening protocol in a single reference center in Brazil. Cardiol Res Pract. 2014;2014:175635. Doi: 10.1155/2014/175635

12 Stümpflen I, Stümpflen A, Wimmer M, Bernaschek G. Effect of detailed fetal echocardiography as part of routine prenatal ultrasonographic screening on detection of congenital heart disease. Lancet. 1996;348(9031):854–857. Doi: 10.1016/S0140-6736(96)04069-X

13 Persico N, Moratalla J, Lombardi CM, Zidere V, Allan L, Nicolaides KH. Fetal echocardiography at 11-13 weeks by transabdominal high-frequency ultrasound. Ultrasound Obstet Gynecol. 2011;37 (03):296–301. Doi: 10.1002/uog.8934

14 Hagemann LL, Zielinsky P. Rastreamento populacional de anormalidades cardíacas fetais por ecocardiografia pré-natal em gestações de baixo risco no município de Porto Alegre. Arq Bras Cardiol. 2004; 82(04):313–319. Doi: 10.1590/S0066-782X2004000400003

15 Nayak K, Chandra G S N, Shetty R, Narayan PK. Evaluation of fetal echocardiography as a routine antenatal screening tool for detection of congenital heart disease. Cardiovasc Diagn Ther. 2016;6 (01):44–49. Doi: 10.3978/j.issn.2223-3652.2015.12.01

16 Perri T, Cohen-Sacher B, Hod M, Berant M, Meizner I, Bar J. Risk factors for cardiac malformations detected by fetal echocardiography in a tertiary center. J Matern Fetal Neonatal Med. 2005;17 (02):123–128. Doi: 10.1080/14767050500043293

17 Ozkutlu S, Akça T, Kafali G, Beksaç S. The results of fetal echocardiography in a tertiary center and comparison of low- and high-risk pregnancies for fetal congenital heart defects. Anadolu Kardiyol Derg. 2010;10(03):263–269. Doi: 10.5152/akd.2010.068

18 Meyer-Wittkopf M, Cooper S, Sholler G. Correlation between fetal cardiac diagnosis by obstetric and pediatric cardiologist sonographers and comparison with postnatal findings. Ultrasound Obstet Gynecol. 2001;17(05):392–397. Doi: 10.1046/j.1469-0705.2001.00381.x

19 Friedberg MK, Silverman NH. Changing indications for fetal echocardiography in a University Center population. Prenat Diagn. 2004;24(10):781–786. Doi: 10.1002/pd.981

20 Sainz JA, Zurita MJ, Guillen I, Borrero C, García-Mejido J, Almeida C, et al. [Prenatal screening of congenital heart defects in population at low risk of congenital defects. A reality today]. An Pediatr (Barc). 2015;82(01):27–34

21 Dervisoglu P, Kosecik M, Kumbasar S. Effects of gestational and pregestational diabetes mellitus on the foetal heart: a cross-sectional study. J Obstet Gynaecol. 2018;38(03):408–412. Doi: 10.1080/01443615.2017.1410536

22 Appiah D, Schreiner PJ, Gunderson EP, Konety SH, Jacobs DJ Jr Nwabuo CC, et al. Association of gestational diabetes mellitus with left ventricular structure and function: the CARDIA Study. Diabetes Care. 2016;39(03):400–407. Doi: 10.2337/dc15-1759

23 Hernandez-Andrade E, Patwardhan M, Cruz-Lemini M, Luewan S. Early evaluation of the fetal heart. Fetal Diagn Ther. 2017;42(03): 161–173. Doi: 10.1159/000477564

24 Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol. 2003;3:21. Doi: 10.1186/1471-2288-3:21-33

25 Prefeitura Municipal do Rio de Janeiro. Secretaria Municipal de Saúde Coordenação de Análise da Situação de Saúde. Indicadores de Saúde de Residentes no Município do Rio de Janeiro, 2010–2019 [Internet]. 2010 [cited 2020 Jan 12]. Available from: http://www.rio.rj.gov.br/dlstatic/10112/7629558/4258614/IndicadoresNascimentoeMortalidade2010_2019_MRJ_06_09_19.pdf

Physical Performance Regarding Handgrip Strength in Women with Polycystic Ovary Syndrome

Desempenho físico na força de preensão manual em mulheres com síndrome dos ovários policísticos

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Abstract

Objective The present study aimed to investigate the physical performance of handgrip strength (HGS) in women with polycystic ovary syndrome (PCOS).

Methods A case-control study that included 70 women with PCOS and 93 age-matched healthy women aged between 18 and 47 years with body mass index (BMI) between 18 Kg/m^2–39.9 Kg/m^2. The serum levels of total testosterone, androstenedione, insulin, estradiol, thyroid-stimulating hormone (TSH), prolactin, sex hormone-binding globulin (SHBG), and 17-hydroxyprogesterone (17-OHP) were measured. The free androgen index (FAI) and the homeostatic model assessment of insulin resistance (HOMA-IR) were calculated. The body composition regions of interest (ROIs) were assessed by dual-energy X-ray absorptiometry (DXA), and the handgrip strength (HGS) was evaluated for both the dominant and the non-dominant hands with a manual Sammons Preston (Bolingbrook, IL, US) bulb dynamometer.

Results Women with PCOS had high serum levels of total testosterone ($p < 0.01$), androstenedione ($p = 0.03$), and insulin ($p < 0.01$), as well as high FAI ($p < 0.01$) and HOMA-IR ($p = 0.01$) scores. Compared with the non-PCOS group, the PCOS group had greater total lean mass in the dominant hand ($p < 0.03$) and greater HGS in both the dominant and the non-dominant hands ($p < 0.01$). The HGS was correlated with lean mass ($p < 0.01$).

Keywords
- handgrip strength
- polycystic ovary syndrome
- body composition
- hyperandrogenism

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Conclusion Women with PCOS have greater HGS. This may be associated with age and BMI, and it may be related to lean mass. In addition, the dominance effect on muscle mass may influence the physical performance regarding HGS in women with PCOS.

Resumo

Objetivo O objetivo deste estudo foi avaliar a força de preensão manual (FPM) em mulheres com síndrome dos ovários policísticos (SOP).

Métodos Estudo de caso-controle que incluiu 70 mulheres com SOP e 93 mulheres saudáveis com idade entre 18 e 47 anos e índice de massa corporal (IMC) de 18 Kg/m^2 a 39.9 Kg/m^2. Foram dosados os níveis séricos de testosterona total, androstenediona, insulina, estradiol, hormônio estimulador da tireoide (HET), prolactina, globulina de ligação ao hormônio sexual (GLHS), e 17-hidroxiprogesterona (17-OHP). Foram calculados o índice de androgênio livre (IAL) e a avaliação do modelo homeostático da resistência à insulina (AMH-RI). As regiões de interesse (RIs) da composição corporal foram avaliadas por absorciometria de raios-x de dupla energia (ARDE), e a força de preensão manual (FPM) das mãos dominante e não dominante foi avaliada com um dinamômetro manual Sammons Preston (Bolingbrook, IL, EUA).

Resultados Mulheres com SOP apresentaram níveis séricos elevados de testosterona total ($p < 0.01$), androstenediona ($p = 0.03$), e insulina ($P < 0.01$), assim como valores altos no IAL ($p < 0.01$) e no AMH-RI ($p = 0.01$). Comparado ao grupo controle, o grupo SOP apresentou maior massa magra total na mão dominante ($p < 0.03$) e maior FPM em ambas as mãos ($p < 0.01$). A FPM foi correlacionada com a massa muscular magra ($p < 0.01$).

Conclusão Mulheres com SOP têm maior FPM, que pode estar associada à idade, ao IMC, e à massa magra. Além disso, o efeito de dominância na massa muscular pode influenciar o desempenho físico na força de preensão manual em mulheres com SOP.

Palavras-chave
- força de preensão manual
- síndrome dos ovários policísticos
- composição corporal
- hiperandrogenismo

Introduction

Polycystic ovary syndrome (PCOS) is a common hormonal disorder among women of reproductive age;[1] it is characterized by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries.[2] The hyperandrogenic manifestations of PCOS include dyslipidemia, insulin resistance, type-2 diabetes mellitus (DM2), obesity, cancer, infertility, and coronary heart diseases.[3] However, in almost every tissue, androgens play an essential role in many physiological processes, such as increases in protein synthesis, muscle function, and bone mineral density. Skeletal muscle is one of the main targets of androgens, which can enhance lean muscle mass and strength.[4]

Handgrip strength (HGS) is a noninvasive measurement of the maximum static force that a hand can squeeze using a dynamometer.[5] It has been employed to predict overall body strength and functional performance in different groups of individuals, as well as to collect information regarding nutritional status, muscle mass, physical function, and health status.[6–8] A recent study[9] showed that lower relative HGS is significantly associated with a higher prevalence of metabolic syndrome in adults, indicating its long-term health implications through life.

Both HGS and skeletal muscle strength are affected by demographic data and socioeconomic variables, such as age, gender, income, and employment. Lifestyle and health behaviors, and health status or comorbidities,[10] as well as several physical factors, such as muscle mass, body mass index (BMI),[7] hand dimensions,[11] and androgens[12] are also relevant. Few studies[13,14] have investigated HGS in women with PCOS, and the results are conflicting.

We hypothesized that some phenotypic characteristics were related to HGS in women with PCOS. Therefore, the present study aimed to investigate HGS in women with and without PCOS, as well as the relationship between the physical performance of maximum voluntary strength of the hand and certain lean mass measurements.

Methods

Experimental Approach to the Problem

Through a secondary analysis of a case-control study, the present study sought to determine if the HGS is different ni women with PCOS and women with regular menstrual cycles. The HGS was initially analyzed for all women included in the study, and then it was paired by BMI. Additionally, through a statistical model, we sought to identify independent HGS determinants. Finally, we investigated the relationships between HGS and lean mass in the dominant and non-dominant hands. The participants were screened clinically and biochemically for enrolment into the PCOS group and the non-PCOS control group. The Review Board of the hospital of

Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (FMRP-USP), Brazil, approved the study (under process number 13475/2009). All of the ongoing and related trials have been registered at the Brazilian Clinical Trials Registry (ReBec) RBR-7p23c3.

Subjects

Our sample consisted of 170 women in reproductive age, aged between 18 and 37 years, with normal (18 Kg/m^2 to 24.9 Kg/m^2), overweight (25 Kg/m^2 to 29.9 Kg/m^2), or obesity ($>$ 30 Kg/m^2) BMIs according to the World Health Organization (WHO), and who had not engaged in regular and systematic physical exercise. These women were divided into 2 groups: the PCOS ($n = 73$) and the non-PCOS ($n = 97$) control group. They were all recruited from February 2010 to December 2013 as previously described.[13] Women with PCOS were selected at the outpatient clinics of the Sector of Human Reproduction of the Department of Gynecology and Obstetrics of FMRP-USP. The control group was recruited among women who went for routine gynecological examinations at the University Hospital and Basic Health Clinic and through public advertisements in the local newspaper and on regional television. The participants underwent transvaginal pelvic ultrasonography examinations with a Voluson 730 Expert instrument (GE Medical Systems, Zipf, Austria) to evaluate the presence of polycystic ovaries. To diagnose PCOS, peripheral blood samples were collected, and thyroid-stimulating hormone (TSH), 17-hydroxyprogesterone (17-OHP), prolactin, and testosterone concentrations were measured. Based on the results, the participants were assigned to the PCOS or non-PCOS groups. The diagnosis of PCOS was based on the presence of at least two of the following three features: chronic anovulation, hyperandrogenism (clinical or biochemical), and polycystic ovaries revealed by ultrasonography. According to the Rotterdam[2] diagnostic criteria, it is possible to identify the composition of four PCOS phenotypes: A – oligo-ovulation or anovulation + clinical and/or biochemical hyperandrogenism + polycystic ovaries; B – oligo-ovulation or anovulation + clinical and/or biochemical hyperandrogenism; C – clinical and/or biochemical hyperandrogenism + polycystic ovaries; and D – oligo-ovulation or anovulation + polycystic ovaries. Women with congenital non-classic adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia, or Cushing syndrome were excluded from the study. The non-PCOS group consisted of women with regular menstrual cycles of 24 to 32 days. Individuals were excluded if they had systemic diseases, used hormonal contraceptives, smoked, or were pregnant. The women were selected regardless of race, social class, or parity. All the selected women provided a written informed consent before they were included. The baseline characteristics included age, height, weight, and BMI, which was calculated as the ratio between the weight and the height squared.

Biochemical Measurements

The serum levels of testosterone, androstenedione, Dehydroepiandrosterone sulfate (DHEAS), and 17-OHP were measured by radioimmunoassay (Immulite1000 Immunoassay System, Siemens, Munich, Germany). Glucose levels were assessed by the glucose oxidase method. Insulin, estradiol (E2), TSH, prolactin, and sex hormone-binding globulin (SHBG) levels were assessed by chemiluminescence (IMMULITE 2000 Immunoassay System; Siemens). The free androgen index (FAI) was determined using the following equation: total testosterone (T) (nmol/L)/SHBG (nmol/L) $\times$ 100;[15] and insulin resistance (IR) was quantified using the homeostatic model assessment of insulin resistance (HOMA-IR) ([(fasting glycemia in mg/dL x 0.05551) x fasting insulin in mU/mL]/ 22.5).[16]

Body Composition

Body composition was assessed by whole-body scan with dual-energy X-ray absorptiometry (DXA) (Hologic 4500 device, QDR Discovery Series, Hologic, Waltham, MA). The analysis was performed using the Hologic Discovery Wi software, version 13.0:5. The examination was conducted by experts at Centro de Ciências das Imagens e Física Médica (CCIFM) of FMRP-USP, following the recommendations of the International Society for Clinical Densitometry (ISCD). The regions of interest (ROIs) for the assessment were total lean mass, distribution of lean mass in the left and right arms, lean mass indices (lean mass [Kg]/height^2 [m^2]), and appendicular lean mass (appendicular lean mass [Kg]/height^2 [m^2]).

Handgrip Strength (HGS)

The HGS test of the upper limb or upper extremity was conducted with a manual Sammons Preston (Bolingbrook, IL, US) bulb dynamometer calibrated in pounds per square inch, with measurements ranging from 10 psi to 30 psi. The HGS was measured three times per hand. One-minute intervals were allowed between the measurements, and the maximum value per hand was used for the analysis.[17] The same investigator evaluated all the patients. Hand dominance was ascertained by asking each subject which hand they used to perform well-learned skills such as writing.[18]

Statistical Analysis

All statistical analyses were performed using the PROC MIXED method of the Statistical Analysis System (SAS) software (SAS Institute Inc., Cary, NC, US) , version 9.4. The Student *t*-test was used to compare the mean variables of both groups independently, and the data are presented as mean $\pm$ standard deviation (SD). To identify the determinant variables for HGS, a multiple linear regression analysis was performed. Appropriately, group, age, BMI, the serum levels of testosterone and of androstenedione, as well as the interactions of these androgens, were considered the independent variables. The model fit was checked considering a graphical analysis of the residuals. Pearson r was used to determine the correlations between HGS and ROIs in the dominant and non-dominant hands. The level of significance was set at 5% ($p < 0.05$) in a two-tailed test.

Results

Of the 170 women selected for the present study, 3 women in the PCOS group and 3 in the non-PCOS group were excluded

Table 1 Laboratory parameters and body composition of the study sample

Variables	PCOS ($N = 73$)	non-PCOS ($N = 97$)	*p*-value
	[median (SD)]	[median (SD)]	
Estradiol (pg/mL)	115.3 (85.0)	120.3 (75.5)	0.71
Testosterone (ng/dL)	91.3 (36.4)	70.6 (28.7)	< 0.01
Free testosterone (nmol/L)	3.1 (1.2)	2.4 (0.9)	< 0.01
Androstenedione (ng/dL)	114.1 (34.7)	100.6 (42.1)	0.03
SHBG (nmol/L)	53.3 (38.5)	62.6 (36.5)	0.14
FAI	8.6 (5.7)	5.3 (4.0)	< 0.01
Glycemia (mg/dL)	102.0 (20.5)	97.5 (18.0)	0.15
Insulin (μIU/mL)	10.8 (13.6)	5.8 (5.1)	< 0.01
HOMA-IR	3.0 (4.3)	1.3 (1.3)	0.01
Lean mass – dominant arm (g)	2,079.5 (493.8)	1,916.8 (425.5)	0.03
Lean mass – non-dominat arm (g)	1,911.7 (557.1)	1,823.8 (392.4)	0.21
Total lean mass (g)	41,856.0 (7405.8)	36,589 (6,602.5)	0.04
Lean mass/height^2 (Kg/m^2)	16.9 (2.8)	16.1 (2.4)	0.09
Appen. lean mass/height^2 (Kg/m^2)	7.1 (1.3)	6.9 (1.1)	0.35

Abbreviations: Appen., appendicular; FAI, free androgen index; HOMA-IR, homeostatic model assessment-insulin resistance; PCOS, polycystic ovary syndrome; SD, standard deviation; SHBG, sex hormone-binding globulin.

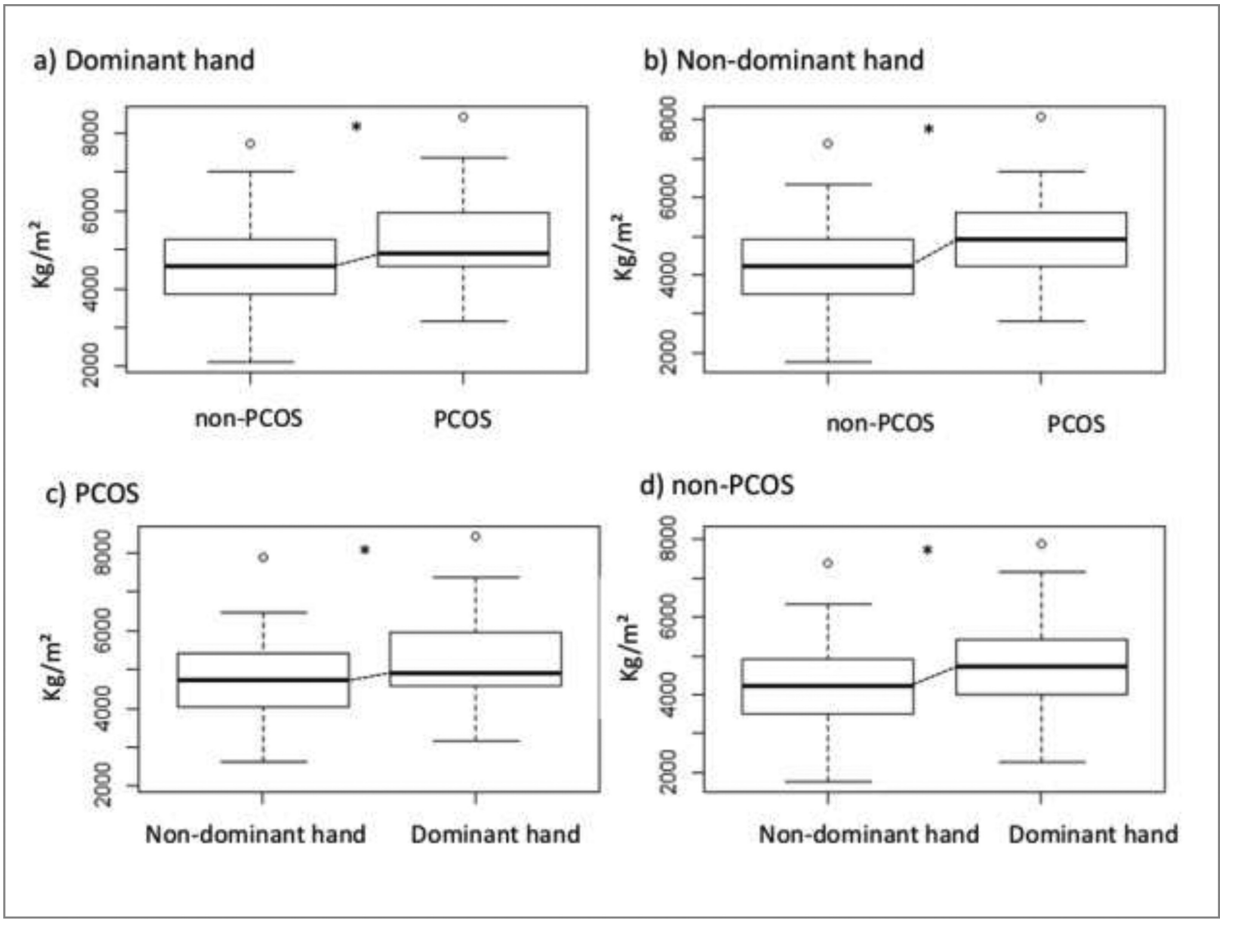

Fig. 1 Grip strength of the dominant and non-dominant hands regarding both study groups. $^*p < 0.01$.

Table 2 Handgrip strength and body composition regarding normal weight, overweight, and obese women in the study groups

	Normal weight		Overweight		Obese	
Variables	PCOS ($n = 22$) [median (SD)]	non-PCOS ($n = 40$) [median (SD)]	PCOS ($n = 21$) [median (SD)]	non-PCOS ($n = 23$) [median (SD)]	PCOS ($n = 27$) [median (SD)]	non-PCOS ($n = 31$) [median (SD)]
HGS – dominant hand	4,469.4 (840.3)	4,569.8 (845.8)	5,457.0 (1,010.4)*	4,486.1 (955.6)	5,551.7 (1,004.7)*	4,817.2 (1,084.8)
HGS – non-dominant hand	4,268.5 (970.9)	4,200.3 (802.2)	4,988.3 (920.8)*	4,335.5 (1135.4)	5,236.5 (986.9)*	4,439.6 (1,059.7)
Lean mass – dominant arm	1,601.2 (214.7)	1,646.7 (244.5)	1,996.1 (286.3)	1,895.4 (305.9)	2,508.2 (386.7)	2,334.1 (386.7)
Lean mass – non-dominat arm	1,510.7 (232.5)	1,590.2 (220.3)	1,816.5 (242.1)	1,808.9 (322.6)	2,289.5 (409.2)	2,182.1 (399.1)
Total lean mass	34,649.7 (3,486.5)	34,525.7 (3,120.6)	39,760.8 (3,187.6)	39,655.0 (3,647.0)	48,930.5 (5,188.7)	4,7017.6 (5,213.9)
Lean mass/height^2	13.9 (1.1)	14.1 (1.1)	16.2 (1.1)	15.9 (1.2)	20.0 (1.5)*	18.8 (1.8)
Appen. lean mass /height^2	5.7 (0.6)	6.0 (0.6)	6.9 (0.6)	6.8 (0.6)	8.6 (0.7)	8.2 (0.8)

Abbreviations: Appen, appendicular; HGS, handgrip strength; PCOS, polycystic ovary syndrome; SD, standard deviation.
Note: *$p < 0.05$.

because they did not adhere to the study. Therefore, in the end, 94 women with regular menstrual cycles and 70 women with PCOS were investigated. According to the 4 PCOS phenotypes defined by the Rotterdam criteria, phenotype A was present in 34 women, phenotype B, in 5 women, phenotype C, in 19 women, and phenotype D, in 12 women. Both study groups had similar age (PCOS: 28.05 ± 5.1 years; non-PCOS: 29.5 ± 5.0 years; $p < 0.12$), height (PCOS: 160.2 ± 0.05 cm; non-PCOS: 160.1 ± 0.05 cm; $p < 0.20$), and weight (PCOS: 75.4 ± 17.6 Kg; non-PCOS: 70.4 ± 16.3 Kg; $p < 0.05$). However, the BMI was higher in the PCOS group (29.2 ± 6.5 Kg/m^2) compared with the non-PCOS group (26.9 ± 5.9 Kg/m^2) ($p < 0.01$). Women with PCOS had increased testosterone and insulin levels, as well as higher FAI and HOMA-IR values ($p < 0.01$, for all) compared with the control group (►**Table 1**). Concerning body composition, the total lean mass was higher in the case than in the control group (►**Table 1**).

Except for nine participants in the PCOS group and 11 participants in the non-PCOS group, the dominant hand was the right hand. None of the participants had tremor, dysmetria, or dysdiadochokinesia. In the PCOS group, the total lean mass was higher in the dominant hand ($p < 0.03$) compared with the non-PCOS group (►**Table 1**). ►**Fig. 1** depicts the HGS statistical analysis for both groups, in the dominant and non-dominant hands.

A total of 62 women (22 PCOS and 40 non-PCOS) had normal BMIs (18 Kg/m^2 to 24.9 Kg/m^2), whereas 44 women (21 PCOS and 23 non-PCOS) were overweight (25 Kg/m^{2}to 29.9 Kg/m^2), and 58 women (27 PCOS and 31 non-PCOS) were obese (> 30 Kg/m^2). By dividing the number of women with PCOS based on the BMI, we found that overweight and obese women with PCOS had higher HGS when compared with non-PCOS women with similar BMI ($p = 0.01$; $p < 0.01$ respectively), and that obese women with PCOS had higher lean mass/height^2 as compared with non-PCOS obese women ($p = 0.02$) (►**Table 2**).

In the statistical modelling herein considered, for the whole sample, BMI and the serum level of androstenedione were predictors of HGS in both hands, but not the serum level of testosterone and the androgen interactions (testosterone and androstenedione) (►**Table 3**). According to the outcomes of the Pearson correlation tests, in the PCOS group, the HGS correlated positively with the ROIs ($p < 0.01$) and lean mass indices ($p < 0.01$) in both hands (►**Fig. 2**). In the non-PCOS group, there was a moderate positive correlation between HGS and lean mass in the dominant hand only ($r = 0.26$; $p = 0.02$).

