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Editorial

Bridging the Gap between Surveillance and Interventions in Latin America Addressing Maternal and Perinatal Morbidity and Mortality

Suzanne Serruya[1] Maria Laura Costa[2] Bremen De Mucio[1] Pablo Duran[1] Claudio Sosa[1] Mercedes Colomar[1] Rodolfo Gomez Ponce de Leon[1] Renato Teixeira Souza[2] Adriana Gomes Luz[2] Jose Guilherme Cecatti[2]

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The Latin American Center for Perinatology-PAHO aims to strengthen healthcare since 1970. For timely surveillance of maternal health, a perinatal information system (SIP) was implemented to enable monitoring trends of severe morbidity/mortality. It is time for integrated interventions to translate surveillance into health policies to address preventable maternal/perinatal deaths.

Regardless of the global progress in reducing maternal mortality from 2000 to 2017, the Sustainable Development Goal target is still far from the objective and if the reduction in mortality is not accelerated, Latin American countries will not meet the global or regional goals agreed. The chance of dying due to maternal causes is 10-fold higher in Latin America when compared with Europe.[1] Preventable mortality is a major concern worldwide, highlighted during the COVID-19 pandemic which resulted in a marked increase in maternal deaths.[2] Health crises expose underlying delays and disparities that need to be addressed.

How many times will we have to report an increase in adverse outcomes during crises? Recent experiences with Influenza (H1N1pdm09) and the Zika virus should have enabled a better response. Latin America has reached its turning point and needs to bridge the gap between surveillance and action to address womeńs health. It should be unacceptable to have cases of eclampsia with no treatment; preeclampsia at term, with no induction of labor; deliveries with no safe blood access, postpartum hemorrhages with no accurate interventions; delayed diagnosis and treatment of sepsis; or no access to modern contraception. Protocols and training must be implemented at all levels of reproductive, maternal and neonatal healthcare.

The Latin American Center for Perinatology, Women's Health and Reproductive Health (CLAP) of the Pan American Health Organization (PAHO) has worked to promote, strengthen and improve motheŕs and newborńs healthcare in the Region since 1970. Perinatal Information System (SIP), among accomplishments, is a free computerized clinical record system implemented in 22 countries under CLAP technical support and is a milestone in the use of systematized information.[3] SIP enables institutions to generate information to monitor the prevalence and trends of severe morbidity and mortality, quality of care, and the need for interventions for local health concerns.[4] SIP has been implemented in a network of maternities from different countries allowing institutions to surveil their own data, perform health system management, implement operational research and train human resources based on identified needs.

There are known differences among countries in the region in terms of social and economic characteristics of the population and also of available resources for maternal and child health care. In addition, there is a general agreement that existing knowledge is already sufficient for facing the challenges of prevention and treatment of causes potentially leading to severe maternal morbidity and mortality but the lack of political willingness and concrete actions to implement the required measures are the main limitations.

In conclusion, considering that CLAP/PAHO activities are feasible based on SIP soundness, as could also be on other national independent initiatives focused on the same goal of surveillance of morbidity, it is time to plan integrated interventions and translate surveillance into public health policies to effectively address preventable maternal

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and neonatal deaths. We urge policymakers, scientific societies and stakeholders to join forces, push toward prioritizing maternity care, and take up the available sources of information to improve womeńs lives in Latin America. This is a necessary condition if we are really willing to reach the Sustainable Development Goals on this topic by 2030.

Conflicts to Interest
None to declare.

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Thyroid Volume in Pregnancy is Associated with Parity, Gestational Age, and Body Mass Index in an Iodine-sufficient Area

O volume tireoidiano em gestantes está associado à paridade, idade gestacional e índice de massa corporal em uma área suficiente em iodo

Mariana Couto Monteiro[1] Gabriela Assayag[1] Ricardo Botler[1] Anice Bergamin[1] Flávia Lúcia Conceição[1] Nathalie Silva de Morais[1] Roberto Perrota de Seixas[2] Tatiana Martins Benvenuto Louro Berbara[1] Annie Schtscherbyna[1] Carolina Martins Corcino[1] Débora Ayres Saraiva[1] Mário Vaisman[1] Patrícia Fátima Santos Teixeira[1]

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Abstract

Objective We compared thyroid volume (TV) and presence of nodular goiter (NG) in pregnant vs. non-pregnant women in an iodine-sufficient area. We also evaluated the relationship between gestational age, parity, and TV in the pregnant women group, and determined the 2.5th and 97.5th percentiles of normal TV in pregnancy.

Methods This cross-sectional study included 299 healthy women (216 pregnant) without previous thyroid diseases. Thyroid ultrasounds were performed and compared between pregnant and non-pregnant women. The range of normal distribution of TV (2.5th and 97.5th percentiles) in pregnancy was determined after excluding individuals with positive thyroid antibodies, NG, and/or abnormal serum thyrotropin (TSH) or free thyroxine (FT4).

Results Thyroid volume was larger among pregnant compared to non-pregnant women (8.6 vs 6.1 cm^3; $p < 0.001$) and was positively correlated with gestational age (rs = 0.221; $p = 0.001$), body mass index (BMI, rs 0.165; $p = 0.002$), and FT4 levels (rs 0.118 $p = 0.021$). Nodular goiter frequency did not differ between the two groups. There was a negative correlation between TV and TSH (rs -0.13; $p = 0.014$). Thyroid volume was lower among primiparous compared to multiparous patients (7.8 vs 8.9; $p < 0.001$) and was positively correlated with parity (rs 0.161; $p = 0.016$). The 2.5th and 97.5th percentiles of TV were 4.23 and 16.47 cm^3, respectively.

Conclusion Thyroid volume was higher in pregnant compared to non-pregnant women and was positively related to parity, BMI, and gestational age in a normal iodine status population. Pregnancy did not interfere with the development of NG.

Keywords
- thyroid volume
- pregnancy
- iodine status
- thyroid nodule
- body mass index

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Resumo

Objetivo Comparamos o volume tireoidiano (VT) e a presença de bócio nodular (BN) em mulheres grávidas e não grávidas em uma área suficiente em iodo. Também avaliamos a relação entre idade gestacional, paridade e VT no grupo de gestantes e determinamos os percentis 2,5 e 97,5 de VT normal na gestação.

Métodos Este estudo transversal incluiu 299 mulheres saudáveis (216 grávidas) sem doenças tireoidianas prévias. Ultrassonografias de tireoide foram realizadas e comparadas entre mulheres grávidas e não grávidas. A faixa de distribuição normal de VT (percentis 2,5 e 97,5) na gestação foi determinada após a exclusão de indivíduos com anticorpos tireoidianos positivos, BN e/ou tireotropina sérica (TSH) ou tiroxina livre (T4L) anormais.

Resultados O VT foi maior entre as gestantes em comparação com as mulheres não grávidas (8,6 vs 6,1 cm3; $p < 0{,}001$) e foi positivamente correlacionado com a idade gestacional (rs = 0,221; $p = 0{,}001$), índice de massa corporal (IMC, rs 0,165; $p = 0{,}002$) e níveis de T4L (rs 0,118 $p = 0{,}021$). A frequência de BN não diferiu entre os dois grupos. Houve correlação negativa entre VT e TSH (rs -0,13; $p = 0{,}014$). O VT foi menor entre as primíparas em comparação com as multíparas (7,8 vs 8,9; $p < 0{,}001$) e foi positivamente correlacionado com a paridade (rs 0,161; $p = 0{,}016$). Os percentis 2,5 e 97,5 de VT foram 4,23 e 16,47 cm3, respectivamente.

Conclusão O VT foi maior em gestantes em comparação com mulheres não grávidas e foi positivamente relacionado à paridade, IMC e idade gestacional em uma população com status iódico normal. A gravidez não interferiu no desenvolvimento de BN.

Palavras-chave

- volume tireoidiano
- gestação
- status iódico
- nódulo tireoidiano
- índice de massa corporal

Introduction

Pregnancy leads to important changes in thyroid physiology, with a higher demand to produce thyroid hormones.[1–5] During pregnancy, higher levels of estrogen increase circulating thyroxine binding globulin levels and decrease thyroid hormones free fractions, which stimulates the hypothalamic-pituitary-thyroid axis. Besides, the placental alfa subunit of human chorionic gonadotropin directly stimulates the thyroid-stimulating hormone (TSH) receptor, increasing thyroid hormone production and thyroid volume (TV). An enlargement of thyroid gland may be associated with physiological thyrotoxicosis during pregnancy due to this excessive stimulus to the gland.[2,4]

The higher demand of thyroid hormone production is fulfilled when there is enough amount of iodine and typical thyroid parenchyma, especially in the absence of autoimmune diseases.[1,3] However, iodine deficiency or excess my compromise the adaptive mechanisms in maternal thyroid function. Pregnancies in conditions of iodine deficiency induce even larger volumes and goitrogenic effects since iodine deficiency is a classical goitrogen factor. In iodine-deficient areas, an increase of 20-30% of TV is reported in pregnant women, compared to non-pregnant women.[1,6]

Other elements such as parity, age, serum TSH levels, and genetic characteristics seem to interfere in maternal TV.[7] However, most studies that evaluated the correlation of these variables with TV were conducted in areas with inadequate iodine intake, which could be a bias.

In this context, we proposed the present study to compare the TV and the presence of nodular goiter (NG) between pregnant and non-pregnant women from an iodine-sufficient area. Furthermore, we aimed to evaluate the relationship between demographic parameters, gestational age, number of previous pregnancies and TV in pregnant women. Finally, we determined the 2.5^{th} and 97.5^{th} percentiles of TV in pregnant women with normal thyroid function and absence of thyroid autoimmune disease, proposing a reference range for TV in women along the different trimesters of pregnancy.

Methods

This was a sectional study enrolling 216 pregnant women aged 18 to 35 years old, without a previous history of thyroid diseases, who were attending obstetric outpatient appointments at four public health basic care units in Rio de Janeiro. All health care units were in urban areas of the state. The inclusion period was from May 2014 to January 2017. The study was approved by the local Research Ethics Committee, and all subjects signed consent forms (CAAE**:** 22546213.0.0000.5275).

Women with any chronic disease, body mass index (BMI) > 40, or any newly diagnosed disease at the first obstetric evaluation were excluded. Patients with multifetal pregnancies or with history of levothyroxine or antithyroid drug use were also excluded. An additional exclusion criterion was the use of drugs or supplements containing iodine.

In order to determine the range of normal distribution of TV in pregnancy, we excluded pregnant women with positive serum thyroid peroxidase antibody (TPOAb) and/ or thyroglobulin antibody (TgAb), NG, and abnormal serum TSH or FT4.

Normal TSH reference range was defined according to the American Thyroid Association recommendations.[8]

Body mass index (BMI) was calculated as weight (Kg) divided by height squared (m^2). Participants were classified as obese according to BMI classification tables specific to pregnant women.[9]

As shown by Saraiva et al., the median ioduria among pregnant women in the same region was 221.0 µg/L, which reflects a sufficient iodine status according to the World Health Organization classification.[10]

A control group with 83 non-pregnant women of similar age was selected. This group did not have known thyroid disease or other chronic conditions and lived in the same region. Also excluded were those who had BMI $> 40\ kg/m^2$ and those taking levothyroxine or supplements containing iodine.

Serum TSH, FT4, TPOAb, and TgAb concentrations were determined by electrochemiluminescence assays with Roche Modular Analytics E170. The reference values, intra- and inter-assay variations were, respectively, TSH: 0.1 to 3.8 mIU/L[11]; 7.2% and 3%; FT4: 0.7 to 1.9 ng/dL; 2.8% and 2.9%; TPOAb: < 34 UI/mL; 6.3% and 7.0%; TgAb: < 115 UI/mL; 4.9% and 6.3%. For non-pregnant women, serum TSH and FT4 reference ranges were 0.4 to 4.3 mUI/L and 0.7 to 1.9 ng/dL.

All participants underwent a thyroid ultrasound evaluation. Considering the pregnant group, the majority (n = 136) was evaluated in the first trimester; however, a group of 37 pregnant patients had US assessment in the second or third trimester. All thyroid ultrasound scans were performed by one of three trained examiners (NSM, PFST, RPS) using a high-frequency SIEMENS-AUSONX 300 (Siemens AG, Munich, Germany) or MYSONO U5 SAMSUNG transducer (12 MHz) (Samsung Electronics Co., Ltd., Suwon-si, South Korea). Thyroid volume was calculated as the summation of each lobe and isthmus volumes, using the formula: length x width x thickness x 0.52.[12] The presence, location and size of thyroid nodules were also evaluated and described. Nodular goiter was defined as the presence of one or more solid lesions $\geq$ 3.0 mm in diameter in both transverse and longitudinal axes. Thyroid nodule volume was calculated by length $\times$ width $\times$ thickness $\times$ 0.52.[12]

Statistical analysis was performed using the IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were described as median (interquartile range) and categorical variables as frequencies. Comparations were performed using the Chi-square and Fisher exact tests for categorical variables. The Mann-Whitney U test was used to compare continuous variables. A p-value < 0.05 was considered significant.

Results

A total of 299 women (216 pregnant) were evaluated. They did not differ regarding age (median age = 28.0 years old in both groups $p = 0.549$) and were also comparable regarding the frequency of overweight and obesity, as depicted in ►**Table 1**. Median serum TSH was lower in the pregnant group compared to the non-pregnant group (1.3 vs 2.0 mUI/L; $p < 0.001$) and, in contrast, median FT4 was higher (1.2 vs 1.0 mUI/L; $p < 0.001$). The frequency of NG as well as the number and volume of thyroid nodules did not differ between the two groups (►**Table 1**).

Table 1 Baseline characteristics of the study population, comparing pregnant and non-pregnant women

	Pregnant	Non-pregnant
Age (years)	28.0 (8.0)	28.0 (7.0)
Overweight (%)	30	33.7
Obesity (%)	16.9	27.7
TSH (mUI /L)	1.35 (1.4)[a]	2.01 (1.8)
FT4 (ng/dL)	1.2 (0.3)[a]	1.0 (1.1)
Thyroid volume (cm^3)	8.6 (3.7)[a]	6.1 (3.2)
Nodular goiter (%)	9.7	16.9
Number of nodules (%)	0.12 (0.06–0.17)	0.28 (0.11–0.46)
Total nodular volume (cm^3)	0.24 (0.32)	0.18 (0.61)

Abbreviations: TSH, thyrotropin; FT4, free thyroxine.
[a]*P*-value < 0.01 compared with the non-pregnant group.
Continuous variables are presented as median (interquartile range).

Thyroid volume was larger among pregnant compared to non-pregnant women (8.6 vs 6.1 cm^3; $p < 0.001$) and was positively correlated with gestational age (rs = 0.221; $p = 0.001$), BMI (rs 0.165; $p = 0.002$) and FT4 levels (rs 0.118 $p = 0.021$). There was a negative correlation between TV and TSH (rs -0.13; $p = 0.014$). Thyroid volume was lower among women in their first trimester of pregnancy compared to those in the second or third trimesters (7.8 vs 8.9; $p < 0.001$) and was positively correlated with the number of previous pregnancies (rs 0.161; $p = 0.016$), as shown in ►**Table 2**.

In order to determine the range of normal distribution of TV in pregnancy, we excluded 43 women with positive serum TPOAb and/ or TgAb, NG, and/or abnormal thyroid function. Among the remaining 173 pregnant women, the 2.5th and 97.5th percentiles of TV were 4.23 and 16.47 cm^3, respectively. There was a tendency for a higher 95th percentile of TV among pregnant women in the second/third trimesters compared to those in the first trimester (17.66 vs 12.63, $p = 0.111$), ►**Table 3**.

Table 2 Correlations between thyroid volume and studied variables in pregnant women

	r^s	*p*-value
Gestational age	+0.221	0.001
Parity	+0.161	0.016
TSH	-0.132	0.014
FT4	+0.118	0.021
Age	+0.124	0.160
BMI	+0.165	0.002

Abbreviations: BMI, body mass index; FT4, free thyroxine; rs, Spearman coefficient score; TSH, thyrotropin.

Table 3 Ranges of distribution of thyroid volume among pregnant women without thyroid diseases

	All pregnant women* (n = 216)	First trimester (n = 136)	Second/third trimester (n = 37)
5^{th}–95^{th}	4.77–12.66	4.88–12.63[a]	4.19–17.66[a]

*Excluded patients with positive serum thyroid peroxidase antibody and/or thyroglobulin antibody, nodular goiter, and abnormal thyroid function. *P*-value = 0.111 comparing pregnant women in the first vs. second/third trimesters.

Discussion

The results of the present study reinforce that, even in iodine-sufficient areas, pregnancy leads to a goitrogenic effect in the thyroid, also associated with higher FT4 and lower TSH levels. This goitrous stimulus persisted into the later stages of pregnancy. Also, a possible cumulative effect may exist with multiple pregnancies. In clinical practice, it may impact the approach to women with NG, since a persistent augment in TV might be expected with pregnancy.

In the studied sample of pregnant women, TV was positively correlated with parity, in consonance with previous studies demonstrating that the goitrogenic effect in the thyroid during pregnancy is not fully reversible after parturition.[12–16] A possible cumulative effect is supported by these results.

In accordance with some previous observations, although parity increases with age, our results indicated that there was no correlation between TV and age per se.[15,17,18] Rotondi et al. also demonstrated that the correlation between TV and the number of term pregnancies was maintained after age adjustment, highlighting parity as an independent variable correlated with TV.[15]

The main difference between our study and other above-mentioned studies is that the majority were performed in iodine-deficient areas.[13–16] This condition has a goitrogenic effect on the thyroid, acting directly in the correlation of different variables and TV.[1,6,19] In this way, iodine deficiency could be an important confounding bias, particularly when considering pregnant patients.

Another study, also conducted in an iodine-sufficient area in Brazil, did not demonstrate a correlation between TV and parity.[20] The authors considered the possibility that iodine sufficiency could have a protective role against the goitrogenic effect of parity. However, they also highlighted that these findings could be due to the uniformity of the sample regarding low parity.

Our data reinforce previous evidence of an association between parity and TV, now demonstrated in an iodine-sufficient area.[10] These results bring to light the idea of an independent effect of pregnancy in the increase of TV. Despite this, we did not find differences in the frequency of NG or the number and volume of thyroid nodules among pregnant and non-pregnant women, which may be a limitation of the study design. A prospective study would be helpful to better evaluate this association.

There were other studies investigating the association between TV and BMI. Most of them suggested that TV is significantly correlated with BMI.[20,21] One of them also demonstrated a significant decrease in TV in obese women who lost > 10% body weight.[21] Our results are in agreement with this evidence, showing a positive correlation between TV and BMI.

Finally, few previous studies have evaluated the normal distribution of TV in pregnant women. The 2.5^{th} and 97.5^{th} percentiles of TV distribution were 4.23 and 16.47 cm^3, respectively. It may help future researchers when designing studies of thyroid morphology in women from the same region and may help to stablish a parameter of normality for TV in pregnancy. Moreover, as expected, there was a tendency to increase the TV values of normality in the second and third trimesters compared to the first trimester, reinforcing once again the idea of the goitrogenic effect of pregnancy.

The limitations of the present study are related to its sectional design since it would be interesting to assess TV evolution, as well as thyroid nodules development, after the delivery. Also, the small sample size should be addressed despite not being impeditive to detecting positive associations. Furthermore, we have only assessed anti-thyroid antibodies levels in the group of pregnant patients.

Conclusion

In conclusion, we demonstrated that pregnancy has a goitrogenic effect over the thyroid, even in pregnant women living in an iodine-sufficient area. TV in pregnancy was positively related to parity, BMI, and gestational age. The found reference range for TV in pregnancy was 4.23 to 16.47 cm^3.

Contributions

All authors contributed to the design of the study, were involved in the data collection, data analysis and/or interpretation. Also, all authors contributed to the writing/substantive editing and review of the manuscript and approved the final draft of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Iron Deficiency Anemia in Pregnancy after Bariatric Surgery: Etiology, Risk Factors, and How to Manage It

Anemia ferropriva na gestação após cirurgia bariátrica: Etiologia, fatores de risco e como tratar

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Abstract

Objective Pregnancy after bariatric surgery is a reality of the 21st century and therefore is essential that all obstetricians know how to manage it. The most prevalent nutritional deficiency is iron deficiency and, consequently, anemia. Although bariatric surgery and pregnancy are already risk factors for anemia, we evaluated in our study if there were any other risk factors and actions to improve hemoglobin levels in this population.

Methods We performed a retrospective cohort study, and performed frequency measurements and analyzes of odds ratio, X^2 and Fisher exact test to evaluate the risk factors.

Results We evaluated 44 pregnancies after bariatric surgery, with an incidence of anemia of 62%, and the only identifiable risk factor for anemia was being black. As for the treatment, the iron salt used for oral supplementation did not associate with anemia risk, and in 27% of the patients, the adjustment of the oral dosage was enough for improvement in hemoglobin levels, but in 36% supplementation with intravenous iron was necessary.

Conclusion Being black is a risk factor for anemia. The type of iron salt does not correlate with the incidence of anemia, and for the treatment and improvement of iron dosages, it seems an effective increase in iron intake.

Keywords
- Bariatric surgery
- Anemia in pregnancy
- Anemia after bariatric surgery

Resumo

Objetivo A gestação após cirurgia bariátrica é uma realidade do século XXI e, portanto, é de suma importância que os obstetras saibam conduzir o pré-natal dessas gestantes. A deficiência nutricional mais prevalente nessa população é a deficiência de ferro, que tem como consequência a anemia. Apesar da própria gestação e da cirurgia serem fatores de risco para anemia ferropriva, realizamos um estudo para avaliar se existem outros fatores que são de risco e quais condutas podem melhorar os níveis de hemoglobina nessa população.

Palavras-chave
- Cirurgia bariátrica
- Anemia na gestação
- Anemia após cirurgia bariátrica

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Métodos Trata-se de um estudo de coorte retrospectiva, e foram realizadas medidas de frequência e análise odds ratio, X^2, e teste de exato de Fisher para a avaliação dos fatores de risco.

Resultados Foram avaliadas 44 gestações após cirurgia bariátrica com incidência de anemia de 62%, sendo que o único fator de risco identificado foi a etnia preta. O sal de ferro utilizado na reposição não se associou com o risco de anemia. Em somente 27% das gestantes o ajuste da dose oral de ferro foi suficiente para corrigir a anemia, enquanto em 36% foi necessária a suplementação com ferro endovenoso.

Conclusão Ser de etnia preta foi fator de risco para anemia após cirurgia bariátrica e o tipo de sal de ferro para suplementação não se correlacionou com a incidência de anemia. Para o tratamento da anemia, somente o ajuste da dose da medicação parece ser suficiente para a resolução desta.

Introduction

Pregnancy after bariatric surgery is a 21st century reality. Although there is still a lack of studies that investigate the prevalence of pregnancy after this surgery, it is well established that the main operated population are women in reproductive age in Brazil and worldwide. Consequently, obstetricians all over the world must know how to assist these women, understanding the risks and possible complications.[1,2]

The most prevalent side effect after bariatric surgery is anemia. Although there are different surgical techniques, all of them are risk factors for anemia. The reduction of gastric fundus decreases chloride acid production, essential for the acid environment necessary for iron absorption. Moreover, there is a decrease of intrinsic factor, responsible for vitamin B12 absorption. Therefore, these women are at risk for both iron and B12 deficiencies. This problem can be intensified during pregnancy, since it increases iron and vitamin B12 consumption, as well as physiologic hemodilution, make pregnancy itself a risk factor for anemia, which is worsened after bariatric surgery.[2,3]

Besides those factors, anemia is still a health problem in Brazil, with a prevalence of almost 25% in women of childbearing age, as shown by a study conducted by the government in 2006. Although data from 2013 and 2014 has shown lower rates of anemia in this population, this index in 2013 was still close to 12%. This risk also surges if the woman is black, of low education, or resident of the North and Northeast regions of the country.[4]

Anemia in pregnancy is deleterious both for the fetus and for the mother since it increases the risk of prematurity, low birthweight, infections, and postpartum hemorrhage. Severe anemia even increased fetal mortality rates, and at long term, behavioral changes.[5,6]

The objective of the present study was to evaluate prevalence, type of anemia, risk factors of severe anemia, need for intravenous iron, oral iron therapy, and perinatal results among pregnant women after bariatric surgery in a university hospital.

Methods

We performed a retrospective cohort study in the Women's Hospital Centro de Atenção Integral da Saúde da Mulher José Aristodemo Pinotti from the University of Campinas. The study was approved by the institution ethical committee under CAAE 29661920.7.0000.5404.

The study included all pregnant women with previous bariatric surgery with singleton pregnancies followed in our prenatal clinic from January 2015 to December 2020. Women who lost antenatal follow-up were excluded from the study. All data was extracted from the electronic medical charts of the patients and included age, ethnicity, marital status, previous pregnancies, type of surgery, interval between surgery and pregnancy, weight before pregnancy, weight gain during pregnancy, medication used and dosage, incidence of gastric symptoms such as nausea and vomiting, acceptance of oral medication, incidence of gestational hypertension and diabetes and need for medical treatment, need for intravenous iron, hemogram, ferritin, iron and B12 dosages during pregnancy (one each trimester), smoking status, gestational age at labor, labor, ultrasound exams (fetus weight, amniotic fluid index, Doppler assessment) birthweight, breastfeeding, and contraception method after birth.

Anemia was defined by hemoglobin levels < 11 g/dL in the 1st and 3rd trimesters and < 10.5 g/dL in the second. Hemoglobin levels > 10g/dl were considered mild anemia, 9 to 10 g/dL was considered moderate anemia, and hemoglobin levels $<$ than 9g/ dL were considered severe anemia. Iron deficiency was defined by levels < 50ug/ dL, ferritin deficiency by levels < 13 ng/dL and B12 < 197 pg/dL. Anemia was also classified as normocytic (mean corpuscular volume [MCV] of 82 to 98 fL) microcystic (MCV < 82 fL) or macrocystic (MCV > 98 fL) and normochromic (mean hemoglobin per red blood cell [MCH] between 27 and 32 pg), hypochromic (< 27 pg) or hyperchromic (> 32 pg). We also analyzed which iron salt patients were taking, since new formulations such as ferric citrate might be more tolerable than iron sulfate, and corelated it with the incidence of anemia.[7–9]

Adequate weight gain was defined by initial pregnancy body mass index (BMI). Patients with a BMI $< 18.5\,kg/m^2$ should gain between 12.5 to 18 kg; those with a BMI between 18.5 and $24.9\,kg/m^2$ should gain between 11.5 and 16 kg; those with a BMI between 25 and $29.9\,kg/m^2$ should gain 7 to 11,5 kg; and those with a BMI $> 30\,kg/m^2$ should gain 5 to 9 kg.[10]

To analyze the data, we used frequency measures, as incidence and prevalence and to corelate date we used measures of chi-squared and Fischer exact test with a significance lever of $p < 0.05$. The software used to perform statistical analyzes of the data was the Statistical analyzes system version 9.2.[11]

Results

We identified 45 patients with 46 pregnancies. One woman had twin pregnancy and another one had an abortion in the 1st trimester (both were excluded). The total analyzed cases were 44 pregnancies. Most patients in our sample were married (70%), white (80%), > 30 years old (70%), non-smokers and did not consume alcohol. In our sample, the type of surgery was described in 27% of the patients, and of them, most were submitted to gastric bypass (58%), the others variated to sleeve or gastric band, and the procedure type did not correlate with anemia incidence. A total of 27% of the patients still had a body mass index (BMI) before pregnancy > 35. The incidence of anemia in our sample was 61% of the patients, 38% of the patients in the 2nd trimester and of 56% in the 3rd trimester. The most common anemia type was microcystic and hypochromic anemia (56%), and iron deficiency was present in most patients with it (72%). Low ferritin levels were also associated with a higher risk of anemia (►**Table 1**).

We correlated the incidence of anemia with the type of iron patients consumed. Most patients consumed iron sulfate, alone or associated with other vitamin supplements. There was no statistically significant difference between the type of iron consumed with the incidence of anemia (►**Table 2**).

Severe anemia was rare in our sample, with an incidence of 2% in the 2nd trimester and of 5% in the 3rd. The most common was mild anemia (Hb levels > 10g/dL) in both the 2nd and in the 3rd trimester. We also evaluated the evolution of hemoglobin levels from the 2nd to the 3rd trimester in patients who presented anemia in the 2nd trimester. A total of 34% of the patients with anemia progressed with lower hemoglobin levels. Intravenous iron was prescribed to 59% of the patients who presented anemia in pregnancy for hemoglobin improvement. In the patients that had an increase in their hemoglobin levels, 36% of them had intravenous iron prescribed, while in 27% the prescription of higher dosages of oral iron was effective. In 13% of the patients there was an association of intravenous iron and improvement of oral iron dosages, and in 13% the polivitamin was associated with another iron supplementation. Macrocytic anemia was not detected in this sample. Of other deficient nutrients, vitamin B12 deficiency had an incidence of 19%. The only factor that was associated with anemia besides iron and ferritin levels was skin color, since being black was a risk factor for it. Weight gain during pregnancy, BMI before pregnancy, and interval between surgery and pregnancy were not correlated with the prevalence of anemia in our study (►**Table 3**).

Table 1 Type and frequency of anemia in pregnant women after bariatric surgery in all trimesters

Anemia ($n = 27$)	Frequency	Percentage
Microcystic and hypocrhomic	15	56%
Normocistyc and normocrhomic	12	44%
Macrocystic and hyperchromic	0	0

Table 2 Iron salt used by the patients during pregnancy and its correlation with the incidence of anemia

Iron salt type ($n = 43$)	Anemia	No anemia	Total
Iron sulfate	7	5	12
Iron glycinate	1	1	2
Iron fumarate	6	4	10
Iron polymaltose	2	1	2
Iron carbonate	1	0	1
Iron fumarate + iron sulfate	8	5	13
Iron sulfate + iron glycinate	2	0	2

Fisher exact test: $p = 0.983$.

Table 3 Variables

Risk factor	Anemia	Non anemia	
Interval between surgery and pregnancy			Fisher exact test $p = 0.6$
< 1 year	0	1	
1 to 5 years	11	6	
> 5 years	15	10	
Ethnic group			$p = 0.026$
White	18	17	
Black	9	0	
Body Mass index (BMI)			Fisher exact test $p = 0.41$
< 25	5	3	
25–30	11	3	
30–35	6	4	
35–40	4	5	
> 40	1	2	
Weight gain during pregnancy			$X^2 = 0.99$ GL = 2 $p = 0.608$
Adequate	12	5	
Inadequate (less than stipulated)	5	4	
Inadequate (More than stipulated)	10	8	

Table 4 Comparison between anemia and no anemia group and neonatal outcomes

Anemia	Yes ($n = 27$)			No ($n = 17$)			Mann-Whitney test for comparison between two groups
	mean	min	max	mean	min	Max	
Fetal weight (g)	2977	2665	3620	2975	1940	3930	$p = 0.95$
1st minute APGAR	8.88	7	10	8.69	6	10	$p = 0.72$
5th minute APGAR	9.68	8	10	9.63	9	10	$p = 0.48$
Height (cm)	47.90	43	51	47.69	45.5	51.5	$p = 0.41$
Gestational age (weeks)	38.85	36	41	38	36	40	$p = 0.33$

The incidence of gestational hypertension or chronic hypertension in this sample was of 13%, and of preeclampsia, 2%. None of the patients required > 1,5 g of methyldopa per day for blood pressure control. Diabetes prevalence was of 25%, and of these, 81% were gestational diabetes. A total of 72% of the patients with diabetes had an adequate treatment with diet only. Diabetes and hypertension did not have statical association with anemia. Regarding fetus development, no major fetal malformations were detected in our study. Considering aneuploids, one patient had a baby with down syndrome, in the anemia group. In our study, newborns from both groups had similar mean birthweight, gestational age at birth, height, and Apgar scores of the 1st and 5th minutes. In both groups, cesarean was the most prevalent delivery form, and the main indication was previous cesarean deliveries (►**Table 4**).

