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Editorial

Premature Ovarian Insufficiency and Bone Health Care: A Concern of the Gynecologist

Insuficiência ovariana prematura e os cuidados com a saúde óssea: uma preocupação do ginecologista

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The greatest increase in bone mass occurs during puberty, and the amount of bone gained during adolescence is the major contribution to the peak bone mass (PBM) that occurs around the age of 30–35 years old. Studies conducted by the National Osteoporosis Foundation have shown the importance of the timing of the PBM, as it determines the phase of the life cycle in which the bone mass is optimized.[1] In healthy girls, the earlier the onset of puberty, the greater the body mass and the bone mineral density (BMD) at the completion of skeletal maturity.[2–5]

The PBM varies according to the location in the skeleton. Estimates based on longitudinal studies performed by the Canadian Multicentre Osteoporosis Study showed the PBM for the lumbar region occurs between 33 and 40 years of age, and that the PBM for the hip occurs between 16 and 19 years of age.[6]

PBM is influenced by genetic factors, nutritional status, adequate endocrine function, and physical activity, and is the major determinant of the future risk of fractures in elderly women.[7] Among the endocrine factors are gonadal, adrenal and pituitary hormones; and, in women, estradiol plays a key role. Estradiol acts on the bones through several mechanisms and exerts an antiresorptive action.[8] According to some authors, estrogens also act on the bones by indirect mechanisms through an action in the muscles by evidencing an interrelationship between mechanical forces and the action of steroids and growth factors on the tissue masses of both the bones and the muscles.[9]

Several clinical situations that lead to hypoestrogenism are associated with BMD loss by leading to osteopenia and osteoporosis. The most typical known situation is the menopausal period. However, when hypoestrogenism occurs in the pubertal period and in adolescence, it may result in a PBM reduction in these young women. Amenorrheic adolescents have a lower BMD compared to those who menstruate regularly. The earlier the hypoestrogenic condition is established and the longer it is extended, the greater the repercussions on bone mass, with an increased risk of fractures. Several conditions can lead to hypoestrogenism in young women, such as hypothalamic amenorrhea, hyperprolactinemia, and premature ovarian insufficiency (POI), among others.[8,10,11]

Premature ovarian insufficiency is a clinical syndrome defined by the depletion of the follicular activity before the age of 40 years old. It is characterized by amenorrhea, increased gonadotrophins (follicle-stimulating hormone [FSH] $>$ 25 mIU/mL) and low levels of estradiol.[11] The incidence of POI in the general population is 1%, and it represents 6% to 10% of the causes of amenorrhea in general, and 10% to 15% of the causes of primary amenorrhea. There is a family history of the disease in 4% of the patients.[11] Patients with POI have a pattern in bone turnover markers similar to the one found in the menopausal state.[12–18] This is an important concern for the health of young women with POI, particularly if they have not yet reached PBM.

Compared to women who experience menopause at normal ages, patients with POI have a 1.5-fold greater risk of fracture.[19] Some studies have shown a lower BMD in women with POI or in the menopause before the age of 45 years old by any etiology. Compared to women who menstruate regularly, women with POI, karyotype 46, XX (mean age: 32 years; range: 20–39 years) had significantly lower BMD Z-scores. About 20% of these women had a BMD Z-score $<$ 2.0, which indicates a low BMD for their age and a fracture risk factor.[20]

A delay in the diagnosis greatly contributes to worsening the BMD.[21] It is very common to find patients with amenorrhea who have already lost precious time in doctors' offices and basic health units without the doctor investigating for a diagnosis of POF. In cases of amenorrhea, the possibility of

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POI should always be considered, and an effective search should be performed regarding the clinical picture (the climacteric symptoms of women) and high dosage of serum FSH. After the POI diagnosis, bone vitality should always be addressed because a loss in bone mass may have already occurred, and this should be a primary concern with the health of young women with POI.[22–24]

The treatment for osteopenia and osteoporosis caused by hypoestrogenism is essential and fundamentally based on the administration of estrogen replacement, which is indicated as a mandatory procedure as long as formal contraindications and patient acceptance are respected.[11,25]

Densitometry is directly related to estradiol levels.[26] Bone mineral density correlates positively with body fat (%), fat distribution and estradiol levels, and estradiol and age were among the factors associated with L2–L4 BMD.[27] Levels below 20 pg/mL may have protective effects on the bone mass. Women with undetectable levels of estradiol ($<$ 5 pg/mL) were at a 2.5-fold higher risk of fracture compared to women with estradiol levels between 5 pg/mL and 25 pg/mL.[28,29]

Thus, smaller estrogen dosages are required to meet bone maintenance needs. Low doses of estrogen, especially when associated with calcium, have a positive effect on bone mass, and its action appears to be predominantly on reabsorption, but not on bone formation after the age of 70 years old.[30]

We must always remember that there are several other goals of hormone replacement therapy (HRT) besides prevention and treatment of secondary bone loss due to ovarian failure. Therefore, the needs of each patient should be taken into account in order to define the estrogen dose to be administered. Further studies are needed to prove the efficacy of lower estrogen doses for cardiovascular protection, vasomotor phenomena, etc.

A three-year prospective randomized clinical trial was conducted by the United States National Institutes of Health (NIH) in young women with POI, karyotype 46, XX, in order to investigate the efficacy of a standardized HRT regime for BMD treatment. The study used transdermal E2 replacement (100 µg/day) with cyclic oral progestogen (10 mg oral medroxyprogesterone acetate daily for 12 days per month). This replacement therapy improved the BMD of the lumbar spine and of the femoral neck, so that at the end of the three-year intervention, the BMD did not differ between women with POI and the control group.[31]

The treatment of POI can have different doses and dosages according to the life period of onset of the disease. There is no evidence of which is the best route, oral or transdermal, and what is the best therapeutic regimen.[11,32–35] In patients diagnosed in the pubertal period and without adequate development of secondary sexual characteristics, puberty should be induced with a low dose of 17β-estradiol and a gradual increase over a period of 2 to 3 years. Progestogens should be used two years after the onset of puberty induction with estradiol or as soon as the first menstrual bleeding occurs. In cases of later diagnosis, and with no remaining concern about growth, the initial estrogen dose may be higher and more rapidly progressive with increases every three to six months until the adult dose is reached. The recommendation is that the hormonal therapy simulates as close as possible the regular levels of ovarian estrogen production and its continuity until the natural menopause age.[11,21]

The use of combined oral contraceptives (COCs) is an alternative to the conventional treatment with natural estrogens. In cases of adolescents, who are still in the development phase of the PBM, some studies have shown that COCs may have a less positive impact on the BMD.[36] However, further studies are needed to prove this effect..

A point to consider is the inclusion or not of BMD in the propaedeutic routine of patients with POI, especially those affected by the disease during adolescence and/or those with additional risk factors. Although BMD measurement is the gold standard for bone mass evaluation, and despite the large number of publications clearly pointing to bone loss, there is no consensus regarding the need to routinely indicate BMD measurement in the evaluation and follow-up of patients with POI.

According to Cox and Liu,[35] "as a consequence of decreased estrogen levels, women with POI often do not achieve peak bone density and may experience loss of bone mass. If hormone therapy is initiated and the woman has not experienced fractures, it is not necessary to do bone mineral density testing."

On the other hand, other authors indicate BMD examination after the diagnosis of POI.[37,38] Torrealday et al[39] suggest that BMD measurement may be useful and should be considered for women with POI already at the beginning of the approach. It should be repeated in those who decide to continue hormone therapy until the equivalent time of menopause for that population. In turn, the European Society for Human Reproduction and Embryology (ESHRE)[11] recommends the initial BMD measurement. If the results are normal and the patient undergoes hormonal therapy immediately upon diagnosis, there is no need to repeat the measurement. If the BMD measurement indicates osteoporosis, once the HRT is initiated, the BMD measurement should be repeated after five years. If the BMD continues to decline even with estrogen therapy, the conduct should be reviewed, and other factors that trigger osteoporosis should be sought.

The cost-benefit of measuring BMD in osteoporosis screening to assess its benefit as a prevention method for fractures in women is questioned. Most cohort studies to assess the use of BMD for this purpose included patients older than 65 years of age.[40] For these patients, by considering the cut-off point of 2 standard deviations, the sensitivity is 9%, the specificity is 99%, and the positive predictive value is 56%. Therefore, the BMD can predict the risk of fracture, but has low accuracy to identify individuals who will (or will not) have fractures.[41]

However, there are currently no alternatives to BMD for this evaluation, since bone turnover markers do not have well-established reference standards yet, given the variations observed among the various studies.[12–18]

In the Brazilian Unified Health System (SUS, in the Portuguese acronym), BMD measurement is authorized in some special situations,[42] including cases of hypogonadism in men and women, postmenopausal women with risk factors, and

to monitor changes in bone mass due to the course of osteoporosis and the different treatments available for this disease. Therefore, there is a possibility of access to the measurement of BMD, even if using public services, but also practical difficulties to perform the exam because it has a high cost and, in Brazil, few public services are available to the population.

Many questions remain unanswered given the lack of scientific evidence:

Are there differences in the behavior of bone mass over time when comparing women with POI and those who experienced menopause at the natural time?

Can we extrapolate to women with POI the sensitivity, specificity and predictive values for predicting fractures obtained with the BMD measurement performed in postmenopausal women?

Is it justified to perform a BMD measurement in young women with POI?

The evidence of the association of hypoestrogenism and low bone density and its association with the increased risk of fractures could be a justification for dispensing patients from undergoing a BMD measurement before starting hormone therapy?

It is known that estrogen therapy may fail in some patients, since other factors may interfere with the maintenance or loss of bone mass. How can we be sure that the patient undergoing hormone therapy will be protected from bone loss if she is not monitored through BMD measurements?

Are there alternative ways to confirm that patients with POI are already losing bone mass without BMD measurements?

Conclusion

In the literature, there are no evidence-based guidelines on criteria to maintain bone health in women with POI. It has not been definitively demonstrated that a reduced BMD in POI is indicative of an association of the disease with an increased fracture risk because the evidence is based on short-term observations and expert opinion. In fact, studies with the clear aim to clarify this cause-effect relationship are difficult to perform because they would involve ethical issues (for example, failure to treat patients on estrogen therapy as a control group), or the high cost and long duration of the follow-up, since the patients should be observed for long periods.

Moreover, the results of BMD studies performed in postmenopausal women cannot be extrapolated to a population of young women with estrogen deficiency before the age of 40 years old in order to predict fractures that will occur 20 to 30 years later, when other risk factors for fractures may be involved.

Despite the lack of such evidence with long-term randomized clinical trials, common sense suggests that the physician should rely on existing data in the literature, especially the guidelines of specialty societies.

The review of the literature shows that the consulted studies are practically consensual about these aspects of the POI approach. Estrogen replacement therapy should begin immediately after diagnosis, obviously respecting the contraindications to its use. The BMD measurement for an initial evaluation before starting hormone therapy would be a good practice. However, if the patient's access to this test is difficult, she can be dispensed by considering the unquestionable benefits of estrogens on bone mass, even in very small doses. The risks of treatment failure should be carefully ascertained in view of the possibility of associated comorbidities or other factors interfering with bone mass.

More than half of the women with POI have inadequate vitamin D levels and low calcium intake. Many are not adherent to hormone therapy, do not exercise regularly, and may be smokers. Therefore, to ensure good bone mass, in addition to hormone therapy, women with POI should maintain a healthy lifestyle that involves physical exercise, abstinence from smoking, a balanced diet with good intake of foods rich in calcium and vitamin D, and weight control.

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Abortion in the Structure of Causes of Maternal Mortality

Aborto na estrutura das causas da mortalidade materna

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Abstract

Objective To study the structure of maternal mortality caused by abortion in the Tula region.

Methods The medical records of deceased pregnant women, childbirth, and postpartum from January 01, 2001, to December 31, 2015, were analyzed.

Results Overall, 204,095 abortion cases were recorded in the Tula region for over 15 years. The frequency of abortion was reduced 4-fold, with 18,200 in 2001 to 4,538 in 2015. The rate of abortions per 1,000 women (age 15–44 years) for 15 years decreased by 40.5%, that is, from 46.53 (2001) to 18.84 (2015), and that of abortions per 100 live births and stillbirths was 29.5%, that is, from 161.7 (2001) to 41.5 (2015). Five women died from abortion complications that began outside of the hospital, which accounted for 0.01% of the total number. In the structure of causes of maternal mortality for 15 years, abortion represented 14.3% of the cases. Lethality mainly occurred in the period from 2001 to 2005 (4 cases). Among the maternal deaths, many women died in rural areas after pregnancy termination at 18 to 20 weeks of gestation ($n = 4$). In addition, three women died from sepsis and two from bleeding.

Conclusion The introduction of modern, effective technologies of family planning has reduced maternal mortality due to abortion.

Keywords
- abortion
- pregnancy
- maternal mortality
- family planning
- sepsis

Resumo

Objetivos Estudar a estrutura da mortalidade materna causada pelo aborto na região de Tula.

Métodos Os registros médicos de mulheres grávidas falecidas, de parto e de pós-parto, de 01 de janeiro de 2001 a 31 de dezembro de 2015, foram analisados.

Resultados No geral, 204.095 casos de aborto foram registrados na região de Tula, em um período de 15 anos. A frequência de aborto foi reduzida a 1/4, passando de 18.200 abortos em 2001 para 4.538 em 2015. A taxa de abortos a cada 1.000 mulheres (com idades entre 15 e 44 anos) diminuiu 40,5% em 15 anos, isto é, de 46,53 (2001) para 18,84 (2015), e a taxa de abortos a cada 100 nascidos vivos e natimortos foi de 29,5%, isto é, de 161,7 (2001) para 41,5 (2015). Cinco mulheres morreram de complicações do aborto que começaram fora do hospital, o que representou 0,01% do número total. No quadro geral de causas de mortalidade materna neste período de

Palavras-chave
- aborto
- gravidez
- mortalidade materna
- planeamento familiar
- sepse

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15 anos, o aborto representou 14,3% dos casos. A letalidade ocorreu, principalmente, no período de 2001 a 2005 (4 casos). Entre as mortes maternas, muitas mulheres morreram em áreas rurais após a interrupção da gravidez, com 18 a 20 semanas de gestação (n= 4). Além disso, três mulheres morreram por sepse, e duas, por sangramento.

Conclusão Com a introdução de tecnologias de planejamento familiar modernas e eficazes, a mortalidade materna devido ao aborto vem sendo reduzida.

Introduction

The Millennium Development Goal 5 calls for a 75% reduction in the maternal mortality ratio (MMR) between 1990 and 2015. Maternal mortality is one of the most important indicators of women's health and the quality of care at national and international levels.[1,2] A decrease in maternal mortality can only happen based on the evaluation of each case at the regional level, which will serve as the basis for developing priority actions that reduce the rate throughout the country.[3] Since 2012, in Russia, birth is recognized as a term for a pregnancy of 22 weeks or more, in which the child's weight at birth is $\geq$500 g (or less than 500 g, in case of multiple births), and the body length of the newborn is $\geq$25 cm (in case the newborn's weight is unknown). The abortion issue always stands out for its socio-political significance, because it is closely connected with the socio-economic situation of the country, the state's attitude toward women's reproductive health, and basic demographics.[4]

Legislative initiatives at the federal and regional levels aimed at reducing the availability of abortion were introduced in Russia with enviable regularity.[4]

This study aimed to analyze and study the structure of maternal mortality due to abortion in the Tula region.

Methods

Maternal death is defined as the death of a woman while pregnant or within 42 days of pregnancy termination, irrespective of the duration and site of pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.[1]

This study analyzed the dynamics and structure of causes of maternal mortality in the Tula region within a period of 15 years, according to government statistics. The data were obtained from official statistics and published national studies. This study retrospectively analyzed anonymized copies of primary medical records, autopsy protocols, forensic examination, and statistical data. Overall, the data were analyzed in 5-year periods: 2001 to 2005, 2006 to 2010, and 2010 to 2015. The present study was approved by the institutional review board and the need to obtain an informed consent from the patients was waived.

We searched for the abortion incidence data in the region of Tula from 2000 to 2015. The data were obtained from official statistics and published or unpublished regional and national studies.

All statistical analyses were performed using the software package Statistical version 6.0 (StatSoft, Tulsa, OK, USA). The results were considered statistically significant when $p < 0.05$.

The study was performed according to the plan of the Tula State University: Project No. 115102710029/ 49–16

Results

In 15 years of the 21st century (2001–2015), in the Tula region, 35 women died for reasons connected with pregnancy, childbirth, and puerperium (42 days after delivery).[5] During the same period, the region had 287,387 living children. When calculating per 100,000 live births, the maternal mortality rate accounted for an average of 12.2%. In the period from 2001 to 2005, the maternal mortality rate was 25.5%; from 2006 to 2010 it was 17.4%; from 2011 to 2015 it was 9.26% per 100,000 live births. Official statistics show that the absolute numbers of live births have a positive trend, particularly in the last 5 years, and the maternal mortality rate decreased by 52.25%.[5]

For 15 years in the Tula region, medical statistics revealed 204,095 abortion cases (►**Table 1**).

The table shows that in 15 years, the abortion rate per 1,000 women of fertile age decreased by 40.5%, and the rate of abortions per 100 live births and stillbirths by 29.5%.