Table 3 Effects of BMI, age, testosterone, androstenedione, and androgen interactions on handgrip strength

Variable	Handgrip strength									
	Dominant hand					Non-dominant hand				
	Sum of square	df	Mean square	F value	Pr > F	Sum of square	df	Mean square	F value	Pr > F
Group	7,035,308.6	1	7,035,308.6	7.81	*< 0.01*	6,110,106.1	1	6,110,106.1	7.25	*< 0.01*
Body mass index (Kg/m^2)	6,350,647.2	1	6,350,647.2	7.05	*< 0.01*	9,090,583.8	1	9,090,583.8	10.79	*< 0.01*
Age (years)	2,269,183.0	1	2,269,183.0	2.52	0.11	603,112.5	1	603,112.5	0.72	0.40
Testosterone (ng/dL)	79,826.2	1	79,826.2	0.09	0.76	281,617.1	1	281,617.1	0.33	0.56
Androstenedione (ng/dL)	3,538,715.9	1	3,538,715.9	3.93	*0.04*	6,899,149.3	1	6,899,149.3	8.19	*< 0.01*
Testosterone* Androstenedione	1,308,819.3	1	1,308,819.3	1.45	0.23	1,632,776.2	1	1,632,776.2	1.94	0.16

Note: *$p < 0.05$.
Pr > F, *p*-value associated with the F statistic; df, degrees of freedom.

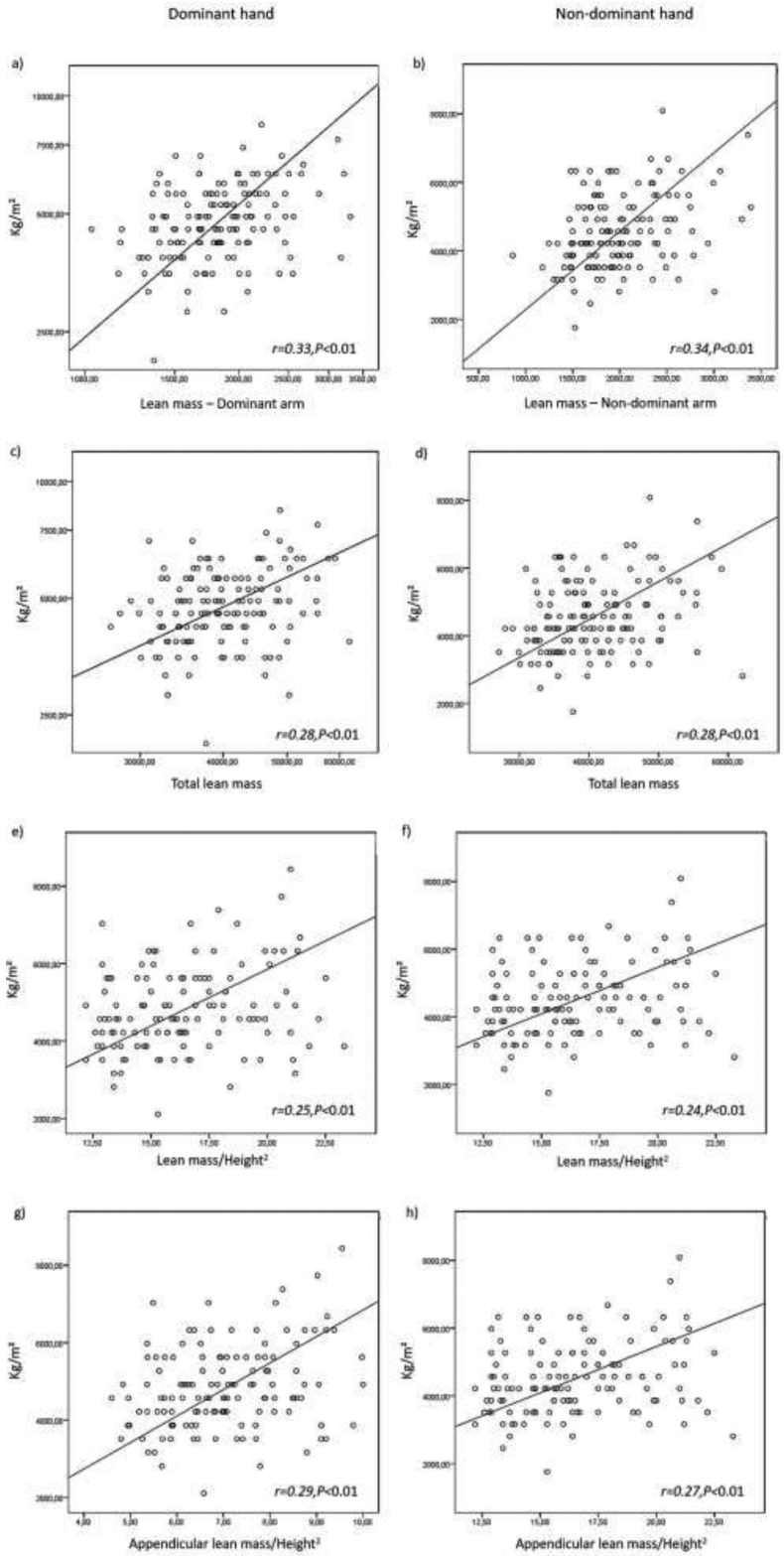

Fig. 2 Relationship between dominant and non-dominant handgrip strength with lean mass indicators in the case group. $^{*}p < 0.01$.

Discussion

In the present study, we have investigated the HGS of the dominant and non-dominant hands, and lean mass indicators in a group of women with PCOS versus a group of healthy women. Additionally, we have explored, in the whole sample, the influence of age, BMI, and hormonal status on muscle strength, as well as the correlation between muscle strength and lean mass indicators in women with PCOS. We have observed, in agreement with a previous study,[19] that the group of women with PCOS in the present study was characterized by having higher levels of

testosterone, androstenedione, and insulin, as well as higher FAI and HOMA-IR values.

In the present study, we concluded that women with PCOS have greater HGS in both hands, and that both study groups havegreater strength in the dominant hand compared with the non-dominant hand. Few studies[20,21] have analyzed muscle strength in women with PCOS with or without physical exercise. In relation to HGS, Soyupek et al.[14] showed that muscle strength did not differ between women with PCOS and age-matched healthy women. A previous study[13] by our group showed that a small sample of women with PCOS had better performance in the dominant hand only,[22] and that excess androgens in cases of PCOS, especially androstenedione, as well as the BMI, could explain the increased muscle strength. In the present study, we have observed that age, BMI and androstenedione, but not testosterone and the interaction of these androgens, were associated with HGS for the whole study sample.

Other studies suggested that age, BMI and sex account for the variances in HGS. Perna et al.[6] observed that the grip strength increased linearly in children and in a quadratic fashion among adults of both genders, and that it peaked in the age group between 30 and 39 years for both men and women, with a gradual subsequent decline. By dividing the patients into subgroups according to BMI, the difference in HGS among women with and without PCOS only occurred when obesity or overweight was present; this difference was not observed among PCOS women with normal weight. Additionally, we have observed that obese women with PCOS have significantly higher lean mass compared with obese non-PCOS controls. The high BMI might be a result of the higher percentage of skeletal muscle mass, which can largely be responsible for body heaviness, but not the percentage of fat mass, thereby resulting in greater HGS.[23] On the other hand, another study[24] verified a weak relationship between HGS and BMI, and that overall muscle function was impaired in obese individuals as compared with their non-obese counterparts, which could explain why adiposity in the obese may be associated with a lower skeletal muscle contractile capacity.

A study[7] also showed different HGS values between genders separated by BMI (low, medium, and high), and evidenced that gender was the most significant factor affecting this variable. These differences between genders may be consistent from childhood to adolescence, between young men and young women, and in different age groups.[6] The gender-related differences in strength may be attributed to the women's tendency to have lower lean body mass,[25] and the upper-body muscularity of men.[26] According to Isen et al.,[27] this gender dimorphism in physical strength between men and women overcomes the differences between the genders in terms of overall body mass and height, and thus likely reflects the higher levels of androgenic hormones.[28] These hormones promote an intense physiological effect on body composition (indeed, testosterone is considered a physiological marker of the body's anabolic state and of muscle strength).[4] Recent studies have shown this association. Scharff et al.[8] observed that after one year of hormonal treatment, grip strength decreased in transwomen (treated with the anti-androgen cyproterone acetate in combination with estradiol valerate), and increased in transmen (treated with testosterone). In transmen only, the change in grip strength was associated with the change in lean body mass. Chiu et al.[12] showed, in a study with a varied sample composed of male and female participants (7,064 people), a positive correlation between serum testosterone levels and grip strength; they also showed that high testosterone levels were negatively associated with low muscle strength. Our results confirmed that lean mass is higher in women with PCOS, and that they had higher androgen levels; however, considering the whole sample, only androstenedione, but not testosterone, as well as the interaction of these androgens, was associated to HGS.

Regarding BMI, obese women with PCOS have significantly higher lean mass. Several studies have shown increased lean body mass in PCOS[29] and classic PCOS,[30] as well as higher lean mass in obese or overweight women with or without PCOS.[31] This difference is reportedly due to fat parameters and insulin,[30] but not to androgens.[29,31] Additionally, the present study showed that in PCOS women, the HGS is positively and moderately correlated with lean mass, more precisely with all the ROIs and lean mass indices. Consistent with these results, other studies showed a site-specific relationship between HGS and muscle mass. Taaffe et al.[32] found that upper-extremity muscle mass had the strongest relationship with HGS, followed by total body muscle mass. Shin et al.[33] demonstrated a positive correlation of HGS with total and appendicular lean mass when controlling for age in postmenopausal women. Several studies support the notion that HGS is positively correlated with muscle mass, especially regarding the upper extremity. Moreover, our results revealed that muscle mass influences HGS in the dominant arm in both groups. There are previous studies that found gain in muscle strength in the dominant arm.[34] The dominance effect on muscle mass has also been demonstrated to be closely related to the muscle function. Dominance naturally influences muscle mass because the dominant arm is physically more active. However, one must be bear in mind that muscle strength results from a combination of the amount of muscle mass and muscle quality.[35]

Some limitations of the present study need to be considered. Although we included volunteers who did not perform regular supervised physical activity, we do not know the participants' exact exercise capacity and muscle endurance, and we have not analyzed the levels of habitual physical activity related to work and to leisure time. In this sense, the present study lacked objective measurements of certain sociodemographic characteristics and socioeconomic status, which might or might not have been important for our final model. In addition, we have not measured or evaluated hand dimensions and other specific anthropometric measurements, such as the forearm. This may have confounded the assessment of muscle performance. Moreover, differences in protocol and HGS measurements used in different studies may affect the precision and reproducibility of the HGS measurements among different study populations.

Conclusion

Our findings indicate that, in comparison to healthy controls, women with PCOS have better physical performance with greater HGS, which may be associated with lean muscle mass. In addition, the dominance effect on muscle mass may influence the physical performance. We also suggest that age and BMI, but not hyperandrogenism, may have important implications in muscle strength. The findings extend the relationships between the physical characteristics and hormonal changes in this syndrome, and provide information about the increased functional capacity in these women, which is usually reduced in individuals with metabolic disorders. It is known that PCOS directly affects body composition, as well as endocrine, metabolic, and cardiovascular system parameters. The simple monitoring of HGS may be a promising tool to optimize, through physical and functional assessments, the multidisciplinary care and management of PCOS. Moreover, further investigations may be beneficial for a better understanding of how lean muscle mass may prevent decline in physical performance among women in reproductive age.

Contributions

All authors were involved in the design and interpretation of the analyses; they contributed to the writing, and read and approved the final manuscript.

Conflicts of Interest

The authors have no conflict of interests to declare.

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References

1 Ding T, Hardiman PJ, Petersen I, Wang FF, Qu F, Baio G. The prevalence of polycystic ovary syndrome in reproductive-aged women of different ethnicity: a systematic review and meta-analysis. Oncotarget. 2017;8(56):96351–96358. Doi: 10.18632/oncotarget.19180
2 Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(01):19–25. Doi: 10.1016/j.fertnstert.2003.10.004
3 Palomba S, Santagni S, Falbo A, La Sala GB. Complications and challenges associated with polycystic ovary syndrome: current perspectives. Int J Womens Health. 2015;7:745–763. Doi: 10.2147/IJWH.S70314
4 Bhasin S, Bross R, Storer TW, Casaburi R. Androgens and muscle. In: Nieschlag E, Behre HM, eds. Testosterone: action, deficiency, substitution. 2nd ed. Berlin: Springer; 1998:209–227
5 Kim CR, Jeon YJ, Kim MC, Jeong T, Koo WR. Reference values for hand grip strength in the South Korean population. PLoS One. 2018;13(04):e0195485. Doi: 10.1371/journal.pone.0195485
6 Perna FM, Coa K, Troiano RP, et al. Muscular grip strength estimates of the U.S. population from the national health and nutrition examination survey 2011–2012. J Strength Cond Res. 2016;30(03):867–874. Doi: 10.1519/JSC.0000000000001104
7 Liao KH. Hand grip strength in low, medium, and high body mass index males and females. Middle East J Rehabil Health.. 2016;3(01):e53229. Doi: 10.17795/mejrh-33860
8 Scharff M, Wiepjes CM, Klaver M, Schreiner T, T'Sjoen G, den Heijer M. Change in grip strength in trans people and its association with lean body mass and bone density. Endocr Connect. 2019;8(07):1020–1028. Doi: 10.1530/EC-19-0196
9 Byeon JY, Lee MK, Yu MS, et al. Lower relative handgrip strength is significantly associated with a higher prevalence of the metabolic syndrome in adults. Metab Syndr Relat Disord. 2019;17(05):280–288. Doi: 10.1089/met.2018.0111
10 Yorke AM, Curtis AB, Shoemaker M, Vangsnes E. Grip strength values stratified by age, gender, and chronic disease status in adults aged 50 years and older. J Geriatr Phys Ther. 2015;38(03):115–121. Doi: 10.1519/JPT.0000000000000037
11 Alahmari KA, Kakaraparthi VN, Reddy RS, Silvian PS, Ahmad I, Rengaramanujam K. Percentage difference of hand dimensions and their correlation with hand grip and pinch strength among schoolchildren in Saudi Arabia. Niger J Clin Pract. 2019;22(10):1356–1364. Doi: 10.4103/njcp.njcp_121_19
12 Chiu HT, Shih MT, Chen WL. Examining the association between grip strength and testosterone. Aging Male. 2019:1–8. Doi: 10.1080/13685538.2019.1632282 [ahead of print]
13 Kogure GS, Silva RC, Picchi Ramos FK, et al. Women with polycystic ovary syndrome have greater muscle strength irrespective of body composition. Gynecol Endocrinol. 2015;31(03):237–242. Doi: 10.3109/09513590.2014.982083
14 Soyupek F, Guney M, Eris S, Cerci S, Yildiz S, Mungan T. Evaluation of hand functions in women with polycystic ovary syndrome. Gynecol Endocrinol. 2008;24(10):571–575. Doi: 10.1080/09513590802288218
15 Cascella T, Palomba S, Tauchmanovà L, et al. Serum aldosterone concentration and cardiovascular risk in women with polycystic ovarian syndrome. J Clin Endocrinol Metab. 2006;91(11):4395–4400. Doi: 10.1210/jc.2006-0399
16 Geloneze B, Repetto EM, Geloneze SR, Tambascia MA, Ermetice MN. The threshold value for insulin resistance (HOMA-IR) in an admixtured population IR in the Brazilian Metabolic Syndrome Study. Diabetes Res Clin Pract. 2006;72(02):219–220. Doi: 10.1016/j.diabres.2005.10.017
17 Heyward VH, Gibson AL. Advanced fitness assessment and exercise prescription. 7th ed. Champaign: Human Kinetics; 2014
18 Abe T, Loenneke JP. Handgrip strength dominance is associated with difference in forearm muscle size. J Phys Ther Sci. 2015;27(07):2147–2149. Doi: 10.1589/jpts.27.2147
19 Stepto NK, Cassar S, Joham AE, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulaemic clamp. Hum Reprod. 2013;28(03):777–784. Doi: 10.1093/humrep/des463
20 Thomson RL, Buckley JD, Moran LJ, et al. Comparison of aerobic exercise capacity and muscle strength in overweight women with and without polycystic ovary syndrome. BJOG. 2009;116(09):1242–1250. Doi: 10.1111/j.1471-0528.2009.02177.x
21 Kogure GS, Silva RC, Miranda-Furtado CL, et al. Hyperandrogenism enhances muscle strength after progressive resistance training, independent of body composition, in women with polycystic ovary syndrome. J Strength Cond Res. 2018;32(09):2642–2651. Doi: 10.1519/JSC.0000000000002714
22 Kogure GS, Picicki FK, Vieira CS, Martins WdeP, dos Reis RM. [Analysis of muscle strength and body composition of women with polycystic ovary syndrome]. Rev Bras Ginecol Obstet. 2012;34(07):316–322. Doi: 10.1590/S0100-72032012000700005
23 Adebisi H, Obaseki CO. Interdependence of body mass index with handgrip strength and endurance among apparently healthy teenagers. Turkish J Kinesiol.. 2018;4(01):1–7. Doi: 10.31459/turkjkin.393476

24 Hulens M, Vansant G, Lysens R, Claessens AL, Muls E, Brumagne S. Study of differences in peripheral muscle strength of lean versus obese women: an allometric approach. Int J Obes Relat Metab Disord. 2001;25(05):676–681. Doi: 10.1038/sj.ijo.0801560
25 Sartorio A, Lafortuna CL, Pogliaghi S, Trecate L. The impact of gender, body dimension and body composition on hand-grip strength in healthy children. J Endocrinol Invest. 2002;25(05): 431–435. Doi: 10.1007/BF03344033
26 Lassek WD, Gaulin SJC. Costs and benefits of fat-free muscle mass in men: relationship to mating success, dietary requirements, and native immunity. Evol Hum Behav.. 2009;30(05):322–8. Doi: 10.1016/j.evolhumbehav.2009.04.002
27 Isen J, McGue M, Iacono W. Genetic influences on the development of grip strength in adolescence. Am J Phys Anthropol. 2014; 154(02):189–200. Doi: 10.1002/ajpa.22492
28 Page ST, Amory JK, Bowman FDB, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab. 2005;90(03):1502–1510. Doi: 10.1210/jc.2004-1933
29 Mario FM, do Amarante F, Toscani MK, Spritzer PM. Lean muscle mass in classic or ovulatory PCOS: association with central obesity and insulin resistance. Exp Clin Endocrinol Diabetes. 2012;120(09):511–516. Doi: 10.1055/s-0032-1309006
30 Aydogdu A, Tasci I, Kucukerdonmez O, et al. Increase in subcutaneous adipose tissue and fat free mass in women with polycystic ovary syndrome is related to impaired insulin sensitivity. Gynecol Endocrinol. 2013;29(02):152–155. Doi: 10.3109/09513590.2012.708802
31 Carmina E, Guastella E, Longo RA, Rini GB, Lobo RA. Correlates of increased lean muscle mass in women with polycystic ovary syndrome. Eur J Endocrinol. 2009;161(04):583–589. Doi: 10.1530/EJE-09-0398
32 Taaffe DR, Cauley JA, Danielson M, et al. Race and sex effects on the association between muscle strength, soft tissue, and bone mineral density in healthy elders: the Health, Aging, and Body Composition Study. J Bone Miner Res. 2001;16(07):1343–1352. Doi: 10.1359/jbmr.2001.16.7.1343
33 Shin H, Liu PY, Panton LB, Ilich JZ. Physical performance in relation to body composition and bone mineral density in healthy, overweight, and obese postmenopausal women. J Geriatr Phys Ther. 2014;37(01):7–16. Doi: 10.1519/JPT.0b013e31828af203
34 Armstrong CA, Oldham JA. A comparison of dominant and non-dominant hand strengths. J Hand Surg [Br]. 1999;24(04): 421–425. Doi: 10.1054/jhsb.1999.0236
35 Barbat-Artigas S, Rolland Y, Vellas B, Aubertin-Leheudre M. Muscle quantity is not synonymous with muscle quality. J Am Med Dir Assoc. 2013;14(11):852.e1–852.e7. Doi: 10.1016/j.jamda.2013.06.003

Sociodemographic and Clinical-pathological Study of Molecular Subtitles of Breast Carcinoma in a Reference Unit of Maranhão

Estudo sociodemográfico e clínico-patológico de legendas moleculares de carcinoma de mama em uma unidade de referência do Maranhão

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Abstract

Objective To evaluate the distribution of the main sociodemographic and clinical-pathological characteristics in women with breast cancer according to the molecular profile by immunohistochemistry.

Methods A cross-sectional, retrospective, analytical and quantitative study was performed, with an analysis of 137 medical records from January 2015 to December 2018 of women attending the High Complexity in Oncology Unit of the city of Imperatriz, state of Maranhão, Brazil. The immunohistochemical profile of tumors based on the estrogen and progesterone receptor, Human Epidermal growth factor Receptor-type 2 (HER2) overexpression and Ki67 cell proliferation index was defined, from which six molecular subtypes were determined: luminal A, luminal B-HER2 negative, luminal B-HER2 positive, triple negative, overexpression of HER2 and inconclusive.

Results A total of 52.6% of the patients were postmenopausal, mean age 52.1 years old, brown (56.2%), had a schooling level $<$ 9 years (40%), staging $>$ IIB (52.6%) and 23.4% had metastasis. Invasive ductal carcinoma accounted for 84.7%, tumor size was 2 to 5 cm (48.9%), with lymph node involvement (56.2%), axillary lymphadenectomy in 67.2%, and mastectomy in 73.7% of the patients. The most frequent molecular subtype was the luminal B-HER2 negative (36.5%), and the luminal A subtype showed characteristics of better prognosis when compared with the others.

Conclusion It was concluded that in the association of molecular subtypes with sociodemographic and clinical-pathological characteristics, there were no statistically significant results obtained, except for complementary therapy, referring to hormone therapy, and there was a high index of metastasis at diagnosis, which was a worrying factor and indicative of failures in the screening and early diagnosis of this population.

Keywords
- breast neoplasms
- immunohistochemistry
- health profile
- oncology
- staging of neoplasms

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Resumo

Objetivo Avaliar a distribuição das principais características sociodemográficas e clínico-patológicas em mulheres com câncer de mama segundo o perfil molecular pela imunohistoquímica.

Métodos Estudo transversal, retrospectivo, analítico, descritivo e quantitativo, com análise de 137 prontuários do período de janeiro de 2015 a dezembro de 2018 de mulheres atendidas na Unidade de Assistência da Alta Complexidade em Oncologia da cidade de Imperatriz, MA, Brasil. Foi definido o perfil imunohistoquímico dos tumores baseado na avaliação dos receptores de estrogênio e progesterona, superexpressão de HER2 e índice de proliferação celular Ki67, de onde foram determinados seis subtipos moleculares: luminal A, luminal B-HER2 negativo, luminal B-HER2 positivo, triplo negativo, superexpressão de HER2 e inconclusivo.

Resultados Foi demonstrado que 52,6% das pacientes eram pós-menopausadas, com idade média de 52,1 anos, pardas (56,2%), tinham grau de escolaridade $<$ 9 anos (40%), estadiamento $>$ IIB (52,6%) e 23,4% tinham metástase. Carcinoma ductal invasivo representou 84,7%, o tamanho tumoral foi de 2 a 5 cm (48,9%), com comprometimento linfonodal (56,2%), com linfadenectomia axilar em 67,2% e mastectomia em 73,7% das pacientes. O subtipo molecular mais frequente foi o luminal B-HER2 negativo (36,5%), e o subtipo luminal A apresentou características de melhor prognóstico em relação aos demais.

Conclusão Concluiu-se que na associação dos subtipos moleculares com as características sociodemográficas e clínico-patológicas não se obteve resultados com significância estatística, exceto para terapia complementar, referente à hormonioterapia, e houve elevado índice de metástase ao diagnóstico, o que representou um fator preocupante e indicativo de falhas no rastreio e diagnóstico precoce dessa população.

Palavras-chave

- neoplasias da mama
- imunohistoquímica
- perfil de saúde
- oncologia
- estadiamento de neoplasias

Introduction

Breast cancer or breast carcinoma is an important public health problem due to its high incidence and mortality, in addition to being the major cause of cancer death in women worldwide.[1] It is the most common malignant disease among women, with an estimated 1,67 million new cases diagnosed worldwide each year.[2] In Brazil, 59,700 new cases of breast cancer are estimated for each year of the biennium 2018–-2019, with an estimated risk of 56.33 cases per 100,000 women. In the state of Maranhão, 720 new cases were estimated, 280 of which for the capital.[3]

Malignant breast neoplasm is not a single disease, since it comprises many biologically distinct entities, with different pathological characteristics and clinical implications.[4] The tumor heterogeneity of this pathology is a major challenge to be faced, since tumors with the same histological types, stages and degrees of differentiation may have different prognostic outcomes and responses to the instituted treatment.[5] Accumulated evidence suggests that this presentation can be justified by the complexity of this neoplasm and the arsenal of molecular changes that lead to different responses to treatment, and should receive different therapeutic strategies.[4,5]

Thus, the precise grouping of breast cancers into clinically relevant subtypes is of particular importance for therapeutic decision-making.[4] After studying several gene expression panels, five intrinsic breast carcinoma subtypes were identified that correlate with the prognosis: Luminal A, Luminal B Human Epidermal growth factor Receptor-type 2 (HER-2) negative, Luminal B HER-2 positive, HER2-enriched and triple-negative. Genomic evaluation is the gold standard for the classification of tumors in these subtypes, but it is complex and has a high cost, making it difficult to use in clinical practice. However, there is a great similarity between its outcomes and the ones provided by immunohistochemistry (IHC), through classic markers like estrogen receptor (ER), progesterone receptor (PR), and HER2. This makes IHC the most used exam for molecular classification, which in turn will guide the target therapies.[6,7]

Nowadays, the expression of ER, PR, HER2 and Ki67 (monoclonal antibody that measures cell growth fraction) receptors, along with the variable clinicopathological data, such as nodal involvement, tumor size, type, grade of tumor and resection margins are commonly used to choose the treatment and predict the prognosis of the disease.[5,7]

Considering the current implications in the therapeutic approach to breast cancer, the performance of studies that provide a better understanding of the distribution of the disease from its heterogeneities in women justifies the present research. Thereby, the objective is to evaluate the distribution of the main sociodemographic and clinical-pathological characteristics in women with breast cancer according to the molecular profile provided by IHC.