Sixty percent of our patients returned to our ambulatory after labor, and of them, 62% were exclusively breastfeeding. A total of 37% had tubal ligation during labor, and 40% of them chose trimestral injections as contraception and 10% intra uterine device (cooper or levonorgestrel).

Discussion

In the present study, we analyzed the prevalence of anemia in pregnant women after bariatric surgery, and the other risk factors associated with it, as the use of different iron salts and what was effective to improve hemoglobin rates. Although some studies have presented weight gain, and an interval between pregnancy and surgery as risk factor for anemia in pregnancy after bariatric surgery, our study has not corroborated such findings, but showed that black women are under a higher risk of anemia.

The incidence of anemia in our sample was of 61%, which is similar to that of other studies that evaluated the incidence of anemia in pregnancy after bariatric surgery. This rate, as expected, is higher than the prevalence of anemia in pregnant women in general, that is, near 42%, since bariatric surgery itself is a risk factor for anemia.[10,12]

Our population was divided into gastric bypass and restrictive procedures. Even though is stipulated that malabsorptive procedures, such as gastric bypass, might be associated with a higher risk of anemia than restrictive procedures, both malabsorptive and restrictive procedures reduce the gastric fundus, responsible for the acid pH necessary for iron absorption; therefore, all procedures might predispose to anemia and that is perhaps why procedure type was not relevant in our sample. Another reason for the type of procedure do not associate with anemia was a limitation of our study that not all patients had their type of surgery described in the medical charts. Although anemia is also associated with a short interval between surgery and pregnancy, it was also not significant in our study since, except for one, all patients had at least 1 year of interval between pregnancy and surgery.[10]

Our study, different from others that evaluated anemia in pregnant women after surgery, analyzed if the type of iron salt has any correlation with the incidence of anemia in this population. It has been considered that some iron salts might be more tolerable than others, since some formulations like iron sulfate may predispose to gastric symptoms. As far as we are concerned, no previous study had made such analyzes in this population. Our data demonstrated that the type of iron salt does not correlate with the incidence of anemia in this specific population. Although women after bariatric surgery had not been previously analyzed, it has been demonstrated that all iron salts seem effective to prevent and treat iron deficiency after bariatric surgery and iron deficiency in pregnancy, and, as concluded by our study, iron deficiency in pregnant women after bariatric surgery.[8,10,13–15]

Like other studies, vitamin B12 and folate anemia were not relevant. For folic acid, this is a result of mainly two factors: first, Brazilian food is enhanced with folate, which decreases the necessity of folic acid, and that pregnant women are advised to take 1 pill of 5 mg daily of folic acid, which is a much higher dosage than required daily. As for vitamin B12, most patients were advised by the gastric surgeon to take vitamin B12 supplementation, especially intramuscular, which might justify the low incidence of anemia.[13]

As a new finding, our study demonstrated that black pregnant women submitted to bariatric surgery had a higher risk of developing anemia in pregnancy than white pregnant women. That is coherent with government data that demonstrated that being black is a risk factor for anemia in the general population, so it is logical that this

applies to pregnant women as well. What raises the question is why: are we not providing the same treatment and assistance according to ethnicity as shown in other studies? Or the access to treatment and healthcare is limited due to social and economic conditions? None of those women had history of sickle diseases or of any other that might justify this prevalence of 100% of anemia. Since these women are at higher risk, we must analyze economic factors and access to medications and care, specially of those patients.[4,16,17]

Although iron deficiency anemia is correlated with low birthweight and preterm birth, in our sample that did not occur, even though bariatric surgery is also a risk for such developments. Major malformations were not detected either and we only had one case of aneuploidy (down syndrome), which is more likely to be associated with maternal age than with the bariatric surgery, since an association of increased risk of aneuploidy after surgery is not described in the literature.[10,13]

Considering the postnatal follow-up, 62% of our patients were exclusively breastfeeding their babies after 40 days, which is unsatisfactory considering that the World Health Organization (WHO) stipulates that exclusive breastfeeding should be maintained up to 6 months old. On the other hand, this is a good result if compared with another study performed in Brazil, in which this rate was near 40%, and it is close to the European rate of 67%. Maternal milk after bariatric surgery is as adequate for the baby as any other women's milk, and therefore we should stimulate considering the benefits for mother and baby like immune protection and nutrition, among others.[18,19]

In the postnatal follow-up, the preferred method was trimestral injection, which is not the method of choice in these patients, due to the weight gain. Most patients after surgery tend not to tolerate this adverse effect and therefore have low adherence to it. The best methods would be long action reversible contraception, especially levonorgestrel intrauterine devices or etonogestrel subdermal implants, since they decrease menstrual bleeding, in a predisposed population for anemia. Unfortunately, subdermal implants are not available in our service.[10]

Our study had some limitations. First, it is a small sample, even though it was possible to obtain statical significance from our data. Second, since this was a retrospective study analyzing medical charts, some data was missing, like type of surgery, which prevents us from making further analyzes. Our hospital is an exclusively obstetrical and gynecology hospital; therefore, we do not have access to their surgery report, and most patients do not know the procedure they were submitted to, which might explain the lack of information. Another limitation of the present study is that we did not have the dosages of elemental iron bioavailability for more accurate data.

In another perspective, our study innovates presenting that all iron salts seem effective in the iron deficiency treatment, and more relevant that changes of the iron salt, it, is improving iron intake. Intravenous treatment is also important and effective, and eventually the only alternative for patients that present many gastric symptoms, which is common in pregnant women and after bariatric surgery.[10]

Our study also innovates demonstrating that ethnicity is also a risk factor for anemia. Studies have showed that ethnicity has an impact in medical treatments and health developments and therefore we need to provide better care for black women.[16,17]

Conclusion

Anemia and iron deficiency are still an important health issue, especially in pregnant women after bariatric surgery. In our sample, the only other risk factor for anemia was being black. To manage it, proper screening and prescription of optimal dosages of iron is essential. As reported, all iron salts seem appropriate for these women.

Contributions

All authors contributed to the design of the study, were involved in the data collection, data analysis and/or interpretation. Also, all authors contributed to the writing/substantive editing and review of the manuscript and approved the final draft of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Obstetric and Perinatal Outcomes in Pregnant Women with Lupus: Retrospective Study in a Portuguese Tertiary Center

Desfechos obstétricos e perinatais de grávidas com lúpus: Estudo retrospectivo em um centro terciário português

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Abstract

Objective Pregnancy in women with lupus poses a higher risk of complications compared with the general population. The present study aimed to determine and describe the obstetric and neonatal outcomes of pregnant women with lupus.

Materials and Methods We conducted an observational retrospective study of pregnant women with the diagnosis of lupus, who were selected and followed at the Maternal-Fetal Medicine Clinic of our institution between January 2013 and July 2018. We analyzed 59 pregnancies and 52 newborns, and collected data regarding sociodemographic features, the preconception period, pregnancy, childbirth, postpartum and the newborn. A descriptive analysis of the variables was performed.

Results In 58% of the cases, the pregnancy was uneventful. We registered flares in 25% of the cases, preeclampsia in 3%, fetal growth restriction in 12%, gestational loss in 10%, preterm labor in 10%, postpartum complications in 20%, and small for gestational age newborns in 17% of the cases.

Conclusions Most pregnancies in women with lupus have favorable obstetric and neonatal outcomes. Prenatal counseling, adequate multidisciplinary surveillance, and optimized treatment of the disease are fundamental pillars for these good results.

Keywords
- lupus erythematosus
- pregnancy
- pregnancy outcome
- neonatal systemic lupus erythematosus
- Resumo

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Resumo

Objetivo A gravidez em mulheres com lúpus representa um risco maior de complicações em comparação com a população em geral. O presente estudo teve como objetivo determinar e descrever os resultados obstétricos e neonatais de gestantes com lúpus.

Materiais e Métodos Realizamos um estudo retrospectivo observacional de gestantes com diagnóstico de lúpus, selecionadas e acompanhadas no Ambulatório de Medicina Materno-Fetal de nossa instituição entre janeiro de 2013 e julho de 2018. Analisamos 59 gestações e 52 recém-nascidos e coletamos dados referentes às características sociodemográficas, período pré-concepcional, gravidez, parto, pós-parto e nascimento. Foi realizada uma análise descritiva das variáveis.

Resultados Em 58% dos casos, a gravidez transcorreu sem intercorrências. Registramos surtos em 25% dos casos, pré-eclâmpsia em 3%, restrição do crescimento fetal em 12%, perda gestacional em 10%, trabalho de parto prematuro em 10%, complicações pós-parto em 20% e recém-nascidos pequenos para a idade gestacional em 17% dos casos.

Conclusões A maioria das gestações em mulheres com lúpus tem resultados obstétricos e neonatais favoráveis. Aconselhamento pré-natal, vigilância multidisciplinar adequada e tratamento otimizado da doença são pilares fundamentais para esses bons resultados.

Palavras-chave

- lúpus eritematoso
- gravidez
- resultado da gravidez
- lúpus eritematoso sistêmico neonatal

Introduction

Systemic lupus erythematosus (SLE) is a chronic, systemic, and immune-mediated disease that mostly affects women of childbearing age.[1]

In the last years, there has been an increase in the overall survival rate, a higher number of pregnancies, and an improvement in obstetric and perinatal outcomes. This was due to greater access to preconception counseling and multidisciplinary surveillance throughout pregnancy, as well as better perinatal care.[2]

However, this disease carries a significant risk of obstetric and perinatal complications, the pathogenesis of which is mainly related to uteroplacental insufficiency, the inflammatory state underlying the disease, and the possibility of maternal immunoglobulin G (IgG) autoantibodies crossing the placental circulation and binding to fetal tissues.[3,4]

Regarding the obstetric complications, there is an increased risk of abortion, preterm birth, fetal death; the hypertensive complications include preeclampsia (PE), eclampsia (E) and/or hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome; other complications include gestational diabetes, fetal growth restriction (FGR), a higher rate of infections, thromboembolic complications, cesarean sections, and postpartum complications, including infection, hemorrhage, and lupus flares.[5–7]

Many predictors of complications and adverse outcomes have been described in the literature, namely: lupus nephritis, damage to other organs (lung, heart, central nervous system), interruption of the medical treatment, active disease in the six months before conception, antiphospholipid syndrome (APS) or the presence of persistent antiphospholipid antibodies, hypocomplementemia, thrombocytopenia, and high levels of anti-double stranded DNA (anti-dsDNA), anti-Sjögren's-syndrome-related antigen A (anti-SSA/Ro), and anti-Sjögren's-syndrome-related antigen B (anti-SSB/La) antibodies.[8,9]

Regarding newborns (NBs) of mothers with SLE, there is an increased risk of several complications, namely: prematurity, low birth weight. and neonatal lupus.[10–12]

The present study aimed to assess the obstetric and perinatal outcomes of pregnant women with SLE.

Materials and Methods

We conducted a retrospective observational study, in which we evaluated pregnant women diagnosed with SLE included in the database of the Materno-Fetal Medicine Clinic of our institution. We included women diagnosed with lupus who had been surveilled in the Obstetrics Department between January 2013 and July 2018. The study included 52 women, totaling 59 pregnancies and 52 NBs. We excluded pregnant women whose birth took place at another institution, as well as women and/or NBs whose clinical files were incomplete or unavailable for consultation.

We collected data regarding sociodemographic features and data relating to the pre-conception period, pregnancy, childbirth, postpartum and NB, and performed a descriptive analysis of the variables using Microsoft Excel 2013 (Microsoft Corp., Redmond, WA, United States) and IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States), version 25.0, with a confidence interval of 95% (95%CI) and a statistical significance level of 0.05. Early abortion was classified as a spontaneous pregnancy loss up to 11 weeks and 6 days; late abortion, as a pregnancy loss between 12 and 21 weeks and 6 days; fetal death, as an

intrauterine death from 22 weeks onwards; and preterm delivery, as those occurring between 22 and 36 weeks + 6 days. Preeclampsia was defined by hypertension and proteinuria and/or organ dysfunction after 20 weeks, in a previously normotensive woman, and gestational hypertension referred to hypertension without proteinuria after 20 weeks, in a previously normotensive woman. Fetal growth restriction was defined through an ultrasound estimate of fetal weight below the 3rd percentile or an ultrasound estimate of fetal weight below the 10th percentile for gestational age along with Doppler changes. Small for gestational age (SGA) was defined as an estimate of fetal weight below the 10th percentile for gestational age without Doppler changes, and large for gestational age (LGA) referred to fetal weight above the 90th percentile for gestational age. We also defined flare as an increase in lupus activity in a patient with inactive disease, and postpartum complications, as hypertensive, hemorrhagic, infectious complications, and postpartum anemia.

The present study was approved by the Ethics Committee of the hospital where it was performed, and international ethical standards were followed.

Results

Starting with the demographic features (►**Table 1**), the mean age of the pregnant women was of 33.5 ± 5.6 (range: 18 to 46) years, 92% were Caucasian, and 8% were of African origin. Regarding parity and previous obstetric history, most women were multiparous (53%), and there was a history of prior abortion in 25% of the cases, half of which were associated with APS; in 7% of the cases, there was a history of fetal death, half of them associated with APS. As far as lupus is concerned, the mean duration of the disease at the beginning of the obstetric follow-up in the Materno-Fetal Medicine Clinic was of 10.0 ± 6.3 (range: 0 to 25) years. The most frequent lupus manifestations were cutaneous, articular, immunological, and hematological (►**Fig. 1**). We registered a thromboembolic history in 14% of the cases and other rheumatologic diseases in 10%.

Before getting pregnant, most women in the sample (76%) did not undergo preconception consultation. Most were singleton pregnancies, but we registered one case of twin pregnancy. Regarding the clinical risk factors (►**Table 1**), most pregnancies started with the disease in an inactive state or in remission (90%). We observed lupus nephritis in the current pregnancy in 10% of the cases, APS in 25%, and hypertension in 10%, which was secondary to lupus nephritis in most cases (67%). Considering the laboratory findings (►**Table 1**), anemia occurred in 14% of the pregnancies, thrombocytopenia, in 7%, hypocomplementemia, in 14%, and proteinuria, in 17%. Regarding the antibody profile, there were positive antiphospholipid antibodies in 29% of the cases, positive anti-ribonucleoprotein (anti-RNP) antibodies in 15%, positive anti-dsDNA in 25%, and positive antinuclear antibodies (ANAs) in 63%, which were anti-SSA in 31% of the cases and anti-SSB in 14% of te cases, the latter always occurring concomitantly with the presence of anti-SSA. We registered some complications of the pregnancy (►**Table 2**), namely hypertensive complications, flares, growing disturbances, and abortive outcome; hypertensive complications were recorded in 10% of the cases, with 3% corresponding to PE and 7%, to gestational hypertension; 25% of the cases had a lupus flare, with the most frequent manifestations being skin rash, joint pain, vasculitis, and worsening of the proteinuria; FGR occurred in 12% of the pregnancies, and we recorded

Table 1 Sociodemographic, clinical, and laboratory features of the study sample

Sociodemographic, clinical and laboratory features	Frequency (n)	%
Sociodemographic features		
Caucasian race	54	92
African origin	5	8
Age: 18–29 years	18	30
Age: 30–39 years	34	58
Age: 40–46 years	7	12
Nulliparous	28	47
Multiparous	31	53
Duration of the disease < 10 years	24	41
Duration of the disease ≥ 10 years	35	59
Clinical features		
Active disease in the preconception period	6	10
Lupus nephritis	6	10
Antiphospholipid syndrome	15	25
Hypertension	6	10
Secondary to lupus nephritis	4	7
Primary	2	3
Laboratory features – analytical alterations		
Anemia	8	14
Leukopenia	3	5
Lymphopenia	3	5
Neutropenia	1	2
Thrombocytopenia	4	7
Hypergammaglobulinemia	1	2
Hypocomplementemia	8	14
Proteinuria	10	17
Not applicable*	3	5
Laboratory features – antibodies		
Antiphospholipid antibodies	17	29
Anti-ribonucleoprotein	9	15
Antinuclear antibodies	37	63
Anti-double stranded DNA	15	25
Anti-Sjögren's-syndrome-related antigen A	18	31
Anti-Sjögren's-syndrome-related antigen B	8	14
Not applicable*	3	5

Note: *Not applicable due to early abortion, and no analytical evaluation was performed ($n = 59$).

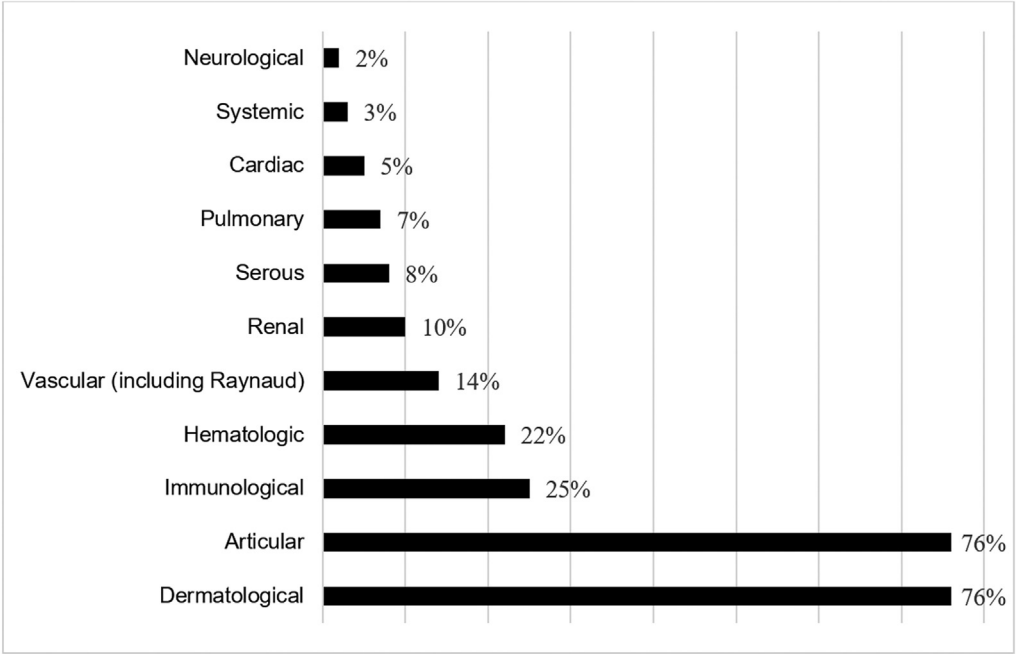

Fig. 1 Preconceptional manifestations of lupus, relative frequency ($n = 59$).

early abortion in 5% of the cases, late abortion in 3%, and fetal death in 2% ($n = 1$). The case of fetal death occurred at 30 weeks, in a fetus with trisomy 18. Delivery was uneventful in most cases. The mean gestational age at delivery was of 38 weeks and 4 days ± 10 days, with preterm delivery occurring in 10% of the cases. We registered normal vaginal delivery in 32% of the cases, delivery assisted by vacuum extraction in 9%, forceps in 9%, forceps after failed vacuum extraction in 6%, and cesarean section in 44% of the cases (planned in 25% and intrapartum in 19% of the cases). The immediate postpartum period was marked by complications in 20% of the cases (►**Table 3**): de novo hypertension in 2%, anemia in 10%, postpartum hemorrhage in 2%, and infection in 7%. We did not observe thromboembolic complications. In the postpartum period, we recorded flares in 2% of the cases, with hematological manifestations.

Table 2 Complications during pregnancy and the postpartum period ($n = 59$)

	Frequency (n)	%
Complications of pregnancy		
Fetal growth restriction	7	12
Gestational diabetes	6	10
Gestational hypertension	4	7
Early abortion	3	5
Preeclampsia	2	3
Late abortion	2	3
Respiratory infection	2	3
Pregnancy cholestasis	2	3
Thromboembolic events	1	2
Fetal death	1	2
Complications of the postpartum period		
Hypertensive (de novo hypertension)	1	2
Anemia	6	10
Hemorrhage	1	2
Infection	4	7
Respiratory	2	3
Urinary	1	2
Surgical wound	1	2

As far as treatment is concerned (►**Table 3**), 19% of the pregnancies occurred in women who were not undergoing any type of treatment. In total, 80% of the medicated women were taking hydroxychloroquine (HCQ), 56% were under corticosteroid therapy with prednisolone, 22% were medicated with azathioprine, 39% were taking acetylsalicylic acid (ASA), and 17%, enoxaparin. During pregnancy, most women were medicated with HCQ (85%) and/or prednisolone (56%), and 25%, with azathioprine, and 3% with tacrolimus. Most pregnant women took ASA (58%), and 32% took enoxaparin. In the postpartum period, therapy was similar to that recorded during pregnancy.

We had a sample of 52 NBs, and 59% of them were female. The mean birth weight was of 2,968 ± 462 g (range: 1,920 g to 3,845 g), with 17% of the cases being SGA. We did not register any LGA NBs. In 90% of the cases, the NBs were hospitalized with their mothers, and 10% needed special neonatal care. Most NBs had no clinical or laboratory alterations. Upon physical examination (►**Table 4**), 31% had jaundice, 2% had exanthema, and 8% had alterations in the primitive reflexes; there were no other relevant changes. Regarding the NBs who underwent analytical evaluation (►**Table 4**), 5% had anemia, 2% had thrombocytopenia, 48%

Table 3 Therapy administered in the preconception period, throughout pregnancy, and the postpartum period ($n = 59$)

Treatment	Preconception: n (%)	Pregnancy: n (%)	Postpartum: n (%)
None	11 (19%)	4 (7%)	4 (7%)
Hydroxychloroquine	47 (80%)	50 (85%)	50 (85%)
Prednisolone	33 (56%)	33 (56%)	34 (58%)
Azathioprine	13 (22%)	15 (25%)	15 (25%)
Tacrolimus	0	2 (3%)	2 (3%)
Acetylsalicylic acid	23 (39%)	34 (58%)	34 (58%)
Enoxaparin	10 (17%)	19 (32%)	18 (31%)

had hyperbilirubinemia, 5% had an increase in gamma-glutamyl-transferase, and 13% had hypoglycemia; the autoimmune profile was determined in a minority of NBs. An electrocardiogram (ECG) was requested in 71% of the NBs, with no alterations in the atrioventricular conduction.

Table 4 Alterations on the physical and laboratory examinations of the newborns

	Frequency (n)	%
Physical examination		
Exanthema	1	2[a]
Jaundice	16	31[a]
Heart murmurs	1	2[a]
Respiratory distress syndrome	1	2[a]
Primitive reflex changes	4	8[a]
Laboratory findings		
Blood count	43	83[a]
Anemia	2	5[b]
Leucopenia	8	19[b]
Platelet count	42	81[a]
Thrombocytopenia	1	2[c]
Liver profile	21	40[a]
Increased transaminases	3	14[d]
Hyperbilirubinemia	10	48[d]
GGT increase	1	5[d]
Antibody profile	5	10[a]
Positive antibodies	3	60[e]
Antinuclear antibodies	3	75[f]
Anti-double stranded DNA	1	50[c]
Anti-Sjögren's-syndrome-related antigen A	1	20[e]
Anti-Sjögren's-syndrome-related antigen B	1	20[e]
Complement dosage	1	2[a]
Hypocomplementemia	1	100[g]
Blood glucose measurement	23	44[a]
Hypoglycemia	3	13[h]

Notes: [a]n = 52; [b]n = 43; [c]n = 2; [d]n = 21; [e]n = 5; [f]n = 4; [g]n = 1; [h]n = 23.

Discussion

In the series herein presented, the percentage of pregnancy loss was of 8%. This value is below the average found in the literature, with values in the order of 20% to 30%, probably related to the lack of records of early abortions.[12,13] There are some identified risk factors for abortion, namely: a history of abortion, proteinuria, APS, AAF, thrombocytopenia, hypocomplementemia, positive anti-dsDNA antibodies, HTA, exacerbations, previous lupus nephritis, PE/E, active disease in the six months before conception, and inaugural SLE in pregnancy.[7,8,14–16]

Of the 5 cases of women with abortion that we recorded, 4 had concomitant APS, and this condition was registered in 25% of the study sample. The association between APS and adverse obstetric outcomes has been described, including miscarriages, FGR, PPT, and hypertensive disorders in pregnancy.[8,14–16]

Recent data report an European rate of prematurity ranging from 5% to 9%, which contrasts with the 30% to 33% reported in the literature regarding the global population of NBs whose mothers have SLE.[17–19] In the sample of the present study, we found 10% of preterm deliveries, a percentage substantially lower than the values reported in the literature concerning the global population with SLE. We highlight that all the preterm NBs in the present series were late preterm.

Several studies[5,7,8,14,20,21] report an association of preterm delivery with some risk factors, namely: high disease activity at conception, positive antiphospholipid antibodies, APS, flares, obstetric history of abortion, thromboembolic complications, previous lupus nephritis, hypertension, PE/E, hypocomplementemia, proteinuria, positive anti-dsDNA antibodies, thyroid disease, and prednisolone treatment dose higher than 15 mg/day.[5,7,8,14,20,21]

Fetal growth restriction occurred in 12% of the cases, which is similar to the values already described, which range from 6% to 30%.[5,12,13,22] The literature describes a relationship between FGR and some predictors, namely: APS, positive antiphospholipid antibodies, hypertension, or lupus nephritis.[9]

As for PE, it occurred in 2 cases (3%), 1 of which overlapped with chronic hypertension. This percentage is in the range of incidence referred in different studies, which is of 3% to 30%,

and is also similar to the percentage found in the population of pregnant women without SLE (~ 5%).[5,12,13,18,22,23] There is a well-described relationship between PE and the existence of lupus nephritis,[14,24] as well as with some other risk factors, such as positive antiphospholipid antibodies, APS, hypocomplementemia, and positive anti-RNP or anti-dsDNA antibodies.[5,8,18,24–26]

In about a quarter of the pregnancies (25%), SLE flares occurred, the most frequent manifestations being cutaneous and articular, which is in agreement with the literature.[9,24]

It is known that active disease in the preconception period is a predictor of the occurrence of flares. In the present study, it is possible that the absence of disease activity before pregnancy, which was observed in most patients (90%), contributed to the low rate of flares (~ 25%), which is comparable to the rates reported in other studies, with an incidence ranging from 10% to 33%.[18,27,28]

Most of the sample of the present study had a mild form of the disease, which was probably the main contributing factor to the considerably favorable results. On the other hand, most patients (85%) received HCQ as part of their treatment during pregnancy, which may have also contributed to the good outcomes obtained.

Hydroxychloroquine was identified as a protective factor against adverse outcomes, especially flares.[29] The literature also associates this drug with possible preventive effects regarding to congenital atrioventricular block, and some studies also report a therapeutic effect on this condition, as well as effects in the reduction if prematurity, FGR and SGA.[8,30,31] In the present study, we did not identify changes in atrioventricular conduction in any of the NBs in the sample.

Flares in the immediate postpartum period were much less significant, with only one case, which occurred in a patient with a record of exacerbation during pregnancy. Some studies have demonstrated that patients with flares during pregnancy have an increased risk of developing postpartum exacerbations.[18]

The rate of SGA NBs in the general population is of ~ 10%.[19] In the present study, we found that 17% of the NBs were SGA, which is in agreement with the results obtained in previous studies (10% to 30%).[10] There are variables associated with SGA NBs, including African origin, prematurity, hypertensive complications or lupus nephritis.[24,26,32]

Neonatal lupus is a rare syndrome, which occurs in 1% to 2% of NBs to mothers with anti-SSA and/or anti-SSB autoantibodies, manifesting more frequently by cardiac, cutaneous, hematological, and hepatic alterations. In the present study, none of the documented alterations in the NB was presumably associated with an autoimmune etiology; as an example, the high incidence of jaundice can be related to hemolytic disease of the NB. However, it should be noted that the manifestations of neonatal lupus can mimic many other neonatal pathologies, possibly appearing at a later stage.

The percentage of NBs in need of special neonatal care was similar to the percentage of general NBs in our institution with this need (10% versus 11%).

The present study incorporates the limitations inherent to a small sample resulting from a retrospective analysis of a single center and for a limited period of time. Other limitations are related to the exclusive access to the records of the NBs during the period of hospitalization, and we did not consult records related to subsequent hospitalizations, follow-up appointments or admissions to the emergency service, which would be of interest, given that the manifestations related to neonatal complications in NBs to mothers with SLE may appear during the first weeks/months of life.[4] The fact that pregnant women who gave birth outside our institution were not included led to the exclusion of part of the pregnancies in follow-up, which constitutes another limitation of the present study, as well as the fact that the absence of electronic clinical records during the study period led to the exclusion of pregnant women and NBs whose handwritten files were not available for consultation or had incomplete data.

Conclusion

In conclusion, we found that most women in this sample had good obstetric and neonatal outcomes, with low rates of abortion, preterm birth, and PE. The most frequent complications were FGR and SGA NBs, but even so, with rates similar to those obtained in other series. The fact that most women had a mild form of the disease and were taking HCQ during pregnancy may have contributed to the good obstetric and neonatal outcomes observed. Thus, although most pregnant women with SLE have favorable obstetric and perinatal outcomes, these women continue to represent a risk group for obstetric complications. To improve obstetric and perinatal outcomes, it is essential to plan the pregnancy during a remission phase of the disease, so that adequate multidisciplinary surveillance of the pregnancy and optimal treatment of the disease can be performed, as well as to plan the delivery in a differentiated perinatal center.

Contributions

All the authors contributed equally to the present paper, namely to the conception and design, data collection or analysis, interpretation of data, writing of the article, and review of the intellectual content. Therefore, all authors approved the final version to be published.

Conflict of Interests

The authors have no conflict of interests declare.

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Adaptation and Validation of the International Pelvic Pain Society's Quality of Life Questionnaire in Portuguese

Adaptação e validação do questionário de qualidade de vida da International Pelvic Pain Society em português

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Abstract

Objective In the present study, our aim was to translate, adapt, and validate the Pelvic Health History Form (a quality of life [QoL] questionnaire) of the International Pelvic Pain Society (IPPS) from English to Portuguese.

Methods The study was approved by the Ethics and Research Committee (CEP, in the Portuguese acronym) and the IPPS. The "Transcultural Adaptation" method comprised 5 stages: translation, synthesis, backtranslation, expert review, and pretest. Cultural adaptation and validation included cognitive interviews and statistical analysis of unanswered items ($>$ 15%) in 14 clinic patients from CPP and endometriosis clinic at Santa Casa de São Paulo.

Results Strong equivalences were established between the USA and Brazil questionnaires in terms of semantics, idioms, experiences, and concepts. Eighteen culturally inappropriate items were identified and adjusted using the revised response rate index. The subjective form underwent rigorous assessments, confirming its accurate measurement of intended targets.

Conclusion The methodology showed efficiency and equivalence, confirming its validity. The user-friendly format and inclusion of translated, adapted, and validated instruments in Portuguese make the form valuable for evaluating pelvic health, with potential for future research.

Keywords
- surveys and questionnaires
- quality of life
- translation
- validation study
- pelvic pain
- chronic pain

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Resumo

Objetivo Realizar a tradução, adaptação e validação do questionário de qualidade de vida Pelvic Health History Form da International Pelvic Pain Society (IPPS, na sigla em inglês) para a língua portuguesa.