Note that deaths due to medical legal (artificial) abortion and abortion on medical and social grounds during the study period were not registered. Regarding maternal deaths due

Table 1 Dynamics of abortion in the Tula region (2001–2015)

	Study time periods (year)		
	2001–2005	2005–2010	2010–2015
Total cases of abortion	93,298	67,457	43,340
Estimated abortion rates per 1,000 women aged 15–44 years	43.94	41.27	29.13
Abortion rate per 100 live births and stillbirths	141.3	97.6	57.3

to complication of abortions that began outside the hospital, five deaths were registered, which accounted for 0.01%. In general, in the structure of maternal mortality causes in these 15 years, abortion accounted for 14.3%.

A significant difference in maternal mortality from abortion was noted over the 5-year periods. During the period from 2001 to 2005, there were 4 cases of maternal deaths (25%), with 6.4% per 100,000 live births; during the period from 2006 to 2010, 1 case was recorded corresponding to 8.3%, with an index equal to 1.45. During 2011–2015, no cases of maternal mortality from abortion were registered.

A detailed analysis of each case found that four of the five women were from rural areas. The average age was 36.6 years (range, 22–41 years). All five women were admitted to the hospital with incipient abortion, of which two were instructed on out-of-hospital intervention. The greatest number of deaths were registered after pregnancy termination at 18 to 20 weeks ($n = 4$), with one case at 10 to 11 weeks.

The direct causes of the deaths of women due to unsafe abortion in three cases were sepsis, multiple organ failure, hemorrhage (two cases), hemorrhagic shock, disseminated intravascular coagulation, and multiple organ failure. All the analyzed observations had underestimated the severity of the patients' condition upon admission to the hospital in terms of bad survey, late diagnosis of sepsis, multiple curettage of the uterus, delay in operational use, and blood transfusion.

Discussion

According to the Ministry of Health, Russia has experienced a steady decline in the absolute number of abortions in 2000 to 2014, going from 1,961,539 in 2000 to 814,162 in 2014 (58.4%). The number of abortions per 100 live births has decreased by 26.8% from 2000 to 2014. In 2014, in the Far Eastern Federal District in Russia, there was a decrease in the number of abortions at 8,675 (absolute number) or 15.5% compared with that in 2013.[6] Therefore, the rate of abortion in the Tula region correlated with the index in Russia and reflects the overall downward trend. Similar dynamics of the frequency of abortions is observed in the countries of the former USSR.[7,8] When comparing the estimated abortion rates per 1,000 women aged 15 to 44 years with European countries during 2010 to 2015, it was established that the figure is lower than that in Eastern Europe at 42% (90% uncertainty interval [UI] 38–51) and Southern Europe at 26% (90% UI 18–57) and higher than that in Northern Europe at 18% (90% UI 17–20) and Western Europe, also at 18% (90% UI 14–31) during the period from 2010 to 2014.[9] The decline in the number of abortions in Russia is confirmed by official statistics and results of sample surveys of women. A particularly rapid decline in abortions is typical in young women; Russia lost the said leadership on the level of teenage pregnancies, and the abortion rate among adolescents in Russia is lower than that of many Western countries. The decomposition of fertility according to the Bongaarts model shows that the role of contraception in the structural methods of family birth control in Russia at present is far superior to the role of induced abortions. The effectiveness of family planning in the country increased.[10]

Despite the decline in abortion rates, their level remains high and is accompanied by adverse changes in their structure, in which the share of spontaneous abortions increased. The proportion of spontaneous abortion was of 12.3% in 2015. The increase in the prevalence of spontaneous abortions shows a decrease in the level of reproductive health of modern Russian women.[11]

In addition, a positive trend is observed on reducing the number of abortions per 1,000 women aged 15–44 years worldwide, that is, 40 in 1990–1994 and 35 in 2010 to 2014. However, due to population growth, the annual number of abortions in the world increased by 5.9 million from 50.4 million in 1990 to 1994 to 56.3 million in 2010 to 2014. In developed countries, the abortion rate decreased by 19 points from 46 to 27. In developing countries, the same slight decrease is noted at 39 to 37 points. Approximately 25% of pregnancies ended in abortion in 2010 to 2014.[9] In France, around 220,000 abortions annually were observed at a steady rate for many decades (prior to 14 weeks of gestation).[12] In Russia, no statistical data were found of abortion with respect to the marital status of women. In the period from 2010 to 2014, 73% of abortions were performed by married women compared with the 27% of unmarried women worldwide.[9]

At the same time, in Russia, an extremely unfavorable growth was observed in 2014 for the maternal deaths from abortions initiated outside the hospital and undetermined cases of abortion (8 cases in 2013 to 11 in 2014; with 0.42 to 0.57 per 100,000 live births, respectively, that is, 35.7%).

The Tula region, as well as all of Russia, has a positive dynamic of reducing maternal mortality due to abortion. In St. Petersburg, there is clearly a strong positive dynamic of reduction of mortality due to abortion, that is, 19.6 per 100,000 in 1988 to 1990, and 2.6 per 100,000 live births in 2006 to 2009.[13]

Mainly in the Tula region, women died from abortion in 2000 to 2005, which roughly coincides with data from other regions in Russia. Hence, for 10 years (1998–2007) in the Kemerovo region, 27 of 145 patients died from sepsis that developed after an abortion.[14] During these years, the maternal death rate from abortions alone took first place in the Khabarovsk region, at 9.3 points in the overall structure, which significantly exceeded the figure for the Russian Federation in 2010 (1.8 per 100,000 live births).[15]

The general trend is that the majority of deaths occurs after abortion at 18–20 weeks of gestation.[14]

Most women who died due to abortion (4 out of 5) lived in rural areas, indicating a lack of aid to rural areas that has been emphasized by many Russian authors. [4,14]

The direct causes of maternal deaths, as a rule, were sepsis and multiple organ failure. The primary role of sepsis as the immediate cause of maternal mortality due to abortion is noted in several other studies, both in the whole territory of Russia or in individual regions.[14–17] The second cause of death was bleeding, which results from the typical underestimation

of the severity of the condition, repeated curettage of the uterine cavity, and later surgery.

One of the target indicators of the state program of healthcare development of the Russian Federation (adopted by the decree of the RF Government No. 2511-p on December 24, 2012) is the proportion of women who decided to carry on with the pregnancy, and the number of women applying for abortion in medical facilities.[10]

Measures to reduce abortion in our country have shifted instead of introducing effective methods of contraception among adolescents and students,[18] it is recommended that abortion be rejected in favor of birth if an unwanted pregnancy occurs.

Conclusion

With the introduction of modern, effective technologies of family planning, abortion lost its role in the structure of maternal mortality in the region of Tula.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Translation and Cultural Adaptation of the Short-Form Food Frequency Questionnaire for Pregnancy into Brazilian Portuguese

Tradução e adaptação cultural da versão curta do Questionário de Frequência Alimentar para gestantes em português do Brasil

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Abstract

Objective To translate and culturally adapt the short-form Food Frequency Questionnaire (SFFFQ) for pregnant women, which contains 24 questions, into Brazilian Portuguese.

Methods Description of the process of translation and cultural adaptation of the SFFFQ into Brazilian Portuguese. The present study followed the recommendation of the International Society for Pharmacoeconomics and Outcomes Research for translation and cultural adaptation with the following steps: 1) preparation; 2) first translation; 3) reconciliation; 4) back translation; 5) revision of back translation; 6) harmonization; 7) cognitive debriefing; 8) revision of debriefing results; 9) syntax and orthographic revision; and 10) final report. Five obstetricians, five dietitians and five pregnant women were interviewed to contribute with the language content of the SFFFQ.

Results Few changes were made to the SFFFQ compared with the original version. These changes were discussed with the research team, and differences in language were adapted to suit all regions of Brazil.

Conclusion The SFFFQ translated to Brazilian Portuguese can now be validated for use in the Brazilian population.

Keywords

- food consumption
- validation studies
- pregnancy
- translation
- adaptation

Resumo

Objetivo Traduzir e adaptar culturalmente, para o português do Brasil, a versão curta do Questionário de Frequência Alimentar (VCQFA), que contém 24 questões, voltado para gestantes brasileiras.

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Métodos Este estudo descreve o processo de tradução e adaptação cultural do VCQFA para o Português do Brasil. Este estudo seguiu as diretrizes da Sociedade Internacional para Farmacoeconomia e Pesquisa de Resultados para tradução e adaptação cultural, e foram realizadas as seguintes etapas: 1) preparação; 2) primeira tradução; 3) reconciliação; 4) tradução retrógrada; 5) revisão da tradução retrógrada; 6) harmonização; 7) discussão cognitiva; 8) análise dos resultados do desdobramento; 9) revisão de sintaxe e ortografia; e 10) relatório final. Cinco obstetras, cinco nutricionistas e cinco gestantes foram entrevistadas para contribuírem com o conteúdo de linguagem do VCQFA.

Resultados Poucas mudanças foram realizadas no VCQFA em comparação com a versão original. Essas mudanças foram discutidas com a equipe de pesquisa, e as diferenças de linguagem foram adaptadas para que o questionário seja adequado a todas as regiões do Brasil.

Conclusão A versão traduzida do VCQFA para o português do Brasil pode ser validada para a população brasileira.

Palavras-chave
- consumo de alimentos
- estudos de validação
- gravidez
- tradução
- adaptação

Introduction

Maternal nutritional status during pregnancy plays an important role in the well-being of both the mother and the fetus.[1] Maternal overnutrition during pregnancy, specifically the consumption of high-calorie foods, is considered a public health concern worldwide. It can lead to obesity and adverse metabolic outcomes in the offspring and infant later in life.[2,3] However, maternal undernutrition is also considered a major contributing factor to adverse pregnancy outcomes.[2]

During pregnancy, in addition to considerations of the quantity and quality of food intake, it is important to aim for adequate weight gain.[4] The Institute of Medicine[4] provides recommendations for adequate weight gain, which are based on prepregnancy body mass index (BMI). For women with normal prepregnancy BMI (18.5–24.9 Kg/m^2), the recommendation of total weight gain during pregnancy is 11.33 Kg to 15.87 Kg; in the second and third trimesters the recommendation is 0.45 Kg (0.36–0.45) per week.[4] In order to achieve these goals, individuals may need to follow a specific dietary or physical activity program.[5,6]

Food frequency questionnaires (FFQs) are considered useful tools for the assessment of dietary intake. They consist of a list of foods and beverages with various options the participant can check to reveal the frequency in which they consume these items.[7] The FFQ is widely used in epidemiological studies aiming to categorize individuals into different levels of dietary patterns and to determine their relationships with health outcomes.[8,9] Many FFQs are validated for Brazilian pregnant women;[10–13] however, most of them are considered lengthy, with around 80 to 100 food categories. Issues with long questionnaires include difficulties in handling data,[14] participant fatigue[15] and lower response rates, especially among the elderly.[16]

The short-form Food Frequency Questionnaire (SFFFQ) contains 24 questions about regular food consumption, which are divided into main groups that focus on fruit, vegetables, fiber-rich foods, high-fat and high-sugar foods, meat, meat products and fish. This questionnaire was developed based on nutritional guidelines for the United Kingdom adult population and was validated and considered an effective method of assessing diet quality.[17] In order to use the SFFFQ in Brazilian pregnant women, the questionnaire needed to be translated and validated for this population. The main objective of the present study was to translate and to culturally adapt into Brazilian Portuguese the SFFFQ for pregnancy.

Methods

The present study was developed with the authorization of the authors of the original version of the SFFFQ,[17] and followed all the steps recommend by Wild et al (2005)[18] for translation and cultural adaptation. The process of how the present study was conducted to obtain the final version of the SFFFQ in Brazilian Portuguese is summarized in ►**Fig. 1**. The original version of the SFFFQ in English was translated to Brazilian Portuguese by two independent researchers, thus creating two different versions (V1 and V2), which were combined into a third version (V3) that was back translated from Brazilian Portuguese to English by two independent translators (►**Fig. 1**).

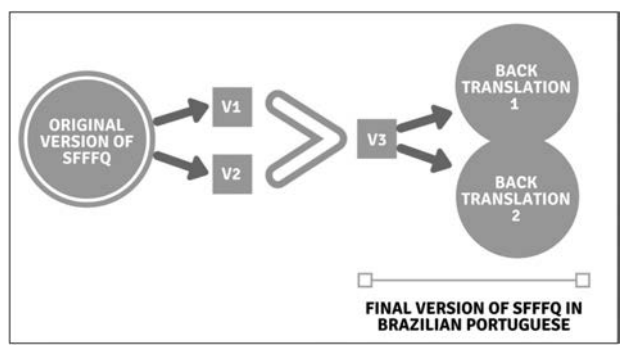

Fig. 1 Process of translation and cultural adaptation of the SFFFQ into Brazilian Portuguese. SFFFQ, short-form Food Frequency Questionnaire; V1, version 1; V2, version 2; V3, version 3.

The present study was developed according to the guidelines laid down in the Declaration of Helsinki, and the cultural adaptation of the SFFFQ for Brazilian pregnant women was approved by the Ethics Committee of the Universidade Estadual de Campinas, Brazil (under CAAE: 62916616.0.1001.5404). Written informed consent was obtained from all participants. Five obstetricians, five dietitians and five pregnant women were interviewed regarding the language content of the SFFFQ, and their opinions were recorded for the cognitive debriefing section of this paper. Then, the final version of the SFFFQ was developed based on the results of the interviews, the discussion with the author of the original SFFFQ validation,[17] and the group's final decision.

Results

The different versions developed as a result of the translation and cultural adaptation of the SFFFQ are presented in ►**Table 1**.

1. Preparation
   We obtained the consent of Cristina Cleghorn, MD (University of Otago) (original author of the validation paper of the SFFFQ in English, to perform the SFFFQ translation and cultural adaptation to Brazilian Portuguese, to apply it among pregnant women.
2. First translation
   The first (V1) and second (V2) versions of the questionnaire translations were done by two independent native Brazilian Portuguese speakers (KTK and DSMP). These translations were considered a draft for the next step.
3. Reconciliation
   Versions V1 and V2 were compared to create the third version in Brazilian Portuguese (V3) by another native Brazilian Portuguese speaker (FGS); at this point, details on language were adjusted to create one document.
4. Back translation
   Two back translations into English were done by two official translators, who were English native speakers with experience in medical terms. These translations were done independently based on V3 to compare with the original version of the SFFFQ. After the back translations, some misinterpretations were identified, and these differences were discussed.
5. Revision of back translation
   The author of the original validation paper of the SFFFQ in English (CLC) and KTK compared the original instrument with the two independent versions of the back translation. The two back translations were slightly different (►**Table 1**), and this stage was based on whether the back translations were correctly interpreted from V3. The result of this step was also incorporated into the final version of the SFFFQ in Brazilian Portuguese.
6. Harmonization
   For this step, the comparison of the back translations of the multiple language versions with each other and the original instrument is recommended. However, the original SFFFQ has not been translated to any other language, so this step was not included in the process.
7. Cognitive debriefing
   For this step, 5 dietitians with a mean age of 42.8 ± 10.8 years and work experience of 15.2 ± 10.1 years, 5 obstetricians with a mean age 40 ± 6.2 years and work experience of 15 ± 6.4 years, and 5 pregnant women with a mean age of 29.4 ± 7.8 years were interviewed. These interviews were recorded in an open questionnaire that captured their suggestions regarding the language and the semantic content of the SFFFQ. All the participants were native Brazilian Portuguese speakers and residents of the Southeastern Region of Brazil (in the city of Campinas, São Paulo).
8. Revision of debriefing results
   The dietitians missed the presence of "eggs" as a protein in the questionnaire, since in Brazil it is very common to have eggs as a main source of protein in a meal.[19] Therefore, this food item was included in the questionnaire. The food "corned-beef" is not considered a common food in Brazil, and was excluded from the questionnaire, and "ham" was transferred from the "meat" category and included under the "processed meat" category, since it is more commonly consumed in this preparation in Brazil. In the same way, the second mention of the word "cream" in the "ice cream/cream" category was excluded, since "cream" is not a common item in the Brazilian diet. ["Canned fruit" was excluded from the category "fruit", as it was considered too sweet, with a high glycemic index, and canned fruit is not a part of Brazil's dietary recommendations for fruit intake. Only "fresh fruit" was considered for this category.[20,21] All the changes were discussed with the research team, and differences in language were adapted to suit all the regions of Brazil.
9. Syntax and orthographic revision
   The syntax and orthographic revision was developed by a Brazilian Portuguese grammar professor with experience in medical terms. The final version of the SFFFQ was reviewed and approved by all authors.
10. Final report

As recommended by Wild et al (2005),[18] the process of translation and cultural adaptation of the SFFFQ into Brazilian Portuguese has been reported to provide guidance for other researchers considering translating the same questionnaire into a different language.

