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Editorial

Surgical Classification of Endometriosis

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Endometriosis is a chronic, benign, estrogen-dependent and multifactorial gynecological disease that mainly affects women of reproductive age. It can be defined by the presence of tissue that resembles the endometrial gland and/or stroma outside the uterus, predominantly although not exclusively, in the female pelvis.[1] It is estimated that 10% of women of reproductive age have this disease, which represents around 176 million women worldwide, generating direct costs to health systems and indirect costs due to reduced productivity, in addition to physical and psychological suffering secondary to pain and infertility, with consequent loss of quality of life.[2]

Given the many difficulties imposed by endometriosis, it has been extensively researched in recent decades.[3,4] Its classification is one of the difficulties faced. A reproducible, easy-to-apply, and well-organized classification system is needed not only to clarify communication between clinicians, but also to standardize the optimal treatment strategy and clinical trials.[2,5]

The National Specialized Commission on Endometriosis of the Brazilian Federation of Gynecology and Obstetrics Associations – FEBRASGO analyzed the different forms of classification chosen by the World Endometriosis Society (WES)[5] with the objective to standardize the current classification nationwide for Brazilian services that diagnose and treat this disease.

As a single classification that evaluates all possible manifestations of endometriosis is lacking, four classifications were standardized, among which: the revised classification of the American Society for Reproductive Medicine (rASRM), the ENZIAN classification, the Endometriosis Fertility Index (EFI) and the American Association of Gynecologic Laparoscopists (AAGL) classification.[2,6–10]

The World Endometriosis Society (WES) published the first international consensus on the classification of endometriosis using a rigorous methodology in 2017.[5] The lack of a classification comprising all aspects of this disease led to the proposal of a combination of the most relevant classifications that could be used by all professionals working with women with endometriosis, from which surgeons can select the appropriate components and ensure its documentation in patients' records.[5]

The initial ASRM Classification proposed a single approach in 1979.[6] The endometriosis stage is derived from a cumulative score according to the location and size of lesions observed during surgery.[2,6] The staging system underwent modifications in 1996 and is currently divided into I (1-5 points, minimal), II (6-15 points, mild), III (16-40 points, moderate) and IV (greater than 40 points, severe).

The advantages of this classification are its global acceptance, being widely used, easy application and the fact of helping patients to easily understand the stage of their disease.[2]

Among the disadvantages are differences between histologically diagnosed endometriosis and the stage made by visualization, its low reproducibility, low correlation between symptoms and its staging, not assessing the severity of pain and infertility, and not considering the presence of deep infiltrating endometriosis in areas such as uterosacral ligaments, bladder, vagina and intestine.[2,6,11,12]

The ENZIAN classification was introduced in 2005 to determine the extent of deep endometriosis during surgical treatment, complementing the rASRM classification. This classification was already revised in 2010 and 2011 to correct its overlap with the rASRM and make it easier to use.[2,7] In

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2021, it was revised again to introduce the evaluation of the forms of peritoneal and ovarian endometriosis, and the assessment of tubal permeability through chromotubation and secondary adhesions.[13] This last review aimed to propose a logical anatomical classification for use by a non-invasive method (magnetic resonance imaging and pelvic ultrasound), preoperatively, enabling a more adequate surgical planning, and intraoperatively, allowing a consistent and clear classification of deep endometriosis. Future studies are needed to assess its clinical validity, accuracy and reproducibility.[2,13]

The advantages are that it describes the retroperitoneal structures, can be determined by imaging modality and used for surgical planning, and the location and extent of the disease are associated with the presence and severity of different symptoms such as pain.[2,5,14]

The following are among the disadvantages: low level of global acceptance due to its complexity; patients' difficulty in understanding the classification informed given the complexity of stages and insufficient knowledge of pelvic anatomy by lay people; the classification will be imprecise if the surgical approach to deep lesions is performed incompletely or if the imaging study is not confirmed in the surgical procedure; and finally, even if the classification is previously made by imaging modality, there is still no scientific evidence on the usefulness of the classification determined by image, although it has great future potential because of the increasing percentage of patients in clinical follow-up of the disease.[2]

Another existing classification, the EFI, aims to develop a Fertility Index in patients with endometriosis, and predict the rate of spontaneous pregnancy in patients with endometriosis undergoing surgical treatment who will not attempt to conceive with assisted reproduction techniques.[8]

The EFI system considers historical factors such as age, duration of infertility and previous pregnancies associated with intraoperative findings. The functional score indicates the situation of pelvic organs for a possible future spontaneous pregnancy. Functional scores are determined by the surgeon and range from 0 to 4 points as follows; absent or nonfunctional as 0, severe dysfunction as 1, moderate dysfunction as 2, mild dysfunction as 3, and normal as 4. Not only the minimal functional score, but also other surgical factors such as the rASRM total score and the rASRM endometriosis lesion score are included. Finally, the final EFI score is calculated by adding the scores from the history and surgical findings that range from 0 to 10 points, with 10 indicating the best prognosis and 0 the worst prognosis.[2,8]

The EFI system has a clear advantage in predicting the outcome of pregnancy and reflects the possible future pregnancy rate better than the rASRM classification, where a score of 6 or more has better RA results than a score of 5 or less.[2,15,16] This classification has already been validated externally numerous times and seems to be an interesting tool for patients with endometriosis and infertility.

However, the EFI system has the following disadvantages: the classification score does not correlate with pain, as it was not designed for this purpose; as the lowest function score is judged subjectively, the total score may vary by surgeon; it is more complex to use than the rASRM classification and the ENZIAN, as it requires the calculation and sum of scores from several categories.[2,8] We believe it is interesting and useful for the group of patients with endometriosis and infertility and for the purpose of calculating probability of a future pregnancy.

In 2010, the AAGL initiated a project to develop a new classification of endometriosis.[9] Thirty endometriosis specialists were asked to assign scores ranging from 0 to 10 points, based on the pain, infertility, and surgical difficulty of patients with endometriosis. In addition, surgical difficulties were categorized into four levels.[9] The visual analogue scale scores and infertility history of patients were collected before surgery for the validation of the scoring system. In 2012, the AAGL Special Interest Group reported that preliminary results presented at the AAGL meeting in Las Vegas were encouraging and the AAGL classification of endometriosis was found to be related to pain, infertility, and surgical difficulty.[11]

The next step was to conduct a prospective multicenter study with more than 1,500 patients to validate this information. According to its authors, it still requires adjustments and improvements so that it is globally accepted and applied, as well as further investigations and discussions about this new classification. However, initial evaluations concluded that this classification allows the identification of objective intraoperative findings that reliably discriminate the levels of surgical complexity better than the ASRM staging system, and the severity stage correlates with the symptoms of pain and infertility with the ASRM stage.[10] Another interesting data of this classification is its easy application in the form of an application with the creation of a final version in pdf, which facilitates storage and a copy for patients (https://apps.apple.com/us/app/aagl-endo-classification/id1592383297 or https://play.google.com/store/apps/details?id = br.com.medicinia.aagl&hl = en&gl = US). AAGL, as one of the largest global Medical Societies in the field of Gynecological Surgery, is putting efforts to test the use of the classification even before surgery, by imaging methods.

In conclusion, the search for better care for patients with endometriosis is constant given the great implications that this disease brings to physical, social, sexual, reproductive and psychological health. Special attention to its classification is needed so we can standardize it globally. In this sense, we believe the classification recently proposed by AAGL may have all the necessary requirements for its wide future use.

Conflicts of Interest:
None to declare.

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Increment of Maternal Mortality Among Admissions for Childbirth in Low-risk Pregnant Women in Brazil: Effect of COVID-19 Pandemic?

Aumento da taxa de mortalidade materna entre as admissões para parto em gestantes de baixo risco gestacional no Brasil: Efeito da pandemia do COVID-19?

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Abstract

Objective To assess the possible impact of the COVID-19 pandemic on maternal mortality among admissions for childbirth in 2020 in relation of the last 10 years.

Methods An ecological study with pregnant women who underwent hospital births at the Brazilian unified public health service (SUS, in the Portuguese acronym) in Brazil from 2010 to 2020. The mortality among admissions for childbirth was obtained based on the number of admissions for childbirth with reported death as outcome divided by the total number of admissions. The underlying gestational risk and route of delivery were considered based on the national surveillance system. The average mortality for the period between 2010 and 2019 (baseline) was compared with the rate of deaths in 2020 (1st pandemic year); the rate ratio was interpreted as the risk of death in 2020 in relation to the average of the previous period (RR), with 95% confidence intervals (CIs).

Results In 2020, the 1st year of the COVID-19 pandemic, 1,821,775 pregnant women were hospitalized for childbirth and 651 deaths were reported, which represents 8.7% of the total hospitalizations and 11.3% of maternal deaths between 2010 and 2020. There was an increase in maternal mortality after births in 2020 compared with the average for the period between 2010 and 2019, specially in low-risk pregnancies, both in vaginal (RR = 1.60; 95%CI:1.39–1.85) and cesarean births (RR = 1.18; 95% CI:1.04–1.34).

Conclusion Maternal mortality among admissions for childbirth according to SUS data increased in 2020 compared with the average between 2010 and 2019, with an increment of 40% in low-risk pregnancies. The increase was of 18% after cesarean section and of 60% after vaginal delivery.

Keywords
- mortality
- maternal
- COVID-19
- postpartum period
- health impact assessment

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Resumo

Objetivo Avaliar os possíveis impactos da pandemia de COVID-19 na mortalidade materna nas admissões para o parto em 2020 em relação ao histórico dos últimos 10 anos.

Métodos Estudo ecológico com gestantes que realizaram parto hospitalar pelo Sistema Unificado de Saúde do Brasil (SUS) de 2010 a 2020. Para obter-se a taxa de mortalidade entre as admissões para o parto, foi utilizado o número de internações para parto que tiveram óbito como desfecho dividido pelo total de internações. O risco gestacional e o tipo de parto foram considerados a partir do sistema de vigilância nacional. A média de mortalidade no período de 2010 a 2019 (linha de base) foi comparada com a taxa de mortalidade pós-parto de 2020 (1° ano pandêmico); a razão das taxas foi interpretada como risco de óbito em 2020 em relação à média no período anterior (RR), com intervalo de confiança (IC) de 95%.

Resultados Em 2020, 1° ano da pandemia de COVID-19, 1.821.775 gestantes foram internadas para o parto e 651 óbitos foram registrados, o que representa 8,7% do total de internações e 11,3% das mortes maternas entre 2010 e 2020. Houve aumento na mortalidade materna após partos em 2020 em relação à média do período entre 2010 e 2019, especialmente em gestações de baixo risco, tanto em partos normais (RR = 1.60; IC95%: 1.39–185) quanto em cesáreas (RR = 1.18; IC95%: 1.04–1.34).

Conclusão A mortalidade entre as admissões para o parto pelo SUS aumentou em 2020 em relação à média de óbitos entre 2010 e 2019, com um incremento de 40% em mulheres de baixo risco gestacional. O aumento verificado foi de 18% após cesárea e de 60% após parto vaginal.

Palavras-chave

- mortalidade materna
- COVID-19
- período pós-parto
- avaliação do impacto na saúde

Introduction

Maternal mortality is a profound violation of the human rights of women, mainly because it is considered preventable in 92% of the cases.[1] Thus, reducing maternal mortality is one of the goals of the World Health Organization (WHO) sustainable development goals for 2030.[2]

In 2020, the Sars-CoV-2 pandemic showed up as a new obstacle to ensuring maternal and fetal health: pregnant and postpartum women were considered an infection risk group for developing more serious complications.[3]

In the same year, a Brazilian study found a12.7% lethality rate due to infection in the obstetric population, higher than in other countries.[4–7] In June 2020, 5 months after the 1st case of COVID-19 in the country, the number of mothers who lost their lives due to the disease already represented 10% of the total annual maternal deaths.[4] Throughout the year, 453 deaths were registered, with a weekly average of 10.5 deaths.[8]

In addition, 4,245 pregnant and postpartum women were infected by COVID-19 in 2020, and 352 of them (7.7%) died. When considering only the gestational period, 3,459 infections and 221 deaths were registered, recording 6.3% of deaths. However, when only puerperal women were considered, 786 infections and 131 deaths were registered, reaching a higher rate (14.3% of the patients died), which suggests that the puerperal period is more lethal than the gestational period.[8]

It is important to emphasize that a large proportion of pregnant and postpartum women who died from COVID-19 infection did not have comorbidities or risk factors; in other words, they did not fit the definition of high-risk pregnancies,[9] when the life or health of the pregnant woman or of the fetus are more likely to be affected than those of the considered population.[10]

Considering the effects of COVID-19 in the Brazilian obstetric population, the present study aims to assess the possible impact of the pandemic on maternal mortality among admissions for childbirth in 2020 in relation to the history of the last 10 years, according to the gestational risk and route of delivery in Brazil.

Methods

This is a quantitative ecological study. The study population consisted of pregnant women who underwent hospital births at the Brazilian Unified Health System (SUS, in the Portuguese acronym), registered in the Hospital Information System (SIH/SUS, in the Portuguese acronym), in the period from 2010 to 2020. Complete data were obtained from health information available in the database of the Information Technology Department of the Brazilian Public Healthcare System (DATASUS, in the Portuguese acronym). Data were exported to Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and were analyzed using the software Stata version 12.0 (StataCorp, College Station, TX, USA).

The population of interest for the study was pregnant women who underwent hospital births at the SUS. The mortality among admissions for childbirth was obtained based on the number of admissions for childbirth who had maternal death as the outcome divided by the total number

of admissions, for each route of delivery, gestational risk, and year of analysis. We used a 10^4 constant. The average mortality for the period between 2010 and 2019 was compared with the maternal mortality rate of 2020. The gestational risk and route of delivery were classified, as recorded at the SIH, in: high-risk vaginal delivery; low-risk vaginal delivery; high-risk cesarean delivery; and low-risk cesarean delivery. This categorization is recorded in the system by the health professional responsible for the assistance, considering the definition of high or low gestational risk.[10]

To analyze a possible effect of COVID-19 on maternal mortality, the period from 2010 to 2019 was considered the baseline, and the year 2020, because of the introduction of COVID-19, the exposure period. So, to measure the impact of 2020 and, indirectly, of the pandemic on mortality among admissions for childbirth, the average mortality in the period between 2010 and 2019 (considered nonexposed period rates) was compared with the mortality presented in 2020 (1st year of the pandemic, considered the exposed period). The rate ratio (RR) was interpreted as the risk of death in 2020 in relation to the average of the previous period. Confidence intervals (CIs) of 95% were estimated, with a significance level of 5%. The analyses were carried out using the Stata statistical program package version 12.0 (StataCorp, College Station, TX, USA) and OpenEpi.

All data is public and available on the Internet with unrestricted access data and without identifying individuals. The present publication is part of a project approved by the Ethical Review Board (No. 4.482.150 of December 2020).

Results

The total number of pregnant women hospitalized for childbirth between 2010 and 2020 was 20,995,023, and 5,761 deaths after birth were recorded (►**Figure 1**). In 2020, the 1st year of the COVID-19 pandemic, 1,821,775 pregnant women were hospitalized for childbirth and 651 deaths were reported, which represents 8.7% of the total hospitalizations and 11.3% of the maternal deaths in the period analyzed.

Besides, maternal mortality in high-risk pregnant women was higher than in low-risk pregnant women, in every route of delivery in the period. The average rate of maternal mortality of low-risk pregnant women from 2010 to 2019 was 2.11 (95%CI: 1.90–2.34) deaths per 10,000 admissions for childbirth, and the average rate of maternal mortality among high-risk pregnant women was 7.37 (95%CI: 6.24–8.66) deaths per 10,000 admissions for childbirth (►**Table 1**).

In 2020, there was an increase in maternal mortality compared with the average of the previous 10 years, with an increment of 40% in low-risk pregnancies. Women with low-risk pregnancies who underwent vaginal delivery had a 60% (RR = 1.6; 95%CI: 1.39–1.85) higher risk of dying in 2020, while those who underwent cesarean deliveries had an 18% higher risk of death (RR = 1.18; 95%CI: 1.04 -1.34) in 2020 when compared with the average between 2010 and 2019 (►**Figure 2**).

Regarding high-risk pregnancies, no significant differences were observed in mortality after vaginal or caesarean delivery in high-risk pregnancies women in the studied period.

Discussion

The present study explored the maternal mortality among admissions for childbirth in the period between 2010 and 2020, focusing on the differences of 2020 compared with a 10-year baseline period. Higher mortality rates in high-risk pregnant women compared with low-risk is a known fact, and the association with cesarean delivery can occur because the conditions of high-risk pregnancy can be configured as indications for surgical delivery.[11–13]Considering this prior knowledge, the increased deaths of low-risk pregnant women, regardless of the route of delivery performed, is remarkable when comparing the period between 2010 and 2019 with the year 2020.

The increase in maternal mortality only in low-risk pregnancies allows us to suggest that the COVID-19 pandemic has been categorized as a threat to the life of this group not known until then, considering that this is a challenging

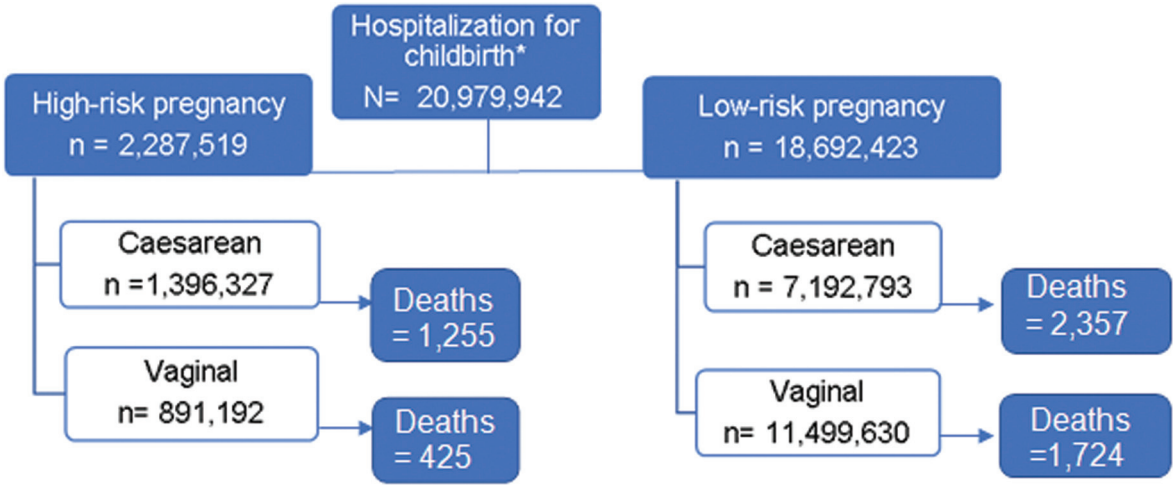

Fig. 1. Absolute number of admissions for childbirth and maternal deaths during hospitalization according to gestational risk and mode of delivery between 2010 and 2020. *Admissions for childbirth at any gestational age were included.

Table 1. Childbirth-related mortality rates in Brazil, according to gestational risk, and rate ratio for 2020 compared with the average for 2010-2019

	Average 2010–2019			2020			
	Hospitalization *n*	Deaths *n*	MR (95%CI)	Hospitalization *n*	Deaths *n*	MR (95%CI)	RR (95% CI)
	1915817	511	2.67 (2.44–2.91)	1821775	651	3.57 (3.31–3.86)	1.34 (1.19–1.50)
Gestational risk/Chilbirth							
Low risk	1,713,766	362	2.11 (1.90–2.34)	1554767	458	2.95 (2.68–3.22)	1.40 (1.21–1.60)
Caesarean	651,916	210	3.22 (3.09–3.36)	673633	256	3.80 (3.35–4.30)	1.18 (1.04–1.34)
Vaginal	1,061,850	152	1.43 (1.36–1.50)	881134	202	2.29 (1.99–2.63)	1.60 (1.39–1.85)
High risk	202,051	149	7.37 (6.24–8.66)	267008	193	7.23 (6.24–8.32)	0.98 (0.79–1.21)
Caesarean	122,792	111	9.04 (8.51–9.58)	168408	146	8.67 (7.32–10.2)	0.96 (0.81–1.14)
Vaginal	79,259	38	4.77 (4.30–5.26)	98600	47	4.76 (3.50–6.34)	0.99 (0.74–1.35)

Abbreviations: MR, Mortality among admissions for childbirth: number of deaths/number of admissions for childbirth x 10,000; RR, relative risk considering 2020 as exposed year and the average of the period between 2010 and 2019 as baseline.

situation for general health, and especially in this group with a higher immune vulnerability.

While maternal mortality in high-risk pregnancies has permanently high rates, mainly due to hemorrhage, sepsis, and hypertensive disorders, low-risk pregnant women have considerably lower mortality rates.[11,14] Thus, the COVID-19 pandemic stood out as a more dramatic and relevant harm to mothers who did not have a previous risk factor of an adverse outcome.

It is important to emphasize that, during the pandemic, prenatal care was highly affected by the fear of pregnant women to seek assistance and by barriers imposed by health care facilities for women.[15,16] The focus on the care of COVID-19-symptomatic individuals in primary care services

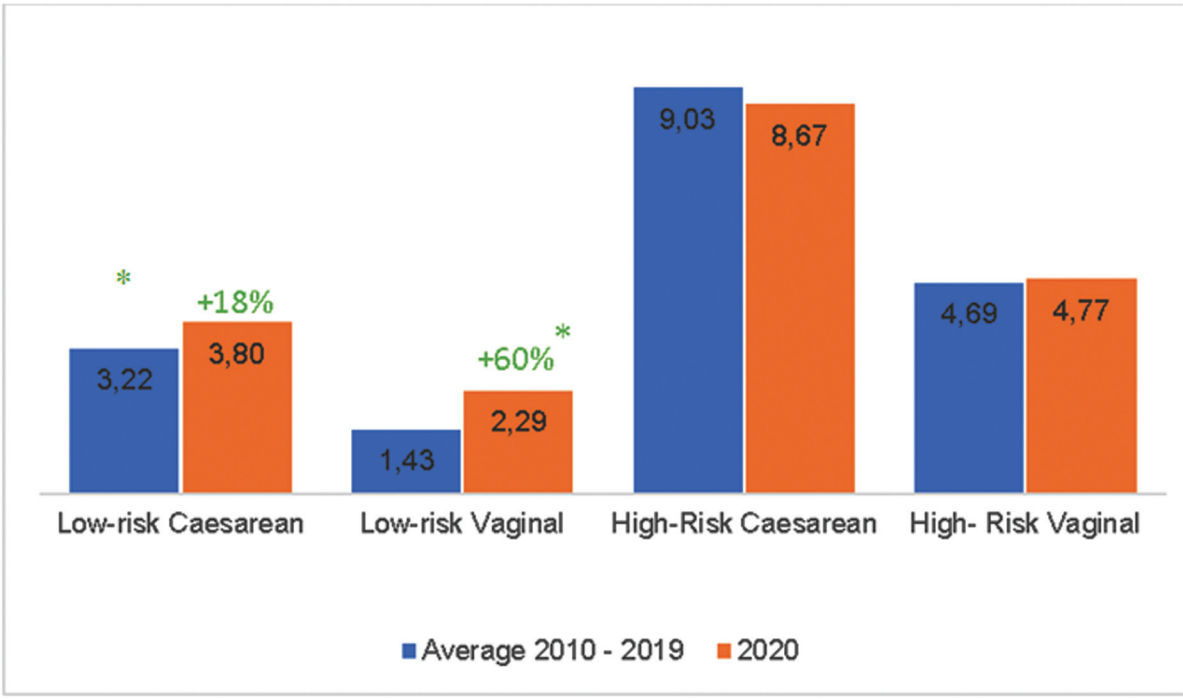

Fig. 2. Mortality among admissions for childbirth performed in Brazil, according to route of delivery and pregnancy risk, 2010-2019 and 2020. *Statistically significant comparison

resulted in the late arrival at hospitals of pregnant women with more serious conditions, which could have been avoided with timely and quality prenatal care.[17] In this context, high-risk pregnant women have become a priority in prenatal consultations, since many health services have changed the management of care for pregnant women, reorganizing the flow and using risk classification screening in order to focus on care for COVID-19 patients.[18] Therefore, the restriction of prenatal care, especially for low-risk pregnant women, as an indirect consequence of the COVID-19 pandemic, leads to losses in the treatment of maternal nutritional deficits, in screening for infections, and even in the classification as high-risk pregnancy if necessary, and may lead to worse maternal outcomes in this group.[19]

In addition, high-risk pregnant women, aware of their most vulnerable health condition, receive greater medical guidance and, associated with the fear of infection with their risk condition, may have followed social isolation and hygiene measures more intensively and, therefore, being less frequently a target of infection and death by COVID-19.[20]

However, it is a fact that, in Brazil, puerperal death by COVID-19 is mainly related to chronic problems in women's health, such as lack of resources, obstetric violence, insufficient beds, and poor-quality prenatal care.[16] Thus, the Brazilian health system was not prepared for all pregnant women to become "high-risk pregnant women" because of COVID-19, requiring greater attention and assistance while the health system was already overloaded. A study carried out with 978 Brazilian pregnant and postpartum women agrees with the present study in concluding that 51.6% of the women who died due to COVID-19 infection did not have comorbidities or risk factors. Besides, the study showed that being black, living in a periurban area, not having access to Family Health Strategy or living $>$ 100km away from the notification hospital were associated with an increased risk of a worse outcome.[9]

Therefore, the precarity of care for pregnant women and the structural racism in pandemic times may have had more impact on the deaths of postpartum women in Brazil than the association between COVID-19 infection and their previous comorbidities. A Brazilian study reinforces the insufficiency of the health system in women's healthcare by showing that 20% of pregnant and postpartum women hospitalized with COVID-19 did not have access to the intensive care unit and (ICU), and a third of them did not have access to mechanical ventilation.[4] An article published in July 2020 in The Lancet has already predicted higher maternal mortality in low- and middle-income countries due to the indirect effect of COVID-19, resulting in lower access to healthcare and to food due to the reorganization around COVID-19. The study found that 60% of additional maternal deaths would be related to basic management of women's healthcare as clean birth environments, parenteral administration of uterotonics, antibiotics, and anticonvulsants.[21] Thus, healthy pregnant and postpartum women who would need minimal assistance ended up being victims of the disorganization of the health system in pandemic times and lost their lives.

Since vaccination was recommended primarily for high-risk pregnant women, this scenario can still be maintained in 2021.[22] Thus, the mortality rates already predicted for high-risk pregnant women would remain the same, regardless of infection by COVID -19, and would increase mortality in low-risk pregnancies, since they were not yet immunized, and the possible infection would add risk to the pregnancy of these women. Therefore, the present analysis is considered preliminary and further studies with a detailed analysis of 2021 are needed to compose a more complete analysis of the pandemic period.

Finally, the increase in maternal mortality among admissions for childbirth occurred both after cesarean delivery and after vaginal delivery. However, it is noteworthy that there was a greater increase after vaginal delivery (60%) compared with cesarean delivery (18%). The literature is conflicting in assessing if the mode of delivery interferes in the maternal mortality during COVID-19 infections. A systematic review of 11,758 pregnant women found that the majority of COVID-19-infected women who died had a cesarean section (58.3%), while 25% had vaginal delivery and 16,7% of the patients were not full-term.[23] However, other systematic reviews have not found significant outcome effects comparing modes of delivery.[24,25]

As for the limitations of the present study, since it is an ecological and exploratory study, comparing 1 year to a period of 10 years, a cause-effect relationship cannot be defined. Also, because of the availability of the data, we considered in comparisons only 1 year (2020) as the risk from the pandemic and did not evaluate the complete trend over the years. In addition, there are limitations inherent to the use of secondary data, depending on the quality of the record carried out and on the impossibility of evaluating the cause of death, as well as the sociodemographic profile of pregnant women, since these data are not available for analysis. Besides, there are few studies on the mortality after birth in hospitalized women, which made the comparison with the literature difficult. However, based on the increased maternal mortality of low-risk pregnancy in Brazil in 2020 compared with the period between 2010 and 2019, it is suggested that this is another unfavorable outcome of the COVID-19 pandemic in the country, since this group was characterized as a risk group for infection.

Conclusion

Maternal mortality among admissions for childbirth according to SUS data increased in 2020 in low-risk pregnancies compared with the average number of deaths between 2010 and 2019. The increase was of 18% after cesarean section and of 60% after vaginal delivery. Regarding high-risk pregnancies, no significant differences were observed. The increase in maternal mortality only in low-risk pregnancies suggests that the COVID-19 pandemic stood out as a more dramatic and relevant harm to mothers who did not have a previous risk factor of an adverse outcome. Since puerperal death due to COVID-19 in Brazil is mainly related to chronic problems in women's health, the precarity of care for pregnant women in pandemic times may have had a greater impact on deaths among admissions for childbirth in Brazil than the association between COVID-19 infection and their previous comorbidities.

Contributions

Michels B. D., Iser B. P. M, and Marin D.F.D. were responsible for the conception and design of the present study. Michels B. D. was responsible for the literature review and for the first version of writing, collection, analysis, and interpretation of data. Iser B. P. M and Marin D.F.D. participated in data analysis and interpretation and performed a relevant critical review of the intellectual content. Michels B. D., Iser B. P. M, and Marin D.F.D. approved the final version presented here.

Conflict of Interests

The authors have no conflict of interests to declare.

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Clinical Presentation, Treatment Outcomes, and Resistance-related Factors in South American Women with Low-risk Postmolar Gestational Trophoblastic Neoplasia

Apresentação clínica, resultados do tratamento e fatores relacionados à resistência em mulheres sul-americanas com neoplasia trofoblástica gestacional pós-molar de baixo risco

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Abstract

Objective There are few multinational studies on gestational trophoblastic neoplasia (GTN) treatment outcomes in South America. The purpose of this study was to assess the clinical presentation, treatment outcomes, and factors associated with chemoresistance in low-risk postmolar GTN treated with first-line single-agent chemotherapy in three South American centers.

Methods Multicentric, historical cohort study including women with International Federation of Gynecology and Obstetrics (FIGO)-staged low-risk postmolar GTN attending centers in Argentina, Brazil, and Colombia between 1990 and 2014. Data were obtained on patient characteristics, disease presentation, and treatment response. Logistic regression was used to assess the relationship between clinical factors

Keywords
- low-risk gestational trophoblastic neoplasia
- molar pregnancy
- South America
- chemotherapy
- resistance-related factors

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and resistance to first-line single-agent treatment. A multivariate analysis of the clinical factors significant in univariate analysis was performed.

Results A total of 163 women with low-risk GTN were included in the analysis. The overall rate of complete response to first-line chemotherapy was 80% (130/163). The rates of complete response to methotrexate or actinomycin-D as first-line treatment, and actinomycin-D as second-line treatment postmethotrexate failure were 79% (125/157), 83% (5⁄6), and 70% (23/33), respectively. Switching to second-line treatment due to chemoresistance occurred in 20.2% of cases (33/163). The multivariate analysis demonstrated that patients with a 5 to 6 FIGO risk score were 4.2-fold more likely to develop resistance to first-line single-agent treatment ($p = 0.019$).

Conclusion 1) At presentation, most women showed clinical characteristics favorable to a good outcome, 2) the overall rate of sustained complete remission after first-line single-agent treatment was comparable to that observed in developed countries, 3) a FIGO risk score of 5 or 6 is associated with development of resistance to first-line single-agent chemotherapy.

Resumo

Objetivo Existem poucos estudos multinacionais sobre os resultados do tratamento da neoplasia trofoblástica gestacional (NTG) na América do Sul. O objetivo deste estudo foi avaliar a apresentação clínica, os resultados do tratamento e os fatores associados a casos de quimiorresistência em NTG pós-molar de baixo risco tratados com quimioterapia de agente único de primeira linha em três centros sul-americanos.

Métodos Estudo multicêntrico de coorte histórica incluindo mulheres com NTG pós-molar de baixo risco com estadiamento International Federation of Gynecology and Obstetrics (FIGO) em centros de atendimento na Argentina, Brasil e Colômbia entre 1990 e 2014. Foram obtidos dados sobre as características do paciente, apresentação da doença e resposta ao tratamento. A regressão logística foi usada para avaliar a relação entre fatores clínicos e resistência ao tratamento de primeira linha com agente único. Foi realizada uma análise multivariada dos fatores clínicos significativos na análise univariada.

Resultados Cento e sessenta e três mulheres com NTG de baixo risco foram incluídas na análise. A taxa global de resposta completa à quimioterapia de primeira linha foi de 80% (130/163). As taxas de resposta completa ao metotrexato ou actinomicina-D como tratamento de primeira linha e actinomicina-D como tratamento de segunda linha após falha do metotrexato foram 79% (125/157), 83% (5⁄6) e 70% (23/33), respectivamente. A mudança para o tratamento de segunda linha por quimiorresistência ocorreu em 20,2% dos casos (33/163). A análise multivariada demonstrou que pacientes com pontuação de risco FIGO de 5 a 6 foram 4,2 vezes mais propensos a desenvolver resistência ao tratamento com agente único de primeira linha ($p = 0,019$).

Conclusão 1) Na apresentação, a maioria das mulheres demonstrou características clínicas favoráveis a um bom resultado, 2) a taxa geral de remissão completa sustentada após o tratamento de primeira linha com agente único foi comparável à de países desenvolvidos, 3) um escore de risco FIGO de 5 ou 6 está associado ao desenvolvimento de resistência à quimioterapia de agente único de primeira linha.

Palavras-chave

- neoplasia trofoblástica gestacional de baixo risco
- gravidez molar
- América do Sul
- quimioterapia
- fatores relacionados à resistência

Introduction

Gestational trophoblastic neoplasia (GTN) is a malignant form of gestational trophoblastic disease with abnormal proliferation of placental trophoblastic cells that secrete persistent amounts of human chorionic gonadotropin (hCG).[1] The clinical presentation of GTN is variable depending on previous pregnancy type, disease extension and histopathological classification. Invasive mole and choriocarcinoma are very responsive to chemotherapy, and hCG values are usually well correlated with the volume of disease. On the other hand, placental site trophoblastic tumor and epithelioid trophoblastic tumor are

relatively chemoresistant and produce less hCG compared with other forms of GTN.[2] In these cases, surgery is often the treatment of choice.[2]

Gestational trophoblastic neoplasia can occur after any type of pregnancy.[3] However, the risk of developing GTN is highest in women with a molar pregnancy. In fact, between 50 and 80% of all GTN cases originate from a hydatidiform mole, and the remainder from a term/preterm pregnancy, miscarriage, or ectopic pregnancy.[4] Between 15 and 20% of patients with a complete hydatidiform mole (CHM) and 1 to 4% of those with a partial mole develop postmolar GTN.[3] These rates may differ from region to region, possibly reflecting differences in the hCG assays and criteria used for the diagnosis of GTN,[5] or even unavailability of demographic data on the entire population.