Métodos Aprovação do Comitê de Ética e Pesquisa (CEP) e consentimento do IPPS. A metodologia "Adaptação Transcultural" foi utilizada em cinco etapas: (I) tradução; (II) síntese; (III) retradução; (IV) revisão pelo comitê de especialistas; (V) pré-teste, seguido de adaptação cultural e validação por meio de entrevista cognitiva e análise estatística da taxa de ausência de respostas $>$ 15% após aplicação do instrumento em 14 pacientes do ambulatório de DPC e endometriose da Santa Casa de São Paulo.

Resultados Equivalências semântica, idiomática, experiencial e conceitual entre o questionário de país fonte (EUA) e alvo (Brasil) foram bem estabelecidas. Dezoito itens culturalmente impróprios, de acordo com o índice de ausência de respostas revisados, adaptados e realizada validade de face e de constructo, avaliando forma subjetiva, confiável que o instrumento mede o que pretende medir.

Conclusão A metodologia utilizada foi eficiente, com boa equivalência com o material de origem concluindo a sua validade. Formulário de formato simples, fácil aplicação e compreensão, composto por diversos instrumentos já traduzidos, adaptados e validados em nossa língua. O formulário auxilia avaliação multidimensional da saúde pélvica destas pacientes e poderá ser utilizado em estudos futuros.

Palavras-chave

- inquéritos e questionários
- qualidade de vida
- tradução
- estudo de validação
- dor pélvica
- dor crônica

Introduction

Chronic pelvic pain (CPP) is a complex and multifactorial condition, defined by the American College of Obstetricians and Gynecologist as pain in the pelvic area that lasts for $\geq$ 6 months, is intermittent or constant, cyclic or noncyclic, and strong enough to cause functional disturbances or require medical care.[1,2] It is a health problem estimated to affect between 6 and 27% of women worldwide.[3] This disease is responsible for 20% of gynecological consultations, and 45% of reduced productivity at work leading to significant socioeconomic expenses and rates of up to 66% of association with anxiety and 63% with depression.[4–6] Its etiology is quite complex due to the interaction between gynecological, gastrointestinal, urological, musculoskeletal, and psychological disorders with potential mechanisms that lead to sensitization of the nervous system.[7] It is estimated that only 30% of the etiologies attributed to CPP are primarily gynecological,[2] with endometriosis as the main cause, with a rate of 24 to 40%.[8] However, CPP of unknown etiology accounts for up to 55% of cases.[5] Additionally, given the variable, multifactorial, and uncertain nature of the etiology of this syndrome, the difficulty in accurately diagnosing it, and considering CPP a condition with symptoms that are associated with behavioral, affective, social, and cognitive consequences, it is of utmost importance to use a specific questionnaire that addresses these domains and is aimed at comprehensively evaluating all aspects related to CPP.[5,9]

The process of translating, adapting and cross-culturally validating a health questionnaire to a new language, culture, or country, requires a unique method that maintains equivalence between the original and the new version.[10,11] Recent reviews in the literature suggest that questionnaire translations should be conducted through guidelines to ensure cultural and linguistic quality. However, current guidelines focus exclusively on the translation and adaptation process, which transforms the questionnaire, but does not cover the validation process that assesses the quality of the questionnaire, which is considered a separate methodological process although both seem to be conjoined.[12]

Moreover, Beaton et al. suggest a cross-cultural adaptation guideline based on the first step of the three stages of the process adopted by the Society for Quality of Life Assessment (IQOLA).These guidelines follow six phases that are very similar among most authors: I – initial translation; II – synthesis of the translation; III – backtranslation; IV – expert committee review; V – test of the prefinal version; VI – submission of the document to the developers or coordination committee for appreciation of the adaptation process.[11]

The validation stage of instrument formation tends to be more contested by reviewers. Several instruments for measuring this validation process were created; however, they were considered somewhat confusing and ended up being based on an empirical demonstration of the adaptation of this instrument in the target population.[10]

Considering the complex nature of CPP, the importance of a precise diagnosis, and the diverse multinational and multicultural characteristics of quality of life questionnaires in their original languages, as well as the necessity to adapt these measures for Brazilian research projects, we undertook the translation, adaptation, and validation process of the Pelvic Health History Form, a quality of life questionnaire revised in June 2019 by the International Pelvic Pain Society (IPPS), specifically for the Portuguese language, aimed at

facilitating the diagnosis of CPP within our settings, which lack dedicated questionnaires available in Portuguese.

The objective of the present study was to carry out the translation, adaptation, and validation of the quality of life questionnaire Pelvic Health History Form of the IPPS into Portuguese.

Methods

A protocol was developed for the translation and validation of the QoL Pelvic Health History Form questionnaire from the IPPS into the Portuguese language. The flowchart outlines the steps involved in this process, with the original English version revised in June 2019 serving as the foundation. Upon submission and approval of the project by the Investigation Review Board (IRB) under CAAE 40166520.8.0000.5479, and with consent from the IPPS, the methodology of "Cross-Cultural Adaptation" was employed following six detailed phases as described below.[10,11] (**Flowchart 1**).

I – Initial translation: the instrument was translated into Portuguese by a bilingual Brazilian translator with an American Translator Association (ATA) English to Portuguese Certification #464880 who worked independently and had no understanding regarding the purpose of the study, generating the Portuguese version (T1).

II – Translation synthesis: the document was then reviewed by a specialist in the field of chronic pelvic pain and gynecology (Ribeiro H. S. A. A.) who was aware of the objective of the study and made her considerations based on her knowledge of the subject in question.

III – Backtranslation: the revised version was backtranslated into English by two other native Portuguese-speaking bilingual individuals, one of them mastering the theme and object of the study in question and the other non-mastering, generating two new versions in English (BT1 and BT2).

IV – Expert Committee: in the prefinal phase, a committee of experts formed by two gynecologists with expertise in CPP (Ribeiro H. S. A. A. and Silva J. C. R.), a physiotherapist (RFC) and two bilingual translators (Brito L. G. O. and Ribeiro P. A. A. G.) compared all versions (T1, BT1, and BT2) with the original in English. Necessary adjustments and adaptations were made to obtain the appropriate prefinal version of the questionnaire in Portuguese.

V – Testing of the Prefinal version: this version of the questionnaire was applied in a self-test format to a sample of 14 women, randomly selected at the Gynecological Endoscopy and Endometriosis Division of Santa Casa de Misericórdia de São Paulo from June 22 to June 29, 2022. Inclusion criteria were patients with complaints of pelvic pain for >6 months, aged between 18 and 45 years old, sexually active, and still in menacme. Exclusion criteria included menopausal patients, prior hysterectomy patients, and patients previously treated for pain with medication or surgery patients.

To assess cultural adaptation and validation, each patient was led to a private room and invited to participate in the study. Patients were explained the purpose of the questionnaire followed by the signing of the informed consent form. The test was applied individually so that the patient herself answered the questionnaire without help. They were instructed to leave the topics they did not understand unanswered. Immediately after each application, semistructured interviews were carried out for a careful analysis of each item, including their responses addressing their understandings and difficulties in interpretation and responses during the previous phase in order to evaluate the semantic, idiomatic, conceptual, and experiential equivalence with the committee of experts. For statistical purposes, positive responses were considered when the patients had a good reaction to the question.

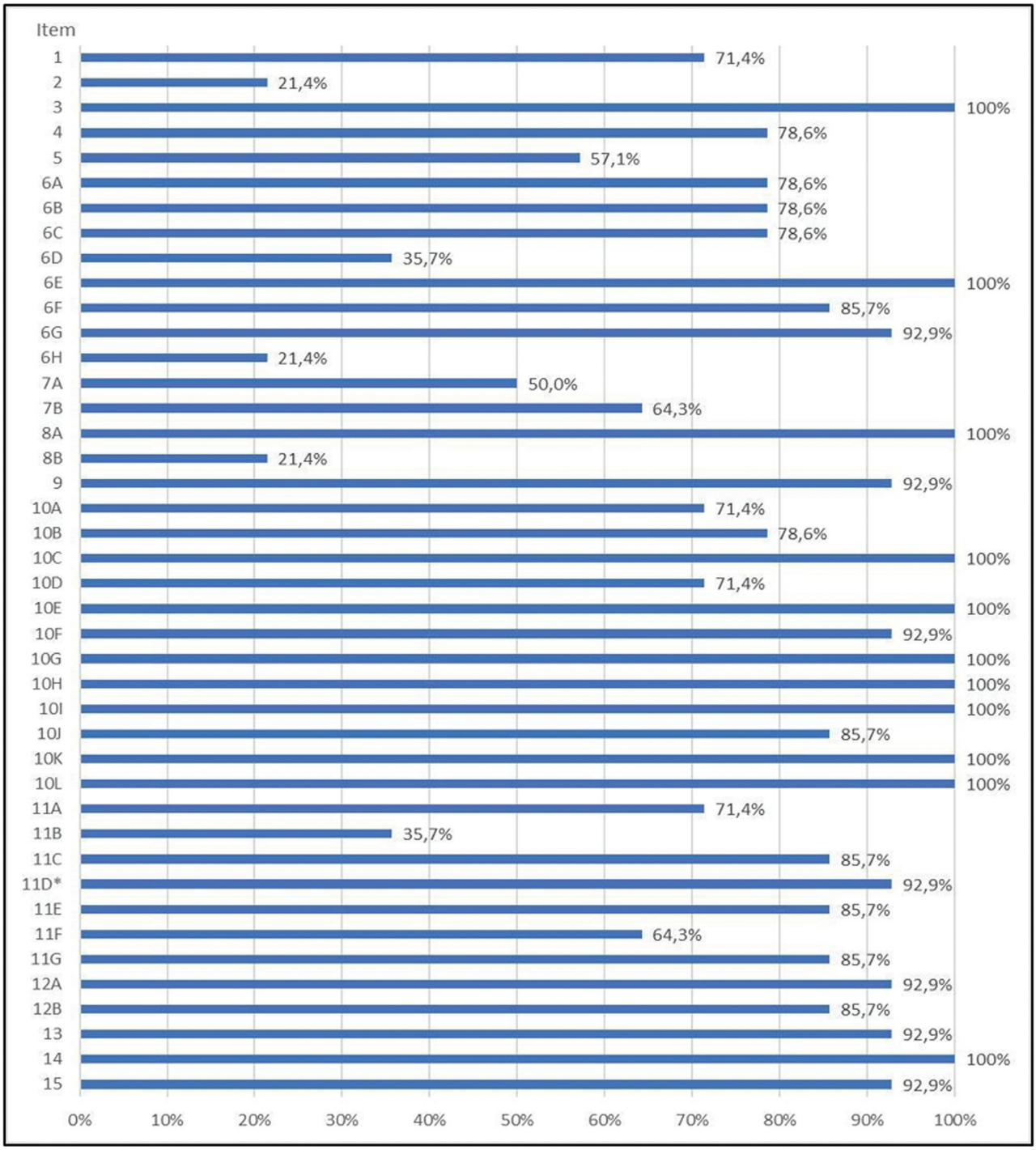
After this step, a statistical analysis of the response rates for each item and subitem of the questionnaire was performed.[12,13] We evaluated the rate of nonresponses in each item and subitems in order to identify which questions would be culturally incompatible (defined as those with $\geq$ 15% of nonresponses), so that they could be adapted appropriately. These questions were selected and reviewed by the expert committee to assess the increased rates of nonresponses, focusing on adapting them culturally, while also preserving the same concept in a manner that the structure and evaluation properties of these questions were not altered. After conducting a comprehensive analysis, the committee of translation experts engaged in insightful discussions to identify areas for enhancement and implement necessary adaptations to the questionnaire. As a result, the final version was successfully completed, ensuring semantic, grammatical, experiential, and conceptual equivalence of the QoL questionnaire in Portuguese. The validated instrument was then submitted to the IPPS for approval and recognition (►**Supplementary Material Annex 1**).

Results

The demographic profile of the sample, as presented in ►**Table 1**, indicated that the patients had a mean age of 34.5 years old (standard deviation [SD]: 8.2), the majority of patients self-identified as white (42.9%) and were married (42.9%), half of the patients reported being sexually active with men (50%), $\sim$ 70% of the sample had completed high school and/or higher education, more than half of the participants (57.1%) were employed outside the home, and an equal percentage (57.1%) lived with a partner.

Following the administration of the instrument and conducting individual interviews for questionnaire analysis, we obtained positive and satisfactory results. Most patients showed good acceptance of the instrument as indicated by their favorable evaluation of the concepts addressed. These findings are summarized in ►**Table 2**, which was created based on the analysis of the questions asked during the semistructured cognitive interviews.

Among the questions that did not receive 100% positive responses, we noticed that in item 4, which asked if patients understood everything they were asked, the majority (64.3%) understood most of the questionnaire. However, some



Flowchart 1 Detailed phases of the process.

patients highlighted flaws and left certain questions blank (items 11 and 12) due to confusion caused by the translated image tables. Regarding item 5, which asked if there were difficulties with any response, 21.4% of the participants experienced difficulties with the response format for item 11, which was based on the McGill pain quality approach. In item 6, which inquired about difficulties with specific words or interpretations, 7.1% of the participants had trouble understanding the word *vesicais* (item 14), which addressed *infecções urinárias frequentes*. Moreover, these observations provide valuable feedback on areas that may require further clarification or refinement in the translated instrument. Regarding the time to complete the form, when asked in question 8 if they found it time-consuming and how long they estimated it took to answer, only 35.7% of the patients did not consider it time-consuming, while 28.6% thought it was time consuming, and 35.7% thought it was just a bit time consuming. Overall, patients were dissatisfied with the time it took to complete the questionnaire. The perception of time varied from 10 to 60 minutes (median of 32.5 minutes), while

Table 1 Demographic dada

	n	%	Mediam/SD/Min-Max
Age (years old)	12	–	34,5 (8,2) (21-44)
Ethnicity	–	–	–
White	6	42.9	–
Black	5	35.7	–
Other	3	21.4	–
Marital status	–	–	–
Single	2	14.3	–
Married	6	42.9	–
Widowed	1	7.1	–
Stable relationship	4	28.6	–
No answer	1	7.1	–
Sexual practice			–
Sexually active with men	7	50.0	–
Sexually active with women	3	21.4	–
Abstinent	3	21.4	–
No answer	1	7.1	–
Level of Education			–
$<$ 12 years of study	2	14.3	–
Complete high school	5	35.7	–
Complete university education	5	35.7	–
No answer	2	14.3	–
Type of work			–
Unemployed	3	21.4	–
Works outside home	8	57.1	–
Homemaker	3	21.4	–
Coexistence			–
Alone	1	7.1	–
Partner	8	57.1	–
Relatives	3	21.4	–
Another family member	2	14.3	–

Abbreviation: SD, standard deviation.

Table 2 Evaluation of positive responses per item n (%) of patients with chronic pelvic pain at the gynecological endoscopy and endometriosis outpatient clinic

Question	*n* (%)
1. Does the questionnaire represent the pain you feel?	14 (100%)
2. Has everything you feel been addressed? Or was something missing?	14 (100%)
3. Do you believe that the instrument will help health professionals to better understand your pain?	14 (100%)
4. Did you understand everything that was asked? If not, what did you not understand?	9 (64.3%)
5. Did you have difficulty with any answers?	3 (21.4%)
6. Did you have difficulty with any specific words or interpretations?	13 (92.9%)
7. Were you embarrassed to answer?	14 (100%)
8. Did you find it time consuming? And how long do you think it took to respond?	4 (28.6%)
9. Do you think the questionnaire could be shortened?	8 (57.1%)
10. What did you think of the questionnaire? Do you believe it will be useful in helping your diagnosis?	14 (100%)

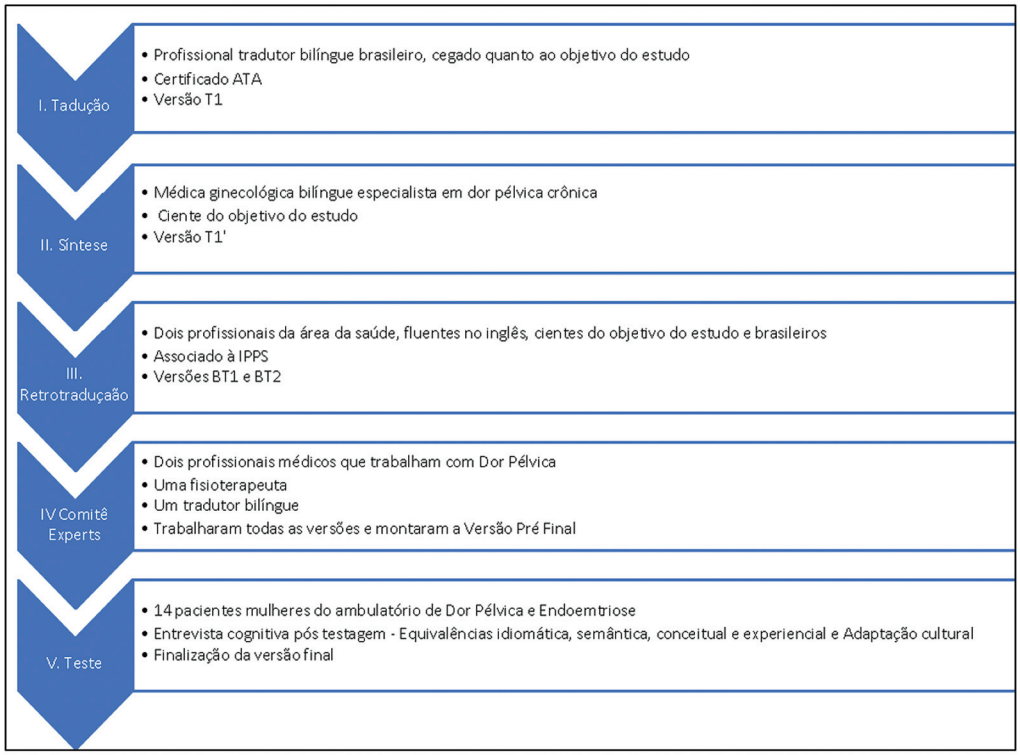


Fig. 1 Percentage of responses per item.

Table 3 Assessment of perception of time in minutes by patients with chronic pelvic pain

	n	median (min–max)	*p-value*
Perception	12	32.5 (10–60)	$< 0.001^{**}$
Real time	13	58.0 (31–75)	

**p-value obtained by the Wilcoxon test.

the reality of scheduled time ranged from 31 to 75 minutes (median of 58.0 minutes). The comparison between the perceived time and the actual scheduled time was assessed using the p-value obtained from the Wilcoxon test, as presented in ►**Table 3**.

A little over half of the participants (57.1%) expressed that, despite its length, the questionnaire should not be shortened. They believed that all the questions included were important, which was evident when asked if they thought the questionnaire could be shortened. During the statistical analysis of the questionnaire responses, we examined a total of 42 items/subitems. Among these, we identified 18 that were deemed culturally inappropriate, based on the criterion of response absence rate > 15%. These findings are depicted in ►**Fig. 1**.

Discussion

Our study was inspired by the understanding of the complexity of CPP and the realization that there is no extensive questionnaire available that could guide us more easily towards the diagnosis of the disease. Therefore, we chose to carry out the translation, adaptation, and validation into Portuguese of the quality of life questionnaire Pelvic Health History Form of the International Pelvic Pain Society revised in June 2019.

The process of cross-cultural adaptation and validation is indeed lengthy, but it holds significant importance in adapting multinational/cultural quality questionnaires and promoting the use of these measurements in Brazilian research projects.

As the literature suggests, the guidelines used in the questionnaire translation process were based on the cross-cultural adaptation of the medical, sociological, psychological, and methodological literature, resulting in a complete adaptation process that conferred a semantic, idiomatic, experiential, and conceptual equivalence between the source country (USA) and target country (Brazil) questionnaires, as well with several other already recognized questionnaires.[10–12,14–19]

The backtranslations demonstrated a high level of agreement with the original English version. Cognitive interviews conducted with semistructured questions indicated excellent acceptability and comprehension of the questionnaire, consistent with previous findings by other researchers (►**Table 2**).[18,19] All respondents regarded the items as relevant (questions 1, 2, and 3), non-offensive (question 7), and useful (question 10). Approximately 64% of the patients found the questions to be easily understandable (question 4), and there were minimal difficulties encountered regarding specific terminology or the interpretation of questions

and answers (questions 5 and 6). None of the participants suggested any modifications to the instrument, although over half of them (64.3%) acknowledged that the questionnaire could be perceived as "time-consuming" or "slightly time-consuming"; however, they did not think it should be reduced (57%).

An important consideration is the method of questionnaire administration. In the literature, we observed that the SF-36 questionnaire was designed to be a straightforward instrument, with clear and easily understandable direct questions, typically administered in a self-report format. A crucial characteristic of a questionnaire is its reasonable application time. In comparison with the translation and validation study of the SF-36, which reported an average application time of 7 minutes, our study recorded an average time of 58 minutes. This discrepancy may explain the higher rate of unanswered questions as the patients did not exhibit difficulties with the questions during the interviews themselves.

The translated questionnaire utilized simple language, making it easy to understand and easy to self-administer. Although a few items analyzed showed a higher rate of unanswered response (above or equal to the acceptable threshold of 15%), primarily in questions related to contact information (item 1), professional contact information (item 2), clinical history (item 4) and surgical history (item 5), menstrual history, birth control, and STIs (items 6A, 6B, 6C, 6D, and 6H), allergies and medications (items 7A and 7B), obstetric history (8B), history, description, and contributing factors of pain (10A , 10B, and 10D), location of pain, intensity scales and treatments performed (11A, 11B, 11D, and 11F), most of these instances were due to a lack of attention, often precipitated by the lengthy completion time of the questionnaire. As identified through the cognitive interview, there was no need to modify the content of the questions or answers, hence only minor text formatting corrections were made.

During the cognitive interview, a comprehensive analysis of all items in the translated questionnaire was conducted, comparing the findings with the completion statistics. The most significant observations were carefully examined and discussed. Regarding item 1, which focused on contact information, although all participants indicated their understanding of the question, many were reluctant to provide personal identification, even though they were assured of data confidentiality. This justified the slightly higher response rate, which remained above the recommended threshold of 15%. Additionally, in this item, it was decided to adapt the response options by including "Portuguese" as an answer choice for preferred language of communication.

Furthermore, in item 6D, where participants were asked about the duration of their menstrual cramps, it was found that 64.3% did not provide a response. Many participants explained that they experienced pain but not specifically cramps. Therefore, it was determined to modify the term to "menstrual pain" instead of "menstrual cramps" to better align with participants' experiences. Regarding the item addressing ethnicity (item 3), although it was considered culturally appropriate based on the response rate, it was decided to adapt it according to the race classification defined by the Brazilian Institute of Geography and Statistics (IBGE, in the Portuguese acronym) to ensure consistency with the categorization of the population. These adaptations and modifications were made to enhance the clarity, relevance, and cultural appropriateness of the questionnaire based on the cognitive interview feedback.

The study findings indicated that the utilization of simple, objective, and direct questions with minimal descriptors was associated with a lower rate of unanswered responses. Notably, items 8A, 10E, 10G, 10H, 10I, 10K, and 10L achieved a complete response rate of 100% without any reported difficulties by the participants

The assessment of pain location, intensity, and characteristics, as well as psychological aspects, were based on questionnaires already recognized, translated, and validated into Portuguese. These included the short version of the McGill Questionnaire, the Visual Analogue Scale (VAS), the short form of the Pain Intensity Scale, the Sexual Function Profile PROMIS version for women, men, and global health, and the Pain Catastrophizing Scale (PCS) and the DASS-2.

Regarding the characteristics of pain in the short version of the McGill questionnaire contained in item 11B, 9 patients (64.3%) did not provide a response. This observation raises several considerations. Notably, the patients encountered the greatest difficulty in answering this particular item, likely due to the complex evaluation format employed in the original proposed form. In addition, the example formatting was less prominent, and there was a formatting error in the answer table, which led to confusion and subsequent difficulty in understanding and responding. In comparison, the other scales mentioned in this form were found to have clearer questions and answers, resulting in a higher response rate (items 11C/D/E and 15). However, since there was no semantic and conceptual difficulty, it was decided to keep the translation according to the original McGill content and highlight only its presentation form to facilitate understanding. The McGill Questionnaire (MPQ) was initially developed in 1970 and has since been considered as an important tool for the quantitative assessment of subjective pain experiences. Its shorter version was developed a decade later (Sort Form-MPQ), consisting of 15 descriptors (11 sensory and 4 affective) and complemented with the VAS and the verbal scale of pain in the present moment (present pain intensity [PPI]). In our questionnaire, derived from this instrument, we maintained the anatomical map from the original version, along with the 15 descriptors and their qualitatively classified intensities (mild, moderate, and severe). Additionally, items were included to assess the duration of the pain, the guided location using the anatomical map, and the VAS. The purpose of this item is to evaluate the location, duration, type, and qualitative intensity of pain. However, the formatting of this item was found to be generalized and visually complex, leading to some confusion during its completion, even among the expert professionals who assisted in validating the questionnaire. Despite this issue, it was determined that the official translation provided by

Menezes Costa et al. in 2011, which had already undergone validation, would be retained for consistency.[20,21]

As mentioned in the translation and validation study conducted by Flynn et al. in 2013, the subitem 11D of our questionnaire includes the SexFS Version 1.0 from PROMIS. This questionnaire was specifically designed to assess sexual function and satisfaction in both males and females, comprising a total of 81 items.[22] The psychometric properties of this instrument were evaluated using both quantitative (development scales) and qualitative (psychometric evaluation) measures, providing researchers with information regarding its reliability and validity as a measure of sexual function and satisfaction for both genders. However, it is worth noting that a criticism of this study is the lack of testing the male version on male participants. The Global Health Scale v1.1, developed by PROMIS, is notable for its ability to assess overall perceptions of physical, mental, and social health using a limited number of items. This scale consists of a total of 10 items and can be completed in a short time, $\sim$ 2 minutes. The scale has been previously translated and validated by Zumpano et al. in 2017. In our questionnaire, the eight items used for scoring are included from this instrument, as well as the item Global 07 from the original scale. However, there are no fields or cutoff points provided for evaluating the results. It should be noted that the global nonscoring question 08, which asks about fatigue, is absent in our version, which may be considered a limitation of the original IPPS questionnaire.[23] The DASS-21 questionnaire, a shortened version of the DASS questionnaire, is included in our questionnaire as item 15. It consists of three subscales, each containing seven items that assess emotional aspects such as depression, anxiety, and stress. The questionnaire consists of a total of 21 items that are rated on a 4-point Likert scale. The translation and adaptation of the DASS-21 to Brazilian Portuguese was conducted by Vignola et al. in 2014,[24] following a methodology similar to the cross-cultural method used in our study. The translation process involved multiple iterations of translation, revision, backtranslation, and finalization. It takes approximately 30 minutes to complete the DASS-21 questionnaire.

It should be noted that in the original IPPS questionnaire, the last item of the DASS-21 questionnaire was replicated, while the last item of the original DASS-21 version contains a different statement. This discrepancy may indicate a potential flaw in the original version of the questionnaire. It was observed that, despite all these QoL questionnaires having their scales and classification scores already predefined, none of these questionnaires (items 11A/D/E and 15) contained in the form provide fields for calculating points, scores, or reference cutoffs to evaluate the results.

During the review of the completed questionnaires, it was noticed that several items, although considered completed, were incomplete, with only the affirmative answer "yes" marked, while the negative response "no" was ignored when the participant did not identify with the question (items 5, 11F, 13, and part of 14) in contrast to Cicconelli, 1997, who suggests that a questionnaire should preferably be presented in a simple format and language, being easy to apply and understand.[15] This may indicate that the extensive format of the form, possibly leading to fatigue, despite being well accepted, and the inclusion of multiple questionnaires within it contribute to the increased completion time.

To assess the acceptability and understanding of the questionnaire, similar to the present study, Hasvik et al. and Zumpano et al. also conducted semistructured cognitive interviews regarding the general meaning of the questionnaire, the explanatory text, the pain descriptors, and the answers (numerical classification).[19,23] The number of patients tested with the prefinal version was also quite variable, ranging from just 5 to even using 100 patients in the surveyed literature.[16,23]

Systematic reviews on the methodological studies related to the development and validation of questionnaires have concluded that there is no established set of criteria to determine the quality of property measures. The literature in this field is highly variable, often relying on expert opinions, even if based on literature reviews.[12,25]

These reviews suggest that if the content validity of a questionnaire is adequate, it can be considered usable, and it is sufficient to test the translated instrument against the original questionnaire for validation purposes. In the case of this questionnaire, which includes several previously translated and validated instruments (SF-McGill, PCS, VAS, PROMIS sexual function, global health, and DASS-21) in Portuguese, we can consider it validated. Therefore, there was no evaluation of the psychometric properties conducted in the present study. However, it is important to acknowledge that this may be considered a weakness of the instrument.

Cicconelli (1997) emphasizes the importance of reproducibility in evaluation instruments, requiring consistent results across multiple administrations for the same patient, assuming their general clinical state remains unchanged. In the present study, the evaluation of reproducibility was not conducted since the questionnaire serves as an identification form and initial anamnesis, rather than a comprehensive instrument intended for repeated administration in the same patients. Furthermore, Cicconelli emphasizes that a measure is considered valid when it effectively measures what it intends to measure. Considering the systematic review by Terwee, which highlights content validity as a crucial property measure, and the absence of a gold standard instrument for criterion validity comparison, face and content validity were thoroughly assessed using a subjective and reliable format, ultimately consolidating the validity of this instrument.

The Pelvic Health History Form in Portuguese will significantly contribute to the diagnosis and appropriate treatment of CPP, leading to improved quality of life for women with CPP. Moreover, its availability will foster research endeavors in Brazil.

Conclusion

The translation and cross-cultural adaptation process demonstrated exceptional efficiency, achieving a high level of equivalence with the source material while preserving both

qualitative and quantitative validity. The resulting questionnaire is presented in a user-friendly format, ensuring ease of application and comprehension. This significant development represents a notable stride forward and its growing presence in the literature, particularly for self-administration in clinical settings while establishing a strong foundation for future studies to build upon.

Contributions

All authors contributed with the project and data interpretation, the writing of the article, the critical review of the intellectual content, and with the final approval of the version to be published.

Conflict of Interest

None to declare.

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Efficacy of Sacrospinous Fixation or Uterosacral Ligament Suspension for Pelvic Organ Prolapse in Stages III and IV: Randomized Clinical Trial

Eficácia da fixação sacroespinhal ou da suspensão do ligamento útero-sacro no prolapso de órgãos pélvicos nos estágios III e IV: Ensaio clínico randomizado

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Abstract

Objective To evaluate the efficacy and outcomes of the surgical treatment for pelvic organ prolapse (POP) in stages III and IV by sacrospinous ligament fixation (SSLF) or uterosacral ligament suspension (USLS) by comparing anatomical and subjective cure rates and quality-of-life parameters (through the version validated for the Portuguese language of the Prolapse Quality of Life [P-QoL] questionnaire) under two definitions: genital prolapse Ba, Bp, and $C < -1$ (stage I) and Ba, Bp, and $C \leq 0$ (stage II).

Materials and Methods After we obtained approval from the Ethics Committee (under CAAE 0833/06) and registered the study in ClinicalTrials.gov (NCT 01347021), 51 patients were randomized into two groups: the USLS group (N = 26) and the SSLF group (N = 25), with follow-up 6 and 12 months after the procedures.