Discussion

This short communication describes the process of translation and cultural adaptation of the SFFFQ to Brazilian Portuguese, as it is considered the first step toward the validation of the questionnaire for Brazilian pregnant women. Dietary patterns during pregnancy may vary in Brazilian pregnant women,[22,23] and different factors influence maternal food intake, such as food price policies and nutritional inequalities.[24,25]

Adequate assessment of the quantity and quality of food intake in pregnant women provides essential information on associations among diet, nutrition and health, the detection of nutrient deficiencies, and the characterization of population

Table 1 Process of translation into Brazilian Portuguese and cultural adaptation of the short-form Food Frequency Questionnaire (SFFFQ) for Brazilian pregnant women

	Original	Version 1 (V1)	Version 2 (V2)	Reconciliation - Version 3 (V3)
1	Fruit (tinned/fresh)	Frutas (enlatadas/frescas)	Frutas (em lata/frescas)	Frutas (enlatadas/frescas)
2	Fruit juice (not cordial or squash)	Suco de frutas (exceto suco concentrado, de caixinha, ou artificial)	Suco de frutas natural (sem contar suco concentrado, de caixinha, ou artificial)	Suco de frutas (exceto suco concentrado, de caixinha, ou artificial)
3	Salad (not garnish added to sandwiches)	Salada (não como ingrediente em sanduíches)	Salada (não como acompanhamento de sanduíches)	Salada (não como ingrediente em sanduíches)
4	Vegetables (tinned/frozen/fresh but not potatoes)	Vegetais (enlatados/congelados/frescos, mas não batatas)	Vegetais (em lata/congelados/frescos, mas não batatas)	Vegetais (enlatados/congelados/frescos, mas não batatas)
5	Chips/fried potatoes	Salgados/Batata frita	Salgados fritos/Batata frita	Salgados/Batata frita
6	Beans or pulses like baked beans, chick peas, dahl	Feijão ou leguminosas cozidas, como grão de bico e lentilha	Feijão ou leguminosas cozidas, como grão de bico e lentilha	Feijão ou leguminosas cozidas, como grão de bico e lentilha
7	Fiber-rich breakfast cereal, like Weetabix, Fruit 'n Fiber, Porridge, Muesli	Cereais ricos em fibras, como aveia e granola	Cereais enriquecidos em fibras, como aveia e granola	Cereais ricos em fibras, como aveia e granola
8	Wholemeal bread or chapattis	Pão integral ou pão sírio de farinha de trigo integral	Pão integral ou pão sírio de farinha de trigo integral	Pão integral ou pão sírio de farinha de trigo integral
9	Cheese/yoghurt	Queijo/iogurte	Queijo/iogurte	Queijo/iogurte
10	Crisps/savoury snacks	Salgadinhos de pacote/petiscos salgados	Salgadinhos de pacote/petiscos salgados	Salgadinhos de pacote/petiscos salgados
11	Sweet biscuits, cakes, chocolate, sweets	Biscoitos doces, bolos, chocolate, doces	Biscoitos doces, bolos, chocolates, doces	Biscoitos doces, bolos, chocolate, doces
12	Ice cream/cream	Sorvete/doce	Sorvete/doce com creme	Sorvete/doce
13	Nonalcoholic fizzy drinks/pop (not sugar free or diet)	Bebidas com gás, como "Aquarius Fresh" ou "H2OH"/refrigerante (sem açúcar ou diet)	Bebidas gaseificadas, como "Aquarius Fresh" ou "H2OH"/refrigerante (sem açúcar, zero ou diet)	Bebidas com gás, como "Aquarius Fresh" ou "H2OH"/refrigerante (sem açúcar, zero ou diet)
14	Whole meats: beef, lamb, pork, ham - steaks, roasts, joints, mince or chops	Carnes: carne de vaca, cordeiro, carne suína, presunto - bifes, assados, mocotó, moída ou costelas	Carnes: carne de vaca, cordeiro, carne suína, presunto - bifes, assados, mocotó, moída ou costelas	Carnes: carne de vaca, cordeiro, carne suína, presunto - bifes, assados, mocotó, moída ou costelas
15	Chicken or turkey – steaks, roasts, joints, mince or portions (not in batter or breadcrumbs)	Frango ou peru – filés, assados, asa/coxa da asa de frango, desfiado ou porção (sem milanesa)	Frango ou peru – filés, assados, asa/coxa da asa de frango, desfiado ou porção (sem milanesa)	Frango ou peru – filés, assados, asa/coxa da asa de frango, desfiado ou porção (sem milanesa)
16	Processed meats/meat products: sausages, bacon, corned beef, meat pies/pasties, burgers	Carnes processadas/preparações com carne: salsichas, bacon, fraldinha, torta de carne/pastéis com carne, hambúrgueres	Carnes processadas/preparações com carne: salsichas, bacon, fraldinha, torta de carne/pastel de carne, hambúrgueres	Carnes processadas/preparações com carne: salsichas, bacon, fraldinha, torta de carne/pastéis com carne, hambúrgueres
17	Chicken/turkey nuggets/twizzlers, turkey burgers, chicken pies, or in batter or breadcrumbs	Frango/*nuggets*, hambúrguer de frango, torta de frango, ou à milanesa	*Nuggets* de frango, hambúrguer de frango, torta de frango, ou à milanesa	*Nuggets* de frango, hambúrguer de frango, torta de frango, ou à milanesa

Table 1 (*Continued*)

	Original	Version 1 (V1)	Version 2 (V2)	Reconciliation - Version 3 (V3)
18	Fish: White fish in batter or breadcrumbs – like 'fish 'n chips'	Peixes: peixe branco à milanesa	Peixes: peixe branco frito à milanesa	Peixes: peixe branco à milanesa
19	White fish not in batter or breadcrumbs	Peixe branco sem milanesa	Peixe branco sem milanesa	Peixe branco sem milanesa
20	Oily fish – like herrings, sardines, salmon, trout, mackerel, fresh tuna (not tinned tuna)	Peixes oleosos – como arenque, sardinha, salmão, truta, cavala, atum fresco (não atum enlatado)	Peixes com alta concentração de óleo – como arenque, sardinha, salmão, truta, cavala, atum fresco (exceto atum em lata)	Peixes oleosos – como arenque, sardinha, salmão, truta, cavala, atum fresco (não atum enlatado)
21	On average, how many portions of FRUIT do you eat a day? (Examples include a handful of grapes, an orange, a glass of fruit juice, a handful of dried fruits).	Em média, quantas porções de FRUTAS você consome por dia? (Por exemplo: um punhado de uvas, uma laranja, um copo de suco de frutas, um punhado de frutas secas).	Em média, quantas porções de FRUTAS você come diariamente? (Por exemplo: um punhado de uvas, uma laranja, um copo de suco de frutas, um punhado de frutas secas).	Em média, quantas porções de FRUTAS você consome por dia? (Por exemplo: um punhado de uvas, uma laranja, um copo de suco de frutas, um punhado de frutas secas).
22	On average, how many portions of VEGETABLES do you eat a day? (Examples include: 3 heaped tablespoons of carrots, a side salad, 2 spears of broccoli).	Em média, quantas porções de VEGETAIS você consome por dia? (Por exemplo: 3 colheres de sopa cheias de cenoura, salada de acompanhamento, 2 ramos de brócolis).	Em média, quantas porções de VEGETAIS você come diariamente? (Por exemplo: 3 colheres de sopa cheias de cenoura, salada de acompanhamento, 2 ramos de brócolis).	Em média, quantas porções de VEGETAIS você consome por dia? (Por exemplo: 3 colheres de sopa cheias de cenoura, salada de acompanhamento, 2 ramos de brócolis).
23	What milk do you usually use or drink, such as in hot & cold drinks or on cereal? (Including tea, coffee, hot milk, milk shakes, or on cereal) Whole/full-fat milk • Semi-skimmed milk • Skimmed milk • Rarely/never use milk • Other (please write its name)	Qual tipo de leite você geralmente consome, quente, frio ou com cereal? (Incluindo leite com chá, leite com café, leite quente, milk shakes, ou com cereal) Leite integral • Leite semidesnatado • Leite desnatado • Raramente/não consumo leite • Outros (por favor, escreva o nome)	Qual tipo de leite você usualmente bebe, quente, frio ou com cereal? (Incluindo leite com chá, leite com café, leite quente, milk shakes, ou com cereal) Leite integral • Leite semidesnatado • Leite desnatado • Raramente/não bebo leite • Outros (por favor, escreva o nome)	Qual tipo de leite você geralmente consome, quente, frio ou com cereal? (Incluindo leite com chá, leite com café, leite quente, milk shakes, ou com cereal) Leite integral • Leite semidesnatado • Leite desnatado • Raramente/não consumo leite • Outros (por favor, escreva o nome)
24	On average, how much alcohol do you drink over a complete seven-day week? (One unit is a standard glass of wine, half a pint of beer or lager, a single measure of spirits, a measure of sherry) I rarely/never drink alcohol • Less than 14 units • Between 14 & 21 units • More than 21 units •	Em média, quanto álcool você consome durante sete dias da semana? (Uma unidade é considerada uma taça de vinho, 250 mL de cerveja, uma dose de bebida destilada (uísque, gim, vodka, rum, cachaça, uma dose de licor) Raramente/não consumo álcool • Menos de 14 unidades • Entre 14 e 21 unidades • Mais de 21 unidades •	Em média, quanto álcool você bebe durante uma semana? (Uma unidade é considerada uma taça de vinho, 250 mL de cerveja, uma dose de bebida destilada (uísque, gim, vodka, rum, cachaça, uma dose de licor) Raramente/não bebo álcool • Menos de 14 unidades • Entre 14 e 21 unidades • Mais de 21 unidades •	Em média, quanto álcool você consome durante sete dias da semana? (Uma unidade é considerada uma taça de vinho, 250 mL de cerveja, uma dose de bebida destilada (uísque, gim, vodka, rum, cachaça, uma dose de licor) Raramente/não consumo álcool • Menos de 14 unidades • Entre 14 e 21 unidades • Mais de 21 unidades •

Table 1 (*Continued*)

	Original	Back translation 1	Back translation 2	Final version
1	Fruit (tinned/fresh)	Fruits (canned/fresh)	Fruits (canned/fresh)	Frutas frescas
2	Fruit juice (not cordial or squash)	Fruit juice (except concentrated juice, in a box, or artificial)	Fruit juice (except concentrated, canned, or artificial juice)	Suco de frutas natural (exceto suco concentrado ou artificial)
3	Salad (not garnish added to sandwiches)	Salad (not as an ingredient in sandwiches)	Salad (not as ingredient in sandwiches)	Salada de folhas (não como ingrediente em sanduíches)
4	Vegetables (tinned/frozen/fresh but not potatoes)	Vegetables (canned/frozen/fresh, but not potatoes)	Vegetables (canned/ frozen/fresh, but not potatoes)	Legumes (enlatados/congelados/frescos, mas não batatas)
5	Chips/fried potatoes	Snacks/Potato chips	Savory snacks/potato chips	Salgados fritos/Batata frita
6	Beans or pulses like baked beans, chick peas, dahl	Cooked beans or legumes such as chick peas and lentils	Beans or legumes cooked, such as chickpeas and lentils	Feijão ou leguminosas cozidas, como grão de bico e lentilha
7	Fiber-rich breakfast cereal, like Weetabix, Fruit 'n Fiber, Porridge, Muesli	Cereals rich in fibers, such as oats and granola	Cereals rich in fiber, such as oatmeal and granola	Cereais ricos em fibras, como aveia e granola
8	Wholemeal bread or chapattis	Whole-wheat bread or whole-wheat pita bread	Whole grain bread or Syrian bread made from whole wheat flour	Pão integral ou pão sírio de farinha de trigo integral
9	Cheese/yoghurt	Cheese/Yogurt	Cheese/yogurt	Queijo/iogurte
10	Crisps/savoury snacks	Snacks in packages/salty snacks	Packaged savory snacks/savory snacks	Salgadinhos de pacote/petiscos salgados
11	Sweet biscuits, cakes, chocolate, sweets	Sweet biscuits, cakes, chocolate, sweets	Sweet biscuits, cakes, chocolate, candies	Biscoitos doces, bolos, chocolates, doces
12	Ice cream/cream	Ice cream/candy	Ice cream/sweet	Sorvete
13	Nonalcoholic fizzy drinks/pop (not sugar free or diet)	Carbonated soft drinks, such as "Aquarius Fresh" or "H2OH"/soft drink (no sugar or diet)	Drinks with gas, such as "Aquarius Fresh" or "H2OH"/soft drinks (without sugar or diet)	Refrigerantes (sem incluir os refrigerantes sem açúcar, zero ou diet)
14	Whole meats: beef, lamb, pork, ham - steaks, roasts, joints, mince or chops	Meats: beef, lamb, pork, ham - steak, roasted, calf's foot, ground beef or ribs	Meat: beef, lamb, pork, ham - steaks, roasts, calf's foot jelly, ground meat, or ribs	Carnes: carne de vaca, cordeiro, carne de porco - bifes, assados, mocotó, moída ou costelas
15	Chicken or turkey – steaks, roasts, joints, mince or portions (not in batter or breadcrumbs)	Chicken or turkey – steak, roasted, wings/chicken wing thigh, shredded or serving (not breaded steak)	Chicken or turkey - fillets, roasts, wing/ wing flat, shredded or a portion (without batter)	Frango ou peru – filés, assados, asa/ coxa da asa de frango, desfiado ou porção (sem ser empanado)
16	Processed meats/meat products: sausages, bacon, corned beef, meat pies/ pasties, burgers	Processed meat/meat preparations: sausages, bacon, thick flank, meat pie/ meat pastry, hamburgers	Processed meat/preparations with meat: sausages, bacon, flank steak, meat pie/ pasty, hamburgers	Carnes processadas/preparações com carne: salsichas, presunto, bacon, torta de carne/pastéis com carne, hambúrgueres
17	Chicken/turkey nuggets/twizzlers, turkey burgers, chicken pies, or in batter or breadcrumbs	Chicken/ nuggets, chicken hamburger, chicken pie or chicken fried steak	Chicken/nuggets, chicken burger, chicken pie or battered chicken	*Nuggets* ou hambúrguer de frango, torta de frango, ou frango empanado

Table 1 (*Continued*)

	Original	Back translation 1	Back translation 2	Final version
18	Fish: White fish in batter or breadcrumbs – like 'fish 'n chips'	Fish: Breaded white fish	Fish: Battered white fish	Peixes: peixe branco empanado
19	White fish not in batter or breadcrumbs	White fish not breaded	White fish without batter	Peixe branco (sem incluir peixe empanado)
20	Oily fish – like herrings, sardines, salmon, trout, mackerel, fresh tuna (not tinned tuna)	Oily fish – such as herring, sardine, salmon, trout, mackerel, fresh tuna (not canned tuna)	Oily fish - such as herring, sardines, salmon, trout, mackerel, fresh tuna (not canned tuna)	Peixes oleosos – como arenque, sardinha, salmão, truta, cavala, atum fresco (não atum enlatado)
21	On average, how many portions of FRUIT do you eat a day? (Examples include a handful of grapes, an orange, a glass of fruit juice, a handful of dried fruits).	On average, how many servings of FRUITS do you consume per day? (For example: a bunch of grapes, an orange, a cup of fruit juice, a bunch of dried fruits).	On average, how many servings of FRUITS do you consume per day? (For example: a handful of grapes, an orange, a glass of fruit juice, a handful of dried fruits).	Em média, quantas porções de FRUTAS você consome por dia? (Por exemplo: um cacho pequeno de uva, uma laranja, um copo de suco de frutas, um punhado de frutas secas).
22	On average, how many portions of VEGETABLES do you eat a day? (Examples include: 3 heaped tablespoons of carrots, a side salad, 2 spears of broccoli).	On average, how many servings of VEGETABLES do you consume per day? (For example: 3 heaping tablespoons of carrots, salad side dish, 2 florets of broccoli).	On average, how many servings of VEGETABLES do you consume per day? (For example: 3 full tablespoons of carrot, an accompanying salad, 2 sprigs of broccoli).	Em média, quantas porções de LEGUMES você consome por dia? (Por exemplo: 3 colheres de sopa cheias de cenoura, salada de acompanhamento, 2 ramos de brócolis).
23	What milk do you usually use or drink, such as in hot & cold drinks or on cereal? (Including tea, coffee, hot milk, milk shakes, or on cereal) Whole/full-fat milk • Semi-skimmed milk • Skimmed milk • Rarely/never use milk • Other (please write its name)	What type of milk do you usually consume, hot, cold or with cereal? (Including milk and tea, milk and coffee, hot milk, milk shakes, or with cereal) Whole milk • Semi-skimmed milk • Skim milk • Rarely/does not consume milk • Others (please, write the name)	What kind of milk do you usually consume, hot, cold, or with cereal? (Including milk with tea, milk with coffee, hot milk, milk shakes, or with cereal) Whole milk • Semi-skimmed milk • Skimmed milk • Rarely/do not drink milk • Other (please write the name)	Qual tipo de leite você geralmente consome, quente, frio ou com cereais? (Incluindo leite com chá, leite com café, leite quente, milk shakes, ou com cereais) Leite integral • Leite semidesnatado • Leite desnatado • Raramente/não consumo leite • Outro (por favor, escreva o nome)
24	On average, how much alcohol do you drink over a complete seven day week? (One unit is a standard glass of wine, half a pint of beer or lager, a single measure of spirits, a measure of sherry) I rarely/never drink alcohol • Less than 14 units • Between 14 & 21 units • More than 21 units •	On average, how much alcohol do you consume during seven days of the week? (one unit is considered a glass of wine, 250 ml of beer, a dose of distilled drink (whisky, gin, vodka, rum, sugarcane brandy, a dose of liquor) Rarely/does not consume alcohol • Less than 14 units • Between 14 and 21 units • More than 21 units •	On average, how much alcohol do you consume over the seven days of the week? (A unit is considered a glass of wine, 250 ml of beer, a shot of distilled drink (whiskey, gin, vodka, rum, brandy, a shot of liquor) Rarely/do not drink alcohol • Less than 14 units • Between 14 and 21 units • More than 21 units •	Em média, quantas doses de bebida alcoolica você consome durante 7 dias da semana? (Uma dose é considerada uma taça de vinho, 250 ml de cerveja, uma dose de licor ou uma dose de bebida destilada, como uísque, gim, vodka, rum, cachaça) Raramente/não consumo álcool • Menos de 14 doses • Entre 14 e 21 doses • Mais de 21 doses •

vulnerability.[26] A study conducted in Brazil showed a different dietary pattern according to the sociodemographic characteristics of pregnant women measured by the FFQ.[23] A restrictive dietary pattern with a low variety of grains, fruits and vegetables was observed in younger Brazilian pregnant women who lived without a partner and attended school or university, while pregnant women with higher maternal age and higher socioeconomic status presented a healthier diet, with more food variety.[23] Therefore, the FFQ has been considered a useful tool to adequately assess maternal dietary habits and to improve the communication between pregnant women and health professionals (dietitians and obstetricians).