Methods

Cross-sectional study, retrospective, quantitative, descriptive and analytical, whose population was formed by all women diagnosed with breast cancer performed between January 2015 and December 2018 ($n = 152$), attended at the High Complexity Assistance Unit on Oncology (UNACON, in the Portuguese acronym), from the city of Imperatriz, state of Maranhão, Brazil. All medical records from patients who had ductal carcinoma in situ ($n = 2$); lobular carcinoma in situ ($n = 3$) and those with incomplete analysis of the immunohistochemical profile ($n = 10$) were excluded; therefore, 137 records were selected for the present study.

Data recruitment was performed through an active search in the medical records of the oncology file of the aforementioned reference center, whose collection of information from patients took place according to a script with a standardized form. The definition of the immunohistochemical profile of the tumors was performed based on the results of reports issued by pathological anatomy services, based on the evaluation of ER and PR, HER2-enriched and Ki67 cell proliferation index. According to the results obtained, six immunohistochemical subgroups were defined: luminal A (RE +, RP +, HER2-), luminal B-HER2 negative (RE+ and/or RP +, HER2-), luminal B-HER2 positive (RE+ and/or RP +, HER2 +), triple-negative or basal-like (RE-, RP-, HER2-), HER2-enriched (RE-, RP-, HER2 +) and Inconclusive (HER2 inconclusive after IHC testing and fluorescent in situ hybridization [FISH]). According to the 2013 St. Gallen Consensus, the Ki67 index is considered as low or negative when < 14% and as positive or high when equal or higher than this value,[6] this being 14% the cutoff value used for the present study.

Sociodemographic variables were analyzed, such as date of diagnosis; age at diagnosis (in years), categorized as ≤ 50 and > 50 years old (cutoff point validated as a marker for menopausal status)[8]; self-reported race; marital status; education level; place of residence; family history of cancer, smoking and drinking; and clinical-pathological characteristics: tumor size; histological type; lymphatic impairment; staging according to the TNM Classification of the American Joint Cancer Committee; presence of metastasis at diagnosis, type of surgery; axillary approach; and complementary therapy. The collected data were stored in a specific database created in Microsoft Excel version 2016 (Microsoft Corporation, Redmond, WA, USA). After checking for mistakes and inconsistencies, statistical analysis of the data was performed in IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA).[9,10]

Initially, descriptive analyzes were performed using relative and absolute frequencies of sociodemographic, clinical and pathological characteristics. To assess possible associations between variables, the chi-squared and Fisher-Freeman-Halton tests were used.[11] All tests were performed at 5% significance.

Research approved by the Ethics and Research Committee through Plataforma Brasil under Statement n°. 3.213.056.

Results

The analysis of the research results showed that the average age at diagnosis was 52.1 years old (standard deviation [SD] = 11.58). Considering the menopausal status, the study showed that 72 (52.6%) patients were diagnosed in the postmenopause; the predominant self-declared race was brown, with 77 patients (56.2%). As for the origin, 83 (60.6%) were from other cities in Maranhão, and Imperatriz had 51 patients (37.2%), and according to marital status, 85 (62%) were married or cohabited. Regarding schooling, 54 (40%) patients had < 9 years of schooling. As there is no information related to smoking, alcohol consumption (current or past) and family history of cancer in all medical records, these data were analyzed in 120 patients. Smoking was denied by 85 (70.8%) patients, alcohol consumption was denied in 79 (65.8%) patients, and the family history of cancer was positive in 62 (51.7%) women. The distribution of the main sociodemographic and clinical characteristics is described in ►**Table 1**.

The pathological characteristics, as described in ►**Table 2**, showed that the prevalent molecular subtype was luminal B-HER2 negative with 50 patients (36.5%). Regarding the type of surgery, 101 (73.7%) patients underwent mastectomy and, according to the histological type, 116 (84.7%) had invasive ductal carcinoma, 7 (5.1%) had another histological type, of which 5 (3.6%) were mucinous carcinoma, 1 (0.7%) invasive clear cell carcinoma and 1 (0.7%) invasive papillary carcinoma.

According to the TNM staging, 72 (52.6%) patients were diagnosed in stage > IIB (advanced).[9] Regarding the tumor size, there was a predominance of tumor between 2 to 5 cm in 67 (48.9%) patients. For lymph node impairment, 77 (56.2%) patients were positive, and metastatic disease at diagnosis was found in 32 women (23.4%), some with > 1 metastatic site involved, the most frequent being bone, with 17 cases (38.5%), pulmonary with 15 cases (38.5%) and hepatic with 7 cases (17.9%). Regarding complementary therapy, almost all patients received at least one type of approach, 89 (45.6%) for chemotherapy, 54 (27.7%) radiation therapy, 47 (24.1%) hormone therapy and 5 (2.6%) did not undergo any type of systemic therapy.

Also, regarding the treatment used, it is possible to highlight that 54 patients (39.4%) underwent breast surgery and radiotherapy, which consists of local treatment of the pathology.

►**Table 3** shows the distribution of the main clinical, sociodemographic and pathological characteristics according to the subtypes of breast cancer classified by IHC. However, in general, most of the variables studied predominated in the HER2 negative luminal B subtype. Even so, relevant results were found in the individual analysis of each molecular subtype in relation to most of the study variables. According to the menopausal status, the predominance of the negative luminal molecular subtype B-HER2 was found both among premenopausal women, with 25 patients (38.5%), and in postmenopausal women, with 25 (34.7%) patients.

Regarding race, regardless of the molecular subtype, the prevalence was of non-white patients (brown, black, yellow and indigenous), however, the largest distribution of white patients was among the negative B-HER2 luminal tumors,

Table 1 Sociodemographic and clinical characteristics of patients

Variables		n	%
Age at diagnosis ($n = 137$)	Average	52.1	–
	Standard deviation	11.8	–
Menopausal State	Premenopause	65	47.4
	Postmenopause	72	52.6
	TOTAL	137	100.0
Race	White	39	28.4
	Brown	77	56.2
	Black	2	1.4
	Yellow	19	14.0
	TOTAL	137	100.0
Regrouped Races	White	39	28.4
	Non-white	98	71.6
	TOTAL		
City	Imperatriz-MA	51	37.2
	Other cities in MA	83	60.6
	Other states	3	2.2
	TOTAL	137	100.0
Marital Status	Unmarried	32	23.4
	Married or Cohabitant	85	62.0
	Divorced	6	4.4
	Widowed	14	10.2
	TOTAL	137	100.0
Level of Schooling	Illiterate	19	14.1
	$<$ 9 years	54	40.0
	9 to 12 years	43	31.9
	$>$ 12 years	19	14.1
	TOTAL	135	100.0
Smoking	Yes (current or past)	35	29.2
	No	85	70.8
	TOTAL	120	100.0
Alcohol Consumption	Yes (current or past)	41	34.2
	No	79	65.8
	TOTAL	120	100.0
Family history of cancer	Yes	62	51.7
	No	58	48.3
	TOTAL	120	100.0

with 11 (78%) tumors of this subtype. The family history of cancer was predominantly positive in most of the molecular subtypes of the study (luminal A, luminal B-HER2 negative, luminal B-HER2 positive and HER2-enriched).

When it comes to tumor size, most of the tumors $>$ 5.0 cm and between 2 to 5 cm were found in luminal B-HER2 negative (40% and 37.3%, respectively); however, tumors $<$ 2 cm were prevalent in the luminal subtype A, with 12 (34.3%) occurrences, which corresponded to 44.4% of the cases related to this subtype.

Table 2 Pathological profile of patients

Variables		n	%
Molecular Subtype	Luminal A	27	19,7
	Luminal B- HER2 negative	50	36.5
	Luminal B- HER2 positive	18	13.1
	Triple-negative	18	13.1
	HER2-enriched	17	12.4
	Inconclusive	7	5.1
	TOTAL	137	100.0
Surgery type	Mastectomy	101	73.7
	Breast-conserving	34	24.8
	Not performed	2	1.5
	TOTAL	137	100.0
Axillary approach	Sentinel node biopsy	20	14.6
	Axillary lymph node dissection	92	67.2
	Not performed	25	18.2
	TOTAL	137	100.0
Histological type	Invasive ductal carcinoma	116	84.7
	Invasive lobular carcinoma	14	10.2
	Others	7	5.1
	TOTAL	137	100.0
TNM staging	$\leq$ II B	65	47.4
	$>$ II B	72	52.6
	TOTAL	137	100.0
Tumor size	$<$ 2 cm	35	25.5
	2 to 5 cm	67	48.9
	$>$ 5 cm	35	25.5
	TOTAL	137	100.0
Lymph node impairment	Positive	77	56.2
	Negative	60	43.8
	TOTAL	137	100.0
Metastasis	Positive	32	23.4
	Negative	105	76.6
	TOTAL	137	100.0
Location of metastasis	Bones	17	43.6
	Lungs	15	38.5
	Liver	7	17.9
	TOTAL	39	100.0
Complementary therapy	Chemotherapy	89	45.6
	Radiation therapy	54	27.7
	Hormone therapy	47	24.1
	Not performed	5	2.6
	TOTAL	195	100.0

Regarding lymph node impairment, it is worth mentioning the positive character, which predominated in the negative subtype B-HER2 with 27 patients (35.1%). Specifically, in relation to the positive luminal B-HER2, 13 patients (72% of

Table 3 Sociodemographic, clinical and pathological profile in relation to the molecular subtype

	MOLECULAR SUBTYPE												
	LA		LB neg		LB pos		HER2-enr		TN		Inc		*p-value*
Age at diagnosis (menopausal status)													
$\leq$ 50 years old	12	18.5	25	38.5	9	13.8	8	12.3	7	10.8	4	6.2	*0.96**
$>$ 50 years old	15	20.8	25	34.7	9	12.5	9	12.5	11	15.3	3	4.2	
Race													
White	9	23.7	11	28.9	6	15.8	6	15.8	3	7.9	3	7.9	*0.56**
Non-white	18	18.2	39	39.4	12	12.1	11	11.1	15	15.2	4	4.0	
Family history of cancer													
Yes	13	21.0	26	41.9	8	12.9	10	16.1	4	6.5	1	1.6	*0.09**
No	9	15.5	19	32.8	7	12.1	6	10.3	12	20.7	5	8.6	
TNM Staging													
$\leq$ II B	18	27.7	24	36.9	7	10.8	6	9.2	6	9.2	4	6.2	*0.20**
$>$ II B	9	12.5	26	36.1	11	15.3	11	15.3	12	16.7	3	4.2	
Tumor size													
$<$ 2 cm	12	34.3	11	31.4	4	11.4	2	5.7	4	11.4	2	5.7	*0.41***
2 to 5 cm	10	14.9	25	37.3	8	11.9	12	17.9	8	11.9	4	6.0	
$>$ 5 cm	5	14.3	14	40.0	6	17.1	3	8.6	6	17.1	1	2.9	
Lymph node impairment													
Positive	11	14.3	27	35.1	13	16.9	11	14.3	11	14.3	4	5.2	*0.38**
Negative	16	26.7	23	38.3	5	8.3	6	10.0	7	11.7	3	5.0	
Metastasis													
Positive	4	12.5	12	37.5	4	12.5	5	15.6	7	21.9	0	0.0	*0.30***
Negative	23	21.9	38	36.2	14	13.3	12	11.4	11	10.5	7	6.7	
Performed chemotherapy													
Yes	18	20.2	25	28.1	14	15.7	13	14.6	14	15.7	5	5.6	*0.14***
No	9	18.8	25	52.1	4	8.3	4	8.3	4	8.3	2	4.2	
Performed radiation therapy													
Yes	12	22.2	23	42.6	8	14.8	4	7.4	6	11.1	1	1.9	*0.39**
No	15	18.1	27	32.5	10	12.0	13	15.7	12	14.5	6	7.2	
Performed hormonotherapy													
Yes	12	25.5	26	55.3	4	8.5	1	2.1	1	2.1	3	6.4	*$<$ 0.001***
No	15	16.7	24	26.7	14	15.6	16	17.8	17	18.9	4	4.4	

Abbreviations: HER2-enr, HER2-enriched; Inc, Inconclusive (Immunohistochemistry + FISH); LA, Luminal A; LB neg, Luminal B- HER2 negative; LB pos, Luminal B- HER2 positive; TN, Triple-negative.
*Chi-squared test.
**Fisher-Freeman-Halton test.

this subtype) presented lymph node positivity, and in relation to luminal A, 16 women (59.2% of this group) presented negative lymph node impairment.

Regarding staging, luminal subtype A deserves to be highlighted, in which most tumors presented in stages $\leq$ IIB, which corresponded to 18 patients (66.7% of this subtype), while for the negative triple subtype, 12 women (66.6% of this group) were $>$ IIB at diagnosis.

Regarding metastasis, most patients who presented positive results of this characteristic at diagnosis belonged to the negative B-HER2 luminal subtype, which corresponded to 12 (37.5%) out of the 32 cases of metastasis recorded in the study. However, in the individual analysis of each subgroup, 7 out of the 18 patients belonging to the triple negative group showed metastasis at diagnosis, a total of 38.8%, which evidenced this subtype with the highest percentage of metastasis. Regarding the inconclusive subgroup, there were no cases of metastasis.

Also, it is possible to highlight that among patients with metastasis, 29 out of 32 (9.6%) underwent mastectomy, 2 (6.2%) conservative surgery, and 1 (3.1%) patient did not receive surgical treatment.

Regarding complementary therapy, the data showed that for chemotherapy, both the luminal groups B-HER2 positive and triple negative showed prevalence of this treatment, performed in 14 of the 18 cases (77.7%) of each subtype. Regarding radiation therapy, it was prevalent in the negative subtype B-HER2, with 23 out of the 54 (42.6%) patients undergoing radiation therapy. Regarding hormone therapy, the analysis of the relationship between this treatment and the molecular subtypes was statistically significant ($p < 0.001$), demonstrating the prevalence of this modality in the negative B-HER2 luminal subtype, with 26 out of the 47 (55.3%) of the hormone therapy performed. On the other hand, in the positive B-HER2 luminal subtype, 14 out of 18 patients (77.7%) did not undergo hormonal therapy, demonstrating that only 4 (22.3%) out of 18 patients received this therapeutic modality.

Discussion

Regarding age, our results are similar to the research that evaluated the profile of patients with breast cancer in Cuiabá, state of Mato Grosso, Brazil, in which the average age of the patients was 51.8 years old.[12] According to Magalhães et al.,[13] this data corroborates with previous studies, which state that the risk of breast cancer increases with age, being relatively rare before the age of 35 years old.

Regarding smoking and alcohol consumption, the results obtained in the present study were similar to other studies performed in Belém, state of Pará,[13] and in São Paulo, state of São Paulo,[14] in which most patients had no history of smoking and alcohol consumption, as highlighted by the authors. These habits are modifiable risk factors, and smokers, ex-smokers and passive smokers are at increased risk of developing cancer, especially after menopause, and alcohol intake is a risk factor for all types of cancer, including breast cancer.[15]

Regarding the level of schooling, the present study corroborates with research that evaluated the epidemiological profile of breast cancer in a reference hospital in the northern region,[14] where > 50% of the patients had not completed elementary and high school. However, it is noteworthy that the percentage of illiterate patients was 3.5% against 14.1% found in our study. This information is relevant in terms of the level of knowledge of the patients about the disease, its prevention and diagnosis, since this level is directly proportional to education.[14]

Regarding marital status, in agreement with the studies by Farina et al., Llanos et al., and Haddad et al.,[12,16,17] most women were married. Marital status is not considered a risk factor for the development of the disease, but the fact of having a partner is associated with better social support, optimism and quality of life among surviving women.[17]

Considering the type of surgery, the results found in the present study showed that 73.7% of the patients underwent radical dissection, which is different from what was found in a study that evaluated the 10-year survival rate in patients with breast cancer in southeastern Brazil, where 53.6% of the women underwent conservative surgery.[18] Radical dissections are indicated in cases of invasive malignant tumors that occupy > 20% of the breast volume;[19] the high percentage of radical mastectomy performed in the present research may be justified by the prevalence of large tumors and in advanced stages of diagnosis.

When it comes to the axillary approach, a Spanish research that evaluated this approach in breast cancer for 20 years concluded that the percentage of axillary lymphadenectomy went from 91% at the beginning of the study to 34% at the end, which was attributed to the introduction of the sentinel lymph node biopsy and international criteria that modified the indication of axillary lymphadenectomy, avoiding morbidities associated with this procedure, especially lymphedema.[20] However, the results of the present study showed that 67.2% of women underwent axillary lymphadenectomy, in contrast to worldwide occurrences.

In the case of the histological type, the study of Pires et al.[21] corroborated with our results, in which 89.38% of the tumors were ductal invasive and 5.09% were lobular invasive; however, 0.66% of the patients had mucinous carcinoma, against 3.6% in the present study. It should be noted that invasive ductal carcinoma, in its pure form or in combination with other types, is the most common form of breast carcinoma reported in the literature.[21]

According to the findings of the present research, for the immunohistochemical profile, the subtypes with the highest frequencies found were the luminal B-HER2 negative and the luminal A. These data corroborate with a large Brazilian multicenter study, which gathered 5,687 cancer cases across the country, whose objective was to identify the distribution of molecular subtypes in the 5 Brazilian regions, where there was the following variation in prevalence: luminal B, from 30.8% to 39.5%, luminal A from 24.1% to 28.8%, and triple negative, from 14% to 20.3%. The classifications adopted were similar to those of the present study in terms of the group of immunohistochemical markers, although there was a divergence between the positive B-HER2 luminal of this study and triple positive.[22]

However, these results were different from international studies, in which they had a prevalence of luminal subtype A, with a frequency that corresponded to from 50 to 70% of cases, to the detriment of 19.7% in the present study.[7,23–25]

Regarding menopausal status and correlation with the molecular subtype, our results differed from that observed by Cintra et al.,[5] who in their study found that the triple negative subtype was prevalent in younger patients, whereas, in the present research, low frequency subtypes in premenopausal women were found in the analysis.

Considering race, the present study was different from other Brazilian studies,[5,26] which evaluated the profile of breast cancer patients, in which most of them were white. However, account should be taken of the miscegenation existing in the national population,[5] which justifies the presence of different results and the possibility of misclassification of the skin color in the present study, since the sample is composed of patients from northeastern Brazil, with a higher prevalence of blacks;[26] however, this group corresponded to 1.4% of the studied sample.

Considering the skin color and the subtype, a higher percentage of non-white skin color was demonstrated in the specific analysis, in the negative triple and a higher percentage of white skin color in the negative B-HER2 luminal. These data were similar to a North American study[27] that evaluated the factors that influence the stage of breast cancer diagnosis and showed a significant prevalence of triple negative in black patients and tumors with positive hormone receptor and negative HER2 in white patients.

The family history of breast cancer, especially when reported in first-degree relatives, is an important risk factor for the onset of the disease, considering that certain genetic alterations increase the risk of developing it. It is noted, however, that $\sim$ 9 out of 10 cases of this pathology occur among women without a family history.[28] In the present study, it was found that most patients had a positive family history and that among the molecular subtypes, the only one that did not show a prevalence of family history was the triple negative. However, it must be clarified that the data collected in the present study can be considered unreliable and/or ignored due to the search for information being restricted to consultation of hospital records.

Ganglion impairment has been recognized as an important prognostic factor in breast cancer, and the presence of positive axillary lymph nodes has been shown to predict increased risk of local and distant recurrence, with direct interference in mortality.[29] In the present study, high rates of lymph node impairment at diagnosis were observed, which corroborates with a bad prognosis in the studied population.

When it comes to tumor size, this is an important prognostic determinant, and together with the status of the axillary lymph node, are the two most important indicators in breast cancer.[21] With the advent of mammography and the greater awareness of the population of its importance, a significant reduction in the size of tumors at the time of diagnosis was observed in some developed countries;[30] however, approximately half of the patients evaluated in the present study had tumors between 2 and 5 cm at the time of diagnosis, which reflected a late diagnosis.

It is important to note that in a specific analysis of each subtype, luminal A showed a prevalence of small tumors and negative nodal involvement, which was compatible with what was described by Barreto-Neto et al.[26] by characterizing luminal subtype A as having the best prognosis, high survival rates and lower recurrence rates.

When it comes to stage at diagnosis, a cross-sectional study performed from 2000 to 2009 involving 87,969 Brazilian women[30] showed that there was a positive association between life in the poorest regions of the country (north, northeast and midwest) and late diagnosis of the disease. This same study demonstrated a gradual reduction in the rate of advanced breast cancer presentation, with a frequency of 59.5% in 2000 and of 50.9% in 2009. However, most patients in the present study were diagnosed in advanced stages of the disease, diverging from the evolutionary character observed in the country. Regarding metastasis at diagnosis, this was high among the population studied, especially when compared with other studies, with 23.4% of patients, while, nationally, percentages of 8.8%, 12.2% and 13.6% were found.[13,14,30] A study performed in a region that has one of the highest mortality rates in the world for breast cancer, sub-Saharan Africa, which brought together 2,558 cases of this tumor diagnosed from 2008 to 2015, showed that 18.4% of patients had metastatic disease in the diagnosis.[31] Advanced diagnosis stage shows greater difficulties and costs in treatment and is associated with greater morbidity and worse survival in high-income countries and in Brazil. Thus, a potential reason for the disproportionately high mortality from breast cancer in Brazil is late diagnosis.[32]

It was observed that in the individual analysis of the molecular subtypes, in the triple negative and HER2-enriched, there were the highest rates of metastasis at diagnosis and, although it did not present statistical significance ($p = 0.30$), this data is in agreement with other studies,[5,33] where these two subtypes were found among the most frequent metastatic disease.

In the case of complementary therapy, radiation therapy was more likely to be performed in patients with B-HER2 negative luminal breast cancer, in divergence from Cintra et al.,[5] in which radiotherapy was more related to luminal subtype A. In this sense, Pires et al.[21] reported that radiation therapy has locoregional control of the disease as its main indication and its use is more common in the postoperative period to decrease the chances of recurrence; however, in some cases, it is used preoperatively to reduce tumor volume. Regarding chemotherapy, its adjuvant form is recommended for the subtypes HER2-enriched, luminal B-HER2 positive and triple negative, and may be prescribed or not for luminal HER2 negative tumors and not indicated for luminal A tumors.[6] The results of the present study corroborated this recommendation, since most of the chemotherapies performed were among the subtypes luminal B-HER2 positive, HER2-enriched and triple negative, although it should be noted that most of the patients with luminal A tumors received this therapy, which can be justified by the inclusion of neoadjuvant chemotherapies in the data collection of the present study.

In the case of hormone therapy, the presence of hormone receptors in tumor cells correlates with the benefit of hormone therapy, which uses substances that inhibit the activity of endogenous hormones progesterone and estrogen in the breast.[21] In agreement with these data, in the present study, the highest frequency of hormone therapy was between the subtypes luminal A and luminal B-HER2 negative, tumors that have hormone receptors. However, in the positive B-HER2 luminal category, despite containing these receptors, only 22.3% of the patients underwent hormone therapy ($p < 0.001$), different from the pattern observed in a German study conducted from 2000 to 2016,[33] in which 67.8% of positive B-HER2 luminal patients received some type of hormone therapy, and the study conducted by Cintra et al.,[5] which demonstrated that 76.7% of the patients belonging to this group received hormone therapy. Such divergence may be justified by the possibility of choosing neoadjuvant chemotherapy, initially, in tumors with some HER2 expression in the patients of the present study.

Regarding the inconclusive subtype, our results were compatible with the research[34] that investigated the clinical-pathological characteristics, treatment patterns and disease outcomes of tumors with doubtful HER2, where these tumors shared a greater similarity with HER2-negative disease. However, it is worth mentioning that the current consensus recommends the repetition of the HER2 test by FISH and/or IHC in equivocal cases, a fact that was demonstrated by the study of Xu et al.,[35] where this recommendation proved that it could clarify $\sim$ 50% of doubtful cases; however, these tumors deserve further study, since there is limited information on the prognosis and the ideal treatment strategy for this population.

Based on these results, it is expected to contribute to the perception of the need to reinforce public health policies aimed at consolidating the national breast cancer screening program, especially for the group of women considered to be at higher risk and living in places with low health care, as they are susceptible to late diagnosis. It is also hoped to have demonstrated the importance of ensuring timely and appropriate treatment for women with breast cancer according to their molecular classification, and it is suggested that, based on the present research, new studies should be performed with a prospective approach with the intention of portraying the current situation in the region studied, considering the limitation of cross-sectional studies, specifically retrospective, as they do not demonstrate the reality of the moment.

Conclusion

With the accomplishment of the present research, it was concluded that:

- The identification of women according to the molecular subtype by means of immunohistochemical classification was mainly in the negative subtype B-HER2.
- Sociodemographic characteristics came from women $>$ 50 years old; brown race; from different cities than the city where the study was performed; married or cohabited; nonsmokers; nondrinkers; and with $<$ 9 years of education; with a positive family history of cancer.
- The clinical-pathological characteristics were of mastectomized women, with axillary lymphadenectomy; carriers of invasive ductal carcinoma, staging $>$ IIB (advanced); tumors from 2 to 5 cm; with lymph node impairment, without metastasis at diagnosis and chemotherapy as complementary therapy.
- That in the association of molecular subtypes with sociodemographic and clinical-pathological characteristics, no statistically significant results were obtained, except for complementary therapy, referring to hormone therapy. However, in the specific clinical analysis, it was observed that luminal subtype A had characteristics of better prognosis in relation to the other subtypes and that there was a failure in the implemented complementary therapy in relation to positive Luminal B-HER2, where the majority did not receive hormone therapy as recommended in the consensus.
- Although it is not part of the objectives of the present study, it was concluded that there was a high rate of metastasis at diagnosis, which is a worrying factor and indicative of failures in screening and early diagnosis of this population.

Contributions

Conception and design: Reis A. P. A. M., Teixeira C. M. S., Medeiros A. R. L., Chaves K. Z. C..

Data collection: Reis A. P. A. M., Melo M. R., Albuquerque C. R..

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Conflict of Interests

The authors have no conflict of interests to declare.