Results There was a significant improvement in the P-QoL score and anatomical measurements of all compartments in both groups after 12 months ($p < 0.001$). The anatomical cure rates in the USLS and SSLF groups, considering stage 1, were of 34.6% and 40% (anterior) respectively; of 100% both for groups (apical); and of 73.1% and 92% (posterior) respectively. The rates of adverse outcomes were of 42% (N = 11) and 36% (N = 11) for the USLS and SSLF groups respectively ($p = 0.654$), and those outcomes were excessive bleeding, bladder perforation (intraoperative) or gluteal pain, and urinary infection (postoperative), among others, without differences between the groups.

Keywords
- pelvic organ prolapse
- pelvic floor disorders
- reconstructive surgical procedures
- patient health questionnaire
- patient-reported outcome measures

* *In memoriam.*

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Conclusion High cure rates in all compartments were observed according to the anatomical criterion (stage I), without differences in P-QoL scores and complications either with USLS or SSLF for the surgical treatment of accentuated POP.

Resumo

Objetivo Avaliar a eficácia e os resultados do tratamento cirúrgico para prolapso de órgãos pélvicos (POP) nos estágios III e IV, por meio da técnica de fixação do ligamento sacroespinal (FLSE) ou suspensão do ligamento útero-sacro (SLUS), ao comparar os índices de cura anatômicos, subjetivos, e os parâmetros de qualidade de vida (por meio do questionário Prolapse Quality of Life [P-QoL] validado para a língua portuguesa) sob duas definições: prolapso genital Ba, Bp e C < -1 (estágio I) e Ba, Bp e C ≤ 0 (estágio II).
Materiais e Métodos Após aprovação do Comitê de Ética (CAAE 0833/06) e registro no ClinicalTrials.gov (NCT 01347021), 51 pacientes foram randomizadas em dois grupos: grupo SLUS (N = 26) e (2) grupo FLSE (N = 25), com seguimento de 6 e 12 meses.
Resultados Houve melhora significativa nas pontuações no P-QoL e nas medidas anatômicas de todos os compartimentos em ambos os grupos após 12 meses ($p < 0{,}001$). As taxas de cura anatômica nos grupos SLUS e FLSE , considerando o estágio 1, foram de 34,6% e 40% (anterior), respectivamente; de 100% em ambos os grupos (apical); e de 73,1% e 92% (posterior), respectivamente. As taxas de resultados adversos foram de 42% (N = 11) e 36% (N = 11), respectivamente, nos grupos SLUS e FLSE ($p = 0{,}654$), e elas foram sangramento excessivo, perfuração da bexiga (intraoperatória) ou dor glútea, e infecção urinária (pós-operatória), entre outras, sem diferenças entre os grupos.
Conclusão Altas taxas de cura em todos os compartimentos foram observadas segundo critério anatômico (estágio I), sem diferença quanto às pontuações no P-QoL e às complicações tanto com SLUS quanto com FLSE para o tratamento cirúrgico de POP acentuado.

Palavras-chave
- prolapso de órgão pélvico
- distúrbios do assoalho pélvico
- procedimentos cirúrgicos reconstrutivos
- questionário de saúde da paciente
- medidas de resultados relatadas pela paciente

Introduction

In high-income countries, individuals are growing ever older, and the need for pelvic organ prolapse (POP) treatment is anticipated to increase in the coming decades.[1] The treatment of the apical compartment is critical to the successful repair of severe POP. The two most commonly used techniques for apical corrections, through vaginal procedures, are uterosacral ligament suspension (USLS) or sacrospinous ligament fixation (SSLF).[2–4] Close to the ischial spines, USLS is an effective intraperitoneal procedure to restore apical support in 98% of women.[5] The second technique is a widely used extraperitoneal procedure with subjective cure rates ranging from 70% to 98%, and objective cure rates ranging from 67% to 97%.[6]

In an attempt to improve the anatomical result of pelvic reconstruction surgeries with native tissues, the use of meshes was propagated with the intention of replacing the injured native tissues, but numerous complications and high rates of reoperations due to exposure, pain, and dyspareunia have been observed.[2–4,7] Because of warnings about the adverse effects of surgical correction with polypropylene meshes,[7] efforts to identify the ideal technique to correct the apical effect by the vaginal access have been undertaken.[7]

Thus, medical societies specializing in such fields have recommended that meshes be used sparingly, with restrictions or not at all. It is possible that researchers in countries such as the United States, Australia, and the United Kingdom have stopped their studies on this topic because of mesh scrutiny.[1,7] Therefore, the objective of the present study was to compare the success rates and outcomes of USLS and SSLF in the surgical treatment of advanced apical POP (stages III and IV) under the subjective (Ba, Bp and C < -1) and anatomical (Ba, Bp and C ≤ 0) cure criteria of the Pelvic Organ Prolapse Quantification (POP-Q) System.[8]

Materials and Methods

The present prospective and randomized trial was performed at Universidade Federal de São Paulo, Brazil, and it was approved by the Research Ethics Committee of said institution (under CAAE 0833/06; CEP 0833/06 [attached document]) and registered on Clinicaltrials.gov (NCT 01347021). The inclusion criteria were patients with apical POP in stages III or IV, aged between 50 and 90 years, who voluntarily agreed to participate and signed the informed consent form. The exclusion criteria were clinico-surgical contraindications (severe comorbidities), apical POP in

stages I and II; previous pelvic radiotherapy or thromboembolic disorders; hormone therapy; endometrial hyperplasia or high-grade squamous intraepithelial lesions of the cervix, vagina, or vulva, or untreated genitourinary infection.

Standard history-taking was performed, as well as a physical examination in the supine and standing positions to stage the POP through the POP-Q according to the recommendations of the International Continence Society (ICS),[8,9] followed by reduction of the prolapse using gauze and a Cheron dressing forceps. The stress test was performed with and without the prolapse reduction to diagnose occult stress urinary incontinence (SUI). If involuntary leakage of urine was observed, a urodynamic study was performed to include the correction of the SUI during the surgical approach. All clinical evaluations were performed by the authors SBM and CCT through sequential randomization (performed by LMO and MMD) and allocation of the sample into two groups. The double-blinded randomization criterion was not applied because the procedures would have had to be explained to the patient and performed by the authors (SBM, CCT, LMO and MMD) in a technically-feasible manner with the scientific rigor of sequential randomization. However, the statistician and the preoperative evaluator were blinded because they did not know to which group the patient would be assigned. The random allocation was sequential and performed 1:1 by drawing lots to avoid possible selection biases, and, in the postoperative evaluation, there was no blinding. The authors state that this does not compromise the outcomes, since the postoperative evaluator was blinded to the other randomization processes. The initial sample consisted of 58 patients with stage III and IV apical POP (according to the POP-Q). Of these, 7 were excluded (leaving 51 randomized patients) (►**Fig. 1**) because they presented stage II apical prolapse. Vaginal hysterectomy (VH) was performed in all

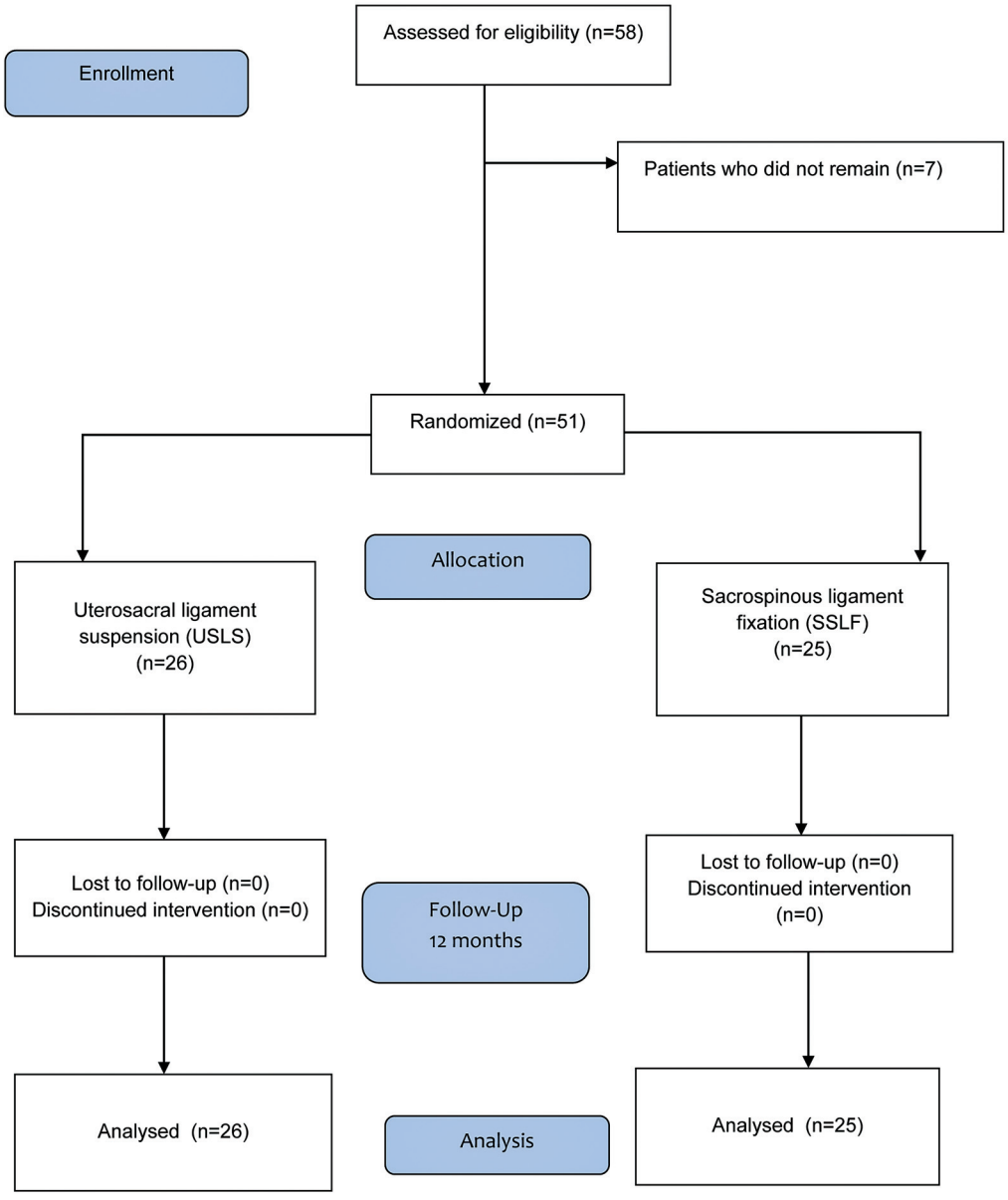

Fig. 1 Flow diagram of the present study.

patients, and correction of SUI with a retropubic midurethral sling when indicated, followed by cystoscopy to assess ureteral integrity and correction of site-specific apical defects through USLS or SSLF. Nine SUI corrections were performed in the USLS group and seven in the SSLF group. All patients underwent posterior colporrhaphy and perineorrhaphy, without the need for a description of the technique, as this was not the technique under comparison in the study hypothesis. The analyses were performed using the intention-to-treat (ITT) principle. In the USLS group, the uterosacral ligaments were identified, seized with an Allis forceps $\sim$ 1 cm medial and posterior to the ischial spine, and repaired, followed by a procedure to correct site-specific defects (in the anterior compartment). After that, the sutures of the uterosacral ligament were passed in the vaginal apex followed by anterior, posterior and perineorrhaphy or colporrhaphy.[10,11] In the SSFL group, correction of site-specific defects (in the anterior compartment) was performed by means of a longitudinal incision of the posterior vaginal wall up to 2 cm from the vaginal apex. Correction of the site-specific defects of the posterior vaginal wall and enterocele was performed, and the knots of polypropylene threads (number 0) were tied, leading the vaginal apex toward the sacrospinous ligament, avoiding excessive traction.[10,11] All patients received intravenous antibiotic therapy (cephalothin and metronidazole) intraoperatively. Meshes were not used to correct pelvic floor defects. Hospital discharge occurred at least 48 hours after surgery, provided the patients were clinically well.

Quality of life was assessed preoperatively, 6, and 12 months after the intervention through the version validated for the Portuguese language of the Prolapse Quality of Life (P-QoL) questionnaire,[12] which determined the criterion of subjective cure. This questionnaire contains 20 questions in 9 domains: general health perception; prolapse impact; role limitations; physical limitations; social limitations; personal relationships; emotions; sleep/energy; and severity measures.[12]

Anatomical success was evaluated by the positions of the vaginal apex, anterior and posterior compartments after 6 and 12 months of follow-up in the two groups. Data from 12 months of follow-up were used to assess both quality of life and the anatomical outcomes, because of the greater practical applicability of the outcomes. However, the authors consider the follow-up of patients to assess long-term efficacy, which was not the objective of the present study. For the assessment of cure ranges, two specific clinical criteria were used: according to the first criterion, those with the highest prolapse point lower than -1 according to the POP-Q were considered cured (stage I). Then, in the second criterion, patients were regrouped and considered cured when the point of greatest prolapse was ≤ 0, (stage II).[8]

The duration of the surgery (time from the first incision to the completion of the suture) and blood loss (hemoglobin and hematocrit levels) were also analyzed pre- and postoperatively. Complications were described according to the terminology of the International Urogynecological Association (IUGA) and ICS.[13]

The sample size (N) was calculated based on the primary objective of the study. According to the literature review, the authors estimated a minimum of 20 patients in each group, with a difference of 25% between them. The level of rejection of the null hypothesis was set at 0.05 or 5% ($\alpha \leq 0{,}05$) and the power of the sample, at 80%.[14] The statistical analyzes were performed using the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States), version 19.0, and the R software (R Foundation for Statistical Computing, Vienna, Austria), version 2.11.1. Quantitative (numerical) variables were calculated as mean, median, minimum and maximum, and standard deviation values. The qualitative (categorical) variables were analyzed by calculating their absolute and relative frequencies (percentage). The Student *t*- and Mann-Whitney tests were used to compare the continuous variables, and the Pearson Chi-squared with the Fisher exact tests, to compare the categorical variables between groups. Analysis of variance (ANOVA) was performed to compare the POP and the P-QoL score between the 2 groups before and 12 months after surgery. The significance level was set at 0.05.

Results

The two groups were homogeneous in terms of age, age at the onset of menopause, number of pregnancies, vaginal or cesarean deliveries, body mass index (BMI), race, smoking status, systemic arterial hypertension, diabetes mellitus, initial stage, previous gynecological surgeries, presence of SUI or occult SUI (►**Table 1**). After 12 months of follow-up, a significant improvement was observed in all anatomical points after the surgeries in both groups (►**Table 2**).

In the evaluation of the compartments, separately, after 12 months of follow-up, with the adoption of anatomical healing patterns of points in a position lower than -1, anatomical cure rates of 34.6% and 40% (for the USLS and SSLF groups respectively) in the anterior compartment and of 100% for both groups in the apical compartment were observed. In the posterior compartment, anatomical healing rates of 73.1% and 92% were observed in the USLS and SSLF groups respectively, with a significant improvement in the posterior compartment (Bp) favorable to the SSLF group ($p = 0.043$) (►**Tables 2** and **3**).

On the other hand, when adopting the presence of prolapse up to the hymenal caruncle as a cure criterion, that is, Ba, Bp or C ≤ 0, we observed cure rates of 88.4% and 84% (for the USLS and SSLF groups respectively) in the anterior compartment, of 88.4% (USLS group) and 96% (SSLF group) in the posterior compartment, and of 100% (both groups) in the apical compartment, with no statistical difference between techniques (►**Table 3**). Therefore, when analyzing the anatomical measurements of the compartments, there was a favorable statistical difference in the SSLF group (posterior compartment), without statistical difference between the groups when analyzing the cure rates. Using the P-QoL, we observed that, after 12 months of follow-up, both procedures were efficient, with a significant improvement in scores in the nine domains evaluated regarding the postoperative and preoperative periods. There were no significant differences when comparing both groups after 12 months of follow-up (►**Table 4**).

Table 1 Preoperative characteristics of the patients

	USLS	SSFL	*p*
Age (years) (min–max) ± SD	68.8 (50–88) ± 10.3	66.6 (53–80) ± 6.9	0.374[a]
Parity (min–max) ± SD	5,0 (1–14) ± 3.4	5,4 (0–15) ± 4.0	0.648[a]
Vaginal deliveries (min–max) ± SD	4,1 (0–14) ± 3.6	4,2 (0–12) ± 3.5	0.864[b]
BMI (Kg/m^2) (min–max) ± SD	26,2 (17.7–38.9) ± 4.7	25,8 (19.4–33.9) ± 3.2	0.760[a]
Race			0.068[c]
White	18 (69.2%)	19 (76%)	
Non-white	8 (31.8%)	6 (24%)	
POP-Q stage			0.312[d]
III	13 (50%)	9 (36%)	
IV	13 (50%)	16 (64%)	
Previous surgeries	5 (19.2%)	7 (28%)	0.460[d]
SUI	15 (57.8%)	16 (64%)	0.645[d]
Overactive bladder	21 (80.8%)	16 (64%)	0.180[d]
Occult SUI	3 (11.5%)	4 (12%)	> 0.999[c]

Abbreviations: BMI, Body Mass Index; min, minimum; max, maximum; POP-Q, Pelvic Organ Prolapse Quantification System; SD, standard deviation; SSLF, sacrospinous ligament fixation; SUI, stress urinary incontinence; USLS, uterosacral ligament suspension.
Notes: [a]Student *t*-test for independent samples; [b]Mann-Whitney test; [c]Fisher exact test or its extension; [d]Pearson Chi-squared test.

Table 2 Position of the anatomical points (POP-Q) pre- and postoperatively after 12 months in both groups

Points	USLS		SSFL		*p*
	Mean ± SD	Min/Max	Mean ± SD	Min/Max	
Aa					
Preop	2.77 ± 0,82	(0/3)	2.48 ± 1.23	(−1/3)	0.827
Postop	−1.15 ± 1.29	(−3/1)	−1.00 ± 1.41	(−3/1)	0.778
p[a]	< 0.001		< 0.001		
Ba					
Preop	4.81 ± 1.44	(1/7)	4.76 ± 2.01	(0/8)	> 0.999
Postop	−1.00 ± 1.26	(−3/1)	−0.80 ± 1.58	(−3/2)	0.791
p[a]	< 0.001		< 0.001		
C					
Preop	5.73 ± 1.54	(3/8)	6.56 ± 1.69	(4/10)	0.481
Postop	−5.46 ± 1.36	(−8/−2)	−5.72 ± 1.28	(−8/−3)	0.324
p[a]	< 0.001		< 0.001		
GH					
Preop	5.15 ± 0.97	(3/6)	4.80 ± 1.12	(3/8)	0.487
Postop	3.31 ± 0.68	(2/5)	3.44 ± 0.71	(2/5)	0.594
p[a]	< 0.001		< 0.001		
PB					
Preop	2.73 ± 0.67	(2/4)	3.04 ± 1.14	(2/7)	0.515
Postop	3.77 ± 0.65	(3/5)	3.80 ± 0.65	(3/5)	0.388
p[a]	< 0.001		< 0.001		

Table 2 (*Continued*)

Points	USLS		SSFL		*p*
	Mean ± SD	Min/Max	Mean ± SD	Min/Max	
TVL					
Preop	8.38 ± 0.70	(7/10)	8.36 ± 0.76	(7/10)	> 0.999
Postop	7.04 ± 1.00	(5/9)	6.92 ± 1.38	(4/9)	0.951
p[a]	< 0.001		< 0.001		
Ap					
Preop	0.96 ± 1.87	(−2/3)	1.56 ± 1.85	(−3/3)	0.481
Postop	−2.19 ± 1.10	(−3/1)	−2.60 ± 0.87	(−3/0)	0.105
p[a]	< 0.001		< 0.001		
Bp					0.141
Preop	2.08 ± 2.86	(−2/6)	3.36 ± 2.45	(−3/8)	
Postop	−1.92 ± 1.41	(−3/2)	−2.48 ± 1.33	(−3/3)	0.043*
p[a]	< 0.001		< 0.001		

Abbreviations: GH, Genital Hiatus; Min, minimum; Max, maximum; PB, Perineal Body; POP-Q, Pelvic Organ Prolapse Quantification System; Postop, postoperatively; Preop, preoperatively; SD, Standard Deviation; SSLF, sacrospinous ligament fixation; TVL, Total Vaginal Length; USLS, uterosacral ligament suspension.
Notes: Values expressed in centimeters (mean ± standard deviation, and minimum and maximum values); [a]Analysis of variance (ANOVA).

Table 3 Cure rate using two different criteria of anatomical and functional cure: POP-Q < −1 or POP-Q ≤ 0

POP-Q	USLS (*N* = 26) N (%)	SSLF (*N* = 25) N (%)	*p*
Ba < −1	9 (34.6%)	10 (40.0%)	0.691[a]
Ba ≤ 0	23 (88.4%)	21 (84.0%)	0.703[a]
C < −1	26 (100.0%)	25 (100.0%)	*
C ≤ 0	26 (100.0%)	25 (100.0%)	*
Bp < 1	19 (73.1%)	23 (92.0%)	0.140[b]
Bp ≤ 0	23 (88.4%)	24 (96.0%)	0.610[b]

Abbreviations: POP-Q, Pelvic Organ Prolapse Quantification System; SSLF, sacrospinous ligament fixation; USLS, uterosacral ligament suspension.
Notes: [a]Pearson Chi-Squared test; [b]Fisher exact test; *Impossibility of performing a statistical analysis for total cure in both groups.

Table 4 Preoperative and postoperative P-QOL scores of women who underwent fixation of the vaginal vault through SSLF USLS

	USLS	SSLF	*p*[a]
	Mean ± SD	Mean ± SD	
General health perception			0.970
Preop	49.0 ± 26.9	52.0 ± 24.9	0.514
Postop	31.7 ± 24.0	22.0 ± 18.1	
p[b]	< 0.001	< 0.001	
Prolapse impact			0.994
Preop	74.3 ± 36.8	76.3 ± 29.6	0.739
Postop	8.9 ± 27.5	1.3 ± 6.6	
p[b]	< 0.001	< 0.001	
Role limitations			0.555
Preop	58.9 ± 38.9	47.4 ± 40.1	
Postop	7.6 ± 27.1	0.6 ± 3.3	0.171
p[b]	< 0.001	< 0.001	

(*Continued*)

Table 4 (*Continued*)

	USLS	SSLF	p^a
	Mean ± SD	Mean ± SD	
Physical limitations			0.444
Preop	60.9 ± 39.4	48.0 ± 42.0	0.297
Postop	5.1 ± 20.4	1.3 ± 6.6	
p^b	< 0.001	< 0.001	
Social limitations			0.771
Preop	44.8 ± 39.8	36.8 ± 38.7	
Postop	0.9 ± 4.5	0.89 ± 4.4	0.204
p^b	< 0.001	< 0.001	
Personal relationships			0.463
Preop	14.1 ± 30.4	24.0 ± 36.3	
Postop	1.2 ± 6.5	1.3 ± 6.6	0.371
p^b	< 0.001	< 0.001	
Emotions			
Preop	62.8 ± 40.9	64.4 ± 37.9	> 0.999
Postop	4.7 ± 19.6	1.3 ± 22.2	0.799
p^b	< 0.001	< 0.001	
Sleep/Energy			0.295
Preop	39.1 ± 34.2	27.1 ± 28.5	
Postop	5.7 ± 15.5	2.6 ± 10.4	
p^b	< 0.001	< 0.001	0.146
Severity measures			0.850
Preop	43.2 ± 32.4	48.3 ± 31.5	
Postop	1.9 ± 1.3	1.3 ± 5.2	0.493
p^b	< 0.001	< 0.001	

Abbreviations: P-QoL, Prolapse Quality of Life questionnaire; Preop, preoperative period; Postop, postoperative period; SD, standard deviation; SSLF, sacrospinous ligament fixation; USLS, uterosacral ligament suspension.
Note: [a,b]Analysis of variance (ANOVA).

The mean duration of the surgery was of 137.6 (range: 80 to 190) minutes in the USLS group, and of 146.9 (range: 80 to 215) minutes in the SSFL group, with no difference between them ($p = 0.299$) (►**Table 5**). There was no statistical differences between the groups regarding the minimal incidence of intraoperative or postoperative complications (►**Table 6**). Subjective cure was determined by the P-QoL, and there was no difference between the groups.

Table 5 Comparison of perioperative results between the USLS and SSFL groups

Variables		USLS Group		SSFL Group		*p*
		Mean ± SD	Min-max	Mean ± SD	Min-max	
Operative Time (minutes)		137.6 ± 29.5	80–190	133.5 ± 33.7	80–215	0.299
Hemoglobin (g/dL)	Preop	13.1 ± 1.1	11.0–15.7	13.1 ± 1.1	10.7–15.4	0.482
	Postop	10.8 ± 1.2	8.6–13.5	11.2 ± 1.6	8.3–14.1	0.448
Hematocrit (%)	Preop	39.1 ± 3.4	34.0–47.4	39.1 ± 3.1	33.6–47.0	0.571
	Postop	32.3 ± 3.7	26.0–40.0	33.4 ± 4.7	24.7–42.6	0.415
Hospital stay (days)		2.3 ± 0.8	2.0–5.0	2.2 ± 0.8	1.0–5.0	0.559

Abbreviations: Min, minimum; max, maximum; Preop, preoperative period; Postop, postoperative period; SD, standard deviation; SSFL, sacrospinous ligament fixation; USLS, uterosacral ligament suspension.
Notes: Values expressed as mean ± standard deviation; hemoglobin and hematocrit levels collected 24 hours after surgery through analysis of variance (ANOVA) with parametric repeated measures.

Table 6 Total number of complications in both groups

	USLS	SSLF	p^a
Intraoperative			
Excessive bleeding	3	1	–
Transfusion	–	–	–
Bladder perforation	–	–	–
Postoperative			
Gluteal pain	–	5	–
Infection	3	1	–
De novo overactive bladder	1	–	–
Thigh paresthesia	1	–	–
Urinary infection	2	3	–
Dyspareunia	1	–	–
Rectal injury (47^{th} postoperative day)[b]	–	1	–
Total	11	11	0.654[a]

Abbreviations: SSLF, sacrospinous ligament fixation; USLS, uterosacral ligament suspension.
Notes: [a]Pearson Chi-squared test; [b]one patient in the SSFL group had an acute abdomen on the 47th postoperative day, with a diagnosis of a perforation lesion measuring ~ 5 cm, located in the middle rectum. The patient underwent exploratory laparotomy with resection of the lesion and colostomy with reconstruction of the intestinal transit in the second stage. The anatomopathological study showed circulatory disturbance, probably due to ischemic injury.

Discussion

The present study evaluated the two most commonly performed surgical correction techniques, one of which is the reconstruction of the pelvic anatomy using native tissues, and the degree of objective (anatomical) and subjective (functional) success in achieving satisfactory results with respect to the most current recommendations on the surgical treatment of POP.[2–4,9,15,16]

Systematic reviews, randomized trials and medical societies found no evidence to support the use of meshes to the detriment of native tissues.[2–4,15–17] Since 2011,[7] many transvaginal mesh products have been removed from the market after the Food and Drug Administration (FDA) announcement that identified serious safety, effectiveness concerns, and complications with the use of transvaginal mesh to treat POP. The outcomes of the present study corroborate global analyzes and recommendations on the surgical treatment for POP. Fortunately, VH and vaginal apex repair to the uterosacral or sacrospinous ligaments (which are relatively low-risk surgeries) are effective treatments for most women with apical POP, according to several authors and supported by renowned medical societies in the field, without the use of synthetic mesh.[2–4,9,15,16]

Studies such as the present, which prove the effectiveness of surgical treatment with the application of traditional techniques in urogynecology, such as fixation of the vaginal vault to the sacrospinous ligament or suspension of the uterosacral ligament to correct even advanced apical prolapses, reinforce the prioritization of the choice and reproducibility of the classic technique in urogynecological surgery for POP.[17–20] Thus, currently there is no indication for the use of screens.[17] In a systematic review published in 2016, Maher et al.[17] found no evidence to support the use of meshes to the detriment of native tissues, which is in line with the results of the present study. The practical applicability of these results enables the advancement and dissemination of knowledge regarding surgical techniques in traditional urogynecology, without detriment to technologies, but with the deserved reservations.[18–20]

Regarding the cure criteria, there is no consensus in the scientific community on success and failure in POP correction surgery. Barber et al.[8] (2009), after a 2-year follow-up of 322 patients in the Colpopexy and Urinary Reduction Efforts (CARE) study, applied 18 different definitions of success after surgery for the correction of POP in stages II to IV, and the treatment success rate varied widely depending on the definition used (range: 19.2% to 97.2%).

In that context, the POP-Q enables more accurate descriptions of the POP stages for diagnosis and follow-up. Despite the fact that most patients are classified as stage II postoperatively, with a surgical outcome between the $+1$ and -1 range of the hymenal ring, they generally remain asymptomatic. Therefore, what would configure an anatomical failure (stage II according to the POP-Q) is classified as a cure according to the patient's subjective criteria, particularly when the prolapse is axial to the hymenal point.[8,21,22]

Based on this scenario, the results of the present study (anterior compartment), showed questionable anatomical cure rates in both groups after one year of follow-up, when considering the cure criterion points of greater POP-Q prolapse below -1 (34.6% and 40%, for USLS and SSLF groups respectively). However, when adopting the hymenal ring as a reference point for healing (Ba ≤ 0), since these patients are

asymptomatic, the cure rates were of 88.4% (USLS) and 88% (SSLF).

In the same direction, Barber et al.[23] (2014) compared patients in stages II to IV submitted to SSLF ($N = 186$) and USLS ($N = 188$), with 2 years of follow-up, and observed recurrence rates of 13.7% and 15.5% respectively, considering $Ba > 0$. Then, the results of the present study were similar to the work by Barber et al.[23], who, after 2 years of follow-up, observed surgical success rates of 59.2% for uterosacral fixation and of 60.5% for sacrospinal fixation, with no difference between the two techniques.

However, Meyer et al.[24] (2020), when reanalyzing data from that study only with patients in stages III and IV, found anterior wall recurrence rates of 16.8% (SSLF) and 17.9% (USLS), and a high rate of patient satisfaction in both groups according to the P-QoL.

The analysis of the apical compartment after the interventions points to the restoration of the anatomy in both groups, with no significant difference. These findings corroborate those of previous studies[2–4,15,16] and enable us to demonstrate that both techniques yield satisfactory surgical outcomes. Choosing to ignore less-rigid cure criteria in the treatment of advanced apical prolapse can provide satisfactory anatomical and surgical outcomes for the patient, especially when native tissues are used for pelvic reconstruction.

On the other hand, in the posterior compartment, a better anatomical result was observed in the SSLF group, with a statistical difference, but no difference in terms of the subjective assessment. This was probably due to to posterior deviation of the vaginal axis: the greater the area of dissection of the posterior compartment, the better the anatomical correction.[24]

In both groups, there was a significant decrease in the size and width of the genital hiatus after reconstruction of the posterior compartment and perineal body, which is considered a high-impact factor in surgical success and decreased recurrence. Inadequate correction of the genital hiatus can therefore impair the surgical outcome in addition to resulting in recurrence of the prolapse.[25,26]

This randomized design, approved by ethics committees and clinical trials plataforms, highlights the methodological rigor and positive impact by offering reliability and resilience of site-specific surgical treatment in advanced POP, in a paradoxical technological appeal and numerous restrictions to synthetic meshes. Synthetic meshes may have their clinical applicability; however, it is increasingly limited due to the high rate of complications.[2–4,7,9,21]

The recommendation to use classic techniques for POP correction is in line with reference medical societies, such as the IUGA,[9] the American College of Obstetricians and Gynecologists (ACOG),[2] the International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique, FIGO, in French),[3] the American Urogynecologic Society (AUGS),[9] as well as regulatory agencies (such as the FDA).[7] Besides that, the present study emphasizes a subjective criterion of cure, valued by the person most interested in the subject, the patient, without detriment to the anatomical criterion.