Gestational trophoblastic neoplasia cure rates are over 90% overall[6] and above 99% in some countries.[7] These good results can be explained by the adequate use of hCG as a biomarker, provision of patient care in specialized centers,[6] identification of prognostic factors for chemotherapy response,[8] and availability of active second- and third-line chemotherapy regimens. In 2000, the International Federation of Gynecology and Obstetrics and the International Society of Gynecological Cancer (FIGO Oncology Committee, 2002)[8] established a combined anatomic staging (stages I, II, III, and IV) and modified World Health Organization (WHO) risk-factor scoring system for classifying GTN as low (< 7) or high (≥ 7) risk for the development of resistance to single-agent chemotherapy.

First-line chemotherapy with either methotrexate (MTX) or actinomycin D (ActD) is the treatment of choice worldwide for patients with low-risk postmolar GTN (score < 7).[7] The most commonly used chemotherapy regimens are MTX (intravenous (IV) or IM), maximum of 25 mg/m^2 daily for 5 days repeated every 2 weeks[9]; 50 mg MTX for 8 days (IM) on days 1, 3, 5, and 7, and with folinic acid (FA) rescue (0.1 mg/kg) on days 2, 4, 6, and 8[10]; ActD 1.25 mg/m^2 (maximum of 2 mg) single IV dose every 2 weeks[11]; and ActD 10 to 12 µg/kg IV for 5 days every 2 weeks.[12] It is important to emphasize that prompt chemotherapy treatment with appropriate regimens and fixed and timely intervals between chemotherapy cycles limits the development of resistance and the exposure of most patients to multi-agent chemotherapy.[13,14]

There are few studies on GTN treatment response in South American patients,[15–18] and most of them are single-center, hospital-based.[19] The difficulties in carrying out multicentric studies in South American countries include socioeconomic and cultural diversities, as well as language barriers (Portuguese, Spanish, English). Given these disparities, the assessment of whether the results of first-line treatment with a single agent are similar or different from those observed in specialized centers in developed countries is relevant. Therefore, the purpose of this study was to assess the clinical presentation, treatment outcomes, and factors associated with chemoresistance in South American patients with low-risk postmolar GTN treated with first-line single-agent chemotherapy.

Methods

This historical, multicentric, cohort study included women with FIGO-defined low-risk postmolar GTN[8] treated from 1990 to 2014 at one of the following South American centers: Centro de Doenças Trofoblásticas de Botucatu, Universidade Estadual de São Paulo —Unesp, São Paulo, Brazil; Durand Trophoblastic Diseases Center in Buenos Aires, Hospital Carlos G. Durand, Buenos Aires, Argentina; and Oncólogos del Occidente S.A. Manizales, Caldas, Colombia). These three centers provide tertiary care and consultation free of charge.

Patients with insufficient clinical information, lost to follow-up before 12 months after serum hCG normalization, having undergone primary hysterectomy, or initially treated outside the centers participating in this study were excluded.

In all study participants, metastases were detected by clinical, gynecological, and imaging examinations. First, transvaginal power Doppler sonography was performed to rule out the presence of pregnancy and residual molar tissue, and to assess the myometrium for invasion and pelvic mass vascularity. A chest X-ray including at least two views (posterior-anterior and lateral) was used to count lung metastases and FIGO scoring. When chest X-rays were normal, no further imaging was ordered, and treatment was promptly indicated. For patients with genital metastases, suspected lung metastasis on chest X-ray, or nodules > 1 cm, a chest tomography was conducted to determine the extent of disease in the lungs.[7] At each of the three participating centers, images of lung metastases were reviewed, and metastatic nodules ≥ 1 cm were counted.[7] Metastases at other sites were investigated as described elsewhere.[17]

The hCG tests used for monitoring response to treatment were Abbott Architect (Centro de Doenças Trofoblásticas de Botucatu) and Roche Elecsys (Durand Trophoblastic Disease Center). At Oncólogos del Occidente S.A., kits by different manufacturers were used (Abbott Architect, Roche Elecsys, Siemens Immulite). However, all hCG tests for each individual patient were performed at the same laboratory to avoid variation among methods and results.

Participants received first-line chemotherapy with 8-day MTX/FA with FA rescue (0.1 mg/kg or 15 mg fixed dose,[10,13] 5-day MTX,[9] 5-day ActD or pulsed ActD each as a 2-week cycle. Multiple cycles of the same chemotherapy regimen were given until hCG remission, resistance development, or substantial toxicity (grades 3–4) (CTCAE, version 5) was reached. Consolidation chemotherapy was administered using the last effective regimen as one cycle to all patients in Argentina, while in Brazil and Colombia, two consolidations cycles were given for stage II or III cases. Patients were advised to use oral contraception throughout GTN treatment and follow up.[19,20]

Remission was defined as 3 normal consecutive serum hCG measurements (< 5 IU/L for Brazil and Colombia; < 2 IU/L for Argentina) taken every 1 to 2 weeks. Cure or sustained complete remission was declared when normal values of hCG were observed for at least 12 months after remission was achieved. Resistance was determined by a hCG plateau of $\pm 10\%$ over 2 weeks or re-elevation in at least one

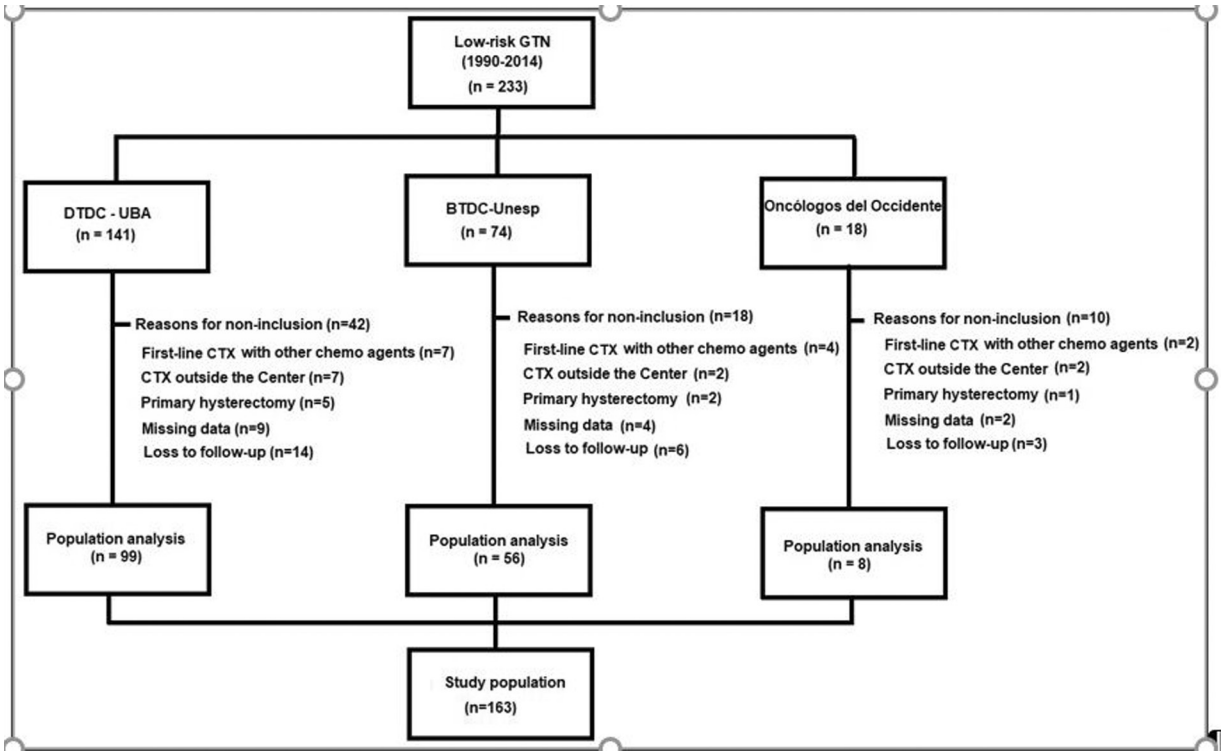

Fig. 1 Patient flow chart.

measurement of the hCG level while the patient was on first-line treatment with MTX or ActD. Second-line treatment consisted of switching the first single agent used (MTX as first-line switched for ActD as second line and vice versa) or capecitabine.[15] All patients either resistant to MTX or with MTX toxicity were eligible for ActD or capecitabine second-line therapy. Two patients received etoposide due to ActD unavailability, and three were given multiagent chemotherapy due to a higher FIGO score (score of 6) or hCG > 30,000 IU/L at the point of resistance to first-line single agent therapy.

The medical records (paper and electronic) of all patients with low-risk postmolar GTN (stages I–III, score < 7) were reviewed. Data on patient characteristics, disease presentation, and treatment response were obtained.

Patient and disease characteristics were assessed based on age, gravidity, parity, molar histology (complete or partial), time between molar evacuation and postmolar GTN diagnosis, interval between GTN diagnosis and chemotherapy initiation, hCG before first-line chemotherapy, presence of metastatic disease, and FIGO stage/risk score.

Response to first-line treatment with MTX or ActD was investigated using the following variables: number of first-line chemotherapy cycles, total number of chemotherapy cycles required to achieve remission, time to remission (interval between first-line chemotherapy initiation and first normal hCG), need for switching to second-line chemotherapy due to resistance to first-line treatment, or occurrence of substantial toxicity, surgery after chemoresistance, and survival rate.

This study was approved by the Research Ethics Committees of all participating institutions.

Statistical analyses were performed using the IBM SPSS Statistics for Windows, version 21.0 software (IBM Corp., Armonk, NY, USA). Univariate analysis was used to assess the associations between clinical factors and resistance to single agent first-line treatment. A multiple logistic regression model was fit to evaluate the associations of resistance to single agent first-line treatment with the clinical factors considered significant ($p < 0.20$) on univariate analysis. Associations were considered significant when $p < 0.05$.

This study was approved by ther ethics committee of the Botucatu Medical School of Universidade Estadual de São Paulo, under protocol no. 563.812 (CAAE 17817613.6.0000.5411), Comité de Bioética Hospital General de Agudos Carlos G. Durand (DI-2018–534-HGACD), and Comité de Ética en Investigación de Oncolólogos del Occidente (IC-FO-003).

Results

Of 233 women diagnosed with FIGO-defined low-risk postmolar GTN, 163 received single agent first-line treatment with either MTX or ActD and were included in the analysis. The remaining 70 women were excluded for the following reasons: first-line treatment with chemotherapy agents other than MTX and ACTD ($n = 13$), initial treatment outside the study Center ($n = 11$), primary hysterectomy ($n = 8$), missing data ($n = 15$), and loss to follow-up < 12 months after serum hCG normalization ($n = 23$) (►**Fig. 1**).

The clinical characteristics of the 163 study participants with low-risk postmolar GTN are shown in ►**Table 1**. The median age (1st, 3rd quartile) of patients was 28 years (21, 33 years) and the median parity (1st, 3rd quartile) was 1 (0, 1). Complete hydatidiform mole was the most frequently

Table 1 Patient and disease characteristics ($n = 163$)

Variables	Summary
Age (years)	28.0 (21.0, 33.0)
Gravidity	2.0 (1.0, 3.0)
Parity	1.0 (0.0, 1.0)
Molar histology	
Partial	27 (16.6%)
Complete	136 (83.4%)
HM evacuation-GTN diagnosis interval (months)	2.3 (1.6, 3.6)
GTN diagnosis- chemotherapy initiation interval (days)	2.0 (0.0–6.0)
Pre-treatment hCG	7,442 (1,693, 29,227)
Pre-treatment hCG	
$< 1{,}000$	31 (19.0%)
$1{,}000 < 10{,}000$	60 (36.8%)
10,000–99,999	62 (38.0%)
$\geq 100{,}000$	10 (6.2%)
Metastatic disease at presentation	51 (31.2%)
FIGO stage	
1	112 (68.7%)
2	3 (1.8%)
3	48 (29.4%)
FIGO risk score	3.0 (1.0, 4.0)
FIGO risk score	
0–2	81 (49.7%)
3–4	61 (37.5%)
5–6	21 (12.8%)
Number of first-line chemotherapy cycles	4.0 (3.0, 7.0)
Total number of chemotherapy cycles to remission	5.0 (3.0–8.0)
Time to hCG remission (weeks)	12.5 (7.7, 19.0)
Switch to second-line treatment	33 (20.2%)
Switch to third-line treatment	2 (1.2%)
Surgery after chemoresistance	11 (6.74%)
Survival rate	163 (100.0%)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; M, hydatidiform mole.
Data are median (25th–75th percentile) or n (%).

observed type of mole (83.4%). The median interval between molar evacuation and postmolar GTN diagnosis (1st, 3rd quartile) was 2.3 months (1.6, 3.6), and hCG level at GTN diagnosis was $< 100{,}000$ IU/L in 94% of patients. At presentation, metastatic disease was observed in 51 patients (31.2%) (48 lung, 2 vagina, and 1 pelvis). Nearly 90% of the women had FIGO risk score < 5.

The following first-line single agent chemotherapy regimens were administered: 8-day MTX/FA ($n = 142$), 5-day MTX ($n = 15$), pulsed ActD ($n = 1$), or 5-day ActD ($n = 5$). Of note, the median interval between GTN diagnosis and initiation of single-agent first-line treatment (1st, 3rd quartile) was 2 days (0–6). The median number of cycles (1st, 3rd quartile) given until hCG normalization or first-line agent resistance was 4 (3, 7). The rates of sustained complete remission with MTX or ActD as first-line treatment, were 79.6%% (125/157) and 83.3% (5%), respectively. Among the 33 patients (20.2%) requiring a switch to second-line treatment, 24 received ActD, 4 capecitabine, 2 etoposide, and 3 multiagent chemotherapy. Failure of second-line single-agent treatment was observed in only 2 patients (1.2%), 1 with 5-day ActD, and the other with capecitabine, who required multiagent chemotherapy to achieve complete remission. Surgery after chemoresistance was performed in 6.7% of patients (9 underwent hysterectomy, and 2 local uterine resection). The median time (1st, 3rd quartile) to reach hCG normalization was 12 weeks (7.7, 19). Gestational trophoblastic neoplasia patients with FIGO risk score 5 to 6 that achieved remission after first- or second-line single-agent chemotherapy accounted for 90.5% (19/21) of the study population (►**Table 1**).

Two patients experienced substantial toxicity during first-line treatment (grade 3 oral mucositis in 1 patient who received 5-day-MTX, and grade 3 nausea/vomiting in 1 patient who received 5-day ActD). However, no failure in first-line single-agent treatment due to chemotherapy-induced toxicity was observed. In these cases, chemotherapy was discontinued, and, because hCG normalization was reached while the patients were recovering from toxicity, chemotherapy was no longer used. All study participants were followed up for at least 12 months after completing chemotherapy. Survival rate between low-risk GTN diagnosis and the end of follow-up was 100% (►**Table 1**).

Univariate analysis showed that a FIGO risk score of 5 to 6 (odds ratio [OR] = 5.75 [95% CI 2.03–16.31], $p = 0.001$), total number of chemotherapy cycles required to achieve remission (1.32 [1.16–1.49], $p < 0.001$), and time to remission (1.07 [1.03–1.11], $p = 0.001$) were identified as significant indicators of resistance to first-line single-agent treatment (►**Table 2**). Multivariate analysis, including the clinical factors considered significant on univariate analysis, demonstrated that patients with a FIGO risk score of 5 to 6 were 4.2-fold more likely to develop resistance to first-line single-agent treatment ($p = 0.019$). Among the patients with a 5 to 6 FIGO score, the rate of chemoresistance to first-line treatment was 52.4% (11/21), whereas in those with a FIGO risk score of 0 to 2 and 3 to 4, it was 16% (13/81) and 14.8% (9/61), respectively.

Discussion

This study including South American women with low-risk postmolar GTN showed that most patients had clinical characteristics favorable to a successful response to treatment. The overall rate of sustained complete remission after first-line single-agent treatment was $\sim$ 80%, and high FIGO scores (5–6) were strongly associated with resistance to first-line single-agent therapy.

Table 2 Univariate associations of resistance to first-line chemotherapy with clinical factors

Variables	OR	95% CI		*P*
Age (years)	0.98	0.94	1.03	*0.488*
Gravidity	0.79	0.58	1.08	*0.146*
Parity	0.80	0.55	1.18	*0.260*
Complete mole	0.87	0.32	2.36	*0.780*
HM evacuation - GTN diagnosis interval (months)	0.97	0.82	1.16	*0.740*
GTN diagnosis-chemotherapy initiation interval (days)	0.97	0.92	1.03	*0.327*
Pretreatment hCG	1.00	1.00	1.00	*0.020*
Pretreatment hCG (Reference $\leq$ 1,000)				*0.140*
[1,000–10,000)	0.45	0.14	1.43	*0.178*
[10,000–100,000)	1.09	0.39	3.04	*0.863*
$\geq$ 100,000	2.29	0.50	10.45	*0.286*
Metastatic disease at presentation	1.26	0.55	2.85	*0.584*
FIGO stage (reference = 1)				*0.715*
2	2.17	0.19	25.03	*0.536*
3	1.29	0.57	2.94	*0.547*
FIGO risk score	1.43	1.10	1.86	*0.007*
FIGO risk score (reference = 0–2)				
3–4	0.91	0.36	2.28	0.833
5–6	5.75	2.03	16.31	0.001
Number of first-line chemotherapy cycles	1.05	0.94	1.17	*0.405*
Total number of chemotherapy cycles to remission	1.32	1.16	1.49	*< 0.001*
Time to hCG remission (weeks)	1.07	1.03	1.11	*0.001*

Abbreviations: CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; HM, hydatidiform mole; OR, odds ratio.

The rates of sustained complete remission with MTX or ActD as first-line treatment were similar to those reported in developed countries[9,13,14,21] and other specialized South American centers as well.[16,18] The excellent overall cure rate found in our study is likely to be explained by the fact that our patients were initially treated in specialized centers. These provide interdisciplinary care, give each patient and their families the information needed to understand the disease and foster awareness of the importance of regular hCG monitoring, as well as actively identifying and recalling patients who miss appointments.[22] These centers perform GTN staging within 1 day after diagnosis so that prompt chemotherapeutic treatment can be started as recommended.[23] Additionally, these centers provide uninsured patients with medical care and chemotherapy drugs free of charge.[17] However, it is worth noting that specialized centers are not found in all Latin American countries, where the time elapsed between GTN diagnosis and treatment initiation is influenced by socioeconomic factors and health policies that do not always prioritize treatment for a rare condition such as GTN.[19] Centralized hCG monitoring has been recommended after molar evacuation, but this is not yet feasible in all countries and regions of South America. Therefore, training physicians for patient referral to a specialized center as soon as hCG plateaus or rises is essential to allow the prompt start of chemotherapy to patients with lower FIGO risk scores (< 5) to quickly achieve therapeutic success.[5,19]

In the majority of our patients, disease duration was less than 4 months, serum hCG level was within the lower range, FIGO risk score was < 5, and the interval between GTN diagnosis and initiation of first-line single agent treatment was short, allowing an excellent response to treatment. Indeed, previous reports have demonstrated that, in women with GTN followed up at specialized centers after molar evacuation, median FIGO risk score is lower and median time interval between molar evacuation and chemotherapy initiation is shorter than in those initially treated in other institutions.[24]

In our patients, treated with either MTX or ActD, the rate of switching to second-line therapy due to the development of resistance to first-line treatment was comparable to those reported with the use of MTX[9,21] and ActD as first-line therapy.[25]

The single-agent ActD regimen has been reported to provide a higher complete remission rate than MTX.[26] However, MTX has been demonstrated to have a more favorable toxicity profile,[18] as it causes no alopecia and has no vesicant properties and reduced risk of vascular disorders, which have all been associated with ActD, particularly the 5-day regimen.[27] These data, added to the fact that ActD is not always

available, have made multi-course MTX and rescue with folinic acid the most commonly used regimen in Latin America, where it is administered in an outpatient setting.[16,18,19,28]

Multivariate analysis revealed that our patients with FIGO risk score of 5 to 6 are significantly more likely to develop resistance to first-line single-agent treatment. This is in line with other reports that show that around 70% of patients in this subset become chemoresistant, and that this is directly related to chemotherapy duration and need for switching to a subsequent more toxic treatment.[1,13] Notably, all our patients who experienced treatment failure with first-line single-agent chemotherapy were cured with sequential single-agent chemotherapy or multiagent chemotherapy with or without the use of salvage surgery.

Several previous investigations have identified pretreatment hCG $>$ 100,000 IU/L,[29] uterine artery pulsatility index $<$ 1,[30] and presence of lung metastases[31] as predictive of resistance to first-line therapy in women with low-risk GTN. However, none of these resistance predictors have been validated.[5] The largest international collaborative study of GTN patients with a FIGO score of 5 to 6 to date[4] reveals that metastatic disease, choriocarcinoma, and pretreatment hCG concentration are significant predictors of resistance to single-agent therapies among these women.[4] However, in our study, FIGO score 5 to 6 was the only factor to reach statistical significance. The fact that hCG at diagnosis was $<$ 100,000 IU/L in the great majority of our patients might explain this finding.

Despite being multicentric, this study is limited by the inherent bias introduced by its retrospective hospital-based design which affect the generalizability of our results. It is noteworthy that the participating centers used different hCG cutoffs to define remission, but this did not affect the assessment of chemoresistance incidence. Other limitations included the small sample size (especially in the scenarios of risk factors for chemoresistance in case of low-risk GTN FIGO risk score of 5–6), and the fact that different first- and second-line regimens were used at the study centers. Additionally, although present in some studies used for comparison, factors related to chemoresistance in low-risk GTN, such as presence of choriocarcinoma, antecedent miscarriage, preterm/term gestation, and ectopic pregnancy, were not addressed herein. Nonetheless, the power of our multivariate analysis on the occurrence of resistance to first-line single-agent treatment was over 95%.

This is the first study to describe low-risk GTN clinical presentation, remission rates, treatment outcomes and resistance risk in South American gestational trophoblastic centers. Our findings may be useful to physicians in guiding decision-making, as they indicate which patients are at a higher risk of resistance and should, therefore, be referred to a specialized center upfront. This can contribute to improve the quality of life of the patients by decreasing exposure to more toxic multiagent therapy and increasing their chance to achieve complete remission more quickly.

Conclusion

In brief, this study of South American women with low-risk of GTN treated in specialized centers led to the following conclusions: 1) at presentation, most patients showed clinical characteristics favorable for a good outcome, 2) the overall rate of sustained complete remission observed after first-line single-agent treatment was comparable to that of developed countries, 3) FIGO risk scores of 5 or 6 are associated with the development of resistance to first-line single-agent chemotherapy.

Contributions

L. A. C. R. conceived and designed the study, reviewed the literature, and collected and managed data from the databases of Durand Trophoblastic Disease Center in Buenos Aires (Carlos G. Durand Hospital), Botucatu Trophoblastic Disease Center (São Paulo State University), and Oncólogos del Occidente S.A. Manizales, Caldas, Colombia; wrote the initial draft of the manuscript. I. M. conceived and designed the study, wrote the manuscript and audited data collected from Botucatu Trophoblastic Disease Center database (São Paulo State University) by L. A. C. R. M. I. B. audited the data collected by L. A. C. R. from the Durand Trophoblastic Disease Center database in Buenos Aires (Carlos G. Durand Hospital) and contributed to data analysis. G. J. helped analyzing data from the Durand Trophoblastic Disease Center database in Buenos Aires (Carlos G. Durand Hospital) and contributed to the manuscript. S. O. helped with the analysis of data from the Carlos G. Durand Hospital database and contributed to the manuscript. C. R. V. M. audited data collected by L. A. C. R. from the database of Oncólogos del Occidente S.A. Manizales, Caldas, Colombia and contributed to the manuscript. R. C. C. contributed to data analysis and interpretation and reviewed the literature for discussion. K. M. E. conceived the analysis strategy and contributed to the manuscript. N. S. H. contributed to data analysis and interpretation and revised the manuscript. M. J. S. supervised the study and revised the manuscript. R. S. B. supervised the study and revised the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Patient Acceptance of Telemedicine in Urogynecology Consultations – A Cross-Sectional Study Performed at a Brazilian Public Institution

Aceitação de telemedicina em consultas de uroginecologia: Estudo transversal em uma instituição pública brasileira

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Abstract

Objective To evaluate the acceptance of telemedicine and determine its associated factors in an urogynecology outpatient clinic of a public hospital in Brazil.

Methods The present was a cross-sectional study performed between June and November 2020. The included patients had their elective appointments postponed due to the coronavirus disease 2019 (COVID-19) pandemic. The variables considered regarding the acceptance of telemedicine were: urogynecologic diagnosis, age, level of schooling, place of residence, access to the internet, type of device used, frequency of internet use, and use of social media platforms. The categorical variables were described by their absolute and relative frequencies. The association among variables was evaluated through the Fisher exact test, and univariate and multivariate analyses, considering the acceptance of telemedicine as the dependent variable.

Results A total of 225 patients were listed, and 182 agreed to participate. The mean age was 59 years old, 81.3% of the patients had access to the internet, and 87.3% of them accepted telemedicine. There were statistically significant associations regarding the acceptance of telemedicine and high levels of schooling ($p < 0.01$), internet access ($p < 0.01$), daily use of the internet ($p < 0.01$), access through personal mobile phone ($p < 0.01$), and access through the participant's own residence ($p < 0.01$). In the univariate and multivariate analyses, only high levels of schooling were associated with the acceptance of telemedicine (Adjusted odds ratio: 4.82; 95% confidence interval = 1.59–14.65).

Palavras-chave
- telemedicina
- estudos de viabilidade
- preferência do paciente
- internet
- ginecologia

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Conclusion Most of the urogynecology patients of a public hospital in a developing country accepted telemedicine. Internet access and level of schooling were the factors associated with the acceptance of telemedicine in urogynecology.

Resumo

Objetivo Avaliar aceitação da telemedicina e determinar seus fatores associados em uma clínica de uroginecologia de um hospital público brasileiro.

Métodos Trata-se de estudo transversal realizado entre junho e novembro de 2020. Foram recrutadas pacientes que tiveram seus atendimentos eletivos adiados devido à pandemia de doença do coronavírus 2019 (*coronavirus disease 2019*, COVID-19, em inglês). As variáveis consideradas para a aceitação da telemedicina foram: diagnóstico uroginecológico, idade, escolaridade, local de residência, acesso à internet, tipo de dispositivo, frequência do uso da internet, e uso de plataformas de redes sociais. As variáveis categóricas foras descritas na forma de suas frequências absoluta e relativa. A associação entre essas variáveis foi avaliada por meio do teste exato de Fisher e análises uni e multivariada, e a aceitação da telemedicina foi considerada a variável dependente.

Resultados Um total de 225 pacientes foram listadas, e 182 concordaram em participar. A idade média das participantes foi de 59 anos; 81,3% delas tinham acesso à internet, e 87,3% aceitaram a telemedicina. Observaram-se associações estatisticamente significativas entre a aceitação e maior escolaridade ($p < 0{,}01$), acesso à internet ($p < 0{,}01$), uso diário da internet ($p < 0{,}01$), acesso por celular próprio ($p < 0{,}01$), e acesso da própria residência ($p < 0{,}01$). Nas análises uni e multivariada, somente alto nível de escolaridade esteve associado à aceitação da telemedicina (razão de probabilidades ajustada: 4,82; intervalo de confiança de 95% = 1,59–14,65).

Conclusão A maioria das pacientes atendidas em um hospital público de um país em desenvolvimento concordaram com a telemedicina. Acesso à internet e nível de escolaridade foram fatores associados à aceitação da telemedicina nessa população.

Keywords
- telemedicine
- feasibility studies
- patient preference
- internet
- gynecology

Introduction

Telemedicine is defined as the use of technology to connect a patient to a healthcare provider.[1] The adoption of this form of care, already widely discussed, became even more relevant after the outbreak of the coronavirus disease 2019 (COVID-19) pandemic in early 2020. The need for social distancing brought up the fact that a significant portion of medical consultations can be performed remotely.[2]

In this context, there has been an effort to implement and accelerate the use of telemedicine in many fields, with further discussions regarding laws and regulations, and the development of evidence-based protocols to guide remote care.

Regarding urogynecology, a guide[3] was recently published to help clinicians provide high-quality care through remote access. Telemedicine is an opportunity to minimize exposure without sacrificing treatments, and it has opened a new door in the field of urogynecology, mainly concerning the follow-up of treatments even after the pandemic.[4,5] A recent study[6] evaluating telemedicine in the postoperative care of pelvic floor dysfunctions showed that telephone follow-up was not inferior to in-person clinic visits regarding patient satisfaction, and there was no difference in clinical outcomes or adverse events among the groups. The leading urogynecologic diagnoses that may demand follow-up during the pandemic are urinary tract infection, urinary incontinence, and pelvic organ prolapse.[7]

In Brazil, before March 2020, telemedicine was only allowed to be used between health care professionals to discuss clinical cases and to promote continuing education in the context of the public health system. The interaction between health professionals and patients was not authorized until an emergency regulation valid only during the COVID-19 pandemic was enacted.[8,9] The health care system in the country is divided between private and public subsystems. Even though the public health system is free and universal, the access to secondary care, such as specialists, is difficult, and often favors those with the ability to pay for the services.[10] Since the regulation, many hospitals have shown interest in implementing telemedicine, but there is no data evaluating how or if public hospitals and their patients are able to use this healthcare modality. There are limiting factors such as the quality of internet connection, the availability of proper devices, and the level of technology literacy among this population. Brazil has more than 212 million inhabitants and has significant levels of social and economic inequality.[11] Among the population aged between 16 and 64 years, there are 140 million social media users, and 94% of them have smartphones.[12] However, women with urogynecological diseases are often older than 60 years, which may be a limiting factor for acceptance and adherence to telemedicine.

Although telemedicine has great potential, there is a lack of data demonstrating its use in Brazil, and we believe it is still underused, especially in the public health system. It is essential to know the resources available, the patterns of internet use, and the interest of the patients in telemedicine to evaluate the feasibility of the implementation of this form of care and how to best approach this population. Furthermore, we intend to demonstrate that patients of the Brazilian public health institutions and those of older ages can engage in this form of care. Therefore, the present study investigates the acceptance of urogynecology telemedicine in a public hospital in Brazil and analyzes its associated factors.

Methods

The present work was a cross-sectional study performed in a urogynecologic outpatient clinic of a public university hospital in the city of Belo Horizonte, state of Minas Gerais, Southeastern Brazil, from June to November 2020. The study was approved by the institutional review board (under CAAE 41733021.7.00005149), and all participants provided informed consent by telephone.

The inclusion criteria were all patients whose urogynecology medical appointment had been postponed due to the COVID-19 pandemic, who were able to be contacted by telephone call, and agreed to participate. The contact data was extracted from the Hospital's records. The patients who did not agree to participate or could not be contacted were not included in the analysis. The sociodemographic data of those who did not accept telemedicine was analyzed once they agreed to participate in the research. Due to the hospital's strategic plan to combat the COVID-19 pandemic, all urogynecologic appointments were considered elective and canceled from March to November 2020. A sample size of 163 was calculated considering a confidence intercal (CI) of 95%, an α error of 0.05, and an estimated proportion of 88% of agreement with telemedicine, based on previous research[13] evaluating the acceptance of telemedicine in urogynecology.

The data was collected through a review of the medical records and structured interviews conducted by telephone. We tried to reach the patients three times, at different times of the day and different days of the week. Two members of the staff of the outpatient clinic performed the interviews, the data was recorded using the Redcap (Vanderbilt University, Nashville, TN, United States) software, and the telephone calls were not recorded nor transcribed. The variables considered regarding telemedicine acceptance were selected based on a previous systematic review conducted by Scott Kruse et al.[14] (2018): primary urogynecologic diagnosis, age, level of schooling, place of residence, access to the internet, type of internet connection, place of access, type of device used, frequency of internet use, and use of social media platforms. The level of schooling was considered "low" if the patients did not have any formal education or had not concluded the equivalent of middle school in the brazilian education system; and "high" if they had concluded middle school or had higher degree of education (high school or college degree). The questions related to internet use and social media platforms could have more than one single answer.

The patients were asked if they agreed with telemedicine care for their condition. We defined this care as a remote appointment made by telephone or video call instead of an in-person visit. They were divided into two groups: those who accepted telemedicine (group 1) and those who did not (group 2).

The statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Window, IBM Corp., Armonk, NY, United States) software, version 21.0. The categorical variables were expressed as absolute and relative frequencies, and age, by the mean and median values. Sociodemographic, clinical, and internet-use variables were tested using the Fisher exact test, and univariate and multivariate logistic regression tests were used to identify possible associations with the agreement or disagreement with telemedicine care. Two continuous variables were converted to binary variables following clinically-relevant criteria: age was categorized as < 50 years or > 51 years, based on the increased prevalence of urogynecological symptoms after this age; and the level of schooling was divided into low or high. Values of $p < 0.05$ were considered statistically significant.

Results

A total of 225 patients had their appointments postponed due to the COVID-19 pandemic. We were able to contact 190, and, of these, 182 agreed to participate (►**Fig. 1**). In total, 35 patients (15.5%) could not be reached by telephone.

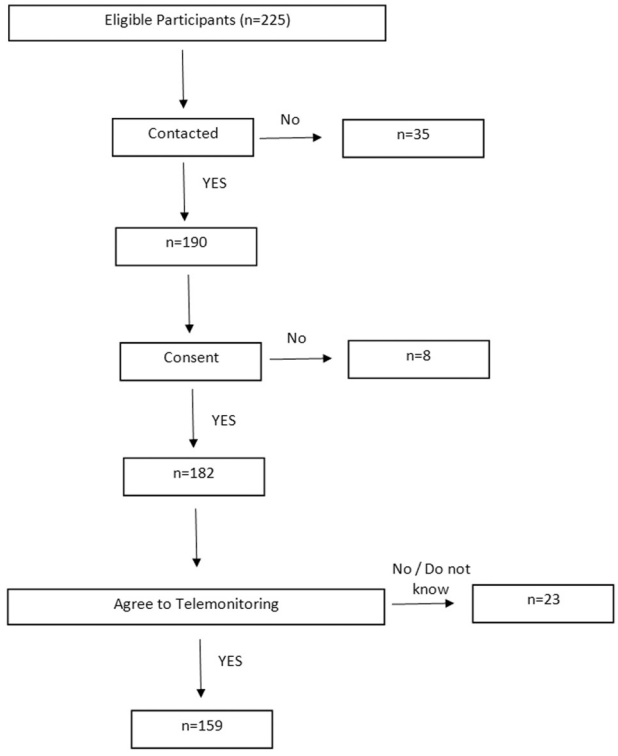

Fig. 1 Flowchart of the steps followed in the present study.

The mean age of the participants was 59 years, ranging from 20 to 87 years, and a median of 60 years. A total of 81.3% of the patients answered that they had internet access. Most participants accessed it mainly through their mobile phones and from their own residence. Regarding the social media platforms, they were used by 97.3% of the patients who had internet access. A total of 76.4% of the sample had the 3 most frequent urogynecologic diagnoses: mixed urinary incontinence, stress urinary incontinence, and overactive bladder. Less frequent diagnoses included pelvic organ prolapse, recurrent urinary tract infection, urinary retention, bladder pain syndrome, vesicovaginal fistula, and vesical endometriosis. A total of 159 (87.3%) participants accepted telemedicine as a form of care for their urogynecological condition; 20 (11%) patients did not accept telemedicine, preferring to be examined in person at the outpatient clinic, and 3 (1.7%) did not know how to answer this question. The acceptance of telemedicine was strongly associated with high levels of schooling, internet access, daily use of the internet, mobile data availability, and internet access from the participant's residence ($p < 0.001$) (►**Table 1**).