During the development of the present study, there were different suggestions made by dietitians, obstetricians and pregnant women about the language content of the SFFFQ. While the dietitians had more comments regarding the food categories and classification, the obstetricians were more concerned with the language content in the questions that were asked. The pregnant women focused on the quantities assessed by the questionnaire and needed clarification on portion sizes. From our perspective, all of them contributed significantly to the development of the final version of the Brazilian SFFFQ.

The present study is similar to various other studies regarding the process of translation and cultural adaptation.[27–29] All the studies followed the recommendation of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) for translating and culturally adapting different questionnaires into Brazilian Portuguese.[27–29] The translated SFFFQ to Brazilian Portuguese can now be validated for use in Brazilian pregnant women.

Transparency Declaration

The lead author states that this manuscript is an honest, accurate, and transparent account of the study being reported. The lead author states that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

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Score Establishment and Brazilian Portuguese version of the Pregnancy Sexual Response Inventory (PSRI)

Definição de escores e versão em português brasileiro do Inventário da Resposta Sexual na Gestação (PSRI)

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Abstract

Objective To establish the Pregnancy Sexual Response Inventory (PSRI) scores for each domain before and during pregnancy, and to publish the Brazilian Portuguese version of the PSRI.

Methods Pregnant women were recruited during antenatal care; the PSRI was administered to 244 women prenatally at Faculdade de Medicina de Botucatu, at Universidade do Estado de São Paulo (UNESP, in the Portuguese acronym). The PSRI scores were estimated based on the Kings Health Questionnaire (KHQ) and the Medical Outcomes Study 36-item short form survey (SF-36). The raw scale type was used to standardize the minimal value and amplitude of each domain. For each domain, the score varied from 0 to 100, and the composite score was obtained as the domain average. The composite score before and during pregnancy was determined by the sum of the scores of all specific domains for each divided by the full domain number. The categorization of the scale into quartiles was established when all PSRI-specific and composite scores were combined.

Results The composite and specific scores for each domain were categorized into quartiles: $0 < 25$ as "very bad;" $25 < 50$ as "bad;" $50 < 75$ as "good" and 75 to 100 as "excellent." The mean scores were lower during pregnancy than before pregnancy in 8 of the 10 domains. The Brazilian Portuguese PSRI version is presented.

Conclusion This study allowed the establishment of the PSRI composite and specific scores for each domain, and the categorization of scores into quartiles: very bad, bad, good and excellent. In addition, the Brazilian Portuguese version of the PSRI is presented in full for application in the Brazilian population.

Keywords
- pregnancy
- sexuality
- questionnaires

Resumo

Objetivo Estabelecer os escores do Inventário da Resposta Sexual na Gestação (PSRI) para cada domínio antes e durante a gravidez, e publicar a versão do PSRI em português brasileiro.

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Métodos Gestantes foram recrutadas durante o cuidado pré-natal; o PSRI foi administrado a 244 mulheres no pré-natal na Faculdade de Medicina de Botucatu da Universidade do Estado de São Paulo (UNESP). Os escores do PSRI foram estimados com base no *Kings Health Questionnaire* (KHQ) e *Medical Outcomes Study 36-item short form survey* (SF-36). O tipo de escala bruta foi utilizado para padronizar o valor mínimo e a amplitude de cada domínio. Para cada domínio, a pontuação variou de 0 a 100, e o escore composto foi obtido pela média do domínio. O escore composto antes e durante a gravidez foi determinado pela somatória dos escores de todos os domínios específicos para cada período dividido pelo número total do domínio. A escala de categorização em quartil foi estabelecida quando todos os escores específicos e compostos do PSRI foram reunidos.

Resultados Os escores compostos e específicos para cada domínio foram categorizados em quartis: 0 < 25 como "muito ruim;" 25 < 5 0 como "ruim;" 50 < 75 como "bom" e 75 a 100 como "excelente." As médias dos escores foram menores durante a gravidez do que antes da gravidez em 8 dos 10 domínios. Foi apresentada a versão PSRI em português brasileiro.

Conclusão Este estudo permitiu o estabelecimento dos escores compostos e específicos do PSRI para cada domínio e a categorização dos escores em quartis: muito ruim, ruim, bom e excelente. Além disso, a versão em português do PSRI é apresentada integralmente para aplicação na população brasileira.

Palavras-chave
- gestação
- sexualidade
- questionários

Introduction

There are several maternal adaptations that involve profound anatomical, physiological, and biochemical changes, which may impact the sexual health of partners during pregnancy.[1]

A systematic review has found a gradual decrease in vaginal intercourse from prepregnancy to the first and third trimesters,[2] and many studies have revealed a reduction in sexual function during pregnancy.[1,3–5]

This topic has attracted researchers' attention due to the increase in the number of epidemiological studies, but data are still limited on the prevalence of sexual dysfunction and concerns about sexual activity in pregnant women, and it remains unclear how to evaluate them. The female sex response cycle proposed by Basson (2000)[6] starts during a neutral phase, and the rewards of emotional closeness serve as the motivational factors that will activate the cycle the next time. This knowledge needs to be included in the instruments used to evaluate the sexual function during pregnancy. Moreover, there are some attitude changes toward sexual function during pregnancy, such as the different sexual responses proposed by Basson (2000),[6] but the methodological limitations (sample sizes, unrepresentative samples, and retrospective data) and inconsistent results of published manuscripts may limit their relevance.[7]

Currently, the instrument "Pregnancy and Sexuality Questionnaire (PSQ)" has been developed to evaluate the subjectivity and complexity of sexual function within pregnancy, although the authors did not list the specific items included in their questionnaire within their article.[8]

The "Female Sexual Function Index (FSFI)" was developed to evaluate female sexual response; however, this questionnaire was not developed for pregnant women.[9] In turn, the Pregnancy and Sexual Function Questionnaire (PSFQ), Portuguese version, was considered adequate for evaluating sexual function during pregnancy.[10]

The Pregnancy Sexual Response Inventory (PSRI) was designed based on the PSQ, a validated instrument for studying sexual relations between partners during pregnancy,[8] and was integrated into the Basson[6] sexual response. This instrument was developed due to the lack of access to the only instrument validated for studying the sexual relationship of partners within pregnancy.

There were five phases in the development of the PSRI: (I) item selection; (2) item development; (3) determination of internal consistency, reliability and convergence; (4) content validity; and (5) determination of inter-interviewer reliability. Internal consistency and reliability were evaluated using Cronbach's α. Inter-interviewer reliability was assessed by evaluating the responses of 18 academics at various institutions using the Kappa Index and Student *t*-test.[11] Furthermore, the PSRI was fully validated in the Brazilian Portuguese language by our current research group and covers different domains of sexual response during pregnancy.[11] Although it is a validated questionnaire, the PSRI had not been published in Portuguese, and thus could not be used to support the clinical diagnosis of sexual function during pregnancy in Brazil and other Portuguese-speaking countries.

The aim of this study was to establish the PSRI composite and specific scores for each domain before and during pregnancy, and to publish the Brazilian Portuguese version of the PSRI.

Methods

Study Population

An observational, cross-sectional, single-center study was performed between January and August 2016 at the Department of Gynecology and Obstetrics at the Faculdade de Medicina de Botucatu (FMB-UNESP, in the Portuguese acronym). This hospital is a tertiary center with a perinatal center of the highest level providing health services to medium- and high-risk obstetrical patients from an area with ~ 500,000 inhabitants, and 1,600 deliveries are performed in it per year. Healthy pregnant women seeking antenatal care were recruited to participate in the current study while waiting for their routine medical check-ups. Any patients who presented systemic illnesses, such as diabetes mellitus, hypertension, hyperlipidemia and thyroid dysfunction, and those who conceived by assisted reproduction techniques were excluded from the current study.

The protocol and the objectives of the study were explained to 370 pregnant women; 249 (67.3%) of them provided a signed informed consent just before the administration of the validated instrument of sexual function - the PSRI. The eligibility criteria included healthy pregnant women who were heterosexual, 18 years of age or older, and in the second or third trimester of pregnancy and who had been sexually active in the previous 4 weeks.

Upon signing the informed consent, the eligible women were interviewed by a trained female interviewer using a paper-and-pencil standardized questionnaire. Interviews were conducted at the prenatal clinic in a private room. All women were assessed with a detailed medical history, including partnership status, education level, religion, employment status, parity, smoking habits, drinking, illicit drugs, planned pregnancy, and condom use, and a comprehensive physical examination was also performed for each woman. Our sample was mostly heterosexual, married, and in female-male relationships. The data were cross-sectional, which means we only collected one questionnaire per woman. Approval for the study was given by the local institutional research bureau under protocol number 161/2012.

Questionnaire

Sexual function was assessed using the PSRI. This semi-structured questionnaire contained 38 questions divided into 12 questions about demographic traits and 26 questions about sexual behavior activity before and during pregnancy. The sexual response questions were grouped in 10 domains; eight of them assessed the women's feelings, and two assessed their perception of her partner's sexual interest. All domains included possible distress items, since it is necessary to investigate sexual dysfunction.

►**Table 1** shows the questions grouped by domain for each period.

Outcome Measures

The primary outcomes were to make possible the establishment of scores to adequately evaluate the PSRI responses, and to publish the Portuguese version of the PSRI for application in the Brazilian population.

Table 1 Description of the grouped questions for each domain before and during pregnancy and the sum of all questions per domain

Domains	Questions Before pregnancy	Questions During Pregnancy	Questions All
PSRI (specific scores) Female perception			
Sexual activity frequency	14a	13, 14b, 14c	13, 14a, 14b, 14c
Desire	21a	21b, 22	21a, 21b, 22
Arousal	18a	18b	18a, 18b
Orgasm	23a	23b	23a, 23b
Satisfaction	15a, 17a	15b, 17b	15a, 15b, 17a, 17b
Dyspareunia	24a	24b	24a, 24b
Intercourse start	25a	25b	25a, 25b
Female difficulties	19a	19b	19a, 19b
Female perception of partners			
Male sexual satisfaction	16a	16b	16a, 16b
Male sexual difficulties	26a	26b	26a, 26b

Abbreviation: PSRI, Pregnancy Sexual Response Inventory.
The numbers followed by letters are the number of questions that appear in the PSRI.

PSRI Composite and Specific Score Establishment

The estimated PSRI scores of sexual behavior considered all answers before and during pregnancy, with the answers divided into each domain according to period. Therefore, 11 questions were analyzed before pregnancy, while 14 questions were analyzed during pregnancy. Two composite scores for the PSRI were established according to both analyzed periods. A score was calculated for each domain in both periods. The 20th question was not included in the score calculation because it was only answered if the 19th question was marked "yes." Demographic characteristics were not included in the PSRI score calculation. The PSRI score estimate was based on the Kings Health Questionnaire (KHQ)[12] and the Medical Outcomes Study, a 36-item short-form health survey (SF-36).[13] The raw scale type was used to standardize the minimal value and amplitude of each domain. For each domain, the score varied from 0 to 100, and the general score was obtained using the domain average. The specific score for each domain was estimated using the SF-36 guidelines.[13] The composite score comprising the periods before and during pregnancy was determined by adding the score of all specific domains for each period divided by the full domain number. Finally, we established the categorization scale into quartiles, once all the PSRI-specific and composite scores were combined (►**Fig. 1**).

I- Características Demográficas	
1- Idade Materna: Idade do Parceiro:	2- Idade Gestacional:
3- Estado Civil: (1) casada/união estável (2) solteira (3) outro_____	4- Nível Educacional: (1) fundamental (2) ensino médio (3) ensino superior
5- Religião: (1) católica (2) evangélica (3) outras_____	6- Você trabalha? (1) não (2) sim, eu tenho um trabalho (3) sim, mas no momento estou desempregada
7- Você tem filhos? (1) não (2) apenas um (3) dois ou mais	8- Você fuma? (1) sim, com alguma ou muita frequência (2) sim, apenas as vezes (3) não
9- Você bebe? (1) sim, com alguma ou muita frequência (2) sim, apenas às vezes (3) não	10- Você usa drogas ilícitas? (1) sim, com alguma ou muita frequência (2) sim, apenas às vezes (3) não
11- Você planejou sua gravidez? (1) sim (2) não	12- Você usa preservativo? (1) sim (2) não
II- Comportamento/Atividade Sexual – antes e durante a gestação	
13- Na sua opinião, a frequência das suas relações sexuais mudou depois que você engravidou? (1) sim, diminuiu (2) não, é a mesma (3) sim, aumentou	14a- Antes da gestação, quantas vezes por semana você tinha relações sexuais? (1) nenhuma (2) 1-2 vezes (3) 3 ou mais vezes
14b- No primeiro trimestre da gestação, quantas vezes por semana você tinha relações sexuais? (1) nenhuma (2) 1-2 vezes (3) 3 ou mais	14c- No momento, quantas relações sexuais você tem por semana? (1) nenhuma (2) 1-2 vezes (3) 3 ou mais
15a- Como você classificaria sua vida sexual antes de você engravidar? (0 = muito ruim, 10 = muito boa) (1) 0-3 (2) 4-7 (3) 8-10	15b- Como você classificaria sua vida sexual atualmente? (0 = muito ruim, 10 = muito boa) (1) 0-3 (2) 4-7 (3) 8-10

Fig. 1 Full version of the Brazilian Portuguese Pregnancy Sexual Response Inventory.

16a- Como você acha que o seu parceiro classificaria a vida sexual dele antes de você engravidar? (1) 0-3 (2) 4-7 (3) 8-10	16b- Como você acha que o seu parceiro classificaria a vida sexual dele atualmente? (1) 0-3 (2) 4-7 (3) 8-10
17a- Você tinha prazer nas suas relações sexuais antes de engravidar? (1) não (2) eu suponho que estava tudo bem (3) sim	17b- Você tem prazer nas suas relações sexuais durante a gestação? (1) não (2) eu suponho que esteja tudo bem (3) sim
18a- Como você classificaria sua excitação antes da gestação? (1) baixa/muito baixa (2) regular (3) excelente	18b- Como você classificaria sua excitação durante a gestação? (1) baixa/muito baixa (2) regular (3) excelente
19a- Você apresentava alguma dificuldade sexual antes da gestação? (1) sim (2) não	19b- Você tem apresentado alguma dificuldade sexual durante a gestação? (1) sim (2) não
20- Essa dificuldades te deixam angustiada? (1) sim (2) um pouco (3) não	21a- Com que frequência você tinha desejo sexual antes da gravidez? (1) nunca/ raramente (2) algumas vezes por semana (3) uma vez por dia
21b- Com que frequência você tem desejo sexual durante a gravidez? (1) nunca/raramente (2) algumas vezes por semana (3) uma vez por dia	22- O que aconteceu com o seu desejo sexual depois que você engravidou? (1) diminuiu (2) é o mesmo (3) aumentou
23a- Com que frequência você alcançava o orgasmo antes da gestação? (1) nunca/raramente (2) as vezes (3) com frequência/com muita frequência	23b- Com que frequência você alcança o orgasmo durante a gestação? (1) nunca/raramente (2) as vezes (3) com frequência/com muita frequência
24a- Você sentia dor durante a relação sexual antes da gestação? (1) sim (2) não	24b- Você sente dor durante a relação sexual durante a gestação? (1) sim (2) não

Fig. 1 (*Continued*)

25a- A relação sexual antes da gestação era iniciada: (1) forçada, sem nenhum desejo (2) geralmente iniciada pelo parceiro (3) espontaneamente ou espontaneamente com estímulo	25b- A relação sexual durante a gestação é iniciada: (1) forçada, sem nenhum desejo (2) geralmente iniciada pelo parceiro (3) espontaneamente ou espontaneamente com estímulo
26a- Na sua opinião, você acha que o seu parceiro estava apresentando alguma dificuldade sexual antes da gestação? (1) sim (2) não	26b- Na sua opinião, você acha que o seu parceiro está apresentando alguma dificuldade sexual durante a gestação? (1) sim (2) não

Fig. 1 (*Continued*)

Portuguese Version

The Brazilian Portuguese version of the PSRI is presented in the same format as the English one.