On the other hand, sample size and sexual function data (most patients no longer had an active sexual life) may be limitations of the present study which may not compromise the scientific quality. The authors believe that the parity of positive cure outcomes analyzed by different anatomical methods, as well as the application of the P-QoL, reinforces the data and alleviates the limitation of the sample. Besides that, due to the objective being the comparison of cure criteria, not the assessment of the superiority or inferiority of a technique, the sample was sufficient according to the statistical recommendation.

The authors point to the need for longer follow-up of patients (undergoing evaluations to provide data for future studies) with a more robust sample from multiple centers to really assess the potential for POP recurrence between the groups.

Due to the current restrictions on the use of synthetic meshes by specialized medical societies, regulatory agencies and several authors, reconstructive pelvic surgery might be moving toward a return to the classic use of native tissues, even in cases o POP in advanced stages.

Conclusion

Both techniques (SSLF and USLS) have high success rates, good satisfactory anatomical and subjective outcomes, and a positive impact on the quality of life of patients with apical POP in stages III and IV.

Contributions

SBM: project development, data collection, writing/proofreading/editing of the manuscript; RAC: project development, proofreading/editing of the manuscript; CCT: project development, data collection, proofreading/editing of the manuscript; GVM: proofreading/editing of the manuscript; LMO: data collection, proofreading/editing of the manuscript; PCFMJ: proofreading/editing of the manuscript; MMD: data collection, proofreading/editing of the manuscript; MJBCG: project development, proofreading/editing of the manuscript and MGFS: project development, writing/proofreading/editing of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Immobilization, Lymphedema, and Obesity are Predictive Factors in the Development of Adhesive Capsulitis in Breast Cancer Patients

Imobilização, linfedema e obesidade são fatores preditivos no desenvolvimento de capsulite adesiva em pacientes com câncer de mama

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Abstract

Objective Adhesive capsulitis is a condition characterized by shoulder pain and stiffness. Breast cancer treatment has been linked to the development of this condition, but its mechanisms are still little known. This study's objective was to identify predictors factors associated with the development of adhesive capsulitis in breast cancer patients.

Methods A case control study was performed with women undergoing treatment for breast cancer in a single center. The sampling was nonprobabilistic and consecutive. Adhesive capsulitis was defined as constant pain associated with decreased active and passive shoulder movement in anterior elevation, external rotation at 0°/90° abduction, and internal rotation at 90° abduction. The study group consisted of patients with shoulder pain and range of motion limitations, while the control group consisted of women without any shoulder abnormalities. Sociodemographic and clinical variables were collected. A univariate logistic regression was used to assess the influence of variables on the studied outcome. For $p < 0.20$, a multivariate logistic regression was used. The probability of null hypothesis rejection was 5%.

Results A total of 145 women were assessed, with 39 (26.9%) on the study group and 106 (73.1%) on the control group. The majority was under 60 years old. In the multivariate analysis, variables correlated to the outcome under study were shoulder immobilization (OR = 3.09; 95% CI: 1.33–7.18; $p = 0.009$), lymphedema (OR = 5.09; 95% CI: 1.81–14.35; $p = 0.002$), and obesity (OR = 3.91; 95% CI: 1.27–12.01; $p = 0.017$).

Conclusion Lymphedema, postsurgery immobilization, and obesity are predictive factors for the development of adhesive capsulitis in breast cancer patients.

Keywords
- breast cancer
- shoulder
- adhesive capsulitis
- obesity
- lymphedema

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Resumo

Objetivo Capsulite adesiva é uma afecção caracterizada por dor e limitação dos movimentos do ombro. O tratamento do câncer de mama está relacionado ao desenvolvimento dessa doença por meio de mecanismos ainda pouco conhecidos. O objetivo do estudo foi identificar os fatores associados ao desenvolvimento de capsulite adesiva em pacientes com câncer de mama.

Métodos Um estudo caso-controle foi realizado com mulheres em tratamento para câncer de mama em um centro único. A amostra foi consecutiva e não-probabilística. A capsulite adesiva foi pré-definida como dor constante e diminuição da amplitude de movimentos em elevação anterior, rotação externa em 0°/90° abdução e rotação interna em 90° abdução. O grupo caso foi constituído por pacientes com dor e limitação de todos os movimentos do ombro, enquanto o controle por pacientes sem qualquer alteração nesta articulação. Variáveis sociodemográficas e clínicas foram coletadas. Foi realizada uma análise de regressão logística univariada para avaliar a influência das variáveis em relação ao desfecho estudado. Para valores de $p < 0,20$, realizou-se a análise de regressão logística multivariada. A probabilidade de se rejeitar a hipótese nula foi de 5%.

Resultados Foram avaliadas 145 mulheres, sendo 39 casos (26,9%) casos e 106 controles (73,1%). Na análise multivariada, as variáveis associadas ao desfecho estudado foram imobilização do ombro (OR = 3,09; 95% IC: 1,33–7,18; $p = 0,009$), linfedema (OR = 5,09; 95% IC: 1,81–14,35; $p = 0,002$) e obesidade (OR = 3,91; 95% IC: 1,27–12,01; $p = 0,017$).

Conclusão Linfedema, imobilização pós-cirúrgica e obesidade são fatores preditores associados ao desenvolvimento de capsulite adesiva em pacientes com câncer de mama.

Palavras-chave

- câncer de mama
- ombro
- capsulite adesiva
- obesidade
- linfedema

Introduction

Adhesive capsulitis (AC) is a condition that causes thickening of the glenohumeral joint capsule, along with constant pain and progressive loss of the shoulder's passive and active range of motion.[1–4] It is prevalent in approximately 2 to 5% of the overall population, especially women aged between 40 and 60 years old.[4] This condition may be classified as primary (idiopathic) or secondary to trauma, surgery, or other comorbidities, such as thyroid conditions, dyslipidemia, diabetes mellitus, Parkinson's, cardiopathies, and breast cancer (BC).[1,3–5]

This type of cancer is highly prevalent worldwide, with 2.3 million new cases reported just in 2020. By 2040, BC is predicted to increase to over 3 million new cases and 1 million deaths every year. It is a heterogeneous condition, morphologically divided into in situ (cancerous cells limited to the basement membrane) and invasive (cancerous cells crossing the basement membrane) carcinoma.[6] There are several conditions that predispose to its development, such as older age, female sex, genetic mutations, previous history of ductal carcinoma in situ, high body mass index (BMI), nulliparity or first pregnancy after 30 years of age, early menarche, history of BC or ovarian cancer in the family, late menopause, exposure to previous thoracic radiation therapy, and slightly elevated combined hormone replacement therapy in postmenopause women.[7,8]

Advancements in the diagnosis and treatment of BC have resulted in a higher survival rate at 5 years (89% in the USA), which has led to an increase in the number of shoulder morbidity cases.[9–11] One of such morbidities is AC,[5,9] which according to Yang et al. accounts for 10.3% of patients treated within a period of 13 to 18 months.[5]

In this setting, despite BC having been established as risk factor for AC, predictive factors for this correlation have not been established. Thus, this study's objective is to identify factors associated with AC development in patients with BC. Our hypothesis is that more aggressive forms of cancer treatment, such as radiation therapy and mastectomy, in addition to immobilization of the shoulder, would favor the development of this condition.

Methods

This is a case control study conducted in a single university hospital, specifically at the Advanced Breast Diagnostics Center (CORA), between September 2020 and March 2021. The study was approved by the Institutional Review Board on June 28, 2020, under the protocol number 4.119.154. All participants signed an informed consent form before data collection began.

About 160 women a month are seen at CORA for BC treatment and investigation. Yang et al.[5] reported AC prevalence in patients treated for BC at 10.3%. Considering the

inclusion and exclusion criteria and assuming α error of 5% and β error of 20% (80% power), the calculated sample size was 145 subjects.

The sampling was nonprobabilistic and consecutive. We defined AC as constant pain associated with decreased active and passive shoulder movement in anterior elevation, external rotation at 0°/90° abduction, and internal rotation at 90° abduction. We did the diagnosis of AC in the BC ambulatory.

Patients over the age of 18 years old undergoing BC treatment and with history of it were included. Furthermore, patients with shoulder pain or limited range of motion before BC treatment, presenting with other BC predisposing conditions, locked dislocation of the shoulder, glenohumeral arthrosis, avascular necrosis of the humeral head, or previous history of trauma/surgery of the affected shoulder were excluded.

After excluding the aforementioned conditions, the case group consisted of BC patients presenting with AC at the time of enrollment, and the control group consisted of BC patients without AC.

Data were collected using a sociodemographic and clinical questionnaire. The questionnaire was applied by researchers individually in a private environment. Patients' charts were also revised to collect relevant data.

After the questionnaire, patients reporting at rest and in motion shoulder pain with the aid of the visual analogue scale for pain underwent physical examination to confirm the AC diagnosis. The diagnosis consisted of active and passive shoulder mobility assessment in dorsal decubitus and hip and knee flexion with a digital Kaptron goniometer model 360 (Kaptron, Porto Alegre, RS, Brazil).

A digital Toledo balance model 9091 (Toledo, São Bernardo do Campo, SP, Brazil), with a calibrated Filizola meter (São Paulo, SP, Brazil) was used to measure patients' weight and height for BMI calculation.

The outcome was AC diagnosis. Independent variables were collected with the applied questionnaire, which contained sociodemographic and clinical variables related to BC.

Sociodemographic variables were age ($<$ or $\geq$ 60 years old); BMI (normal/overweight/obesity); race (white/nonwhite); marital status (married/divorced/widowed/single); monthly income (in minimum wages); level of education (illiterate/elementary school/middle school/highschool/higher education), and dominance (right or left-handed).

The relevant clinical data were: side (right/left/bilateral); biopsies (½ to 3/over 4); breastfeeding (yes/no); menopause (yes/no); previous hormone replacement therapy (yes/no); stage at time of diagnosis (early/advanced); chemotherapy (yes/no); radiation therapy (yes/no); endocrine therapy (yes/no); surgery (yes/no); and shoulder immobilization (yes/no). For patients undergoing mastectomy: type of mastectomy (quadrantectomy/mastectomy), lymph nodes dissection (no/sentinel/axillary emptying), and development of lymphedema after surgery (yes/no). For patients undergoing immobilization: time of immobilization (1–3 or $\geq$4 weeks).

Categorical variables were described with absolute (n) and relative frequency (%), and quantitative variables were described with average and standard deviation. Homogeneity among subjects in the study and control groups was analyzed with the Student *t*-test for continuous variables and the Pearson Chi-squared test for categorical variables. The univariate logistic regression analysis test was used to assess the influence of predictor variables for the development of AC, for variables with $p < 0.20$, a multivariate logistic regression analysis test was used (odds ratio, OR, and 95% confidence interval, CI). Excel 2007 (Microsoft Corp. Redmond, WA, USA) and the Statistical Package Social Sciences (SPSS, IBM Corp. Armonk, NY, USA), version 22.0 were used for tabulating data and statistical analysis, respectively.

Results

A total of 175 patients with BC were recruited, but 30 were excluded due to presenting shoulder pain with a history of trauma or other joint conditions and without motion limitation. 145 patients remained, 39 of which were in the study group (26.9%) and 106 in the control one (73.1%). Please refer to ►**Table 1** for BC patients' sociodemographic and clinical data.

Table 1 Breast cancer patients' sociodemographic and clinical data for case ($n = 39$) and control ($n = 106$) groups

Variables	Case n (%)	Control n (%)	Total n (%)	p^*
Sociodemographic variables				
Age group				
$<$ 60 years	33 (84.6)	72 (67.9)	105 (72.4)	0.059
$\geq$ 60 years	6 (15.4)	34 (32.1)	40 (27.6)	
BMI				
Normal	6 (15.4)	40 (37.7)	46 (31.7)	0.018
Overweight	14 (35.9)	36 (34.0)	50 (34.5)	
Obesity	19 (48.7)	30 (28.3)	49 (33.8)	
Race				
White	16 (41.0)	36 (34.0)	52 (35.9)	0.432
Not white	23 (59.0)	70 (66.0)	93 (64.1)	

Table 1 (*Continued*)

Variables	Case n (%)	Control n (%)	Total n (%)	p^*
Marital status				
Married	18 (46.2)	48 (45.3)	66 (45.5)	0.971
Divorced	6 (15.4)	16 (15.1)	22 (15.2)	
Widow	4 (10.3)	14 (13.2)	18 (12.4)	
Single	11 (28.2)	28 (26.4)	39 (26.9)	
Monthly income				
None	2 (2.6)	10 (5.9)	12 (5.0)	0.259
Up to 1 MW	16 (42.1)	56 (54.9)	72 (51.4)	
2 or 3 MW	18 (47.4)	37 (36.3)	55 (39.3)	
$\geq$ 4 MW	3 (7.9)	3 (2.9)	6 (4.3)	
Education				
Illiterate	1 (2.6)	5 (2.9)	6 (2.8)	0.234
Elementary school	5 (12.8)	22 (21.2)	27 (18.9)	
Middle school	6 (15.4)	16 (15.4)	22 (15.4)	
Highschool	26 (66.7)	51 (49.0)	77 (53.8)	
Higher	1 (2.6)	12 (11.5)	13 (9.1)	
Dominance				
Right-handed	36 (92.3)	101 (95.3)	137 (94.5)	0.487
Left-handed	3 (7.7)	5 (4.7)	8 (5.5)	
Clinical breast data				
Affected breast				
Right	18 (46.2)	52 (49.1)	70 (48.3)	0.618
Left	18 (46.2)	50 (47.2)	68 (46.9)	
Both	3 (7.7)	4 (3.8)	7 (4.8)	
Number of biopsies				
1	12 (30.8)	50 (47.2)	62 (42.8)	0.206
2 to 3	23(59.0)	47 (44.3)	70 (48.3)	
$\geq$ 4	4 (10.3)	9 (8.5)	13 (9.0)	
Breastfeeding				
Yes	36 (92.3)	90 (84.9)	126 (86.9)	0.241
No	3 (7.7)	16 (15.1)	19 (13.1)	
Menopause				
Yes	30 (76.9)	82 (77.4)	112 (77.2)	0.956
No	9 (23.1)	24 (22.6)	33 (22.8)	
Chemotherapy				
Yes	33 (84.6)	89 (84.0)	122 (84.1)	0.924
No	6 (15.4)	17 (16.0)	23 (15.9)	
Radiotherapy				
Yes	35 (89.7)	71 (67.0)	106 (73.1)	0.006
No	4 (10.3)	35 (33.0)	39 (26.9)	
Endocrinotherapy				
Yes	25 (64.1)	65 (61.3)	90 (62.1)	0.760
No	14 (35.9)	41 (38.7)	55 (37.9)	

(*Continued*)

Table 1 (*Continued*)

Variables	Case n (%)	Control n (%)	Total n (%)	p^*
Previous hormone replacement therapy				
Yes	1 (2.6)	10 (9.4)	11 (7.6)	0.166
No	38 (97.4)	96 (90.6)	134 (92.4)	
Breast cancer stage				
Initial	23 (59.0)	60 (56.6)	83 (57.2)	0.798
Advanced	16 (41.0)	46 (43.4)	62 (42.8)	
Surgery				
Yes	38 (97.4)	80 (75.5)	118 (81.4)	0,003
No	1 (2.6)	26 (24.5)	27 (18.6)	
Type of surgery				
Quadrantectomy	18 (47.4)	39 (48.8)	57 (48.3)	0.567
Mastectomy	20 (52.6)	41 (51.3)	61 (51.7)	
Lymph node dissection				
No	5 (13.2)	15 (18.8)	20 (17.0)	0.537
Sentinel	9 (23.7)	23 (28.7)	32 (27.1)	
Axillary dissection	24 (63.2)	42 (52.5)	66 (55.9)	
Immobilization				
Yes	22 (56.4)	26 (24.5)	48 (33.1)	<0.001
No	17 (43.6)	80 (76.5)	97 (66.9)	
Immobilization time				
1 to 3 Weeks	8 (36.4)	11 (42.3)	19 (39.6)	0.675
$\geq$ 4 Weeks	14 (63.6)	15 (57.7)	29 (60.4)	
Lymphedema				
Yes	13 (34.2)	8 (11.2)	21 (18.6)	0.001
No	25 (65.8)	72 (88.7)	97 (81.4)	

Abbreviations: BMI, body mass index; MW, minimum wage; n, absolute frequency; SD, standard deviation. **Notes:** * Pearson chi-square test for categorical variables.

For the case group, according to the visual analogic scale (VAS), the mean pain scores at rest and at motion were 4.21 and 7.38, respectively. The mean passive range of motion was 121.8° of anterior elevation, 53.4° and 53.5° of external rotation at 0°/90° of abduction, and 57.9° of internal rotation. Univariate analysis (►**Table 2**) showed the following predictor variables with $p < 0.20$: age group $\geq$60 years old (0.052); obesity ($p = 0.006$); monthly income $\geq$4 minimum wages ($p = 0.153$); previous hormonal replacement therapy ($p = 0.197$); radiation therapy ($p = 0.010$), surgery ($p = 0.015$), immobilization ($p < 0.001$), and lymphedema ($p = 0.002$).

Multivariate logistic regression is demonstrated in ►**Table 3**. Shoulder immobilization (OR = 3.13; 95% CI:

Table 2 Final univariate logistic regression model for the development of adhesive capsulitis in breast cancer patients

Variables	Case	Control	OR	95% CI		*p*
				Inferior	Superior	
Sociodemographic data						
Age group						
$<$ 60 years	33	72	1.00			
$\geq$ 60 years	6	34	2.60	0.99	6.79	0.052
BMI						
Normal	6	40	1.00			

Table 2 (*Continued*)

Variables	Case	Control	OR	95% CI		*p*
				Inferior	Superior	
Overweight	14	36	1.63	0.70	3.79	0.257
Obesity	19	30	4.22	1.50	11.86	0.006
Race						
White	16	36	1.35	0,64	2.88	0.432
Not white	23	70	1.00			
Marital status						
Married	18	48	0.95	0.39	2.31	0.918
Divorced	6	16	0.95	0.30	3.07	0.938
Widow	4	14	0.73	0.20	2.70	0.634
Single	11	28	1.00			
Monthly income						
None	2	10	1.00			
Up to 1 MW	16	56	1.43	0.28	7.19	0.665
2–3 MW	18	37	2.43	0.48	12.28	0.282
$\geq$ 4 MW	3	3	5.00	0.55	45.39	0.153
Education						
Illiterate	1	5	1.00			
Elementary school	5	22	1.14	0.11	11.99	0.915
Middle school	6	16	1.87	0.18	19.53	0.599
Highschool	26	51	2.55	0.28	22.97	0.404
Higher	1	12	0.42	0.02	8.05	0.562
Dominance						
Right-handed	36	101	0.59	0.14	2.61	0.491
Left-handed	3	5	1.00			
Clinical breast data						
Affected breast						
Right	18	52	0.46	0.09	2.26	0.341
Left	18	50	0.48	0.10	2.36	0.366
Both	3	4	1.00			
Number of biopsies						
1	12	50	0.54	0.14	2.05	0.366
2 to 3	23	47	1.10	0.31	3.96	0.883
$\geq$ 4	4	9	1.00			
Breastfeeding						
Yes	36	90	2.13	0.59	7.77	0.250
No	3	16	1.00			
Menopause						
Yes	30	82	0.98	0.41	2.34	0.956
No	9	24	1.00			
Chemotherapy						
Yes	33	89	1.05	0.38	2.89	0.924

(*Continued*)

Table 2 (*Continued*)

Variables	Case	Control	OR	95% CI		*p*
				Inferior	Superior	
No	6	17	1.00			
Radiotherapy						
Yes	35	71	4.31	1.42	13.10	0.010
No	4	35	1.00			
Endocrinotherapy						
Yes	25	65	1.13	0.53	2.41	0.760
No	14	41	1.00			
Previous hormone replacement therapy						
Yes	1	10	0.25	0.03	2.04	0.197
No	38	96	1.00			
Breast cancer stage						
Initial illness	23	60	1.00			
Advanced disease	16	46	1.10	0.52	2.32	0.798
Surgery						
Yes	38	80	12.35	1.62	94.44	0.015
No	1	26	1.00			
Type of surgery						
Quadrantectomy	18	39	1.00			
Mastectomy	20	41	1.06	0.49	2.29	0.888
Lymph node dissection						
No	5	15	1.00			
Sentinel	9	23	1.17	0.33	4.19	0.805
Axillary dissection	24	42	1.71	0.55	5.30	0.350
Immobilization						
Yes	22	26	3.98	1.84	8.62	<0.001
No	17	80	1.00			
Immobilization time						
1 to 3 Weeks	8	11	1.00			
$\geq$ 4 Weeks	14	15	1.28	0.40	4.12	0.675
Lymphedema						
Yes	13	8	4.68	1.74	12.61	0.002
No	25	72	1.00			

Abbreviations: BMI, Body Mass Index; CI, confidence interval; MW, minimum wages; n, absolute frequency; OR, odds ratio; SD, standard deviation.

Table 3 Final multivariate logistic regression model for the development of adhesive capsulitis in breast cancer patients

Variables	OR	95% CI		*p*
		Inferior	Superior	
Age group				
$\geq$ 60 years old	2.48	0.76	8.08	0.132
BMI				
Obesity	3.91	1.27	12.01	0.017

Table 3 (*Continued*)

Variables	OR	95% CI		*p*
		Inferior	Superior	
Monthly income				
$\geq$ 4 SM	3.64	0.28	47.64	0.325
Radiotherapy				
Yes	1.21	0.28	5.32	0.801
Previous hormone replacement therapy				
Yes	5.11	0.41	64.01	0.206
Surgery				
Yes	8.20	0.99	68.01	0.059
Immobilization				
Yes	3.13	1.30	7.52	0.011
Lymphedema				
Yes	4.60	1.59	13.28	0.005

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

1.30–7.52; $p = 0.011$), lymphedema (OR = 4.60; 95% CI: 1.59–13.28; $p = 0.005$), and obesity (OR = 3.91; 95% CI: 1.27–12.01; $p = 0.017$) showed statistically significant association with the AC outcome.

Discussion

We investigated predictor factors for AC as outcome in patients undergoing treatment for BC. Predictive variables were obesity, shoulder immobilization, and lymphedema. Our initial hypothesis of radiation therapy and mastectomy associated with the outcome was not verified. The hypothesis was considered partially accepted, as shoulder immobilization was associated with the outcome.

Obesity is a world health issue correlating with several organic dysfunctions, including upper extremity pain.[12] It is part of the metabolic syndromes, a set of risk factors for cardiovascular outcomes and type 2 diabetes mellitus.[13] The latter are established predictors for the development of AC, as well as dyslipidemia.[1,3] In agreement with Kingston et al.,[2] our study verified an association between obesity and AC. Thus, women diagnosed with BC must be instructed to manage body weight during treatment to prevent this shoulder condition.

Glenohumeral joint immobilization has been reported in the literature as a risk factor for AC,[14,15] which has also been verified in our study. Furthermore, Recchia et al. showed significant correlation between upper extremity morbidity and a decrease in quality of life after BC treatment.[16] Thus, the recommendation for BC patients following surgery should be a short splinting period followed by early movement of the shoulder. This would lead to improvement in shoulder pain and mobility.[17]

A systematic review by Yang et al. concludes that implementing an exercise program before BC surgery focusing on shoulder motion may benefit ipsilateral upper extremity recovery.[18] In a study of BC survivors, Reigle and Zhang point out that patients who adhere to a postsurgery rehabilitation program may improve their functional abilities.[19]

However, no association between immobilization time and the development of AC was verified in women with BC, which is not in agreement with other studies demonstrating this relation.[17,20,21] Only 48 patients in our study underwent immobilization and were consequently analyzed under variable "immobilization time." This accounted for 33.1% of the total sample (22 cases and 26 controls) and only 14 cases underwent splitting for $\geq$4 weeks. This small subgroup may have favored a type II error of false-negative findings.

Another significant predictive factor for the development of AC in BC was lymphedema. In our study, 34.2% of the case group patients had previous history of lymphedema, in agreement with literature findings of approximately 20% BC-related lymphedema patients presenting with ipsilateral AC.[22,23] The therapy for this type of cancer directly involves all neuromusculoskeletal shoulder tissues, which accounts for the reason why BC survivors develop weakness, fatigue, reduced motion, and lymphedema.

This damage to the shoulder complex may be associated with diagnoses such as AC and postmastectomy syndrome.[9,24] Lymphedema does not usually present with pain but it is often correlated with various inflammatory processes that are related either to surgery or to other BC treatments, which could contribute to the development of several shoulder conditions, such as AC.[22]

It is important to note that our study's objective was to find the association between predictor variables in women treated for BC and AC development. Oncologists seeing such patients should be able to recognize potential associated factors, diagnose AC with no delay, and refer them to specialized treatment. Orthopedists, on their end, should be aware of AC as one of the complications for BC treatment and use the therapy methods available to improve quality of

life for affected women.[25] Patients under treatment for BC must be encouraged to exercise their shoulders after surgical procedures, be it in physiotherapy or hydrotherapy sessions, especially obese patients who developed lymphedema during treatment.

Despite our contribution to the clarification of AC in patients under treatment for BC, this study has some limitations. It is an analytical case-controlled study, and, as such, susceptible to a memory bias. Due to its design, it cannot investigate any cause and effect relationship. Furthermore, nonprobabilistic sampling at a BC-treatment specialty center may have imposed a selection bias, which did not allow for all patients presenting with the condition to be included in the study.

However, using a control group of BC patients without AC allowed for the comparison of the obtained data, aiding in improving scientific knowledge of this incapacitating joint condition's development in patients who are already facing the burden of a malignant condition. Additionally, the sampling was conducted with a minimum of two controls for each eligible case.

Conclusion

Shoulder immobilization, lymphedema, and obesity are predictive factors for the development of AC in women with BC.

Contributions

All of the authors contributed with the project and data interpretation, the writing of the article, the critical review of the intellectual content, and with the final approval of the version to be published.

Conflict of Interests

The authors have no conflict of interests to declare.

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Assessing Endoscopic Suture Performance of Gynecology and Obstetrics Residents Following Methodic Training

Avaliando a performance em sutura endoscópica de residentes de ginecologia e obstetrícia após treinamento metódico

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Abstract

Objective To evaluate the performance of residents in gynecology and obstetrics before and after practicing laparoscopic sutures, to establish when the training shows the best results, in addition to comparing whether being in different years of residency influences this progression.

Methods A prospective cohort study involving 32 medical residents evaluated with a pretest to establish their previous knowledge in laparoscopic suture. This test consisted of knotting two wires, one made of polypropylene and the other of polyglactin, with a blocking sequence of five semi-knots. We set a 30-minute limit to complete the task. Then, the residents held four training meetings, focusing on suture, Gladiator rule, knot, and symmetries, in addition to executing blocking sequences. A second test to establish progress was performed.

Results Regarding the time spent to make the stiches using polyglactin wire, a statistically significant time improvement ($p < 0.01$) was observed, with a 10.67-minute pretraining median (mean 12.24 minutes) and a 2.53-minute posttraining median (mean 3.25 minutes). Regarding the stitches with polypropylene wire, a statistically significant time improvement ($p < 0.05$) was also observed, with a 9.38-minute pretraining median (mean 15.43 minutes) and a 3.65-minute posttraining median (mean 4.54 minutes). A total of 64.2% of the residents had been able to make the knot with polypropylene previously. One hundred percent were able to complete the task in the posttest.

Conclusion Model training using the Gladiator rule for laparoscopic suture improves the knotting time with statistically similar performance, regardless of the year of residency, after systematic training.

Keywords
- suture techniques
- medical education
- in-service training
- simulation training
- laparoscopy

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Resumo

Objetivo Avaliar a performance de residentes em ginecologia e obstetrícia antes e depois de praticarem suturas laparoscópicas, com o intuito de estabelecer quando o treinamento mostra os melhores resultados, comparando se estar em diferentes da residência influencia essa progressão.

Métodos Um estudo coorte prospectivo envolvendo 32 médicos residentes avaliados com um teste pré-treinamento para avaliar seus conhecimentos prévios em sutura laparoscópica. Esse teste consistia em atar nós em dois fios, um de polipropileno e o outro de poliglactina, com uma sequencia de bloqueio de cinco seminós. Definiu-se um limite de 30 minutos para se completar a tarefa. Depois, os residentes tiveram quatro reuniões de treinamento, focadas em sutura, técnica da Regra do Gladiador, nós e simetria, executando, ainda, uma sequência de pontos. Um segundo teste foi feito para avaliar o progresso.

Resultados Com relação ao tempo para realizarem os pontos com fio de poliglactina, uma melhora de tempo estatisticamente significativa ($p < 0.01$) foi observada, com uma mediana de 10.67 minutos no pré-treinamento (média de 12.24 minutos) e uma mediana de 2.53 minutos no pós-treinamento (média de 3.25 minutos). Com relação ao fio de polipropileno, uma melhora de tempo estatisticamente significativa ($p < 0.05$) também foi observada, com uma mediana de pré-treinamento de 9.38 minutos (média de 15.43 minutos) e uma mediana de pós-treinamento de 3.65 minutos (média de 4.54 minutos). Um total de 64.2% dos residentes foram capazes de realizar os nós com polipropileno inicialmente. Cem por cento do residentes foram capazes de completar a tarefa no pós-teste.

Conclusão O modelo de treino usando a técnica da Regra do Gladiador para sutura laparoscópica melhora o tempo de atar nós com uma performance estatisticamente similar, não havendo diferenças quanto ao ano da residência, após treinamento sistematizado.

Palavras-chave

- técnicas de sutura
- educação médica
- capacitação em serviço
- treinamento por simulação
- laparoscopia

Introduction

In recent years, the exponential growth in medical technologies has brought a range of new tools to the repertoire of minimally invasive gynecological surgery. Laparoscopic surgery has become an integral part of this practice, with benefits well documented in the literature.[1,2] Thus, it is necessary to create effective and reproducible training protocols for residents in laparoscopic surgery. The traditional Hallsteadian training model has been used by several academic centers during training in laparoscopic surgery.[3,4] Unfortunately, this method has been shown to be highly subjective and ineffective.[5] Some characteristics of laparoscopy are not suitable for this method, such as the slower learning curve to develop the hand-eye coordination necessary to operate by a video monitor, the interpretation of the limitations of the two-dimensional image, the reduction of tactile feedback and the fulcrum effect.[6] It should also be noticed that when a novice surgeon has to develop these skills in the operating room, the cost of surgery and operative time significantly increase.[7]

Currently, most surgical educators understand that basic skills in laparoscopy should be taught initially outside the operating room; most surgical training programs use a variety of models, including inanimate models, virtual reality, training in live animals or in corpse.[8] Simulation-based training has been shown to improve the residents' laparoscopic skills and can also be used to assess their proficiency objectively.[9,10] Laparoscopic training based on proficiency was developed for training boxes (box training – BT), which proved to be an effective method to develop laparoscopic surgical skills.[11,12]

The suture consists of processes of knotting and closing of a blocking sequence; this task was initially considered a major limiting factor in laparoscopic surgeries, but now it is considered a basic skill to perform these procedures. The wires used have several specific characteristics that directly influence the difficulty of the suture (mono or multifilament; absorption rate; elasticity; tensile strength; easy handling and duration of the inflammatory reaction).[13]

The objective of the present study was to evaluate the amount of time taken to make surgical laparoscopic knots using 2 different types of wires (polyglactin multifilament and polypropylene monofilament) with the previous knowledge of medical residents in gynecology and obstetrics compared with the time taken after participating in 4 training sessions in systematic BTs using the Gladiator rule and to compare the individual performances and those among different groups of

residents according to their years into the residency program (PGY-1/R1, PGY-2/R2 and PGY-3/R3).