A multivariate analysis was performed for the level of schooling to compare it with other demographic variables (►**Table 2**). A multivariate analysis was performed for the level of schooling to compare it with other demographic variables. Only high level of schooling was associated with the acceptance of telemedicine in both univariate (odds ratio [OR]: 5.18; 95%; CI¼1.77–15.16; $p<0.01$) and multivariate analysis (OR: 4.82; 95 CI¼1.59–14.65; $p<0.01$).

Table 1 Sociodemographic, diagnosis, and internet accessibility according to acceptance of telemedicine care

Variables	Group 1 ($n = 159$)	Group 2 ($n = 20$)	p-value*
Age			
< 50	49	2	0.052
>51	110	18	
Education Level			
Low education	55	14	<0.01
High education	102	6	
Local of Residency			0.717
Same city of the hospital	102	14	
Metropolitan area	38	5	
Distant city	17	1	
Diagnosis/Follow-up			0.550
Urinary Incontinence[α]	122	16	
Pre-operative care	3	0	
Post-operative follow-up	33	1	
Overactive Bladder	18	3	
Stress incontinence	22	1	
Mixed Incontinence	46	11	
Pelvic Organ Prolapse[α]	14	3	
Pre-operative care	2	1	
Post-operative follow-up	5	0	
Conservative treatment	7	2	
Urinary retention	3	0	
Recurrent urinary tract infection	5	0	
Other	10	0	
Internet Access			<0.01
Yes	141	6	
No	17	13	
Daily Use of Internet			<0.01
Yes	123	4	
No	18	5	
Device			<0.01
Personal mobile phone	127	4	
Family's or friend's mobile phone	18	2	
Tablet	9	0	
Computer	40	2	
Place of Access			<0.01
Own residence	118	4	
Family's or friend's residence	6	1	
Workplace	9	0	
Any place with internet	45	2	

Group 1: Accepted Telemedicine; Group 2–No Accepted Telemedicine; *Chi-square and Fisher Test; [α]Grouped variables.

Discussion

Although telemedicine in Brazil is recent and probably underutilized in public hospitals, we found that most participants were interested and agreed to have their urogynecological condition monitored through this type of care. Among the associated factors, the level of schooling presented the strongest association with the acceptance of telemedicine. The factors involved in the non-acceptance of telemedicine included low level of schooling, lack of internet access, and lack of daily internet use. We believe our sample was representative of the studied population, once it comprised the number of patients usually seen in personal appointments for three months.

The World Health Organization (WHO) considers that telehealth plays an essential role in achieving universal access to health in a cost-effective manner, especially in the developing world.[15] Although it is believed that low- and middle-income countries can benefit more from remote access to health care services, its use for urogynecological patients has mainly been studied among educated women living in economically-developed countries.[16] The difficulties in effectively implementing its use were studied by Scott Kruse et al.[14] (2018) in a systematic review, and they included concerns about data privacy and confidentiality; the patient's age and level of schooling; computer access; bandwidth of dwelling; and resistance to change. A review[17] on the use of telehealth in urology showed similar results and

Table 2 Univariate and Multivariate Analysis for age, educational level, residence and diagnosis associated with telemedicine

Variables	Crude OR (95%CI)	*p*-value	Adjusted OR (95%CI)	*p*-value
Age				
> 51	0.26 (0.05-1.20)	0.086	0.4 (0.08-1.96)	0.264
Education Level				
High education	5.18 (1.77-15.16)	<0.01	4.82 (1.59-14.65)	<0.01
Local of Residency				
Metropolitan area	0.95 (0.31-2.85)	0.931	1.04 (0.32-3.34)	0.942
Distant city	2.05 (0.25-16.83)	0.500	2.36 (0.26-20.89)	0.438
Diagnosis/Follow-up				
Pelvic Organ Prolapse	0.57 (0.03-10.06)	0.702	0.63 (0.15-2.70)	0.542

OR: Odds Ratio; CI: Confidence Interval; Adjusted for: age, educational level, local of residence and diagnosis/follow-up; $n = 159$.

mentioned access to the internet, familiarity, and ease of use with technology as barriers to its implementation on the part of the patients. The results of the present study are similar to those of other studies in the published literature. We found that the level of schooling was the most substantial limiting factor associated with the acceptance of telemedicine in our population, even though the confidence intervals in the multivariate analysis are wide, which can reduce the precision of our effect estimate. We believe this is due to the fact that lower levels of schooling are associated with lower ability to communicate through and use the technological resources available. Most of the participants in the present study were considered to have high levels of schooling, although in Brazil, 6.6% of the population (14 million people) is deemed illiterate, and most of them are users of the public health system.[18] We have observed that the schooling profile of these users has been changing in recent years and could explain the findings of the present study.

Most patients interviewed had access to the internet through a mobile phone. This corroborates with the data from 2016 by the WHO, which acknowledges that mobile phone subscription rates in low- and middle-income countries are similar to those in high-income countries, alongside much lower access to other technological sources, such as computers or fixed broadband.[14] The use of mobile technology to deliver health care has been proven to be beneficial.[19] Karageorgos et al.[20] (2019) evaluated the use of mobile technologies in developing countries, and concluded that telehealth effectively motivated patients suffering from chronic diseases to adhere to treatment, attend appointments, and improve their lifestyle habits. In urogynecology, the use of mobile technology was studied in the follow-up of conservative treatment of urinary incontinence and demonstrated positive results, with improvement in symptoms and quality of life scores.[19,20]

The use of social media platforms is also becoming more popular. In the medical field, they represent a source of information to the patients on their condition and have the potential of improving the patients' satisfaction, sense of belonging, autonomy, and empowerment.[21] Alas et al.[22] (2013) analyzed the usefulness of social media in urogynecology, and concluded that a significant proportion of the information available regarding incontinence, pelvic floor prolapse, and urogynecology in the most popular platforms are not medically relevant. Therefore, physicians must incorporate this growing source of information into their daily practice and make an effort to ensure that accurate information is available to their patients. A multicenter survey conducted by Mazloomdoost et al. (2016)[21] demonstrated that 74.1% of women presenting to urogynecology practices reported having at least one social networking account, and 76.4% of the women most often used the internet for personal reasons, including medical inquiries. Almost the totality of patients with internet access in the present study accessed social media platforms regularly, and these platforms could also be used to to access and deliver healthcare.

The limitations of the present study include the fact that the interviews were performed during a period when the patients had their in-office visits canceled and no perspective for the return of the activities, which could have biased them to agree with telemedicine. Also, the invitation made by telephone call limited the recruitment of the patients, once we could not confirm the contact data previously. We did not include the non-responders in the sociodemographic analyses, which could be considered a response bias, since only patients who had access to a telephone were interviewed. We only included patients from a single center in the Southeastern region of Brazil, and we cannot extend our results to different parts of the country. We did not evaluate the efficiency and feasibility of telemedicine itself, thus, and further studies are necessary to determine its use among this population. The present study enabled us to recognize the profile of patients who could benefit from telemedicine in a public hospital in Brazil. Our next step will be to implement telemedicine care for these patients.

Conclusion

In conclusion, the present study demonstrated that patients of a public hospital in a developing country have the resources and the desire to take part in

telemedicine consultations. Internet access, daily use, access through their personal mobile phone, access from the participant's residence, and level of schooling were the factors associated with the acceptance of telemedicine in urogynecology.

Contributions

Macharet DVDL: project development, data collection, data analysis, manuscript writing. Mendes LN: project development, data collection, data analysis, manuscript editing. Oliveira WCS: data collection, data analysis. Pereira GMV: project development, data analysis, manuscript editing. Monteiro MVC: project development, data analysis, manuscript editing.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Histological and Immunohistochemical Characteristics for Hereditary Breast Cancer Risk in a Cohort of Brazilian Women

Características histológicas e imunohistoquímicas para risco hereditário de câncer de mama em uma coorte de mulheres brasileiras

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Abstract

Objective The study aimed to characterize the clinical, histological, and immunohistochemical profile of women with invasive breast cancer, according to the risk for Hereditary Predisposition Breast and Ovarian Cancer Syndrome in a Brazilian population.

Methods This is a retrospective study performed from a hospital-based cohort of 522 women, diagnosed with breast cancer treated at an oncology referral center in the Southeast region of Brazil, between 2014 and 2016.

Results Among the 430 women diagnosed with invasive breast cancer who composed the study population, 127 (29.5%) were classified as at increased risk for hereditary predisposition to breast and ovarian cancer syndrome. There was a lower level of education in patients at increased risk (34.6%) when compared with those at usual risk (46.0%). Regarding tumor characteristics, women at increased risk had higher percentages of the disease diagnosed at an advanced stage (32.3%), and with tumors $>$ 2cm (63.0%), with increased prevalence for both characteristics, when compared with those at usual risk. Furthermore, we found higher percentages of HG3 (43.3%) and K_i-67 $\geq$ 25% (64.6%) in women at increased risk, with prevalence being about twice as high in this group. The presence of triple-negative tumors was observed as 25.2% in women at increased risk and 6.0% in women at usual risk, with the

Keywords
- breast cancer
- hereditary breast and ovarian cancer syndrome
- cohort studies
- immunohistochemistry
- genetic counseling

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prevalence of absence of biomarkers being 2.5 times higher among women in the increased risk group.

Conclusion From the clinical criteria routinely used in the diagnosis of breast cancer, the care practice of genetic counseling for patients at increased risk of hereditary breast cancer in contexts such as Brazil is still scarce.

Resumo

Objetivo O presente estudo buscou caracterizar o perfil clínico, histológico e imunohistoquímico de mulheres com câncer de mama invasivo segundo o risco para a Síndrome de Predisposição Hereditária ao Câncer de Mama e Ovário em uma população brasileira.

Métodos Trata-se de um estudo retrospectivo realizado a partir de uma coorte hospitalar composta por 522 mulheres diagnosticadas com câncer de mama entre 2014 e 2016 assistidas em um centro de referência oncológica localizado na região sudeste brasileira.

Resultados Entre as 430 mulheres diagnosticadas com câncer de mama invasivo que compuseram a população de estudo, 127 (29,5%) foram classificadas como de risco aumentado para a síndrome de predisposição hereditária ao câncer de mama e ovário. Verificou-se menor nível de escolaridade nas pacientes com risco aumentado (34,6%) quando comparadas àquelas consideradas como de risco habitual (46,0%). Quanto às características do tumor, as mulheres de risco aumentado apresentaram maiores percentuais de doença diagnosticada em estádio avançado (32,3%) e com tumores $>$ 2cm (63,0%), com prevalência aumentada para ambas as características, quando comparadas àquelas de risco habitual. Ainda nas mulheres de risco aumentado, foram encontrados maiores percentuais de GH3 (43,3%) e K_i-67 $\geq$ 25% (64,6%), com prevalência cerca de duas vezes maior neste grupo. A presença de tumores triplo-negativos foi observada em 25,2% nas mulheres de risco aumentado e 6,0% nas mulheres de risco habitual, com prevalência de ausência de biomarcadores 2,5 vezes maior entre as mulheres do grupo de risco aumentado.

Conclusão A partir dos critérios clínicos rotineiramente utilizados no diagnóstico do câncer de mama, a prática assistencial do aconselhamento genético para as pacientes com risco aumentado de câncer de mama hereditário em contextos como o do Brasil ainda é escarça.

Palavras-chave
- câncer de mama
- síndrome hereditária de câncer de mama e ovário
- estudos de coorte
- imuno-histoquímica
- aconselhamento genético

Introduction

Breast cancer has a multifactorial etiology associated with hormonal, reproductive, genetics, lifestyle-related factors, and it is more frequent in post-climacteric women.[1] Most of these tumors originate in the ductal epithelium and acquire an invasive capacity. However, other histological types are found due to the great heterogeneity and different carcinogenic profiles of the tumors.[2]

Molecular biology has allowed the investigation of several genes associated with carcinogenesis, including the analysis of gene expression profiles of breast cancers, which makes it possible to correlate them with disease prognosis and with response to treatment.[3] In clinical practice, the immunohistochemical technique enables a quick, simple, and low-cost analysis of the expression of proteins that compose the tumor; additionally, it can evaluate the tumor grade and identify the molecular subtypes of breast cancer.[4]

Some characteristics of the breast tumor are essential for the clinical follow-up of the patients. The cell proliferation marker K_i-67 has an increased expression in breast tumors that may be associated with a higher risk of recurrence and worse prognosis.[5] The histological grade given by the Nottingham Classification System refers to the sum of the tubular grade, nuclear grade, and mitotic index scores, indicating the degree of differentiation of the tumor tissue, which also influences the prognosis. Furthermore, it is noteworthy that the size of the tumor is related to the probability of recurrence and lymph node involvement.[4]

The hereditary condition is the cause identified in 10 to 25% of breast and ovarian cancers, involving mutations in genes of high and moderate penetrance, such as the *BRCA1* and *BRCA2* genes.[6] The National Comprehensive Cancer Network (NCCN) defines criteria that help identify women prone to hereditary breast cancer. These criteria take into account the clinical manifestation of pre-climacteric ages and more aggressive breast carcinogenesis, with a

prevalence of bilaterality, triple-negative subtype tumors diagnosed up to 60 years old, Ashkenazi Jewish ancestry, and an association with other malignant neoplasms that affect family members, such as ovarian, endometrial, pancreas, bowel, prostate, and male breast cancer.[7–9]

Furthermore, the NCCN (2020)[9] and other medical organizations suggest potential candidates to specialists that would benefit from genetic testing and counseling, based mainly on personal and family history of cancer.[8–10] Family history is an important means used to identify individuals at risk of hereditary cancer; however, recommendations based on family history for genetic screening may be limited due to a poor family history, limited to first-degree relatives or to information inconsistently documented by professionals.[7,9–11]

Therefore, frequent reviews of the recommendation guidelines to assess Hereditary Breast and Ovarian Cancer (HBOC) syndrome have been performed to advance the diagnosis and management of women with HBOC syndrome, which has enabled the incorporation of new and more comprehensive criteria.[6,10]

In Brazil, there are few studies on the genetic profile of patients and family members at risk for HBOC syndrome.[12] This study seeks to characterize the clinical, histological, and immunohistochemical profile of women with invasive breast cancer, according to the risk for HBOC syndrome in a Brazilian population.

Methods

This is a retrospective study, performed from a hospital-based cohort, consisting of 522 women diagnosed with breast cancer between 2014 and 2016, and treated at an oncology referral center in the Zona da Mata of Minas Gerais, in the southeastern region in Brazil.

Sociodemographic, clinic, and pathological data were extracted from medical records, and additional information was obtained through interviews with patients, as well as from analysis of pathological anatomy and immunohistochemical test results.

Through the criteria used to assess hereditary breast cancer risk, recommended by the NCCN (2020),[9] women were classified into two categories: increased and usual risk for hereditary breast cancer. The group with increased risk for hereditary breast cancer considered the presence of at least one of the clinical criteria for HBOC Syndrome, such as: age at diagnosis $\leq$ 45-years-old; triple-negative subtype diagnosed in women aged $\leq$ 60 years; diagnosis of breast cancer between 46–50-years-old, with at least one first or second-degree relative with malignant neoplasm in the breast or ovary; and a personal history of breast cancer with the presence of secondary malignant tumor in the same organ.[9] The group with usual risk for hereditary breast cancer was considered as the same found in the asymptomatic female population, which has environmental and hormonal factors as the main risk conditions for the development of the disease.

The study excluded women with in situ breast cancer ($n = 42$) and those without information about at least one of the biomarkers of the tumor for estrogen, progesterone, and HER-2 ($n = 50$).

The characterization of the pathological profile of breast carcinoma was performed using the following variables: stage at diagnosis (early – I, intermediate – II, advanced stage – III and IV), histological type (ductal, lobular, others), tumor size ($\leq$ 2 cm, $>$ 2 cm), lymph node involvement, histological grade (HG1–well differentiated, HG2–moderately differentiated, HG3–poorly differentiated), K_i-67 cell proliferation index ($<$ 25%, $\geq$ 25%). Considering the relationship between the increased expression of K_i-67 and HG3, according to Gong et al.[5] and Delpech et al.[13] perineural invasion, vascular invasion, inflammatory infiltrate, multifocality, multicentricity, intraductal component, estrogen and progesterone hormone receptors (HR), HER-2 receptor, and immunohistochemical biomarkers (present: HR $\pm$ and HER-2+ or HR+ and HER-2-; absent: HR- and HER-2). And considering the presence of HER-2- only in tumors reported as 2+ or 3+ with confirmation by in situ hybridization technique.[14]

From analyses stratified according to risk for hereditary breast cancer, the mean and respective 95% confidence interval (95% CI) for age at diagnosis, as well as absolute numbers and percentages for categorical variables were presented. The difference in the distribution of categorical variables according to the risk for hereditary breast cancer was assessed using the chi-square test (χ^2), and the significance level considered was 5%. For these variables were estimated the prevalence ratios (PR) and the respective 95% confidence interval (95% CI). The analysis was performed using the STATA (StataCorp. College Station, TX, USA) software, version 16.0.

The study was approved by the Research Ethics Committee of Federal University of Juiz de Fora (CEP/UFJF), CAAE: 5342919.0.0000.5147.

Results

Among the 430 women diagnosed with invasive breast cancer who composed our study population, 127 (29.5%) were classified as at increased risk for HBOC Syndrome, according to the criteria recommended by the NCCN (2020).[9] For women at increased risk, the mean age was 42 years (95% CI: 40.9–44.0), and for those with usual risk, it was 63 years (95% CI: 61.9–64.2).

The majority of women were white (72.3%), with more than eight years of education (55.8%), and users of the public health service (60.5%). There was a lower level of education in patients at increased risk (36.4%) when compared with those considered to be at usual risk (46.0%) (PR = 0.70; 95% CI: 0.52–0.96) (►**Table 1**).

Most of the investigated patients did not mention a history of breast cancer in the family (69.5%). However, for women at increased risk, 39.4% had a positive history of cancer in up to third-degree relative. When we considered only first-degree relatives with breast cancer in the group of women at increased risk (20.5%), a 50% higher prevalence was found in the increased risk group than in the usual risk group (PR = 1.5; 95% CI: 1.09–2.14). Regarding

Table 1 Sociodemographic characteristics and family history of cancer according to the risk of predisposition for Hereditary Breast-Ovarian Cancer Syndrome (HBOC) in women treated

Variables			Usual risk		Increased risk			PR[b] (95% CI)
	n*	%	n	%	n	%	P[a]	
Age at diagnosis								
≥ 50 years old	299	69.5	282	93.1	17	13.4	0.000	1.00
< 50 years old	131	30.5	21	6.9	110	86.6		14.8 (9.3–23.6)
Skin color								
White	311	72.3	226	74.6	85	66.9	0.16	1.00
Non-white	113	26.3	72	23.8	41	32.3		1.33 (0.98–1.80)
Education (in years)								
> 8	240	55.8	158	52.0	82	64.6	0.05	1.00
≤ 8	183	42.6	139	46.0	44	34.6		0.70 (0.52–0.96)
Health service								
Private	170	39.5	124	40.9	46	36.2	0.40	1.00
Public	260	60.5	179	59.1	81	63.8		1.15 (0.85–1.56)
Family history of breast cancer								
Absent	299	69.5	222	73.3	77	60.6	0.01	1.00
Present	131	30.5	81	26.7	50	39.4		1.48 (1.11–1.98)
First-degree relative with breast cancer[c]								
Absent	368	85.6	267	88.0	101	79.5	0.02	1.00
Present	62	14.4	36	12.0	26	20.5		1.53 (1.09–2.14)

Abbreviations 95% CI, 95% confidence interval; PR, prevalence ratios.
Notes:
[a]chi-square (X^2) test, $p < 0.05$
[b]prevalence ratio calculated only for valid data
[c]first-degree relatives: parents, children, and siblings of the patient
*the difference in totals (N) is due to incompleteness of information.

anatomopathological characteristics of the population of the study, it was observed that 74.4% had early-stage/intermediate type, 82.3% had invasive ductal histological type, tumor size > 2 cm (54.2%), non-involved lymph nodes (50.9%), histological grade 2 (37.7%), and K_i-67 < 25% (48.1%) (►**Table 2**).

There was a significant difference between the groups regarding staging, tumor size, histological grade, and K_i-67 index. Women at increased risk had higher percentages of diagnosed disease at an advanced stage (32.3%), with tumors > 2cm (63.0%), and an increased prevalence (~1.4 times) for both characteristics, when compared with those at usual risk.

Also in women at increased risk, higher percentages of HG3 (43.3%) and K_i-67 ≥ 25% (64.6%) were found, with a prevalence about twice as high in this group (PR = 2.64 and 2.03, respectively). On the other hand, in women at usual risk, higher percentage of more differentiated tumors was identified, with HG2 (38.0%) and K_i-67 < 25% being intermediate or low (54.8%).

There was no significant difference in the distribution of histological types between groups. The lymph node involvement was 56.0% in women at increased risk, and 46.2% in women at usual risk, although it was also statistically insignificant (►**Table 2**).

Regarding estrogen and/or progesterone hormone receptors (HR), an absence of HR expression was found in 30.0% of the women at increased risk, compared with 11.0% of women at usual risk ($p < 0.01$), with a prevalence about two times higher in the increased risk group. Higher percentages of HER-2 expression negativity were also observed in both groups (increased risk: 81.8% vs. usual risk: 80.9%), with no significant difference between groups (►**Table 2**).

The biomarkers (HR and/or HER-2) used to classify breast cancer subtypes through the immunohistochemical technique had a percentage of 88.4 in the study population. However, its distribution was significantly different between the groups, with an absence of expression of biomarkers, that is, triple-negative tumors in 25.2% of women at increased risk, and 6.0% in women at usual risk, with a prevalence of absence of biomarkers 2.5 times higher among women in the increased risk group.

The other variables related to tumor characteristics did not show a significant difference in distribution according to the groups considered (►**Table 2**).

Table 2 Histological and immunohistochemical characteristics of the breast tumor, according to the risk of predisposition for Hereditary Breast-Ovarian Cancer Syndrome (HBOC) in women treated

Variables			Usual risk		Increased risk			
	n*	%	n	%	n	%	P[a]	PR[b] (95% CI)
Stage at diagnosis[c]								
Early stage/intermediate	320	74.4	234	77.2	86	67.7	0.04	1.00
Advanced	110	25.6	69	22.8	41	32.3		1.39 (1.02–1.88)
Histological type								
Invasive lobular	34	7.9	27	9.0	7	5.5	0.51	1.00
Others	40	9.3	28	9.2	12	9.5		1.46 (0.65–3.28)
Invasive ductal	354	82.3	246	81.2	108	85.0		1.48 (0.75–2.92)
Tumor size								
$\leq$ 2cm	195	45.3	148	48.8	47	37.0	0.04	1.00
$>$ 2cm	233	54.2	153	50.5	80	63.0		1.42 (1.05–1.93)
Compromised lymph nodes								
No	219	50.9	163	53.8	56	44.0	0.07	1.00
Yes	211	49.1	140	46.2	71	56.0		1.32 (0.98–1.77)
Histological grade (HG)[d]								
HG 1	90	20.9	75	24.8	15	11.8	$<$0.01	1.00
HG 2	162	37.7	115	38.0	47	37.0		1.74 (1.03–2.93)
HG 3	125	29.1	70	23.0	55	43.3		2.64 (1.60–4.36)
Ki67								
$<$ 25%	207	48.1	166	54.8	41	32.3	$<$0.01	1.00
$\geq$ 25%	204	47.5	122	40.3	82	64.6		2.03 (1.47–2.80)
Perineural invasion								
Absent	388	90.2	271	89.4	117	92.0	0.39	1.00
Present	42	9.8	32	10.6	10	8.0		0.79 (0.45–1.38)
Vascular invasion								
Absent	334	77.7	234	77.2	100	78.7	0.73	1.00
Present	96	22.3	69	22.8	27	21.3		0.94 (0.66–1.35)
Inflammatory infiltrate								
Absent	319	74.2	229	75.6	90	71.0	0.31	1.00
Present	111	25.8	74	24.4	37	29.0		1.18 (0.86–1.62)
Multifocality								
Absent	387	90.0	276	91.1	111	87.4	0.25	1.00
Present	43	10.0	27	8.9	16	12.6		1.30 (0.85–1.97)
Multicentricity								
Absent	416	96.7	295	97.4	121	95.3	0.27	1.00
Present	14	3.3	8	2.6	6	4.7		1.47 (0.79–2.75)
Intraductal component								
Absent	320	74.4	228	75.2	92	72.4	0.54	1.00
Present	110	25.6	75	24.8	35	27.6		1.11 (0.80–1.53)
Hormone receptors								
Present	357	83.0	268	88.4	89	70.0	$<$0.01	1.00
Absent	71	16.5	33	11.0	38	30.0		2.15 (1.62–2.85)
HER-2								
Present	74	17.2	51	16.8	23	18.1	0.55	1.00
Absent	348	80.9	245	80.9	103	81.1		1.05 (0.7–1.53)
Biomarkers[e]								
Present	380	88.4	285	94.0	95	74.8	$<$0.01	1.00
Absent	50	11.6	18	6.0	32	25.2		2.56 (1.95–3.36)

Abbreviations 95% CI, 95% confidence interval; PR, prevalence ratios. Notes:
[a]chi-square (X^2) test, $p < 0.05$.
[b]Prevalence ratio calculated only for valid data.
[c]Stage at diagnosis: early stage (I); intermediate (II); advanced (III and IV).
[d]Histological grade: HG1: well differentiated; HG2: moderately differentiated; HG3: poorly differentiated.
[e]Present biomarkers: HR $\pm$ and HER-2+ or HR+ and HER-2-; absent biomarkers: HR- and HER-2- (triple negative).
*The difference in totals (N) is due to incompleteness of information.

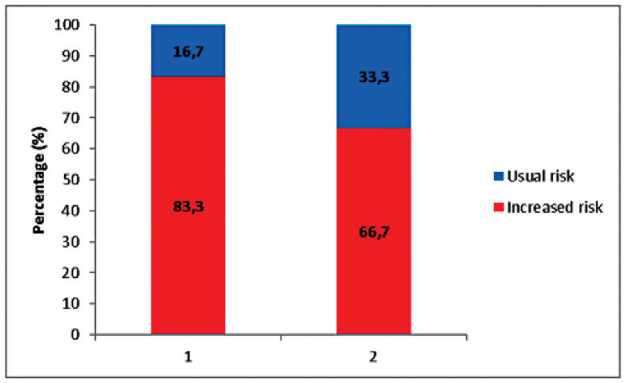

Fig. 1 K_i-67 $\geq$ 25% with absent biomarkers (Column 1); and K_i-67 $\geq$ 25% and absent HR (Column 2) with simultaneous occurrence for each considered group.

►**Figure 1** shows the distribution of the tumors' histological and immunohistochemical characteristics with simultaneity of occurrence between the following variables: K_i-67 $\geq$ 25%, absents biomarkers, and absents HR for each group considered.

When considering K_i-67 $\geq$ 25% and absent biomarkers, a percentage of 83.3 versus 16.7% was observed in the increased and usual risk groups, respectively. Higher percentages were also observed in the increased risk group when K_i-67 $\geq$ 25% and absent HR (66.7%) were compared simultaneously to the usual risk group (33.3%).

Discussion

Women in the increased risk for hereditary breast cancer group represented 29.5% of the study population and had a mean age of 42 years at diagnosis, which is far below the mean age of the group considered as usual risk (62 years), according to the results found in other studies.[15]

Between 10 to 25% of breast and ovarian neoplasms are considered hereditary and will manifest earlier in women with some risk factors related to this heredity, that is, history cases of breast, ovarian, and male breast cancers due to the detection of some genetic alteration, especially in the *BRCA1* and *BRCA2* genes, which reinforces the benefit that these women would have when performing an improved screening.[6,7,10]

In our study, the frequency of women at increased risk for clinical criteria for HBOC syndrome was higher than reported in the literature, which generally addresses Caucasian populations from Europe and the United States. Moreover, it should be noted that divergence of some criteria and guidelines between referral institutions can make it difficult to reach a consensus on the identification of eligible patients for investigation of hereditary cancer.[10]

In Brazil, access to risk evaluation for hereditary cancers and genetic screenings is limited. Brazilian experts propose recommendations to expand early diagnosis, risk management, and treatment of hereditary breast cancer, as well as provide epidemiological information about the Brazilian population. The identification of women at increased risk for hereditary breast cancer allows patients and their physicians to assess the available options to mitigate the risk of developing breast cancer, including more frequent screening, chemoprophylaxis, and even prophylactic mastectomy.[6]

For hereditary breast cancer, family history is the most accepted risk factor among the scientific community, with a risk increase of 2 to 4 times in the presence of family members affected by breast cancer, especially if they have been diagnosed at an early age.[7,10,16] In this study, family history—specifically the presence of affected first-degree relatives—was evaluated, observing a higher prevalence of these conditions in the group of women at increased risk. When genetic inheritance is strongly transferred between first-degree relatives, the relative risk of developing breast cancer in pre-climacteric women becomes higher.[16]

Regarding sociodemographic characteristics, white skin color was the most prevalent among the women evaluated. However, there was a higher number of non-white women in the increased risk for hereditary breast cancer group. It is noteworthy that the worst prognostic features for breast cancer, such as younger age, late diagnosis, and triple-negative tumors, are more frequent in black women.[17]

Nevertheless, the study performed by Fejerman et al. (2009) [18] showed that for every 25% increase in European ancestry, there was a 20% increase in the risk of breast cancer. It is known that the Brazilian population is mainly composed of European, African, and Amerindian ancestral roots, among others, presenting a high genomic diversity.[19] However, little is known about the profile of genetic ancestry in the Brazilian population related to breast cancer. In the only study with this approach in a Brazilian population identified in our literature review, Fernandes et al. (2016),[12] observed some trends or associations related to genetic ancestry with more aggressive cancer behavior, including higher histological grade in patients whose African component was greater. Nonetheless, this investigation was performed in a cohort that may not represent the diversity of the Brazilian population.

The higher education level predominant in the group of women at increased risk ($p = 0.05$) may highlight the relationship between educational level and socioeconomic status—which also interferes with greater access to information about the risk factors that permeate the development of cancer—and access to preventive measures, particularly important in women with hereditary predisposition to breast cancer.[19,20]

In addition to a family history of cancer, tumor characteristics can be of considerable importance in women at increased risk for hereditary breast cancer, where histopathological findings can be potentially useful in predicting the presence of germline mutation, along with the already mentioned criteria for predisposition to HBOC syndrome.[21] Furthermore, some characteristics of breast cancer are considered prognostic factors of the disease, including the histological type, tumor size, lymph node involvement, and histological grade.[4] They may also present histological and molecular differences that are related to sporadic and hereditary cancers, helping define characteristics that are more prevalent in women at risk for HBOC syndrome.[22–24]

Studies show that tumors related to HBOC syndrome are often larger, less poorly differentiated, with high cell proliferation markers, predominance of the invasive ductal histological type, and triple-negative subtype, leading to a more aggressive form of the disease.[22–26] This study corroborates these results, as there was a higher prevalence of advanced ductal carcinomas, tumor size greater than 2 cm, lymph nodes involvement, poorly differentiated tumors, K_i-67 $\geq$ 25%, and triple-negative subtype in the increased risk group.

It is known that advanced stages influence the therapeutic options and prognosis of patients, and among the histological types, invasive ductal carcinoma is the most common, accounting for approximately 70% of all prevalent cases of breast cancer.[20] In this study, a higher prevalence of the invasive ductal histological type was also observed in both the increased risk and usual risk groups (85.0%; 81.2%, respectively). In general, women affected by invasive ductal carcinoma have greater lymphatic involvement, which was also observed in the study population in general.[21–27] However, there was no data regarding when the study population was stratified by risk of hereditary cancer.

The histological grade (HG) of the invasive carcinomas is an important feature and must be evaluated to guide the therapeutic approach and predict the prognosis.[28] In the increased risk group, the frequency of HG3 was higher ($p < 0.01$), as well as K_i-67 $\geq$ 25% ($p < 0.01$), compared with the usual risk group. The literature points to higher HG and K_i-67 values in women with hereditary predisposition.[5,29,30]

In the study of Mavaddat et al. (2012),[21] performed by the Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* (CIMBA), HG3 tumors were identified in 77.0% and 50.0% of women with mutations in the *BRCA1* and *BRCA2* genes, respectively.

Newman (2015)[31] suggests an inverse correlation between low incidence and higher breast cancer mortality rates in African American women compared with white women, with a 67% higher risk of death due to breast cancer among African American women.

Regarding hormone receptors (HR), the higher frequency of cases with absence HR was observed in the increased risk for hereditary breast cancer group, compared with the usual risk group ($p < 0.01$), which reinforces the premise that women at risk for hereditary predisposition are more prone to estrogen receptor negativity.[30] The presence of hormone receptors in tumor tissue is related to indicators of good prognosis, with a lower histological grade and lower rates of cell proliferation.[3,4,18]

The higher prevalence of triple-negative subtypes tumors, characterized by the absence of hormone receptors and HER-2, in women at increased risk (PR = 2.56; 95% CI: 1.95–3.36) also corroborates findings in the scientific literature. In the meta-analysis performed by Tun et al. (2014),[32] it was observed that in a population with increased risk characteristics, women with triple-negative breast cancer are 5.7 times more likely to have a hereditary predisposition compared with the non-triple-negative immunophenotype. Fernandes et al. (2019)[33] performed the same analysis, and their results showed the presence of tumors with HG3 in 56.5% and 25.0% of women with mutations in the *BRCA1* and *BRCA2* genes, respectively, thus corroborating the higher frequency of this finding in women at risk of HBOC syndrome.

As observed in the study by Fernandes et al. (2019),[33] most cases of triple-negativity occur in women with hereditary mutations in the *BRCA1* and *BRCA2* genes (51.1%). Moreover, according to data presented by Young et al. (2009),[34] women with this subtype of breast cancer diagnosed in pre-climacteric age should be candidates of a risk assessment test for HBOC, even in the absence of a family history of breast and ovary cancer. Therefore, the NCCN guidelines recommend a genetic investigation for all triple-negative breast cancer aged $\leq$ 60 years.[9]

When evaluating the simultaneous occurrence of some characteristics in the categorized groups, we sought to verify that the information routinely collected at the time of diagnosis could favor the identification of women at increased risk for HBOC. Higher percentages were observed in the increased risk group, when compared with those of the usual risk group, regarding the presence of K_i-67 $\geq$ 25% in triple-negative tumors (83.3% vs. 16.7%), K_i-67 $\geq$ 25% and absence of hormone receptors (66.7% vs. 33.3%). The data presented suggests that a high K_i-67 proliferation index with the absence of expression of biomarkers could be clinical indicators of increased risk for HBOC.