Statistical Analyses

The sample size was calculated according to the 40% prevalence of sexual dysfunction in pregnant women, with a margin of error of 10% and a reliability of 95%.[14] Thus, the minimum sample size was determined to be184 participants.

Comparisons between means of the domain values classified by both analyzed periods were assessed by paired *t*-test at a significance level of 5%. All data were analyzed using the software Statistical Analysis System (SAS) for Windows, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

►**Fig. 2** provides an overview of the study sample collection.

The Brazilian Portuguese PSRI, a validated questionnaire, is shown in ►**Fig. 1**. Two hundred and forty-nine pregnant women completed the PSRI, with 49 in the second trimester of pregnancy, 200 in the third trimester of pregnancy and 5 excluded from the final sample because their questionnaires were incomplete. ►**Table 2** represents the demographic features of our full sample. The mean maternal age of the 244 participants was 26 years (SD = 5.4, Min = 20.6, Max = 31.4). At study inclusion, the mean gestational age was 34.8 weeks of pregnancy (SD = 3.5, Min = 25.0, Max = 42.0). The majority of our sample (63.1%) was married

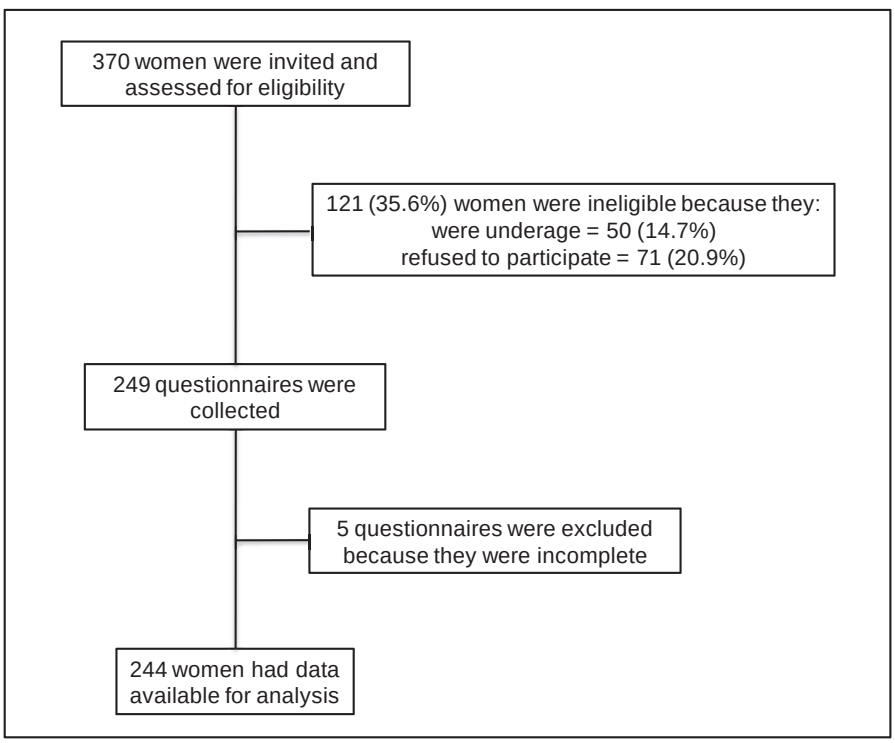

Fig. 2 Flow-diagram describing the process for recruitment of the pregnant women.

Table 2 Descriptive demographic characteristics of pregnant women

Variables	f (%)
Partnership status	
Married/Living together	154 (63.1)
Single	71 (2.1)
Other	19 (7.8)
Sociodemographic factors	
Education Level	
Basic Level	99 (40.6)
High School	120 (49.2)
College/University	25 (1. 2)
Religion	
Catholic	113 (46.3)
Brazilian Protestants	95 (38.9)
Other/No religion	36 (14.8)
Employment status	
Student	72 (29.5)
Employed	86 (35.2)
Not employed	86 (35.2)
Children	
No	128 (52.5)
Just one	71 (29.1)
Two or more	45 (18.4)
Smoke	
Often/Very often	20 (8.2)
Sometimes	21 (8.6)
No	203 (83.2)
Drink	
Often/Very often	2 (0.8)
Sometimes	11 (4.5)
No	231 (94.7)
Illicit drugs	
Often/Very often	5 (2.0)
Sometimes	2 (0.8)
No	237 (97.1)
Family planning knowledge	
Planned pregnancy	
Yes	109 (44.7)
No	135 (55.3)
Contraceptive methods*	
No	199 (81.6)
Yes, stopped before pregnancy	28 (11.5)
Very often	17 (7.0)

Abbreviation: f, frequency of clinical characteristics of the study population.

or living together, primigravida (52.5%) and had studied until elementary school (59.4%). From our sample, 40.6% were Catholic, 38.9% were Brazilian Protestants, and the rest answered another or no religion. A high proportion of the respondents were students (29.5%) and employed full- or part-time (35.2%). Only a small percentage (16.8%) reported smoking at least half a pack of cigarettes per day, and 94.7% responded that they did not drink alcohol even socially. A history of illicit drug use was observed in 2.8% of all respondents. A high percentage of our sample (55.3%) declared that pregnancy was unplanned, and 81.6% did not use condoms. Additional assessed demographics can be seen in ►**Table 2**.

Composite and Specific Scores Measured by Domains for PSRI

►**Fig. 3** shows the questions grouped by each domain and by each period, and the composite score for the PSRI specific score measurements before and during pregnancy in the studied population. As the options for the PSRI answers are graduated from minimal to maximal values, "0" is considered the worst and "100" the best. These values are the inverse of the KHQ, for which the answer options are graduated from "best" to "worse" values.

The score was categorized into quartiles by sexual response as follows: $0 < 25$ as "very bad," $25 < 50$ as "bad," $50 < 75$ as "good" and 75 to 100 as "excellent." Using this established quartile-categorized score for PSRI composite scores before and during pregnancy allowed us to accurately identify the quality of the answers of each domain and the sum of the domains of the composite score (►**Fig. 3**).

Influence of Pregnancy on Sexual Response as Evaluated by the PSRI

►**Table 3** shows the results of the specific and composite scores before and during pregnancy. During pregnancy, the specific scores were lower than before pregnancy in almost all of the PSRI domains (sexual activity frequency, arousal, orgasm, satisfaction, dyspareunia, intercourse start, female difficulties and male sexual satisfaction) ($p < 0.05$), thus suggesting a negative impact of pregnancy on sexual function response. A significant increase in the desire score was observed, but no significant difference in male sexual difficulties was shown between the periods. The composite score of sexual activity as evaluated by the PSRI showed a significant decrease from pre-pregnancy (mean score = 83 "excellent") to during pregnancy (mean score = 66 "good").

Discussion

Sexual function during pregnancy is an aspect of quality of life. The World Health Organization defined sexual health as "a state of physical, emotional, mental, and social wellbeing related to sexuality."[15] Sexual dysfunctions are defined as disorders related to both sexual desire and sexual satisfaction for several reasons.[16]

Pregnancy is a process of alteration experienced by women, and as a consequence, sexual life also changes during pregnancy,[17] although there is a lack of specific instruments in the literature to confirm the influence of pregnancy on sexual function. Many non-specific questionnaires to characterize this adjustment of sexual function in pregnant women have been published.[18] The FSFI questionnaire has been used to

PSRI Specific Score	
Before pregnancy	**During pregnancy**
Frequency score $FS = \frac{(Q14a - 1)}{2} x\ 100$	Frequency Score $FS = \frac{[(Q13 + Q14b + Q14c) - 3]}{6} x\ 100$
Desire Score $DS = \frac{(Q21a - 1)}{2} x\ 100$	Desire Score $DS = \frac{[(Q21b + Q22) - 2]}{4} x\ 100$
Arousal Score $AS = \frac{(Q18a - 1)}{2} x\ 100$	Arousal Score $AS = \frac{(Q18b - 1)}{2} x\ 100$
Orgasm Score $OS = \frac{(Q23a - 1)}{2} x\ 100$	Orgasm Score $OS = \frac{(Q23b - 1)}{2} x\ 100$
Satisfaction Score $SS = \frac{[(Q15a + Q17a) - 2]}{4} x\ 100$	Satisfaction Score $SS = \frac{[(Q15b + Q17b) - 2]}{4} x\ 100$
Dyspareunia Score $DyS = (Q24a - 1) x\ 100$	Dyspareunia Score $DyS = (Q24b - 1) x\ 100$
Intercourse Start Score $ISS = \frac{(Q25a - 1)}{2} x\ 100$	Intercourse Start Score $ISS = \frac{(Q25b - 1)}{2} x\ 100$
Female Difficulties Score $FDS = (Q19a - 1) x\ 100$	Female Difficulties Score $FDS = (Q19b - 1) x\ 100$
Male sexual satisfaction score $MSSS = \frac{(Q16a - 1)}{2} x\ 100$	Male sexual satisfaction score $MSSS = \frac{(Q16b - 1)}{2} x\ 100$
Male difficulties score $MDS = (Q26a - 1) x\ 100$	Male difficulties score $MDS = (Q26b - 1) x\ 100$
Composite Score* measurements $\textbf{Composite Score} = \frac{FS + DS + AS + OS + SS + DyS + ISS + FDS + MSSS + MDS}{10}$	
* The composite score must be applied for each period: before and during pregnancy. FS: Frequency sexual activity score; DS: Desire score; AS: Arousal score; SS: Satisfaction score; DyS: Dyspareunia score; ISS: Intercourse Start score; FDS: Female difficulties score; MSSS: Male sexual satisfaction score; MDS: Male difficulties score.	

Fig. 3 Pregnancy Sexual Response Inventory I composite and specific scores for each domain before and during pregnancy.

assess sexual function, showing low values in the third trimester.[19,20] However, it is essential to emphasize that the current and most frequent use of the FSFI is for non-pregnant women, for whom it was designed and validated. The PSRI is a specific questionnaire that was designed to consider the influence of pregnancy on sexual behavior using a self-evaluation before and during pregnancy. This differences in the design and drafting of the questionnaires need to be taken into account when considering the disparities in the results published in various articles, which result in a lack of consensus.

The findings presented here in our study using the PSRI indicate that the composite and specific scores for each

Table 3 Pregnancy Sexual Response Inventory composite and specific scores before and during pregnancy

Domains	Before pregnancy	During pregnancy	*p* Value
	Mean ± SD	Mean ± SD	
Frequency score	72.95 ± 28.63	43.83 ± 29.4	0.00 *
Desire score	48.58 ± 42.23	63.61 ± 27.7	0.02 *
Arousal score	79.18 ± 27.1	54.63 ± 31.56	0.00 *
Orgasm score	95.55 ± 16.57	72.95 ± 34.04	0.00 *
Satisfaction score	86.3 ± 19.68	64.06 ± 30.58	0.00 *
Dyspareunia score	89.68 ± 30.48	70.11 ± 45.86	0.00 *
Intercourse start score	85.23 ± 23.24	81.67 ± 24.5	0.01 *
Female difficulties score	92.52 ± 26.34	67.61 ± 46.88	0.00 *
Male sexual satisfaction score	82.74 ± 30.69	49.46 ± 40.85	0.00 *
Male sexual difficulties score	97.15 ± 16.66	95.73 ± 20.25	0.13
Composite score	82.99 ± 9.76	66.25 ± 15.14	0.00 *

Abbreviation: SD, standard deviation. *$P<0.05$.

domain and from prepregnancy to pregnancy were established. The scores were significantly different and categorized into quartiles by sexual response as follows: $0 < 25$ as "very bad," $25 < 50$ as "bad," $50 < 75$ as "good" and 75 to 100 as "excellent" for before and during pregnancy. The results indicated that lower composite and specific scores occurred during pregnancy than before pregnancy in almost all PSRI domains (sexual activity frequency, arousal, orgasm, satisfaction, dyspareunia, intercourse start, female difficulties and male sexual satisfaction).

These results may indicate the negative impact of pregnancy on sexual function response. However, some authors demonstrated no difference in general scores between the 1st and 2nd trimesters but a significant association between decreased intercourse frequency and trimesters.[4] Galazka et al (2015)[5] found that desire, arousal, lubrication, orgasm, satisfaction, pain and sexual activity frequency decrease as gestation advances. Most of our findings are in line with the recent literature, which characterizes the perinatal period by a low sex drive.[21,22] Women also seem to report higher levels of FSD female sexual dysfunction and low sexual desire, which is potentially associated with overall physical discomfort.[23,24]

Our results suggest that it is possible to quantitatively assess the impact of pregnancy on sexual response through score estimations before and during pregnancy, allowing comparisons of women's real sexual state during different pregnancy periods. As hypothesized, the PSRI scores could allow us to understand the influence of pregnancy on sexual health not only in qualitative but also in quantitative parameters for each domain. By using scores, clinicians can better plan and implement strategies and health programs targeted at improving sexual health for pregnant partners.

Identifying pregnant women who experience sexual distress and referring them to appropriate resources could help to minimize sexual and relationship problems during pregnancy.[25] These strategies are important not only for clinical assistance but also to teach and train undergraduates of medicine because most of them do not feel comfortable or confident, and they lack specific knowledge and skills to address questions related to sexual problems within pregnancy.[26]

Despite fears and myths about sexual activity during pregnancy, maintaining sexual interactions throughout the pregnancy and postpartum period can promote sexual health, well-being and a greater depth of intimacy. An open discussion about the expected changes in sexual health could provide guidance for couples, as well as promote rigorously designed, evidence-based studies to further elucidate our understanding of sexual function during pregnancy and postpartum.[27]

Although far from conclusive, these results are consistent with the hypothesis that a clinical diagnostic assessment using PSRI scores enables and facilitates an understanding of the current pregnancy sexual response and changes in sexual response before and during pregnancy. Our results, in particular, can indicate that clinical scores may represent a key strategy for implementing specific health programs to improve sexual health for pregnant partners.

As with many studies, it is important to consider the potential strengths and weaknesses of the clinical PSRI scores, as well as their use in further clinical practice and research implications.

The current study's strength relies on the use of a validated instrument to assess sexual function during pregnancy.[11] We acknowledge that using additional questionnaires to evaluate the sexual symptoms and quality of life of the participants could have enriched our study. Finally, the current study's limitations involve our sample, which mostly comprised heterosexual married women, which prevents our findings from being extrapolated to a broader population of pregnant women. More studies involving women of other social and cultural contexts are needed to confirm such findings. As the PSRI is a generic questionnaire, its value for pregnancy comorbidities should be investigated.

Despite these limitations, the current study advances the understanding of the inter-relationships between maternal sexual response before and during pregnancy. As such, our findings regarding the clinical scores for the potential classification of pregnant women's sexual dysfunction may have implications for evidence-based practice in preventative and intervention efforts, as well as in scientific study. The ultimate goal would be to implement early treatment and support (ideally before pregnancy) to improve the couple's sexual health outcomes. Further studies are needed to establish the cutoff score to be used to indicate normal sexual function during pregnancy and sexual dysfunction during pregnancy.

Nonetheless, there are several important clinical implications of our findings. First, the current study enriches the literature because a validated questionnaire can establish clinically meaningful scores, supporting the efforts of other nations to translate and apply such instruments in specific pregnancy comorbidities. Additionally, we can encourage healthcare providers to use the PSRI scores for composite and specific domains to determine the influence of pregnancy on each one of the sexual response domains. Finally, the PSRI is a unique validated instrument designed specifically to evaluate at the same time the sexual response before and during pregnancy.

The Brazilian Portuguese version of the PSRI is published within the current manuscript, which allows Portuguese speakers to administer the questionnaire during antenatal care. According to the results, pregnant women or couples would be referred to a sexologist.

Conclusion

This study allowed the establishment of PSRI composite and specific scores for each domain, between 0 and 100, and the categorization of scores into quartiles: very bad, bad, good and excellent. In addition, the Portuguese version of the PSRI is presented in full for application in the Brazilian population.

Contributors

Rudge C. V. C., Calderon I. M. P., Almeida A. P. M., Piculo F., Rudge M. V. C. and Barbosa A. M. P. contributed with the project and interpretation of data, writing of the article, critical review of the intellectual content and final approval of the version to be published.

Conflicts of Interest

No conflicts of interest have been declared by the authors.

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Which mode and potency of electrocoagulation yields the Smallest Unobstructed Area of the Fallopian Tubes?

Qual modo e potência produzem a menor área de não-obstrução nas tubas de Falópio?

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Abstract

Objective To determine which mode and potency of electrocoagulation, using a modern electrosurgical generator, yields the smallest unobstructed area of the Fallopian tubes.