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References

1 Ferreira LF, Petel LA, Fernandes SS. A história natural do câncer de mama na paciente jovem: revisão de literatura. Femina. 2011;39 (11):527–531

2 Rupp J, Hadamitzky C, Henkenberens C, Christiansen H, Steinmann D, Bruns F. Frequency and risk factors for arm lymphedema after multimodal breast-conserving treatment of nodal positive breast Cancer - a long-term observation. Radiat Oncol. 2019;14 (01):39. Doi: 10.1186/s13014-019-1243-y

3 Ministério da Saúde Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2018: incidência de câncer no Brasil [Internet]. Rio de JaneiroINCA2017 [cited 2019 Mar 12]. Available from: https://portaldeboaspraticas.iff.fiocruz.br/wp-content/uploads/2019/10/estimativa-incidencia-de-cancer-no-brasil-2018.pdf

4 Dai X, Li T, Bai Z, Yang Y, Liu X, Zhan J, Shi B. Breast cancer intrinsic subtype classification, clinical use and future trends. Am J Cancer Res. 2015;5(10):2929–2943

5 Cintra JRD, Teixeira MT, Diniz RW, Junior HG, Florentino TM, Freitas GF, et al. Immunohistochemical profile and clinical-pathological variables in breast cancer. Rev Assoc Med Bras (1992). 2012;58(02): 178–187. Doi: 10.1590/S0104-42302012000200013

6 Serra KP, Ramalho S, Torresan R, Vassalo J, Sarian LOZ, Silva GRP, Derchain S. [The new classification of breast cancers: finding the

luminal A]. Rev Bras Ginecol Obstet. 2014;36(12):575–580. Doi: 10.1590/SO100-720320140005158
7 Vallejos CS, Gómez HL, Cruz WR, Pinto JA, Dyer RR, Velarde R, et al. Breast cancer classification according to immunohistochemistry markers: subtypes and association with clinicopathologic variables in a peruvian hospital database. Clin Breast Cancer. 2010;10 (04):294–300. Doi: 10.3816/CBC.2010.n.038
8 Anderson WF, Jatoi I, Devesa SS. Distinct breast cancer incidence and prognostic patterns in the NCI's SEER program: suggesting a possible link between etiology and outcome. Breast Cancer Res Treat. 2005;90(02):127–137. Doi: 10.1007/s10549-004-3777-3
9 Hortobagyi GN, Connolly JL, D'Orsi CJ, et al. Breast. In: Amin MB, editor. AJCC cancer staging manual. 8th ed. London: Springer; 2017:589–636
10 Corp IBM. IBM SPSS Statistics for Windows. Version 24.0 [software] Armonk: IBM Corp; 2016
11 Gibbons JD, Chakraborti S. Nonparametric statistical inference. 5th ed. Boca Raton: CRC Press; 2010
12 Farina A, Almeida LLR, Paula LEJ, Medeiros RV, Silva MR, Sommavilla SB. Perfil epidemiológico, clínico, anátomo patológico e imunohistoquímico das pacientes com câncer de mama em Cuiabá (MT). Rev Bras Mastol. 2016;27(01):74–79. Doi: 10.5327/Z201700010017RBM
13 Magalhães G, Brandão-Souza C, Fustinoni SM, Matos JC, Schirmer J. Perfil clínico, sociodemográfico e epidemiológico da mulher com câncer de mama. Rev Pesqui. 2017;9(02):473–479
14 Rocha FS, Silva WS, Nascimento ER, Bacciotti AM. Epidemiological profile of breast cancer in a reference hospital in the north region. Mastology. 2018;28(03):169–175. Doi: 10.29289/25945394201800 00413
15 Setiawan VW, Monroe KR, Wilkens LR, Kolonel LN, Pike MC, Henderson BE. Breast cancer risk factors defined by estrogen and progesterone receptor status: the multiethnic cohort study. Am J Epidemiol. 2009;169(10):1251–1259. Doi: 10.1093/aje/kwp036
16 Llanos AAM, Chandwani S, Bandera EV, Hirschfield KM, Lin Y, Ambrosone CB, Demissie K. Associations between sociodemographic and clinicopathological factors and breast cancer subtypes in a population-based study. Cancer Causes Control. 2015; 26(12):1737–1750. Doi: 10.1007/s10552-015-0667-4
17 Haddad NC, Carvalho ACA, Novaes CO. Perfil sociodemográfico e de saúde de mulheres submetidas à cirurgia para câncer de mama Materiais e métodos. Rev HUPE. 2015;14(Suppl 1):28–35. Doi: 10.12957/rhupe.2015.17923
18 Fayer VA, Guerra MR, Cintra JRD, Bustamante-Teixeira MT. Ten-year survival and prognostic factors for breast cancer in the southeast region of Brazil. Rev Bras Epidemiol. 2016;19(04): 766–778. Doi: 10.1590/1980-5497201600040007
19 Migowski A, Stein AT, Ferreira CBT, Ferreira DMTP, Nadanovsky P. Guidelines for early detection of breast cancer in Brazil. I - Development methods. Cad Saude Publica. 2018;34(06):e00116317. Doi: 10.1590/0102-311X00116317
20 García-Novoa A, Acea-Nebril B, Casal-Beloy I, Bouzón-Alejandro A, Garea CC, Gómez-Dovigo A, et al. El declive de la linfadenectomía axilar en el cáncer de mama. Evolución de su indicación durante los últimos 20 años. Cir Esp. 2019;97(04):222–229. Doi: 10.1016/ j.ciresp.2019.01.010
21 Pires EDLS, Morais LM, Pires ADLS, Matsuda LO, Matsuda JB, Alves ARM. Prognostic factors in breast cancer: from staging to the immunohistochemical profile of patients with breast cancer in a reference hospital of Ceara - Brazil. Int Arch Med Microbiol. 2018; 1(01):1–5. Doi: 10.23937/iamm-2017/1710005
22 Carvalho FM, Bacchi LM, Pincerato KM, Van de Rijn M, Bacchi CE. Geographic differences in the distribution of molecular subtypes of breast cancer in Brazil. BMC Womens Health. 2014;14:102. Doi: 10.1186/1472-6874-14-102
23 Cherbal F, Gaceb H, Mehemmai C, Saiah I, Bakour R, Rouis AO, et al. Distribution of molecular breast cancer subtypes among Algerian women and correlation with clinical and tumor characteristics: a population-based study. Breast Dis. 2015;35(02):95–102. Doi: 10.3233/BD-150398
24 Park S, Koo JS, Kim MS, Park HS, Lee JS, Lee JS, et al. Characteristics and outcomes according to molecular subtypes of breast cancer as classified by a panel of four biomarkers using immunohistochemistry. Breast. 2012;21(01):50–57. Doi: 10.1016/j.breast.2011.07.008
25 Blows FM, Driver KE, Schmidt MK, Broeks A, van Leeuwen FE, Wesseling J, et al. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. PLoS Med. 2010;7(05):e1000279. Doi: 10.1371/journal.pmed.1000279
26 Barreto-Neto NJS, Pinheiro AB, Oliveira JF, et al. Perfil epidemiológico dos subtipos moleculares de carcinoma ductal da mama em população de pacientes em Salvador, Bahia. Rev Bras Mastologia. 2014;24(04):98–102. Doi: 10.5327/Z201400040002RBM
27 Franzoi MA, Schwartsmann G, de Azevedo SJ, Geib G, Zaffaroni F, Liedke PER. Differences in breast cancer stage at diagnosis by ethnicity, insurance status, and family income in young women in the USA. J Racial Ethn Health Disparities. 2019;6(05):909–916. Doi: 10.1007/s40615-019-00591-y
28 Ito EJ, Safar AS. Epidemiological profile of the mastology clinic in a university of Paraná. Mastology. 2017;27(04):293–299. Doi: 10.29289/2594539420170000199
29 Tonellotto F, Bergmann A, de Souza Abrahão K, de Aguiar SS, Bello MA, Thuler LCS. Impact of number of positive lymph node and lymph node ratio on survival of women with node-positive breast cancer. Eur J Breast Health. 2019;15(02):76–84. Doi: 10.5152/ ejbh.2019.4414
30 Abrahão KdeS, Bergmann A, Aguiar SS, Thuler LCS. Determinants of advanced stage presentation of breast cancer in 87,969 Brazilian women. Maturitas. 2015;82(04):365–370. Doi: 10.1016/j. maturitas.2015.07.021
31 Joko-Fru WY, Miranda-Filho A, Soerjomataram I, Egue M, Akele-Akpo M-T, N'da G, et al. Breast cancer survival in sub-Saharan Africa by age, stage at diagnosis and human development index: A population-based registry study. Int J Cancer. 2020;146(05): 1208–1218. Doi: 10.1002/ijc.32406
32 Dos-Santos-Silva I, De Stavola BL, Renna NL Junior, Nogueira MC, Aquino EML, Bustamente-Teixeira MT, Silva GA. Ethnoracial and social trends in breast cancer staging at diagnosis in Brazil, 2001-14: a case only analysis. Lancet Glob Health. 2019;7(06):e784-–e797. Doi: 10.1016/S2214-109X(19)30151-2
33 Ignatov A, Eggemann H, Burger E, Ignatov T. Patterns of breast cancer relapse in accordance to biological subtype. J Cancer Res Clin Oncol. 2018;144(07):1347–1355. Doi: 10.1007/s00432-018-2644-2
34 Tong Y, Chen X, Fei X, Lin L, Wu J, Huang O, et al. Can breast cancer patients with HER2 dual-equivocal tumours be managed as HER2-negative disease? Eur J Cancer. 2018;89:9–18. Doi: 10.1016/j.ejca.2017.10.033
35 Xu FP, Wang K, Xu J, Chen J, Zhang Y-F, Wu H-M, et al. Impact of repeat HER2 testing after initial equivocal HER2 FISH results using 2013 ASCO/CAP guidelines. Breast Cancer Res Treat. 2017;166 (03):757–764. Doi: 10.1007/s10549-017-4479-y

Reproductive Outcomes in Cases of Subclinical Hypothyroidism and Thyroid Autoimmunity: A Narrative Review

Resultados reprodutivos nos casos de hipotireoidismo subclínico e autoimunidade tireoidiana: Uma revisão narrativa

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Abstract

Thyroid diseases are relatively common in women in the reproductive period. It is currently understood that clinically-evident thyroid disorders may impair ovulation and, consequently, fertility. However, to date it has not been proven that high serum levels of thyroid-stimulating hormone and/or positivity for antithyroid antibodies are associated to a reduction in fertility, mainly in the absence of altered thyroxine levels. The present comprehensive review aims to present current data on the association between subclinical hypothyroidism and/or thyroid autoimmunity and reproductive outcomes.

Keywords

- thyroid diseases
- thyroid function tests
- thyroid hormones
- hypothyroidism
- autoimmunity
- female infertility

Resumo

As doenças da tireoide são relativamente comuns em mulheres no período reprodutivo. Atualmente, entende-se que distúrbios da tireoide clinicamente evidentes podem prejudicar a ovulação e, consequentemente, a fertilidade. No entanto, não se provou até o presente que níveis séricos altos do hormônio estimulador da tireoide e/ou positividade para anticorpos antitireoidianos estão associados a uma redução na fertilidade, sobretudo na ausência de níveis alterados de tiroxina. Esta revisão narrativa tem como objetivo apresentar dados atuais sobre a associação entre hipotireoidismo subclínico e/ou autoimunidade tireoidiana e resultados reprodutivos.

Palavras-chave

- doenças da tireoide
- testes de função da tireoide
- hormônios da tireoide
- hipotireoidismo
- autoimunidade
- infertilidade feminina

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Introduction

The thyroid gland is responsible for regulating several mechanisms of human physiology, which include the reproductive function. Thyroid hormones are involved in the modulation of the hypothalamic-pituitary-gonadal axis and, despite the lack of consistent scientific evidence, it is currently understood that clinically evident thyroid disorders may impair ovulation and, consequently, fertility.[1] Thyroid diseases are relatively common in women in the reproductive period. A significant association between clinical thyroid disorders and abnormalities of the reproductive system has been largely confirmed: both primary hyperthyroidism and hypothyroidism have been documented to produce variable degrees of gonadal dysfunction. Nevertheless, the impact of subclinical thyroid dysfunction and/or thyroid autoimmunity (TAI) on fertility and reproductive outcomes is not consensual, although they may be related to infertility and the risk of spontaneous pregnancy loss.[1,2] As a matter of course, subclinical hypothyroidism (SCH) has been defined as a level of thyroid stimulating hormone (TSH) going over the upper threshold of 4.5 mIU/L to 5.0 mIU/L in the setting of a normal level of free thyroxine (fT4).[3] Nonetheless, the limits commonly vary among studies, and it has been suggested that the upper cutoff for TSH should be set at 2.5 mIU/L, based on the observation that 95% of asymptomatic people have that level or even lower levels of TSH.[4] Regarding thyroid diseases, in addition to idiopathic changes in function, situations resulting from the presence of autoantibodies are quite common, such as Hashimoto thyroiditis and Graves disease. Currently, at least three anti-thyroid antibodies can be evaluated in human serum: the thyroid globulin antibody (TGAb), the thyroid peroxidase antibody (TPOAb), and the thyrotropin receptor antibody (TRAb). However, presenting anti-thyroid antibodies is not sufficient to develop autoimmune thyroid disease, which pathophysiology is not yet fully understood. Thus, the clinical relevance of presenting positive antibodies without an established disease is still questionable, including the influence on fertility.[5] The present narrative review aims to present the current data on the association between SCH and/or TAI and reproductive outcomes. Our objective is to help clinicians decide the medical approach to women attempting to conceive and presenting those conditions, based on hierarchized evidence. However, once the levels of evidence do not provide a definitive judgment about the quality of the studies included nor they constitute a final recommendation,[6] clinicians may apply individualization as the main key for their critical appraisal in treatment decisions.

Methods

Using the keywords *subclinical hypothyroidism*, *thyroid autoimmunity*, and *infertility*, we searched for clinical trials, controlled clinical trials, meta-analyses, and randomized controlled trials on the following databases: PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Cochrane Gynecology and Fertility Group specialized register, and clinicaltrials.gov. No date or language restrictions were applied to the search. A total of 13 studies were primarily selected for this review.[7–19] The references of the selected studies were also checked, and seven more relevant articles were included.[20–26] The evidence was hierarchized according to the Oxford Centre for Evidence-based Medicine's 2011 Levels of Evidence[6] by the first author (BRC), and checked by the second author (APN); there were no discordances between them or between them and the other authors.

Subclinical Hypothyroidism

Subclinical hypothyroidism is a condition in which the level of TSH is elevated, but the level of fT4 is normal. It represents an early, mild thyroid failure, and affects up to 10% of the adult population.[27] However, its clinical significance has not been consistently proven. Raber et al[7] followed 223 women for up to 5 years, and they observed lower conception rates among women who never achieved a basal TSH < 20 mUI/L with fT4 therapy, and, then, they suggested a negative effect of such findings on reproductive function (level 4). Moreover, the meta-analysis of two studies[21] showed a significant decrease in the rates of miscarriage (relative risk [RR]: 0.18; 95%; 95% confidence interval [95%CI]: 0.08–0.39; $p < 0.01$) and preterm delivery (RR: 0.41; 95%CI: 0.24–0.68; $p = 0.0005$) in women with SCH treated with levothyroxine (LT4) (level 1). However, contrary to those authors, preconception TSH ≥ 2.5 mIU/L was not associated to time to biochemical pregnancy (odds ratio [OR]: 1.09; 95%CI: 0.90–1.31), pregnancy loss (RR: 1.15; 95%CI: 0.86–1.54) or live births (RR: 1.01, 95%CI: 0.89–1.14) among 1,193 women with normal fT4 (0.7 ng/dL to 1.85 ng/dL) and a history of either one or two previous pregnancy losses, even if they were positive for anti-thyroid antibodies (TGAb ≥ 115 - IU/mL and/or TPOAb ≥ 35 IU/mL), and after adjusting for age and body mass index. The authors also attempted to determine a TSH cut-off affecting the continuation of pregnancy, but an additional analysis of both TSH tertiles and continuous TSH did not result in differences between women with TSH ≥ 2.5 mIU/L and those with TSH < 2.5 mIU/L (level 2).[12] There are some studies evaluating the effect of LT4 in women with subclinical hypothyrodism undergoing assisted reproductive treatments, like in vitro fertilization (IVF), with conflicting results.[8,10,15,22,26] According to Kim et al,[10] women with subclinical hypothyroidism undergoing assisted reproductive techniques presented with similar clinical pregnancy rates when compared with controls, despite the significant differences in the number of good-quality embryos, implantation rates, and live-birth rates (RR: 1.8; 95%CI: 1.0–3.25; $p = 0.05$; and RR: 2.13; 95%CI: 1.07–4.21; $p = 0.03$ respectively).[10] However, the miscarriage rate was significantly lower in the LT4 group (no miscarriages *versus* 33,3% in the control group; $p = 0.021$) (level 2). In another trial,[8] LT4 or placebo were initiated one month before IVF and were maintained throughout pregnancy. The number of follicles punctured, mature oocytes, and the fertilization, pregnancy, and delivery rates were significantly higher in the treatment group. Moreover, the miscarriage rate was significantly lower in the intervention group (level 1).[8] In a cohort study by Cai et al,[15] 270 women with SCH supplemented with LT4 before IVF were compared with 200 age-matched euthyroid women who underwent classical IVF or intracytoplasmic sperm injection (ICSI). In

total, 176 out of 270 women completed all pregnancy visits of the study, and were included in the final analysis. In the SCH treated with LT4 and euthyroid groups of women who underwent IVF in the same period, the overall rates of clinical pregnancy (44.31% versus 38.36%; $p = 0.251$ respectively) and miscarriage (10.3% versus 10.7%, $p = 0.39$ respectively) were similar (level 3).[15] Moreover, another study[12] demonstrated that the treatment with LT4 lead to the same rates of clinical pregnancy, miscarriage, and live births, which were independent of TSH levels, in women with SCH. There were no differences between the groups regarding the total number of oocytes retrieved and good-quality embryos (level 2).[12] To enhance the challenge, two recent meta-analysis have shown that LT4 supplementation in women with SCH can significantly reduce the risk of miscarriage after assisted reproductive technologies (ARTs) in almost 50% (RR: 0.51; 95%CI: 0.32–0.82), but not the rate of preterm birth (RR: 1.13; 95% CI: 0.65–1.96). In women with TAI, LT4 supplementation reduced the risks of pregnancy loss (RR: 0.61; 95%CI: 0.39–0.96; $p = 0.03$) and preterm birth (RR: 0.49; 95%CI: 0.30–0.79; $p = 0.003$) in naturally-conceived pregnancies, but not in pregnancies achieved by ARTs (level 1).[17] These results support previous similarly-designed studies (level 1).[16,22] As a matter of fact, the last Cochrane review[23] concluded that evidence is not sufficient to support the recommendation of one prepregnancy or mid-pregnancy intervention over another, in cases of SCH (level 1). Given that their findings were only based on two trials with a moderate risk of bias, and that new trials have been published after that, the conclusion of a reduction in preterm birth and a trend toward reduced miscarriage with the use of LT4 therapy should be taken with caution when deciding to treat euthyroid women. More recently, a Cochrane systematic review[18] evaluated the LT4 treatment in subfertile women with SCH undergoing ARTs. Only in one study involving 64 women with both subclinical hypothyroidism and positive or negative TPOAb, LT4 replacement provided an improvement in the rate of live births (RR: 2.13; 95%CI: 1.07–4.21), with similar miscarriage rates (RR: 0.11; 95%CI: 0.01–1.98) (level 1).[18] Nevertheless, the authors could not draw clear conclusions due to the low to very low quality of the evidence reported.

Finally, according to the American Society for Reproductive Medicine,[3] evidence that SCH (defined as TSH > 2.5 mIU/L with a normal level of fT4) affects fertility or induces miscarriages is insufficient. In the absence of specific recommendations for women attempting pregnancy, there is a suggestion to use pregnancy thresholds to minimize the potential risks associated with SCH. The American Thyroid Association[2] has published recommendations on the thresholds; briefly, in the absence of TAI, LT4 replacement is recommended for women presenting with TSH > 10.0 mIU/L (strong recommendation, but based on low-quality evidence), and could be considered for those presenting with TSH ≥ 4.0 mIU/L and < 10.0 mIU/L (weak recommendation, also based on low-quality evidence).

Thyroid Autoimmunity

Thyroid autoimmunity seems to be relatively common among women of reproductive age, and it might be associated with subfertility and adverse pregnancy outcomes, like miscarriage, recurrent miscarriage and preterm birth. Although not consensual, the literature suggests that the administration of LT4 can improve reproductive outcomes in women with normal thyroid function and positive thyroid autoantibodies (level 1).[9,20,28]

First of all, the association between TAI and impaired fertility is still to be proven. In the study by Plowden et al,[12] TAI (TGAb ≥ 115 IU/mL and/or TPOAb ≥ 35 IU/mL) was examined in relation to time to biochemical pregnancy, pregnancy loss, and live birth among women with normal fT4 with one or two previous pregnancy losses. The authors did not find a significant delay in pregnancy (OR: 1.11; 95%CI: 0.88–1.40), higher risk of pregnancy loss (RR: 0.90; 95%CI: 0.61–1.33) or impaired live birth rate in women with circulating anti-thyroid antibodies (RR: 1.04; 95%CI: 0.90–1.20), even after adjusting for age and body mass index (level 2).[12]

Addiotnally, according to van den Boogaard et al,[9,29] no association was found between TAI and the rates of clinical pregnancy after IVF in the meta-analysis of seven studies (OR: 0.71; 95%CI: 0.36–1.4). However, the same study found elevated odds for unexplained subfertility (OR: 1.47; 95%CI: 1.06–2.02; $p = 0.02$), miscarriage (OR: 3.73; 95%CI: 1.83–7.6; $p = 0.0003$), recurrent miscarriage (OR: 2.26; 95%CI: 1.46–73.5; $p = 0.0003$), and preterm delivery (OR: 1.93; 95%CI: 1.08–3.47; $p = 0.03$) among euthyroid women positive for thyroid autoantibodies (level 1).[9,29]

In the same sense, the meta-analysis[20] of seven homogeneous cohort studies demonstrated a significant elevation in the odds of miscarriage among subfertile women presenting with thyroid autoantibodies (OR: 3.15; 95%CI: 2.23–4.44; $p < 0.001$), especially TPOAb, but such an association was not proven by analyzing the three eligible studies involving women with recurrent pregnancy loss. Moreover, the authors found a 2-fold increase in the odds of preterm birth in the presence of TAI (OR: 2.07; 95%CI: 1.17–3.68; $p = 0.01$), with a significant 52% reduction in the relative risk of miscarriage (RR: 0.48; 95% CI: 0.25- 0.92; $p = 0.03$) and a 69% reduction in the relative risk of preterm birth (RR: 0.31 95%CI: 0.11–0.9; $p < 0.05$) when LT4 was supplemented in women with thyroid autoantibodies (level 1).[20] Finally, in a recent meta-analysis, Dong et al[19] showed an association between TAI and recurrent pregnancy loss (OR: 1.94; 95%CI: 1.43–2,.4), but LT4 did not improve the pregnancy outcomes (level 1).[19]

Despite the aforementioned findings, Vissenberg et al[21] could not demonstrate the benefits of treating euthyroid women with positive thyroid autoantibodies with LT4 (level 1).[21] In a preview cohort study, Raber et al[7] did not find a significant association between the presence of TPOAb and TGAb and pregnancy or abortion rates in infertile women with or without SCH followed-up for more than 5 years (level 4). In accordance to those results, Dhillon-Smith et al[25] could not find significant differences in the rates of live births after at least 34 weeks of pregnancy by using 50 µg of LT4 once a day, started before conception and continued throughout pregnancy, among euthyroid women with TPOAb with a history of miscarriage or infertility. There was also no significant effect of LT4 on other pregnancy or neonatal outcomes, including the incidence of miscarriage and preterm birth (level 1).[25]

Another trial[14] evaluated the treatment with LT4 initiated between 2 and 4 weeks before the controlled ovarian hyperstimulation for IVF and continued through the end of pregnancy in women with normal thyroid function who tested positive for TPOAb. The LT4 treatment did not reduce rates of miscarriage or improved the rates of live births compared with the usual care (level 1).[14] A recent Cochrane Systematic Review[18] also showed no differences in miscarriage rates or live-birth rates with the LT4 treatment or placebo in a similar group of women undergoing ARTs (level 1).

Beside all the lack of evidence to support the use of LT4 in euthyroid women with positive antibodies, Bartáková et al[11] analyzed the reproductive outcomes of 258 women up to 47 months after an episode of spontaneous abortion in the first trimester, and 43% of them were "positive for thyroid disorders" (level 3). Despite the fact that they found a significantly lower rate of secondary infertility among women treated with LT4 when compared with the controls and untreated women (4.1% versus 10.9% versus 21.1% respectively), such a finding was not clear when they compared the controls to treated and untreated positive women together (10.9% versus 9.9% respectively). The authors concluded that screening for thyroid disorders in women after spontaneous abortion and treatment with LT4 is cost-saving and improves the subsequent pregnancy rate.

In the absence of specific recommendations for women attempting pregnancy, some defend the use of pregnancy thresholds to minimize the potential risks associated with TAI. According to the most recent American Thyroid Association (ATA) recommendations,[2] pregnant women presenting with TSH $>$ 2.5 mIU/L should be regularly evaluated for TPOAb; briefly, for those TPOAb-positive, LT4 therapy is recommended if TSH $\geq$ 4.0 mIU/L (strong recommendation, based on moderate-quality evidence), and could be considered for those presenting with TSH $>$ 2.5 mIU/L and $<$ 4.0 mIU/L (weak recommendation, also based on moderate-quality evidence).