Methods

The study is a prospective cohort, in which all residents in gynecology and obstetrics from the residency program at Maternidade Escola Assis Chateaubriand (MEAC) were selected, totaling 32 residents, ten R1, twelve R2, and ten R3. This service currently has a structured service for minimally invasive gynecological surgery and a specialization service (R4) in gynecological endoscopy. The inclusion criteria were to be a MEAC resident doctor, to be available to carry out the evaluations and training, and to carry out the pre and posttraining. Ethical approval was obtained under the register 55770422.0.0000.5050, issued by the Ethical Committee from Maternidade Escola Assis Chateaubriand at Universidade Federal do Ceará.

The resident doctors were initially submitted to a pretraining that consisted of making two blocking sequences, which could be composed of five semi-knots. Participants should use a polyglactin, multifilament, absorbable and synthetic wire, 0 (COVIDIEN) for the first blocking sequence, and a polypropylene wire, monofilament and non-absorbable, 2–0 (SURGIPRO II - COVIDIEN) for the second sequence in a maximum time of 30 minutes (min) for both knots, only with their previous knowledge. Romeu and Minelli Gladiator rule was used to teach trainees how to tie intracorporeal knots.[14]

Next, we made 4 laparoscopic suture training meetings, each one with an emphasis on a specific skill: 1st meeting - horizon, home base and Gladiator rule (above and below the wire); 2nd meeting – ambidextrous, semi-knot, and semi-key; 3rd meeting – blocking sequence H3H2, H2H1SSB; 4th meeting - blocking sequence. Simulation models of the abdominal cavity, support model for the realization of the knots, 1 laparoscopic needle holder and a Maryland forceps were used in the training.[14] After training, a second test was performed in the same pattern as the previous one, and the time to make the knot was again evaluated.

Due to changes in rounds and difficulties in attending training, our sample was reduced to 10 R3, 5 R2, and 5 R1. Data collection was performed during the months of November and December 2018 and January 2019.

Regarding the statistical analysis of the numerical variables, the data will be presented in mean and standard deviation, and in median. In the categorical variables, the data will be exposed in frequency and prevalence rate to investigate associations between the variables evaluated and the result of the pretraining test in comparison with the posttraining test and among the groups of residents (PGY-1, PGY-2, and PGY-3). In the analysis of the characteristics of the groups, the Kruskall-Wallis test and the paired Student *t*-test were used, conditioned to the adherence of the data to the Gaussian distribution. A significance level of 5% was adopted. Statistical analyses were performed using the Jamovi statistical software version: 0.9.5.12 and Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA).

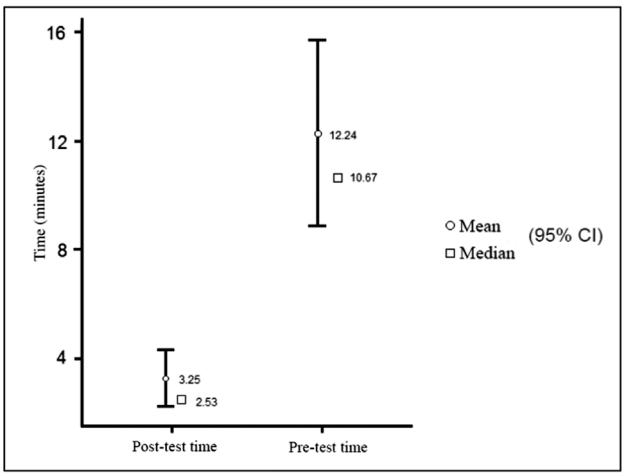

Fig. 1 Pre vs Post training time using polyglactin wire.

Results

The results obtained by comparing the pre and posttraining times for making a knot with polyglactin wire (►**Fig. 1**) showed a statistically significant improvement, with an initial median of 10.67 minutes and a mean of 12.24 minutes, which evolved to a median of 2.53 minutes and mean of 3.25 minutes (►**Table 1**).

In regard to statistical analysis, these results are statistically significant, with $p < 0.01$ (►**Table 2**).

The time evaluation using the polypropylene wire (►**Fig. 2**) presented a median of 9.38 minutes with a mean of 15.43 minutes in the pretraining, which evolved to a median of 3.65 minutes with a mean of 4.54 minutes posttraining (►**Table 3**).

These results are also statistically significant, with $p < 0.05$ (►**Table 4**).

During pretraining evaluations, 64.2% of the residents were able to make a knot with polypropylene wire. In contrast, 100% of the residents were able to complete the task posttraining. The proportion of residents who managed to make the knot before and after training was also evaluated. In pretraining evaluation, the result was not different

Table 1 Pre and post training time using polyglactin wire

	n	Mean(min)	Median	SD	SS
Pre training time	23	12:24	10:67	8.36	1.743
Post training time	23	3:25	2:53	2.56	0.534

Abbreviations: SD, standard deviation; SS, statistical significance.

Table 2 Wilcoxon test – polyglactin wire

			Statistics	*p*
Post training time	Pre training time	Wilcoxon W	2.00	< 0.01

Table 3 Pre and posttraining time using polypropylene wire

	n	Mean(min)	Median	SD	SS
Pre training time	23	15:43	9:38	11.89	2.480
Post training time	23	4:54	3:65	3.47	0.723

Table 4 Wilcoxon test – polypropylene wire

			Statistics	*p*
Post training time	Pretraining time	Wilcoxon W	16.00	< 0.01

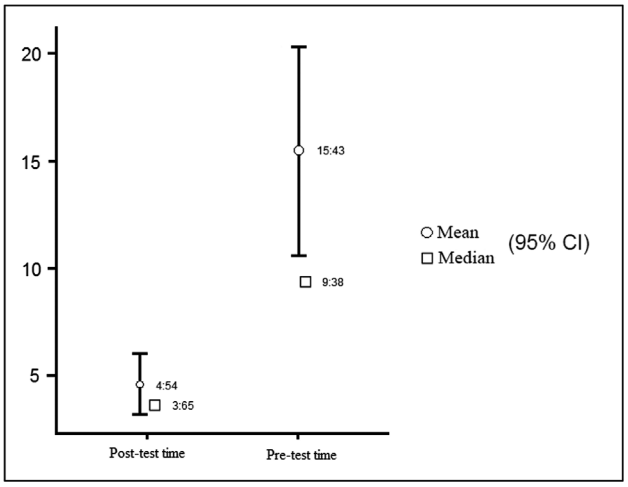

Fig. 2 Pre vs Post training time using polypropylene wire.

from 50%, without statistical significance ($p = 0.210$). In the posttraining, the result was different from 50%, with statistical significance ($p < 0.01$). Therefore, there was a significant evolution in all groups after training. We also evaluated time improvement by comparing the groups in different years of residence (PGY-1, PGY-2, and PGY-3). The assessment showed improvement by reducing the time to perform uniform knots among the residency groups but did not show statistical evidence regarding skill enhancement.

Discussion

Our study demonstrated a significant time improvement in making laparoscopic surgical knots performed by a resident doctor, after four training sessions in laparoscopic sutures. These performances' improvement results were observed using polyglactin or polypropylene wire. We observed at the beginning of the study, before the resident doctors underwent training, that only 64.2% were able to make the knot with polypropylene. The greater ease with multifilament sutures was very clear, limiting the residents' competence to make knots with monofilament sutures. In the literature, we find several references that describe different specific characteristics of the wires used in sutures that directly influence the difficulty of their manipulation (mono or multifilament; absorption rate; elasticity; tensile strength; easy handling and duration of the inflammatory reaction).[13] Thus, there is an urgent need for the resident physician to acquire competence and proficiency in performing laparoscopic sutures with different types of wires available.

The conformation of the knot is a key point, and its security is defined as a sequence of knots that does not untie or slip and opens before the wire breaks or does not slip by > 3 mm.[13,15,16] More recently, with dynamometric evaluation, the safe knot was redefined as the greatest pressure sustained by it until it slips, fails, or the suture breaks.[17] According to our data, systematic training with mentors in a simulated BT environment is able to increase the proficiency of resident physicians in a few sessions. We observed in the posttraining evaluations, performed after 4 training sessions in laparoscopic sutures, that 100% of the students were able to successfully perform a suture also with polypropylene wire.

The traditional Halstedian learning model—"seeing one, making one, teaching one"—has been challenged recently. The learning opportunity in the operating room has decreased, mainly because of time pressure, cost, and, above all, bioethical and medical-legal issues.[6] The best way to develop laparoscopic surgical skills and overcome this learning curve seems to be by participating in formal training in a specialized surgical skills laboratory.[5,6] Laparoscopic suture, for example, is an advanced laparoscopic skill that allows the

surgeon to expand the application in various dimensions of video surgery.[8] However, it consists of a skill that is difficult to develop and requires many hours of specialized training.[9]

Suturing and tying knots are essential skills in most surgical procedures for tissue apposition and hemostasis.[5] We recognize as fundamental the need for all surgeons to understand and master the correct combinations of surgical knots.[10] When a suture fails, the consequences can be disastrous, with possible massive bleeding, evisceration and dehiscence of the vaginal dome.[13] Many different training systems have been designed and manufactured to allow students and surgeons to acquire some skill in handling dedicated equipment and performing laparoscopic surgical procedures. These different training systems can be separated into physical simulation (box trainer or animal model) and systems that use virtual software.[11,12,18–24]

In addition to an adequate environment and simulation materials for training in laparoscopic sutures, it is essential that we have standardization and methodization in teaching and learning technologies. In our study, all training was based on the Gladiator rule. In 2017, Romeo et al. studied 2,000 thousand knots made by experienced and trained surgeons using the Gladiator's suturing technique followed by tests with a dynamometer and concluded that the blocking sequences composed of 5 semi-knots or semi-keys had the best results withstanding pressures greater than 30 Newtons (safe pressure for gynecological procedures).[18]

In our study, when evaluating groups of resident physicians from different years, we observed that there was no statistically significant difference in the improvement of suturing time. These findings are similar to those from Galvão-Neto et al., who demonstrated that previous medical experience is valid only when medical decision-making is necessary and does not seem to be relevant in the final result in a scenario of simulation of skills.[11,12] We conducted our training based on the Gladiator rule, a methodology already validated by Liceaga et al., in 2013, with good results in teaching.[19]

The results of substantial time improvement to perform the suture found in our study corroborate with the findings by Assencio et al., who also used the Gladiator rule. However, they performed 14 hours of theoretical and practical training with polyglactin wire. In our study, unlike Assencio et al., each resident underwent only 1 hour and 20 minutes of practical training, and we also tested the knotting of polypropylene thread. According to our findings, we dare to infer that shorter, fractional training, focused on mentored and systematized practice would have a similar result in improving time in knotting. We demonstrated that, at the end of the training, both residents of the first year without experience in laparoscopy and those in more advanced periods reached proficiency without a statistically significant difference in number and in resistance of the stitches, creating less dispersion and more homogeneous results. We believe, therefore, that it is fundamentally and fully possible to learn the intracorporeal suture at the beginning of the endoscopic learning curve and not only in the case of an experienced and skilled surgeon. In fact, it must be considered that also during basic operative procedures, the surgeon may unexpectedly need the ability to intracorporeal suture. The technique taught during this type of course, as demonstrated in the present work, is essential to improve dexterity and coordination, especially among inexperienced laparoscopists.

Another observation of our study was the proportional time decrease to perform the suture with polypropylene when compared with polyglactin. Therefore, the hypothesis is refuted that it is impossible to improve the quality of the suture with different materials, with different physical and chemical characteristics for beginners. In this way, the possible use of different materials in different situations is made available to inexperienced surgeons, increasing their effectiveness and safety of laparoscopic sutures.

Although it was not the objective of the study's outcome, our results somehow corroborate with the literature regarding the effectiveness of BTs for the training of laparoscopic skills such as psychomotor control, spatial orientation and improvement of two-dimensional vision, basic concepts for the development of laparoscopic suture.[19–23]

Despite the evidence on simulated training, its implementation is unfortunately still not systematic. Among the difficulties in implementing this training, we can mention the required time for training, the high cost of training material and the lack of access to the simulators.[24,25] Teaching surgical skills has undergone severe changes after the development of laparoscopy, when it was necessary to develop new teaching protocols to improve efficiency and safety in surgeries. Our study corroborated with the findings of other studies, emphasizing the need for this type of training protocol, and once again validating its use in in-service training.[26]

Conclusion

We find that the training for laparoscopic suture skills using the Gladiator rule improves the knotting time performed by trainees with both polyglactin and polypropylene wires. Furthermore, regardless of the year of resident physicians, the improvement was the same after methodical training.

Contributions

All of the authors contributed to the conception of project and data analysis and interpretation, the writing of the article and approved the final version to be published.

Conflict of Interests

The authors have no conflict of interests to declare.

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Prognostic Impact of AGR3 Protein Expression in Breast Cancer: A Systematic Review and Meta-analysis

Impacto prognóstico da expressão da proteína AGR3 no câncer de mama: Uma revisão sistemática e metanálise

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Abstract

Objective To investigate the clinicopathological significance and prognosis of the expression of the anterior gradient 3 (AGR3) protein in women with breast cancer.

Data Sources The PubMed, CINAHL, EMBASE, Scopus, and Web of Science databases were searched for studies published in English and without restrictions regarding the year of publication. The search terms were: *breast cancer* AND *anterior gradient 3* OR *AGR3 expression*.

Study Selection We included observational or interventional studies, studies on AGR3 protein expression by immunohistochemistry, and studies on invasive breast cancer. Case reports, studies with animals, and reviews were excluded. In total, 4 studies were included, containing 713 cases of breast cancer.

Data Collection Data were extracted on clinicopathological characteristics and survival. A meta-analysis of the prevalence of AGR3 expression was performed according to the clinicopathological characteristics, hazard ratios (HRs), and overall survival and disease-free survival.

Data Synthesis The expression of AGR3 was found in 62% of the cases, and it was associated with histological grade II, positivity of estrogen and progesterone receptors, low expression of ki67, recurrence or distant metastasis, and lumen subtypes. In patients with low and intermediate histological grades, AGR3 expression was associated with worse overall survival (HR: 2.39; 95% confidence interval [95%CI]: 0.628–4.159; $p = 0.008$) and worse disease-free survival (HR: 3.856; 95%CI: 1.026–6.686; $p = 0.008$).

Conclusion The AGR3 protein may be a biomarker for the early detection of breast cancer and predict prognosis in luminal subtypes. In addition, in patients with low and

Keywords
- breast neoplasms
- human AGR3 protein
- immunohistochemistry
- prognosis
- survival

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intermediate histological grades, AGR3 protein expression may indicate an unfavorable prognosis in relation to survival.

Resumo

Objetivo Investigar o significado clinicopatológico e prognóstico da expressão da proteína *anterior gradient 3* (AGR3) em mulheres com câncer de mama.

Fontes de Dados Utilizamos as bases de dados PubMed, CINAHL, EMBASE, Scopus e Web of Science para pesquisar estudos em inglês, sem restrições quanto ao ano de publicação. Os termos buscados foram: *breast cancer* AND *anterior gradient 3* OR *AGR3 expression*.

Seleção dos Estudos Foram incluídos estudos observacionais ou intervencionais, estudos sobre a expressão da proteína AGR3 por imuno-histoquímica, e estudos sobre câncer de mama invasivo. Excluíram-se relatos de casos, estudos com animais e revisões. Quatro estudos foram selecionados, que continham 713 casos de câncer de mama.

Coleta de Dados Foram extraídos dados relativos a características clinicopatológicas e sobrevida. A metanálise da prevalência da expressão de AGR3 foi realizada conforme as características clinicopatológicas, razões de risco (RRs) e sobrevida global (SG) e sobrevida livre de doença (SLD).

Síntese dos Dados Encontrou-se expressão de AGR3 em 62% dos casos, que se associou com grau histológico II, positividade de receptores de estrogênio e progesterona, baixa expressão de ki67, recorrência ou metástase à distância e subtipos luminais. Em pacientes com graus histológicos baixo e intermediário, a expressão de AGR3 conferiu pior SG (RR: 2,39; intervalo de confiança de 95% [IC95%]: 0,628–4,159; $p = 0,008$) e pior SLD (RR: 3,856; IC95%: 1,026–6,686; $p = 0,008$).

Conclusão A AGR3 pode ser um biomarcador para a detecção precoce do câncer de mama e predizer o prognóstico em subtipos luminais. Em graus histológicos baixo e intermediário, a expressão da proteína AGR3 pode indicar um prognóstico desfavorável em relação à sobrevida.

Palavras-chave
- câncer de mama
- proteína humana AGR3
- imuno-histoquímica
- prognóstico
- sobrevida

Introduction

Breast cancer is of great epidemiological relevance due to the high rates of mortality and morbidity in the world. In 2020, breast cancer represented the main cause of death due to cancer among women, affecting $\sim$ 2.3 million new cases.[1]

With advances in large-scale techniques, gene expression signatures capable of stratifying breast cancer into molecular subtypes that aid in diagnosis, response to treatment, and prognosis have been proposed. Through these analyses, breast cancers have been stratified into four subtypes: luminal A, luminal B, human epidermal growth factor receptor-2 positive (HER2 +), and basal-like.[2,3] Despite the translational application of the molecular stratification of breast cancer, many patients develop resistance to treatments and recurrence, which instigates research that seeks new biomarkers of prognosis and response to chemotherapy.[4]

Anterior gradient 3 (AGR3) is a member of the protein disulfide isomerase (PDI) gene family. In recent years, the protein encoded by this gene has attracted the attention of researchers due to its role in the process of carcinogenesis.[5] The clinical relevance of AGR3 has been demonstrated in several cancers, including ovarian cancer,[6,7] prostate cancer,[8] intrahepatic cholangiocarcinoma, hepatocellular carcinoma,[9] and breast cancer.[5,10–13] Scientific evidence has suggested that AGR3 has prognostic value in ovarian and breast cancers.[6,14] In ovarian cancer, AGR3 is upregulated in the serous[6] and clear-cell subtypes,[7] and high levels of AGR3 are a predictor of better survival.[6] In breast cancer, AGR3 is considered a potential biomarker for early detection in blood and tissue[5,11] and for prognosis.[13]

The role of AGR3 in the clinic of breast cancer remains nuclear,[5,12] due to the limited studies that present the clinicopathological and prognostic relevance of this protein.[5] However, the evidence suggest that AGR3 may be associated with oncogenesis, and it has been pointed out as a potential therapeutic target and prognostic biomarker for patients with breast cancer. According to these precedents, the objective of the present systematic review and meta-analysis was to investigate the clinicopathological significance and

prognosis of the expression of the AGR3 protein in women with breast cancer.

Materials and Methods

The present systematic review and meta-analysis was performed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[15] statement and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group.[16] In adition, the study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021244277).

An electronic search was performed on the PubMed, CINAHL, EMBASE, Scopus, and Web of Science databases. Searches on Google Scholar and the primary study reference list were also conducted to identify additional studies. The search terms were: *breast cancer* AND *anterior gradient 3* OR *AGR3 expression*. The search strategies for each database are presented in **chart 1**.

The inclusion criteria were: 1) observational or interventional studies involving the expression of the AGR3 protein in women with breast cancer; 2) studies evaluating the prognostic capacity of the AGR3 protein expression by immunohistochemistry; and 3) studies on invasive breast cancer; moreover, there were no restrictions regarding language or the year of publication of the studies. The following were excluded: dissertations, theses, case reports, studies with animals, reviews, editorials, letters to the editor, and duplicate studies found in more than one database.

Titles and abstracts were read using the Rayyan (Rayyan Systems Inc., Cambridge, MA, United States) software. The studies retrieved were analyzed by the authors, the selected articles were read in full, and the inclusion and exclusion criteria were applied. Doubts and/or disagreements about the articles were discussed by the research team.

The following data were extracted: author and year of publication, study design, country, number of patients, age of the patients, methods of evaluation and results of AGR3 expression in women with breast cancer, and clinical results (clinicopathological characteristics and survival).The clinicopathological characteristics included: age, histological grade, estrogen receptor (ER), progesterone receptor (PR), HER2, K_i−67, recurrence or distant metastasis, and molecular subtypes (luminal A, luminal B, HER2+, and triple-negative). The data collected on survival were: overall survival (OS) and disease-free survival (DFS).

The risk of bias was assessed using the Cochrane's Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) tool.[17] Eight methodological domains were evaluated: 1) bias due to confounding; 2) bias in the selection of participants into the study; 3) bias in the measurement of interventions; 4) bias due to departures from the intended interventions; 5) bias due to missing data; 6) bias in the measurement of outcomes; 7) bias in the selection of the reported result; and 8) overall bias. Each domain was classified as presenting "low risk of bias," "moderate risk of bias," "serious risk of bias," and "critical risk of bias."

The methodological quality of the studies was evaluated using the software application of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach (https://gdt.gradepro.org/app/#),[18,19]

Chart 1 Search strategies used in each database

Databases	Search Strategy
MEDLINE/PubMed	*Search: ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) AND ((("anterior"[All Fields] OR "anteriores"[All Fields] OR "anteriorization"[All Fields] OR "anteriorized"[All Fields] OR "anteriors"[All Fields]) AND ("gradient"[All Fields] OR "gradient s"[All Fields] OR "gradients"[All Fields]) AND "3"[All Fields]) OR ("AGR3"[All Fields] AND ("express"[All Fields] OR "expresse"[All Fields] OR "expresses"[All Fields] OR "expressing"[All Fields] OR "expressions"[All Fields] OR "gene expression"[MeSH Terms] OR ("gene"[All Fields] AND "expression"[All Fields]) OR "gene expression"[All Fields] OR "expressed"[All Fields] OR "expression"[All Fields])))* ***Total: 32***
CINAHL	*Boolean/Phrase: Breast Cancer AND AGR3 OR Anterior gradient 3* ***Total: 3***
EMBASE	*1 breast cancer/394079* *2 Anterior gradient 3.mp./12* *3 AGR3.mp./94* *4 2 or 3/94* *5 1 and 4/12* ***Total: 12***
Scopus	*TITLE-ABS-KEY ((breast cancer) AND (Anterior gradient 3 OR AGR3))* ***Total: 29***
Web of Science	*((breast cancer) AND (AGR3 OR Anterior gradient 3))* ***Total: 40***

which considers four categories: high, moderate, low, and very low quality.[20] Thus, the quality of the evidence was classified into these aforementioned categories.

Meta-analyses were conducted using the random effects model on coded data stratified by the expression of AGR3. The meta-analysis of prevalence of AGR3 expression was performed according to clinicopathological characteristics, hazard ratios (HRs) and OS and DFS analyses. The data were expressed graphically in forest plots, with estimates on the prevalence and HRs with 95% confidence intervals (95%CIs). The degree of heterogeneity among the studies was estimated by the statistical values of I^2: $<25\%$ – low heterogeneity;, 25% to 50% – moderate heterogeneity; and $>50\%$ –high heterogeneity.[21] Publication bias was assessed using the Egger test and funnel plot asymmetry. All analyses were performed using the STATA (StataCorp LLC, College Station, TX, United States) software, version 16.0.

Results

A total of 116 articles were identified in the 5 databases evaluated. After the careful process of screening and removing duplicates, 69 articles were selected and had their titles and abstracts read; then, 9 articles were selected for full-text reading, and 4 articles presented the eligibility criteria and were included in the present systematic review and meta-analysis.[5,10,11,13] The article selection process is illustrated in a flowchart prepared in accordance with the PRISMA statement (►**Fig. 1**).

The excluded articles and the reasons for the exclusions are presented in **chart 2**.

Four studies were evaluated using the GRADE approach and ROBINS-I. The GRADE score indicated that three studies showed moderate quality of evidence[5,11,13] and one study, showed poor quality (►**Table 1**).[10] The results of the risk of bias assessment are shown in ►**Fig. 2**.

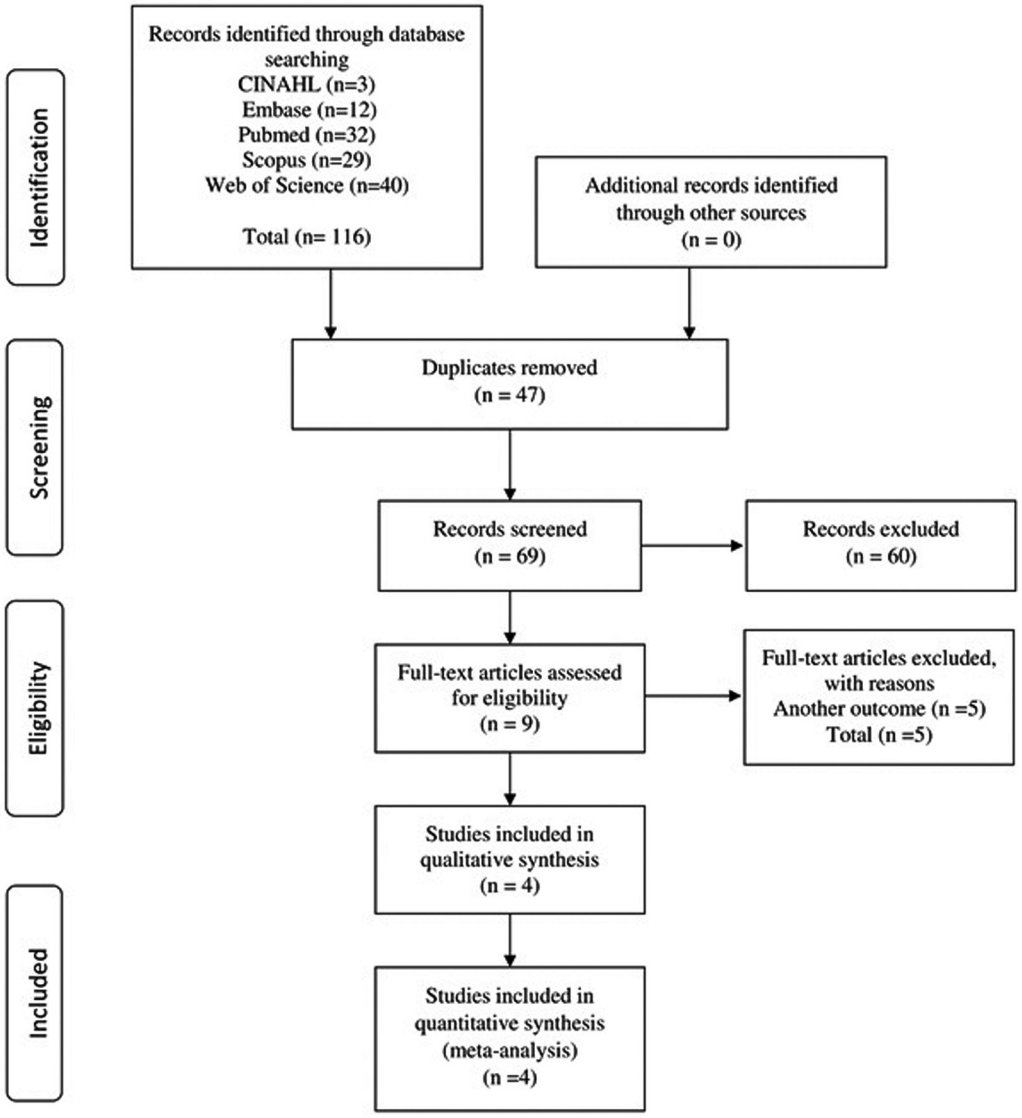

Fig. 1 Flowchart of the process of selection of studies.

Chart 2 Excluded articles and reason for exclusion

Number	Title	Reason for exclusion
1	Jian, Lei et al. AGR3 promotes estrogen receptor-positive breast cancer cell proliferation in an estrogen-dependent manner. *Oncology Letters*, v. 20, n. 2, p. 1,441–1,451, 2020.	Another outcome
2	Umesh, Anita et al. Identification of AGR3 as a potential biomarker though public genomic data analysis of triple-negative (TN) versus triple-positive (TP) breast cancer (BC). *Journal of Clinical Oncology*, v. 30, n. 27, supplement 31, 2012.	Another outcome
3	Obacz, Joanna et al. The role of AGR2 and AGR3 in cancer: similar but not identical. *European Journal of Cell Biology*, v. 94, n. 3–4, p. 139–147, 2015.	Another outcome
4	Obacz, Joanna et al. Extracellular AGR3 regulates breast cancer cells migration via Src signaling. *Oncology Letters*, v. 18, n. 5, p. 4,449–4,456, 2019.	Another outcome
5	PERSSON, Staffan et al. Diversity of the protein disulfide isomerase family: identification of breast tumor induced Hag2 and Hag3 as novel members of the protein family. *Molecular Phylogenetics and Evolution*, v. 36, n. 3, p. 734–740, 2005.	Another outcome

A funnel plot was developed to assess the publication bias (►**Fig. 3**). This analysis revealed a symmetrical pattern, and there was no evidence of a notable publication bias that could confuse the results. The Egger test ruled out the apparent bias in studies that analyzed the expression of AGR3 in women with breast cancer ($p = 0.105$).

The present systematic review included four studies,[5,10,11,13] comprising a total of 713 cases of breast cancer from Germany,[11] the United Kingdom,[10] the Czech Republic,[5] and China.[13] The characteristics of each study are shown in **table 1**.

The studies included showed results of the prevalence of AGR3 expression in women with breast cancer that were included in the meta-analysis.[5,10,11,13] The prevalence of AGR3 expression was of 62%, as shown in ►**Fig. 4**.

The results of the meta-analysis of the prevalence of AGR3 expression according to the clinicopathological variables are summarized in ►**Table 2**. The type-II histological grade (65%; $p = 0.048$; $I^2 = 95.33\%$),[5,11,13] ER positivity (72%; $p = 0.000$; $I^2 = 98.53\%$),[5,11,13] PR positivity (69%; $p = 0.000$; $I^2 = 96.74\%$),[5,11,13] negativity of Ki-67 expression (52%; $p = 0.015$; $I^2 = 90.16\%$),[5,13] recurrence or distant metastasis

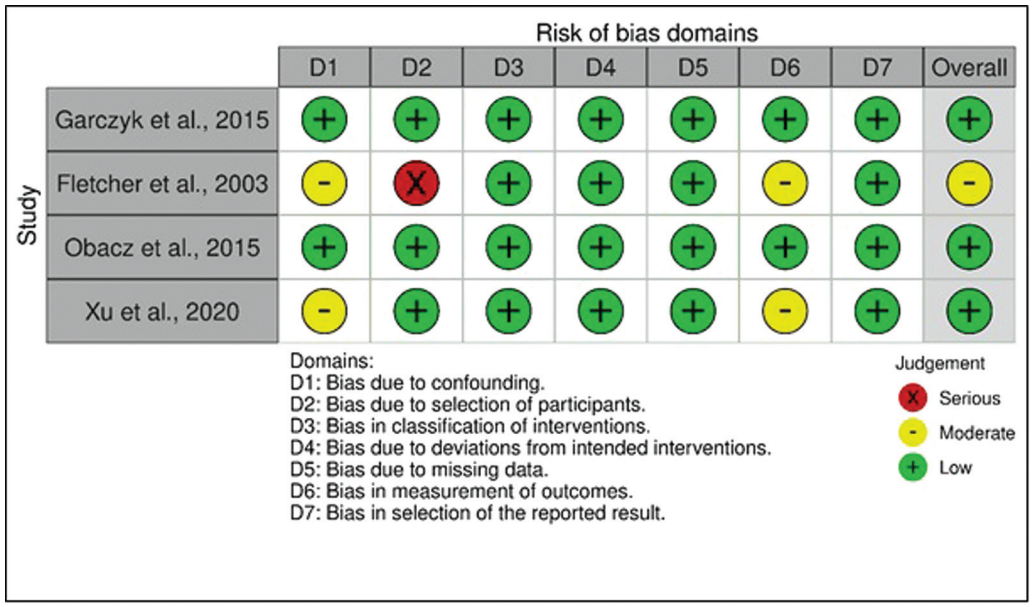

Fig. 2 Summary of the authors' judgments about each item of the risk of bias assessment for each included study.