Methods In an experimental study, tubes from 48 hysterectomies or tubal ligation were evaluated. Tubes were randomly allocated to one of the following groups: group A) 25 W x 5 seconds ($n = 17$); group B) 30 W x 5 seconds ($n = 17$); group C) 35 W x 5 seconds ($n = 18$), group D) 40 W x 5 seconds ($n = 20$); group E) 40 W x 5 seconds with visual inspection (blanch, swells, collapse) ($n = 16$); group F) 50 W x 5 seconds ($n = 8$). Bipolar electrocoagulation was performed in groups A to E, and monopolar electrocoagulation was performed in group F. Coagulation mode was used in all groups. Digital photomicrography of the transversal histological sections of the isthmic segment of the Fallopian tube were taken, and the median percentage of unobstructed luminal area (mm^2) was measured with ImageJ software (ImageJ, National Institutes of Health, Bethesda, MD, USA). The Kruskal-Wallis test or analysis of variance (ANOVA) was used for statistical analysis.

Results Ninety-six Fallopian tube sections were analyzed. The smallest median occluded area (%; range) of the Fallopian tube was obtained in the group with 40 W with visual inspection (8.3%; 0.9–40%), followed by the groups 25 W (9.1%; 0–35.9%), 40 W (14.2; 0.9–43.2%), 30 W (14.2; 0.9–49.7%), 35 W (15.1; 3–46.4%) and 50 W (38.2; 3.1–51%). No statistically significant difference was found among groups ($p = 0.09$, Kruskal-Wallis test).

Keywords
- tubal ligation
- fulguration
- occlusion

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Conclusion The smallest unobstructed area was obtained with power setting at 40 W with visual inspection using a modern electrosurgical generator. However, no statistically significant difference in the unobstructed area was observed among the groups using these different modes and potencies.

Resumo

Objetivo Determinar em qual modo e potência, usando unidades geradoras modernas de eletrocoagulação, produz a menor área de não-obstrução das tubas de Falópio.
Métodos Num estudo experimental, tubas uterinas derivadas de 48 histerectomias ou ligadura tubária foram avaliadas. As tubas foram alocadas aleatoriamente para um dos seguintes grupos: grupo A) 25 W x 5 segundos ($n = 17$); grupo B) 30 W x 5 segundos ($n = 17$); grupo C) 35 W x 5 segundos ($n = 18$), grupo D) 40 W, 5 segundos ($n = 20$); grupo E) 40 W x 5 segundos inspeção visual (branqueia, incha e colapsa) ($n = 16$); grupo F) 50 W x 5 segundos ($n = 8$). A eletrocoagulação bipolar foi usada nos grupos de A a E, e a eletrocoagulação monopolar, no grupo F. O modo de coagulação foi utilizado em todos os grupos. Cortes histológicos transversais do segmento ístmico das tubas de Falópio foram corados e fotografados digitalmente, e a percentagem da área luminal (mm^2) não-obstruída foi medida com o software ImageJ (ImageJ, National Institutes of Health, Bethesda, MD, USA). O teste de Kruskal-Wallis ou ANOVA foram usados para a análise estatística.
Resultados Noventa e seis cortes histológicos de tubas de Falópio foram analisados. A mediana da menor área não-obstruída (%; amplitude) da tuba de Falópio foi obtida no grupo 40 W com inspeção visual (8,3%; 0,9–40%), seguido do grupo 25 W (9,1%; 0–35,9%), 40W (14,2; 0,9–43,2%), 30 W (14.2; 0,9–49,7%), 35 W (15,1; 3–46,4%) e 50 W (38,2; 3.1–51%). Não houve diferença significativa entre os grupos ($p = 0,09$, teste de Kruskal-Wallis).
Conclusão A menor área não-obstruída foi obtida com a potência de 40 W com inspeção visual usando um gerador moderno de eletrocirurgia. Contudo, nenhuma diferença significativa na área não-obstruída foi observada entre os grupos usando esses modos e potências.

Palavras-chave
- ligadura tubária
- fulguração
- oclusão

Introduction

Tubal ligation is an effective form of permanent female contraception. In the world, it is the most commonly used method of permanent contraception selected by women aged between 15 and 49 who are married or in union.[1] In the United States, it is the second most commonly used form of contraception.[2] Among the different methods of tubal ligation, the monopolar electrocoagulation has the lowest long-term failure rate,[3] but has been associated with thermal injury to the bowel and is rarely used.[4] Laparoscopic bipolar coagulation is a safe technique according to the American College of Obstetricians and Gynecologists (ACOG) practice bulletin.[4] The ACOG recommends that at least 3 cm of the isthmic portion of the Fallopian tube must be completely coagulated.[4] According to Soderstrom et al,[5] they were able to verify that with 35 W of potency, 100% of the tubes had a complete occlusion of the lumen, while with 25 W, none of the tubes had a complete occlusion. Nonetheless, the 95% confidence interval (CI) of the data derived from Soderstrom et al[5] revealed a wide range in both groups: 100% (5 out of 5: 95% CI 56.6–100) using bipolar coagulation at 35 W, while zero cases had a total occluded area with 25 W (0 out of 5: 95% CI 0–43).

The use of inline ammeter has been advocated when tubal ligation is performed, since visual inspection is not accurate to identify the complete fulguration of the Fallopian tube.[5,6] The use of inline ammeter is not recommended or mentioned by the Brazilian Health Ministry[7] or the Brazilian Federation of Gynecologists and Obstetricians (FEBRASGO, in the Portuguese acronym).[8]

Modern electrosurgical generators (solid-state electrosurgical generators) provide constant power output by measuring the output voltage and current and adjusting the drive signal to compensate for changes in the equivalent load impedance.[9] Therefore, it is necessary to provide evidences that the current practice of tubal ligation without inline ammeter, using the bipolar mode in a modern electrosurgical generator, delivers enough energy to collapse the lumen of the Fallopian tube. The objective of this study is to determine which configuration and power setting of electrocoagulation, using a modern electrosurgical generator, yield the smallest unobstructed area of the Fallopian tubes.

Methods

Study Design and Setting

This experimental study took place between April 1st 2010 and December 30th 2011, at Hospital Femina located in Porto Alegre, Rio Grande do Sul, Brazil.

Fallopian Tubes

The Fallopian tubes were obtained from consecutive women who were scheduled for tubal ligation or hysterectomy for benign conditions. Subjects were invited to participate in the study and gave their written consent. The inclusion criteria consisted in normal Fallopian tubes and age $\leq$ 50 years-old. Those who had gynecologic cancer, hydrosalpinx, isthmic segment of the Fallopian tube $<$ 3 cm and abnormal anatomy of the Fallopian tube were excluded. These surgeries were performed by one of the authors (Campagnolo M.I.), or by another surgeon previously instructed about the protocol.

Randomization

The randomization list was generated by an online program (www.randomization.com) using blocks of four. The randomized list was kept in sequenced sealed envelopes, which were opened at the beginning of the surgery.

Intervention

During the procedure, each tube was randomly allocated to one of the following groups: group A) 25 W x 5 seconds; group B) 30 W x 5 seconds; group C) 35 W x 5 seconds; group D) 40 W x 5 seconds; group E) 40 W x 5 seconds visual inspection (blanch, swells, collapse); group F) 50 W x 5 seconds. All groups used the coagulation mode, because it is not possible to use the cutting mode in bipolar electrocoagulation. Bipolar electrocoagulation was applied in groups A to E, and monopolar electrocoagulation was performed in group F.

Electrocoagulation was performed in the coagulation mode using the WEM Model SS-501S electrosurgical generator (WEM Equipamentos Eletrônicos Ltda, Ribeirão Preto, SP, Brazil) with the Edlo bipolar forceps Ref. 14.1048 (EDLO, Canoas, RS, Brazil), or the Rhosse monopolar forceps Ref. 12231 (Rhosse, Ribeirão Preto, SP, Brazil). Bipolar coagulation of the tubes was performed on an auxiliary table after the uterus was removed. Due to the characteristics of the monopolar system, electrocoagulation of the Fallopian tubes was performed before the removal of the uterus. Monopolar coagulation has been considered the most efficient method, as described in the literature,[3] and was limited to eight samples.

Fulguration of the tubes was performed on 3 contiguous areas, at least 3 cm in length, as recommended in the literature.[10]

Outcome/Data Sources/Measurements

The mean occluded area of the Fallopian tube after fulguration in each group was the main outcome. This outcome was analyzed in terms of mm^2 and percentage of the transversal section of the Fallopian tube that was unobstructed. The time to achieve the collapse of the Fallopian tube in group E was analyzed in seconds. To analyze these variables, the coagulated tubes were resected and fixed in a formaldehyde (10%) solution and embedded in paraffin for histological analysis. The paraffin blocks were cut 4 µm thick and stained with hematoxylin and eosin.

The data sources were obtained after microscopic analysis of four transversal sections taken from each block. The section with the highest thermal injury, according to Soderstrom et al,[5] was chosen for digital photomicrography. Digital pictures were taken using an Olympus BX51 microscope (Olympus Optical Co., Tokyo, Japan) connected to a digital color camera/Q-Color 5 (Olympus, Waltham, MA 02453, USA). The images were obtained with a UPlanFI 4X objective lens (Olympus, Waltham, MA, USA) (resolution: 2.75 µm), at a size of 2,560 $\times$ 1,920 pixels (resolution: 1 mm = 590 pixels), under standard lighting conditions.

To reduce bias, each slide was coded, and the unobstructed area of the lumen was blindly analyzed for the outcomes (open luminal area in mm^2 and percentage of area that was open in the lumen). These outcomes were analyzed with ImageJ software, v1.43j (ImageJ; National Institutes of Health, Bethesda, MD, USA). Briefly, a circle was drawn around the lumen of the Fallopian tube. The outside area was cleared, and the image was converted into 8 bits. The image was adjusted for a threshold, using a dark background. Next, the region of interest (ROI) manager was activated and saved in a file. From the ROI manager, the software calculated the total and relative open area of the section.

Sample Size

The sample size was calculated based on data previously published[5] and using the formula described in the literature for superiority trial for continuous outcome.[11] The following parameters were used: an α error of 0.05, power of 0.8, median lumen occlusion (100%) using bipolar coagulation at 35 W, an expected reduction of the mean occluded area by 85% with lower potencies (25 W), and a standard deviation of 10. The standard deviation value was obtained from a pilot study in tubes that used visual fulguration. These figures yielded a sample size of a minimum of eight cases in each group.

Statistical Methods and Ethics

GraphPad Prism version 6 for Macintosh (GraphPad Software, Inc., San Diego, CA, USA) was used for statistical analysis of the variables, using the Kruskal-Wallis test. Gaussian distribution of the data was verified by the D'Agostino & Pearson omnibus normality test. Ethnicity was analyzed using descriptive statistics. This study was submitted and approved by the Research Ethics Committees of Hospital de Clínicas de Porto Alegre and Grupo Hospitalar Conceição, under the numbers 09–624 and 09–253, respectively.

Results

Fifty-nine women were invited to participate in the study, and 11 were excluded (6 had a short isthmic segment; 5 had abnormal anatomy of the Fallopian tube). Forty-eight women, that is, 96 Fallopian tubes were fulgurated; 88 were submitted to bipolar and 8 to monopolar coagulation. Four tubes were discarded after randomization for technical problems during

Table 1 Baseline characteristics of the studied population

Parameter	Group of fulguration settings						P^i
	25 W[a]	30 W[b]	35 W[c]	40 W[d]	40 Wv[e]	50 W[f]	
Age[g]	40.7(8)	37.6(7.7)	43.6(8.8)	37.1(8.2)	40.4(8.3)	40(4)	0.5
Gestations[g]	3.2(1.5)	2.9(1.5)	2.8(1.2)	3.3(0.9)	2.8(1.2)	1.5(1.7)	0.3
Parity[g]	3.2(1.5)	2.8(1.6)	2.5(1.3)	3.1(1.3)	2.6(1.1)	1.5(1.7)	0.4
Ethinicity[h]							
Caucasian	3	9	5	3	6	2	
Non-caucasian	11	2	3	5	2	2	
Tubes from							
Abd hysterec	5	4	4	3	0	8	
Vag hysterec	3	3	6	4	6	0	
BTL-Abdomen	8	10	7	12	9	0	
BTL-Vaginal	1	0	0	0	1	0	
BSO	0	0	1	1	0	0	
Total *n* of tubes	17	17	17	18	15	8	

Abbreviations: Abd hysterec., abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; BTL, bilateral tubal ligation; Vag hysterec., vaginal hysterectomy.
[a]25 W x 5 seconds—bipolar;
[b]30 W x 5 seconds—bipolar;
[c]35 W x 5 seconds—bipolar;
[d]40 W x 5 seconds—bipolar;
[e]40 W visual inspection—bipolar;
[f]50 W x 5 seconds—monopolar;
[g]numbers are given as means (standard deviation);
[h]each Fallopian tube of a patient was randomized to a different group;
[i]analysis of variance (ANOVA).

histopathology processing (one in the 35W, 2 in the 40W and 1 in the 40 W visual). The characteristics of the groups are depicted in ►**Table 1**.

The median [range] unobstructed area (mm^2) of each group was: A= 0.13 [0–3.96], B= 0.17 [0.01–3.3], C= 0.33 [0.03–4.61], D= 0.22 [0–3.53], E= 0.27[0.01–.45] and F = 0.94 [0.08–2.67]. No statistical significance was found ($p = 0.3$—Kruskal-Wallis test—►**Fig. 1A**). In contrast, the smallest median unobstructed area considering the percentage of the total area (%) of the Fallopian tube was obtained in group E (40 W visual inspection—8.3%; range from 0.9–40%), although no statistically significant difference was found among the groups ($p = 0.09$, Kruskal-Wallis test—►**Fig. 1B**). The mean (SD) time of coagulation for each grasp in group E was 3.8 (1) seconds. The largest median unobstructed area was obtained with the monopolar method with 38.2% (range 3.1–51%—►**Fig. 1B**). Examples of tubal occlusion with different power settings are depicted in ►**Fig. 2**.

Discussion

The new feature of modern electrosurgical generators, where constant electronic adjustments provide constant power through different tissue changes, leads us to investigate if total fulguration of the Fallopian tube, using different potencies and modes of fulguration settings presented herein, could be achieved without the use of an inline ammeter.

We were not able to find any statistical difference among groups. The bipolar mode, independently of the wattage used, yielded a median occluded area of 85% or more, while the 40 W with visual inspection provided around 92% of occlusion. Occlusion of the luminal area close to 0% (0– 1%) was observed in one sample of the 25 W group (0%), one in the 30 W (0.9%), one in the 40 W (0.7%) and one in the 40W visual inspection (0.9%). These findings may be explained by the high-peak bursts that desiccate the outer layers of the tube too quickly and prevents the deep penetration of the energy. This phenomenon may explain the smallest coagulation area (around 61%) obtained with monopolar coagulation, which used 50W.

Based on our findings, it seems reasonable to follow the international recommendations to use an inline ammeter, which is incorporated with most bipolar generators in the US, to confirm total occlusion.[5,12] This recommendation is based on a review of 2,267 procedures done before 1987, where failures on tubal ligation were observed.[13] In 1989, Soderstrom et al,[5] using 5 tubes derived from hysterectomy, demonstrated that bipolar system using 35 W in the coagulation mode yielded complete coagulation of the Fallopian tube. Likewise, using 20 tubes, complete coagulation of the Fallopian tube was obtained with 25 W in the cutting mode. These results were based on an old Kepplinger and Valleylab generators.[5]

Modern electrosurgical generators have electronic adjustments, which provide constant power through different

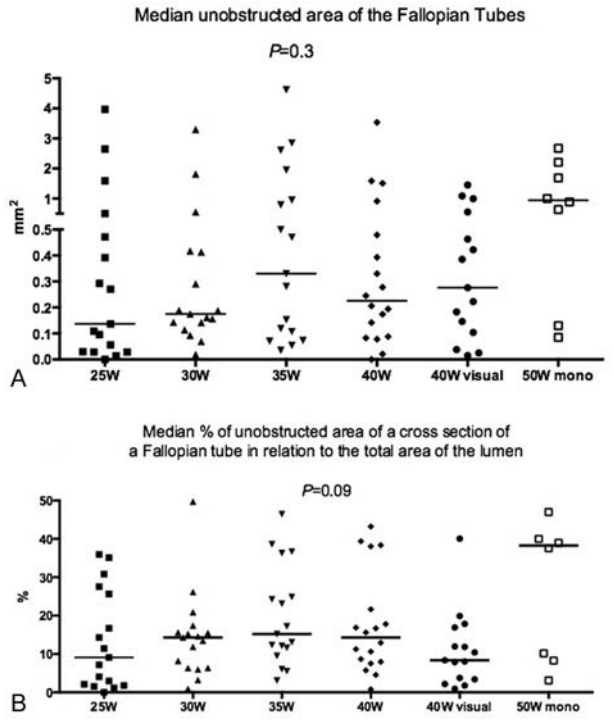

Fig. 1 Median area (**A**) and percentage of the total area (**B**) of a transversal section of the Fallopian tube that was unobstructed by different configurations and power settings (W). The bars represent the median value. The statistical analysis was performed using the Kruskal-Wallis test. The area was calculated using ImageJ software. Mono: monopolar fulguration.

tissue changes, and can offer up to 40 W. These new electrosurgical generators have a computer-controlled tissue feedback response system that senses tissue impedance and corrects the energy flow.[14] In contrast, modern electrosurgical generators do not offer "pure cut" in the bipolar mode, thus the use of an inline ammeter seems to be necessary to indicate when the current through the Fallopian tube has ceased flow.