Practical Aspects

In the absence of sufficiently consistent scientific evidence on the approach of thyroid function in women attempting to conceive, and considering the aforementioned findings, we propose the following practical aspects:

1. Healthy women actively attempting to conceive should not be evaluated for thyroid disorders (strong recommendation, evidence of moderate quality);[12]
2. Infertile women should be evaluated for thyroid disorders;[3]
3. In infertile women presenting with TSH $>$ 2.5 mIU/L, evaluate the TPOAb:
   (a) The LT4 therapy is recommended (strong recommendation, evidence of low to moderate quality) for women presenting:
      i. TPOAb-positive, TSH $\geq$ 4.0 mIU/L;
      ii. TPOAb-negative, TSH $>$ 10.0 mIU/L;
   (b) The LT4 therapy may be individually considered (weak recommendation, evidence of moderate quality) for women presenting:
      i. TPOAb-positive, TSH $>$ 2.5 mIU/L and $<$ 4.0 mIU/L;
      ii. TPOAb-negative, TSH $\geq$ 4.0 mIU/L and $<$ 10.0 mIU/L;[2]
4. The LT4 therapy is not recommended (strong recommendation, evidence of high quality) for women presenting:
   (a) TSH $\leq$ 2.5 mIU/mL;
   (b) TPOAb-negative, TSH $<$ 4.0 mIU/L.[2]

Laboratorial Pitfalls

Thyroid function tests (TFTs) are routinely ordered, but the evaluation and interpretation of the results may be difficult at times due to technical problems. The pitfalls in the hormonal evaluation can be preanalytical, analytical, and postanalytical. The preanalytical factors include age, pregnancy, use of medications (such as oral contraceptives and biotin), genetic mutations, systemic diseases, and critical illnesses. The analytical errors occur due to heterophile antibodies and macro-TSH. The postanalytical errors include wrong registration of the result by the laboratory, mistakes in the units of the parameter checked, and failure to identify the normal data.[28,30] Thus, before taking clinical decisions, it is important that the physician become aware of those challenges and repeat the test in case of doubt.

Final Considerations

The decision to treat SCH, particularly in women attempting pregnancy and infertile women, remains controversial, since the current understanding of the effect of thyroid dysfunction and/or autoimmunity on reproductive outcomes is based largely on low quality evidence. For this reason, the findings on the reproductive influence of SCH and TAI should be considered with care. Also because of the lacking evidence, the treatment with LT4 should not be established as a routine for women with SCH or those positive for thyroid autoantibodies as isolated findings, even assuming that potential benefits may outweigh the potential risks. As a matter of fact, the use LT4 will certainly benefit pregnant women with clinical hypothyroidism, and is an accepted strategy for those with a combination of TAI and elevated TSH. The treatment may be extended with caution and informed consent when that combination is found in subfertile women or those attempting pregnancy, but future better-designed studies are expected to support strong recommendations. Finally, screening for thyroid dysfunctions may be considered reasonable in women who are attempting to conceive and in the initial stage of pregnancy, but this is not consensual. Regarding the treatment with LT4, it is well established only in cases of clinical hypothyroidism, but it should be accepted in the following situations: 1) SCH associated to infertility; 2) TAI with TSH $\geq$ 4.0 mIU/L; or 3) when TSH $>$ 10.0 mIU/L. Therefore, it should not be a rule for subclinical conditions, especially in the absence of autoimmunity. In the case of an individualized treatment for those who are candidates for maternity, we suggest that the same guidelines provided for pregnancy should be followed.

Conflict of Interests
The authors have no conflict of interests to declare.

References

1 Gracia CR. Thyroid in Reproduction. Semin Reprod Med. 2016;34 (06):315–316. Doi: 10.1055/s-0036-1593490

2 Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27(03):315–389. Doi: 10.1089/thy.2016.0457

3 Practice Committee of the American Society for Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: a guideline. Fertil Steril. 2015;104(03):545–553. Doi: 10.1016/j.fertnstert.2015.05.028

4 Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al; Guidelines Committee, National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid. 2003;13(01):3–126. Doi: 10.1089/105072503321086962

5 Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev. 2014;13(4-5):391–397. Doi: 10.1016/j.autrev.2014.01.007

6 Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, et al. The 2011 Oxford CEBM Evidence Levels of Evidence: introductory document [Internet]. 2011 [cited 2020 May 12]. Available from: https://www.cebm.net/2011/06/2011-oxford-cebm-levels-evidence-introductory-document/

7 Raber W, Nowotny P, Vytiska-Binstorfer E, Vierhapper H. Thyroxine treatment modified in infertile women according to thyroxine-releasing hormone testing: 5 year follow-up of 283 women referred after exclusion of absolute causes of infertility. Hum Reprod. 2003;18(04):707–714. Doi: 10.1093/humrep/deg142

8 Abdel Rahman AH, Aly Abbassy H, Abbassy AAE. Improved in vitro fertilization outcomes after treatment of subclinical hypothyroidism in infertile women. Endocr Pract. 2010;16(05):792–797. Doi: 10.4158/EP09365.OR

9 van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M, et al. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Hum Reprod Update. 2011; 17(05):605–619. Doi: 10.1093/humupd/dmr024

10 Kim CH, Ahn JW, Kang SP, Kim SH, Chae HD, Kang BM. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril. 2011;95(05):1650–1654. Doi: 10.1016/j.fertnstert.2010.12.004

11 Bartáková J, Potluková E, Rogalewicz V, Fait T, Schöndorfová D, Telička Z, et al. Screening for autoimmune thyroid disorders after spontaneous abortion is cost-saving and it improves the subsequent pregnancy rate. BMC Pregnancy Childbirth. 2013;13:217. Doi: 10.1186/1471-2393-13-217

12 Plowden TC, Schisterman EF, Sjaarda LA, Zarek SM, Perkins NJ, Silver R, et al. Subclinical hypothyroidism and thyroid autoimmunity are not associated with fecundity, pregnancy loss, or live birth. J Clin Endocrinol Metab. 2016;101(06):2358–2365. Doi: 10.1210/jc.2016-1049

13 Busnelli A, Paffoni A, Fedele L, Somigliana E. The impact of thyroid autoimmunity on IVF/ICSI outcome: a systematic review and meta-analysis. Hum Reprod Update. 2016;22(06):775–790. Doi: 10.1093/humupd/dmw019

14 Wang H, Gao H, Chi H, Zeng L, Xiao W, Wang Y, et al. Effect of levothyroxine on miscarriage among women with normal thyroid function and thyroid autoimmunity undergoing in vitro fertilization and embryo transfer: a randomized clinical trial. JAMA. 2017; 318(22):2190–2198. Doi: 10.1001/jama.2017.18249

15 Cai Y, Zhong L, Guan J, Guo RJ, Niu B, Ma YP, et al. Outcome of in vitro fertilization in women with subclinical hypothyroidism. Reprod Biol Endocrinol. 2017;15(01):39. Doi: 10.1186/s12958-017-0257-2

16 Li J, Shen J, Qin L. Effects of levothyroxine on pregnancy outcomes in women with thyroid dysfunction: a meta-analysis of randomized controlled trials. Altern Ther Health Med. 2017;23(02):49–58

17 Rao M, Zeng Z, Zhao S, Tang L. Effect of levothyroxine supplementation on pregnancy outcomes in women with subclinical hypothyroidism and thyroid autoimmuneity undergoing in vitro fertilization/intracytoplasmic sperm injection: an updated meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2018;16(01):92. Doi: 10.1186/s12958-018-0410-6

18 Akhtar MA, Agrawal R, Brown J, Sajjad Y, Craciunas L. Thyroxine replacement for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism. Cochrane Database Syst Rev. 2019;6(06):CD011009. Doi: 10.1002/14651858.CD011009.pub2

19 Dong AC, Morgan J, Kane M, Stagnaro-Green A, Stephenson MD. Subclinical hypothyroidism and thyroid autoimmunity in recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril. 2020;113(03):587–600.e1. Doi: 10.1016/j.fertnstert.2019.11.003

20 Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ. 2011; 342:d2616. Doi: 10.1136/bmj.d2616

21 Vissenberg R, van den Boogaard E, van Wely M, van der Post JA, Fliers E, Bisschop PH, et al. Treatment of thyroid disorders before conception and in early pregnancy: a systematic review. Hum Reprod Update. 2012;18(04):360–373. Doi: 10.1093/humupd/dms007

22 Velkeniers B, Van Meerhaeghe A, Poppe K, Unuane D, Tournaye H, Haentjens P. Levothyroxine treatment and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction technologies: systematic review and meta-analysis of RCTs. Hum Reprod Update. 2013;19(03):251–258. Doi: 10.1093/humupd/dms052

23 Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E. Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. Cochrane Database Syst Rev. 2013; (05):CD007752. Doi: 10.1002/14651858.CD007752.pub3

24 Negro R, Schwartz A, Stagnaro-Green A. Impact of levothyroxine in miscarriage and preterm delivery rates in first trimester thyroid antibody positive women with TSH less than 2.5 mIU/L. J Clin Endocrinol Metab. 2016;101(10):3685–3690. Doi: 10.1210/jc.2016-1803

25 Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, et al. Levothyroxine in women with thyroid peroxidase antibodies before conception. N Engl J Med. 2019; 380(14):1316–1325. Doi: 10.1056/NEJMoa1812537

26 Rao M, Zeng Z, Zhou F, Wang H, Liu J, Wang R, et al. Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity: a systematic review and meta-analysis. Hum Reprod Update. 2019;25(03):344–361. Doi: 10.1093/humupd/dmz003

27 Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism: a review. JAMA. 2019;322(02):153–160. Doi: 10.1001/jama.2019.9052

28 Garg MK, Mahalle N, Hari Kumar KVS. Laboratory evaluation of thyroid function: dilemmas and pitfalls. Med J DY Patil Univ. 2016;9(04):430–436

29 van den Boogaard E, Vissenberg R, Land JA, van Wely M, ven der Post JA, Goddijn M, et al. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Hum Reprod Update. 2016;22(04):532–533. Doi: 10.1093/humupd/dmw003

30 Vandendriessche B, Lapauw B, Kaufman JM, Fiers T. A practical approach towards the evaluation of aberrant thyroid function tests. Acta Clin Belg. 2020;75(02):155–162. Doi: 10.1080/17843286.2019.1577531

Update on Thrombocytopenia in Pregnancy

Atualização sobre trombocitopenia na gravidez

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Abstract

Thrombocytopenia, defined as platelet count $< 150{,}000\ mm^3$, is frequently diagnosed by obstetricians since this parameter is included in routine surveillance during pregnancy, with an incidence of between 7 and 12%. Therefore, decisions regarding subsequent examination and management are primordial. While most of the cases are due to physiological changes, as gestational thrombocytopenia, other causes can be related to severe conditions that can lead to fetal or maternal death. Differentiating these conditions might be challenging: they can be pregnancy-specific (pre-eclampsia/HELLP syndrome [hemolysis, elevated liver enzymes, low platelets]), or not (immune thrombocytopenia purpura, thrombotic thrombocytopenic purpura or hemolytic uremic syndrome). Understanding the mechanisms and recognition of symptoms and signs is essential to decide an adequate line of investigation. The severity of thrombocytopenia, its etiology and gestational age dictates different treatment regimens.

Keywords
- thrombocytopenia
- pregnancy
- preeclampsia
- HELLP syndrome
- thrombotic microangiopathy

Resumo

Trombocitopenia, definida como uma contagem de plaquetária $< 150.000\ mm^3$, é frequentemente diagnosticada pelos obstetras, uma vez que este parâmetro está incluído na vigilância de rotina durante a gravidez, com uma incidência de entre 7 e 12%. Assim, decisões relativas à avaliação e orientação subsequentes são primordiais. Embora a maioria dos casos ocorra devido a alterações fisiológicas, como a trombocitopenia gestacional, outras causas podem estar relacionadas com condições graves que podem levar à morte fetal ou materna. Distinguir entre estas entidades pode ser desafiante: elas podem ser específicas da gravidez (pré-eclâmpsia/síndrome HELLP [*hemolysis, elevated liver enzymes, low platelets*]) ou não (púrpura trombocitopênica imune, púrpura trombocitopênica trombótica ou síndrome hemolítico urêmico). Compreender os mecanismos e reconhecer os sinais e sintomas é essencial para decidir uma adequada linha de investigação. A severidade da trombocitopenia, a sua etiologia e a idade gestacional ditam regimes de tratamento diferentes.

Palavras-chave
- trombocitopenia
- gravidez
- pré-eclâmpsia
- síndrome HELLP
- microangiopatia trombótica

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Introduction

Thrombocytopenia, defined as platelet count of $< 150{,}000\ mm^3$, is a frequent diagnosis during pregnancy, occurring in 7 to 12% of pregnancies.[1,2] Mild thrombocytopenia corresponds to platelet count $> 100{,}000\ mm^3$, moderate between 50,000 and $100{,}000\ mm^3$, while severe thrombocytopenia relates to platelets $< 50{,}000\ mm^3$.[3] It may be related to physiologic changes or pathological conditions, some of which are unique to pregnancy and may pose significant risk to both mother and child.[1]

Thrombocytopenia typically results in mucosal bleeding consequent to primary hemostasis defect.[1,4] As so, clinical presentation includes epistaxis, gingival bleeding or abnormal uterine bleeding; other common signs are petechiae and ecchymosis. Life-threatening bleeding is infrequent and is restricted to patients with extremely low platelet levels, presenting as hematuria, gastrointestinal bleeding and, rarely, intracranial hemorrhage.[1] However, platelet count $> 50{,}000\ mm^3$ is mostly asymptomatic, if their function is normal.[3] In pregnancy, most cases of thrombocytopenia are due to hemodilution and increased platelet destruction. Decreased production is not common, and when it occurs, it is mainly associated with nutritional deficiencies.[1] A complete medical history including medication, medical conditions and physical exam are mandatory. Laboratory testing should include complete blood count, peripheral blood smear, liver and renal function tests, coagulation study, antiphospholipid antibodies, antinuclear antibodies, human immunodeficiency virus (HIV) serology, hepatitis C antibody and hepatitis B surface antigen.[2,5]

Physiological Changes during Pregnancy

It is usual to find low platelet count in pregnant women, beginning in the first trimester and gradually decreasing through gestation, with nadir at delivery.[6] This condition is due to physiological hemodilution, increased platelet activation and clearance, and transient flow sequester in placental circulation.[7] A recent retrospective cohort study of 4,568 women evaluated the course of platelet count throughout uncomplicated pregnancies. Comparing with the mean platelet count in nonpregnant women ($273{,}000\ mm^3$), pregnant women had decreased count since the first trimester, worsening during gestation. Twin pregnancies had a lower platelet count during pregnancy and at delivery compared with single pregnancies, possibly due to greatest plasma volume or larger placental size.[6,8]

Pregnancy-Related Conditions

Gestational Thrombocytopenia

Gestational thrombocytopenia (GT) is the most common etiology of thrombocytopenia during gestation, occurring in 5 to 11% of pregnancies.[1,9] It is responsible for 75 to 80% of all thrombocytopenias in pregnant women, and its pathogenesis most likely results from hemodilution and accelerated platelet clearance.[1,3,9,10] There is no personal history of thrombocytopenia outside pregnancy, but the risk of recurrence is 14.2 times higher among women with previous GT.[1,6,11] Gestational thrombocytopenia can occur at any point of pregnancy, but it is most frequent during mid-to late-second or third trimester.[11] In the setting of thrombocytopenia in pregnancy, it is indicated a complete blood count and examination of the peripheral blood smear, to exclude pseudothrombocytopenia due to EDTA platelet clumping.[1,8] Stable platelet count $> 100{,}000\ mm^3$ in asymptomatic pregnant women are due to GT and do not require further investigation nor specific intervention other than periodic monitoring.[1,3,8,9,12] There is no evidence of the ideal frequency of platelet count, but a monthly platelet count is suggested. This is a diagnosis of exclusion, with no specific laboratory tests.[1] Other causes should be considered if there is a platelet count $< 100{,}000\ mm^3$, as only between 1 and 5% of GT cases develop platelet count below this value (although some authors suggest investigation if platelet count is $< 70{,}000\ mm^3$).[5,6,8,10] Most international guidelines suggest excluding epidural anesthesia with a platelet count between $< 70{,}000$ and $80{,}000\ mm^3$, due to epidural hematoma risk and spinal cord compression; however, others accept lower platelets (50,000 to $70{,}000\ mm^3$), provided that there is no suspicion of pre-eclampsia (PE) or hemolysis, elevated liver enzymes and low platelets syndrome (HELLP syndrome).[1,8,12] An anesthetic evaluation during the third trimester of pregnancy is advised in cases of moderate to severe thrombocytopenia.[3] Steroids should be considered with platelets $< 50{,}000\ mm^3$, as the diagnosis of immune thrombocytopenic purpura (ITP) cannot be excluded; in GT, there is no response to steroids or intravenous immunoglobulin (IVIg).[3,12] Interventions as elective cesarean delivery are not indicated and there is no risk of maternal bleeding complications nor fetal hemorrhage, since this condition is not associated with neonatal thrombocytopenia).[1,3,5] Recovery to normal platelet count occurs within between 1 and 2 months of delivery, so a platelet count is recommended 6 weeks after birth.[3,10,12]

Pre-eclampsia

Hypertensive disorders of pregnancy are responsible for 5 to 21% of maternal thrombocytopenia.[1] Pre-eclampsia is characterized by new onset hypertension after 20 weeks of pregnancy associated with at least one additional feature: proteinuria, thrombocytopenia ($< 100{,}000\ mm^3$), renal insufficiency, impaired liver function, pulmonary edema and/or new onset of headache.[13] Nearly 50% of PE cases develop thrombocytopenia and it might be one of the earliest signs and preceding hypertension in PE, being considered a severe feature of this condition.[1,9,10,12,13] Typically, a sudden decrease in platelet count should lead to PE hypothesis. Hemorrhage seldom occurs, unless in the presence of disseminated intravascular coagulopathy (DIC).[1] The pathogenesis of thrombocytopenia in these cases is due to thrombotic microangiopathy (TMA), owing to injured endothelium causing platelet aggregation and adhesion, enhancing platelet consumption, and thrombin generation in small vessels.[3,9,12] Characteristic alterations include schistocytes on peripheral blood smear, elevated bilirubin and lactate dehydrogenase (LDH), with decreased haptoglobin.[12] Treatment is delivery, ideally at or after 34 weeks of gestation; expectant management of PE with severe features before 34 weeks depends on maternal and fetal

stability and is based on strict selection criteria.[13] Platelet transfusions are reserved for patients with active bleeding or undergoing cesarean delivery, to increase maternal platelet count > 50,000 mm^3. However, the benefit is temporary, due to accelerated platelet destruction.[1] Thrombocytopenia in the setting of PE or HELLP syndrome may improve more quickly with corticosteroids, but no differences were found in terms of maternal mortality or morbidity.[1,5,14] Decrease in platelet count is often seen for between 24 and 48 hours postpartum, improving rapidly thereafter, unlike other TMAs.[15]

Hemolysis, elevated liver enzymes and low platelets syndrome

Hemolysis, elevated liver enzymes and low platelets syndrome syndrome is characterized by platelet count < 100,000 mm^3, elevated liver function tests and microangiophatic hemolytic anemia (MHA), related to endothelial damage and coagulation activation.[13,16,17] Hemolysis, elevated liver enzymes and low platelets syndrome may result from a continuum of PE, in 10% of cases, or might occur without pre-eclamptic features, like hypertension and proteinuria, in up to 15% of cases.[12,13] Besides being more frequent in the third trimester, it can present first postpartum, in 30% of the cases.[16] Clinical manifestations include upper abdominal pain, nausea, vomiting, malaise, headache and, rarely, jaundice.[17] This condition imposes an aggressive management, as DIC occurs in 20% of cases, which can lead to massive hemorrhage, placental abruption and hepatic rupture, implying high maternal morbidity and mortality.[3,17] Delivery is the only treatment, regardless of the gestational age.[13] Similarly to PE, there is insufficient evidence to support the use of corticosteroids in HELLP management, and 90% of patients will have platelet count > 100,000 mm^3 with supportive care within the first postpartum week. In case of DIC, fresh frozen plasma with or without cryoprecipitate may be required.[10,13,14,17]

Acute Fatty Liver of Pregnancy

This rare life-threatening condition (6–14:100,000 pregnancies) typically occurs in the third trimester and seems to be related to estrogen elevation in late pregnancy, fatty acid metabolism disorder and mitochondrial dysfunction.[18] Clinical manifestations include abdominal pain, malaise, anorexia, nausea and vomiting. As this condition progresses, liver failure and encephalopathy may ensue. Blood pressure usually is in the normal range.[8,17] Analytically, there is severe hypoglycemia, hyperuricemia, elevated transaminases and bilirubin, renal impairment, coagulopathy, and thrombocytopenia (present in < 50% of cases).[5] Patients can be diagnosed according to the Swansea criteria and acute fatty liver of pregnancy (AFLP) can be confirmed with hepatic biopsy, demonstrating microvesicular steatosis.[17] Severe HELLP syndrome is the main differential diagnosis, but hypoglycemia and coagulopathy are key features of AFLP.[10,17] Early delivery is mandatory, and supportive care may be required for several days or weeks, including correction of coagulopathy and dialysis.[17] Some authors suggest plasmapheresis, implying a mortality rate of 17%, compared with 81% in those with supportive care only.[18]

Medical Conditions

Primary Immune Thrombocytopenia

Primary immune thrombocytopenia, also known as ITP, is an acquired autoimmune disorder characterized by production of antiplatelet antibodies causing isolated thrombocytopenia, accounting for between 1 and 4% of pregnancy thrombocytopenia.[1–3,9] Impaired platelet production by thrombopoietin also plays a role.[3,4] Preconception or early pregnancy platelet count is important in distinguishing ITP from GT, since ITP typically presents prior to pregnancy or during the first trimester.[8,9,12] Similarly to GT, ITP diagnosis is based mainly on the exclusion of other causes of isolated thrombocytopenia, as definitive diagnostic tests are lacking.[1,8] Initial evaluation should include a complete medical history, full physical examination, full blood count and peripheral blood film, to exclude pseudothrombocytopenia or TMA (►**Table 1**).[7] Assays for the detection of antiplatelet antibodies lack both sensitivity and specificity, so they should not be performed.[1,3] Thrombocytopenia < 100,000 mm^3 is suggestive of ITP, and < 50,000 mm^3 is almost definitely related to this condition.[1] An international consensus suggests that pregnant patients with a suspicious history of ITP or with a platelet count < 80,000 mm^3 should be investigated for possible ITP.[7] Owing to transplacental passage of maternal IgG antiplatelet antibodies, there is a risk of fetal and neonatal thrombocytopenia. Although maternal platelet count does not predict fetal platelet count, there are some warning factors: a previously affected sibling is the strongest predictor of neonatal thrombocytopenia; and maternal antiplatelet circulating antibodies are reversely correlated to neonatal platelet count.[2,8,19] A retrospective case study showed that almost one-fifth of infants will develop platelet count < 150,000 mm^3.[20] Neonatal platelet count < 30,000 mm^3 occurs approximately in between 1 and 5% of newborns, but severe hemorrhagic complications like intracranial hemorrhage are rare (< 1%). There is no evidence that cesarean delivery reduces the risk of intracranial hemorrhage.[2,3,10] Pregnancy surveillance should be managed combining obstetric and hematology settings: expert opinion suggests every trimester assessment in asymptomatic women in remission; if platelet count is < 80,000 mm^3, weekly monitoring should be considered, especially after 34 weeks.[1,2,10] Usually, no treatment is required during pregnancy, since most cases present with platelet count > 70,000 mm^3; however, at least between 15 and 35% may require treatment before labor.[3,10] Most women do not have bleeding complications, although there is a slight increase in postpartum hemorrhage, especially if platelet count is < 20,000 mm^3.[8,12] In fact, in a cohort study, 21% of women with severe thrombocytopenia had postpartum bleeding.[21] Accordingly, clinical practice guidelines from the American Society of Hematology advise treatment until 36 weeks or sooner if: delivery is imminent, or if platelet count falls < 30,000 mm^3; < 50,000 mm^3 near delivery; or if the patient is symptomatic.[5] Vaginal delivery is considered safe between > 20,000 and 30,000 mm^3; and operative vaginal or cesarean delivery with 50,000 mm^3. So, before delivery, the platelet count should be maintained > at 50,000 mm^3.[3,8,12] If ITP is suspected, fetal scalp electrodes

Table 1 Recommended tests x Associated conditions

Recommended tests	Associated conditions
CBC and peripheral blood smear	Pseudothrombocytopenia, pancytopenia, hemolysis
Reticulocyte count	Hemolysis, hypertensive disorders
Coagulation screening (PT/PTT) and fibrinogen	DIC, severe liver disease
Liver function	Preeclampsia, HELLP syndrome
LDH	Hemolysis
Viral serologies (HIV,HCV)	Viral infection
Renal function	HUS, TTP, DIC
Optional	
ANA/APS	Systemic lupus erythematosus, antiphospholipid syndrome
ADAMTS13 activity & antibody	TTP
H. pylori testing	H. pylori infection
Thyroid function	Thyroid disorders
Immunoglobulin levels	Immunodeficiency disorders

Abbreviations: ANA, anti-nuclear antibodies; APS, antiphospholipid antibodies; CBC, complete blood count; DIC, disseminated intravascular coagulopathy; HELLP, hemolysis, elevated liver enzymes, low platelets; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; PTT, partial thromboplastin time; PT, prothrombin time; TTP, thrombotic thrombocytopenia purpura.

and operative vaginal delivery such as vacuum or forceps should be avoided.[2]