In a retrospective analysis performed by Liang et al. (2020),[35] the authors evaluated the interaction between K_i-67 and HG in the prognostic of different subtypes of breast cancer. The results indicated that K_i-67 expression was significantly associated with HG in all breast cancer patients, and that patients with increased K_i-67 or HG3 had reduced recurrence-free survival and a worse prognosis.[5,13,35]

It is important to highlight that these characteristics alone provide relevant information at the time of the diagnosis. This was demonstrated in the study performed by Pérez-López et al. (2016),[36] when considering tumor size, lymph node involvement HG3, and independent prognostic factors. In the same study, the high K_i-67 score increased the risk of breast cancer mortality by 2.7 times.[36]

Most of the Brazilian studies published so far regarding HBOC syndrome have been performed with specific populations, that is, with young women diagnosed with breast cancer and/or with an investigation of specific gene regions.[37,38] Therefore, there is a need to obtain more consistent data related to HBOC syndrome from patients and their families in Brazil.

The identification of patients and family members at risk for hereditary cancer is essential, as the cumulative vital risk is much higher in affected people. This identification makes it possible to know the risk that family members are exposed to, through screening measures that allow for an early diagnosis and the implementation of appropriate follow-up and treatment protocols, which can improve the outcome of the disease in patients and their families.[39]

A study conducted in the United States found that, in one year, only 8% of 603 women referred for genetic counseling,

according to the NCCN criteria, attended the exam. This exemplifies how genetic counseling is still underused, even in developed countries.[11] Studies highlight the importance of providing patients better information about the genetics of cancer and the risk of hereditary cancer, as well as the role of the genetic counseling service, more specifically disease management, and therapeutic approaches that could implement greater demand for these services.[11] In studies on the assistance of specialized genetic services in Brazil, Llerena (2002)[40] and Horovitz et al. (2012),[39] highlighted the inadequate number of geneticists doctors available, the centralization of services in the private system, usually located in urban centers, and the scarcity of geneticists in the public health system, being available only in some research institutions and universities. Furthermore, the profession of genetic counselor is still not recognized in Brazil, despite the involvement of many health professionals with specialty in genetics.

As a limitation of the study, we emphasize that genetic screening was not performed in the investigated population, particularly in relation to the *BRCA* genes, which would enable a better characterization of the increased risk for hereditary breast cancer, and the associations raised. It is worth mention the high cost of the test to assess pathogenic mutations in the *BRCA1* and *BRCA2* genes, which makes its use very restricted in countries with limited sources, such as Brazil.

In this regard, information on tumor histopathology, routinely collected at the time of diagnoses, such as histological grade, the status of estrogen, progesterone, or HER-2, as well as identification of cell proliferation markers, can be incorporated into the criteria already recommended for investigation of the risk of hereditary breast and ovarian cancer, aiming to strengthen and expand the adoption of a practical strategy for genetic evaluation in patients with breast cancer. This becomes particularly important for countries in which specialized genetic services are scarce, financial resources for health are limited and concentrated in more developed regions, and where public and private health systems have major restrictions on coverage of such molecular analyzes, such as in Brazil and other Latin American countries.[12]

Conclusion

The results of this study allow the characterization of the clinical, histological, and immunohistochemical profile of women with breast cancer in a Brazilian hospital-based cohort, according to the risk of hereditary breast cancer. The findings show the possibility of considering, even if only in a complementary way, the frequency of some of these characteristics to help identify and manage women with clinical suspicion of hereditary breast cancer. In this regard, there is a higher frequency of tumors with HG3, K_i-67 $\geq$ 25%, absence of hormone receptors, and HER-2, and family history of breast cancer in women classified in this study as at increased risk for HBOC syndrome. Based on the clinical criteria routinely used in the diagnosis of breast cancer, this study collaborated to guide the care practice of genetic counseling for patients at increased risk of hereditary breast cancer in contexts such as in Brazil. Therefore, it guides the indication of women to undergo genetic evaluation and who, consequently, could benefit from these more specific therapies. It also contributes to the risk management of their families, enabling the application of specific preventive measures.

Contributions

Freitas analyzed the data, and promoted the conception and design of the article. Guerra helped in the analysis and writing of the article. Fayer and Campos participated in data collection. Cintra contributed to the screening of patients in the cohort and the collection of clinical information. Warren contributed substantially to the interpretation of the data and performed a critical review of its intellectual content. Ervilha participated in the data collection and writing of the article. De Paula acted in the graphic presentation of the results, and Teixeira performed a relevant critical review of the intellectual content presented with approval of the final version to be published.

Conflict of Interests

The authors have no conflict of interests to declare.

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Immature Platelet Fraction and Thrombin Generation: Preeclampsia Biomarkers

Fração de plaquetas imaturas e geração de trombina: Biomarcadores da pré-eclâmpsia

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Abstract

Preeclampsia, a human pregnancy syndrome, is characterized by elevated blood pressure and proteinuria after the 20th week of gestation. Its etiology remains unknown, and its pathophysiological mechanisms are related to placental hypoperfusion, endothelial dysfunction, inflammation, and coagulation cascade activation. Recently, the role of the complement system has been considered. This syndrome is one of the main causes of maternal and fetal mortality and morbidity. This article discusses the hypothesis of preeclampsia being triggered by the occurrence of inadequate implantation of the syncytiotrophoblast, associated with bleeding during the first stage of pregnancy and with augmented thrombin generation. Thrombin activates platelets, increasing the release of antiangiogenic factors and activating the complement system, inducing the membrane attack complex (C5b9). Immature platelet fraction and thrombin generation may be possible blood biomarkers to help the early diagnosis of preeclampsia.

Keywords
- platelets
- platelet activation
- hypertension pregnancy-induced
- blood coagulation
- complement system proteins

Resumo

A pré-eclâmpsia, uma síndrome da gestação humana, é caracterizada por elevação da pressão arterial e proteinúria patológica após a 20ª semana de gestação. Sua etiologia permanece desconhecida, e seus mecanismos fisiopatológicos estão relacionados à hipoperfusão placentária, disfunção endotelial, inflamação, e ativação da cascata de coagulação. Recentemente, o papel do sistema do complemento foi considerado. Essa síndrome é uma das principais causas de morbidade e mortalidade materna e fetal. Este artigo discute a hipótese de a pré-eclâmpsia ser desencadeada pela ocorrência da implantação inadequada do sinciciotrofoblasto, associada ao sangramento durante o primeiro trimestre da gravidez com aumento da geração de trombina. A trombina ativa plaquetas, aumentando a liberação de fatores antiangiogênicos na circulação e ativando o sistema do complemento, especialmente o complexo de ataque de membrana (C5b9). Portanto, a fração de plaquetas imaturas e a geração de trombina podem ser possíveis biomarcadores sanguíneos para auxílio no diagnóstico precoce da pré-eclâmpsia.

Palavras-chave
- plaquetas
- ativação plaquetária
- hipertensão induzida pela gravidez
- coagulação sanguínea
- proteínas do sistema do complemento

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Introduction

Hypertensive disorders are very frequent complications in pregnancy. It is one of the main causes of maternal and fetal morbidity and mortality.[1,2] Preeclampsia (PE) is characterized by elevated blood pressure and pathological proteinuria after the 20th week of pregnancy. The incidence varies depending on where the study is being performed, but it is estimated to compromise from 2 to 8% of pregnancies.[1,3,4] The etiology is unknown, and its pathophysiological mechanisms are related to placental hypoperfusion, endothelial dysfunction, oxidative stress, inflammation, and coagulation changes.[5–14]

Theory

Defective implantation of the syncytiotrophoblast and bleeding in the first trimester of pregnancy contribute to increased thrombin generation, causing increased platelet activation and release of antiangiogenic factors in the maternal circulation (such as sFLT-1). The activation of platelets also triggers the complement system, membrane attack complex (C5b9) (►**Fig. 1**).

Discussion

Platelets and Preeclampsia

Hemostatic changes occur during pregnancy, shifting the balance in favor of hypercoagulability with an increased thrombosis risk.[15] These changes are aggravated in PE, as there is an abnormal activation of the hemostatic and immune system, which are responsible for most complications of the disease. In pregnant women with hypertensive disorder, especially PE, the total number of platelets and platelet parameters modifications, including the mean platelet volume (MPV) and the immature platelet fraction (IPF), platelet activation markers, and the complement system. Mean platelet volume, platelet distribution width (PDW), and IPF values are proportionally increased in relation to the severity of preeclampsia when compared with pregnant women without PE.[16–21] Thrombocytopenia results from increased platelet activation, aggregation, and consumption, and it maybe considered a platelet activation marker.[22,23]

Platelets play an important role in the pathophysiology of PE, being responsible for coagulation and participating as an important inflammatory mediator. There is evidence of PE with platelet activation and increased platelet surface markers (CD62P) when comparing women with PE to healthy women.[24–26] In addition, there is an increase in CD41 expression in pregnant women with PE, evidencing platelet activation.[25]

Platelet and Thrombin Generation

Platelet activation may be due to increased thrombin generation. Thrombin is a multifunctional protease, responsible for coagulation cascade and one of the most potent platelet activators. Activation through thrombin generation causes degranulation and platelet activation, which displaces adhesion receptors to the cell surface and releases hemostatic and inflammatory mediators in the bloodstream, facilitating cell adhesion.[27–30] It is known that uterine bleeding or bruising at the moment of the syncytiotrophoblast implantation are associated with the development of PE and generates excess thrombin.[31] Bleeding in the first 20 weeks of pregnancy is a common complication, affecting about 1 in 5 pregnant women.[32] It has clinical relevance, as these patients develop an increased risk for unfavorable outcomes, mainly placental abruption, low birth weight, and premature birth.[33,34] As bleeding in pregnant women can be used as an early marker of placental dysfunction, there are studies associating bleeding with the development of PE.[25] However, findings remain conflicting. On the one hand, some authors disclosed a 35 to

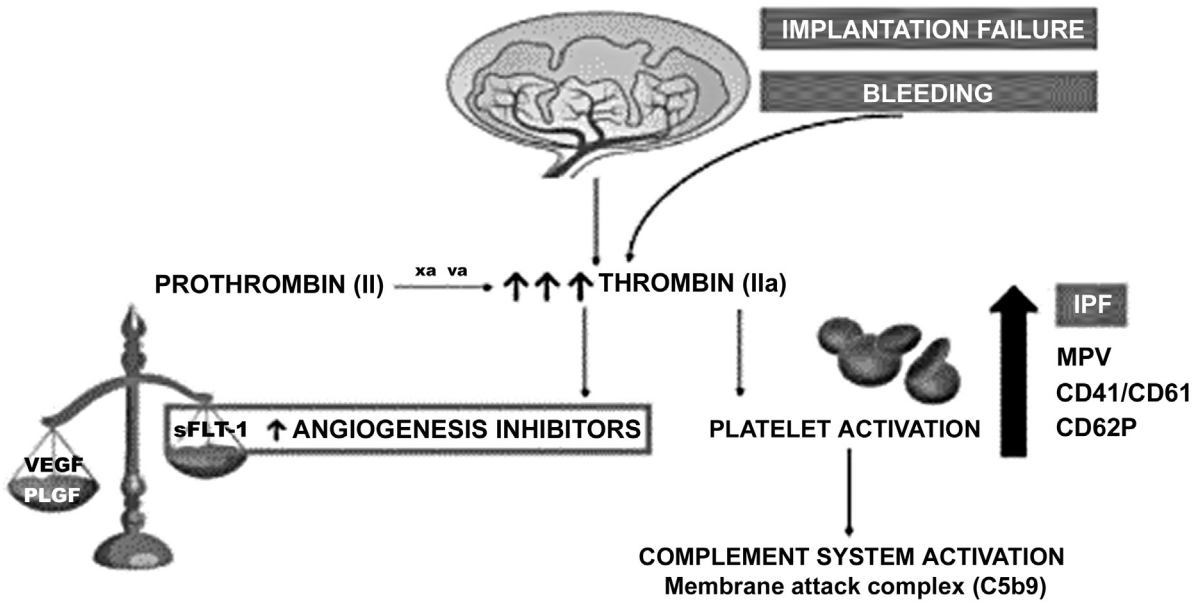

Fig. 1 Scheme of the theory.

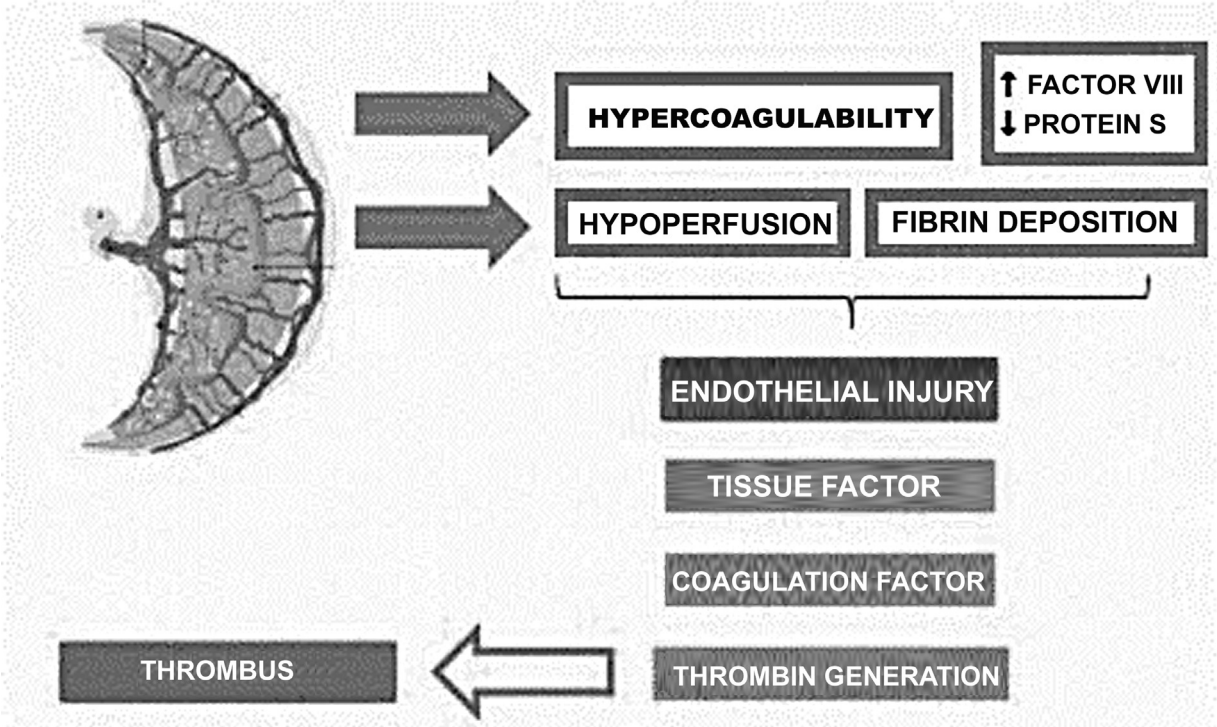

Fig. 2 Factors involved in thrombus generation in preeclampsia.

40% increase in the risk of developing PE in patients with mild bleeding in the first stage of pregnancy when compared with pregnant women who did not present bleeding.[35,36] On the other hand, Smits et al.[31] found no association between bleeding (mild or severe) and the development of PE in primiparous women at low risk. However, among women with bleeding disorders, the results indicated that the analysis of intensity, pattern, and frequency of bleeding may indicate the risk of subsequent development of PE.

There are some studies showing association between thrombin generation increase and the pathogenesis of PE.[37,38] The excess of thrombin generated due to hemorrhage during placental development increases the expression of soluble feline McDonough sarcoma-like tyrosine kinase-1 (sFlt-1) by the trophoblast through the activation of the PAR-1/NADPH oxidase/ROS signaling pathway (specific receptors activated by proteinase).[39]

There is evidence shown by the increased generation of thrombin in pregnant women with PE.[40,41] This activation induces neutrophil recruitment, activation, and oxidation. The excess of tissue factor binds to platelets, causing ADP release. This release increases thrombin generation, which has a high affinity for PAR-1 in the syncytiotrophoblast, platelets, and neutrophils, thus causing cell activation.[39]

Thus, thrombin increases the secretion of sFlt-1. Soluble feline McDonough sarcoma-like tyrosine kinase-1is a receptor protein produced by syncytiotrophoblast, and its concentration in normal pregnancies is only a few times higher than that of placental growth factor (PlGF). It is related to the maternal endothelial dysfunction, a PE feature.[5,42] In hypoxia or inadequate perfusion of the placenta, the trophoblast produces a large quantity of sFlt-1, and its concentration in the maternal bloodstream is, at least, 12 times higher than the concentration of PlGF.[43]

Increased SFlt-1 in maternal circulation is one of the elements that determines the PE maternal multisystemic syndrome. These changes in sFlt-1 concentration precede the onset of clinical and laboratory symptoms in preeclamptic women by $\sim$ 5 to 6 weeks.[44] Therefore, laboratory tests to measure platelet activation and thrombin generation along with the sFlt-1 measurement could contribute to an early diagnosis of PE syndrome (►**Fig. 2**).

Platelets and Complement System Activation

In addition, evidence brought by few studies shows the involvement of the excessive increase in tissue factor (TF) with the activation of proteins C3 and C5 of the complement system. This activation is probably due to the stress generated by the syncytiotrophoblast. Although TF is important for placental development, its increase during trophoblast implantation and tissue hemorrhage exarcebates the activation of coagulation cascade, which has been the first hypothesis of abnormal implantation of trophoblast.[45]

The activated platelets trigger the alternative complement pathway, especially the membrane attack complex (C5b9). And the activation of complement proteins may help to trigger PE and hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome. Burwick et al.[46] showed an increase in plasma concentration of C5b9 complement proteins in patients with gestational hypertension. The activation of the membrane attack complex in hypertensive disorders reflects endothelial dysfunction and systemic inflammation (►**Fig. 3**).

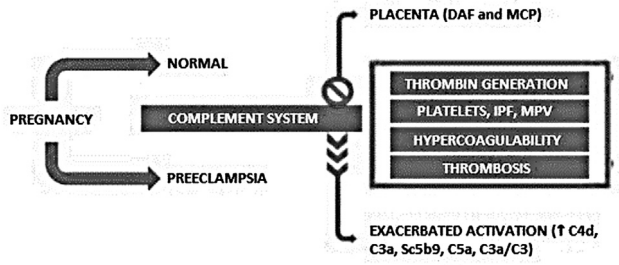

Fig. 3 Complement cascade in normal pregnancy and preeclampsia.

Conclusion

Platelets play a fundamental role in the pathophysiology of PE. We suggest that platelet activation in preeclamptic pregnancy is caused by the excess generation of thrombin associated with bleeding in the first trimester, increasing the release of antiangiogenic factors and activating the complement system before the onset of the clinical symptoms of the syndrome. Although platelet activation and increased IPF is confirmed in pregnant women who develop PE, these tests are not routinely performed for diagnosis. Laboratory essays for measuring IPF and thrombin generation are simple and easily accessible in laboratories that use advanced technology to perform them. They may be useful for the early diagnosis of this syndrome and the management of patients. Therefore, we believe further studies focused on these laboratory tests are required to enable early diagnosis and treatment of the disease.

Conflicts of Interests

The authors have no conflict of interests to declare.

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Non-pharmacological Interventions for Improving Sleep Quality During Pregnancy: A Systematic Review and Meta-Analysis

Intervenções não-farmacológicas para melhoria da qualidade do sono durante a gravidez: Uma revisão sistemática e metanálise

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Abstract

Objective To investigate the effect of non-pharmacological interventions to improve sleep quality during pregnancy.

Data sources A search was made in the NCBI/PubMed, ClinicalTrials.gov, Embase, BVS, and Web of Science databases. There were no limitations regarding language, sample size, and type of non-pharmacological intervention. We have included prospective clinical trials between July 2014 and July 2019.

Selection of studies This study was registered in the Prospective International Registration of Systematic Reviews (PROSPERO) database was performed. Publication bias was also assessed with funnel plots. the primary outcome was the total score in the Pittsburgh Sleep Quality Index (PSQI) before and after intervention. Risk of bias and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria were used for assessing methodological quality. From the 28 retrieved studies, we have selected 8 for qualitative analysis and 6 for meta-analysis.

Data collection Two independent reviewers performed the study selection. In the case of disagreement, a third senior reviewer was consulted. The study was initially assessed based on the title, followed by abstract. Lastly, the full text was assessed to be included.

Data Synthesis A significant improvement on the sleep quality (PSQI score) was observed when all interventions were grouped (MD = -3.03, 95%CI -4.15 to -1.92, $n = 623$, $i^2 = 84\%$, $p < 0.001$). Analysis by subgroup (music listening: MD = -1.96, 95% CI -3.27 to -0.65, $n = 207$, $i^2 = 67\%$, $p = 0.003$ and other interventions: MD = -3.66, 95% CI -4.93 to -2.40, $n = 416$, i2 = 80%, $p < 0.001$) showed an improvement, with high

Keywords
- sleep quality
- non-pharmacological interventions
- pregnant women
- systematic review
- meta-analysis

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heterogeneity. Risk of bias has shown performance and detection bias for almost studies, and GRADE evidence was very low for all analyzed variables.

Conclusion Non-pharmacological interventions—listening to music, physical exercise, relaxation exercises, lettuce seed, sleep hygiene, and acupressure—are effective for improving sleep quality during pregnancy.

Resumo

Objetivo Investigar o efeito de intervenções não-farmacológicas para melhorar a qualidade do sono durante a gravidez.

Fontes dos dados Uma busca foi feita nas bases de dados NBCI/PubMed, ClinicalTrials.gov, Embase, BVS, e Web of Science. Não houve limitações quanto ao idioma, tamanho da amostra e tipo de intervenção não-farmacológica. Incluímos estudos clínicos prospectivos entre julho de 2014 e julho de 2019.

Seleção dos estudos Foi realizado um registro no banco de dados *Prospective International Registration of Systematic Reviews* (PROSPERO). O viés de publicação foi avaliado com gráficos de funil. O desfecho primário foi a pontuação total do *Pittsburgh Sleep Quality Index* (PSQI) antes e depois da intervenção. O risco de viés e os critérios *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) foram usados para avaliar a qualidade metodológica. Dos 28 estudos encontrados, selecionamos 8 para análise qualitativa e 6 para a metanálise.

Coleta de dados Dois revisores independentes realizaram a seleção dos estudos. Em caso de discordância, um terceiro revisor foi consultado. Inicialmente o estudo foi avaliado com base no título e resumo. Para a inclusão, foi avaliado o texto completo.

Síntese dos dados Uma melhora significativa na qualidade do sono (PSQI score) foi observada quando todas as intervenções foram agrupadas (MD = -3.03, 95% CI -4.15 a -1.92, $n = 623$, $i^2 = 84\%$, $p < 0.001$). A análise por subgrupo (escutar música: MD = -1.96, 95% CI -3.27 a -0.65, $n = 207$, $i^2 = 67\%$, $p = 0.003$ e outras intervenções: MD = -3.66, 95% CI -4.93 a -2.40, $n = 416$, i2 = 80%, $p < 0.001$) também mostrou uma melhora da qualidade do sono, porém com alta heterogeneidade. A análise do risco de viés mostrou que quase todos os estudos avaliados apresentaram viés de desempenho e detecção, e o nível de evidência GRADE foi muito baixo para todas as variáveis analisadas.

Conclusão Intervenções não-farmacológicas - ouvir música, exercícios físicos, exercícios de relaxamento, sementes de alface, higiene do sono e acupressão - são eficazes para melhorar a qualidade do sono durante a gravidez.

Palavras-chave

- qualidade do sono
- intervenções não-farmacológicas
- gestantes
- revisão sistemática
- metanálise

Introduction

Sleep quality and sleep routine are significantly affected by the hormonal, physical, and psychological changes that occur during pregnancy. It has been described that increased progesterone and estrogen levels, as well the discomfort caused by fetal growth and fetal movements, lumbar pain, gastroesophageal reflux, nocturnal cramps, frequent urination, and concerns inherent to the baby's health have a negative influence on subjective sleep quality.[1,2]

Studies have shown that poor sleep quality in pregnant women varies from 39.6 to 89.3%, and it is observed that sleep disorders seem to worsen throughout pregnancy.[3–5] Poor sleep quality during pregnancy impacts on labor, and maternal and fetal heath. It has been demonstrated that the quality of sleep during late pregnancy may predict the length of labor and mode of labor.[6,7] Low birthweight and Apgar scores are significantly correlated with duration of sleep.[8] Furthermore, poor sleep quality impacts on the woman's quality of life[9] and increases the risk of gestational diabetes, hypertensive disorders, and postpartum depression.[10–13]

Some sleep medications, such as flurazepam, temazepam, and mefloquine, have their use contraindicated for having teratogenic effects.[14] Other drugs, like zolpidem, are not teratogenic but may cause adverse maternal-fetal outcomes such as preterm delivery.[15] In addition, pregnant women are generally cautious about the use of drugs during pregnancy. Thus, given the health-related consequences of sleep disorders and the difficulty of using sleep-improvement drugs during pregnancy, there has been a growing interest in non-pharmacological interventions to improve sleep quality during pregnancy.

Here, we aim to investigate the effect of non-pharmacological methods for improving sleep quality in pregnancy by a systematic review and meta-analysis.

Methods

Protocol and Registration

A systematic review was conducted, and it was registered in the Prospective International Registration of Systematic Reviews (PROSPERO) () database with register number CRD42018092004.

Eligibility criteria

The inclusion criteria were defined using the P (participants) I (intervention) C (comparison) O (outcome) S (study design) strategy. We have included pregnant women that were submitted to non-pharmacological interventions (with a control group without intervention or with the usual care) during pregnancy for sleep improvement (via the Pittsburgh Sleep Quality Index [PSQI] or other methods as the mean outcome) in prospective clinical trials (CTs) between July 2014 and July 2019. There were no limitations regarding language, study sample size, and type of non-pharmacological intervention.

Search Strategy and Study Selection

The following databases were consulted: NCBI/PubMed, ClinicalTrials.gov, Embase, Biblioteca Virtual em Saúde-BVS and Web of Science, and the following medical scientific terms (Medical Subject Headings - MeSH) with their synonyms were considered for the development of the search strategy: *Sleep Quality*, Pregnant women. The following search strategy was developed on the PubMed database and modified according to each database requirement: ([*sleep quality*) AND (Pregnant Women [MeSH Terms]) OR *Pregnant Women* (Title/Abstract) OR *Women*, *Pregnant* (MeSH Terms) OR *Women*, *Pregnant* (Title/Abstract) OR *Pregnant Woman* (MeSH Terms) OR *Pregnant Woman* (-Title/Abstract) OR Woman, Pregnant (MeSH Terms) OR *Woman*, *Pregnant* [Title/Abstract]).

Two independent reviewers (D. S. M. P. and C. B.) performed the study selection and, in the case of disagreement on the final inclusion of a study, a third senior reviewer (F. G. S.) was consulted. The study was initially assessed based on the title, followed by abstract. Lastly, the full text was assessed to be included. The references listed in the selected articles were also consulted, aiming to find any other study that had not been previously identified by the search strategy. Study authors were contacted whenever necessary for further clarification or information regarding their articles.

Outcomes

The data of sleep quality assessed by the PSQI total score, as well as the number of participants were extracted from each study included in the meta-analysis. The PSQI was developed in 1989 by Buysse et al.[16] to assess sleep quality during the last four weeks of pregnancy. The PSQI is a self-report questionnaire with 19 items, which measures 7 components of sleep quality: subjective sleep quality, sleep latency (time necessary to fall asleep and frequency of not falling asleep in 30 minutes), sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. The components are scored between 0 and 3, and the total score is obtained by the sum of the 7 components with a value range of 0 to 21. Total score > 5 is clinically classified as poor sleep quality.

Two reviewers (D. S. M. P. and C. B.) independently assessed the risk of bias in the included studies using the Cochrane risk-of-bias assessment tool.[17] Disagreements were resolved by consultation with a third reviewer (L. G. B.), and consensus was obtained through discussion. About the overall quality of the body of evidence for the review outcomes, we used the Easy Grade Pro software (Orbis Technologies, Inc., Annapolis, MD, USA). The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria consider study limitations, consistency of effect, imprecision, indirectness, and publication bias.

Statistical Analysis

The meta-analysis was performed for at least two studies that could be grouped into a single forest plot. For continuous outcomes, the mean difference with 95% confidence intervals was calculated. We stipulated a 5% significance level. Heterogeneity was calculated by the I^2 test, and if values were over 50%, a random-effect model was performed. The outcomes were divided according to the type of intervention (music intervention and other interventions) for subgroup analysis to reduce heterogeneity. The data were tabulated and analyzed using the RevMan 5.3 software (The Cochrane Collaboration, Copenhagen, Denmark).

A forest plot was performed to evaluate the relative strength of the intervention effect. Funnel plots were built to assess publication bias. For database validation, the first author has inserted the data, and a second author (C. B.) revised the database to identify possible inconsistencies or typos.

Results

A total of eight studies were retrieved after study selection; six of them were suitable for meta-analysis. Search history and screen process of the articles were detailed in the flow diagram presented in ►**Figure 1**.

All studies included in the meta-analysis were randomized clinical trials and used the PSQI total score to measure sleep quality. The other two studies included in qualitative review were non-randomized clinical trials,[18,19] one of which used the PSQI as a categorical variable (with score ranging from 7 to 21 labeled as moderate-to-severe insomnia), and the other used a custom-designed questionnaire to evaluate sleep quality.[19] Studies were performed in six countries. Sampling for these studies ranged from 42 to 134 in the intervention group, and 42 to 101 in the control group, comprising 1,020 pregnant women. Non-pharmacological interventions studied to improve sleep quality were listening to music ($n = 2$),[20,21] physical exercise ($n = 2$),[19,22]

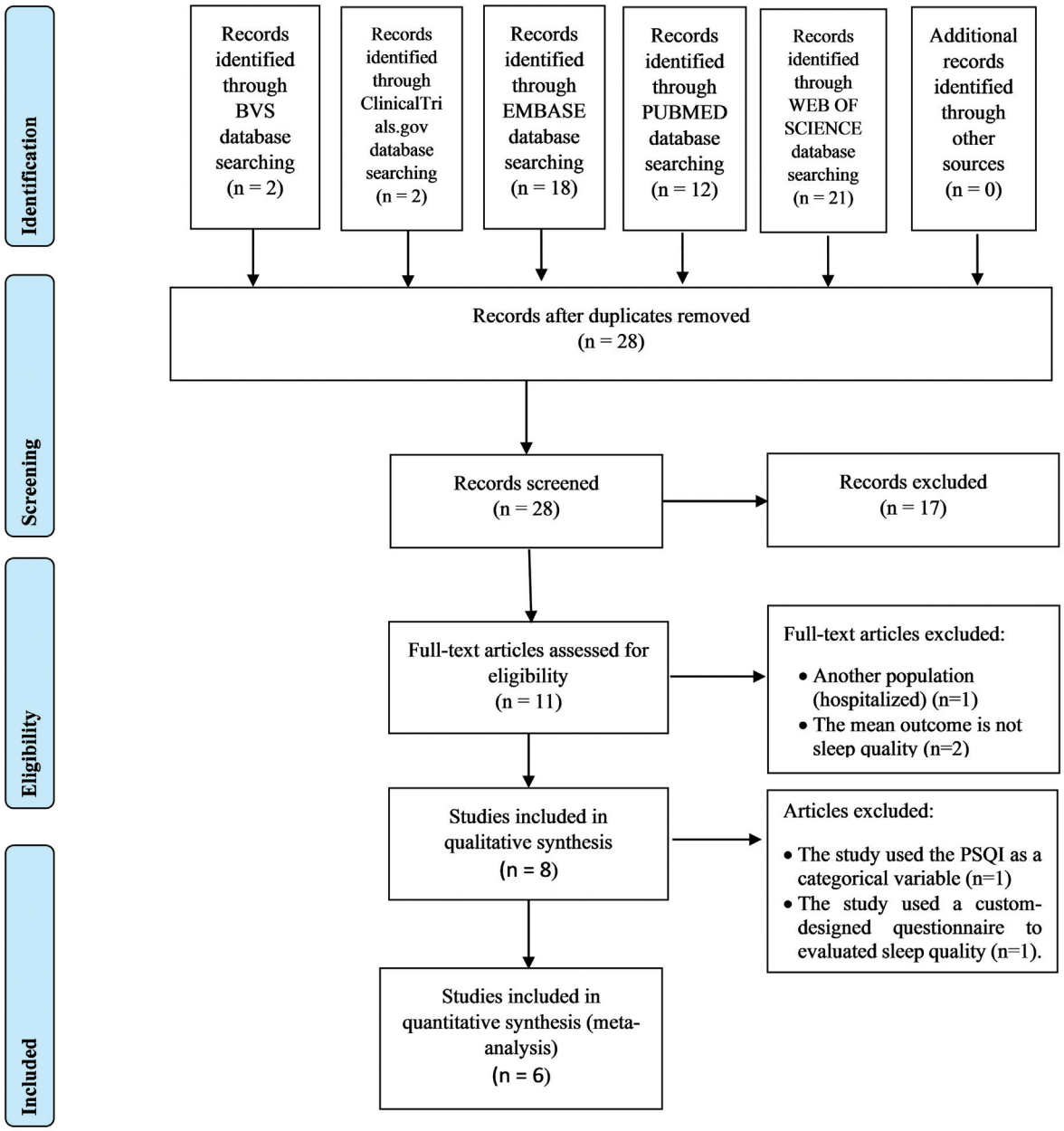

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart of the study screen process.

relaxation exercises,[23] lettuce seed,[24] sleep hygiene,[25] or acupressure.[18] Treatment duration varied across the studies. Other details of the studies included in the review were described in ►**Table 1**.

►**Figure 2** illustrates the risk of bias assessment of the included studies. All studies in the meta-analysis described the random sequence generation method and allocation concealment. Given the type of interventions used, only one study has blinded the participants,[24] and almost all studies were classified as high risk of bias. Similarly, most of the studies did not blind the investigators. We classified the studies as having a low risk of bias for incomplete outcome when they reported the adherence and/or dropout rates; and if they properly use methods to control the attrition, and if they did not have inappropriate methods for imputing missing data. In relation to selective reporting, we scored all studies as low risk of bias, because the trials selected reported all predetermined outcomes. Other bias sources were not identified in the trials.

We observed a very low evidence quality and the main limitations of the included studies were also evaluated, according to GRADE criteria. The details regarding quality of evidence can be found in ►**Table 2**. Indirect evidence was not serious at the trial that studied music listening, but very serious in the other interventions.

From 28 retrieved studies, we have selected 8 for qualitative analysis and 6 for meta-analysis (►**Fig. 3**), comprising 1,020 pregnant women.