Unfortunately, an inline ammeter is not sold in Brazil, and the only orientation given by the Brazilian Health Ministry and other institutions, such as the Brazilian Federation of Gynecologists and Obstetricians (FEBRASGO, in the Portuguese acronym), is that the procedure should be performed with bipolar mode.[7,8] This lack of details could be related to the report that bipolar coagulation system is highly effective for bilateral tubal ligation, if a segment of $\geq$ 3 cm is coagulated.[13]

The strengths of this study are the calculated sample size and the use of ImageJ software to quantify the unobstructed area of the Fallopian tube. Using an α error of 0.05 and data on unobstructed area (mm^2), post-hoc analysis revealed a power of 95.7% comparing groups 40 W visual inspection *vs* 50 W and 94.2% comparing 40 W *vs* 50 W. ImageJ provides an unbiased quantification of the open area, and this approach and this approach is likely to be superior to visual inspection.[15] Initially, we used the histological grading described by Soderstrom et al,[5] but the high inter- and intraobserver variation (data not shown) led us to use the ImageJ software, a widely used software for this and other purposes.[16–19]

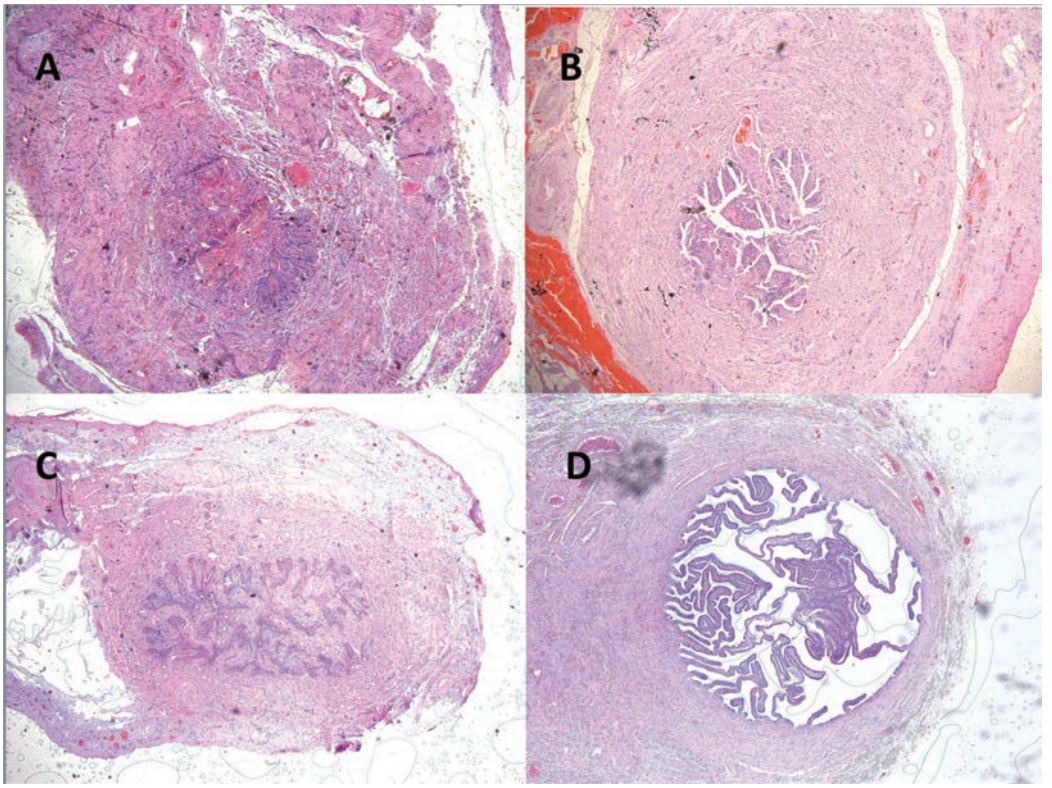

Fig. 2 Photomicrograph of representative sections stained with hematoxylin & eosin. Total occlusion of the Fallopian tube using 25 W (**A**) and 40 W visual (**C**). Partial occlusion of the lumen of the Fallopian tube using 40 W (**B**); inadequate occlusion of the lumen of the Fallopian tube using monopolar fulguration at 50 W (**D**). Magnification was 200x.

The main weakness of the study is the degree of thermal injury. The histological analysis was done after the electrocoagulation was performed. It has been shown that complete occlusion may take up to 8 weeks to occur.[20] Therefore, our data may underestimate the real rate of the tubal occlusion. Another minor weakness is the lack of external validity. Just one electrosurgical generator was used, so no extrapolations can make to other models.

Although no significant difference was found among the groups, the mean occluded area was higher in the monopolar mode, and this was an unexpected finding. This study brings new data about the monopolar occlusion rate at 50 W, which was thought to be the best method for tubal occlusion. Different settings for tubal fulguration, such as lower wattage and longer time, may be sought to reach the best occlusion rate without using an inline ammeter. A low-cost alternative for the Brazilian population may be the use of an ammeter plier in one of the cables of the bipolar.

Conclusion

In summary, the modern electrosurgical generator used herein yielded a similar degree of damage on the Fallopian tube independently of the configuration and power setting used, and none of these settings reached a mean occluded area of 100%.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Contributions

Campagnolo M. I., Reis R., Santos M. O., Kliemann L. M. and Savaris R. F. contributed with project and interpretation of data, writing of the article, critical review of the intellectual content and final approval of the version to be published.

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External Quality Monitoring of the Cervical Cytopathological Exams in the Rio de Janeiro City

Monitoramento externo da qualidade dos exames citopatológicos cervicais na cidade do Rio de Janeiro

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Abstract

Objective To discuss the implementation and contributions of the External Quality Monitoring in the city of Rio de Janeiro and to analyze the performance of the main providers of cervical cytopathology in this city from September 2013 to March 2017, here referred to as "Alpha laboratory" and "Beta laboratory."

Methods Observational, cross-sectional, retrospective study using information from the Cervical Cancer Control Information System (SISCOLO, in the Portuguese acronym), municipal coordination module, External Quality Monitoring report. The proportions of false positives, false negatives, unsatisfactory samples and rejected samples were estimated. The agreement among the observers was analyzed through the Kappa index and the reduction of disagreements in the period for each laboratory studied, comparing the results of each cycle.

Results A total of 19,158 examinations were selected, of which 19,130 (99.85%) were monitored, 16.649 (87, 03%) were reviewed by the External Quality Monitoring Unit, 2,481 (12,97%) were rejected and 441 (2,65%) were considered unsatisfactory. The "Beta laboratory" presented excellent concordance in all cycles; the "Alpha laboratory" had good concordance in the first two cycles (K = 0.76 and 0.79), becoming excellent in the following four cycles. The average Kappa index was 0.85, with median of 0.86. The percentage of diagnostic disagreement was 6.63% of the reviewed exams, of which 5.38% required a change of conduct

Conclusion External Quality Monitoring is an exercise in diagnostic improvement, and its implementation was fundamental to ensure the reliability of the cytopathological exams in the city of Rio de Janeiro.

Keywords
- quality control
- cytodiagnosis
- uterine cervical neoplasms
- mass screening

Resumo

Objetivo Discutir a implementação e as contribuições do Monitoramento Externo da Qualidade na cidade do Rio de Janeiro e analisar o desempenho dos principais

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provedores de citopatologia cervical nessa cidade no período de setembro de 2013 a março de 2017, aqui denominado "laboratório Alfa" "e" "laboratório Beta."

Métodos Estudo observacional, transversal, retrospectivo, utilizando informações do Sistema de Informação de Controle do Câncer do Colo do Útero (SISCOLO), do módulo de coordenação municipal, e do relatório de Monitoramento da Qualidade Externa. As proporções de falsos positivos, falsos negativos, amostras insatisfatórias e amostras rejeitadas foram estimadas. A concordância entre os observadores foi analisada através do índice Kappa bem como a redução de divergências no período para cada laboratório estudado, comparando os resultados de cada ciclo.

Resultados Foram selecionados 19.158 exames, dos quais 19.130 (99,85%) foram monitorados, 16.649 (87, 03%) foram revisados pela Unidade de Monitoramento da Qualidade Externa, 2.481 (12,97%) foram rejeitados e 441 (2,65%) foram considerados insatisfatório. O "laboratório Beta" apresentou excelente concordância em todos os ciclos; o "laboratório Alfa" apresentou boa concordância nos 2 primeiros ciclos ($K = 0,76$ e 0,79), tornando-se excelente nos 4 ciclos seguintes. O índice Kappa médio foi de 0,85, com mediana de 0,86. O percentual de discordância diagnóstica foi de 6,63% dos exames revisados, dos quais 5,38% necessitaram de mudança de conduta.

Conclusão O Monitoramento Externo da Qualidade é um exercício de aprimoramento diagnóstico, e sua implementação foi fundamental para garantir a confiabilidade dos exames citopatológicos no município do Rio de Janeiro.

Palavras-chave
- controle de qualidade
- citodiagnóstico
- neoplasias do colo do útero
- triagem em massa

Introduction

With ~ 530,000 new cases per year worldwide, cervical cancer is the fourth most common form of cancer among women, accounting for the deaths of 266,000 women per year.[1] In Brazil, it is the third most frequent type of cancer, with an adjusted mortality rate for the world population of 4.98 per 100 thousand women in 2015.[2] A total of 16,370 new cases are estimated for the 2018/2019 period, 490 in the Rio de Janeiro city.[3]

It is possible to reduce the incidence and mortality due to cervical cancer with early detection through screening, diagnostic confirmation and treatment of precursor lesions in a timely manner. The strategy used in Brazil for its screening is cytopathologic examination of the uterine cervix in women aged 25 to 64 years, with intervals of 3 years, after 2 negative annual tests.

The specific clinical course to be adopted based on the results of these tests is based on the Brazilian Nomenclature for Cervical Cytopathological Reports[4] and must follow the recommendations of the Brazilian Guidelines for the Screening of Cervical Cancer, reviewed in 2016.[5]

With the development of the Cervical Cancer Control Information System (SISCOLO, in the Portuguese acronym) in 1999, in a partnership between the National Cancer Institute José Alencar Gomes da Silva (INCA, in the Portuguese acronym) and the Information Technology Department of the Unified National Health System (DATASUS, in the Portuguese acronym), it became possible to manage and monitor cervical cancer control actions throughout the country. The SISCOLO allows the preparation of reports, among them the External Quality Monitoring (MEQ, in the Portuguese acronym).[6]

Through the analysis of the MEQ, it was observed that most of the Brazilian laboratories present quality indicators of the cervical cytopathological exam outside the recommended standards.[7,8] This test presents a variable sensitivity, mainly due to the subjectivity of the analysis, which can cause intra- and interobserver errors. As a strategy to ensure the continuous improvement of the quality of cervical cytopathology, the Ministry of Health proposed the implementation of MEQ, which consists of a review of the cytopathological exams by a laboratory other than the one that performed the first reading.[9,10]

In Brazil, the concern with the quality of these examinations was made official with ministerial order nº. 79, of July 6, 1998,[11] joint ministerial order Nº. 92, of 2001,[12] the National Program for the Control of Cervical and Breast Cancer, launched on March 22, 2011[13] and the Federal decree nº. 3,388 of December 30, 2013.[14]

The MEQ in Municipality of Rio de Janeiro (MRJ, in the Portuguese acronym) was implemented in 2013 following the recommendations made by INCA. The flow was agreed between representatives of the Primary Care Superintendency, the Cancer Technical Area Management (GCA, in the Portuguese acronym).) and the External Quality Monitoring Unit (UMEQ, in the Portuguese acronym), with adaptations over the years for the needs identified posteriorly.

At each cycle, between the fifth and tenth working days of the current month, the municipal coordination sends the "External Quality Monitoring File" and the "list of exams to be reviewed" to the UMEQ, and the "list of exams to be reviewed" to the monitored laboratory.

The monitored laboratory delivers the slides listed to the UMEQ within 10 days (from the receipt of the list), and the

slides are packed in appropriate and labeled transport boxes, organized in ascending numerical order and in correspondence with the copies of the reports. The carton must be completely filled, void spaces are filled with bubble wrap or similar so there is no loss of sequence during transport.

The UMEQ reviews the exams within 30 calendar days (preanalytical, analytical and postanalytical phases), which can be extended to 45 days if there are more than 2,500 exams to be reviewed, considering the technical limit of 2,500/month established by it. At the end of the review, the UMEQ returns all the slides with identification of the discordant ones (clinically relevant) accompanied by the reports of the MEQ.

If there is interest of the monitored laboratory, because it does not comply with the UMEQ report, a consensus meeting must be held for joint analysis of the discordant cases, to be scheduled by the monitored laboratory, sending to the UMEQ an Excel listing and the slides to be analyzed within 5 working days prior to the meeting.

Once the definitive reports have been released, the UMEQ prepares the final report and generates the files "Exports and Outpatient Production Report (BPA, in the Portuguese acronym) of the MEQ," closing the corresponding competence, and sends them to the Municipal Health Secretariat of Rio de Janeiro (SMS-RJ, in the Portuguese acronym).

The municipal coordination evaluates the new reports and sends them to the General Coordinators of Primary Care of the Planning Areas (CAPs, in the Portuguese acronym), assigning to the Primary Health Care Units (APS, in the Portuguese acronym), for active search, a list of women with an indication to repeat cytopathological exam or colposcopy, according to the MEQ result. This list is accompanied by a personalized invitation letter, prepared by the Technical Area of Cancer Management, in agreement with the UMEQ and the monitored laboratories, clarifying to the women about the quality control process and requesting their attendance at the APS to perform a new exam of control or be scheduled to the secondary reference unit. In cases of repetition of the exam, the GCA send to the units the definitive results to be registered, informed and delivered after counseling with an attending professional.

Three units of secondary referral in cervical pathology in the city of Rio de Janeiro participated in the process welcoming women with a change of diagnosis after MEQ for diagnostic investigation, with a schedule made by the management of the cancer technical area. Until 2016, this schedule was made by e-mail, being included in the Regulation Center System (SISREG, in the Portuguese acronym) in 2017. Parallel to the scheduling, the GCA sends to the secondary unit the nominal listing, results (original and MEQ) and guidelines regarding the reception of these women.

From September 2013 to March 2017, it was possible to improve the External Quality Monitoring, increase the number of cycles, strengthen the partnerships involved in the process, evaluate the performance in the cervical cytopathology diagnosis of the two main laboratories contracted that provide this service to the public primary health care units in the city of Rio de Janeiro, discuss the difficulties in the process and their contributions to the quality line of cervical cancer care.

The objective of this study was to present the experience of the city of Rio de Janeiro in the performance of the MEQ from September 2013 to March 2017, and the performance of the participating laboratories, analyzing the interobserver agreement, proportions of unsatisfactory exams, rejected samples, false-negative and false-positive tests over time.

Methods

A descriptive, observational, cross-sectional, retrospective study was performed using information from the SISCOLO, municipal coordination module of Rio de Janeiro, MEQ report of the cervical samples evaluated by the two main laboratories that provide this service to the public primary health care network in the city of Rio de Janeiro and the exams reviewed by the UMEQ.

The sample consisted of 16,649 records of cervical cytopathological examinations performed by the participating laboratories, reviewed in the MEQ, from September 2013 to March 2017, including all the exams entered in SISCOLO in this period. Those inserted in the period after March 2017 and those that were not included in this database were excluded.

The data was collected from the synthetic reports of each MEQ using aggregate records of the results of the monitored laboratory and review.

The cytopathological examinations of the cervix were considered as rejected when they were outside the minimum criteria necessary for the UMEQ review; unsatisfactory when reading was impaired by the presence of acellular or hypocellular material ($<$ 10% of the smear); when there was presence of blood, pyocytes, drying artifacts, external contaminants or intense cellular superposition, not allowing a diagnostic conclusion normal;[9–15] when results were within the limit of normality; when there was inflammation, benign cellular alterations and when they were positive according to the Brazilian Nomenclature for Cytopathological Reports.[9]

Discordant exams, with a change of diagnostic category implying a change in clinical behavior after the execution of the MEQ, were classified as: false negatives, those whose monitored laboratory classified as normal or benign alteration, and after the review, the result was atypical squamous cells of unknown significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells, cannot rule out high-grade squamous intra-epithelial lesion (ASC-H), more severe or unsatisfactory results and false-positive results when the monitored laboratory defined the outcome as ASC-US, LSIL, ASC-H or more severe outcomes and, after review, the report was unsatisfactory, normal, or benign. Cases with change in diagnosis without causing change in clinical behavior were also considered discordant.

For the analysis of agreement among the observers, based on each MEQ performed, the Kappa (K) index was used. The statistical method Kappa is divided into six categories, according to ►**Table 1**.

The proportions of false positives, false negatives, unsatisfactory samples and rejected samples were estimated, as well as the reduction of disagreements for each laboratory.

Table 1 Kappa (K) interpretation

Kappa interpretation	
K = 1	Perfect agreement
0.80 < K < 1	Excellent agreement
0.60 < K < 0.80	Good agreement
0,40 < K < 0.60	Moderate agreement
0 < K < 0.40	Poor agreement
K = 0	No agreement

Source: Landis and Koch (1977).[16]

After the collection and analysis of the records of the SISCOLO Synthetic Quality External Monitoring Reports, the information was tabulated in a Microsoft Excel (Microsoft Corp., Redmond, WA, USA) spreadsheet.