Table 1 Characteristics of the studies included in the systematic review and meta-analysis

Reference	N/age	Study design/ follow-up	Immunohistochemical staining	AGR3 expression	Conflict of interests	Ethical approval	Quality of the evidence (GRADE)
Obacz et al., 2015[5] (Czech Republic)	129/29 to 84 (median: 57) years	Cohort/ 10 years	Tumor samples were fixed in 10% neutral buffered formalin for 24 hours and then embedded in paraffin wax. Immunohistochemical analysis was performed on 4-µm thick sections cut from formalin-fixed paraffin-embedded archival tissue blocks, mounted on slides, deparaffinized in xylene, and rehydrated in phosphate-buffered saline through a graded ethanol series.	104/129	No	Yes	⊕⊕⊕⊖ moderate
Fletcher et al., 2003[10] (United Kingdom)	58/< 50 years versus 50 years	Not reported	Immunohistochemical analysis was performed on formalin-fixed paraffin-embedded tissue microarrays containing 1-mm sections of breast carcinoma tissues from 60 donors. Slides were deparafinized by two 5-minute washes in xylene, then rehydrated through successive graded ethanol solutions and washed for 5 minutes in phosphate-buffered saline.	43/58	No	Yes	⊕⊕⊖⊖ Low
Garczyk et al., 2015[11] (Germany)	190 **Age:** Less than 54,5 years of age versus 54,5 years	Cohort 138.5 (range: 1–218) months	Immunohistochemical analysis was performed according to the manufacturer's instructions (DAKO 5001; DAKO, Glostrup, Denmark). Heat-induced epitope retrieval was performed in 10-mm citrate buffer (pH 6.0) for 10 minutes using a pressure cooker. Formalin-fixed, paraffin-embedded sections (3 µm) were incubated for 45 minutes with mouse monoclonal anti-AGR3-antibody (1:1000; ab82400, Abcam, Cambridge, United Kingdom).	104/190	No	Yes	⊕⊕⊕⊖ moderate
Xu et al., 2020[13] (China)	336*/52 years, which ranged from 28 to 89 years	Cohort/ 5–146 months	All procedures were performed in Benchmark XT (Roche, Basel, Switzerland). Antigen retrieval was performed in citrate buffer at 121°C for 2 minutes 15 seconds. After retrieval, sections were steeped in 3% H2O2 buffer for 25 minutes and in 10% goat serum buffer for 25 minutes. Then, the sections were steeped in primary antibody against AGR3 (1:100, HPA053942, Sigma, St. Louis, MO, United States) at 4°C for 1 night.	129/336	No	Yes	⊕⊕⊕⊖ moderate

Abbreviations: AGR3, anterior gradient 3; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations.
Note: *Invasive ductal carcinoma. GRADE Working Group grades of evidence: high quality – further research is very unlikely to change our confidence in the estimate of effect; moderate quality – further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality – further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality – we are very uncertain about the estimate.

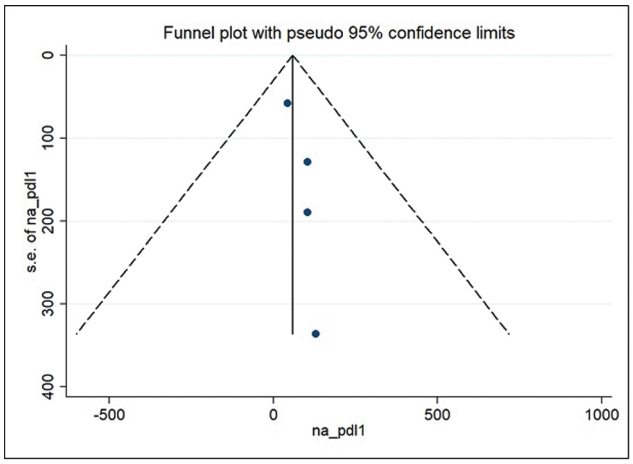

Fig. 3 Funnel plot for the studies included in the meta-analysis.

(55%; $p = 0.001$; $I^2 = 0\%$).[13] and luminal subtypes A (46%) and B (48%) ($p = 0.000$; $I^2 = 94.06\%$)[13] have been associated with positive AGR3 expression in women with breast cancer.

Information about the association regarding AGR3 expression and OS[5,11,13] and DFS[5,13] in women with breast cancer are shown in ►**Table 3**.

►**Fig. 5** shows the combined HR and forest plots for survival based on AGR3 expression. The result of the meta-analysis revealed that AGR3 expression was associated with a worse OS (HR: 2.39; 95%CI = 0.63–4.16; $p = 0.008$)[11,13] and DFS (HR: 3.86; 95%CI = 1.03–6.69; $p = 0.008$).[13] In addition, the final result of the meta-analysis indicated that AGR3 expression was associated with poorer survival in low- and intermediate-grade tumors (HR: 2.80; 95%CI = 1.30–4.30; $p = 0.000$) (►**Fig. 5**). No heterogeneity was observed among the included studies ($I^2 = 0.0\%$).

Table 2 Meta-analysis of AGR3 expression and clinicopathological features of breast cancer

Analysis	Proportion (%) Of AGR3	*p-value* for overall effect	Heterogeneity I^2 (%)/*p*-value	References
Age (in years)				
< 50	0.44%	0.068	0%/$p = 0.00$	13
≥ 50	0.34%			
Histological grade				
I	0.44%	0.048	95.33%/$p = 0.00$	5,11,13
II	0.65%			
III	0.24%			
Estrogen receptor				
(–)	0.12%	0.000	98.53%/$p = 0.00$	5,11,13
(+)	0.72%			
Progesterone receptor				
(–)	0.22%	0.000	96.74%/$p = 0.00$	5,11,13
(+)	0.69%			
MIB1/Ki-67 expression				
Low	0.52%	0.015	90.16%/$p = 0.00$	5,13
High	0.41%			
HER2				
(–)	0.60%	0.059	92.36%/$p = 0.00$	5,11,13
(+)	0.33%			
Recurrence or distant metastasis				
No	0.34%	0.001	.%, $p = 0.00$	13
Yes	0.55%			
Molecular subtypes				
Luminal A	0.46%	0.000	94.06%, $p = 0.00$	13
Luminal B	0.48%			
HER2+	0.11%			
Triple-negative	0.15%			

Abbreviations: AGR3, anterior gradient 3; HER2, human epidermal growth factor receptor-2.
Notes: I^2: heterogeneity between groups; $p < 0.05$: statistically significant; observation: prevalence data and I^2 were extracted from the meta-analysis graphs.

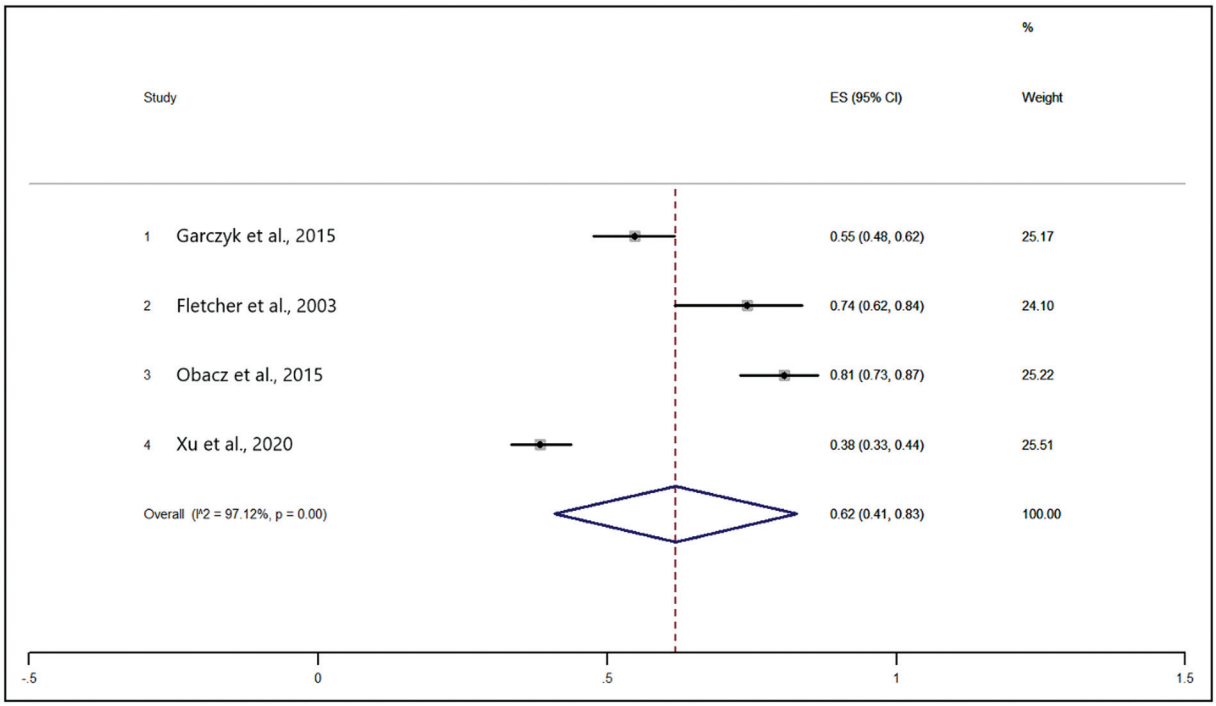

Fig. 4 Forest plots of the prevalence (%) of anterior gradient 3 (AGR3) expression in women with breast cancer.

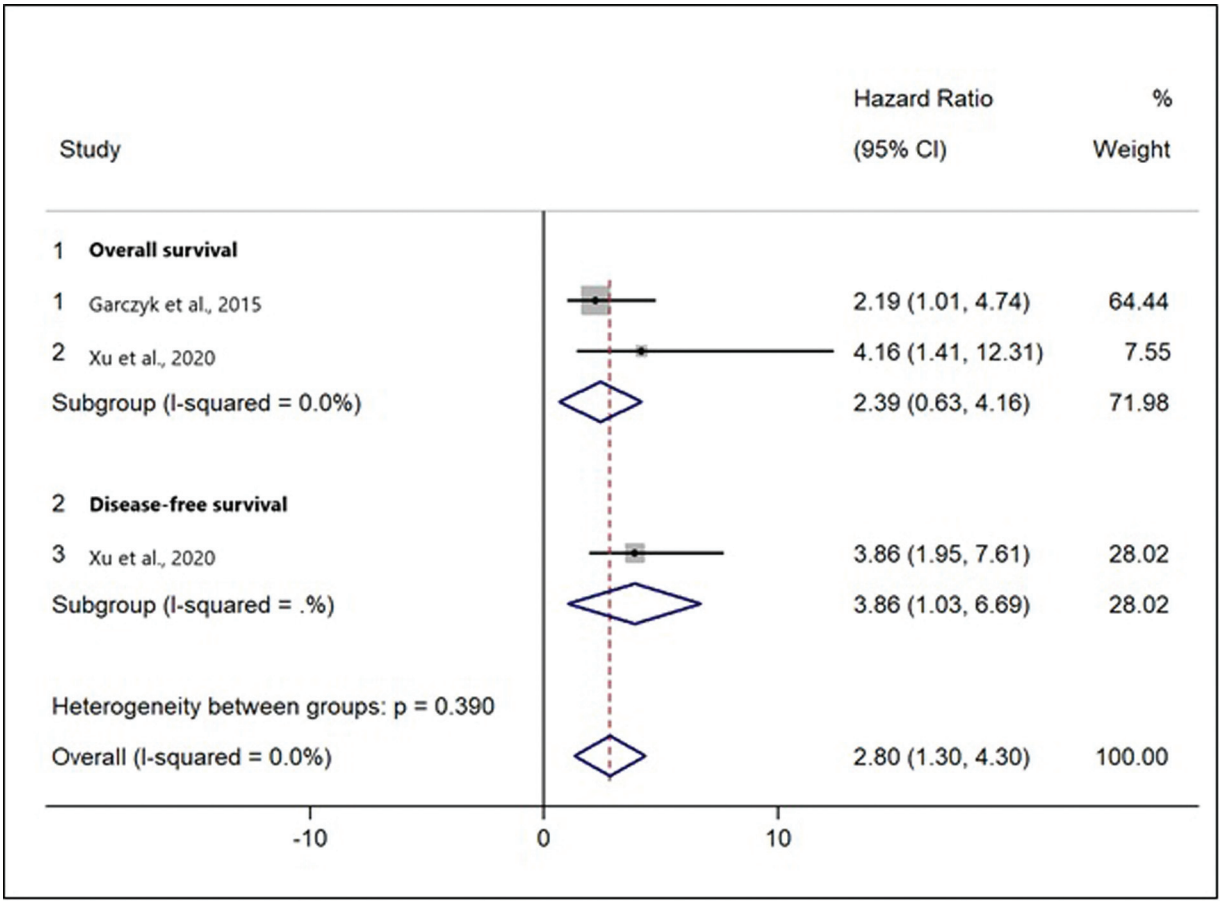

Fig. 5 Forest plots of the hazard ratios (HRs) for survival based on the expression of AGR3.

Table 3 Association between survival and AGR3 expression in women with breast cancer

Global survival	
Obacz et al., 2015[5]	Determination of overall survival by Kaplan–Meier analysis in patients with "high" AGR3 expression and patients with "low" AGR3 expression using Breslow test ($p = 0.111$).
Garczyk et al., 2015[11]	Patients with low and intermediate grade tumors showing high AGR3 expression had an unfavorable outcome (mean tumor-specific survival: 142.5 ± 9.6 months; 95%CI: 123.8–161.2) compared with those with low AGR3 expression (mean tumor-specific survival: 181.7 ± 10.1 months; 95%CI: 162.0–201.4). The Cox regression model confirmed AGR3 to be a putative independent marker of unfavorable prognosis in low- and intermediate-grade breast tumors (multivariate HR: 2.186; 95%CI: 1.008–4.740; $p < 0.05$).
Xu et al., 2020[13]	IDC patients of grades I-II: in the multivariate Cox regression analysis, we found that AGR3 expression was an independent predictor for overall survival (HR: 4.161; 95%CI: 1.406–12.312; $p < 0.010$).
Disease-free survival	
Obacz et al., 2015[5]	Determination of progression-free survival by Kaplan–Meier analysis in patients with "high" AGR3 expression (more than 50% of positive cells) and patients with "low" AGR3 expression (less than 50% of positive cells) using Breslow test ($p = 0.037$)
Xu et al., 2020[13]	IDC patients of grades I-II: in the multivariate Cox regression analysis, we found that AGR3 expression was an independent predictor for disease-free survival (HR: 3.856; 95%CI: 1.953–7.613; $p < 0.001$)

Abbreviations: 95%CI, 95% confidence interval; AGR3, anterior gradient 3; HR, hazard ratio; IDC, invasive ductal carcinoma.

Discussion

Currently, there are studies that point out the potential of AGR3 in breast carcinogenesis.[5,10,11,13] The present systematic review and meta-analysis evaluated 713 cases and found a high prevalence of AGR3 protein expression in patients with breast cancer. The AGR3 protein was associated with positivity of estrogen and progesterone receptors, histological grade II, low expression of Ki-67, recurrence or distant metastasis, and luminal subtypes. In addition, AGR3 has a prognostic value for conferring worse OS and DFS in patients with histological grades I and II.

In the present study, we observed a prevalence of AGR3 positivity of 62% in breast cancer, which demonstrates the relevance of this protein in breast carcinogenesis, confirming the predominant expression previously reported.[5,11] The expression of AGR3 in general seems to be associated with a less aggressive phenotype, with hormone receptor positivity, low histological grade, and low proliferation rate. The association of AGR3 with the positivity of estrogen and progesterone receptors demonstrates that there is a close relationship between AGR3 and the luminal subtypes.[5,11,13] This interaction has often been reported[10,11,13,14] and, in conjunction with the other histological and proliferative characteristics, it suggests that AGR3 is associated with less aggressive cancers that are generally responsive to treatment and therefore have a favorable result.[5]

The findings of the present study indicate that the expression of AGR3 was reduced for the triple-negative subtype of breast cancer. This finding is in line with that of another recent study that analyzed AGR3 mRNA gene expression in breast cancer cell tissues.[12]

Although AGR3 expression has been associated with less aggressive clinicopathological features in breast cancer, paradoxically, in the present study, we have identified the association of AGR3 expression with distant recurrence and/or metastasis and an unfavorable outcome in relation to survival, demonstrating the complexity of that molecule. In luminal subtype B, high AGR3 expression was associated with high risk of recurrence and metastasis and poor prognosis in patients with invasive breast carcinoma.[13] In addition, AGR3 appears to have protumor functions in breast cancer, by regulating the adhesion and migration processes of tumor cells through the activation of Src kinases.[22]

The result of the meta-analysis revealed that AGR3 expression was associated with worse OS[11,13] and DFS[13] in low- and intermediate-grade cancers. Garczyk et al.[11] suggested a prooncogenic impact of AGR3 in tumors of low and intermediate histological grade, and they also highlighted the potential of AGR3 for the early detection of breast cancer, with high specificity (of 92.5%) and sensitivity (of 35%).

Regarding the therapeutic potential, a recent study[13] concluded that, in patients with luminal subtype B and histological grades I and II, the AGR3 expression conferred an unfavorable prognosis and suggested that this patients should be treated with 5-fluoropyrimidine chemotherapy, but not taxane. The authors[13] warned that AGR3 can promote tumor progression, through processes of proliferation, invasion, and resistance to chemotherapy.

The present research confirmed the association of AGR3 with important features in the breast cancer clinic, such as hormone receptors, proliferation index, and prognosis. The AGR3 protein may be a biomarker of poor prognosis in low- and intermediate-grade tumors and luminal subtypes, representing an interesting tool for the clinical management of this population. Considering the recent development in cancer research, understanding the functions of AGR3 would be inevitable for the development of predictive tools for prognosis and new target therapies.[14] In addition, AGR3 can serve as a biomarker in the early detection of breast cancer and to predict the clinical outcome.[14]

The present systematic review and meta-analysis has certain limitations. Firstly, we included only four studies, and the size of the sample of one of them was small. Secondly, although no evidence of publication bias was verified by the Egger test, exclusion of unpublished data and gray literature may have introduced selection bias in the analysis.

The present review also has strengths. Firstly, the research was conducted in five important databases in health sciences, and there was scientific rigor in the analysis process. Secondly, there was no restrictions on the year of publication and language. Thirdly, all references included were full-text articles published in peer-reviewed journals. In addition, the studies reported no conflicts of interest and were approved by ethics committees. Although the results of the present systematic review should be interpreted with caution, the evidence presented at the moment may serve as a guide for future research and also for the clinical practice.

Conclusion

The AGR3 protein may be a biomarker to predict prognosis in luminal subtypes. In addition, in patients with tumors of low and intermediate histological grades, AGR3 expression may indicate unfavorable prognosis in relation to OS and DFS. Although the present study indicates that AGR3 may be promising to predict prognosis in luminal subtypes, we highlight the need for more high-quality studies to confirm these findings, and these should be considered when making decisions regarding the prediction of diagnosis and prognosis in breast cancer.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

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Male Infertility – What about Mental Health?

Infertilidade Masculina – E a Saúde Mental?

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Dear Editor,

Infertility is the inability to achieve a clinical pregnancy even after engaging in regular and unprotected sexual intercourse for 12 months[1,2] during the fertile days; roughly 8% to 12% of couples of reproductive age worldwide are believed to be affected by infertility. While males are solely responsible for around 20% to 30% of infertility cases, overall, they contribute to half of the cases.[2] It is well known that infertility may induce stress on couples who fail to conceive, but it is unclear whether psychological stress causes infertility.[3] Determining the emotional and psychological impact of male infertility and knowing whether it can improve outcomes if addressed is one of the priorities of male infertility research.[4] Infertile men generally suffer silently, and consequently report lower levels of psychological distress in questionnaires;[5] considering that the concepts of male fertility and virility are part of the perception of masculinity, it is not illogical to assume that there is a social concern that could influence male sexual and reproductive health.[6] A study[7] has found that the pessimism and psychological distress reported by male partners in couples undergoing in vitro fertilization had a negative linear correlation with clinical pregnancy. This might be due to the fact that psychological stress reduces sperm count, progressive motility, and increases abnormal morphology.[8] Another study[9] found an inverse relationship between erectile dysfunction and quality of life measured through the fertility quality of life tool (FertiQoL) and a significant relationship between depression and erectile dysfunction. Additionally, a prospective study[10] suggested infertile men are generally less healthy than their fertile counterparts when considering overall health.

It is unclear whether psychological interventions would be helpful to infertile males; a meta-analysis[11] found a non-significant relationship regarding psychological interventions and depressive symptoms and anxiety in men from infertile couples. However, a systematic review[12] found cognitive behavioral therapy and mind-body interventions proved to be effective psychological interventions, with some positive effects on anxiety, pregnancy rates or marital function, and that coping therapy may be used to reduce stress and anxiety in the waiting period before the pregnancy test.

Male infertility is a clinical challenge; in its guidelines,[13] the European Association of Urology (EAU) recommends that infertile males undergoing fertility therapy should be referred to a mental health professional to undergo different strategies, such as psychoeducation and psychotherapy interventions; nevertheless, the male infertility guidelines[14] of the American Urological Association (AUA) and the American Society for Reproductive Medicine (ASRM) do not include any recommendation related to mental health.

Therefore, male infertility is not only a physical problem; it has emotional and psychological implications. Infertile men can suffer in silence, and psychological stress can negatively affect sperm quality, pregnancy outcomes, and overall quality of life. Although there is conflicting evidence regarding the effectiveness of psychological interventions for infertile men, some studies suggest that cognitive-behavioral therapy and mind-body interventions may be beneficial. However, the current male infertility guidelines differ in their recommendations regarding mental health interventions.

In the Latin American context, male infertility poses significant challenges, as it impacts countless couples due to cultural barriers, limited access to healthcare, socioeconomic disparities, and environmental influences. The ideal conditions for couples trying to conceive involve a supportive and understanding environment that fosters open discussions about infertility. Urgent action and comprehensive strategies are needed to improve sexual and reproductive health outcomes.

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To conclude, further research is needed to determine the best approach to treat the psychological impact of male infertility, and healthcare professionals should be aware of the potential mental health implications and consider referral to a mental health professional as appropriate.

Conflict of Interests

The authors have no conflict of interests to declare.

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FEBRASGO POSITION STATEMENT

Trauma and pregnancy

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The National Specialized Commission on High-Risk Pregnancy of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) and the Brazilian Society of Integrated Trauma Care (SBAIT) endorse this document. Content production is based on scientific evidence on the proposed theme and the results presented contribute to clinical practice.

Key points

- The incidence of trauma during pregnancy is 6-8% (severe forms of trauma: 3-6%).
- Of pregnant women who need hospitalization due to trauma, 60% progress to delivery.
- Pregnant women are 1.6 times more likely to die in a trauma situation.
- The anatomical and physiological alterations of pregnancy interfere with the repercussions and the approach to trauma.
- Domestic violence represents the most common trauma mechanism for pregnant women and triggers several obstetric complications. Ideally, it should be identified during antenatal care.
- The diagnosis of placental abruption in car accidents deserves special attention.
- Ultrasound in the trauma room enables action in trauma care, and as a quick mechanism, the necessary information about the fetus and pregnancy (fetal FAST).
- Most imaging exams required for good trauma care do not represent harm to the pregnancy.
- Antenatal care plays an important role in preventing trauma during pregnancy.
- The joint action of the trauma surgeon and the obstetrician is recommended in the care of traumatized pregnant women, especially in severe cases and in pregnant women over 20-24 weeks.

Recommendations

- When caring for pregnant women who suffered severe trauma, especially after 20 weeks, the uterus must be moved to the left to decompress the inferior vena cava.
- Pregnant women victims of severe trauma must receive priority care in trauma centers with obstetric support. If unavailable, prioritize a referral to trauma centers.
- In view of the need to perform chest drainage in pregnant women over 20 weeks, this should be done in the 3rd or 4th intercostal space anterior to the mid-axillary line to avoid diaphragmatic elevation typical of pregnancy.
- Fluid and transfusion replacement – if needed – should be based on the shock index and favor blood transfusion over the massive use of crystalloids.
- In car accidents involving pregnant women, even if the abdomen is not reached, the diagnosis of placental abruption should be pursued.
- In car accidents, consider the observation with continuous fetal monitoring for a minimum period of six hours.
- Perimortem cesarean section should be indicated in pregnant women with a uterus above the umbilicus if there is no return to maternal spontaneous circulation after four minutes of cardiopulmonary resuscitation (CPR) or if it is not possible to estimate the duration of cardiopulmonary arrest (CPA).
- Screening for obstetric violence should occur systematically during the first antenatal visit and be repeated every trimester and at the postpartum visit.
- The obstetrician should advise about the correct use of the seat belt during antenatal care.

Background

The incidence of trauma during pregnancy is around 6-8%, and when considering serious forms of trauma, it affects 3-6% of all pregnancies.[1,2] Three to four trauma occurrences in pregnant women per 1,000 will require hospitalization and 60% of these will prog-

ress to delivery. Severe trauma represents the main cause of non-obstetric maternal death in the world.[1,3] Compared to non-pregnant women, pregnant women are twice as likely to suffer severe trauma and 66% more likely to progress to death.[4] Pregnancy currently represents an isolated predictor of post-trauma mortality, and pregnant women are 1.6 times more likely to die than non-pregnant women.[3,5] Thus, knowledge of the particularities of this dyad and the specific aspects of pregnancy in trauma are of interest to obstetricians and trauma surgeons.[1,2]

Can pregnancy interfere with trauma care?

Several physiological alterations during the pregnancy-puerperal cycle may interfere in the care and management of the pregnant woman victim of trauma. These physiological alterations can simulate pathological conditions that are found in trauma and confuse the physician during care because of the potential to simulate normal situations.[2,5,6] Chart 1 summarizes these alterations with the respective possible interferences in the management of these traumas.

Chart 1. Physiological changes during pregnancy and possible implications for trauma care

Physiological changes	Clinical implications
Cardiovascular Blood volume ↑↑ x erythrocyte mass ↑ Heart rate ↑ (15-20 bpm) ↓ Blood pressure (2nd trimester) Plasma volume ↑ (30%-40%) ↓↓ Peripheral resistance ↑ Uterine volume (3rd trimester) → cava compression (pregnant woman in supine position)	Physiological "anemia" (normal hemoglobin ≥ 11 g/dL) Difficulty in diagnosing hypovolemic shock ↓ Venous return when patient in supine position (↓ preload)
Pulmonary Elevation of the diaphragmatic dome by 4 cm Functional residual capacity ↓ 20% Inspiratory capacity ↑	Respiratory alkalosis Lower apnea time tolerance
Renal ↑ Glomerular filtration ↑ Plasma volume	↓ Creatinine, urea and plasma uric acid
Coagulation ↑ Factors I, VII, VIII and X and XII ↑ Fibrinogen ↑ Von Willebrand Factor Resistance to activated C protein	↑ Risk of thromboembolism
Gastrointestinal ↑ Gastrin ↓ Esophageal sphincter activity ↓ Gastrointestinal motility	↑ Production of gastric secretion ↑ Risk of bronchoaspiration

Source: Prepared by the Assistance Group for Trauma in Pregnant Women (CNEGAR-Febrasgo and SBAIT).

Cardiovascular system

The cardiovascular system undergoes profound changes during the pregnancy-puerperal cycle, either by the influence of placental hormones and nitric oxide, the placentation process or even the anatomical alterations resulting from uterine growth, especially after 20 weeks. The main characteristics found in pregnancy are increased heart rate (increasing up to 32 weeks) and plasma volume, which determine the progressive increase in cardiac output during pregnancy. There is also a reduction in peripheral vascular resistance determining a decrease in arterial blood pressure, particularly in the second trimester of pregnancy. From 20 weeks onwards, the gravid uterus prevents normal venous return to the heart when the pregnant woman assumes the supine position, determining compression of the inferior vena cava. This situation is circumvented when the pregnant woman assumes the left lateral decubitus. In trauma care, especially in severe cases, this condition is very relevant, as it determines the need for alternative positions for adequate medical care, ideally the decubitus with an angle of 20° to the left or with manual decompression of the uterus to the left side. Special attention should be given to patients who may have spinal cord trauma compromising the thoracic and/or lumbar spine. In these cases, en bloc mobilization or manual displacement only of the uterus represent the appropriate maneuvers, avoiding trunk movement.[5]

Another important context related to increased plasma volume is blood hemodilution. This condition occurs due to a much higher plasma increase than the erythrocyte volume during pregnancy. Thus, a condition of normality is observed in the face of lower hemoglobin and hematocrit concentrations than those usually found outside of pregnancy ("physiologic anemia" of pregnancy). Hemoglobin concentration decreases from 13 g/dL (usual situation outside pregnancy) to 11 g/dL in the first trimester and 10.5 g/dL in the second and third trimester of pregnancy. Faced with such repercussions, it is important to emphasize that more than laboratory alterations, in the face of trauma in pregnant women, we must use hemodynamic parameters. The quantification of diuresis is characterized as one of the main hemodynamic variables during the initial care of trauma victims.[4]

Respiratory system

Pregnant women undergo marked changes in their thoracic anatomy. These modifications involve both an increase in the anteroposterior and transverse diameters of the thorax by approximately 2 centimeters and a diaphragmatic elevation of up to 4 centimeters. Therefore, technical care at the time of drainage should be reinforced, such as digital exploration of the

cavity before insertion of the chest drain, as this can contribute to reduce accidents during the procedure, such as, for example, the placement of the drain in the abdominal cavity. Depending on the uterine volume and elevation of the diaphragm, the higher insertion, above the 5th intercostal space, will make the procedure safer.[7] Progesterone, by stimulating the respiratory center, plays an important role in increasing the current volume (or tidal volume). This change determines the condition of hyperventilation, which is important to facilitate gas exchange during pregnancy, although it leads to a condition of physiological respiratory alkalosis (with a decrease in pCO2 to less than 30 mmHg). This process is naturally compensated for by the excretion of bicarbonate (whose concentration decreases in the plasma), so that the pH does not change.[7] Table 1 summarizes the alterations found in the blood gas analysis of pregnant women.