A significant improvement on the sleep quality (PSQI score) was observed when all interventions were grouped

Table 1 Summary of clinical trials that assessed the effect of non-pharmacological strategies for improving sleep quality

Study ID	Country	Year	Sample size, N		Participant criteria	Intervention		Instrument
			Intervention	Control		Strategies/Intervention	Duration	
Özkan and Rathfisch[23]	Turkey	2018	42	42	3rd trimester, $\geq$ 20 y, primiparous, singleton, HRP, GA 28–34 weeks, pre-pregnancy BMI $\leq$ 25 kg/m^2, neck circumference < 38 cm, and no RLS.	Listening to a relaxation exercises CD before sleeping. The CD comprised a 4-minute introduction, 10-minute of information on deep relaxation PE and points to consider during PE, 30-minute introduction to relaxation, and the last 30 minute includes relaxation music.	4 weeks	PSQI
Pour et al.[24]	Iran	2018	50	50	20–45 y, singleton pregnancy, GA 12–36 weeks, with insomnia and PSQI score > 5.	IG received capsules containing 1000 mg of lettuce seed daily. CG received placebo capsules containing starch.	2 weeks	PSQI
Rodriguez-Blanque et al.[22]	Spain	2018	67	67	GA 12–20 weeks, without any absolute contraindications for PE*.	IG took part in the SWEP program, performing three 1-hour sessions/week water exercises. CG followed the usual recommendations, including emphasis on the positive effects of PE.	17 weeks	PSQI
Sönmez and Derya[25]	Turkey	2018	64	64	Diagnoses of RLS, literate, at 3rd trimester, HRP, using iron supplementation, without sleep disorder.	IG received sleep hygiene training. A sleep hygiene training booklet was issued after training, and 2 weeks later, during a home visit, participants received a counseling service on sleep hygiene.	4 weeks	PSQI
Kocsis et al.[19]	Romania	2017	79	53	HRP, 18–40 y, GA 18–22 weeks, BMI < 35 kg/m^2, parity < 3.	IG followed a specific PE program under strict instruction by a PE training specialist. The PE program structure involved 2-hour training sessions twice a week. PE included posture correction, preserving muscle tone, and strengthening pelvic and posterior muscles, breathing exercises, and relaxation techniques.	10 weeks	CDQ**
Neri et al.[18]	Italy	2016	134	101	HRP, singleton pregnancy, ability to understand Italian, with feelings of anxiety and poor sleep quality.	IG was advised by a midwife (trained by an expert acupuncturist) to wear a soft rubber pin kept in place by an adhesive plaque able to exert acupressure on Point 7 of the heart meridian.	2 weeks	PSQI
Shobeiri et al.[20]	Iran	2016	42	44	PSQI score > 5, 18–35 y, GA 30–34 weeks, singleton pregnancy, no drug addiction, not taking drugs affecting sleep quality, avoiding antidepressants use, without mental/physical disorders, access to an audio player at home.	IG received music therapy counseling in two weekly sessions, with each session lasting 60 minutes, in groups of 5–7 people. The music therapy method was passive music-listening (instrumental music by Kitaro, a Japanese composer and performer).	4 weeks	PSQI
Liu et al.[21]	Taiwan	2016	61	60	PSQI score > 5, > 18y, GA 18–34 weeks.	IG was instructed to listen to at least one disc (30-minute) of the five prerecorded CDs compiled by the researcher or a minimum 30 minute of their preferred music per day at bedtime for 2 weeks. CG received the usual prenatal care.	2 weeks	Chinese version of the PSQI

Abbreviations: BMI, body mass index; CD, compact disk; CDQ, custom-designed questionnaire; CG, control group; GA, gestational age; HRP, habitual risk pregnancy; IG, intervention group; PE, physical exercise; PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome; SWEP, study of water exercise in pregnancy.

*Described by the American College of Obstetricians and Gynecologists.

**Involved general perception of sleep quality and quantity, number of awakenings, difficulty falling asleep, insomnia, restless sleep, snoring, diurnal sleep, and consequences of inadequate sleep.

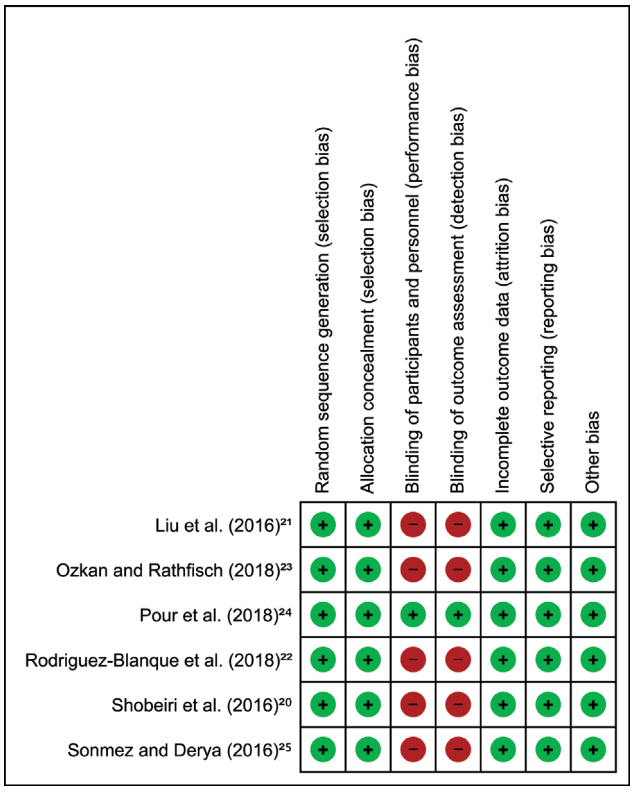

Fig. 2 Risk of bias summary: review authors' judgements about each risk of bias domain. Based on the Cochrane risk-of-bias assessment tool. Green color indicates low risk of bias; red color means indicates risk of bias.

(mean difference [MD] = -3.03, 95% confidence interval [CI] -4.15 to -1.92, $n = 623$, $i^2 = 84\%$, $p < 0.001$). We also performed two subgroups of analyses based on the interventions: music listening and other interventions. Analysis by subgroup (music listening: MD = -1.96, 95% CI -3.27 to -0.65, $n = 207$, $i^2 = 67\%$, $p = 0.003$ and other interventions: MD = -3.66, 95% CI -4.93 to -2.40, $n = 416$, $i^2 = 80\%$, $p < 0.001$) showed an improvement on sleep quality, with high heterogeneity. The risk of bias has shown good performance, however with some bias present in the majority of studies, GRADE evidence was low for all analyzed variables. The assessment of publication bias was demonstrated in the funnel plot (►**Fig. 4**), which suggests absence of publication bias, given the symmetry displayed.

Discussion

Our systematic review has demonstrated that non-pharmacological interventions improved sleep quality during pregnancy. Several studies have demonstrated that women during pregnancy experienced a poor sleep quality, and this may be a target of intervention given the disturbers of sleep can predict adverse maternal and fetal outcomes;[26–31] however, to our knowledge, this is the first review to evaluate the effects of lifestyle interventions for promoting sleep quality improvement during pregnancy. We have also calculated the risk of bias of these studies and the quality of

Table 2 Grading of Recommendations Assessment, Development, and Evaluation criteria for Pittsburgh Sleep Quality Index score among the eligible randomized controlled trials

Certainty assessment						Participants, n (before and after)		Absolute effect (95% CI)	Certainty
Number of studies	Study design	Risk of bias	Inconsistence	Indirect evidence	Imprecision	IC	CG		
Non-pharmacological interventions - Music listening									
2	Randomized clinical trial	Severe[a]	Severe[b]	Not severe	Severe[c]	103	104	MD **−1.96** (−3.27 to −0.65)	⊕OOO Very low
Non-pharmacological interventions - Other interventions									
4	Randomized clinical trial	Severe[a]	Severe[b]	Too severe[d]	Severe[c]	208	208	MD **−3.66** (−4.93 to −2.4)	⊕OOO Very low

Abbreviations: CI, confidence interval; CG, control Group; IC, intervention group; MD, mean difference.
Explanations: a. Lack of blinding was present in all RCTs; b. Heterogeneity varied from 67–80% even after using random-effect models; c. Sample size for each group in total is less than 400 individuals; d. Indirect evidence due to different populations (one study is from patients with restless leg syndrome) and this subgroup analysis also present different interventions (four in total).

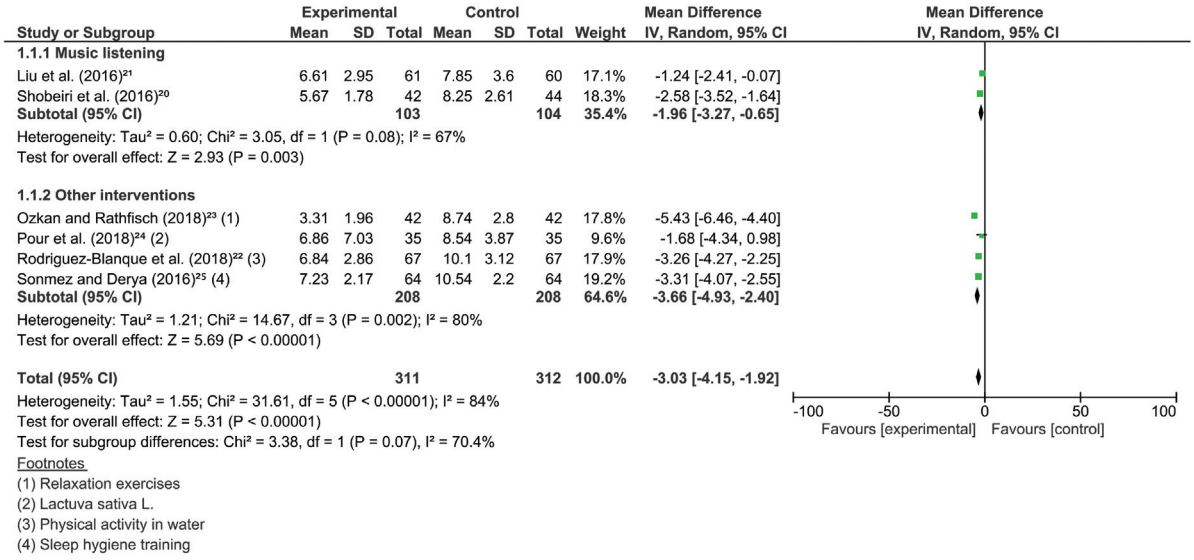

Fig. 3 Forest plot of all non-pharmacological interventions and their subgroups, outcome: sleep quality (measured by PSQI total score).

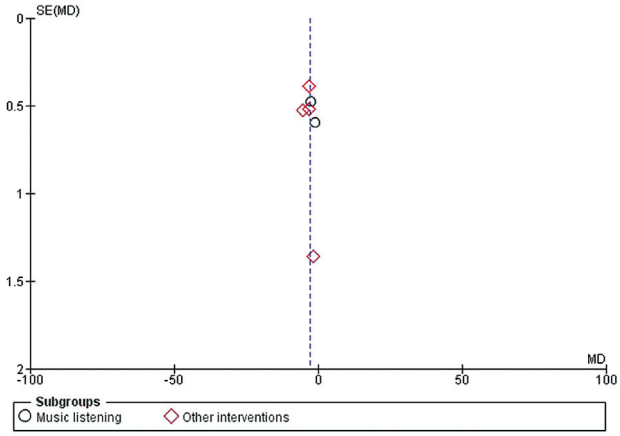

Fig. 4 Funnel plot estimating the risk of publication bias.

evidence using GRADE, giving an idea about the level of information provided in these studies.

The PSQI total score was the instrument assessed as a measure of sleep quality in our findings. Many studies in this field are based on self-reported measures of sleep quality, and although there is variation in the agreement between subjective and objective sleep measures,[6,32,33] the use of subjective parameters is an accurate predictor of complications in pregnancy and the postpartum period.[34–36]

Given the importance of methodological quality in the validity of computed tomography (CT) results, it is crucial to evaluate the risk of bias. Here, five of the six studies included in the quantitative analysis had high risk of bias in at least one domain, predominantly related to lack of blinding. However, given the nature of the interventions, most of the studies could not blind the participants. Our assessment also found that risk of bias among investigators could have been avoided if an investigator blinded to the group allocations had been recruited for data collection. However, as PSQI is a structured questionnaire, possibly minimal bias was introduced by the lack of a blinded investigator.

Our systematic review included studies from six different countries, but from two regions (Europe and Middle East), limiting the representativeness of our sample. In this sense, we need to be cautious in extrapolating these data to the general population. In addition, future higher-quality studies should provide a detailed of non-pharmacological measures for sleep improvement in other populations.

One study in our meta-analysis was conducted on women with diagnoses of restless legs syndrome (RLS). This condition is well explored during pregnancy and has been demonstrated to be more frequent during pregnancy than in the general population,[37] RLS has also been associated with decreased sleep quality.[38–40]

A recent meta-analysis of sleep quality during pregnancy[28] has indicated a mean PSQI score of 6.07 and a 1.68-point increase in the mean PSQI score from the second to third trimester. In our findings, there was a decrease of 3.03 points in the mean difference of PSQI total score, suggesting that lifestyle interventions during pregnancy may be an important way to minimize the sleep disturbances of pregnant women.

The subgroup analysis showed that listening to music was effective in improving sleep quality in pregnancy. However, it is worth noting that there is a low level of scientific evidence in this statement.

Interestingly, despite the benefits of non-pharmacological measures demonstrated in the current meta-analysis, this approach is still little used in clinical practice.

This study has some limitations that should be considered. First, the low number of well-controlled trials using non-pharmacological interventions for sleep problems in pregnant women that are available to be included in a meta-analysis. Moreover, we could not extract any quantitative data from two eligible studies.[18,19] The main reasons were that one study[18] used the PSQI as a categorical variable

(% of women with a PSQI score ranging 7–21), and although the authors answered our e-mail, they did not provide any additional data. The other study used a custom-designed questionnaire to evaluate sleep quality[19]; as a result, the parameters that assessed sleep quality are different from those of the PSQI. The eligible studies had considerable differences between the intervention type, time and duration, and the population studied. Consequently, our results should be analyzed carefully. Moreover, the sample size for each group was < 400 participants, and the heterogeneity was 67 to 84%, even after using random-effect models, rendering the strength of recommendation weak. As the number of studies were not sufficient to perform a meta-regression or sensitivity analysis, we need to be cautious about the generalizability of data. Despite these limitations, our findings identify strategies that may be adopted in prenatal care and should be considered by health professionals aiming to improve sleep patterns during pregnancy and also for avoiding possible adverse effects related to sleep disturbances, not only in pregnancy but also postpartum.

Conclusion

Safe strategies for improving sleep quality in pregnant women should be emphasized during prenatal care. The current analysis shows that non-pharmacological interventions (listening to music, physical exercise, relaxation exercises, lettuce seed, sleep hygiene, and acupressure) are effective for improving sleep quality during pregnancy. Although the evidence quality was very low. Moreover, lifestyle interventions and the encouragement of health behaviors during the gestational period may contribute to avoiding adverse outcomes for mother and fetus. Furthermore, considering the high prevalence of poor sleep in pregnant women and the limitations in drug use during the gestational period, future investigations that consider lifestyle modifications for improving sleep in other populations should be performed. Finally, further studies examining the potential effect of non-pharmacological approaches in postpartum women should be conducted, once the prevalence of poor sleep quality is also increased during the postpartum period.

Conflict of Interests

The authors have no conflict of interests to declare.

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Sentinel Lymph Node Biopsy in Endometrial Cancer – A Systematic Review and Quality Assessment of Meta-Analyses

Biópsia do linfonodo sentinela no câncer de endométrio – Uma revisão sistemática e avaliação da qualidade de meta-análises

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Abstract

Objective To assess the quality of recent meta-analyses reviewing the diagnostic utility of sentinel node biopsy in endometrial cancer.

Methods With the MeSH terms *endometrial neoplasms* and *sentinel lymph node biopsy*, PubMed and Embase databases were searched on October 21, 2020, and again on November 10, 2021, with meta-analysis and publication date filters set to since 2015. The articles included were classified with the A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) assessment tool.

Results The database searches found 17, 7 of which, after the screening, were selected for full review by the author, finally extracting six meta-analyzes for quality analysis. The rating with the AMSTAR 2 assessment tool found that overall confidence in their results was critically low.

Conclusion This study found that the quality of recent meta-analyses on the utility of the staging of endometrial cancer with sentinel node biopsy, evaluated by the AMSTAR 2 assessment tool, is classified as critically low, and, therefore, these meta-analyses are not reliable in the summary of their studies.

Keywords

- neoplasms
- uterus
- endometrium
- sentinel lymph node
- biopsy
- endometrial neoplasms

Resumo

Objetivo Avaliar a qualidade de meta-análises recentes que revisaram a utilidade diagnóstica da biópsia do linfonodo sentinela no câncer de endométrio.

Métodos Com os termos MeSH *endometrial neoplasms* e =*biópsia do linfonodo sentinela*, as bases de dados PubMed e Embase foram pesquisadas em 21 de outubro de 2020 e novamente em 10 de novembro de 2021, com filtros de meta-análise e data de publicação configurados para desde 2015. Os artigos incluídos foram classificados com o instrumento de avaliação *A Measurement Tool to Assess Systematic Reviews* (AMSTAR 2).

Palavras-chave

- neoplasias
- útero
- endométrio
- linfonodo sentinela
- biópsia
- neoplasias endometriais

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Resultados As pesquisas de banco de dados encontraram 17 artigos, sete dos quais, após a triagem, foram selecionados para revisão completa pelo autor, extraindo finalmente 6 meta-análises para análise de qualidade. A classificação com a ferramenta de avaliação AMSTAR 2 descobriu que a confiança geral em seus resultados era criticamente baixa.

Conclusão Este estudo constatou que a qualidade de meta-análises recentes sobre a utilidade do estadiamento do câncer de endométrio com biópsia do linfonodo sentinela, avaliada pela ferramenta de avaliação AMSTAR 2, é classificada como criticamente baixa e, portanto, essas meta-análises não são confiáveis no resumo de seus estudos.

Introduction

Endometrial cancer is the most common gynecological cancer in rich countries.[1] Overall survival is considered good because its diagnosis usually happens in the early stages, with the disease confined to the uterus, and surgery is often curative.[2]

The standard surgical procedure, when indicated, is an extra-fascial total hysterectomy with bilateral salpingo-oophorectomy.[1] Lymphadenectomy is included for staging; it used to be performed in all cases, but, now, a more selective approach is preferred.[3] Node-positive documentation identifies a high-risk population and helps tailor adjuvant therapy for node-negative results, potentially reducing the need for external radiation therapy.[4] The therapeutic utility of lymphadenectomy is controversial; two randomized controlled trials showed no therapeutic benefit in early endometrial cancer,[5,6] but, instead, it is associated with significant morbidity, up to a 50% risk of lymphedema,[7] increased risk of bleeding, intraoperative injury, and increased surgical time.[8] Sentinel node biopsy offers relevant information, and it is a useful procedure to determine lymph node involvement in cases of early endometrial cancer,[3,9] with a lower risk of lymphedema.[9]

To evaluate the quality of each meta-analysis included in this study, the A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) tool, which allows critical evaluation of systematic reviews that include randomized or non-randomized studies as well as those with both designs in care interventions, was used.[10] This instrument considers that all its items used to assess systematic reviews are important, but that seven of them can critically affect the validity of a review and its conclusions. These items correspond to the existence of a protocol registered before the beginning of the review, adequate bibliographic search, justification for the exclusion of each of the studies, the risk of bias of each study included in the review, suitability of the methods of meta-analysis, consideration of risk of bias when interpreting the results of the review, and assessment of the presence and possible impact of publication bias.[10]

Methods

A search of publications was conducted using the MeSH terms *endometrial neoplasm* and *sentinel lymph node biopsy* in the PubMed and Embase databases on October 21, 2020, and, again, on November 10, 2021, with the filters of meta-analysis and publication date set to since 2015. The retrieved articles were screened by the title and abstract independently, with another evaluator agreeing to read the entire article in case of discrepancy and make their decision after this reading. The articles selected for this screening were studied by the author, who read the complete articles and determined their relevance for the review; those that were finally extracted were classified with the AMSTAR 2 evaluation tool.

Results

The database searches found 17 articles, 7 of which were selected, after the screening, for full review by the author. Finally, six of them were included for quality analysis. ►**Figure 1** shows that the excluded publication did not report the results of the sentinel node biopsy in endometrial cancer separately (the results were combined with those for cervical cancer).[11]

A meta-analysis that included prospective cohort studies to evaluate sentinel lymph node biopsy in stage I high-grade endometrial cancer patients found a false negative rate of 8% (95% confidence interval [CI], 4–16%).[12] Other results of this study, as well as those of a study in laparoscopic surgery,[13] and two meta-analyses from 2017[14,15] are shown in **Chart 1**. The study by Lin et al.[14] also evaluated the laparoscopic surgery subgroup that had the best sensitivity within the sentinel node mapping surgical options with 96% (95% CI: 88–99%).

Sentinel node biopsy was superior to lymphadenectomy in detecting positive pelvic nodes, but there was no difference in detecting positive para-aortic nodes in two meta-analyzes that analyze this issue.[16,17] **Chart 2**. The classification of the items with the AMSTAR 2 assessment tool are shown for each study in **Chart 3**.

Discussion

Most patients with endometrial cancer present without lymph node metastases, with tumor confined to the uterus (about 75% stage I of the International Federation of Gynecology and Obstetrics [FIGO] classification) that has a rate of overall survival greater than 90%.[18]

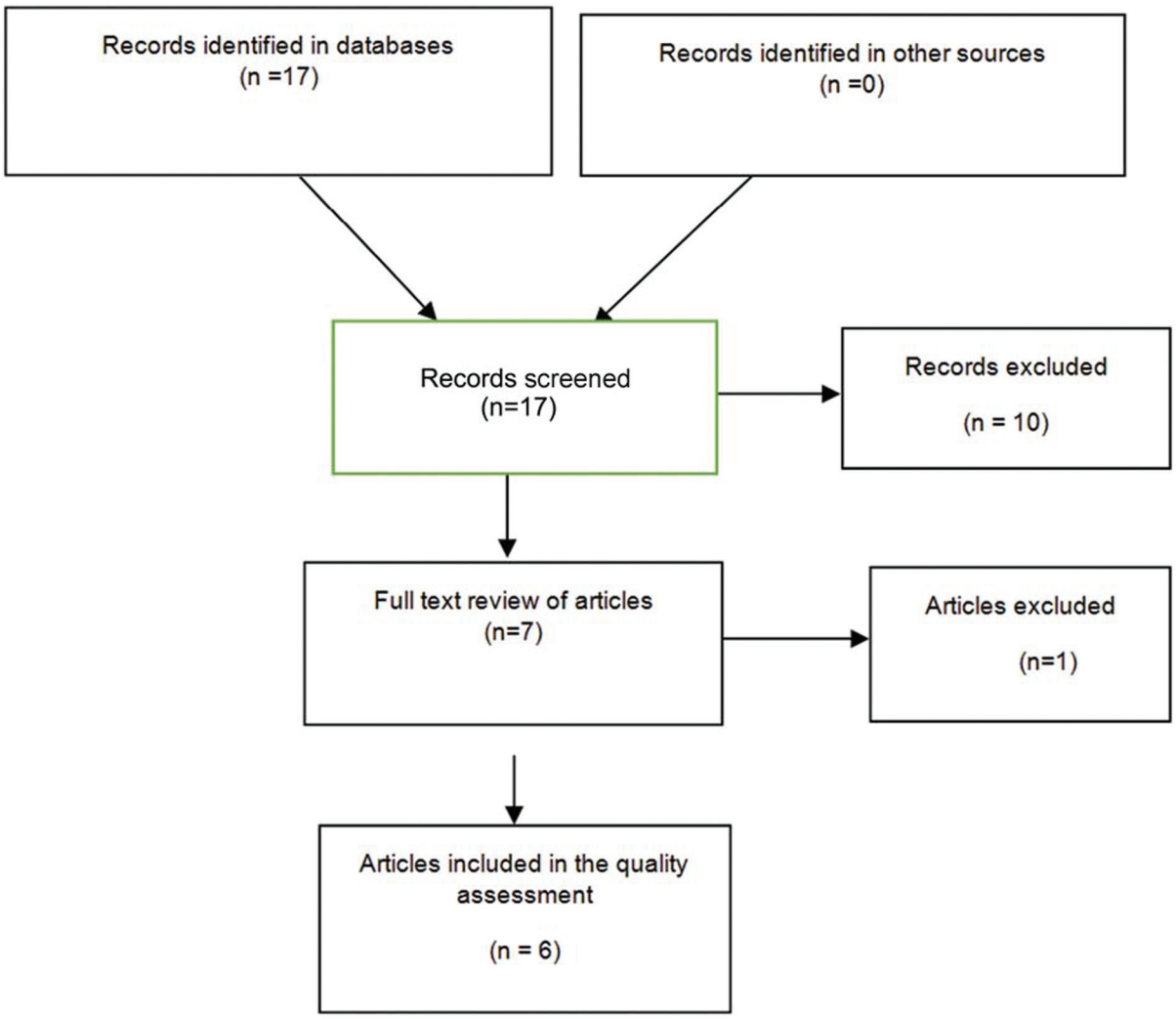

Fig. 1 Information flow through the different phases of the systematic review.

Chart 1 Meta-analyses reporting the detection rate and sensitivity of sentinel node biopsy in endometrial cancer

Author	Detection rate (%) (95% CI)	Sensitivity (%) (95% CI)
Marchocki et al.[12]	91 (85–95)	92 (84–96)
Wang and Liu[13]	96 (95–98)	96.3 (94–98)
Lin et al.[14]	83 (80–86)	91 (87–95)
Bodurtha Smith et al.[15]	81 (77–84)	96 (91–98)

Abbreviation: CI, confidence interval.

Chart 2 Detection of pelvic and para-aortic nodes comparing sentinel node biopsy with lymphadenectomy in endometrial cancer

Author	Pelvic nodes Odds ratio (95% CI)	Paraortic nodes Odds ratio (95% CI)
Gu et al.[16]	2.00 (1.21–3.32); $p = 0.007$	0.62 (0.24–1.64); $p = 0.34$
Bogani et al.[17]	2.03 (1.30–3.18); $p = 0.002$	0,93 (0,39–2.18); $p = 0.86$

Abbreviation: CI, confidence interval.

The acceptance of sentinel node mapping within the National Comprehensive Cancer Network (NCCN) guidelines as a procedure to be considered in the surgical staging of endometrial cancer apparently confined to the uterus, without evidence of metastasis in the images and without evidence of extrauterine disease in surgery,[3] confirms the indication of this procedure in surgical practice given the difficulty in selecting cases for lymphadenectomy, as well as the lack of benefit in early stages when this surgical procedure is performed, evidenced in randomized studies, and its high rate of complications. Sentinel node mapping can allow staging with a simple, rapid procedure and a lower risk of complications.[1] However, the speed of its acceptance does not seem consistent with the currently available evidence. The inclusion of sentinel node mapping in endometrial

Chart 3 Assessment of each domain in the meta-analyses rated with the critical evaluation tool for reviews AMSTAR 2

Question/author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Classification
Marchocki et al.[12]	Y	Y	N	N	Y	N	Y	Y	N	N	N	N	N	N	N	Y	CL
Wang and Liu[13]	Y	N	N	N	Y	Y	N	N	P	N	Y	Y	N	N	Y	Y	CL
Lin et al.[14]	N	N	N	N	Y	Y	N	P	P	N	N	N	N	N	N	N	CL
Bodurtha Smith et al.[15]	N	Y	N	N	Y	Y	N	Y	P	N	N	N	Y	Y	N	Y	CL
Gu et al.[16]	Y	Y	N	N	Y	Y	Y	N	N	N	N	N	N	N	N	Y	CL
Bogani et al.[17]	Y	P	N	P	N	N	Y	Y	N	N	N	N	N	N	N	Y	CL

Abbreviations: CL, critically low; N, no.; P, partial yes; Y, yes

cancer in clinical practice has a low level of evidence derived mainly from observational studies, and it is desirable to have more randomized studies to support its acceptance as an alternative in the staging of this pathology. However, it is a story that begins to seem to the current standard use of the sentinel node in the staging of axillary nodes in clinically node-negative early breast cancer,[19] in which its use was extended to the clinical setting, without high-level studies, despite the insistence on the need for randomized studies but that was able to demonstrate their advantages in the following years.[20] For greater safety with this new surgical option, it is recommended that surgeons developing this technique adhere to an algorithm that includes a thorough evaluation of retroperitoneal lymph nodes, selective or side-specific lymphadenectomy, if there is no identified mapping within a hemipelvis, and removal of all suspicious lymph nodes regardless of the mapping.[21]

The quality evaluation of each study found the general confidence of their results to be critically low according to the AMSTAR 2 tool. This means that the review has more than one critical flaw and should not be relied upon to provide an accurate and complete summary of the available studies.[10] Among the critical domains, those corresponding to items 9 and 13 of the AMSTAR 2 listing refer to the risk of biases, which are present in all the meta-analyses evaluated here in different magnitudes, except for the one by Bodurtha Smith et al.[15] for the consideration of these risks in the analysis of the results of the review. These items that assess the risk of bias are given priority in the classification because of the inclusion in the reviews of non-randomized studies.

Meta-analyses are important components of scientific information in evidence-based medicine.[22] The number of these reviews has increased steadily, but their quality has not always kept pace with this number.[23] To this issue, many instruments have been designed to evaluate the different aspects of a review, AMSTAR 2 allows a more detailed evaluation of systematic reviews that include non-randomized studies, which are increasingly being incorporated into these studies.[10]

The limitations of this study are due to the design of the AMSTAR 2 tool in the evaluation of the planning and performance of the reviews. As a new tool that includes non-randomized studies in systematic reviews, it is necessary to wait for the feedback of users of the instrument to consider making modifications.[10]

Conclusion

The current study found that the quality of recent meta-analyses on the utility of sentinel node biopsy in the staging of endometrial cancer, evaluated by the AMSTAR 2 assessment tool — which allows evaluating systematic reviews that include non-randomized studies — is classified as critically low, and, therefore, these meta-analyses are not reliable to be used in the summary of their studies.

Conflicts to Interest

The authors have no conflict of interests to declare.

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The Effects of Hysterectomy on Urinary and Sexual Functions of Women with Cervical Cancer: A Systematic Review

Os efeitos da histerectomia nas funções urinárias e sexuais de mulheres com câncer cervical: Uma revisão sistemática

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Abstract

Objective This systematic review aims at describing the prevalence of urinary and sexual symptoms among women who underwent a hysterectomy for cervical cancer.

Methods A systematic search in six electronic databases was performed, in September 2019, by two researchers. The text search was limited to the investigation of prevalence or occurrence of lower urinary tract symptoms (LUTS) and sexual dysfunctions in women who underwent a hysterectomy for cervical cancer. For search strategies, specific combinations of terms were used.

Results A total of 8 studies, published between 2010 and 2018, were included in the sample. The average age of the participants ranged from 40 to 56 years, and the dysfunctions predominantly investigated in the articles were urinary symptoms ($n = 8$). The rates of urinary incontinence due to radical abdominal hysterectomy ranged from 7 to 31%. The same dysfunction related to laparoscopic radical hysterectomy varied from 25 to 35% and to laparoscopic nerve sparing radical hysterectomy varied from 25 to 47%. Nocturia ranged from 13%, before treatment, to 30%, after radical hysterectomy. The prevalence rates of dyspareunia related to laparoscopic radical hysterectomy and laparoscopic nerve sparing radical hysterectomy ranged from 5 to 16% and 7 to 19% respectively. The difficulty in having orgasm was related to laparoscopic radical hysterectomy (10 to 14%) and laparoscopic nerve sparing radical hysterectomy (9 to 19%).

Conclusion Urinary and sexual dysfunctions after radical hysterectomy to treat cervical cancer are frequent events. The main reported disorders were urinary incontinence and dyspareunia.

Keywords
- uterine cervical neoplasms
- hysterectomy
- lower urinary tract symptoms

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Resumo

Objetivo Essa revisão sistemática visa descrever a prevalência de sintomas urinários e sexuais entre mulheres submetidas à histerectomia por câncer cervical.

Métodos Uma pesquisa sistemática foi realizada em seis bases de dados eletrônicas, em setembro de 2019, por dois pesquisadores. A busca foi limitada à investigação da prevalência e ocorrência de sintomas do trato urinário baixo e disfunções sexuais em mulheres após histerectomia por câncer cervical. Como estratégia de busca foi utilizada uma combinação específica de termos apenas em inglês.

Resultados Um total de 8 estudos, publicados entre 2010 e 2018, foram incluídos na amostra. A idade média dos participantes foi de 40 a 56 anos, e as principais disfunções investigadas pelos artigos foram sintomas urinários ($n = 8$). Na literatura analisada, as taxas de incontinência urinária ligadas à histerectomia abdominal radical variaram de 7 a 31%. A mesma disfunção, para histerectomia radical laparoscópica, variou de 25 a 35%, e de 25 a 47% para histerectomia radical laparoscópica poupadora de nervo. A taxa de noctúria variou de 13%, antes do tratamento, a 30%, após histerectomia radical. A prevalência de dispareunia associada à histerectomia radical laparoscópica foi de 5 a 16%. Já a taxa de dispareunia relatada pós-histerectomia radical laparoscópica poupadora situou-se entre 7 e 19%. A dificuldade de alcançar o orgasmo foi relatada após histerectomia radical laparoscópica, variando de 10 a 14%, e também na histerectomia radical laparoscópica poupadora de nervo, variando de 9 a 19%.

Conclusão Disfunções urinárias e sexuais após histerectomia para tratamento do câncer cervical são eventos frequentes. As principais desordens relatadas foram incontinência urinária e dispareunia.

Palavras-chave

- neoplasias do colo do útero
- histerectomia
- sintomas do trato urinário inferior

Introduction

Cervical cancer is the fourth most common female cancer worldwide and the second in low/middle-income countries (LMICs).[1] In Brazil, it is the third most frequent and the fourth leading cause of death for women.[2] The treatment of cervical cancer begins with surgery or radiation therapy, with or without chemotherapy. Surgery is indicated in the early stages. Surgical technique is selected according to disease staging: cervical conization, total simple hysterectomy, or radical hysterectomy.[3] Among radical hysterectomies, the most common is the type III technique, involving more extensive removal of the upper vagina, as well as uterosacral ligaments and bilateral parametrium.[4]

Although there is a high survival rate for treated, early-stage, node-negative cervical cancer, radical hysterectomy leads to a major morbidity, in particular, regarding the urinary and sexual functions.[5–8] In addition, despite the early transient changes in pelvic organ functions, after radical hysterectomy, the long-term prevalence of symptoms and the extent of morbidity associated with the procedure have not been well established.[9] Selcuk et al.[9] affirm that hysterectomy impacts on the quality of life (QoL), regarding aspects of pelvic floor functions, especially in women submitted to radical hysterectomy. Urinary symptoms (retention, urgency) and sexual dysfunctions are as uncomfortable as challenging to overwhelmed patients.[9]

Surgical treatment of women with cervical cancer causes significant injury to the pelvic floor. In fact, hysterectomy impairs the anatomical relationship between the pelvic organs (bladder, uterus, bowel, and vagina), supportive structures, and local nerve supply, which disrupts the pelvic floor normal function.[5] It is thought that surgical damage to the pelvic autonomic nerves plays a critical role in urinary and sexual dysfunctions.[5,8,10,11]

Differences on the surgical procedures will involve varying degrees of dissection and disruption of the neuroanatomy of the pelvic organs. Such variations are important to be pointed out, for they may be related to the studied outcomes. Thus, we aimed at this systematic review to describe the prevalence of urinary and sexual symptoms among women who underwent a hysterectomy for cervical cancer.