If the maternal count is $< 80{,}000\ mm^3$ in labor, a cord sample should be collected to check the baby's count, since it is difficult to exclude ITP. Until the fetal count is known, intramuscular vitamin K should be postponed.[3,8] Prednisolone and IVIg are considered first-line options.[5] In a retrospective study from two tertiary hospitals, there was no significant difference in maternal platelet response between the two.[22] Treatment should start with prednisolone, starting with 20 mg daily, increasing to 60 mg if there is an inadequate response in 1 week; the steroid dose should be tapered to the lowest effective dosage.[3,7] Some international guidelines recommend an initial dose of 1 mg/Kg, but there is no evidence that higher doses are more effective.[5,8] Platelet response is usually seen in between 4 and 14 days, and the same corticosteroid dosage should be maintained for 21 days before tapering.[1,2] Toward being able to receive epidural anesthesia, prednisolone can be initiated 10 days prior to anticipated delivery with between 10 and 20 mg/day in women with platelet count $< 80{,}000\ mm^3$.[5] In cases of inadequate response to steroids or if a rapid response is needed, IVIg has a rapid effect in increasing platelet count in between 1 and 3 days and a peak response within between 2 and 7 days. It is recommended 1 g/Kg as a one-time dose, and retreatment may be required every 2 to 4 weeks; increase in platelet count usually lasts 1 to 3 weeks. If there is no response, the next-line option is a combined prednisolone and IVIg treatment. IV immunoglobulin G anti-RhD treatment experience is limited.[1–3,7,8] Second-line treatments might be needed in women with platelet count $< 20{,}000$ to $30{,}000\ mm^3$ or $< 50{,}000\ mm^3$ near delivery, besides steroid or IVIg therapy. Medication used in nonpregnant women lack safety data in pregnancy. Immunosuppressants as azathioprine and cyclosporine have been used in pregnancy with acceptable side effects, but with delayed response, 3 to 6 months. Rituximab's response occurs in between 1 and 8 weeks, and can be considered in severe cases.[7,8] Splenectomy can be considered, preferably during the second trimester, as first trimester surgery is linked to risk of miscarriage and surgery during third trimester is technically difficult. Romiplostin and eltrombopag, thrombopoietin-receptor agonists, lack safety data in pregnancy, so their routine use during pregnancy is not yet recommended.[8] Nevertheless, Rodriguez Nuñez et al.[23] reported nine ITP cases treated during pregnancy with romiplostin, which was considered as an alternative option, without serious maternal or fetal side effects; nonetheless, the majority of pregnant women were treated after 20 weeks. Eltrombopag has also been safely used during pregnancy.[24] Platelet transfusions are not routinely recommended, as they will not provide long-term response, but should be available in the setting of significant bleeding or if platelet count is $< 50{,}000\ mm^3$ near delivery, in combination with IVIg.[2,5,8] Each unit of platelet concentration is expected to increase platelet count by 7,000 to $10.000\ mm^3$ in 1 hour in a 75-Kg individual.[2] Platelet count will not improve spontaneously after birth, unlike GT.[12] Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided during the postpartum period since there is an elevated hemorrhagic risk.[7]

Thrombotic Microangiopathies

Thrombotic microangiopathy can be pregnancy-related, such as preeclampsia and HELLP, or rarely nonpregnancy-related (for which pregnancy acts as a trigger), like thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS). Both are characterized by endothelial damage, microvascular thrombosis, consumptive thrombocytopenia, and intravascular hemolytic anemia.[15] Unlike pregnancy-related TMA, which rarely occurs before the second trimester, TTP/HUS can present

at any point during pregnancy and postpartum. In TTP, the mainstream form of presentation occurs after 30 weeks of pregnancy; HUS presents mostly postpartum.[25–27] In the setting of severe thrombocytopenia, even when considering preeclampsia or HELLP syndrome, an hemolysis screening including LDH levels and blood film should be requested.[17] In pregnancy with TMA, the stillbirth rate is high, $\sim$ 40%, caused by microvascular thrombosis, placental ischemia and infarction.[12] It is recommended to check regularly for signs of fetal distress or intrauterine growth restriction with uterine artery Doppler ultrasound. Premature delivery may be appropriate due to fetal prognosis.[12,17] Unlike PE/HELLP syndrome, the TTP/HUS disease course is not influenced by delivery.[12,15] Clinical persistence or deterioration between 48 and 72 hours postpartum should prompt TTP/HUS as a possible diagnosis, since PE/HELLP features improves within this period.[10,17]

Thrombotic Thrombocytopenia Purpura

Thrombotic thrombocytopenia purpura is a rare (1 in 25,000 pregnancies) life-threatening blood disorder, in which microthrombi develop in small blood vessels due to lack of ADAMTS13 enzyme activity, leading to persistence of ultra-large multimeters of von Willebrand factor, activating platelet receptors and consequently platelet aggregation.[3,15,17] The characteristic pentad includes MHA, thrombocytopenia, neurological symptoms/signs, renal dysfunction and fever.[3,15] However, up to 35% of patients lack some of the typical signs. Neurological symptoms may include several manifestations from headache to coma.[12] Mutations in the *ADAMTS13* gene are responsible for congenital deficiency of von Willebrand factor-cleaving protein (Upshaw-Schulman Syndrome). More frequently, an acquired form occurs due to autoantibody production that blocks enzyme activity. These two different etiologies can be distinguished by the presence of the inhibitor.[3] The diagnosis of TTP may be confirmed by reduced ADAMT13 activity ($<$ 10%) and/or by the presence of IgG antibodies to ADAMTS13. Additionally, laboratory findings include evidence of MHA, normal coagulation tests (TTP/HUS are not associated with coagulopathy) and increased serum creatinine.[12,15,17]

Plasmapheresis allows antibody removal in the acquired form. Fresh frozen plasma should be infused until platelet count is restored and the LDH level is reduced. Immunosuppression is also required in immune-mediated TTP, with steroids and azathioprine. Monoclonal antibody against CD20 (rituximab) is considered standard of care in the general population, but during pregnancy it is usually initiated postpartum, for safety issues. In congenital forms, fresh frozen plasma is enough to augment ADAMTS13 levels.[3,15] Once platelet count is restored, the frequency of plasmapheresis or plasma infusion will depend on subsequent platelet count and ADAMTS13 activity levels.[17] Platelet transfusions may precipitate central nervous system (CNS) symptoms, so they are contraindicated.[3,15] Pregnancy may trigger both acquired and congenital TTP. The risk of acquired TTP recurrence is reported to be $\sim$ 50%, and the risk of congenital TTP relapse is 100%, if no prophylaxis measures are taken, as reported in a Japanese series.[26,28] Some authors suggest low dose aspirin associated with prophylactic low molecular weight heparin in high thrombotic risk women during pregnancy.[17] This approach, including regular plasma therapy in congenital TTP, has been associated with 100% live births and maternal survival.[26] In congenital cases, if term is achieved, delivery is advisable by 37 weeks and induction of labor and vaginal delivery is encouraged.[17] In the acquired type, ADAMTS13 activity should be monitored in early pregnancy and at least each trimester; if the ADAMTS13 activity falls to $<$ 10%, plasma therapy with regular plasmapheresis and azathioprine as a steroid-sparing treatment should be considered. Rituximab can be used before conception to normalize ADAMTS13 levels in acquired cases.[17,26]

Hemolytic Uremic Syndrome

The clinical presentation of HUS is similar to that of TTP (MHA and thrombocytopenia), but with a poor renal prognosis, since the risk of end-stage renal disease is between 44 and 55%.[27] Infection is the main cause during childhood, due to Shiga-toxin production by E.coli O157:H7.[29] The atypical form is linked to a congenital defect that results in dysregulation of the alternate complement system pathway, known as complement-mediated HUS (CM-HUS).[12,15,17] Indeed, pregnancy is a potent complement activator, accounting for 7% of CM-HUS cases.[30]

This is an exclusion diagnosis, after ruling out TTP as well as other TMA causes.[15,17] Complement genetic testing can be performed to support the diagnosis.[25] Initial therapy includes plasmapheresis and fresh frozen plasma, and dialysis is frequently necessary.[12] Plasmapheresis is often ineffective, since the risk of end-stage renal disease is similar between patients who underwent plasmapheresis and those who did not, as shown by Bruel et al.[27] Eculizumab, a monoclonal anti-C5 inhibitor, is approved for CM-HUS in nonpregnant women and has been safely used in paroxysmal nocturne hemoglobinuria during pregnancy.[31] This complement inhibitor treatment is promising, since renal recovery may be achieved if eculizumab is started early. So, if CM-HUS is highly suspected, eculizumab should be started promptly.[15,27] A recent Russian series reports 35% maternal and 25% fetal mortality in CM-HUS.[30] Fetal outcomes seem better than in TTP, possibly because most cases present postpartum.[15] The risk of relapse and of chronic kidney disease should be discussed in women with history of CM-HUS, and a recommended approach is to restart eculizumab at the first sign of relapse.[15] Other authors suggest to start eculizumab in the second trimester, until the postpartum period, in women who are not already on complement inhibition therapy, as it can be difficult to anticipate relapse by routine laboratory tests in time to avoid serious maternal and fetal complications.[17]

Secondary Immune Thrombocytopenia and Systemic Conditions

Viral infections can cause transient thrombocytopenia. Human immunodeficiency virus (HIV) and cytomegalovirus are frequent underlying agents, and thrombocytopenia is thought to be caused through antibodies cross-reacting with platelets.[2,3]

Several medications can cause drug-induced thrombocytopenia, including unfractionated heparin (incidence of between 3 and 6%), penicillin, cephalosporins and NSAIDs.[2,3] A careful medication history is crucial for diagnosis. Antiphospholipid syndrome (APS) is an autoimmune disease characterized by arterial and venous recurrent thrombosis and/or recurrent early pregnancy loss, fetal loss or pregnancy morbidity related to placental insufficiency or pre-eclampsia.[32] Thrombocytopenia is a frequent clinical manifestation (20–40% of APS cases), mostly $> 70{,}000\ mm^3$.[33] Catastrophic APS, a rare acute multiorgan failure due to small vessels occlusion, may include thrombocytopenia in 60% of cases. Triggers are identified in 50% of cases, such as infections, surgery or obstetrics morbidity.[32,33] Pregnancy may also be a risk for acute "flares" of systemic lupus erythematosus, which might be associated to thrombocytopenia.[5] Disseminated intravascular coagulopathy implies an activation of the coagulation system leading to microvascular thrombus and multiple organ failure, mainly in the setting of placental abruption, uterine rupture, amniotic embolus and PE/HELLP syndrome. There will be thrombocytopenia, increase of the prothrombin time, partial thromboplastin time, decreased fibrinogen and increased fibrin degradation products like D-dimers.[12] Disseminated intravascular coagulopathy requires aggressive management, including fresh frozen plasma, cryoprecipitate and platelet transfusion.[3] Primary bone marrow disorders, such as myelodysplastic syndrome and acute leukemia, are extremely rare, but should be considered in the setting of pancytopenia, after exclusion of more frequent diagnosis such as nutritional deficiencies (folate or B12).[2,8] Vitamin B12 plays a vital role in DNA synthesis, and hematopoietic precursor cells are extremely sensitive to B12 deficiency. B12 deficiency should be suspected in the setting of prior bariatric surgery, inflammatory bowel disease, *Helicobacter pylori* infection, use of metformin or proton pump inhibitors, vegan diets or pernicious anemia.[34]

Heritable Platelets Function Disorders

Bernard-Soulier Syndrome

This autosomal recessive disorder affects $< 1{:}1{,}000{,}000$ individuals and is characterized by qualitative and quantitative defects of the platelet membrane glycoprotein Ib-IX-V complex.[9,35] Clinical manifestations include thrombocytopenia, prolonged bleeding time and the presence of giant platelets. Pregnancy course may be normal, but there might be severe bleeding during the peripartum period.[9,35] Primary postpartum bleeding has been reported in 33%, and secondary in 40% of pregnancies, leading in some cases to hysterectomy. Neonatal hemorrhagic complications such as intracranial bleeding may occur due to alloimmune thrombocytopenia. The use of rFVIIA associated with tranexamic acid is recommended, but DDAVP and platelet transfusions might be needed. The third stage of labor should be actively managed with uterotonics to avoid uterine atony. The safest mode of delivery is yet to be determined.[35]

Glanzmann Thrombasthenia

Glanzmann thrombasthenia is an autosomal recessive condition characterized by a deficiency or dysfunction of glycoprotein IIb-IIIa receptors on platelet, which is a receptor of fibrinogen, interfering with platelet aggregation, leading to prolonged bleeding time.[36] These individuals have normal platelet count and morphology, but there is no platelet aggregation. It is also associated with bleeding during pregnancy and the peripartum period. Different treatments have been proposed to prevent hemorrhage, such as platelet transfusion, recombinant factor VIIa concentrate and plasmapheresis, but due to the rarity of this disorder, recommendations are difficult to implement. Temporary fetal thrombocytopenia related to the presence of maternal HPA antibodies to platelet glycoproteins may lead to in utero death due to intracranial hemorrhage. There are no benefits in performing caesarean section to prevent neonatal morbidity/mortality.[9,36]

Conclusion

Gestational thrombocytopenia is by far the most common cause of thrombocytopenia during pregnancy and does not imply any fetal or maternal risk. The diagnosis of ITP, an immune-mediated condition, is one of exclusion; nevertheless, in almost two-thirds of cases there is a prepregnancy diagnosis. Most of the cases do not require treatment. Pre-eclampsia and HELLP syndrome are associated with thrombocytopenia, and early delivery may be necessary. Thrombotic microangiopathy due to TTP and CM-HUS occurs seldomly in pregnancy. Distinction from PE and HELLP syndrome may be challenging, and a multidisciplinary approach is often necessary. Intensive care management and close monitoring can help improve pregnancy outcomes. The prognosis for future pregnancies must be discussed with these women. The paucity of literature on the use of innovating effective agents in ITP and HUS (as thrombopoietin-receptor agonists or eculizumab), implies difficult decisions concerning risks of fetal and maternal outcomes associated with disease progression, against safety issues of their usage during pregnancy.

Conflict of Interests

The authors have no conflict of interests to declare.

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References

1 Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin no. 207: thrombocytopenia in pregnancy. Obstet Gynecol. 2019; 133(03):e181–e193. Doi: 10.1097/AOG.0000000000003100

2 Baucom AM, Kuller JA, Dotters-Katz S. Immune thrombocytopenic purpura in pregnancy. Obstet Gynecol Surv. 2019;74(08): 490–496. Doi: 10.1097/OGX.0000000000000697

3 Myers B. Review thrombocytopenia in pregnancy. Obstet Gynaecol. 2009;11:177–183. Doi: 10.1576/toag.11.3.177.27502
4 Zainal A, Salama A, Alweis R. Immune thrombocytopenic purpura. J Community Hosp Intern Med Perspect. 2019;9(01):59–61. Doi: 10.1080/20009666.2019.1565884
5 Rajasekhar A, Gernsheimer T, Stasi R, James AH. 2013 clinical practice guide on thrombocytopenia in pregnancy. Washington (DC): American Society of Hematology; 2013
6 Reese JA, Peck JD, Deschamps DR, McIntosh JJ, Knudtson EJ, Terrell DR, et al. Platelet counts during pregnancy. N Engl J Med. 2018; 379(01):32–43. Doi: 10.1056/NEJMoa1802897
7 Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019;3(22):3780–3817. Doi: 10.1182/bloodadvances.2019000812
8 Eslick R, McLintock C. Managing ITP and thrombocytopenia in pregnancy. Platelets. 2020;31(03):300–306. Doi: 10.1080/09537104.2019.1640870
9 Valera MC, Parant O, Vayssiere C, Arnal JF, Payrastre B. Physiologic and pathologic changes of platelets in pregnancy. Platelets. 2010; 21(08):587–595. Doi: 10.3109/09537104.2010.509828
10 Cines DB, Levine LD. Thrombocytopenia in pregnancy. Blood. 2017;130(21):2271–2277. Doi: 10.1182/blood-2017-05-781971
11 Rottenstreich A, Israeli N, Levin G, Rottenstreich M, Elchalal U, Kalish Y. Clinical characteristics, neonatal risk and recurrence rate of gestational thrombocytopenia with platelet count $<100 \times 10^9$/L. Eur J Obstet Gynecol Reprod Biol. 2018;231:75–79. Doi: 10.1016/j.ejogrb.2018.10.026
12 Ciobanu AM, Colibaba S, Cimpoca B, Peltecu G, Panaitescu AM. Thrombocytopenia in Pregnancy. Maedica (Bucur). 2016;11(01): 55–60
13 Wisner K. Gestational hypertension and preeclampsia. MCN Am J Matern Child Nurs. 2019;44(03):170. Doi: 10.1097/NMC.0000000000000523
14 Woudstra DM, Chandra S, Hofmeyr GJ, Dowswell T. Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy. Cochrane Database Syst Rev. 2010;(09): CD008148. Doi: 10.1002/14651858.CD008148.pub2
15 Neave L, Scully M. Microangiopathic hemolytic anemia in pregnancy. Transfus Med Rev. 2018;32(04):230–236. Doi: 10.1016/j.tmrv.2018.08.002
16 Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018;72(01): 24–43. Doi: 10.1161/HYPERTENSIONAHA.117.10803
17 Thomas MR, Robinson S, Scully MA. How we manage thrombotic microangiopathies in pregnancy. Br J Haematol. 2016;173(06): 821–830. Doi: 10.1111/bjh.14045
18 Ding J, Han LP, Lou XP, Geng LN, Liu D, Yang Q, et al. Effectiveness of combining plasma exchange with plasma perfusion in acute fatty liver of pregnancy: a retrospective analysis. Gynecol Obstet Invest. 2015;79(02):97–100. Doi: 10.1159/000368752
19 Khaspekova SG, Shustova ON, Golubeva NV, Naimushin YA, Larina LE, Mazurov AV. Circulating antiplatelet antibodies in pregnant women with immune thrombocytopenic purpura as predictors of thrombocytopenia in the newborns. Platelets. 2019;30(08): 1008–1012. Doi: 10.1080/09537104.2018.1557615
20 Loustau V, Debouverie O, Canoui-Poitrine F, Baili L, Khellaf M, Toubul C, et al. Effect of pregnancy on the course of immune thrombocytopenia: a retrospective study of 118 pregnancies in 82 women. Br J Haematol. 2014;166(06):929–935. Doi: 10.1111/bjh.12976
21 Care A, Pavord S, Knight M, Alfirevic Z. Severe primary autoimmune thrombocytopenia in pregnancy: a national cohort study. BJOG. 2018;125(05):604–612. Doi: 10.1111/1471-0528.14697
22 Sun D, Shehata N, Ye XY, Gregorovich S, de France B, Arnold DM, et al. Corticosteroids compared with intravenous immunoglobulin for the treatment of immune thrombocytopenia in pregnancy. Blood. 2016;128(10):1329–1335. Doi: 10.1182/blood-2016-04-710285
23 Rosa María RN, Laura RL, Ángeles PB, Laura LB. Use of Romiplostim during pregnancy as a rescue therapy in primary immune thrombocytopenia: Literature review and case description. Platelets. 2020;31(03):403–406. Doi: 10.1080/09537104.2019.1615613
24 Ferreira IJMCF, Sousa F, Vasco EM, Areia ALFA, Moura JPAS, Carda J, Ribeiro L. Severe immune thrombocytopenia in pregnancy treated with Eltrombopag - A case report. J Gynecol Obstet Hum Reprod. 2018;47(08):405–408. Doi: 10.1016/j.jogoh.2018.06.010
25 Gupta M, Govindappagari S, Burwick RM. Pregnancy-associated atypical hemolytic uremic syndrome: a systematic review. Obstet Gynecol. 2020;135(01):46–58. Doi: 10.1097/AOG.0000000000003554
26 Scully M, Thomas M, Underwood M, Watson H, Langley K, Camilleri RS, et al; collaborators of the UK TTP Registry. Thrombotic thrombocytopenic purpura and pregnancy: presentation, management, and subsequent pregnancy outcomes. Blood. 2014; 124(02):211–219. Doi: 10.1182/blood-2014-02-553131
27 Bruel A, Kavanagh D, Noris M, Delmas Y, Wong EKS, Bresin E, et al. Hemolytic uremic syndrome in pregnancy and postpartum. Clin J Am Soc Nephrol. 2017;12(08):1237–1247. Doi: 10.2215/CJN.00280117
28 Fujimura Y, Matsumoto M, Kokame K, Isonishi A, Soejima K, Akuyama N, et al. Pregnancy-induced thrombocytopenia and TTP, and the risk of fetal death, in Upshaw-Schulman syndrome: a series of 15 pregnancies in 9 genotyped patients. Br J Haematol. 2009;144(05):742–754. Doi: 10.1111/j.1365-2141.2008.07515.x
29 Sacerdoti F, Scalise ML, Burdet J, Amaral MM, Franchi AM, Ibarra C. Shiga toxin-producing escherichia coli infections during pregnancy. Microorganisms. 2018;6(04):111. Doi: 10.3390/microorganisms6040111
30 Kozlovskaya NL, Korotchaeva YV, Bobrova LA. Adverse outcomes in obstetric-atypical haemolytic uraemic syndrome: a case series analysis. J Matern Fetal Neonatal Med. 2019;32(17):2853–2859. Doi: 10.1080/14767058.2018.1450381
31 Sharma R, Keyzner A, Liu J, Bradley T, Allen SL. Successful pregnancy outcome in paroxysmal nocturnal hemoglobinuria (PNH) following escalated eculizumab dosing to control breakthrough hemolysis. Leuk Res Rep. 2015;4(01):36–38. Doi: 10.1016/j.lrr.2015.05.001
32 Sammaritano LR. Antiphospholipid syndrome. Best Pract Res Clin Rheumatol. 2020;34(01):101463. Doi: 10.1016/j.berh.2019.101463
33 Funke A, Danowski A, de Andrade DCO, Rêgo J, Levy RA. A importância de reconhecer a síndrome antifosfolípide na medicina vascular. J Vasc Bras. 2017;16(02):140–149. Doi: 10.1590/1677-5449.011416
34 Govindappagari S, Nguyen M, Gupta M, Hanna RM, Burwick RM. Severe vitamin B12 deficiency in pregnancy mimicking HELLP syndrome. Case Rep Obstet Gynecol. 2019;2019:4325647. Doi: 10.1155/2019/4325647
35 Peitsidis P, Datta T, Pafilis I, Otomewo O, Tuddenham EGD, Kadir RA. Bernard Soulier syndrome in pregnancy: a systematic review. Haemophilia. 2010;16(04):584–591. Doi: 10.1111/j.1365-2516.2009.02137.x
36 Wijemanne A, Watt-Coote I, Austin S. Glanzmann thrombasthenia in pregnancy: Optimising maternal and fetal outcomes. Obstet Med. 2016;9(04):169–170. Doi: 10.1177/1753495X16655021

Preeclampsia as an Inaugural Manifestation of Primary Hyperparathyroidism: A Case Report

Pré-eclâmpsia como manifestação inaugural de hiperparatiroidismo primário: Um caso clínico

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Abstract

Primary hyperparathyroidism is an endocrine disorder characterized by hypercalcemia and elevated or inappropriately normal levels of parathyroid hormone. The diagnosis is based on a biochemical evaluation, and a neck ultrasound is the first choice during pregnancy to access the parathyroid glands. Manifestations during pregnancy are rare and can be present with life-threatening complications, so the diagnosis is challenging. The conservative treatment is limited, and there is not enough data about its safety and efficacy during pregnancy. Surgery is the only curative treatment, and a parathyroidectomy performed during the second or third trimesters is considered safe. Recently, some authors suggested an association between primary hyperparathyroidism and preeclampsia. We describe a case of preeclampsia with severe features at 27 weeks of gestational age. The severity of the preeclampsia motivated an early termination of the pregnancy by cesarean section. During the postpartum period, the patient presented life-threatening complications, such as severe hypercalcemia and acute pancreatitis. An ultrasound exam found two parathyroid nodules, suggestive of parathyroid adenomas. The patient recovered after the pharmacological correction of the calcemia levels.

Keywords

- preeclampsia
- primary hyperparathyroidism
- hypercalcemia
- parathyroid adenomas

Resumo

O hiperparatiroidismo primário é um distúrbio endócrino caraterizado pela elevação do cálcio sérico associada a níveis de paratormona elevados ou inapropriadamente normais. O diagnóstico é baseado em análises bioquímicas, e, na gravidez, o exame de imagem de primeira linha é a ecografia cervical. É uma doença rara na gravidez, e pode se apresentar com complicações ameaçadoras de vida, pelo que o seu diagnóstico é desafiante. O tratamento médico disponível é limitado, havendo poucos dados relativos à sua eficácia e segurança na gravidez. A cirurgia é o único tratamento curativo, e pode ser realizada no segundo ou terceiro trimestres. Tem sido descrita uma

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- pré-eclâmpsia
- hiperparatiroidismo primário
- hipercalcemia
- adenomas paratiróideos

relação entre hiperparatiroidismo primário e pré-eclâmpsia. Apresenta-se um caso de uma grávida de 27 semanas com pré-eclâmpsia com critérios de gravidade, o que obrigou ao término da gravidez por cesariana. Verificou-se agravamento clínico no período pós-parto, com aparecimento de complicações graves, tais como hipercalcemia grave e pancreatite aguda. Ecograficamente, constataram-se duas massas paratiróideias sugestivas de adenomas da paratiroide. A doente recebeu tratamento médico, e teve melhora apenas após a correção dos níveis de cálcio sérico.

Introduction

Primary hyperparathyroidism (PHP) is the unregulated overproduction of parathyroid hormone (PTH) resulting in abnormal calcium homeostasis. It is very rare during pregnancy, and its exact incidence is unknown.[1] Most patients are asymptomatic, but if symptoms develop, they can mimic certain physiological alterations of pregnancy, such as nausea, vomiting, anorexia, weakness, fatigue and neurological/psychiatric manifestations, which can delay the diagnosis. The complications can be life-threatening, and they include nephrolithiasis, bone disease, pancreatitis, depression, uremia, seizures and coma.[2] Some authors suggest a possible association between PHP and preeclampsia (PE). Hultin et al.[3] reported a six-fold increased risk of developing PE in women with PHP. Schnatz and Thaxton[4] estimate that PE occurs in 25% of pregnant women with PHP. Acute pancreatitis during pregnancy is also a rare entity, with an incidence of 0.02% to 0.1%, and it is even rarer when associated to PHP.[5] The authors describe a case of preeclampsia with severe features, with the onset of acute pancreatitis after delivery, and the diagnosis of two parathyroid adenomas.