Table 1. Blood gas changes found during pregnancy

	Non-pregnant	Pregnant
PO_2 (mmHg)	75 to 100	105 ↑
PCO_2 (mmHg)	37 to 40	27 to 32 ↓
Arterial pH	7.35 to 7.40	7.40 to 7.45 ↑
Bicarbonate (mmol/L)	22 to 26	18 to 21 ↓

Source: Adapted from Greco et al. (2019).[8]

On the other hand, these changes, which are harmonically compensated under normal conditions, may influence pregnant women's response to conditions of low oxygenation or apnea. Thus, they are less adaptable to longer periods of apnea, becoming more vulnerable to hypoxia. This aspect cannot be overlooked in trauma care during pregnancy.

Renal system

With the increase in cardiac output and the decrease in peripheral resistance, there is a concomitant increase in renal plasma flow and glomerular filtration rate.

Plasma creatinine concentration reaches average values of 0.5-0.8 mg/dL, while uric acid concentration drops to levels below 3 mg/dL in the first trimester, rising slightly in the third trimester of pregnancy.[3,9]

Coagulation system

Important alterations occur in pregnant women's blood clotting, leading to the condition of hypercoagulability. There is an increase in fibrinogen, which can reach 400-600 mg/dL, an increase in clotting factors (factors I, VII, VIII, X, XII) and a decrease in thrombolytic factors. Although these alterations are important to avoid greater blood loss in the physiological process of childbirth and puerperium, they determine a greater thromboembolic risk for pregnant and puerperal women, especially when associated with trauma mechanisms such as fractures, bleeding and/or resulting from long periods of immobilization.

Gastrointestinal system

The gastrointestinal system (esophagus, stomach, gallbladder and intestine) remains atonic throughout pregnancy because of hormonal action, particularly progesterone, on the smooth muscles of these organs. This alteration is associated with the gradual growth of the gravid uterus, which determines an increase in abdominal pressure. In view of this situation, the relaxation of the gastroesophageal sphincter and the increase in intra-abdominal pressure favor situations of reflux and, in case of trauma care, a greater risk of aspiration of gastrointestinal contents.[6] This should be particularity monitored closely in the trauma care room, as well as in surgeries and intensive care units.

What are the possible mechanisms of trauma in pregnant women?

The main mechanisms of trauma in pregnant women are: domestic violence, car accidents, falls, penetrating/perforating trauma, attempted murder, burns and inhalation of toxic substances and/or gases.[1,8,10,11]

Domestic violence

Domestic violence very likely represents the main cause of trauma to pregnant women. Approximately 4-8% of pregnant women suffer some type of violence during their pregnancy.[11] These numbers can be much higher if underreporting is taken into account. Most cases of domestic violence originate from intimate partner violence, and the resulting injuries are frequently found in the head and neck region, and also on the back.[2] The risks to pregnancy inherent to intimate partner violence go beyond the trauma and may mean an increase in intercurrences in the pregnancy-puerperal cycle, namely: fetal growth restriction, anemia, smoking, prematurity, stillbirth, premature rupture of membranes and placental abruption.[5,12,13] In the face of suspected domestic violence, it is important that the health professional and/or the health unit perform the compulsory notification to the police authority in accordance with Ordinance GM/MS No. 78, of January 18, 2021,[14] in line with Article 4 of Law number 10.778, of November 24, 2003.[15]

Car accidents

Car accidents represent a significant portion of trauma in pregnant women and are the most related to blunt injuries (55-70%).[16] Around 200-300 pregnant women/100,000 live births are involved in car accidents. However, more than 50% of them reported not having

been properly instructed about the use of seat belts by their physicians.[2,10,16] Another important aspect mainly related to serious accidents is the use of drugs and alcohol, as approximately 45% of serious car accidents involving pregnant women are associated with alcohol use.[4] In this type of accident, direct blunt trauma to the fetus is uncommon, given the protective role played by the uterus and annexes to the fetus, thus, the worst consequence is the possibility of placental abruption, which is also the most feared mechanism of fetal compromise.[2,13,17] Placental abruption can occur in up to 40% of pregnant women that are seriously injured in car accidents.[2] Although placental abruption is more common in severe trauma, it can also occur in apparently mild trauma.[17] In severe trauma suffered by pregnant women over 35 weeks, the occurrence of splenic and hepatic injuries is more common, because of the greater congestion of these organs during the pregnancy period.[16]

Falls

Due to joint instability, pregnant women are more susceptible to falls. Although frequent, they do not usually lead to fetal risk, given the protection offered by the uterine cavity. It is believed that one in four pregnant women will have at least one fall during pregnancy.[18,19] Most falls occur at home, and falls from one's own height are frequent. About 39% involve stairs.[20] Fractures of the extremities are common, most commonly involving the lower limbs. Unfavorable obstetric effects involving falls are premature birth (RR: 4.4), placental abruption (RR: 8), fetal distress (2.1), fetal hypoxia (2.9) and stillbirth (2.0).[12,21]

Burns

Injuries caused by burns have different mechanisms from those of other forms of trauma: direct thermal injury to the tissue, injury due to inhalation in the lungs, and accumulation of toxic substances in the bloodstream. The estimated incidence of burns is 0.17 per 100,000 pregnancies. The impact of the burn will depend on the depth and extent of the affected area. When the affected area exceeds 40% of the body surface, fetal mortality can reach 100%.[1] The mortality rate can also be influenced when the pregnant woman inhales smoke, as the inhalation of carbon monoxide freely crosses the placental barrier and avidly binds to fetal hemoglobin, triggering tissue hypoxia.[16,21]

Penetrating/perforating trauma

Penetrating/perforating trauma is mainly related to stab and firearm injuries. It is uncommon during pregnancy (2.3 per 100,000 live births) and associated with low rates of maternal mortality.[1,18] This characteristic is attributed to displacement of the abdominal viscera. However, perinatal mortality can reach 40% and results from prematurity or direct fetal injury.[1,21]

What is the role played by ultrasound in the trauma room?

Ultrasound in the trauma room in non-pregnant patients is a very important element in the surgeon's decision-making, especially in assisting victims of abdominal and thoracic injuries with hemodynamic instability. The so-called FAST is a quick test that looks for the presence of fluid collected in the abdominal region, and more currently in the abdominal and thoracic regions (eFAST).[22]

The eFAST consists of: 1) longitudinal view in the right upper quadrant for analysis of the liver, right kidney and Morrison's pouch; 2) longitudinal view in the left upper quadrant to analyze the spleen, left kidney and splenorenal space; 3) transversal views in the suprapubic region for analysis of the bladder and uterine and rectouterine pouch (impaired analysis during pregnancy); 4) transverse subxiphoid view to investigate pericardial effusion and injuries in the left lobe of the liver; and 5) longitudinal views in the right and left thoracic apexes and bases to search for pneumothorax and/or presence of fluid. This exam should last between 3-5 minutes and is very accurate in detecting bleeding and free fluid in the cavities.[22,23]

In the same logic of rapid evaluation during pregnancy, it is possible to use ultrasound in the trauma/emergency room for a primary fetal analysis (fetal FAST). Within the concept of multidisciplinary trauma care for pregnant women, it can be an important instrument in detecting fetal elements that are determinant for decision-making, even if it is not carried out by obstetricians. Like eFAST, fetal FAST must adhere to very objective fetal data: presence of fetal heartbeat, placental position, subjective assessment of amniotic fluid volume, and assessment of femur length. The measurement of the femur is the best isolated measurement for estimating gestational age in the third trimester (femur > 4 centimeters = viable fetus). The exam should not extend over time in search of complementary information, such as diagnosis of estimated due date, objective determination of amniotic fluid volume and assessment of fetal circulation, which should be secondary assessments to the initial care.[24,25]

What obstetric repercussions can we expect in the case of trauma?

The main obstetric complications for pregnant women in the case of trauma are: miscarriage, prematurity, placental abruption, rupture of ovular membranes, uterine rupture and fetal death. These complications vary according to gestational age, trauma mecha-

nism, severity and, evidently, the degree of maternal instability in relation to the trauma.[12] Some deserve consideration.

Placental abruption in pregnant women with trauma

Placental abruption is a serious obstetric condition due to the maternal, fetal and neonatal morbidity and mortality it entails. It occurs in the second half of pregnancy with an incidence of 2-10 cases/1,000 live births.[26] One of the causes of placental abruption is mechanical trauma. It is the most common complication in pregnant women victims of this type of trauma, and can occur even in less serious situations. Evidently, the increase in the severity of the trauma increases the percentage of occurrence of this pathology.[12] Placental abruption is present in 40% of the cases of car accidents with severe trauma to the pregnant woman. However, even in less severe abdominal trauma, we can find an association with placental abruption in 3% of cases.[26] Two main mechanisms are involved in the genesis of placental abruption in cases of car accidents: the increase in negative pressure imposed on the abdomen and placental traction/tension failure, which does not follow uterine movement. Due to these factors, shear forces cause cleavage of the decidual-placental interface and subsequent detachment of the placenta from its insertion bed. An important fact to be highlighted is that the detachment caused by the uterine movement can be delayed, which should be taken into account in the monitoring of fetal vitality in these situations.[6,12] The diagnosis of placental abruption is clinical. Acute, intense and non-rhythmic abdominal pain is the main clinical predictor of an unfavorable outcome. However, depending on the level of consciousness at which the pregnant woman is admitted, it will not be a plausible parameter for evaluation. Sudden bleeding of variable volume, increased uterine sensitivity, hypertonia, tachysystole, maternal hypotension and changes in fetal vitality culminating in fetal death may be present in the clinical picture.[26] Ultrasound has low sensitivity (25-60%) for identification of retroplacental hematoma in its initial phase. In the case of acute bleeding, an isoechogenic image is formed, with the placenta making it difficult to identify. In cases of placental abruption that culminate in fetal death, the degree of bleeding and the percentage of detached placental area are significant. In all cases of fetal death identified in the first steps of care to the trauma victim, severe placental abruption should be strongly suspected. In these cases, it is considered that > 50% of placental separation occurred, and 20% of cases are associated with disseminated intravascular coagulation. Massive bleeding can be hidden with little or no exteriorization via the vagina, which makes the clinical diagnosis of placental abruption more difficult. Hence the alert for fetal death as a sign of hemorrhagic severity in the context of trauma. The occurrence of Couvelaire's uterus is also a constant concern in this scenario. Blood infiltration alters the activity of myometrial fibers, making the response to drugs to correct atony less effective. It presents a high risk of evolving, with the need for hysterectomy to contain the bleeding. After maternal stabilization, continuous cardiotocographic monitoring should be established for at least four to eight hours. It is an instrument for immediate detection of deterioration in fetal vitality, with a high possibility of having placental abruption in its genesis. The tachysystole pattern can also be a predictor of placental abruption. When ≥ 6 contractions/hour are recorded, the possibility of extending continuous fetal monitoring for up to 24 hours is suggested.[25] Laboratory tests should be requested to assess volume loss and the degree of shock: blood gas analysis, complete blood count, coagulogram, blood typing, lactate and the best predictor of coagulopathy, fibrinogen. However, note that at the beginning of the hemorrhagic condition, laboratory tests do not reliably reflect the acute blood loss (which may be hidden and massive in some cases). They are suitable for post-transfusion control. The level of fibrinogen has the best correlation with the severity of the shock. Fibrinogen levels < 200 mg/dL have a positive predictive value of 100% for identifying severe conditions. The expected goals during treatment with the patient are: hemoglobin > 8 g/dL, hematocrit from 21% to 24%, platelets > 50 thousand, fibrinogen > 200 mg/dL and TAP and APTT < 1.5 times the control values.

Uterine rupture

Uterine rupture is a rare event associated with trauma (<1%). It may be secondary to perforations by pelvic bone fragments or related to direct trauma in major accidents, especially in the third trimester. Although uncommon and given the pelvic congestion, it is usually severe.[12]

Which imaging exams can and should be performed in the care of pregnant victims of trauma?

Most imaging exams indicated for adequate trauma care in pregnant women are not associated with greater risk and can be performed when necessary. The acceptable level of fetal irradiation, particularly in the first trimester, is up to 50 mGy or 5 rad.[27-29] The vast majority of tests used in the management of pregnant women with trauma have fetal radiation below the maximum level, as demonstrated in table 2.[27]

During admission to the trauma room, imaging tests should be objective in order to identify potentially

Table 2. Fetal radiation doses in common exams in the trauma room

Exam	Fetal dose (mGy)
Head or neck CT scan	0.001-0.01
Extremity x-ray	< 0.001
2-view chest x-ray	0.0005-0.01
Abdominal or pelvic X-ray	0.1-3.0
Chest tomography	0.1-0.66
Lumbosacral spine X-ray	1-10
Abdominal tomography	1.3-35
Pelvic tomography	10-50

Source: Adapted from Committee Opinion No. 723 (2017).[27]

lethal injuries.[28] Among them, the following are performed in a protocol manner:

1. Anteroposterior chest X-ray (assess fractures, pneumothorax or hemothorax, diaphragmatic hernia);
2. Anteroposterior pelvic X-ray (assess fractures and pelvic instability);
3. e-FAST (assess the presence of pneumothorax and free fluid in the pericardial sac and abdominal cavity).

Tomography represents the gold standard examination for identifying central nervous system and spinal cord injuries, and for investigating intracavitary bleeding, and it contributes to surgical planning. However, the patient's hemodynamic stability is essential to perform such an examination. Pelvic and/or abdominal tomography should not be avoided due to pregnancy, even under the assumption that the radiation reaches the fetus, in view of its importance for detecting visceral injuries.[28,29]

X-ray exams must be requested so that musculoskeletal injuries can be identified and treated. As long as the team is trained and there is possibility, the fetal FAST is performed for guidance on fetal viability and vitality. Magnetic resonance imaging in pregnant women has no complications for the fetus. Gadolinium should not be used as a contrast method, as it is associated with inflammatory processes and stillbirth. In scenarios of stability and low suspicion of multiple injuries, MRI may represent a reasonable substitute for tomography, in view of its quality of soft tissue images and fetal non-irradiation.[27]

What obstetric approaches are necessary for pregnant trauma victims?

Assessment of fetal vitality

Note that the focus of care for pregnant women victims of trauma is the maintenance of maternal life. Fetal evaluation measures should be taken particularly after maternal stabilization and/or in extreme cases, such as perimortem cesarean section in the case of CRA.[11] The main method described for assessing fetal vitality in traumatized pregnant women, especially after 24-26 weeks, is continuous antepartum cardiotocography. This method is particularly important in the case of major car trauma, where the chance of developing placental abruption is greater. It should be started as soon as maternal conditions allow and performed at least six hours after admission (as long as the pregnant woman has not associated bleeding and/or uterine contractions). The safe time of this assessment is discussed. Some services may suggest a follow-up of up to 24 hours, particularly in cases of suspected placental abruption or genital leakage (fluid or blood). However, most recommendations do not exceed eight hours of maintenance of this monitoring.[30,31] Since most severe traumas are attended by trauma centers without maternity units and a neonatal intensive care unit, the transfer of these pregnant women to greater centers with this complexity should be recommended as soon as maternal conditions allow.[30]

Medicines

The use of corticosteroids and magnesium sulfate should be considered when premature birth is a possibility, as it will bring benefits in terms of morbidity and mortality of children born prematurely to these mothers. However, an important alert: childbirth, especially when necessary due to a serious maternal condition, should not be postponed to perform these therapies.[32]

Perimortem cesarean section

Perimortem cesarean section is considered a resuscitation maneuver in pregnant women. It is indicated if there is no return to maternal spontaneous circulation after four minutes of CPR or if it is not possible to estimate the patient's CPA time.[33] In all cases, it should only be performed if the uterine fundus extends above the umbilical scar, aligning the possibility of fetal viability and that the uterine fundus at this time represents an important factor of compression to the inferior vena cava, interfering with maternal venous return.[34] After the procedure, with uterine emptying, there is an increase in pre-cardiac load, and maternal blood flow is more easily reestablished, favoring the return of spontaneous circulation and the reduction of CPA time. A review of cases that included 38 patients showed that 12 out of 20 pregnant women duly monitored showed return of spontaneous circulation soon after delivery and, of these, 30 resulted in a viable newborn after delivery.[34] The early performance of perimortem cesarean section facilitates resuscitation efforts and decreases the risk of fetal anoxia. However, it is important to emphasize that fetal viability or vitality does not influence the indication of the procedure. Thus, fetal monitoring is not recommended during care.

Prophylaxis of RH isoimmunization

Fetomaternal hemorrhage occurs in 10-30% of pregnant trauma patients. Rh-negative pregnant women should receive anti-D immunoglobulin (Rh-D) in the condition of trauma with risk of maternal-fetal blood exchange. The appropriate dose of anti-D immunoglobulin depends on the amount of exposure. A standard dose of 300 µg anti-D immunoglobulin will protect up to 30 mL of fetal blood, but abdominal trauma can often exceed 30 mL of fetal blood in maternal circulation. Therefore, blunt abdominal trauma is more likely to require more than one dose of anti-D immunoglobulin.[31,35] The administration of anti-D immunoglobulin is recommended within 72 hours to avoid future anti-Rh sensitization. When this is not possible, it is still recommended to perform it in longer terms, even incurring less effectiveness.[35]

What is the role played by the obstetrician in preventing trauma during pregnancy?

Antenatal approach to domestic violence

Antenatal care can play a fundamental role in creating awareness about the signs, types and degrees of domestic violence and in order that the signs of violence, even incipient, are perceived. Creating a safe environment in which women can understand, recognize and report violence is fundamental to fight it. Furthermore, it is a way to offer proper multidisciplinary care to those who have suffered violence.[36] The training of professionals to recognize, offer embracement and respond to violence is fundamental for the implementation of screening for these occurrences during antenatal care. Screening should occur periodically; during the first antenatal visit, and repeated every quarter and at the postpartum visit.[37] There is no consensus on which is the best approach among the different options described in the literature, but it should be one that: 1) promotes preventive actions with educational interventions; 2) promotes channels of communication with the patient, so that she feels safe and embraced; 3) involves a multidisciplinary team; and 4) results in good adherence by the team, which can identify the different types of violence (physical, psychological, sexual, patrimonial and moral). During the service, the team must be prepared to deal with the spontaneous report of domestic violence or with the performance of direct and indirect questions for risk assessment. Chart 2 shows suggestions for a direct and indirect approach to screening for violence against women.[37] In addition to a direct or indirect approach, it is important to be aware of signs that lead to the suspicion of violence, such as the presence of the following: chronic, vague and repetitive disorders; late entry into antenatal care; very controlling companion; recurrent urinary tract infection (no secondary cause found); chronic pelvic pain; irritable bowel syndrome; disorders in sexuality; complications in previous pregnancies, recurrent miscarriages; depression; anxiety; history of suicide attempt; physical injuries that are not adequately explained.[38]

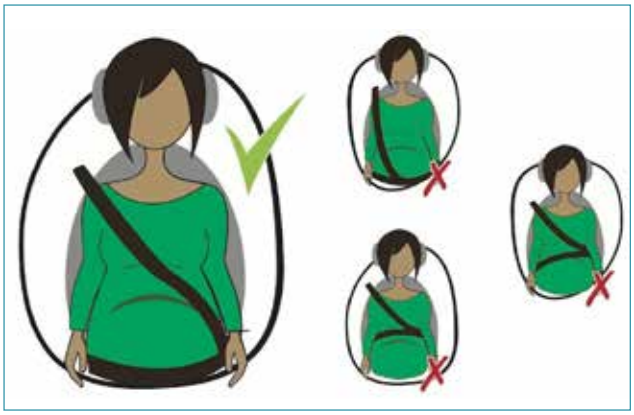
Chart 2. Suggestions for screening for violence against women

Direct questions
• As you may know, nowadays it is not uncommon to hear about people who have been physically, psychologically or sexually assaulted throughout their lives, and we know that this can affect their health, even years later. Has this ever happened to you?
• I have seen problems like yours in people who are physically abused. Did this happen to you?
• Does someone hit you?
• Have you ever been forced to have sex with someone?
Indirect questions
• Is everything okay at home with your partner?
• Are you having problems with family relationships?
• Do you feel humiliated or attacked?
• Do you think problems at home are affecting your health?
• Do you and your husband (or son or father or relative) fight a lot?
• When you argue, does he get aggressive?

Antenatal approach to falls and car accidents

The obstetrician's preventive action in the event of trauma during pregnancy mainly refers to educational aspects about behaviors that may put pregnant women and the fetus at risk.[17] The hormones produced during pregnancy act on the joints, increasing ligament laxity; fetal growth and weight gain can cause changes in body dynamics and balance axis; the action of progesterone on the central nervous system can decrease the level of attention. These physiological changes during pregnancy predispose to the occurrence of accidents and should be discussed during antenatal care. As mentioned, the hormonal action on the joints, associated with uterine growth and the change in the pregnant woman's center of gravity leads to greater exposure to falls and eventual fractures of the extremities. Thus, it is very important that the antenatal care professional recommends the use of more comfortable and stable shoes during pregnancy, as well as domestic care with carpets and safety on stairs.[6] Although car accidents are an important cause of trauma during pregnancy, the need for proper use of seat belts is little discussed during antenatal care. Many pregnant women even stop using it due to discomfort or fear of hurting the fetus. Less than 50% of pregnant women who had accidents and were questioned about use of the seat belt reported having received guidance during antenatal

care. When they use it, a significant portion of women does it inadequately.[3,6,21] The use of seat belts should always be advised, even if the pregnant woman is not driving the vehicle. The pelvic part of the belt should fit under the abdomen and across the upper thighs, and the thoracic part should cross the middle of the shoulder, passing between the breasts and lateral to the abdomen. None of the straps should pass over the gravid uterus (Figure 1), or even be placed behind the chest, arm or pelvis, under penalty of compromising the safety of the mother and fetus. In vehicles equipped with an airbag, the seat must be moved as far as possible to allow safe contact with the steering wheel and pedals. An important recommendation in car accidents regards the role of the airbag. There are no studies demonstrating that its opening can trigger traumatic uterine injuries, and it constitutes a fundamental element in the prevention of severe brain trauma. Therefore, the attitude of deactivating this vehicle safety device should be strictly discouraged.[3] Regarding the use of bicycles and motorcycles, information should be given about the greater risk of falls due to modifications of the body axis and that direct impacts on the abdomen in an eventual fall can cause complications to the fetus.



Source: https://bestcarseathub.com/blog/wearing-a-seat-belt-during-pregnancy-how-you-may-be-doing-it-wrong/

Figure 1. Correct seat belt use during pregnancy

Cell phone use while driving has been identified as an important cause of car accidents and seems to play a similar role to the use of alcohol in the loss of necessary attention.

Final considerations

Trauma during pregnancy is an important topic for both the trauma surgeon and the obstetrician due to the great reciprocal influence. Its incidence is between 6% and 8% of all pregnancies and represents the main reason for maternal death from non-obstetric causes. Pregnancy is seen as an isolated predictor of post-trauma death, as pregnant women are twice as likely to suffer severe trauma and 1.6 times as likely to die. In addition, pregnant women who suffer severe trauma have a 60% chance of progressing to childbirth. The definition of referral is also important. It is recommended that pregnant women who suffer severe trauma are ideally referred to a trauma center with an integrated maternity. If unavailable, care for the mother should be the priority. During the care of pregnant women victims of severe trauma, no exam that is necessary for an adequate evaluation is contraindicated and ultrasound plays an important role in the trauma room both in the evaluation of traumatic injuries and in rapid fetal evaluation. The main motivating mechanism of trauma in pregnant women is domestic violence. It is believed that 4-8% of pregnant women experience domestic violence. The obstetrician plays a fundamental role during antenatal care in detecting these cases, since violence often occurs in the intimacy of the victim's home. In these situations, an active search is recommended. Antenatal care is also equally important as an opportunity to provide guidance on the need to use the seat belt and safe shoes. Pregnancy is a great challenge in the face of trauma, given the presence of anatomical and physiological changes typical of this period, as well as the very presence of the maternal-fetal dyad that can substantially interfere with adequate medical care.

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- **Case reports:** They are of interest if well documented from a clinical and laboratory point of view and should contain new or unexpected aspects in relation to cases already published. Authors should indicate this information in the referral letter. The text of **Introduction** and **Discussion** sections must be based on an up-to-date literature review.
- **Review articles:** Spontaneous contributions are accepted, including integrative, scoping, or systematic reviews with or without meta-analyses. Narrative reviews will only be accepted exceptionally, given the questionable scientific evidence they represent. The methods and procedures adopted to obtain data inserted in the text must be described and based on recent references, including the current year. As this is still subject to controversy, the review should discuss trends and lines of investigation in progress. In addition to the review text, the synthesis and conclusions must be presented.
- **Letters to the Editor:** Must address editorial matters or not, but present relevant information to readers. The letters may be summarized by the editorial board, always keeping the main points. In the case of criticism or comments on published works, the letter is sent to the authors of the cited article so their response can be published simultaneously. All data presented in the letter must be fully citable and cited in the supporting reference list (unpublished data should not be described in the letter).
- **Editorial:** By invitation of the editor only.

OBS. Manuscripts containing results of original clinical or experimental research have priority for publication

Manuscript structure

Title

When writing a scientific article, the researcher must pay attention to the title of the manuscript. The title is the business card of any publication. It should be prepared with great care and preferably be written only after the article is finished. A good title adequately describes the content of the manuscript. It is usually not a sentence, as it does not contain the subject or arranged verbs and objects. **Abbreviations, chemical formulas, excess of adjectives, names of cities and institutions, among others, should be avoided in titles.** The titles of manuscripts submitted to the RBGO must contain a maximum of 18 words.

Abstract

The abstract must provide the context or basis for the study, establish the objectives, basic procedures of the methodology used, main results and main conclusions. It should emphasize new and important aspects of the study or observations. As abstracts are the only substantive part of the article that is indexed in many electronic databases, authors must ensure they accurately reflect the content of the article and highlight the research contribution/innovation to the topic. Abbreviations, symbols and references should not be used in the abstract. In case of original articles from clinical trials, the authors must inform the registration number at the end of the abstract.

1. Abstract: for original articles

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

Objective: Retrospective on the topic and the question posed by researchers.

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

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

Conclusion: What was the conclusion; the answer to the question asked.

2. Abstract: for systematic review articles

Abstracts of systematic review articles submitted to the RBGO must be structured in six sections and contain a maximum of 250 words:

Objective: State the main objective of the article.

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

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

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

Data synthesis: Present the main results of the review and the methods employed to obtain them.

Conclusions: State the main conclusions and their clinical utility.

3. Abstract: for integrative/scoping reviews

It must contain the essence of the article, covering the purpose, method, results and conclusions or recommendations. Expose enough detail so readers can decide on the convenience of reading the entire text (word limit: 150).

NOTE: An abstract in Portuguese may be optionally added by the authors.

Keywords

The keywords of a scientific work indicate the thematic content of the text they represent. The identification of thematic content, the indexing of the work in databases and the quick location and retrieval of the content are considered the main objectives of the mentioned terms. The keyword systems used by the RBGO are DeCS (Health Sciences Descriptors – Lilacs Indexer) and MeSH (Medical Subject Headings – MEDLINE-PubMed Indexer). Five descriptors that represent the work must be chosen on these platforms.

Manuscript body

Manuscripts submitted to the RBGO should have a maximum of 4,000 words. Tables, charts and figures in the **Results** section, as well as references, are not counted.

Introduction

This part of the article prepares the reader to understand the investigation and the justification for its development. It should include the current state of knowledge on the subject, offering only strictly relevant and up-to-date references. The content to be reported in this section should provide context or background for the study, that is, the nature of the problem and its importance, and state the specific purpose, research objective, or hypothesis tested in the study or observation. The research objective is the final part of the introduction and both the main and secondary objectives must be clear and any analyzes in a pre-specified subgroup must be described. The introduction should not include data or conclusions from the work being reported.

Methods

The **Methods** section of a scientific work aims to present the study in a clear and concise way so that it is understandable and can be replicated. It should state how, when and where the study was developed. The

method comprises the material and procedures adopted in the study in order to be able to answer the main question of investigation. The **Methods** section should be structured starting with the type of study design, to show if it is appropriate to achieve the research objective; the research setting (the place and time in which it was developed); the data collection; the intervention to be performed and evaluated (if any) and also the alternative intervention; the statistical methods used and the ethical aspects of research.

NOTE: the RBGO joined the initiative of the International Committee of Medical Journal Editors (ICMJE) and the EQUATOR Network, aimed at improving the presentation of research results. Check related interactive guides:

Randomized clinical trial:

http://www.equator-network.org/reporting-guidelines/consort/

Systematic reviews and meta-analyses:

http://www.equator-network.org/reporting-guidelines/prisma/

Observational studies in epidemiology:

http://www.equator-network.org/reporting-guidelines/strobe/

Qualitative studies:

http://www.equator-network.org/reporting-guidelines/srqr/

Results

The purpose of the **Results** section is to show the findings of the research. These are original data obtained and synthesized by the author in order to provide an answer to the question that motivated the investigation. Results should be presented in a logical sequence in the text, tables and illustrations, mentioning the most important findings first. Whenever appropriate, the statistical significance of results should be indicated. All information in tables or illustrations should not be repeated in the text, and only important observations should be emphasized or summarized. Additional or supplementary materials and technical details may be placed in an appendix, accessible via a link, that will not interrupt the flow of the text. When data are summarized in the **Results** section, numerical results must be presented not only in derived values (e.g. percentages) but also in absolute values from which the derived values were calculated, and specify the statistical methods used to analyze them. Only the tables and figures necessary to explain the argument of the work and to assess its basis should be used. When scientifically appropriate, analyzes of data with variables such as age and sex should be included. The limit of a maximum of five tables, five charts or five figures must not be exceeded. Tables, charts and/or figures must be included in the body of the manuscript and do not account for the requested limit of 4,000 words. For clarification on the resolution of figures, please check https://www.ncbi.nlm.nih.gov/pmc/pub/filespec-images/.

Discussion

In the **Discussion** section, new and important aspects of the study and the conclusions derived from them should be emphasized. Data or other information presented in the **Introduction** or **Results** sections should not be repeated in detail. In experimental studies, it is useful to start the discussion with a brief summary of the main findings, compare and contrast the results with those of other relevant studies, state the limitations of the study and explore the implications of the findings for future research and clinical practice. Claiming precedence and alluding to incomplete works should be avoided, as well as discussing data not directly related to the results of the research presented. New hypotheses may be proposed when justified, but they must be clearly qualified as such. The last paragraph of the **Discussion** section should include the information of the study that relatively contributes to new knowledge.

Conclusion

The **Conclusion** section is intended to relate the conclusions to the objectives of the study. Authors should avoid unsubstantiated statements and conclusions not appropriately supported by their data. In particular, authors should avoid making claims about economic benefits and costs unless their manuscript includes economic analysis and appropriate data.

References

In manuscripts submitted to the RBGO, authors must number references in order of entry in the work and use these numbers for citations in the text. An excessive number of references should be avoided, selecting the most relevant for each statement and giving preference to more recent works. Do not use citations of difficult to access, such as abstracts of works presented at conferences, theses or publications with restricted circulation (not indexed). Cite primary and conventional references (articles in scientific journals and textbooks). References such as "unpublished observations" and "personal communication" should not be used. Authors' publications (self-citation) should only be used if there is a clear need and they are related to the topic. In this case, include only original works published in regular journals (do not cite chapters or reviews) among the bibliographic references. The number of references should be limited to 35, except for review articles. Citations of references must be placed after the period in superscript, without space after the last word (sequential and numerical citations). Authors are responsible for the accuracy of data contained in the references. To format your references, check **Vancouver:** https://www.ncbi.nlm.nih.gov/books/NBK7256/.

Submission of manuscripts

Articles must be submitted electronically, according to instructions available on the website: http://mc04.manuscriptcentral.com/rbgo-scielo.

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