Methods

This study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist.[12]

A systematic search of the MEDLINE/Pubmed, SCIELO, LILACS, CINAHL, SCOPUS, and WEB OF SCIENCE databases was performed from September 1 to 7, 2019 by two researchers (M. A. F. and L. G. B. M. M.) to retrieve all the manuscripts that contained information on the prevalence of urinary disorders and sexual symptoms in women after cervical cancer hysterectomy. A manual search of reference lists was also performed. For search strategies, the following combinations of terms were used: *hysterectomy* OR *hysterectomy, vaginal*

AND *uterine cervical neoplasms* OR *cervical cancer* OR *cervical neoplams* OR *genital neoplams, female* AND *pelvic floor disorders* OR *pelvic floor*, *hysterectomy* OR *hysterectomy, vaginal* AND *pelvic floor disorders* OR *pelvic floor*, *hysterectomy* OR *hysterectomy, vaginal* AND *uterine cervical neoplams* OR *cervical cancer* OR *cervical neoplasms* OR *genital neoplams*, female AND *diurnal enuresis* OR *nocturnal enuresis* OR *urine* AND *sexual dysfunction* OR *dyspareunia* OR *sexual behavior* OR *libido* OR *orgasm*/ *hysterectomy* OR *hysterectomy*, *vaginal* AND *diurnal enuresis* OR *nocturnal enuresis* OR *urine* AND *sexual dysfunction* OR *dyspareunia* OR *sexual behavior* OR *libido* OR *orgasm*.

The search was limited to the investigation of prevalence or occurrence of LUTS and sexual dysfunctions in women who underwent a hysterectomy for cervical cancer. There was no limit regarding the publication period. Articles were excluded if they were duplicates, reviews, case studies, or commentaries.

We included randomized controlled trials (RCTs) and observational studies. The PICO criteria determined all parameters: women, aged between 18 and 65 years, who underwent hysterectomy with pelvic and/or paraaortic lymphadenectomy for cervical cancer (IA2, IB1, IB2, IIA, IIB), with or without radiotherapy (RT) or chemotherapy (QT), and who indicated urinary and sexual symptoms. Studies comparing surgical techniques for treating cervical cancer for assessing the onset of urinary or sexual dysfunctions were also included.

In the initial research, 4,015 studies were identified, out of which 3,886 duplicates were excluded. One hundred and ten out of 128 articles screened for eligibility were excluded, after the reading of the abstract, as well as 54 reviews, 22 case-studies, and others 34 papers, which did not meet the research goal. Twenty-seven articles were potentially eligible for inclusion in this review and, therefore, were read in full. After reading and analyzing them, 19 studies were excluded, resulting in 8 articles included in this review (►**Fig. 1**).

The search was conducted from the 1st to 7th of September 2019 by two authors (M. A. F. and L. G. B. M. M.). The JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data was used by the former author for assessment of risk of bias of the selected studies (criteria and appraisals are provided in supporting information) (►**Charts 1** and **2**). According to this instrument, each question presents four options: yes (Y), no (N), unclear (U), and not applicable (N/A). The calculation of the percentage of risk of bias was established out of the amount of Y that was selected in the checklist. When the N/A response was selected, the question was not considered in the calculation, according to the guidelines of the Joanna Briggs Institute.[13] Up to 49% of the calculation was considered a high risk of bias. From 50 up to 70%, the risk was considered moderate, and above 70%, the risk of bias was considered low.[13]

The critical evaluation was discussed with the other authors who agreed with the study appraisals. A standardized data extraction sheet was developed and filled in, to extract data concerning the study design, population and sample, results, outcomes, and conclusions.

Symptoms of urinary and sexual dysfunction were those described by the *International Urogynecological Association (IUGA)/International Continence Society (ICS)*.[14] Data on urinary and sexual symptoms researched in the articles should be recorded and reported as: (1) the subject's observations (symptoms); (2) quantification of symptoms; (3) clinician's observations (anatomical and functional); (4) quality of life; and (5) socioeconomic measures.[15]

Primary outcomes: prevalence of urinary symptoms (lower urinary tract symptoms, urinary incontinence, stress urinary incontinence, urge urinary incontinence, nocturia, and urinary tract infections) before and after hysterectomy. Prevalence of sexual symptoms (sexual dysfunction, dyspareunia, difficulty in having orgasm) before and after hysterectomy.[14]

Secondary variables: age, type of surgery, instruments used to measure symptoms and period in which symptoms were measured.

Finally, data were categorized and organized in tables and figures, according to prevalence, associated factors, and impact on quality of life. A qualitative synthesis of all the studies was performed and included in the final sample, describing the study results organized by study characteristics and quality appraisal, prevalence, risk factors, and impact on urinary and sexual symptoms and on quality of life. After these evaluations, the selected studies were submitted to a statistical analysis to verify the possibility of constructing a meta-analysis, which would increase the accuracy and the evidential power of the results. However, this step was not possible due to heterogeneity of the methods, study samples, questionnaires, definition of symptoms, and reporting of results.

Results

Study Characteristics and Quality Appraisal

According to the search strategy adopted, 4,015 studies were identified, 3,886 of which were duplicates and, therefore, excluded. Title and abstracts of the 128 remaining papers were assessed to determine whether the study was adequate to be included, resulting in 110 articles excluded. Thus, 27 articles were fully evaluated for eligibility and 19 studies were excluded according to the eligibility criteria.

A total of 8 studies, published between 2010 and 2018, were included in the sample. The average age of the participants ranged from 40 to 56 years and the dysfunctions predominantly investigated by the articles were urinary symptoms ($n = 8$). Five studies reported, in addition to data related to voiding dysfunction, female sexual dysfunction.[9,16–38] Only five studies used validated questionnaires in their data collections, the rest used standardized instruments in their respective collection fields (►**Charts 1** and **2**). The studies had a variation in patient follow-up from 3 months to 9 years. Most studies were performed in Europe.[16,27,38,39]

Four retrospective cohort studies have reported oncological results and complications from various treatment modalities for various stages of cervical cancer.[9,27,36,37] Prospective cohorts, on the other hand, assessed the influence of

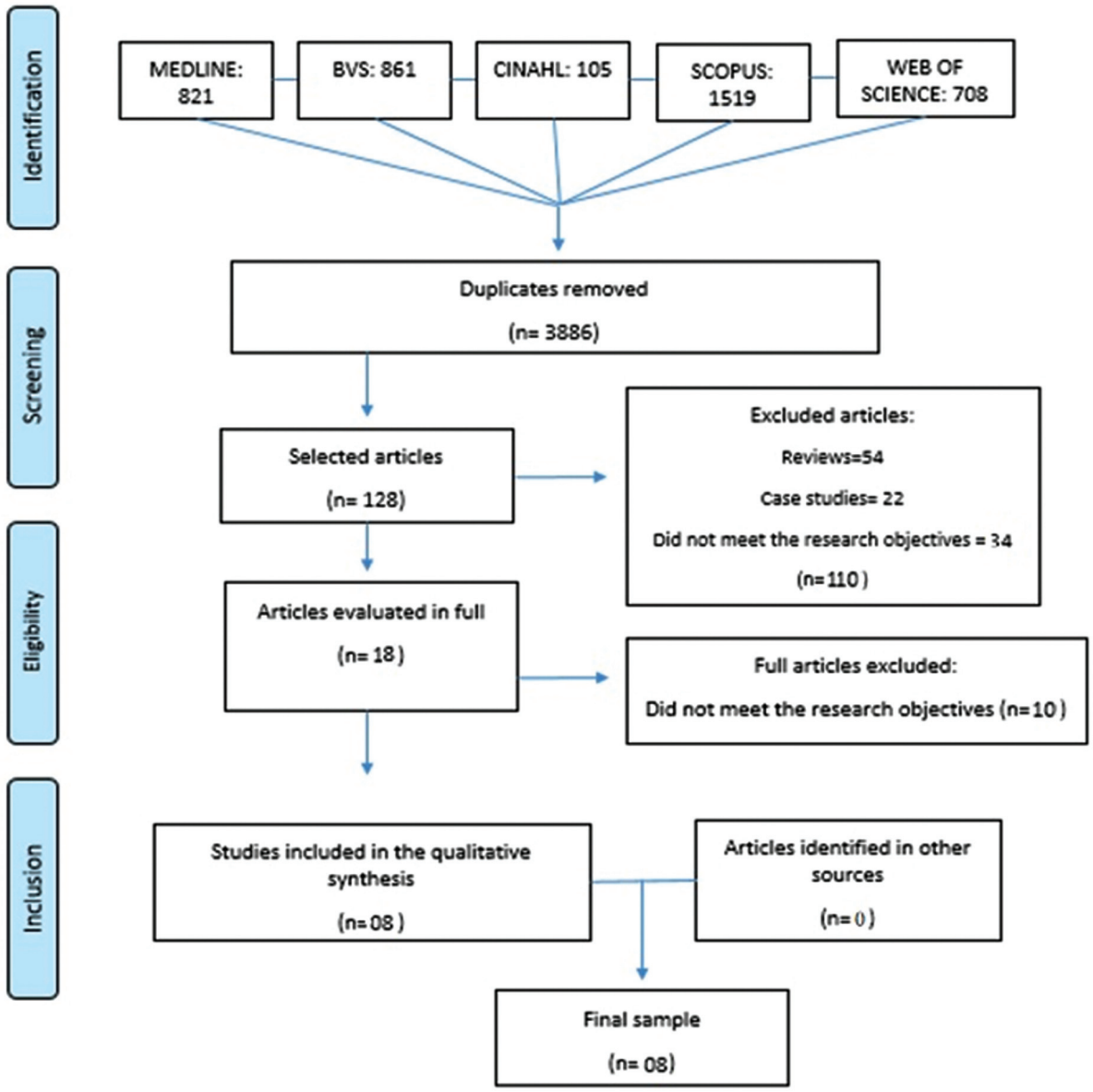

Fig. 1 Flow referring to the selection process of the systematic review studies, adapted from PRISMA-ScR.

hysterectomy on the pelvic floor regarding morbidity secondary to urinary and sexual symptoms.[16,22,38,39]

The cross-sectional study that comprised the sample in this review was part of an original study and used questionnaires to assess urinary and sexual symptoms in women undergoing hysterectomy, with a follow-up of up to 9 years.[16]

►**Charts 1** and **2** list publications that show the prevalence of urinary and sexual dysfunctions posthysterectomy. It is noteworthy that there are methodological differences between the studies regarding the following aspects: study designs, reason for the hysterectomy (type of cancer), surgical route (abdominal, laparoscopic, vaginal, etc.), age of the women, time of surgery, and questionnaires used and follow-up period.

Prevalence of Urinary Symptoms

The rates of urinary incontinence due to radical abdominal hysterectomy ranged from 7 to 31%. The same dysfunction related to laparoscopic radical hysterectomy varied from 25 to 35%, and from 25 to 47% when related to laparoscopic nerve sparing radical hysterectomy, varied. Finally, relating stress urinary incontinence to radical abdominal hysterectomy, rates vary from 7 to 11%. Supracervical hysterectomy, in turn, when related to the rates of appearance of stress incontinence, had no variation (11%), urge incontinence ranged from 7, before surgery, and 45%, after surgery, in radical abdominal hysterectomy, and 5% after supracervical hysterectomy. Nocturia ranged from 13, before treatment, to 30% after the radical hysterectomy (►**Charts 1** and **2**).

Prevalence of Sexual Symptoms

The prevalence rates of dyspareunia related to laparoscopic radical hysterectomy and laparoscopic nerve sparing radical hysterectomy ranged from 5 to 16% and 7 to 19% respectively. The difficulty in having orgasm was related to laparoscopic

radical hysterectomy (10 to 14%) and laparoscopic nerve sparing radical hysterectomy (9 to 19%) (►**Charts 1** and **2**, supplementary material).

Evaluation of Studies

All 8 articles were analyzed, according to the type of study, through the JBI critical appraisal checklist, which aims at assessing the methodological quality of a study and determining the extent to which the authors addressed the possibility of bias in its design, conduct and analysis. Within the sample of this review, seven articles had a low risk of bias, and one article showed a moderate risk of bias (►**Charts 1** and **2**, supplementary material).

Discussion

This systematic review was designed to assess the prevalence of urinary and sexual symptoms after the different types of hysterectomy. It was agreed that the observations or symptoms of the patients should include evaluations with validated questionnaires; however, three of the selected studies used non validated questionnaires. There is a critical need for validated and reliable instruments for symptom assessment in all types of pelvic floor disorders, which may include standardized interviews, questionnaires, symptom diaries, and other techniques for collecting qualitative and quantitative data.[19]

The importance of using validated questionnaires in scientific research consists of attending to what the researcher proposes to unveil and of having coherence in the methodological processes and consistency of the results, allowing to analyze the existence of a logic between the proposed instruments and the objectives of research. The use of validated instruments in health studies is imperative to verify the need for intervention in some process. It is necessary to guarantee two characteristics of the measuring instruments: validity and reliability. Ensuring the validity of the instrument means statistically proving that the questionnaire really measures what it proposes, and reliability can be defined as the reproducibility of that measure.[20]

In addition, in three studies, patients already had urinary and/or sexual symptoms before the surgical procedure.[16,21–23] Epidemiological studies show that the prevalence of voiding complaints among women aged 40 to 56 years can vary between 7 and 47% (►**Charts 1** and **2**, supplementary material), and the prevalence of sexual symptoms in the same age group varies between 5 and 19% (►**Charts 1** and **2**, supplementary material). Pelvic floor dysfunctions usually occur due to multiparity, obesity, previous pelvic surgery (such as hysterectomy), and behavioral factors. These changes lead to dysfunctions such as urinary (UI) and fecal (IF) incontinence, pelvic organ prolapses (POPs), constipation, and sexual dysfunctions.[24]

Hysterectomy remains the main treatment modality for early cervical cancer, due to the effects of radiation on ovarian function and vaginal mucosa integrity. Although the 5-year survival is greater than 90% for negative lymph node disease, the procedure causes significant morbidity for patients, including on the pelvic floor, such as, for example, urinary and sexual dysfunctions.[25] Many studies in this review pointed out that any type of hysterectomy can result in more pelvic floor symptoms.[9,21,26]

Although the literature mentions hysterectomy as a risk factor for the development of urinary dysfunctions, these symptoms are frequently related to other factors, such as pregnancy, childbirth, and climacteric period. Chen et al.[39] reported bladder dysfunction in oncological patients related to pathological changes in the detrusor muscle and injuries to bladder autonomic innervation by vaginal, paravaginal, and parametrial resection. These changes can lead to increase of urinary frequency, urinary urgency, and decrease of bladder compliance, symptoms that could persist for 6 to 12 months after surgery.

A study that compared the prevalence of these disorders among women with cervical cancer who underwent surgery and radiotherapy found that there were urinary complications in both groups, but sexual disorders, in the radiotherapy group, were more exacerbated in young and obese patients, while surgery-related disorders were more prevalent in the elderly and obese.[27] This data corroborates with the literature, when it states that some clinical and demographic characteristics may be associated with increased intensity of bladder and sexual symptoms in patients with gynecological cancer, such as, obesity and a low level of education.[28]

Cosson et al. (2001)[22] also stated that many long-term complications, which appear in the first 4 years after hysterectomy, cannot be attributed to the intervention. There are confounding factors, such as age and hormonal changes.[22] In the writing stages of this review, a shortage of studies about these factors was noted. They are relevant considering the sample profile and high climacteric symptoms prevalence. Therefore, we emphasize the need for more studies evaluating such variables.

When it comes to laparoscopic hysterectomies, we noticed that the variations in the rates of voiding dysfunction were much more significant than the rates of sexual problems presented by women. In addition, this type of surgery, compared with other surgical techniques, causes less morbidity to the female pelvic floor.[21]

Sensory innervation lesion of the bladder, as well as damage to the autonomic pelvic plexus, can occur during hysterectomy, resulting in urinary dysfunction. Terminal bundles of the bilateral plexuses innervate the vagina and the proximal bladder and can be damaged during surgery, resulting in a defective closing mechanism of the proximal urethral sphincter.[29]

The same authors also emphasize that radical hysterectomy for the treatment of cervical cancer causes significant morbidity to the pelvic floor, and this is related to the radicality of the parametrial and vaginal resection with partial denervation resulting from the pelvic viscera and it is not just explained by the removal of the uterus.[29,30] In addition, when surgery is associated with adjuvant radiotherapy, the prevalence of self-reported urinary and sexual symptoms increases.[29]

The results obtained in this review also show that the treatment against early cervical cancer results in an increase

of the sexual and urinary symptoms of the patients, regardless of the surgical procedure.[22]

There may be consequences after hysterectomy, in the quality of the woman's sexual life, in her emotional conditions, and in the quality of the relationship established with her partner. The need to perform this surgery, in many cases, causes conflicting, traumatic, insecure emotions, and anxiety, generating important changes in sexual patterns and desire.[31]

In Brazil, each year, many women receive an indication for hysterectomy. In 2017, 122 hysterectomies were performed per 100 thousand women over the age of 20 years. It is estimated that between 20 and 30% of women will undergo this procedure until the 6th decade of life.[32] These patients may present changes in self-image and depressive symptoms, due to conceptions about the uterus that are closely linked to the woman's sexuality.

In addition to the emotional aspects, anatomical changes also occur in the pelvis, which can lead to changes in the size and diameter of the vagina (leading to difficulty in vaginal penetration and dyspareunia) and reduction of circulating hormone levels (leading to decreased sexual desire, vaginal dryness, and lower frequency of orgasms). Our results are in accordance with the literature, observing an increase in the prevalence rates of dyspareunia and orgasmic difficulties in all types of hysterectomies performed.[31]

In most developed countries, cancer is the second leading cause of death, preceded only by cardiovascular disease, and there is epidemiological evidence that this trend is emerging in developing countries.[1] The number of cancer deaths in the world is expected to increase 45% between 2007 and 2030 (from 7.9–11.5 million deaths), influenced, in part, by the increase in population and global aging.[34] The incidence of cancer tends to increase with age, probably due to the accumulation of risk factors for some specific cancers.[34] This susceptibility of the elderly can occur due to the duration of carcinogenesis, the vulnerability of the elderly tissues to environmental carcinogens, and other transformations that favor the development and growth of tumors.[35]

Gynecological cancer survivors face several barriers with regard to identification and treatment of pelvic floor disorders, including communication issues between patient and health professional.[40] Hence, we highlight the importance of multidisciplinary programs to prevent and treat this group, providing information and strategies to improve vaginal symptoms and to improve sexual health.

Although most cervical cancer patients are not elderly, we need to be attentive to postoperative care for hysterectomized patients. This review indicates the importance of a thorough investigation involving the adverse effects of the treatment of hysterectomy. The quality of life should be increasingly valued, to the detriment of life in conditions limited or disabled. In this sense, the need for health assistance in the monitoring of these patients after the cancer diagnosis (both before and after surgery) is highlighted, to help with all these needs.

Regarding oncological patients, the biopsychosocial dimension must be considered. Thus, the literature indicates fear of disease recurrence, shame of urinary symptoms, reduced sexual function and vaginal motility, dyspareunia, and low sex drive.[41] Some of these subjects were addressed in the articles of our review, which reinforce the relevance of strategies to prevent harm to the psychological health of that group.

The limitations of this study were the inclusion of papers with non-comparable types of hysterectomies, with different follow-up times and measurement of different variables, and the inclusion of studies with a low level of evidence. Additional studies are needed to investigate the impact on the productivity of these patients' work, the causal relationships of the dysfunctions with the occupation and the carrying out of preventive interventions and conservative treatments aimed at this population.

Conclusion

The urinary and sexual dysfunctions in hysterectomized women are frequent events. The main diseases reported in the studies were urinary incontinence, which had a prevalence variation between 7, in radical abdominal hysterectomy, and 47%, in laparoscopic radical hysterectomy (including stress and urge incontinence), and dyspareunia. The latter ranged from 5, in laparoscopic radical hysterectomy, to 19%, in laparoscopic nerve sparing radical hysterectomy.

Conflict of Interests

The authors have no conflict of interests to declare.

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Medical Residents, the Group and the Formation of Professional Identity During the COVID-19 Pandemic

Médicos residentes, o grupo e a formação da identidade profissional durante a pandemia do COVID-19

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Abstract

Residency is still considered the gold standard for quality medical training, and acquiring a professional identity as a specialist is one of its central elements. Residents obtain this identity through both the educational environment and direct interaction with peers and supervisors. However, modifications in health care and educational routines during the recent coronavirus disease 2019 (COVID-19) pandemic have significantly impaired these channels. This study is part of a qualitative research project to analyze professional identity formation in a medical residency program in obstetrics and gynecology at a public hospital in southern Brazil. The authors conducted 28 semi-structured interviews with medical residents and preceptors, as well as a focus group with the residents, which was recorded, transcribed, and analyzed in an effort to construct major analytical categories. Restricted movement and physical contact have forced the use of alternative means of interpersonal interaction, such as communication through social media or instant messaging applications. This has also affected educational activities, such as morning rounds, lectures, and seminars. These changes represent a significant impact, especially in Brazil, where physical proximity is an important cultural feature, even in the work and school environments. We speculate that this new type of virtual interaction will also affect the formation of professional identity among obstetrician-gynecologists. These findings suggest that medical residency programs should be attentive to changes in resident training to ensure that the specialist profile and the expected skills, which are consolidated over many years, are not lost.

Keywords

- medical residency
- professional identity
- educational environment

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Resumo

A residência médica ainda é considerada o padrão-ouro para a formação médica de qualidade, sendo o processo de construção da identidade profissional de um médico especialista um de seus elementos centrais. Os residentes obtêm essa identidade, entre outros fatores, por meio do ambiente educacional e da interação direta com colegas e supervisores. No entanto, as modificações nas rotinas assistenciais e educacionais durante a recente pandemia de *coronavirus disease 2019* (Covid-19) prejudicaram significativamente esses canais. Este estudo faz parte de um projeto de pesquisa qualitativa com o objetivo de analisar a formação da identidade profissional em um programa de residência médica em ginecologia e obstetrícia em um hospital público do sul do Brasil. Os autores realizaram 28 entrevistas semiestruturadas com médicos residentes e preceptores, bem como um grupo focal com residentes. Tanto as entrevistas como as reuniões com o grupo focal foram gravadas, transcritas e analisadas no esforço de construir categorias analíticas. Foi identificado que o movimento restrito e o contato físico forçaram o uso de meios alternativos de interação interpessoal, como a comunicação por meio de mídias sociais ou aplicativos de mensagens instantâneas. Isso também afetou as atividades educacionais, como as rounds, palestras e seminários. Essas mudanças representam um impacto significativo, principalmente no Brasil, onde a proximidade física é uma importante característica cultural, mesmo em ambientes de trabalho e de estudo. Conjectura-se que esse novo tipo de interação virtual também afetará a formação da identidade profissional entre os ginecologistas-obstetras. Esses achados sugerem que os programas de residência médica devem estar atentos às mudanças na formação dos residentes para garantir que o perfil do especialista e as competências esperadas, consolidadas ao longo de muitos anos, não sejam perdidos.

Palavras-chave

- residência médica
- identidade profissional
- ambiente educacional

Introduction

Due to the growing complexity of health care, physician training has been modified to include the skills necessary for new and constantly changing scenarios.[1,2] The coronavirus disease 2019 (COVID-19) pandemic represents one of the most important health crises in recent human history. In medical education, these changes have forced adaptations in curriculum design regarding new skills, interpersonal relationships, teaching strategies, and the need for community interventions.[3,4] For physicians in training, such as medical residents, the pandemic has also led to direct changes in work and leisure routines, social interaction, and their own health care. In addition to the inevitable stress that arises from training in a medical specialty, these young physicians are overwhelmed with concerns about how to address the health care of the population and how to deal with the dangers of contagion, both for themselves and those close to them.[5,6] In other words, in addition to resident burnout, which has already reached epidemic levels in recent years, the pandemic has added a further destabilizing factor.[7–10]

Recently, professional identity formation has been studied as a crucial element in the long trajectory of medical education.[11] Thus, *becoming a doctor* in such a disruptive and uncertain context may deserve greater attention by researchers committed to medical education.

This study is part of a broader, qualitative research project that seeks to analyze the formation of professional identity among gynecology-obstetrics residents in a public hospital in Brazil. Medical residents and preceptors in this program were interviewed, and their interviews were recorded, transcribed, and analyzed using NVivo software (QSR International, Doncaster, Australia). This study was approved by the institutional research ethics committee (protocol no. CAAE 27172919.6.0000.5327).

After some initial interviews, it was clear that the pandemic had definitely affected this process.

Healthcare and Educational Changes in Brazil due to the Pandemic

Following its spread from China, the COVID-19 pandemic hit Brazil in late February 2020, with the first case confirmed on February 26, and the first death recorded on March 17. Although there were enormous contrasts in the epidemiological characteristics of the disease's progress, all regions of the country were severely affected, and there were significant changes in the functioning of healthcare networks. In view of this situation, the National Medical Residency Commission (CNRM, an organ linked to the Ministry of Education that is responsible for regulating medical residency) issued a technical note on May 2020 featuring recommendations regarding the development of residence program activities during the COVID-19 pandemic.[12] In general, this document has guided the medical residency commissions of each

institution and the State Medical Residency Commissions (CEREMs) about how to make residency activities more flexible to minimize the harmful effects to physicians during the specialization process. At the same time, it called on medical residents of all specialties to actively engage in health care activities aimed at the pandemic in their cities. In the same vein, the Brazilian Federation of Obstetrics and Gynecology Associations (FEBRASGO), a scientific entity that represents Brazilian gynecologists and obstetricians and is involved in the training of specialists in the area, issued its own recommendations seeking, among other points, to minimize the loss of surgical skills due to the pandemic.[13]

The Hospital de Clínicas de Porto Alegre, a university hospital, is one of the largest centers for training medical specialists in southern Brazil. The institution had been preparing for the pandemic since January 2020, establishing contingency plans with staggered restrictions for assistance activities, including specific flows for each stage according to criteria that considered the number of occupied hospital beds and the spread of the disease in the state of Rio Grande do Sul and the city of Porto Alegre, where this study was conducted. The first officially registered case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at the institution occurred on March 11, 2020, and the first death, 2 weeks later.

Since residence programs generally begin in early March, the new residents arrived at the height of all this activity. Although the official reception was still festive, including hundreds of photos shared on social media, the hospital moved to its first contingency level on March 15, limiting a number of assistance activities and the circulation of people through the hospital, which affected the patients and the medical teams. As the pandemic progressed, restrictions were implemented in residence program teaching activities and, in conformity to local health regulations, bars, restaurants, and other public places were closed to reduce crowds.

Professional Identity: The Case of Obstetrics and Gynecology Residency

This exceptional scenario has had repercussions even on specialties that are not traditionally involved in epidemiological problems. Obstetrics and gynecology, for example, is essentially a medical specialty in women's health. The competency matrix, which serves as a guide for the almost 300 residency programs in obstetrics and gynecology in Brazil, was defined through recent CNRM legislation.[14] This detailed document divides the competences to be achieved into several axes of care according to each year of the residency. Although it does not establish a minimum number of expected procedures, there is a clear indication that the resident must master certain techniques, which presupposes having acquired such competence through exhaustive training.

As in any other surgical specialty, it requires, in addition to knowledge and attitudes, the development of a series of motor skills, which residents obtain through continuous exposure to a significant and varied number of situations in which they can exercise their clinical reasoning in an appropriate, independent, and safe way for their patient and themselves.[15]

In this complex trajectory towards specialized medical practice, the interrelationship of peers plays a crucial role. Although the formation of a physician's professional identity involves an eminently individual path, it always occurs alongside others who are undergoing the same situation. For newcomers, being accepted into a peer community that has a structured professional identity can pose additional stress during the transition from student to doctor. This is true among the residents and the health team members they relate to professionally. In other words, becoming a doctor is also directly linked to the process of appearing like a doctor to other people. Thus, forming a group of residents has been a hallmark of medical residency since its beginning.[16] In other words, the formation of professional identity is a two-way street: from the inside out (the doctor must *feel* like a doctor) and from the outside in (other people must *see* him or her as a doctor).

Although the millennials' way of learning has led to changes in teaching and medical residency in recent years, some traits, such as group support, have remained equally important despite generational differences and increasing technological sophistication.

Regardless of preparation, which can begin prior to entering medical school, the transition from being a student to a resident is still a huge challenge in any specialty.[17] Despite previous familiarity with some of the activities of medical school, being registered with state agencies and "having the seal", that is, formal authorization to practice medicine, puts professional activity in a different perspective.

Likewise, coexistence and relationships with new colleagues—some completely unknown and others who were former competitors for a place in the program—is an important element in this equation. Interaction between colleagues in outpatient clinics, in the operating room, on duty and in seminars is not only inevitable, but it can also help residents bear the moments of stress and emotional overload that occur during the program. Often, it is this type of connection that allows young doctors to satisfactorily reach the end of their journey toward obtaining the title of specialist after finishing the residency program.

Following the rapid expansion of information, communication, and technology resources, there seems to be no doubt that this generation has a different learning style than its predecessors.[18–20] Nevertheless, despite such autonomous learning and skill development, interpersonal relationships and collaborative work among peers remain among the most important pillars in resident training, although different programs do not always recognize them in the same way.[21]

The Particularities of Brazilian Programs

The medical field in Brazil reflects certain particularities observed in the country as a whole. Deciphering Brazilian culture has, in itself, been a constant challenge for generations of anthropologists. However, despite great regional

diversity, we can say that Brazilian culture has a more permissive tendency than many other countries, both in romantic relationships and in friendships.[22] Among other characteristics, it is a culture marked by physical proximity; for example, greetings with hugs and kisses are not unusual.

This greater permissiveness in interpersonal relations is also reflected in the work environment. In medical residencies, for example, new friends are made quickly through numerous social activities during the program, although mainly outside the formal structure. The welcoming rituals for new residents, reception parties, and other informal gatherings that occur in the first weeks of the program are good examples of this. Such events, especially among residents of the same year, become habitual and strengthen friendships and the feeling of belonging to the larger group. These feelings continue even after the residents go their separate ways as trained professionals. The testimonies of two final-year residents illustrate this dimension well:

"Towards the end of the first year, we start working together, with two first-year residents and one second-year resident. But there was always this thing about 'after our shift, let's go out and get something to eat, after our shift let's go out and...'"

"To deal with stress, I talk to my fellow residents. We have a very good group, my colleagues from the same year. We're pretty united. We try to help each other. Just yesterday, two colleagues were going through some situations and we [said] 'Let's go have some coffee together, let's go have lunch together', we help each other a lot. And this is in addition to family support"

(these and the following quotes have been translated from Portuguese).

During a medical residency program, any activity can have an educational role, even informal ones and those involving interpersonal and group relationships. It is also in these environments that information about jobs, courses, publications, and articles of interest are exchanged. As Bonet[23] notes in his study on the training of family physicians in Argentina and Brazil, it is interesting to observe the different environments in which professional socialization takes place. It is in these spaces that, more or less explicitly, the transmission of values and performance standards occurs. Thus, the group of residents becomes the space in which they share their personal stories and reveal their personalities in a more open way, without the risk of being judged by preceptors. In fact, it is when residents share their problems with the group, such as difficulties with patients or conflicts within the staff, that they receive collective support. As a second-year resident reports:

"I was having a very stressful month that was turned around by my great team. I had an episode that I guess should be called burnout, in which I found myself yelling at a patient. I understood I was in a bad environment. But my colleagues took me aside and said: 'What's going on? Let's sit down and talk.' And then I was able to get myself together, and the month ended very well."

Obviously, the group dynamics depend essentially on how these relationships are established and maintained over time. On one hand, there can be a spirit of camaraderie and cooperation, but on the other, overexposure can be dangerous because it reveals weaknesses, faults, or other behaviors that are considered out of step with the group's principles. These discrepancies, if striking, can even compromise a resident's participation in the group. This is because, despite theoretically enjoying independence, more flexible limits, and their own set of values, groups of residents assume a position of relative submission to the larger structure of the residency program. In other words, there is a permanent tension between the central core of the program and the groups of residents who, being the weak end, are "shaped" by the more consolidated and, therefore, more powerful group.

Two residents' reflections about how a colleague abandoned the program the previous year are very enlightening about this type of thinking:

"The eight of us who entered [the program] are progressing, for better or worse, by leaps and bounds, but, when necessary, we get together and hammer things out. I think the group we have now is very good, we help each other. Still, there are, of course, differences, little intrigues, but I think that, in general, it is a supportive group. There was a resident who requested a transfer to another state, and, recently, one of our oldest residents gave up, taking a test for another specialty. And there was another one who gave up at the beginning of the year and is doing another clinical specialty. These people did not feel at home in our program."

"Two colleagues ended up quitting the program. I think it was because of a number of things. I think the first one gave up because she didn't really fit in; she gave up in July. I think it's because she didn't really like what she was doing. But the second one, I think, was because of built-up pressure. She had a sick relative and the pressure her colleagues–her teammates–put on her was also great."

Even in this environment, interesting changes have occurred more recently regarding group formation. The growing and widespread use of technology has proven inexorable in all dimensions of our lives. Interpersonal and intergroup communication should be highlighted, especially during the pandemic, which has required physical distancing as a way to reduce disease transmission. Communication through platforms such as Facebook, Instagram, and applications—such as WhatsApp and Telegram—have become very popular, especially among young people. With these tools, unlimited instant text and voice messages, images, and videos can be exchanged virtually for free.

Thus, other forms of interpersonal communication had to be quickly created to ensure a sense of interactivity and belonging, which is essential for medical residency. *"They [only] had 2 weeks of residency! Many people can't make it to meetings. For example, what brought my group together was this: scheduling a happy hour to talk trash about the professors together, call each outer out, to get together, we did that a whole lot. So, now, we can very easily resolve our problems, trade shifts, and admonish each other. [The new residents] often have to go before the full group to ask to trade shifts."*

In this context, there was a rush toward online communication tools and virtual meetings. Although most of these

applications have been used routinely for several years, the lockdown has intensified their use. What was formerly resolved in person began happening online—even the most common questions. As one resident said: "*WhatsApp saved us!*" Nevertheless, she pointed out that "*it's not the same thing, but you can still feel supported.*"

The changes in these relationships seem to indicate adjustments in both form and content. They were creative adaptations implemented very quickly during an uncertain situation and an urgent need for interaction. Thus, a quick solution for a communication problem has now assumed the characteristics of professional identity formation.

Assessing the real impact of these changes will require, in addition to a longer follow-up time, a more comprehensive and careful perspective.

Conflict to Interests

The authors have no conflict of interests to declare.

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Dydrogesterone as an Option in the Medical Treatment of Endometriosis: A Brief Comment

Didrogesterona como opção no tratamento clínico da endometriose: Um breve comentário

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Dear Editor,

Endometriosis-related pain and morbidity are assumed to cause substantial impact on quality of life. Due to its chronicity, the disease is expected to be clinically managed in a long-term individualized plan, considering easy access, cost-effectiveness, acceptance, and adherence, regardless of surgical interventions, when (and if) they are necessary.