Case Description

A 40-year-old primigravida presented to our emergency department with headache, nausea, vomiting and upper abdominal pain at 27 weeks of gestational age. Upon examination, her blood pressure was elevated (162/98 mmHg), and the laboratory tests showed a random proteinuria of 3.30 g/L and an urine protein/creatinine ratio of 3.32 mg/dL. She was immediately admitted and received antihypertensive drugs (metildopa and nifedipine), betamethasone to promote fetal lung maturity, and magnesium sulfate for fetal neuroprotection. After 24 hours, the patient presented with uncontrolled hypertension despite the medical treatment, persistent abdominal pain, vomiting, peripheral edema, and behavioral alterations. A neurological examination was performed, revealing language abnormalities and impairment in performing simple tasks. A brain computed tomography (CT) disclosed no alterations. The urine protein excretion continued to rise, without other abnormal blood test results. An urgent cesarean section was performed due to PE with severe features. The newborn was a female, with a birth weight of 775 g, and APGAR score of 6/8/9. The neonate was transferred to the neonatal intensive care unit, and during admission she suffered from multiple prematurity complications, such as hyaline membrane disease III, jaundice, sepsis, peripheral cyanosis and anemia. The newborn presented with neonatal hypocalcemia, with no signs of tetany and with no specific treatment required. Due to the severity of the case, the puerpera was transferred to the intensive care unit for monitoring, where she presented clinical deterioration during the following 6 days, with resistant hypertension, anasarca, respiratory insufficiency, pericardial effusion, and delirium. The patient maintained persistent upper abdominal pain associated with fever, elevated white blood count (22,600/uL) and hyperamylasemia (584 U/L). An abdominal ultrasound revealed signs of uncomplicated pancreatitis. During the pancreatitis study, we found severely elevated levels of calcium (14 mg/dL) and serum PTH (616 pg/mL). A cervical ultrasound and a CT scan were then performed, and revealed the presence of 2 parathyroid masses with $10 \times 9 \times 12$ mm and $20 \times 14 \times 17$ mm, suggesting a parathyroid multipleadenoma. With the collaboration of the Endocrinology Department, the patient was diagnosed with PHP, and the treatment was initiated with a single dose of zolendronic acid and cinacalcet (30 mg orally every 12 hours). After the correction of the calcemia levels, the patient stabilized. The molecular screening was negative for multiple endocrine neoplasia syndrome type 1 (MEN1) and cell division cycle 73 (CDC73). The patient was discharged 13 days after delivery, and was scheduled for short-term outpatient follow-up and elective parathyroidectomy, with gradual clinical improvement. The newborn was discharged after 91 days.

Discussion

We present a case of PE with severe features in a primigravida of 27 weeks, with clinical deterioration in the postpartum period and the finding of severe hypercalcemia due to parathyroid multiple adenomas. Preeclampsia is a multisystem pregnancy disease that develops after 20 weeks of gestation. It is characterized by the onset of hypertension and proteinuria, or, in the absence of proteinuria, the finding of maternal-organ dysfunction. It is a major cause of maternal and fetal morbidity and mortality.[3]

The etiology of PE is not completely understood. Several mechanisms of disease have been proposed, such as chronic uteroplacentar ischemia, immune maladaptation, very-low-density lipoprotein toxicity, genetic imprinting, increased trophoblast apoptosis or necrosis, an exaggerated maternal inflammatory response, and an imbalance of angiogenic factors.[6]

Researchers have highlighted major risk factors, but have not yet provided the definitive causes of this multifactorial disease.[3]

An increased risk of PE has been showed in women with PHP, and patients with PHP frequently suffer from hypertension.[2,7] The link between these two disorders seems to be the interaction of PTH with the renin-aldosterone system, the sympathetic nervous system, and the vascular endothelium.[8]

Primary hyperparathyroidism is a relatively common endocrine disease. However, it is rare in pregnancy, with an incidence of around 8 cases per 100 thousand people annually.[7] There are less than 200 cases reported in literature.[2]

A diagnosis of PHP should be considered when a patient presents with elevated serum ionized calcium with a normal or elevated PTH. The cervical ultrasound is the first-line imaging technique in pregnancy for the diagnosis and location of parathyroid masses.

The diagnosis of PHP can be challenging during pregnancy, due to the wide range of presentations, which vary from nonspecific discomfort to end-organ damage.[9] Moreover, PHP is related to the presence of nonspecific symptoms that may mimic certain physiological changes that occur during pregnancy, such as nausea, vomiting and fatigue. This can lead to a delay in the diagnosis and management of this important disease during pregnancy.

High clinical suspicion and early diagnosis are of outmost importance and pose a clinical challenge, because of the rarity and nonspecific manifestations of this disease.

The most common cause is a solitary parathyroid adenoma, representing 80% to 85% of all cases, followed by parathyroid hyperplasia and multiple adenomas (15% to 20%), and parathyroid cancer ($< 1\%$).[10] The rare possibility of familial hypocalciuric hypercalcemia and hereditary syndromes, such as MEN-1 or MEN-2 and familial parathyroid hyperplasia syndromes, should be considered, particularly in women in reproductive age or younger.[11]

In the case herein reported, a diagnosis of multiple adenomas was made only after delivery, and, due to the severity of the manifestations and the age of the patient, it was crucial to exclude hereditary syndromes.

In 2/3 of the cases, PHP can lead to serious maternal complications, including acute pancreatitis, which is a sign of disease severity, nephrolithiasis, hyperemesis, hypercalcemia crisis, and so forth.[2,11]

As in the case reported by Dale et al.,[12] our patient also presented with pancreatitis, due to hyperparathyroid-induced hypercalcemia. But in contrast to the study by Dale et al.,[12] the patient in our case was diagnosed with pancreatitis after delivery and not previously, but both cases were well managed with supportive care.

In our case, the diagnosis of acute pancreatitis led us to the finding of severe hypercalcemia, and, subsequently, to the diagnosis of two parathyroid masses.

Preeclampsia in patients with PHP can lead to severe complications, such as intracerebral hemorrhage, retinal hemorrhage and hypertensive crisis.[9,13]

In the case herein reported, uncontrolled hypertension and the occurrence of acute neurological symptoms led us to exclude other pathologies, such as cerebrovascular event, posterior reversible encephalopathy syndrome, and cerebral venous sinus thrombosis.

Unlike the cases reported by Ghaznavi et al.[11] or Alharbi et al.[7] our patient suffered from severe neurological impairment, with full recovery after the treatment.[7,11]

Dale et al.[12] did not describe any important complications in the postpartum period. In our case, the clinical deterioration occurred after delivery, with complications such as anasarca, respiratory insufficiency, and pericardial effusion.[12]

Perinatal complications can occur in up to 80% of the fetus/neonates of mothers who did not undergo treatment for PHP, including fetal growth restriction, neonatal hypocalcemia, permanent hypocalcemia, tetany and death.[11,14,15] Neonatal hypocalcemia due to fetal parathyroid-gland suppression in the setting of maternal hypercalcemia is usually transient, as it was in our case, and with favorable evolution. The fetus also had growth restriction (percentile 2).[11]

There are no guidelines available for the management and treatment of PHP during pregnancy. The guidelines for the management of patients with PHP published in 2014 did not include recommendations for pregnant women.[16]

The treatment should be individualized, and should consider the symptoms, complications, gestational age and maternal and fetal estimated risk. A multidisciplinary team including an endocrinologist is of extreme importance.

Hypercalcemia can be reasonably managed with conservative treatments, such as hydration, calcitonin, cinacalcet and bisphosphonates. However, surgery is the only definitive treatment for parathyroid adenomas. A minimally-invasive parathyroidectomy during the second trimester is the therapeutic gold standard.

Due to the severity of the hypercalcemia and the clinical instability, the patient was medically treated with zolendronic acid and cinacalcet, and the surgery was postponed. She is waiting for elective surgery.

This patient presented late in the second trimester of pregnancy with symptoms, and this is consistent with the majority of the cases reported in the literature.[7,17–20]

Contrary to many described cases, including those reported by Ghaznavi et al.,[11] the case herein reported occurred in a previously healthy woman with no personal or familial clinical history until the onset of a severe event that led to the diagnosis.[11]

An accurate diagnosis is essential for the adequate treatment. Due to the multiple and nonspecific clinical manifestations, allied to the fact that this condition is rare during pregnancy, the diagnosis in our case was delayed until severe complications developed, with rapidly deterioration of the clinical state of the patient. A high level of suspicion for the diagnosis and a multidisciplinary management are mandatory.

We report a challenging case due to its singularities, such as an atypical inaugural manifestation in a previously healthy woman with no familial history, the severity of the neurological impairment, the presence of multiple parathyroid adenomas, and the need to postpone the first-line treatment; the patient was pharmacologically managed until

recovery. Primary hyperparathyroidism is an endocrine disease that is rare during pregnancy. The diagnosis is challenging due to the lack of symptoms or their similarity to the physiological alterations that occur during pregnancy.[21]

Conclusion

If not promptly diagnosed and treated, PHP can be associated with significant maternal and fetal morbidity and mortality. An association between PHP and PE has been reported. Untreated hypercalcemia can be life-threatening, and can induce the onset of PE, which is a major cause of maternal and fetal mortality. Surgery is the gold-standard treatment for PHP, and is considered safe during the second and third trimesters of pregnancy. The report of the present case is important to raise awareness among physicians that severe PE can be caused by PHP, and its early diagnosis and treatment can prevent important consequences.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Heath H III, Hodgson SF, Kennedy MA. Primary hyperparathyroidism. Incidence, morbidity, and potential economic impact in a community. N Engl J Med. 1980;302(04):189–193. Doi: 10.1056/NEJM198001243020402

2 Liu Y, Wang JN, Huang Y, Zhu Y-H, Liu RL, Xu CF, Li X. Acute pancreatitis and preeclampsia induced by parathyroid sdenoma in pregnancy: a case report and literature review. Int J Clin Exp Med. 2016;9(11):22652–22655

3 Hultin H, Hellman P, Lundgren E, Olovsson M, Ekbom A, Rastad J, Montgomery SM. Association of parathyroid adenoma and pregnancy with preeclampsia. J Clin Endocrinol Metab. 2009;94(09):3394–3399. Doi: 10.1210/jc.2009-0012

4 Schnatz PF, Thaxton S. Parathyroidectomy in the third trimester of pregnancy. Obstet Gynecol Surv. 2005;60(10):672–682. Doi: 10.1097/01.ogx.0000180889.23678.fb

5 Ducarme G, Maire F, Chatel P, Luton D, Hammel P. Acute pancreatitis during pregnancy: a review. J Perinatol. 2014;34(02):87–94. Doi: 10.1038/jp.2013.161

6 Wisner K. Gestational hypertension and preeclampsia. MCN Am J Matern Child Nurs. 2019;44(03):170. Doi: 10.1097/NMC.0000000000000523

7 Alharbi BA, Alqahtani MA, Hmoud M, Alhejaili EA, Badros R. Preeclampsia: a possible complication of primary hyperparathyroidism. Case Rep Obstet Gynecol. 2016;2016:7501263. Doi: 10.1155/2016/7501263

8 Perkovic V, Hewitson TD, Kelynack KJ, Martic M, Tait MG, Becker GJ. Parathyroid hormone has a prosclerotic effect on vascular smooth muscle cells. Kidney Blood Press Res. 2003;26(01):27–33. Doi: 10.1159/000069761

9 Hong MK, Lin YC, Wei YC, Chu TY. Parathyroid adenoma with hypertensive crisis and intracerebral hemorrhage mimicking hemolysis, elevated liver enzymes, low platelets syndrome. Obstet Gynecol. 2011;117(2 Pt 2):498–500. Doi: 10.1097/AOG.0b013e3182061fc2

10 Som M, Stroup JS. Primary hyperparathyroidism and pregnancy. Proc Bayl Univ Med Cent. 2011;24(03):220–223. Doi: 10.1080/08998280.2011.11928719

11 Ghaznavi SA, Saad NMA, Donovan LE. The biochemical profile of familial hypocalciuric hypercalcemia and primary hyperparathyroidism during pregnancy and lactation: two case reports and review of the literature. Case Rep Endocrinol. 2016;2016:2725486. Doi: 10.1155/2016/2725486

12 Dale AG, Holbrook BD, Sobel L, Rappaport VJ. Hyperparathyroidism in pregnancy leading to pancreatitis and preeclampsia with severe features. Case Rep Obstet Gynecol. 2017;2017:6061313. Doi: 10.1155/2017/6061313

13 Yilmaz BA, Altay M, Değertekin CK, Çimen AR, Iyidir ÖT, Biri A, et al. Hyperparathyroid crisis presenting with hyperemesis gravidarum. Arch Gynecol Obstet. 2014;290(04):811–814. Doi: 10.1007/s00404-014-3297-2

14 Cooper MS. Disorders of calcium metabolism and parathyroid disease. Best Pract Res Clin Endocrinol Metab. 2011;25(06):975–983. Doi: 10.1016/j.beem.2011.07.001

15 Gonzalo García I, Robles Fradejas M, Martín Macías MLA, Ciganda AB, Beaskoetxea ZB, Pérez ER, et al. Primary hyperparathyroidism in pregnancy treated with cinacalcet: a case report. J Obstet Gynaecol. 2018;38(01):132–134. Doi: 10.1080/01443615.2017.1325862

16 Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, Potts JT Jr. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3561–3569. Doi: 10.1210/jc.2014-1413

17 Shangold MM, Dor N, Welt SI, Fleischman AR, Crenshaw MC Jr. Hyperparathyroidism and pregnancy: a review. Obstet Gynecol Surv. 1982;37(04):217–228. Doi: 10.1097/00006254-198204000-00002

18 Parham GP, Orr JW Jr. Hyperparathyroidism secondary to parathyroid carcinoma in pregnancy. A case report. J Reprod Med. 1987;32(02):123–125

19 Higgins RV, Hisley JC. Primary hyperparathyroidism in pregnancy. A report of two cases. J Reprod Med. 1988;33(08):726–730

20 Trebb C, Wallace S, Ishak F, Splinter KL. Concurrent parathyroidectomy and caesarean section in the third trimester. J Obstet Gynaecol Can. 2014;36(06):502–505. Doi: 10.1016/S1701-2163(15)30564-8

21 Kort KC, Schiller HJ, Numann PJ. Hyperparathyroidism and pregnancy. Am J Surg. 1999;177(01):66–68. Doi: 10.1016/s0002-9610(98)00302-x

Short-term Prophylaxis for Delivery in Pregnant Women with Hereditary Angioedema with Normal C1-Inhibitor

Profilaxia de curto prazo para o parto em grávidas com angioedema hereditário com inibidor de C1 normal

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Abstract

Objective To verify the efficacy of short-term prophylaxis for vaginal or cesarean section childbirth with plasma-derived C1-inhibitor concentrate in pregnant women. They should have hereditary angioedema (HAE) and normal plasma C1-inhibitor.

Methods Case report of pregnant women diagnosed with HAE with normal C1-inhibitor who had been treated with intravenous C1-inhibitor concentrate for prophylaxis of angioedema attacks when hospitalized for delivery. The exon 9 of the Factor 12 (*F12*) genotyping gene was performed by automatic sequencing in all patients.

Results Three cases of pregnant women with HAE with normal serum level of C1-inhibitor are reported. The genetic test detected the presence of a pathogenic mutation in the *F12* gene. Deliveries occurred uneventfully and patients had no HAE symptoms in the following 72 hours.

Conclusion C1-inhibitor concentrate could be useful to prevent angioedema attacks during and after delivery.

Keywords
- angioedema
- estrogens
- edema
- pregnancy
- prophylaxis

Resumo

Objetivo Verificar a eficácia da profilaxia de curto prazo para o parto vaginal ou cesáreo com inibidor de C1 derivado de plasma concentrado em mulheres grávidas. Eles devem ter angioedema hereditário e inibidor normal de C1 no plasma.

Métodos Relato de caso de gestantes diagnosticadas com angioedema hereditário com inibidor de C1 normal que foram tratadas com inibidor intravenoso de concentrado de C1 para profilaxia de ataques de angioedema quando hospitalizadas para o parto. O exon 9 do gene de genotipagem do fator 12 (*F12*) foi realizado por sequenciamento automático em todos os pacientes.

Palavras-chave
- angioedema
- estrogênios
- edema
- gravidez
- profilaxia

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Resultados Três casos de gestantes com angioedema hereditário com nível sérico normal de inibidor de C1 são relatados. O teste genético detectou a presença de uma mutação patogênica no gene *F12*. Os partos ocorreram sem intercorrências e as pacientes não apresentaram sintomas hereditários de angioedema nas 72 horas seguintes.

Conclusão O concentrado de inibidor de C1 pode ser útil para prevenir ataques de angioedema durante e após o parto.

Introduction

Hereditary angioedema (HAE) is a rare disease, and its prevalence is estimated to be $\sim$ 1:50,000 inhabitants. It is a genetic disorder of autosomal dominant inheritance. It is defined by the quantitative and/or functional deficiency of C1 esterase inhibitor (C1-INH), or with normal C1-INH and alteration in genes encoding Hageman factor XII (*FXII*) of the blood coagulation cascade.[1,2] It leads to edema attacks in the skin and submucosa, in the regions of the face, extremities, genitalia, oropharynx, larynx, tongue, airway and gastrointestinal tract with risk of death from airway obstruction.[1,2]

The association between the disease and the estrogen hormone is the main feature of HAE with normal C1-INH. Elevated levels of this hormone in pregnancy, or the use of oral contraceptives, stress and menstrual cycles are triggers of this type of HAE.[1,3,4] Thus, symptoms may become more frequent and severe during pregnancy, delivery, postpartum and lactation in women with HAE.[5,6]

Pregnant women with HAE with low level or functional deficiency of C1-INH should be treated with plasma-derived C1 inhibitor concentrate until 6 hours before delivery and could be repeated as needed, as well as 72 hours after the delivery.[1] The hospital where the delivery will take place should have short-term preventive medications such as plasma-derived C1 inhibitor concentrate and trained personnel for the care of patients with HAE.[4–6]

There is no data regarding plasma-derived C1 inhibitor concentrate short-term prophylaxis for HAE with normal C1-INH. The objective of the present study was to verify the efficacy of short-term prophylaxis of attacks in vaginal or cesarean delivery with plasma-derived C1-inhibitor concentrate in three pregnant women with HAE and normal C1-inhibitor confirmed by molecular mutation analysis of the *F12* gene.

Description of Cases

We report three pregnant patients diagnosed with HAE and *F12* gene mutation attending the Immunology Division of the Hospital de Clínicas of the Universidade Federal do Paraná in 2018. All three had normal serum levels of C1-INH and C4. Of these, 2 are first cousins (patients 1 and 2) and they all agreed to participate in the present study and signed the informed consent form. Exon 9 genotyping, as well as its flanking regions and splicing sites of the *F12* gene, was performed by automated sequencing on an ABI 3500 Genetic Analyzer sequencer (Applied Biosystems, Foster City, CA, USA).

Patient 1

Female, 31 years old, primiparous. She reports clinical signs of HAE for 9 years, usually marked lip and facial edema, requiring medical attention and treated with corticosteroids, adrenaline and antihistamines. She did not identify any triggering factors.

Menarche at 15 years old, and she started contraception at 19 years old. At 29 years old, she became pregnant and reported left lower eyelid edema, lasting 5 hours and without treatment, sagging spontaneously.

Mutation search for the factor XII *F12* gene revealed the presence of the c.983C > A mutation in pathogenic heterozygosis (p.Thr328Lys) and confirmed the hypothesis of HAE without C1-INH deficiency.

Plasma-derived C1 esterase inhibitor, 1,000 IU, was administered intravenously 6 hours before cesarean section for short-term prophylaxis at delivery and postpartum. There were no complications during the surgical procedure and within 72 hours, subsequently.

Patient 2

Female, 44 years old, menarche at 12 years old. She reported lip and facial edema in the first pregnancy, 22 years ago. After this period, she had monthly angioedema attacks in the extremities and abdominal pain. During the attacks, she was treated with adrenaline and corticosteroids, unsuccessfully. The contraceptive was the only medication for continuous use. At 38 years old, she had severe upper airway edema requiring orotracheal intubation and hospitalization for 4 days, and no triggers could be pointed out.

A search for mutation of factor XII *F12* gene confirmed the presence of the mutation c.983C > A in pathogenic heterozygosis (p.Thr328Lys) and confirmed HAE with no C1-INH deficiency.

When she was 43 years old, at the end of the pregnancy, she reported edema in the hands and legs. Fetal echocardiography showed subcutaneous edema and increased echogenicity in intestinal loops with increased peristalsis. The patient was hospitalized for dyspnea and successfully treated with fresh plasma.

The cesarean section at the 39th gestational week was performed for fetal malformation. The patient received 1,000 IU of intravenous C1-INH inhibitor 1 hour before the

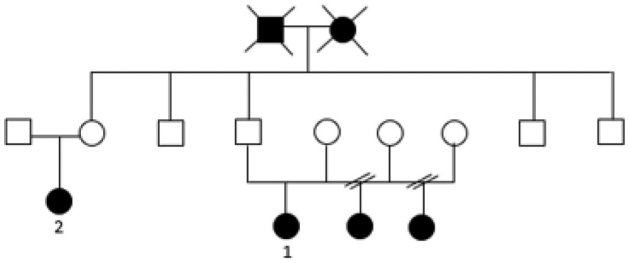

Fig. 1 Family Heredogram (Patients 1 and 2).

cesarean section without complications during the procedure and 72 hours postpartum (►**Fig. 1**).

Patient 03

Female, 20 years old, primiparous, single HAE case in the family. Menarche at 11 years old. Abdominal pain began in childhood and, from the age of 15 years old, monthly edema attacks of lips, tongue, face, eyelids, hands, and feet lasting from 3 to 4 days without improvement and no response to adrenaline and corticosteroids. She was treated with fresh plasma with improved outcomes.

Mutation search for the factor XII *F12* gene confirmed the presence of the mutation c.983C > A in pathogenic heterozygosis (p.Thr328Lys) and confirmed HAE without C1-INH deficiency.

She got pregnant at 19 years old and reported 2 episodes of foot edema and mild lip edema, without medical complications, improving in 12 hours. The patient received intravenous C1 inhibitor, 1,000 IU, 1 hour before vaginal delivery for short-term prophylaxis. During the labor and postpartum, the patient was in good general condition, and 2 days after the delivery she had edema attacks in her left hand (►**Table 1**).

Discussion

Hereditary angioedema with normal C1-INH was first described in the year 2000.[6] As noted, it is rare, mainly affects women, and is characterized by normal C1-INH levels and activities[7] and by mutations in the *F12* gene.[8]

A predominance in females is associated with the estrogen hormone, a hallmark of HAE with normal C1-INH.[5,7] Estrogen has a regulatory role in the synthesis of FXII protein, as well as of several genes and proteins of the coagulation cascade and of the kallikrein-kinin system, increasing synthesis of bradykinin, kallikrein, vascular permeability and consequently causing edema.[9] This association is important in worsening the attacks in women, ranging from childhood, puberty, menses, pregnancy and menopause.[1]

Short-term prophylaxis with C1-INH concentrate administration up to 6 hours before the procedure or having a dose of C1-INH concentrate available in the delivery room is recommended to prevent a possible bout of edema during childbirth in women with HAE with C1-INH deficiency, but not for HAE with normal C1-INH.[3,7]

The present report of three pregnant patients demonstrated the efficacy and safety of plasma-derived C1-INH as short-term prophylaxis for HAE with normal C1-INH. There was no severe edema during vaginal delivery and/or cesarean section after the intravenous use of C1-INH concentrate. Surgical stress and mechanical abdominal trauma for cesarean delivery or genital mechanical trauma for normal delivery may be triggering factors for HAE.[10]

In the postpartum period, special attention should be given to edema triggers.[10] Postpartum seizures usually occur within 72 hours of delivery and can have serious consequences.[1] Patients show different symptoms in the attacks (left lower eyelid edema, left hand edema, vaginal bleeding and hypotension) starting 48 hours after delivery, demonstrating the need for protective medication immediately after delivery.[7] C1-INH concentrate shortens the duration of attacks by about one third and also reduces the time for the onset of symptom relief.[11]

The reported cases bring to light the discussion of preventive therapy of a complex and serious situation, which is the occurrence of HAE attacks during pregnancy and childbirth. Although used in a minority of cases, these should be adequately selected and their diagnosis confirmed by molecular tools. C1-INH concentrate can produce satisfactory results in symptomatic relief and improvement of the quality of life of the patients, especially postpartum. In Brazil, C1-INH concentrate is approved; however, it is not yet included in the list of high-cost drugs provided by the government and only by demand of judicial request to the public health system.[1]

Conclusion

In conclusion, short-term prophylaxis using C1-INH concentrate in vaginal or cesarean delivery could be useful in pregnant patients with HAE and normal C1-INH. Larger

Table 1 Laboratory workout

	Case 1	Case 2	Case 3	Reference values
C4 Complement Fraction (mg/dL)	22	27	19	10–40
Quantitative C1 Inhibitor (mg/dL)	26	20	28.8	21–39
Functional C1 Inhibitor (%)	81	85	71	70–130

studies may verify how C1-INH prevents attacks of HAE in pregnant women with HAE and normal C1-INH.

Conflict of Interests

The authors have no conflict of interests to declare.