A better health-related quality of life is the main goal of the endometriosis treatment. It may be reached, individually, by relieving chronic pelvic pain, either acyclic, dysmenorrhea or dyspareunia, reducing the use of analgesics, and eventually protecting fertility. The optimized treatment of the disease often combines hormonal and surgical approaches, but the current literature[1] shows an inclination towards the use of medical strategies as first choices, ultimately postponing, or even avoiding, the need for surgery.

Aiming to inhibit the growth of endometriotic lesions, medical alternatives like selective progesterone receptor modulators, antiangiogenic factors and immunomodulators have been studied in recent years.[2] As a matter of fact, estrogens combined with progestagens or progestagens alone still seem to be the most used agents to suppress ovarian function and disease activity,[2] but there is a lack of comparative information to determine a best choice among the available molecules. Despite the different potencies to suppress the hypothalamic-pituitary-ovarian axis, progestagens in general may be similarly effective to control endometriosis. Individualization of the treatment is, then, expected to be the less expensive, with minimal adverse effects and maximal adherence.[3,4]

Dydrogesterone is a retroprogesterone characterized by high selectivity for progesterone receptors and potent progestagenic activity. According to the medical leaflet, it may be prescribed in two regimens in the treatment of endometriosis, namely: a cyclical regimen, from the 5th to the 25th days of the menstrual cycle, and a continuous one, both with daily doses ranging from 10 mg to 30 mg.[5] However, knowledge on the comparative efficacy of the two protocols is also scarce, and the recently published ORCHIDEA Study[1] brought interesting data to light.

As the primary outcome, a significant decrease in the intensity of chronic pelvic pain was observed among women receiving dydrogesterone in the daily doses of 20 mg or 30 mg. By assessing women experience after treatment cycle 6, it was also observed a reduction in the number of days of analgesics use, and the severity of dysmenorrhea, as much as improvements in sexual well-being.1 In other words, the study pointed to a comparable gain in quality of life between the two daily doses, whether in cyclical or continuous regimens, at least for the first 6 months.[4]

Regarding adverse events, the ORCHIDEA Study[1] found mild uterine bleeding as the most frequent one (1.1%), as it is expected for other progestagen-only treatment regimens, especially in the continuous model. However, despite being related to a better control of uterine bleeding, vaginal discharge and irritation, and coital well-being, than other progestagens, adverse events like headache, dizziness, abdominal pain, flatulence, and nausea may be more frequent with dydrogesterone,[6] and this must be better evaluated in future well-designed studies.

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The earlier results of the application of dydrogesterone in women with endometriosis were published more than four decades ago,[7] but such a use has been notedly explored with more interest in the last fifteen years. The study by Trivedi et al. (2007)[8] was the first to convincingly demonstrate significant improvements in pelvic pain, dysmenorrhea and dyspareunia, and a 74% rate of satisfaction in the postlaparoscopic follow-up at 3 to 6 months.

A recently published meta-analysis[9] of 19 studies (1,709 women) confronted different regimens of dydrogesterone to gonadotropin-releasing hormone (GnRH) agonists, aromatase inhibitors or anti-progestagens against endometriosis. Despite the suggestion that dydrogesterone is the most effective among them for dysmenorrhea, little could be obtained regarding definite conclusions, since the available studies are generally small, non-randomized and heterogeneous. Of note, a special view on the efficacy of dydrogesterone to treat sexual dysfunction in women with endometriosis is expected from large cohorts with long term follow ups, since the preliminary data are encouraging.[10] Following the same reasoning, the ability of dydrogesterone to prevent the increase in size of ovarian endometriomas must be reassured by robust studies.[11]

It is true that the absence of clinically relevant activity on estrogen, glucocorticoid, mineralocorticoid, or androgenic receptors may be a positive characteristic of dydrogesterone in currently recommended daily doses versus other progestagens. In addition to favoring the lower occurrence of adverse events, that pharmacological profile may be safer for women in childbearing age, in the absence of contraception.[6,12] Moreover, the good oral bioavailability and the theoretical lower risk of developing breast or endometrial cancer compared to other progestagens[6] are aspects to be considered for a first clinical treatment choice.

However, it should be argued that any progestagen may be initially considered sufficient against the symptoms of endometriosis. Then, what is expected from science is to fill the gaps by the confrontation of different progestins commonly used for treating endometriosis, such as the contemporary dienogest,[13] or the molecules from previous generations.

The information available to date is still insufficient to establish the clinical superiority of one molecule over the others. The ORCHIDEA Study[1] reported that dydrogesterone may relieve endometriosis-related chronic pelvic pain for at least 6 months of use in the regimen of preference. As aforementioned, the best progestagen for the treatment of endometriosis will be the one that is affordable, efficient, and well-accepted by each woman. Therefore, dydrogesterone is as welcome as any other progestagen in the search for the best individualized approach.

Conflict of Interests

The author has no conflict of interests to declare.

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Difficulties in the Management of Placenta Accreta Spectrum Disorders are not Confined to Low-/Middle-Income Countries: A Possible Usefulness of Simulation Training

AS dificuldades no manejo dos distúrbios do espectro da placenta acreta não se limitam aos países de baixa/média renda: Uma possível utilidade do treinamento de simulação

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Dear Editor,

Aguilera et al.[1] clearly illustrated some difficulties in the management of placenta accreta spectrum (PAS) disorders in low-/middle-income countries (LMICs), with special emphasis on the low rate of presurgical diagnosis. This naturally forced obstetric surgeons to handle "unexpected PAS disorders" on an emergency basis, and this situation may also be true in high-income countries (HICs).

The recommendation of Aguilera et al.[1] is to provide periodic education for professionals who may have to deal with PAS disorders, and we believe that this is true in both LMICs and HICs. Therefore, we believe that simulation training might become an important tool.

Simulation should cover what to do when encountering "unexpected PAS disorders" during delivery/surgery for the following reasons: first, the surgery for PAS disorders is still life-threatening.[2] A study[2] has shown that 82 deaths were associated with surgery for PAS disorders during a 5-year period in 16 countries on 3 continents. Importantly, the insufficient experience/knowledge on the part of the surgeons accounted for many of the deaths.[2]

Secondly, even though in many HICs planned surgery for diagnosed cases may now be performed by a multidisciplinary team in a well-prepared manner, presurgical diagnosis of PAS disorders is still difficult, so not all PAS disorders are diagnosed preoperatively.[2] Aguilera et al.[1] reported that approximately a half of the surgeries were performed at night; this may be an extreme, but any obstetrician, including those less experienced, might encounter it incidentally during cesarean section.

Third, PAS disorders are not common; therefore, not every obstetrician will observe cases of them in their practices. The simulation training hitherto focuses on "common procedures" such as laparoscopic surgery, vacuum or forceps delivery, or cosmetics-oriented skin closure, which are all "everyday-practice procedures". That may be the reason why simulation training for PAS disorders has been less frequently provided.

Surgery for PAS disorders requires experienced hands.[3,4] One may not be able to perform it solely based on simulation training. However, since any obstetrician might encounter a patient with an undiagnosed PAS disorder during cesarean

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section, for example, and since inexperience cannot become an excuse for an inability to handle the situation, obstetricians may benefit from simulation training on how to deal with an unexpected PAS disorder on an emergency basis.

It is beyond the scope of this letter to discuss what is required for the training and how to provide it. However, we believe that the following may become goals of the simulation training; trainees can: 1) intra-surgically diagnose the condition as placenta percreta: understand that the following two strongly indicate very severe conditions, i.e., the placenta being discernable from the uterine serosa and the presence of engorged vessels; 2) know how and when to add uterine compression sutures; 3) effectively insert an intrauterine hemostatic balloon; 4) perform compression of the abdominal aorta compression; and 5) know how and when to perform hysterectomy. Regarding hysterectomy, subtotal hysterectomy or an amputation-first procedure[3] may be sufficient, considering the emergency and depending on the situation. Simulation is expected to be performed both at an individual or team level and also scientific-meeting level, because with the management of an unexpected PAS disorder should be understood and shared by individuals, teams, and obstetric societies. Some internet-based educational tools (including ours, regarding Bakri-balloon-insertion)[5] may be useful additions to the simulation training. Bearing the final goals of simulation training in mind, one can create/modulate/devise the actual simulation program depending on the situations that are specific to each region of the world.

The good patient outcomes shown by Aguilera et al.[1] have impressed us: lower levels of massive bleeding, lower rate of surgical complications, and, importantly, no maternal deaths. The authors[1] considered that this was due to "experienced hands": the obstetric surgeons in their hospital had no choice but to perform many difficult surgeries; thus, they were used to performing cesarean hysterectomy for PAS disorders. However, we believe that no surgeon begins their career with "experienced hands". Patients may die during surgery for PAS disorders. One may not have experienced hands, but, depending on the situation, be obliged to perform surgery for PAS disorders regardless of this. Simulation training may be of great help, and much discussion is needed as to how, when, and to whom the training should be provided.

Conflict of Interests

The authors have no conflict of interests to declare.

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FEBRASGO POSITION STATEMENT

Screening, diagnosis and management of hyperthyroidism in pregnancy

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The National Commission Specialized in High Risk Pregnancy of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) and the Thyroid Department of the Brazilian Society of Endocrinology and Metabology (SBEM) endorse this document. The production of content is based on scientific evidence on the proposed theme and the results presented contribute to clinical practice.

Key points

- The physiological changes of pregnancy that interfere with the production, release and availability of the active form of hormones interfere with the diagnosis and management of hyperthyroidism during pregnancy.
- Gestational thyrotoxicosis or transient hyperthyroidism, the most common cause of hyperthyroidism in pregnancy, is related to the increased production of human chorionic gonadotropin (hCG) and may persist until week 18.
- Untreated hyperthyroidism can have fetal, neonatal, and maternal effects.
- The obstetrician must be aware of the fetal, neonatal and/or maternal risks caused by the drug treatment of hyperthyroidism during pregnancy.
- Graves' disease (GD) is the main pathology etiologically associated with hyperthyroidism in pregnancy.
- The diagnosis of hyperthyroidism in pregnancy is preferably made by measuring free thyroxine (FT4) and thyroid-stimulating hormone (TSH).
- The measurement of anti-TSH receptor antibody (TRAb) allows the diagnosis of GD, which is an important cause of hyperthyroidism.
- Propylthiouracil (PTU) is the first-choice drug for the treatment of hyperthyroidism in pregnancy in the first trimester, while methimazole (MMZ) is used in the second and third trimesters and puerperal period.
- The use of antithyroid drugs (ATD) is allowed during breastfeeding.
- Radioactive iodine (^{131}I) should not be used during pregnancy or breastfeeding.

Recommendations

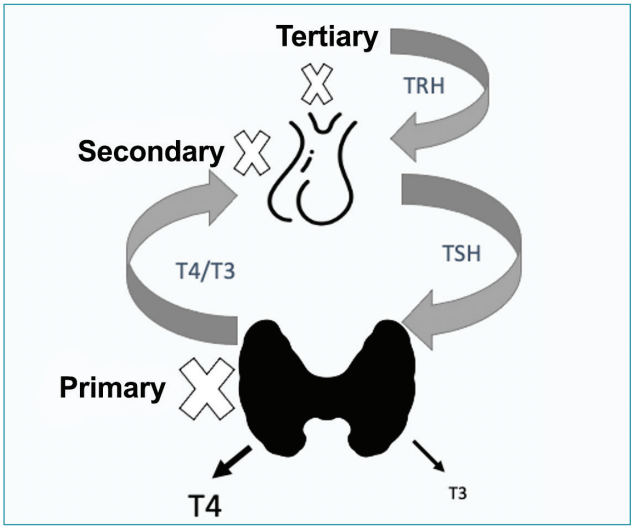
- The diagnosis of hyperthyroidism should be confirmed when TSH is suppressed (<0.1 mUI/L) and FT4 is above the upper limit of normality of the lab kit used.
- The use of ATDs for the treatment of gestational thyrotoxicosis or subclinical hyperthyroidism is not recommended.
- In case of suspicion of gestational thyrotoxicosis, whenever possible, GD should be ruled out with the measurement of TRAb.
- All overt hyperthyroidism should be treated during pregnancy, given the fetal, neonatal and maternal risks of the disease.
- The doses of ATDs (PTU and MMZ) should be the lowest possible to maintain FT4 levels at the upper limit of normality of the lab kit used, considering the passage of these medications through the placenta and the risk of fetal hypothyroidism.
- The recommended doses of PTU are 200-400 mg daily, divided into three daily intakes. Propylthiouracil has less teratogenicity and greater side effects than MMZ. It is preferably used in the preconception period and in the first trimester of pregnancy. Methimazole, in turn, is recommended in doses of 10-30 mg daily, taken in a single dose. Methimazole is preferably used in the second and third trimesters of pregnancy, and during breastfeeding.
- Pregnant women with hyperthyroidism should be followed up in high-risk antenatal care. Barring other complications, they should have follow-up appointments every other week until week 28 and weekly visits from then until delivery.
- Treatment of the hyperthyroid phase of postpartum thyroiditis with ATDs is not recommended.

Background

During pregnancy, there is an increase in the stimulation of the hypothalamic-pituitary-thyroid axis through different mechanisms:[1]

- Increase in the serum concentration of estrogens, accompanied by an increase in thyroid hormone binding globulin (TBG - thyroxine binding protein) and consequent reduction in the free fractions of thyroid hormones (THs);
- Greater iodine clearance;
- Greater degradation of THs by placental deiodinases;
- Increase in the serum concentration of hCG that stimulates the thyroid tissue by cross-reacting with the TSH receptor, which can generate goiter and transient gestational hyperthyroidism.

This stimulus to the axis explains why pregnant women, especially in the first trimester, have lower TSH concentrations than non-pregnant women.[1] Metabolic demands are greater in the first trimester of pregnancy, a critical period for the occurrence of thyroid dysfunctions, given the changes in the stimulation of the thyroid gland. All changes described in the physiology of the hypothalamic-pituitary-thyroid axis ensure the supply of TH to the fetus, especially in the period when the fetal thyroid is not functionally mature yet. Although the development of the gland begins at week 8, it functions fully only between weeks 18-20, therefore, until that moment, the fetus is totally dependent on the placental transfer of maternal THs. There is a compensatory mechanism via feedback between the thyroid, pituitary and hypothalamus that regulates glandular functioning. Knowing this mechanism helps to find the cause of a possible dysfunction (Figure 1).



TRH: thyrotropin releasing hormone; TSH: thyroid stimulating hormone; T4: thyroxine; T3: triiodothyronine.
Source: prepared by the Working Group for Thyroid Dysfunctions in Pregnancy (Brazilian Society of Endocrinology and Metabology – SBEM).

Figure 1. Schematic representation of the hypothalamic-pituitary-thyroid axis indicating the types of hypothyroidism

Due to the previously mentioned physiological changes during pregnancy, the reference values for TSH, FT4 and total T4 (T4T) must be adjusted.[2] In relation to TSH, this means that if we reduce 0.4 mU/L of the lower reference limit stated by the lab kit, the TSH level for the diagnosis of hyperthyroidism would be <0.1 mU/L for most laboratories. This is a recommendation from the American Thyroid Association (ATA) and proved to be adequate as a determinant of the specific reference range for pregnant women in a recent study of a healthy population in Rio de Janeiro.[2,3] Thyrotoxicosis is a clinical syndrome characterized by hypermetabolism and hyperactivity resulting from exposure to excessive amounts of THs. The main cause of thyrotoxicosis is the hyperfunction of the thyroid gland, called hyperthyroidism, which is characterized in the laboratory by a reduction in TSH levels with or without an increase in TH concentration.[4]

How can hyperthyroidism present during pregnancy and what are its main etiologies?

Grave's disease of autoimmune etiology is the most common pathological cause of hyperthyroidism in pregnancy, representing 95% of cases. It occurs in 0.4-1% of women before pregnancy and in approximately 0.2% during pregnancy. Gestational transient thyrotoxicosis (GTT) or transient gestational hyperthyroidism, is the main differential diagnosis of GD and the most common clinical condition, occurring in up to 5% of pregnancies and limited to the first half of pregnancy. This condition is characterized by a reduction in TSH, with or without an increase in FT4. Elevated hCG at the beginning of pregnancy is the cause of thyroid stimulation, causing mild and transient hyperthyroidism, which may be associated with hyperemesis gravidarum. There is a greater risk for GTT in conditions of high hCG concentration, such as twin pregnancy, hydatidiform mole, and choriocarcinoma.[4]

Other causes of hyperthyroidism in pregnancy are toxic adenoma, subacute thyroiditis, multinodular or iatrogenic goiter due to excessive ingestion of THs.[2,5] Hyperthyroidism can manifest itself in pregnancy as:

- **Overt hyperthyroidism**, characterized by reduced TSH and elevated TH levels, especially FT4;
- **Subclinical hyperthyroidism**, characterized by reduced TSH and normal THs.

The possible scenarios in pregnant women with hyperthyroidism are correlated with the time of diagnosis, previous and/or current treatment and the quality of metabolic control (Chart 1) (Figure 2).

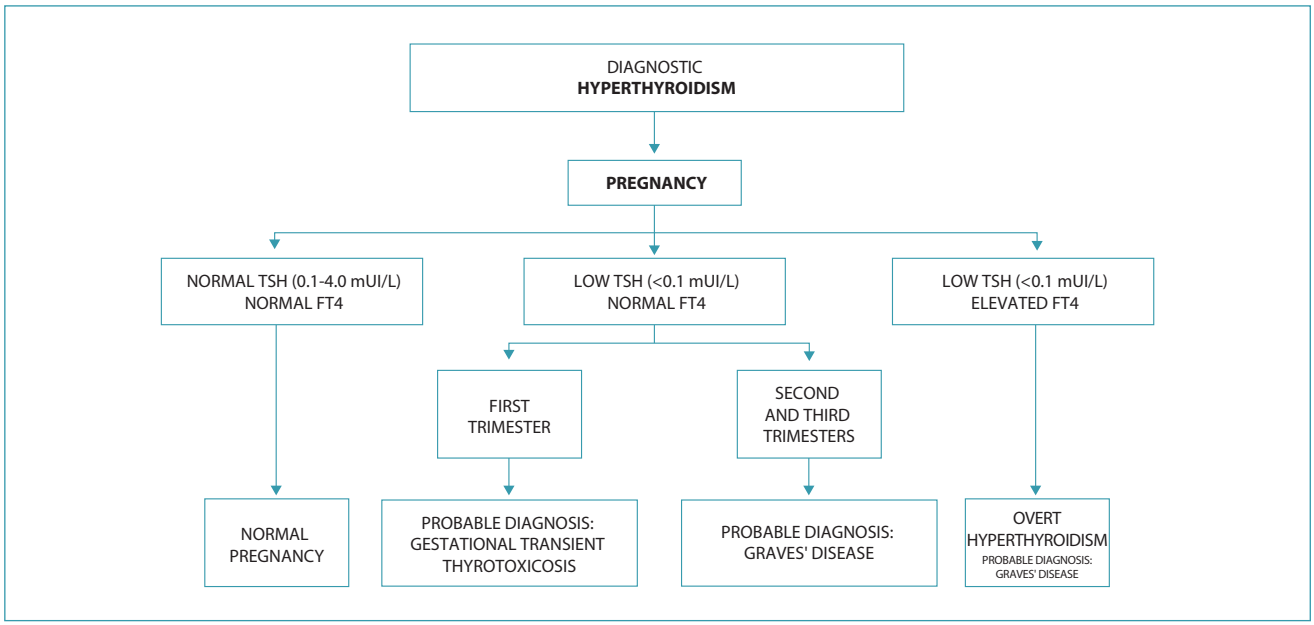
Hyperthyroidism with diagnosis prior to pregnancy

- *GD in remission:* when the pregnant woman was diagnosed with GD, underwent clinical treatment

Chart 1. Diagnoses related to hyperthyroidism in pregnancy that may impact clinical management

	Diagnosis	TSH	T4L	TRAB
Hyperthyroidism diagnosed prior to pregnancy	GD in remission	Normal	Normal	Not necessary
	GD after treatment with RAI or surgery, on FT4 therapy	Normal	Normal	Request
	Controlled GD in use of low doses of ATD	Normal	Normal	Request
	Uncontrolled GD on high doses of ATD	Low	Elevated	Request
	Other causes of hyperthyroidism (TMNG or TNG	Normal or reduced	Normal or elevated	Not necessary
Hyperthyroidism diagnosed in pregnancy	Subclinical hyperthyroidism Probable diagnosis: GTT	<0.1 mU/L	Normal	Request only if there is suspicion of GD
	Clinical hyperthyroidism Probable diagnosis: GD	<0.1 mU/L	Elevated	Request

TSH: thyroid stimulating hormone; FT4: free thyroxine; T4T: total thyroxine; T3T: total triiodothyronine; GD: Graves' disease; RAI: radioactive iodine therapy; LT4: levothyroxine; ATD: antithyroid drug; TMNG: toxic multinodular goiter; TNG: toxic nodular goiter; GTT: gestational transient thyrotoxicosis
Source: Prepared by the Working Group for Thyroid Dysfunctions in Pregnancy (CNEGAR and Brazilian Society of Endocrinology and Metabolism – SBEM).



TSH: thyroid stimulating hormone; FT4: free thyroxine.
Source: Prepared by the Working Group for Thyroid Dysfunctions in Pregnancy (CNEGAR and Brazilian Society of Endocrinology and Metabolism – SBEM).

Figure 2. Diagnostic hyperthyroidism

with an ATD and is in remission after discontinuing the drug, maintaining normal thyroid function. This patient should have her thyroid function monitored during pregnancy and if normal, there is no need for additional fetal testing or monitoring. The postpartum period requires special care given the higher risk of GD recurrence and postpartum thyroiditis.

- *GD after treatment with ^{131}I or surgery:* when the patient needs replacement with levothyroxine. Monitoring of TRAb is necessary, as it may be elevated even after treatment, which increases the risk of fetal hyperthyroidism via placental passage.
- *GD using low doses of ATD:* when the patient being treated for GD with low doses of ATD – 5-10 mg of MMZ or 50-200 mg of PTU – is under control and wants to become pregnant or is pregnant. Antithyroid drugs may be withheld depending on recurrence risk factors.
- *GD using high doses of ATD:* when the patient has difficulty controlling hyperthyroidism, definitive therapy with ^{131}I or surgical excision may be recommended before pregnancy. If she becomes pregnant inadvertently, the recommendation is to maintain the drug.
- *Patients with hyperthyroidism due to other causes such as toxic multinodular or nodular goiter:* in this situation, definitive treatment is suggested before pregnancy and if the patient becomes pregnant before that, it is recommended to maintain drug therapy without the need for TRAb monitoring.

Hyperthyroidism diagnosed during pregnancy

- *Subclinical hyperthyroidism* presents with TSH < 0.1 mIU/L and normal FT4, and the diagnosis is laboratory confirmed. The patient should not be treated with ATD and the differential diagnosis between GTT and GD is important.
- *Overt hyperthyroidism* presents with TSH < 0.1 mIU/L and elevated FT4. The most likely diagnosis is GD. It is important to define the etiology with the measurement of TRAb to evaluate treatment and perform fetal monitoring.

Which symptoms in pregnant women should make the health professional suspect hyperthyroidism?

The signs and symptoms of hyperthyroidism are linked to a clinical state of hypermetabolism. A hypermetabolic state should be suspected when the pregnant woman has palpitations and/or tachycardia, irritability, aggressiveness, restlessness, fine tremors, sweating, hot skin, and weight loss or weight gain less than expected. Evidently, as these are non-specific symptoms, they can go unnoticed, particularly during pregnancy. More specific findings include goiter, ophthalmopathy and pretibial myxedema suggestive of GD.[6,7]

Which TSH and FT4 values make the diagnosis of hyperthyroidism?

The laboratory diagnosis of hyperthyroidism during pregnancy is defined as reduced TSH and elevated FT4 levels using specific reference values for pregnant women.[8] Note that reference values for thyroid function during pregnancy are different because of the typical physiological changes of pregnancy and the characteristics of laboratory assays used in this evaluation. Furthermore, iodine sufficiency in the population and race can also influence these parameters. Specialist societies recommend that reference values for pregnant women are determined for each population according to each trimester and using specific assays.[2,6] In case this reference curve is unavailable, the following can be considered:

TSH

By knowing that the TSH is low in the first trimester of pregnancy given the high concentrations of hCG and there are difficulties in obtaining a standardization, the lower limit of normality can be considered as 0.1 mIU/L.[7,9]

From the second trimester onwards, TSH concentrations increase slightly, and the lower limit of normality in pregnant women can be considered the same used for non-pregnant individuals.[2] Patients diagnosed with GD hyperthyroidism have TSH < 0.1 mU/L and often undetectable TSH.

T4T

The T4T concentration increases progressively until week 16, when it stabilizes influenced by the increase in TBG. From that period until delivery, consider 1.5 times the reference values provided by the laboratory for non-pregnant people. Therefore, a high concentration of T4T is expected during a normal pregnancy, that is, values at the upper limit or even above the usual reference values.[2,6,10]

FT4

The gold standard for dosing FT4 is by liquid chromatography mass spectrometry or equilibrium dialysis or ultrafiltration, which eliminate any interference.[2] However, these methodologies are costly and not available in most laboratories. The widely used automated immunoassays suffer interference from excess TBG, particularly from the second trimester, providing false low FT4 values.

Although there are difficulties both physiological of pregnancy and related to variations imposed by the laboratory method used, the best option for the diagnosis of overt hyperthyroidism in pregnant women is through elevated concentrations of FT4 above the upper limit of the laboratory reference considered, in conjunction with low or suppressed TSH.

Should GTT be treated with ATDs?

Antithyroid drugs are not recommended for the treatment of GTT, because in this condition, spontaneous normalization of TH concentrations occurs until the end of the first trimester and may persist until week 18 of pregnancy, and these drugs are associated with congenital malformations and fetal hypothyroidism.[2]

How should the management in the face of a diagnosis of subclinical hyperthyroidism be?

Pregnant women with subclinical hyperthyroidism have TSH suppressed and thyroid hormone levels (FT4) within the reference value for pregnant women. The most important issue is to define the differential diagnosis between GTT and other forms of mild hyperthyroidism, among which the most common is GD. Whenever possible, this initial follow-up should be performed by the obstetrician in partnership with the endocrinologist. Careful anamnesis and physical examination with emphasis on GD stigmata (goiter and ophthalmopathy) should be performed, and the TSH and FT4 dosage should be repeated. The measurement of TRAb and T3 can help in etiological diagnosis. In GTT, the clinical picture is generally milder and may overlap

with signs and symptoms of hyperemesis gravidarum (nausea and vomiting in early pregnancy with weight loss > 5%, dehydration and ketonuria); there is no previous history of thyroid disease and no GD stigmata such as goiter and ophthalmopathy.[9] However, GD can also manifest in a milder form during pregnancy, including subclinical hyperthyroidism; in this case, the patient usually has a previous history of thyroid disease, with or without a goiter and ophthalmopathy.

The presence of circulating TRAb confirms GD.[9]

What subsidiary exams should be requested to define the etiologic diagnosis of hyperthyroidism?

The etiological diagnosis of hyperthyroidism during pregnancy is essential, because it requires different treatments and has different prognoses (Chart 2). The main diagnostic test is the TRAb measurement, particularly in the case of overt hyperthyroidism, since it is sensitive and specific for GD. In the absence of TRAb, an important increase also in T3 concentrations (total or free) in relation to T4 suggests GD. The level of T3 is slightly elevated in <20% in women affected by GTT.[10,11] Thyroid ultrasound may be useful when the etiologic suspicion is a toxic multinodular goiter or toxic adenoma (Plummer's disease).[10,11] Scintigraphy is absolutely contraindicated in pregnancy. It is important to warn that the use of biotin should always be suspended before blood collection for these measurements, as most tests to assess thyroid function suffers interference, which mimics clinical hyperthyroidism with TSH suppression, FT4 elevation and positive TRAb.[12] It is also recommended to stop taking vitamins at least 48 hours before blood collection.

Chart 2. Differential diagnosis between GD and GTT

	Graves Disease	TTG
TRAb	Positive	Negative
T3	Elevated	Normal
T3:T4	Elevated	Low
T4L	Greatly increased	Slightly increased
TSH	Suppressed	Low or suppressed

GTT: gestational transient thyrotoxicosis; GD: Graves' disease; TSH: thyroid stimulating hormone; TRAb: thyrotropin receptor antibody; T3: triiodothyronine; FT4: free thyroxine; T3:T4: ratio between T3 and T4 concentrations
Source: Prepared by the Working Group for Thyroid Dysfunctions in Pregnancy (CNEGAR and Brazilian Society of Endocrinology and Metabology – SBEM).

Which patients with hyperthyroidism should be treated during pregnancy?

Overt hyperthyroidism is associated with unfavorable outcomes in pregnancy if left untreated. Poor thyrotoxicosis control is associated with fetal loss, gestational hypertension, prematurity, low birth weight, intrauterine growth restriction, thyrotoxic crisis, and maternal congestive heart failure.[13] Patients with overt hyperthyroidism should be treated, while those with subclinical hyperthyroidism and/or GTT should undergo symptomatic treatment and monitoring.[2]

How should care for patients diagnosed with subclinical hyperthyroidism be?

Since there is no evidence of worsening of maternal or fetal outcomes in pregnant women with subclinical hyperthyroidism,[11,14] ATD treatment is not recommended for them. Although worsening or progression to overt hyperthyroidism during pregnancy is uncommon, TSH and FT4 should be monitored every four weeks in order to identify patients who progress unfavorably.[2] The measurement of TRAb is important for the etiological diagnosis of subclinical hyperthyroidism. In case of positive TRAb, if concentrations are greater than three times the upper limit of normality, a new measurement should be taken between weeks 18-22, when the fetal thyroid is fully formed. Monitoring of TRAb should be performed as it is known to cross the placenta.[2] In cases of GD, special care should be taken after delivery given the higher recurrence of the disease in the postpartum period, and the patient should be referred to an endocrinology service for monitoring thyroid function during this period. Gestational transient thyrotoxicosis is another cause of subclinical hyperthyroidism in pregnancy, so thyroid function (TSH, FT4) should be monitored every four weeks until normalization occurs, usually around weeks 14-18. After normalization of thyroid function and if there are no associated diseases, the pregnant woman can undergo regular follow-up. Special attention should be taken when there is an association with hyperemesis gravidarum; in these cases, control of vomiting and intravenous hydration may be needed. Some cases may require hospitalization.[2,15] In cases of tachycardia with discomfort for the pregnant woman and elevated FT4, symptomatic drugs, such as beta-blockers, can be used. The medication of choice is propranolol, administered in doses of 10-40 mg every eight hours for a short time, until the FT4 level is normalized.[2] As prolonged use of propranolol during pregnancy has been associated with fetal bradycardia, neonatal hypoglycemia and fetal growth restriction, it should be used for the shortest possible time.[16]

What preconception care should be taken in women with hyperthyroidism?

Pregnancy planning should be discussed extensively between a woman of childbearing age with hyperthyroidism and her physician. It is important to inform the teratogenic and obstetric risks of hyperthyroidism, as well as its complex treatment during pregnancy. The institution of treatment is recommended, and the

woman should be in stable euthyroidism on low doses of ATD (5-10 mg daily of MMZ or 50-200 mg of PTU) before considering conception. This state is considered when two consecutive tests with a minimum interval of one month in between show euthyroidism.[2,6] Particularly in conditions where the disease is difficult to control with ATDs, definitive treatment with ^{131}I or thyroidectomy should be offered prior to conception. It is important to remember that in cases of treatment with ^{131}I, even if control of hyperthyroidism is achieved in the short/medium term, there is a high chance of immunological worsening with high titers of circulating TRAb in response to therapy, which may last for a few months. Women who have been treated for at least six months with low doses of ATDs – 5-10 mg/day of MMZ or 100-200 mg/day of PTU – and are well controlled may have medication discontinuation considered in the first trimester, in view of the teratogenic potential of these drugs, provided they are regularly monitored for thyroid function.[7,17]

What should be the type of antenatal care follow up in pregnant women with hyperthyroidism?

Pregnant women with overt hyperthyroidism, in view of the complexity of medication adjustment and maternal and fetal risk, should be followed up in high-risk antenatal care. In this follow-up, permanent interaction between the obstetrician and endocrinologist is necessary, as well as special monitoring of the fetus.[2,6]

How should the drug treatment of hyperthyroidism diagnosed in pregnancy be?

Propylthiouracil and MMZ are the drugs available for the treatment of hyperthyroidism during pregnancy. Because of adverse effects, especially the possibility of congenital malformations and fetal hypothyroidism, it is recommended to use the lowest possible dose, keeping the mother slightly thyrotoxic in order to preserve fetal thyroid function, as ATDs cross the placental barrier.[10,18] The dose depends on the level of FT4. Doses vary between 5-30 mg daily of MMZ (average of 10-20 mg), in a single daily dose, and between 100-600 mg of PTU daily (average of 200-400 mg), divided into two to three daily intakes.[2] Initial doses of ATDs should be proportional to the severity of thyrotoxicosis, as measured by the FT4 level. Chart 3 shows a suggestion of doses for MMZ and PTU adapted from the ATA guideline for the treatment of hyperthyroidism and thyrotoxicosis for non-pregnant women and adjusted to doses recommended for pregnant women (Figure 3).[5] Propylthiouracil is the drug of choice when therapy is required up to week 16 of pregnancy, given the lower risk and lower severity of associated congenital malformations. In case it is necessary to maintain the ATD after week 16, PTU can be replaced by MMZ because of the higher risk of hepatotoxicity attributed to PTU. However, the change of medication can lead to uncontrolled hyperthyroidism. Thus, each pregnant woman should be evaluated individually to decide on the need to change medications. The dose equivalence between MMZ and PTU is 1:20 (5 mg of MMZ is equivalent to 100 mg of PTU).[2] If treatment begins after week 16 of pregnancy, it is recommended to start therapy with MMZ.[2] There is a tendency for improvement of GD during pregnancy due to immunological changes of this period and the increase in the TBG binding hormone; for this reason, ATD doses need to be reviewed at each visit, and a 30-50% dose reduction is recommended when FT4 level reaches the upper limit of normality.[5] The use of ^{131}I is contraindicated during pregnancy, as it crosses the placental barrier and causes fetal hypothyroidism and also by exposing the fetus to radiation. Thyroidectomy during pregnancy may be indicated if there are serious adverse effects related to ATDs and when the therapeutic goals of controlling hyperthyroidism cannot be achieved even with high doses of ATDs (>40 mg of MMZ or 600 mg of PTU).[2] If necessary, the best time for thyroidectomy is the second trimester of pregnancy. Preparation can be performed with beta-blockers. Special care should be taken in pregnant women with very high TRAb (>3 times the reference value), as the reduction in TRAb after surgery is slow and, even with successful control of maternal hyperthyroidism, there may still be a risk of fetal hyperthyroidism, requiring fetal monitoring.[2]

How should the treatment be for women who were already medicated for hyperthyroidism and get pregnant?