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References

1 Giavina-Bianchi P, Arruda LK, Aun MV, et al. Diretrizes brasileiras para o diagnóstico e tratamento do angioedema hereditário-2017. Arq Asma Alerg Imunol. 2017;1(01):23–48. Doi: 10.5935/2526-5393.20170005

2 Valle SOR, França AT, Campos RA, Grumach AS. Angioedema hereditário. Rev Bras Alerg Imunopatol. 2010;33(03):80–87

3 Sim DW, Park KH, Lee JH, Park JW. A case of type 2 hereditary angioedema with SERPING1 mutation. Allergy Asthma Immunol Res. 2017;9(01):96–98. Doi: 10.4168/aair.2017.9.1.96

4 Caballero T, Farkas H, Bouillet L, Bowen T, Gompel A, Fagerberg C, et al; C-1-INH Deficiency Working Group. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. J Allergy Clin Immunol. 2012;129(02): 308–320. Doi: 10.1016/j.jaci.2011.11.025

5 Zuraw BL, Bork K, Binkley KE, Banerji A, Christiansen SC, Castaldo A, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. Allergy Asthma Proc. 2012;33(Suppl 1):S145–S156. Doi: 10.2500/aap.2012.33.3627

6 Bouillet L, Gompel A. Hereditary angioedema in women: specific challenges. Immunol Allergy Clin North Am. 2013;33(04): 505–511. Doi: 10.1016/j.iac.2013.07.006

7 Riedl MA. Hereditary angioedema with normal C1-INH (HAE type III). J Allergy Clin Immunol Pract. 2013;1(05):427–432. Doi: 10.1016/j.jaip.2013.06.004

8 Bork K, Wulff K, Meinke P, Wagner N, Hardt J, Witzke G. A novel mutation in the coagulation factor 12 gene in subjects with hereditary angioedema and normal C1-inhibitor. Clin Immunol. 2011;141(01):31–35. Doi: 10.1016/j.clim.2011.07.002

9 Bork K. Hereditary angioedema with normal C1 inhibitor. Immunol Allergy Clin North Am. 2013;33(04):457–470. Doi: 10.1016/j.iac.2013.07.002

10 Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy. 2018;73(08):1575–1596. Doi: 10.1111/all.13384

11 Gompels MM, Lock RJ, Abinun M, Bethune CA, Davies G, Grattan C, et al. C1 inhibitor deficiency: consensus document. Clin Exp Immunol. 2005;139(03):379–394. Doi: 10.1111/j.1365-2249.2005.02726.x

Medical Treatment for Ectopic Pregnancy during the COVID-19 Pandemic

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Dear Editor,

The incidence of ectopic pregnancy is 2%, and during the COVID-19 pandemic, it became a challenge for obstetricians.[1] Ectopic pregnancy is the main cause of mortality in the first trimester of gestation. Therefore, early diagnosis and treatment should be performed to avoid morbidity and mortality. Early diagnosis is not common because pregnant women hesitate to seek medical assistance. Therefore, social isolation could postpone the diagnosis. To avoid this and encourage consultation, pregnant women should be informed of the risk factors for ectopic pregnancy, such as previous ectopic pregnancy, history of salpingitis, infertility, and others. On the other hand, patients with no risk factors should see a physician in case of first trimester bleeding.

Once diagnosis is confirmed, physicians should select the best applicable treatment, which should include outpatient management. As health systems are overburdened during the COVID-19 pandemic and personal protective equipment are limited, avoiding a surgical procedure becomes more necessary.[2]

Methotrexate (MTX) treatment must be considered carefully, as incorrect dosage could lead to more risks for the patient. This may include failure of the treatment and a consequent emergent procedure for possible hemorrhage, as well as exposure of the patient to medical treatment with the potential risk of immunodeficiency. Therefore, medical treatment should be performed only in patients with the following inclusion criteria: unruptured ectopic pregnancy, hemodynamically stable, tubal pregnancy $\leq$3.5 cm, β-hCG levels $\leq$ 5,000 mUI/ml, and absence of embryonic cardiac activity detected by transvaginal ultrasonography. The exclusion criteria are as follows: intrauterine pregnancy; evidence of immunodeficiency, anemia, leukopenia, or thrombocytopenia; sensitivity to methotrexate (MTX); active pulmonary disease; active peptic ulcer disease; hepatic and renal dysfunction; decreasing levels of β-hCG at 24/48h before treatment; breastfeeding; and refusal to accept blood transfusion.[3]

Once the patient was selected, the next step was to define the MTX regimen: single dose of MTX 50 mg/m^2, two doses (50 mg/m^2 on days 1 and 4), multiple doses (MTX 1 mg/kg on days 1, 3, 5, and 7 and folinic acid 0.1 mg/mg on days 2, 4, 6, and 8). The single dose is the most commonly used regimen in patients with tubal pregnancy. Follow-up could be performed by telemedicine, with a focus on the β-hCG levels on days 4 and 7 after MTX regimen. If the levels decrease by more than 15% between days 4 and 7, the response is considered favorable. The patient should be followed up with β-hCG titers every week until the levels become negative. On the other hand, if the β-hCG level decrease by less than 15% between days 4 and 7, this indicates that an increase in MTX dose is necessary.[3]

Expectant management can be performed in patients with declining β-hCG levels at an interval of 24/48 hours before treatment. The main criteria for expectant management are unruptured ectopic pregnancy, hemodynamically stable, declining levels of β-hCG at an interval of 24/48 hours, β-hCG levels $\leq$ 2,000 mUI/ml, tubal pregnancy diameter $\leq$ 3.5 cm, and absence of embryonic cardiac activity detected by transvaginal ultrasonography.[4] The surveillance is performed to check β-hCG levels every week until the titers become negative.

Surgery for tubal pregnancy should be performed in patients with ruptured tubal pregnancy, high levels of β-hCG, adnexal mass $>$ 3.5 cm, and presence of live embryo. Patients diagnosed with COVID-19 should undergo laparoscopy because the MTX regimen could reduce immunity, and active pulmonary disease is a contraindication for MTX.

In most cases of non-tubal ectopic pregnancy (cervical, cesarean scar, interstitial and ovarian pregnancy), the standard treatment is surgery, such as hysterectomy. Some procedures alternative to surgery include local injection of MTX guided by transvaginal ultrasound, systemic medical treatment with MTX, and embolization of uterine arteries. Management in cases of interstitial, cervical, and cesarean scar pregnancies should always be on a case by case basis. When the embryo has

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a heartbeat, transvaginal ultrasonography-guided local treatment with MTX injection into the gestational sac at a dose of 1 mg/kg is the first-line treatment. Systemic treatment with MTX is performed in cases in which the embryo has no heartbeat. Medical treatment will depend on the initial β-hCG titer. For titers $<$ 5,000 mIU/mL, a single dose of MTX 50 mg/m^2 is recommended. On the other hand, if β-hCG titers are $>$ 5,000 mIU/ml, a multiple-dose MTX protocol is recommended.

In summary, clinical treatment of ectopic pregnancy by MTX or expectant management is an alternative during the COVID-19 pandemic. An early diagnosis and appropriate selection of treatment options are critical for the success of the treatment.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Cecchino GN, Araujo Júnior E, Elito Júnior J. Methotrexate for ectopic pregnancy: when and how. Arch Gynecol Obstet. 2014; 290(03):417–423. Doi: 10.1007/s00404-014-3266-9

2 Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJCOVID-19 Systematic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet. 2020;395 (10242):1973–1987. Doi: 10.1016/S0140-6736(20)31142-9

3 Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 191: tubal ectopic pregnancy. Obstet Gynecol. 2018;131(02):e65–e77. Doi: 10.1097/AOG.0000000000002464

4 Silva PM, Araujo Júnior E, Cecchino GN, Elito Júnior J, Camano L. Effectiveness of expectant management versus methotrexate in tubal ectopic pregnancy: a double-blind randomized trial. Arch Gynecol Obstet. 2015;291(04):939–943. Doi: 10.1007/s00404-014-3513-0

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FEBRASGO POSITION STATEMENT

Vaccination in pregnant and postpartum women

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The National Specialty Commission for Vaccines of the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO) endorses to this document. The content production is based on scientific studies on a thematic proposal and the findings presented contribute to clinical practice.

Key points:

- Alert gynecologists and obstetricians about the importance of vaccinating pregnant and postpartum women;
- Address immunological changes in pregnancy and the puerperal period and susceptibility to infections;
- Highlight the maternal and fetal advantages of vaccination during pregnancy and lactation and offer tools that help obstetricians to convince their patients to adhere to vaccination;
- Describe the vaccines routinely recommended during pregnancy and puerperal period;
- Address vaccines given sporadically during pregnancy and puerperal period;
- Alert about contraindicated vaccines during pregnancy and inform risks of inadvertent use;
- Address future perspectives on the vaccination of pregnant women.

Recommendations:

- In pregnancy and the puerperal period, the practice of vaccination is essential, aiming at maternal and conceptus health. It should be part of the checklist of recommendations of gynecologists and obstetricians.
- Changes in cellular immunity lead to a greater susceptibility of pregnant women to infections such as influenza, with progression to severe forms of the disease. At the same time, pregnant women respond effectively to vaccination and produce antibodies appropriately.
- When pregnant women are vaccinated, there is a significant improvement in maternal and newborn health related to these infections. Note that by vaccinating the pregnant woman, the conceptus is protected because of the transplacental passage of antibodies. This is also true for breast milk. Perhaps this is the best argument for increasing adherence to immunization.
- Vaccines recommended during pregnancy are: influenza, dTpa (diphtheria, tetanus and pertussis) and hepatitis B (if the three doses have not been received previously).
- In some clinical or epidemiological conditions, inactivated vaccines, such as hepatitis A, pneumococcal and meningococcal viruses, may be recommended. These inactivated vaccines are indicated if there is a high risk of infection by these agents.
- The yellow fever vaccine, although of live attenuated viruses, may be given in pregnancy if the epidemiological risk justifies it. The use in women breastfeeding babies under six months is contraindicated.
- Triple viral, HPV, chickenpox and dengue vaccines are contraindicated during pregnancy. In case of inadvertent use, pregnancy must be maintained because the potential risks do not justify extreme measures.
- Vaccines for respiratory syncytial virus and group B streptococcus for specific use in pregnant women are in an advanced stage of development.

Clinical context

While death is the most extreme consequence of vaccine-preventable infections, there are hundreds of thousands of secondary hospitalizations due to these diseases each year.[1]

Immunological and physiological changes during pregnancy cause greater susceptibility to infectious conditions with increased morbidity and mortality[2], as occurred in the influenza A-H1N1 pandemic in 2009.[3] When a pregnant woman acquires an infection, in addition to her health , there is a risk for compromising the health of the conceptus, for example, malformations, delayed intrauterine growth, premature birth, neonatal and late infectious manifestations, and even death.

In this sense, immunizing the pregnant woman is the primary action to prevent harm to the binomial.[4] Since more than 90% of pregnant women in Brazil attend prenatal consultations seeking care to ensure their health and of their conceptus, this is a unique moment to guarantee the vaccination of women and their family in a broad health promotion strategy.[5]

In general, seroconversion by immunization during pregnancy is similar to that of women outside the pregnancy-puerperal cycle.[6] In addition, immunizing the pregnant woman is the beginning of the process of protecting this conceptus even before birth, through transplacental transfer of IgG antibodies, thereby offering passive protection for up to 12 months until the child is adequately immunized.[7,8]

Unfortunately, immunization rates in pregnancy are below the desired in the world. In a study conducted in 2016, in the city of São Paulo, only 68.4% of pregnant women received the recommended vaccines.[9] Several factors may explain the poor compliance with official recommendations. Concerns about the safety of the mother or the newborn (NB) and the ignorance of vaccine recommendations by health professionals and pregnant women seem to be the most important factors for low adherence.[8]

The ideal is to update the vaccine before conception, but as about half of pregnancies in the country are unplanned, Gynecologists and Obstetricians (GO) must incorporate the vaccine practice as an item of the prenatal consultation, indispensable for promoting the health of the binomial, using enlightening and compelling arguments that reinforce the adherence to vaccines by these pregnant women. The puerperal period is another moment of health care and a great opportunity to update women's vaccination.[10,11]

Through bibliographic review in the PubMed database between 2010 and 2020 using the keyword "maternal immunization", in addition to national vaccination recommendations in the pregnancy-puerperal cycle, we highlight here the main points to strengthen the knowledge and practice of GOs that assist pregnant and postpartum women, definitively incorporating immunization as a routine practice of the pregnancy-puerperal cycle.

Why incorporate the vaccine recommendation in gynecologist and obstetrician consultations?

Because vaccines are important prevention tools and must integrate the health planning of all individuals, men and women, from birth to old age. However, vaccinating women has a range of benefits. It contributes to their protection, avoids congenital infections, allows the transmission of antibodies to the fetus, prevents the transmission of diseases to the infant and to others under their care, whether at home, in the nursery, at school, hospitals. Therefore, specific guidelines on immunization for adult women are essential.[12]

Historically, there was no culture in which GOs participated effectively in immunization guidance, and only tetanus vaccination remained in pregnant women treated in the public service. In the last decade, these professionals began to be guided to participate effectively in immunization programs.[10] Initially, the licensing of HPV (human papilloma virus) vaccines in 2007 placed women as the main target population. In 2009, the dreaded H1N1 influenza pandemic occurred; pregnant women were in the risk group for complications and death, and started to be immunized routinely. The third event was the epidemic of neonatal deaths from pertussis, experienced in Brazil from 2011. The main strategy for controlling this situation is the vaccination of pregnant women at each pregnancy for the protection of the newborn, which has become a rule for the public system since the end of 2014.[10]

The need to maintain high levels of vaccination coverage in the population and the use of periodic booster doses to maintain many infectious diseases controlled is well known. Gynecologists and Obstetricians are the main physicians with access to an important part of the population, women, for a long period of their lives, and must offer this periodic guidance.[10]

Although the application of vaccines is not a medical act, the prescription is, remembering that every action must be documented in medical records.

How to sensitize pregnant and postpartum women in order to increase adherence to vaccination?

Some of the reasons for poor adherence are the lack of information on the susceptibility and the greater potential for severity of some infections in pregnant women, the fear of possible side effects of vaccines, harm to the fetus, in addition to the lack of information on the beneficial potential effect achieved with maternal immunization. Obstacles, especially for the most vulnerable, are the action of anti-vaccine groups and currently, fake news disseminated through social networks and the internet. The lack of patient guidance by the attending physician, either due to ignorance or negligence, is also noteworthy.[8]

The American College of Gynecology and Obstetrics[13] suggests some measures for a better maternal acceptance of vaccination:

- Education: insufficient knowledge about the susceptibility and morbidity of vaccine-preventable diseases and risks and benefits of vaccination are modifiable barriers to improve adherence to vaccination;
- Recommendation: the verbal communication provided by a physician seems to be the biggest mo-

tivator for the acceptance of vaccination by pregnant women;
- Standardize: obstetricians should adopt the approach to prevent maternal and child infectious diseases through vaccination as a routine or protocol in their first prenatal consultation;
- Improve convenience: obstetricians have the opportunity to consult pregnant women frequently and are seen as reliable sources of information. One way to guarantee vaccination is to offer vaccines in the same place where prenatal consultations are held.

What vaccines are recommended during pregnancy and when should they be taken?

Influenza, hepatitis B (for those not previously immunized) and dTpa (diphtheria, tetanus and pertussis) are the vaccines indicated during pregnancy.[14]

The **influenza** vaccine is recommended for every pregnant woman, every pregnancy, in any gestational phase, preferably in the period that precedes the circulation season of the influenza virus in the region. Its protection lasts between six to 12 months after application. The vaccine is also recommended for postpartum women up to 45 days after delivery, offering no risk to breastfeeding. Pregnant women have a higher risk for complications after influenza infections, namely hospitalization, admission to intensive care units and death. In addition, there is a greater risk for premature birth, low birth weight, fetal death and also risk for complications in newborns. Immunization against influenza during pregnancy-puerperal period protects the fetus in the first six months of life, since they are at greater risk of hospitalization and death from the disease, and no influenza vaccine is licensed in this age group because of the low immunogenicity of current formulations. Two vaccines are licensed and available in Brazil: in the public service, the trivalent (a strain of influenza A-H1N1, one of A-H3N2 and a variant of influenza B), and in the private service, the quadrivalent (a strain of a second strain B), which increases the protection spectrum.[14-16]

The **dTpa** vaccine should be given after the 20th week of pregnancy, sufficient to induce protection against neonatal tetanus in pregnant women with a previous history of complete immunization (three doses) with vaccines containing the tetanus component, or who have received two doses of dT previously. In cases of incomplete or unknown vaccination history, two doses of dT and the dTpa must be guaranteed. Women who did not receive the dTpa during pregnancy should be vaccinated in the immediate postpartum period.[10,12,15,16]

Pertussis is a serious disease, where the bacteria *Bordetella pertussis* is especially virulent when it affects young infants in the first months of life. Routine dTpa vaccination during pregnancy reduces the child's risk of contracting whooping cough by approximately 90% in the first months of life.[17-19] This disease is transmitted through respiratory droplets from nearby infected individuals. The immunization strategy, called cocoon or cocooning, consists of the immunization of all those who live with the young infant and therefore, represent the greatest risk of transmitting the disease in the domestic environment, which is considered the main epidemic unit of the disease.

The **hepatitis B** vaccine complete schedule includes three doses (zero-one-six months) that can be started in the first trimester. If there is no previous vaccination proof, or an incomplete vaccination schedule, the orientation is to start the schedule or complete the missing doses.[16] In the absence of prophylaxis, the risk of the newborn being infected by the hepatitis B virus due to intrauterine and mainly perinatal exposure to HBsAg and HBeAg positive parturient women is 70%-90%, falling to 5%-20% in parturient women who are HBsAg positive and HBsAg negative. Vertical transmission is associated with a higher risk for chronic infection in children. As a result, vaccination of pregnant women protects the mother from acquiring the virus during pregnancy, as well as the conceptus.[15,16] Special attention should be given to women at a higher risk for hepatitis B virus infection during pregnancy, such as: household contact members or sexual partners who are positive for hepatitis B surface antigen; more than one partner in the six months before pregnancy; recent treatment for sexually transmitted infection; current or recent injecting drug users; people living with chronic liver disease; people living with HIV; travelers to areas of high endemicity.[17]

What vaccines are given eventually during pregnancy?

Inactivated vaccines (hepatitis A, pneumococcal, meningococcal conjugate or MenACWY and meningococcal B) do not have theoretical risks for neither the pregnant woman nor the fetus. Currently, these vaccines are offered only at private clinics. Despite insufficient data on the safety of the HAV hepatitis A vaccine during pregnancy, in Brazil, there are several situations in which the risk of exposure to the virus is high. In such cases, vaccination during pregnancy should be considered, for example, women who live in inadequate sanitation conditions, or in the presence of disease outbreaks.[10,12,15]

The sequential schedule with 13-valent pneumococcal and 23-valent polysaccharide conjugate vaccines should be considered in women with clinical risk factors for invasive pneumococcal disease, such as pregnant women with chronic heart disease, chronic

lung disease, diabetes, chronic liver disease, cochlear implant, congenital and/or acquired immunodeficiencies, sickle cell disease or other hemoglobinopathies and anatomical or functional asplenia.[15,20,21]

Similarly, mono (C) or quadrivalent (A, C, W, Y) and meningococcal B vaccines do not have safety data regarding their use during pregnancy, although in situations of epidemiological risk, the possibility of vaccination should be evaluated.[15,20,21]

Which vaccines are contraindicated during pregnancy?

The HPV vaccine and attenuated vaccines (chickenpox, triple viral - MMR and dengue), composed of live attenuated viruses, are contraindicated because they may represent a theoretical risk of transmission of the vaccine virus to the fetus. They should be recommended in the preconception period, puerperal period, in the presence or not of breastfeeding.[14-16]

As the yellow fever vaccine consists of live attenuated virus, it is usually contraindicated in pregnant women. In situations where the risk of infection outweighs the potential risks of vaccination, it may be recommended during pregnancy. For pregnant women traveling to countries that require the International Certificate of Vaccination or Prophylaxis, they can be exempted from vaccination by the attending physician if there is no risk of contracting the infection. It is contraindicated in nursing mothers until the baby is six months old, but if vaccination cannot be avoided, breastfeeding should be suspended for ten days.[10,12,14]

The dengue vaccine is contraindicated both during pregnancy and in the puerperal period.[10,12,14,15]

Which vaccines are currently being developed for use in pregnancy?

New vaccines are at different stages of development with the main purpose of preventing neonatal infectious diseases. Among them, vaccines against respiratory syncytial virus (RSV), group B streptococcus (GBS), herpes simplex virus (HSV) and cytomegalovirus (CMV) stand out as diseases for which vaccines are currently unavailable.[8] The respiratory syncytial virus is the main cause of lower respiratory tract infections in infants and children under two years of age, age groups in which infections are more severe, especially in premature newborns and infants. Premature newborns or those with underlying severe chronic heart or lung disease are at higher risk for severe RSV infection leading to hospitalization and death. As most cases of severe RSV infection occur in the first three months of life, it is unlikely that immunization of infants can provide sufficient and timely protection. Therefore, maternal immunization is considered an adequate strategy for the prevention of RSV disease in young children.

Group B streptococcus infection is a major cause of pneumonia, meningitis and sepsis in newborns. Due to the early onset of the disease, the administration of a GBS vaccine for newborns at birth does not generate an immune response quickly enough to prevent a high lethality infection. Thus, maternal immunization is identified as a potential strategy to prevent neonatal disease (early-onset disease), when associated with the use of intrapartum antibiotic prophylaxis administered to GBS positive parturient women in prenatal screening, in addition to preventing the late-onset disease (>7 to 90 days of age) as well.

Due to the risks of neonatal herpes and congenital CMV, these vaccines are being evaluated with priority for seronegative women before pregnancy.[15]

Final considerations

Women who are planning to become pregnant or who are already pregnant become more receptive to immunization, especially when informed about the goal of making the gestation period as safe and healthy as possible, and about the benefits to their baby. However, there are still low rates of adherence to prenatal vaccination, especially among pregnant women with low socioeconomic status, low education, some racial and ethnic groups, and alternative behaviors. For this reason, the theme of immunizations in preconception, pregnancy and puerperal periods must be addressed in consultations with the gynecologist, obstetrician and pediatrician. These are unique moments in women's life that should be valued by all health professionals, especially by gynecologists/obstetricians, who must include immunizations as part of their clinical practice.

References

1. National Foundation for Infectious Diseases. Adult vaccination saves lives [Internet]. Bethesda: NFID; 2012 [cited 2020 Aug 20]. Available from: https://www.nfid.org/wp-content/uploads/2019/08/cta-adult.pdf
2. Robinson DP, Klein SL. Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis. Horm Behav. 2012;62(3):263-71. doi: 10.1016/j.yhbeh.2012.02.023
3. Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet. 2009;374(9688):451-8. doi: 10.1016/S0140-6736(09)61304-0
4. United Nations. The Millenium Development Goals Report 2015 [Internet]. New York: United Nations; 2015 [cited 2020 Aug 20]. Available from: https://www.un.org/millenniumgoals/2015_MDG_Report/pdf/MDG%202015%20PR%20Global.pdf
5. Leal MC, Esteves-Pereira P, Viellas EF, Domingues RMSM, Nogueira da Gama SG. Assistência pré-natal na rede pública do Brasil. Rev Saúde Pública. 2020; 54:8. doi: 10.11606/s1518-8787.2020054001458
6. Bischoff AL, Folsgaard NV, Carson CG, Stokholm J, Pedersen L, Holmberg M, et al. Altered response to A(H1N1)pnd9 vaccination in pregnant women: a single blinded randomized controlled trial. PloS One. 2013;8(4):e56700. doi: 10.1371/journal.pone.0056700

7. Robinson DP, Klein SL. Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis. Horm Behav. 2012;62(3):263-71. doi: 10.1016/j.yhbeh.2012.02.023
8. Abu-Raya B, Maertens K, Edwards KM, Omer SB, Englund JA, Flanagan KL, et al. Global perspectives on immunization during pregnancy and priorities for future research and development: an international consensus statement. Front Immunol. 2020;11:1282. doi: 10.3389/fimmu.2020.01282
9. Rocha BCCR, Carvalheira APP, Ferrari AP, Tonete VLP, Duarte MTC, Parada CMGL. Cobertura vacinal e fatores associados em puérperas de município paulista. Ciênc Saúde Coletiva. 2020;21(7):2287-92. doi: 10.1590/1413-81232015217.16862015
10. Neves N, Kfouri R. Vacinação na mulher. Rio de Janeiro: Elsevier; 2016.
11. ACOG Committee Opinion No. 772: immunization implementation strategies for obstetrician-gynecologists. Obstet Gynecol. 2019;133(3):e254-9. doi: 10.1097/AOG.0000000000003130
12. Lajos GJ, Fialho SCAV, Teixeira JC. Imunização na gravidez, puerpério e amamentação. In: Federação Brasileira das Associações de Ginecologia e Obstetrícia (FEBRASGO). Programa vacinal para mulheres. São Paulo: FEBRASGO; 2017. p. 128-38. (Série Orientações e Recomendações FEBRASGO; no. 13).
13. American College of Obstetricians and Gynecologists. ACOG Committee Opinion no. 558: integrating immunizations into practice. Obstet Gynecol. 2013;121(4):897-903. doi: 10.1097/01.AOG.0000428788.74725.90
14. Ministério da Saúde. Calendário nacional de vacinação 2020 [Internet]. Brasília (DF): Ministério da Saúde; 2020 [cited 2020 Apr. 21]. Available from: https://www.saude.go.gov.br/files/imunizacao/calendario/Calendario.Nacional.Vacinacao.2020.atualizado.pdf.
15. Kfouri RA, Martins CMR, Lajos GJ, Giamberardino HIG, Cunha J, Pereira LDC, et al. Imunização na gestação, pré-concepção e puerpério: Documento Técnico. São Paulo: SBP/SBIm/FEBRASGO; 2020.
16. Calendário de vacinação SBIm gestante: recomendações da Sociedade Brasileira de Imunizações (SBIm) – 2020/2021. São Paulo: SBIm; 2020 [cited 2020 Oct 31]. Available from: https://sbim.org.br/images/calendarios/calend-sbim-gestante.pdf.
17. Tan TQ, Flaherty JP, Gerbie MV. The vaccine handbook: a practitioner's guide to maximizing use and efficacy across lifespan. New York: Oxford University Press; 2018.
18. Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of vaccination during pregnancy to prevent infant pertussis. Pediatrics. 2017;139(5):e20164091. doi: 10.1542/peds.2016-4091
19. Kaczmarek MC, Ware RS, McEniery JA, Coulthard MG, Lambert SB. Epidemiology of pertussis-related paediatric intensive care unit (ICU) admissions in Australia, 1997-2013: an observational study. BMJ Open. 2016;6(4):e010386. doi: 10.1136/bmjopen-2015-010386
20. Ministério da Saúde. Anexo V - Instrução normativa referente ao calendário nacional de vacinação 2020. 2020 [cited 2020 Oct 31]. Available from: https://saude.es.gov.br/Media/sesa/Calend%C3%A1rio%20de%20Vacina%C3%A7%C3%A3o/INSTRUCAO%20NORMATIVA%202020.pdf
21. Sociedade Brasileira de Imunizações (SBIm). Calendários de vacinação pacientes especiais [Internet]. São Paulo: SBIM; 2020 [cited 2020 Oct 31]. Available from: https://sbim.org.br/images/calendarios/calend-sbim-pacientes-especiais-v2.pdf

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