For patients at low risk for GD recurrence who are euthyroid and get pregnant while on low doses of ATDs (5-10 mg MMZ or 50-200 mg PTU), discontinuation of ATDs and observation of thyroid function are suggested. It is important to take into account other factors associated with disease recurrence, such as high levels of TRAb, use of ADT for less than six months, suppressed TSH while using ATD, voluminous goiter, presence of ophthalmopathy, and the need for higher doses than 5-10 mg MMZ or 50-200 mg PTU (Chart 4). In cases of high risk for recurrence, the suggestion is to maintain PTU or change MMZ to PTU in the 1:20 ratio. Hyperthyroidism may improve during pregnancy, leading to the need for lower doses of ATDs or even discontinuation of medication. For this reason, dose adjustments based on serial laboratory evaluations should be made throughout pregnancy.[2]

Chart 3. Suggested MMZ and PTU doses for the start of treatment in pregnant women according to FT4 level

FT4 (number of times the upper normal limit)	METHIMAZOLE MG	PROPYLTHIOURACIL MG
Up to 2 times	5-10	100-200
2-3 times	10-20	200-400
Above 3 times	20-30	400-600

FT4: free thyroxine.
Source: Adapted from Ross et al.[5]

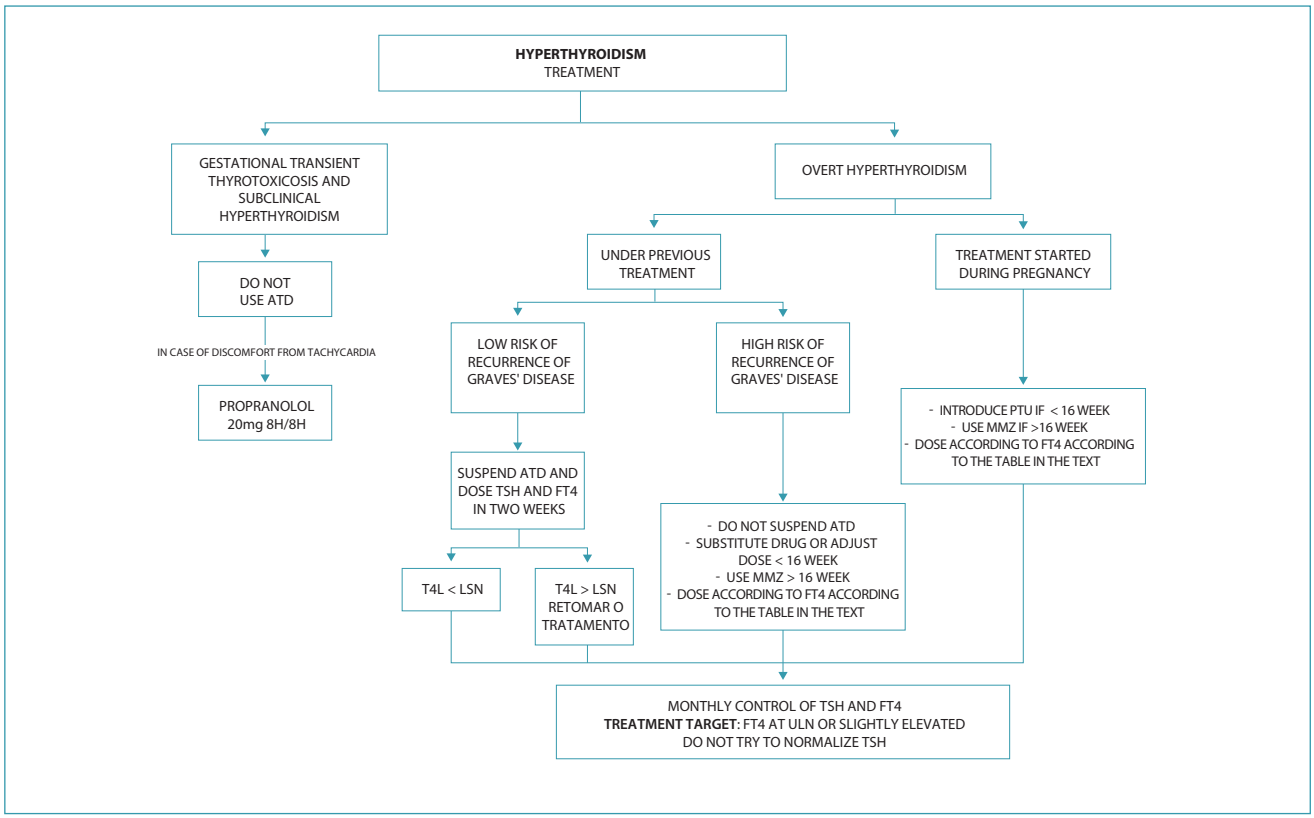
Chart 4. High-risk criteria for GD recurrence after withdrawal of ATDs in pregnant women

Elevated TRAb levels (3 times the upper limit of normal)
Use of ATDs for less than 6 months
TSH suppressed in use of ATDs
Voluminous goiter
Graves' ophthalmopathy
Need for higher doses than 5-10 mg of MMZ or 50-200 mg of PTU

MMZ: methimazole; PTU: propylthiouracil; GD: Graves' disease; ATDs: antithyroid drugs; TRAb: anti-TSH receptor antibody; TSH: thyroid stimulating hormone.
Source: Prepared by the Working Group for Thyroid Dysfunctions in Pregnancy (CNEGAR and Brazilian Society of Endocrinology and Metabology – SBEM).

What are the maternal-fetal adverse effects of antithyroid drug treatment?

Antithyroid drugs are the mainstay of hyperthyroidism treatment in pregnancy. The most used drugs are PTU and MMZ, and both fundamentally interfere in the process of thyroid hormone formation, inhibiting its synthesis. However, they can produce undesirable effects. Side effects occur in 3-5% of mothers and are mostly eruptive allergic reactions or gastrointestinal symptoms, which can be controlled with symptomatic drugs (antihistamines) or by switching between ATDs. However, in 0.1-0.15%, they can lead to serious effects such as agranulocytosis and liver failure. These two effects are an absolute contraindication for the use of ATDs and if they occur with the use of one drug, switching to the other is not recommended. The patient should be urgently referred to a specialized service, and thyroidectomy can be considered, ideally in the second trimester. All pregnant women using ATDs should be warned that in the presence of flu-like signs and/or symptoms such as fever and odynophagia, there is a possibility of agranulocytosis, and blood count should be collected, ATD discontinued and antibiotic therapy started immediately if the diagnosis is confirmed.[17,19] The effects on the fetus are due to the transplacental



TSH: thyroid stimulating hormone; FT4: free thyroxine; ATD: antithyroid drug; PTU: propylthiouracil; MMZ: methimazole; ULN: upper limit of normality. Source: Prepared by the Working Group for Thyroid Dysfunctions in Pregnancy (CNEGAR and Brazilian Society of Endocrinology and Metabology – SBEM).

Figure 3. Hyperthyroidism - treatment

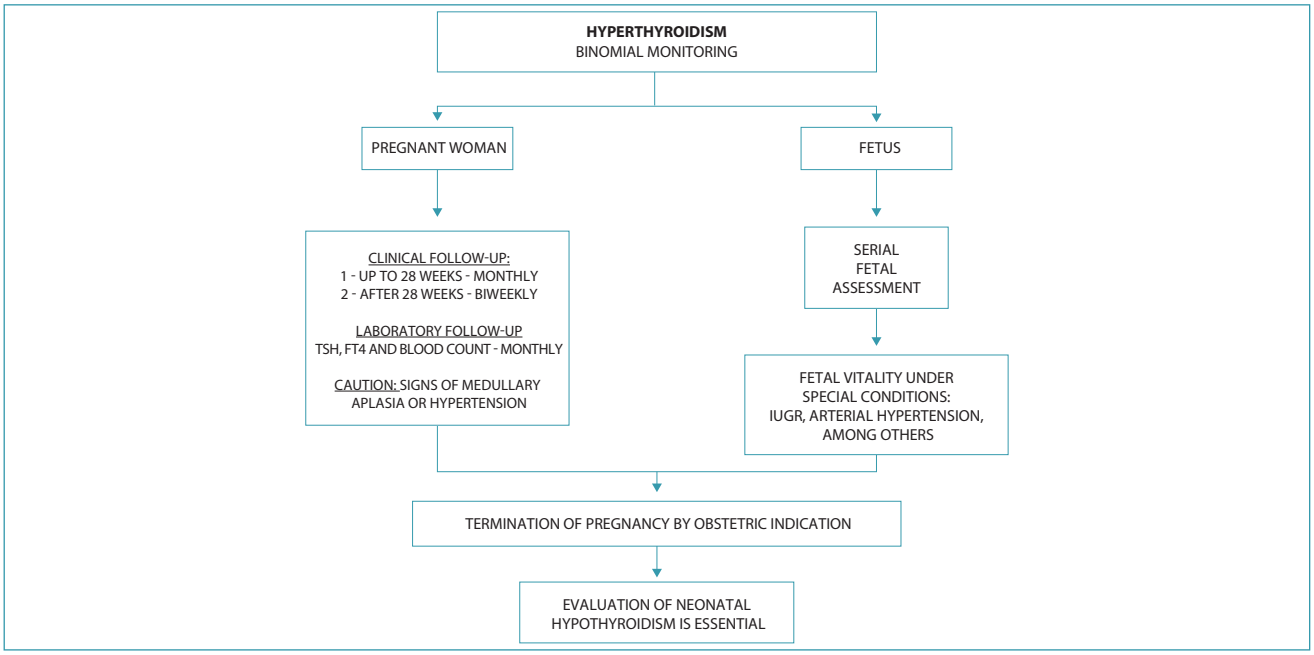
passage of these medications. In the first trimester, we are faced with teratogenic effects. Methimazole leads to complications in 2-4% of pregnancies. The best known malformation is aplasia cutis, although other malformations have been described, namely cloacal and esophageal atresia, defects in the formation of the abdominal wall and malformations of the eyes, heart and urinary system. Propylthiouracil can also lead to fetal malformations in 2-3%. The malformations we can find are cervical cysts and male urinary tract abnormalities. Note that malformations related to PTU are usually less severe than those triggered by MMZ.[19-21] In addition to interfering with fetal formation, when these medications cross the placental barrier, they can interfere with fetal thyroid hormone synthesis, causing fetal hypothyroidism. Thus, precise management of these medications during pregnancy is essential. The dose of ATDs should be the minimum necessary. Propranolol can also be used to control the symptoms of hyperthyroidism. If this use is extended over long periods, it can cause fetal growth restriction, fetal bradycardia and neonatal hypoglycemia.[21]

How to monitor the treatment for hyperthyroidism and what is the laboratory goal to be achieved?

The goal during treatment of hyperthyroidism in pregnancy is to maintain FT4 concentrations at the upper limit of normal or slightly elevated. This way, excessive treatment with ATDs will be avoided and consequently, fetal hypothyroidism. Monitoring should be done every 2-4 weeks until the pregnant woman is on a stable dose of ATD. Then, follow-up can be done every four weeks. The TSH can remain low or undetectable for weeks, even after FT4 has decreased. Therefore, TSH should not be a follow-up parameter during treatment. Hyperthyroidism in pregnant women will be well controlled in the presence of FT4 at the upper limit of normal (or slightly elevated), even with TSH still low.[2,8] Patients with GD should measure TRAb in the first trimester. If concentrations are greater than three times the upper limit of normal, a new measurement should be taken between weeks 18-22, when the fetal thyroid is fully formed. The TRAb level should be monitored as it is known to cross the placenta. If high TRAb titers persist, fetal goiter assessment and monitoring should be performed given the higher risk of fetal and neonatal hyperthyroidism. If titers become negative or decrease, the risk of maternal-fetal complications is lower.[2,22]

How and at what intervals should maternal-fetal follow-up be performed?

As a general rule, multidisciplinary follow-up involving the obstetrician and endocrinologist in high-risk antenatal care is advised. Appointments should be carried out every other week until week 28, and weekly until delivery. The fetus should be monitored for formation, growth, and signs of hypothyroidism or hyperthyroidism throughout pregnancy. After week 28, in specific situations – such as fetal growth restriction – it is recommended to include periodic assessments of fetal vitality (Figure 4).[5,6]



TSH: thyroid stimulating hormone; FT4: free thyroxine; IUGR: intrauterine growth restriction.
Source: Prepared by the Working Group for Thyroid Dysfunctions in Pregnancy (CNEGAR and Brazilian Society of Endocrinology and Metabology – SBEM).

Figure 4. Hyperthyroidism – Monitoring the binomial

How to diagnose and manage fetal hyperthyroidism or hypothyroidism?

Fetal hyperthyroidism typically manifests with persistent fetal tachycardia (FHR > 170 bpm) for more than 10 minutes in pregnant women with GD. Other fetal clinical signs can be: fetal growth restriction, fetal goiter, accelerated bone maturation and in more extreme cases, congestive heart failure and hydrops. Fetal hyperthyroidism is triggered by the passage of TRAb through the placental barrier, excessively stimulating the formation and release of THs from the fetus. These pregnant women must be monitored in a particular way by an experienced fetal medicine team. This condition can even extend to the neonatal period, and there must be strict monitoring by the obstetrician and neonatologist. A condition that should be considered as high risk is the scenario of women with a previous diagnosis of GD who underwent ^{131}I or thyroidectomy prior to pregnancy. As these women no longer use ATDs, they may continue to produce TRAb, causing fetal and/or neonatal hyperthyroidism.[6,23,24] Fetal hypothyroidism is usually manifested by fetal goiter, as a result of the passage of ATDs or rarely, by the passage of inhibitory TRAb, which would decrease the production of THs by the fetus. The pregnant woman must be accompanied by an experienced fetal medicine team. Cordocentesis or the measurement of THs in amniotic fluid for the diagnosis of fetal hypothyroidism is extremely controversial, as is the administration of levothyroxine in amniotic fluid.[6] In case of massive fetal goiter, the need for EXIT (ex-utero intrapartum treatment) at delivery should be discussed.

How to prescribe treatment for hyperthyroidism during lactation?

Antithyroid drugs are secreted into breast milk, although in very low concentrations. Breastfeeding is safe with doses up to 20 mg/day of MMZ and 450 mg/day of PTU.[2] Antithyroid drugs should be taken immediately after breastfeeding.[10] The preference for MMZ is due to the side effects associated with PTU.[5] Monitoring the infant's thyroid function is not necessary, as there is no evidence that ATD use leads to hypothyroidism or impairment in the child's growth and neurocognitive development.[25] Since there are not enough data showing that hyperthyroidism interferes with lactation, it should be treated according to its diagnosis.[2] Treatment with ^{131}I can only be indicated after breastfeeding has been discontinued for at least three months and breastfeeding should not be resumed,[26] as the concentration of radioactive iodine in the mammary gland may increase the risk for future breast cancer.[27] Propranolol can be used during breastfeeding without risk to the child or interference with lactation ability. However, atenolol is not recommended as it is secreted into breast milk, causing bradycardia and hypoglycemia in the infant.[28]

How should care to postpartum women with thyrotoxicosis be?

Thyrotoxicosis that appears in the postpartum period is often caused by postpartum thyroiditis (PPT), defined as autoimmune thyroid dysfunction in the first year postpartum, excluding GD.[8,25] Another possibility is the recurrence or activation of GD in the postpartum period. It is important to differentiate between these two main causes. The incidence of PPT is extremely variable, reaching about 15% of cases.[2] It most often affects women with a previous history of PPT, who have positive antithyroid antibodies before pregnancy (under treatment with levothyroxine or in euthyroidism), with another associated autoimmune disease (insulin-dependent diabetes, rheumatoid arthritis, etc.) or even with GD in remission.[29] The typical clinical picture begins with a toxic phase, clinical and laboratory hyperthyroidism, followed by hypothyroidism and later recovery of thyroid function. Thyroid function shows suppressed TSH and elevated FT4 level, defining thyrotoxicosis (toxic phase) and the presence of antithyroid antibodies, particularly the antithyroperoxidase (anti-TPO) antibody, characterizes PPT. The thyrotoxicosis phase is usually mild and self-limiting, lasting from one to three months, when the patient may experience palpitations, tremors, fatigue and nervousness. At this stage, it is important to differentiate it from GD triggered in the postpartum period (Figure 1) (Chart 5).

Chart 5. Differential diagnosis between postpartum thyroiditis and Graves' disease

	Postpartum thyroiditis	Graves disease
Onset after delivery	<3 to 6 months	>3 to 6 months
TRAb	Negative	Positive
Anti-TPO	Present	May be present
T3:T4	Low (T4 >>T3)	Elevated (T3>>T4)
Thyroid vascularization	Normal	Increased

TRAb: anti-TSH receptor antibody; anti-TPO: antithyroperoxidase antibody; T3:T4: ratio of triiodothyronine and thyroxine concentrations.
Source: Prepared by the Working Group for Thyroid Dysfunctions in Pregnancy (CNEGAR and Brazilian Society of Endocrinology and Metabology – SBEM).

The hyperthyroid phase of PPT usually appears in the first few months after delivery, while GD can appear after this period (three months after delivery).[30] Given the destructive process of PPT, higher concentrations of T4 are observed in relation to T3, while in GD, there is a predominance of higher concentrations of T3 than T4. The presence of TRAb favors the diagnosis of GD. Scintigraphy should be avoided due to the passage of the radioisotope into breast milk. If it is essential for the

diagnosis, the option is to use 99mTc or ^{123}I, with shorter half-lives, and breast milk should be removed and discarded for 1-5 days, respectively, until breastfeeding is resumed.[31] Treatment of the toxic phase of PPT can be instituted to mitigate the clinical picture by using beta-blockers, which are not contraindicated during breastfeeding. The dose of propranolol is given according to symptoms, starting with 10mg three times a day. Atenolol, on the other hand, should be avoided, as it is secreted into breast milk, causing bradycardia and hypoglycemia in the infant. The use of ATDs is contraindicated in PPT.[2] Monitoring with TSH and FT4 should be performed every 4-8 weeks.[29] The concern after the hyperthyroid phase is hypothyroidism, which may be more symptomatic, occurring 3-12 months after delivery.[2] Treatment with levothyroxine should be started if the patient has significant symptoms, if she is breastfeeding, if the TSH elevation continues for more than six months, and especially if she is planning a new pregnancy. Levothyroxine withdrawal can be planned after 6-12 months of treatment. Monitoring of TSH and FT4 should be done annually given the high risk of developing permanent hypothyroidism after PPT.[2,6]

Final considerations

Hyperthyroidism in pregnancy represents a major challenge for both the obstetrician and the endocrinologist. Pregnancy changes in thyroid hormone physiology, fetal, neonatal and maternal complications of untreated disease, fetal and maternal repercussions, as well as the details of drug treatment during pregnancy are important aspects that should be on the radar of this follow-up treatment. In the first trimester of pregnancy, gestational thyrotoxicosis, present in up to 5% of pregnancies, stands out. Its etiopathogenesis is primarily related to the production of hCG, leads to symptoms usually more related to hyperemesis gravidarum and does not require treatment with antithyroid drugs. An important aspect is the differentiation with GD diagnosed during pregnancy. In general, GD is the most associated pathology with hyperthyroidism in pregnancy. This aspect also brings the effects of TRAb on fetal thyroid function, as these antibodies cross the placental barrier. Untreated hyperthyroidism is linked to a series of complications, such as: fetal loss, hypertension, prematurity, fetal growth restriction, fetal hyperthyroidism, thyrotoxic crisis, maternal congestive heart failure and maternal death, the latter being rare. Thus, adequate treatment of hyperthyroidism during pregnancy is important. However, the drugs from the thiamine class available for this treatment, PTU and MMZ, are potential teratogenic substances that can cause fetal hypothyroidism and goiter, and are related to several side effects in pregnant women, some very serious, such as hepatitis and pancytopenia. Other more effective treatments, such as ^{131}I, are proscribed during pregnancy and breastfeeding as they can lead to fetal and neonatal thyroid injury. Surgery represents a greater risk in pregnancy and should be indicated in very specific situations. With all this dynamics, drug treatment with the lowest possible dose of medication is necessary during pregnancy. Systematic laboratory control of collateral and fetal effects and careful obstetric follow-up are also essential. Childbirth does not necessarily represent a relief, as the rebound of the autoimmune system - suppressed during pregnancy - and the return to normal conditions of production and peripheral transport of TH can trigger new cases of GD and worsen the existing GD. Finally, it is important to emphasize that drug treatment of hyperthyroidism does not contraindicate breastfeeding, but additional care must be taken.

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Instructions to Authors

Scope and policy

The material submitted for analysis cannot be simultaneously submitted for publication in other journals or previously published. In the selection of manuscripts for publication, are evaluated the originality, relevance of the theme, quality of the methodology used, and adequacy to the editorial standards adopted by the journal. The published material becomes intellectual property of the Brazilian Journal of Gynecology and Obstetrics and Febrasgo.

Manuscripts evaluation

The manuscripts submitted to the journal are received by the Editorial Office that checks the mandatory documentation and examines if the editorial norms contained in the Instructions to Authors have been fulfilled. If the process is in compliance, the manuscript is sent to the Editor-in-Chief, who will make a merit evaluation of the material. If the Editor-in-Chief concludes the work is in favorable scientific and technical conditions, the manuscript is forwarded to the Associate Editors, who will designate reviewers (double mind process) to evaluate it. Then, the reviewers' opinions and editor's instructions are sent to authors to inform them about changes to be made. Then, the authors resubmit the text with the suggested changes within the requested deadline. When resubmitting the manuscript, the requested corrections should be highlighted in yellow. In cases of disagreement with the suggestions, observations should be included in the comments balloons. Be assertive and punctual with the inquiry, and support the hypothesis with references.

IMPORTANT! Authors must comply with the deadlines, since non-attendance will result in delay of manuscript publication or even archiving of the process. At any point in the process of analysis and editing of the text, the authors may request the process suspension and withdrawal of the manuscript, except when it is accepted for publication. The concepts and statements contained in the articles are of the authors' responsibility.

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When submitting a manuscript to RBGO, attach the documents listed below on the ScholarOne submission platform. Note that not attaching the documents will result in cancellation of the submitted process. Mandatory documentation for online submission:

- Authorization of copyright transfer signed by all authors (scanned and attached as supplementary document) **Model;**
- In accordance with chapter XII.2 of Res. CNS 466/2012, in Brazil, research involving human subjects needs to inform the registration number referring to the Certificate of Ethical Assessment (CAAE) or the approval number of the research (CEP/CONEP) in the Ethics Committee. International manuscripts must present local ethical documentation to proceed with the submission process;
- Cover Letter: written to justify the publication. The authors should be identified, together with the title of the team that intends to publish, origin institution of the authors and intention of publication;
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Title Page

- Title of the manuscript in English with a maximum of 18 words;
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Instructions to Authors

The Brazilian Journal of Gynecology and Obstetrics publishes the following categories of manuscripts:

Original Articles, complete prospective, experimental or retrospective studies. Manuscripts containing original clinical or experimental research results have priority for publication.

Case Reports, of great interest and well documented from the clinical and laboratorial point of view. In the letter of referral, authors should indicate new or unexpected aspects in relation to already published cases. The text of Introduction and Discussion sections should be based on an updated bibliographic review.

Review Articles, including comprehensive reviews, meta-analysis or systematic reviews. Spontaneous contributions are accepted. The methods and procedures adopted for obtaining the text should be described, and based on recent references, including the current year. As this subject is still subject to controversy, the review should discuss the trends and lines of research under way. In addition to the text of the review, there should be an abstract and conclusions. See the 'Instructions to Authors' section for information on the text body and title page;

Letters to the Editor, dealing with editorial matters or not, but presenting relevant information to readers. Letters can be summarized by the editor, but maintaining the main points. In case of criticism to published works, the letter is sent to the authors so their reply can be published simultaneously;

Editorial, only at the publisher's invitation.

Title

When writing a scientific article, the researcher should focus on the manuscript title, which is the business card of any publication. It should be elaborated very carefully, and preferably written only after the article finalization. A good title adequately describes the manuscript content. Generally it is not a phrase, because it does not contain the subject, only verbs and arranged objects. Titles rarely contain abbreviations, chemical formulas, adjectives, names of cities, among others. The title of manuscripts submitted to RBGO must contain a maximum of 18 words.

Abstract

The abstract should provide the context or basis for the study, establish the objectives, basic procedures, main outcomes and key findings. It should emphasize new and important aspects of the study or observations. Since the abstract is the only substantive part of the article indexed in many electronic databases, authors should ensure it reflects the article content in an accurate and highlighted manner. Do not use abbreviations, symbols and references in the abstract. In case of original articles from clinical trials, authors must inform the registration number at the end of the text.

Informational abstract of structured type of original articles

Abstracts of original articles submitted to RBGO must be structured in four sections and contain a maximum of 250 words:

Objective: What was done; the question posed by the investigator.

Methods: How it was done; the method, including the material used to achieve the objective.

Results: What was found, the main findings and, if necessary, the secondary findings.

Conclusion: The conclusions; the answer to the question asked.

Informational abstract of structured type of systematic review articles

Among the included items are the review objective to the question asked, data source, procedures for selecting the studies and data collection, the results and conclusions. The abstracts of systematic review articles submitted to RBGO must be structured in six sections and contain a maximum of 250 words:

Objective: Declare the main purpose of the article.

Data sources: Describe the data sources examined, including the date, indexing terms, and limitations.

Selection of studies: Specify the number of studies reviewed and the criteria used in their selection.

Data collection: Summarize the conduct used for data extraction and how it was used.

Data synthesis: State the main results of the review and the methods used to obtain them.

Conclusions: Indicate the main conclusions and their clinical usefulness.

Informational abstract of unstructured type of review articles, except systematic reviews and case studies

It shall contain the substance of the article, covering the purpose, method, results and conclusions or recommendations. It exposes enough details so readers can decide on the convenience of reading the full text (Limit of words: 150).

Keywords

The keywords of a scientific paper indicate the thematic content of the text they represent. The main objectives of the aforementioned terms are the thematic content identification, indexing of the work in databases, and rapid location and retrieval of contents. The keyword systems used by RBGO are DeCS (Health Sciences Descriptors - Lilacs Indexer) and MeSH (Medical Subject Headings - MEDLINE-PubMed Indexer). Please choose five descriptors that represent your work on these platforms.

Manuscript body (Manuscripts submitted to RBGO must have a maximum of 4000 words. Note that tables, charts and figures in the Results section and References are not counted).

Introduction

The **Introduction** section of a scientific article has the purpose of informing what was researched and the reason for the investigation. This part of the article prepares the reader to understand the investigation and justification of its realization. The content informed in this section should provide context or basis for the study (i.e. the nature of the problem and its importance); state the specific purpose, research objective, or hypothesis tested in the study or observation. The study objective usually has a more precise focus when formulated as a question. Both the primary and secondary objectives should be clear, and any analyzes in a pre-specified subgroup should be described; provide strictly relevant references only and do not include data or conclusions of the work being reported.

Methods

According to the Houaiss dictionary, **Methods** "is an organized, logical and systematic process of research". The method comprises the material and procedures adopted in the research in order to respond to the central research question. Structure the Methods section of RBGO starting with the study design; research scenario (place and period in which it was performed); sample of participants; data collection; intervention to be evaluated (if any) and the alternative intervention; statistical methods used and the ethical aspects of the study. When thinking about the writing of the study design, reflect if it is appropriate to achieve the research objective, if the data analysis reflects the design, and if what was expected with use of the design was achieved to research the theme. Following, the guidelines used in clinical or epidemiological research that should be included in the section Methods of manuscripts sent to RBGO:

Types of study (adapted from Pereira, 2014*):

Case Report (Case study): In-depth investigation of a situation in which one or a few people are included (usually up to ten);

Case series: A set of patients (for example, more than ten people) with the same diagnosis or undergoing the same intervention. In general, these are consecutive series of patients seen in a hospital or other health institution for a certain period. There is no internal control group formed simultaneously. The comparison is made with external controls. The name of external or historical control is given to the group used to compare the results, but that was not constituted at the same time within the study: for example, the case series is compared with patients from previous years.

Transversal (or Cross-sectional) study: Investigation to determine prevalence; examine the relationship between events (exposure, disease, and other variables of interest) at any given time. Cause and effect data are collected simultaneously: for example, the case series is compared with patients from previous years.

Case-control study: Particular form of etiological investigation of retrospective approach in which the search of causes starts from the effects. Groups of individuals, respectively with and without a particular health problem are compared in relation to past exposures in order to test the hypothesis that exposure to certain risk factors is the contributing cause of the disease. For example, individuals afflicted with low back pain are compared with an equal number of individuals (control group) of the same sex and age, but without low back pain.

Cohort study: Particular form of investigation of etiological factors in which the search of effects starts from the cause; therefore, the opposite of case-control studies. A group of people is identified, and pertinent information on the exposure of interest is collected, so the group can be monitored over time, checking those who do not develop the disease in focus, and if the prior exposure is related to occurrence of disease. For example, smokers are compared to nonsmoker controls; the incidence of bladder cancer is determined for each group.

Randomized study: This has the connotation of an experimental study to evaluate an intervention hence the synonym of *intervention study*. Can be performed in a clinical setting; sometimes referred to simply as clinical trial or clinical study. It is also conducted at the community level. In clinical trials, participants are randomly assigned to form groups called study (experimental) and control (or testimony), whether submitted or not to an intervention (for example, a drug or vaccine). Participants are monitored to verify the occurrence of outcome of interest. This way, the relationship between intervention and effect is examined under controlled observation conditions, usually with double-blind evaluation. In the case of a **randomized study**, inform the number of the Brazilian Registry of Clinical Trials (REBEC) and/or the number of the International Clinical Trials Registration Platform (ICTRP/OMS) on the title page.

Ecological study: Research performed with statistics: the unit of observation and analysis is not constituted of individuals, but of groups of individuals hence the synonyms: study of groups, aggregates, clusters, statistics or community. For example, research on the variation of mortality coefficients for diseases of the vascular system and per capita consumption of wine among European countries.

Systematic Review and Meta-analysis: Type of review in which there is a clearly formulated question, explicit methods are used to critically identify, select and evaluate relevant research, and also to collect and analyze data from the studies included in the review. There is use of strategies to

limit bias in the localization, selection, critical evaluation and synthesis of relevant studies on a given topic. Meta-analysis may or may not be part of the systematic review. Meta-analysis is the review of two or more studies to obtain a global, quantitative estimate of the question or hypothesis investigated; and employs statistical methods to combine the results of the studies used in the review.

Source: *Pereira MG. Artigos Científicos – Como redigir, publicar e avaliar. Rio de Janeiro: Guanabara-Koogan; 2014.

Script for statistical review of original scientific papers

Study objective: Is the study objective sufficiently described, including pre-established hypotheses?

Design: Is the design appropriate to achieve the proposed objective?

Characteristics of the sample: Is there a satisfactory report on the selection of people for inclusion in the study? Has a satisfactory rate of responses (valid cases) been achieved? If participants were followed up, was it long and complete enough? If there was a pairing (eg. of cases and controls), is it appropriate? How did you deal with missing data?

Data Collection (measurement of results): Were the measurement methods detailed for each variable of interest? Is there a description of comparability of the measurement methods used in the groups? Was there consideration of the validity and reproducibility of the methods used?

Sample size: Has adequate information on sample size calculation been provided? Is the logic used to determine the study size described, including practical and statistical considerations?

Statistical Methods: Was the statistical test used for each comparison informed? Indicate if the assumptions for use of the test were followed. Was there information about the methods used for any other analysis? For example, subgroup analysis and sensitivity analysis. Are the main results accompanied by accuracy of the estimate? Inform the p value and confidence interval. Was the alpha level informed? Indicate the alpha level below which the results are statistically significant. Was the beta error informed? Or indicate the statistical power of the sample. Has the adjustment been made to the main confounding factors? Were the reasons that explained the inclusion of some and the exclusion of others described? Is the difference found statistically significant? Make sure there are sufficient analyzes to show the statistically significant difference is not due to any bias (eg. lack of comparability between groups or distortion in data collection). If the difference found is significant, is it also relevant? Specify the clinically important minimal difference. Make clear the distinction between statistically relevant difference and relevant clinical difference. Is it a one- or two-tailed test? Provide this information if appropriate. What statistical program is used? Inform the reference where to find it, and the version used.

Abstract: Does the abstract contain the proper article synthesis?

Recommendation on the article: Is the article in acceptable statistical standard for publication? If not, can the article be accepted after proper review?

Source: *Pereira MG. Artigos Científicos – Como redigir, publicar e avaliar. Rio de Janeiro: Guanabara-Koogan; 2014.

IMPORTANT!

RBGO joined the initiative of the International Committee of Medical Journal Editors (ICMJE) and the EQUATOR Network, which are aimed to improve the presentation of research results. Check the following international guides:

Randomized clinical trial:
http://www.consort-statement.org/downloads/consort-statement

Systematic reviews and meta-analysis: http://www.scielo.br/pdf/ress/v24n2/2237-9622-ress-24-02-00335.pdf

Observational studies in epidemiology: strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf

Qualitative studies: http://intqhc.oxfordjournals.org/content/19/6/349.long

Results

The purpose of the Results section is to show the study findings. It is the original data obtained and synthesized by the author with the aim to answer the question that motivated the investigation. For the writing of the section, present the results in logical sequence in the text, tables and illustrations, first mentioning the most important findings. Do not repeat all information of the tables or illustrations in the text. Emphasize or summarize only important observations. Additional or supplementary materials and technical details may be placed in an appendix where they will be accessible without interrupting the flow of the text. Alternatively, this information may be published only in the electronic version of the Journal. When data are summarized in the results section, provide numerical results not only in derived values (eg. percentages), but also in absolute values from which the derivatives were calculated, and specify the statistical methods used for their analysis. Use only the tables and figures necessary to explain the argument of the work and evaluate its foundation. When scientifically appropriate, include data analysis with variables such as age and sex. Do not exceed the maximum limit of five tables, five charts or five figures. Tables, charts and/or figures should be included in the body of the manuscript and do not count the requested limit of 4000 words.

ATTENTION!

In Case Studies, the Methods and Results sections should be replaced by the term Case Description.

Discussion

In the **Discussion** section, emphasize the new and important aspects of the study and the conclusions derived therefrom. Do not repeat details of data or other information presented in the introduction or results sections. For experimental studies, it is useful to begin the discussion by briefly summarizing the main findings, comparing and contrasting the results with other relevant studies, stating the limitations of the study, and exploring the implications of the findings for future research and clinical practice. Avoid claiming precedence and referring to incomplete studies. Do not discuss data not directly related to the results of the presented study. Propose new hypotheses when justifiable, but qualify them clearly as such. In the last paragraph of the Discussion section, cite which information of your work contributes relatively to advancement of knowledge.

Conclusion

The **Conclusion** section has the function of relating the conclusions to the objectives of the study, but authors should avoid unfounded statements and conclusions not adequately supported by data. In particular, authors should avoid making statements about economic benefits and costs unless their original includes economic analysis and appropriate data.

References

A study is based on the results of other research that preceded it. Once published, it becomes support for future work on the subject. In the report of their research, authors state the references of prior works consulted that they deem pertinent to inform readers, hence the importance of choosing good References. Properly chosen references lend credibility to the report. They are a source for convincing readers of the validity of facts and arguments presented.

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Please check the Vancouver Citation Style to format your references.

*The Instructions to Authors of this journal were elaborated based in the literary work ***Artigos Científicos: Como redigir, publicar e avaliar de Maurício Gomes Pereira, Editora Guanabara Koogan, 2014.***

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