All information extracted from the system was analyzed and considered in secrecy, maintaining their anonymity, in order not to entail risks and damages to the participants. The project was approved by the Research Ethics Committee of the Municipal Health Secretariat of Rio de Janeiro on 08/29/2017-CAAE 70812117.6.0000.5279.

Results

Between September 2013 and March 2017, 12 cycles of MEQ of cervical cytopathology were performed in the city of Rio de Janeiro, with the participation of the two main laboratories contracted, here called "Alpha laboratory" and "Beta laboratory," with six cycles each.

A total of 19,158 exams were selected by SISCOLO, of which 19,130 (99.85%) were monitored, 16,649 (87.03%) were reviewed by the UMEQ, 2,481 (12.97%) were rejected and 441 (2.65%) were considered unsatisfactory (►**Table 2**).

The concordance between observers (monitored laboratory and reviewer) was evaluated using the statistical method Kappa (K), with a mean of 0.85 and median of 0.86 showing excellent agreement. The "Beta laboratory" presented excellent agreement in all MEQs, with Kappa ranging from 0.85 to 0.89. The "Alpha laboratory" presented good agreement (Kappa from 0.76–0.78) in 2 cycles of the 2015 MEQ, becoming excellent in the last cycle of the 2015 MEQ, 2016 and 2017, with Kappa varying from 0.81 to 0.92 (►**Table 3**). Of the 16,650 examinations reviewed, there was concordance in 15,546 (93.40%), and disagreement in 1,104 (6.63%), of which 895 (5.38%) indicated a change of conduct (►**Table 3**).

Of the 441 (2.65%) unsatisfactory results, the UMEQ diagnosed 11 (0.06%) atypical epithelial changes (2.5%), 5 (0.00%) in the "Beta laboratory" and 6 (0.00%) in the "Alpha laboratory" (►**Figs. 1** and **2**).

The highest percentage of agreement between observers in the 2 monitored laboratories was observed between the normal results and benign alterations—7,438 (92.54%) in the "Beta laboratory, 3,146 (86.64%) in the" Alpha laboratory—and the highest diagnostic disagreement occurred in the results of atypical glandular cells (AGC), 164 (61.88%) and 21 (43.75%), respectively (►**Figs. 1** and **2**).

In 4 out of 8 (50%) invasive carcinoma results, the "Beta laboratory" was in disagreement with the UMEQ regarding the results of 2 high-grade squamous intraepithelial lesion (HSIL) and 2 HSIL/HSIL microinvasion without change of care conduct. In the "Alpha Laboratory" there was 100% agreement (►**Figs. 1** and **2**).

Table 2 Records of the external reports of Quality External Monitoring (SISCOLO) with selected results, monitored results, revised results, unsatisfactory results, rejected samples and their percentages, by laboratory and monitoring cycle

Laboratory Monitoring cycle	SRs n	MRs n (%)	RRs n (%)	URs n (%)	RSs n (%)
BETA laboratory 092013	1,933	1,930 (99.84)	1,632 (84.56)	44 (2.70)	298 (15.44)
BETA laboratory 042014	771	768 (99.61)	738 (96.09)	42 (5.69)	30 (3.91)
BETA laboratory 122014	3,339	3,333 (99.82)	1,421 (42.63)	34 (2.39)	1,912 (57.37)
BETA laboratory 102015	2,041	2,041 (100.00)	1,996 (97.80)	20 (1.00)	45 (2.20)
BETA laboratory 012016	4,007	4,005 (99.95)	3,886 (97.03)	75(1.93)	119 (2.97)
BETA laboratory 032017	1,796	1,795 (99.94)	1,773 (98.77)	23 (1.30)	22 (1.23)
ALPHA laboratory 012015	433	433 (100.00)	427 (98.61)	9 (2.11)	6 (1.39)
ALPHA laboratory 042015	1,201	1,200 (99.92)	1,170 (97.50)	29 (2.48)	30 (2.50)
ALPHA laboratory 092015	1,168	1,168 (100.00)	1,154 (98.72)	24 (2.08)	15 (1.28)
ALPHA laboratory 012016	546	546 (100.00)	544 (99.63)	7 (1.29)	2 (0.37)
ALPHA laboratory 052016	1,208	1,197 (99.09)	1,195 (99.83)	17 (1.42)	2 (0.17)
ALPHA laboratory 012017	715	714 (99.86)	714 (100.00)	20 (2.80)	0 (0.00)
Total	19,158	19,130 (99.85)	16,650 (87.03)	344 (2.07)	2,481 (12.97)

Abbreviations: MRs, monitored results; RSs, rejected samples; RRs, revised results; SISCOLO, Cervical Cancer Control Information System (in the Portuguese acronym); SRs, selected results; URs, unsatisfactory results.

Table 3 Concordance in the results of cervical cytopathological examinations and disagreement with change of conduct by laboratory and monitoring cycle

Laboratory monitoring cycle	Concordant n (%)	Discordant n (%)	Discordant with change of conduct n (%)	Total	Kappa
BETA laboratory 092013	1,551 (95.04)	81 (4.96)	74 (4.53)	1,632	0.88
BETA laboratory 042014	682 (92.41)	56 (7.59)	39 (5.28)	738	0.85
BETA laboratory 122014	1,327 (93.38)	94 (6.62)	73 (5.14)	1,421	0.84
BETA laboratory 102015	1,863 (93.34)	133 (6.66)	106 (5.41)	1,996	0.87
BETA laboratory 012016	3,666 (94.34)	220 (5.66)	180 (4.63)	3,886	0.87
BETA laboratory 032017	1,681 (94.81)	92 (5.19)	83 (4.68)	1,773	0.88
ALPHA laboratory 012015	367 (85.95)	60 (14.05)	46 (10.77)	427	0.76
ALPHA laboratory 042015	1,050 (89.74)	120 (10.26)	93 (7.95)	1,170	0.79
ALPHA laboratory 092015	1,086 (94.11)	68 (5.89)	56 (4.85)	1,154	0.88
ALPHA laboratory 012016	503 (92.46)	41 (7.54)	31 (5.70)	544	0.82
ALPHA laboratory 052016	1,083 (90.63)	112 (9.3)	89 (7.45)	1,195	0.81
ALPHA laboratory 012017	687 (96.22)	27 (3.78)	23 (3.22)	714	0.92
Total	15,546 (93.40)	1,104 (6.63)	895(5.38)	16,650	0.85

Review Laboratory / Monitored Laboratory	Unsatisfactory	Normal	Benign changes	ASC-US	ASC-H	LSIL	HSIL	HSIL/HSIL-MICROINVASIVE	Epidermoid cancer	AGC-US	AGC-H	AIS	Invasive adenocarcinoma	Atypical undifined cells*	Atypical undifined cells**	Other neoplasm	Reject sample	Total samples	Total samples excluding rejected
Unsatisfatory	227	2	28	4	0	0	0	0	0	1	0	0	0	0	0	0	51	313	262
Normal	0	38	290	3	1	0	0	0	0	0	0	0	2	0	0	0	56	390	334
Benign changes	11	94	7400	126	10	45	7	0	0	8	1	0	1	0	0	0	1627	9330	7703
ASC-US	0	0	123	1188	74	260	17	0	0	15	2	0	0	0	4	0	358	2041	1683
ASC-H	0	0	3	17	175	4	82	3	0	2	2	0	1	0	0	0	63	352	289
LSIL	0	0	7	33	10	572	52	1	0	0	0	0	0	0	0	0	142	817	675
HSIL	0	0	3	0	13	5	174	4	1	1	0	0	0	0	0	0	41	242	201
HSIL/HSIL-microinvasive	0	0	0	1	1	0	9	14	0	0	0	0	0	0	0	0	10	35	25
Epidermoid cancer	0	0	0	0	0	0	2	2	4	0	0	0	0	0	0	0	3	11	8
AGC-US	0	0	24	59	11	3	4	0	0	89	6	1	0	1	8	0	68	274	206
AGC-H	0	0	2	0	15	0	12	2	0	4	12	9	0	0	3	0	7	66	59
AIS	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1
Invasive adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Atypical undifined cells*	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Atypical undifined cells**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other neoplasms	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	238	134	7880	1431	310	889	359	26	5	120	23	11	4	1	15	0	2426	13872	11446

Fig. 1 Synthetic external monitoring report produced by the cervical cancer information system (SISCOLO). Distribution of cytopathological results diagnosed by the review laboratory and the monitored laboratory (Beta), from September 2013 to March 2017.
Abbreviations: ASC-US, atypical squamos cells of undetermined significance not possible High grade lesion, ASC-H: atypical squamos cells of undetermined significance cannot exclude High grade lesion, LSIL: low grade squamous intrapithelial lesions, HSIL: High grade squamous intrapithelial lesions, HSIL/HSIL-microinvasor: High grade squamous intrapithelial lesions with suspeccious of microinvasion, AGC-US, atypical glandular cells of undetermined significance; AGC-H, atypical glandular cells cannot exclude high-grade glandular lesion; AIS, endocervical adenocarcinoma in situ; AI, adenocarcinoma invasor. *atypical undifined cells of undeterminated significance not possible high grade lesion; **atypical undifined cells of undeterminated significance cannot exclude high grade.

Review Laboratory / Monitored Laboratory	Unsatisfactory	Normal	Benign changes	ASC-US	ASC-H	LSIL	HSIL	HSIL-HSIL-MICROINVASIVE	Epidermoid cancer	AGC-US	AGC-H	AIS	Invasive adenocarcinoma	Atypical undifined cells*	Atypical undifined cells**	Other neoplasm	Reject sample	Total samples	Total samples excluding rejected
Unsatisfatory	*104*	0	69	3	1	1	1	0	0	0	0	0	0	0	0	0	1	180	179
Normal	0	*8*	30	0	0	1	0	0	0	0	0	0	0	0	0	0	0	39	39
Benign changes	2	29	*3138*	33	11	20	5	0	0	2	0	0	0	0	0	0	10	3250	3240
ASC-US	0	1	159	*854*	28	127	14	0	0	13	0	0	0	0	0	0	5	1201	1196
ASC-H	0	0	7	12	*97*	2	42	0	0	2	0	0	1	0	1	0	1	165	164
LSIL	0	0	1	21	7	*213*	16	0	0	1	0	0	0	0	0	0	1	260	259
HSIL	0	0	0	0	9	0	*60*	3	0	0	0	0	0	0	0	0	1	73	72
HSIL/HSIL-microinvasive	0	0	0	0	0	0	1	*4*	0	0	0	0	0	0	0	0	0	5	5
Epidermoid cancer	0	0	0	0	0	0	0	0	*1*	0	0	0	0	0	0	0	0	1	1
AGC-US	0	0	11	6	0	0	0	0	0	*24*	1	0	0	0	1	0	0	43	43
AGC-H	0	0	0	0	1	0	1	0	0	0	*3*	0	0	0	0	0	0	5	5
AIS	0	0	0	0	0	0	0	0	0	0	0	*0*	0	0	0	0	0	0	0
Invasive adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	0	*0*	0	0	0	0	0	0
Atypical undifined cells*	0	0	0	0	0	0	0	0	0	0	0	0	0	*0*	0	0	0	0	0
Atypical undifined cells**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	*0*	0	0	0	0
Other neoplasms	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	*0*	0	1	1
Total	106	38	3415	929	154	364	140	7	1	42	4	0	2	0	2	0	19	5223	5204

Fig. 2 Synthetic external monitoring report produced by the cervical cancer information system (SISCOLO). Distribution of cytopathological results diagnosed by the review laboratory and the monitored laboratory (Alpha), January 2015 to January 2017.
Abbreviations: ASC-US, atypical squamos cells of undetermined significance not possible High grade lesion, ASC-H: atypical squamos cells of undetermined significance cannot exclude High grade lesion, LSIL: low grade squamous intrapithelial lesions, HSIL: High grade squamous intrapithelial lesions, HSIL/HSIL-microinvasor: High grade squamous intrapithelial lesions with suspeccious of microinvasion, AGC-US, atypical glandular cells of undetermined significance; AGC-H, atypical glandular cells cannot exclude high-grade glandular lesion; AIS, endocervical adenocarcinoma in situ; AI, adenocarcinoma invasor. *atypical undifined cells of undeterminated significance not possible high grade lesion; **atypical undifined cells of undeterminated significance cannot exclude high grade.

From the 1,683 (14.7%) ASC-US results from the "Beta laboratory," the UMEQ diagnosed 17 (0.14%) as HSIL, 17 (0.14%) as AGC and 4 (0.03%) as atypical undetermined cells; in 1,196 (22.9%) ASC-US results of the "Alpha laboratory," the UMEQ diagnosed 14 (0.02%) as HSIL and 13 (0.02%) as AGC. In 675 (5.8%) LSIL results from the "Beta laboratory," the UMEQ diagnosed 52 (0.45%) as HSIL, 10 (0.08%) as ASC-H and 1 (0.00%) as HSIL/HSIL microinvasion; and in 259 (4.97%) results of the "Alpha laboratory," the UMEQ diagnosed 16 (0.30) as HSIL, 7 (0.01%) as ASC-H and 1 (0.00%) as AGC. In these cases, there was delay in the care delivery according to the established recommendations (►**Figs. 1** and **2**).

The 209 (1.83%) false-negative results from the Beta laboratory were distributed in 133 (1.16%) ASC-US, 45 (0.39%) LSIL, 11 (0.10%) ASC-H, 7 (0.06) HSIL, 10 (0.08%) AGC and 3 (0.03%) invasive adenocarcinoma, and in the "Alpha laboratory, there were 78 (1.50%) false-negative results, with 36 (0.69%) cases of ASC-US, 22 (0.42%) LSIL, 12 (0.23%) ASC-H, 6 (0.12%) HSIL, 2 (0.04) AGC (►**Figs. 1** and **2**).

The 162 (1.42%) false-positive results from the Beta laboratory were distributed in 123 (1.07%) ASC-US, 3 (0.03%) ASC H, 7 (0.06) LSIL, HSC and 26 (0.23%) AGC, and in the "Alpha laboratory" were 178 (3.42%) being 159 (3.06%) ASC-US, 7 (0.13%) ASC-H, 1 (0.02%) LSIL, 6 (0.12%) HSIL and 2 (0.04%) AGC (►**Figs. 1** and **2**).

There was a change in clinical behavior in 895 (5.38%) of the 1,104 (6.63%) results with a discordant diagnosis from 2013 to 2017. In the "Beta laboratory" 555 (5.91%) clinical conduct changes occurred in 676 (5.91%) discordant results. Of these, 178 (1.56%) were false-negative results that should have repeated cytology in 6 to 12 months; 31 (0.27) were false-negative results that should have performed colposcopy; 162 (1.42%) were false-positive results that required only the recommended screening and 11 (0.10%) were negative reports given on unsatisfactory slides that should have been collected again in 6 to 12 weeks. In the "Alpha laboratory," there were 338 (6.50%) changes in clinical behavior in the 428 (8.22%) discordant results. Of these, 58 (1.11%) were

false-negative results that should have repeated the cytology in 6 to 12 months, 20 (0.38%) were false-negative results that should have performed the colposcopy, 178 (1.42%) were false positives that only needed the recommended screening and 2 (0.10%) were negative reports given on unsatisfactory slides that should have been collected again in 6 to 12 weeks (►**Figs. 1** and **2**).

Discussion

The implementation of the MEQ of the cervical cytopathological exams in the city of Rio de Janeiro followed the recommendations from INCA, started in 2013. The participation of the laboratories was progressive, and the joint work was decisive to overcome the difficulties encountered. Since then, the MEQ has been performed systematically.

The diversity of methods used for the MEQ in other countries, the peculiarity of the model adopted in Brazil and the little literature on the subject make it difficult to compare with the results obtained by other authors.

The UMEQ evaluation process had three phases: preanalytical, analytical and postanalytical, which defined the examinations reviewed or rejected for nonconformities, unsatisfactory, false negatives and false positives.[9]

A total of 19,130 cervical cytopathological exams were monitored at the 2 participating laboratories, with rejection of 2,481exams (12.97%), which were not reviewed by the External Quality Monitoring Unit (UMEQ) for presenting unconformities. Considering the whole sample, this indicator was well above the acceptable level (0.1%),[9] and was strongly influenced by the performance of the "Beta laboratory," which showed rejection of 2,426 out of 13,872 monitored tests (17.49%), and mainly in the third cycle, in which 1,912 out of 3,333 examinations were rejected (57.37%). Educational interventions were performed, which resulted in a drop in the rejection percentage of this laboratory to 1.23% in the last cycle studied. This fact reinforces the importance of the actions of permanent education, quality assurance of the cervix cytopathological exam. The "Alpha laboratory" presented rejection of 55 out of 5,258 tests (1.05%), not impacting the result of this indicator.

Of the 16,650 cervix cytopathological exams reviewed by the UMEQ in the period, 441 (2.65%) were considered unsatisfactory, of which 239/ out of 11,446 (2,08%) came from the "Beta laboratory," and 179 out of 5,203 (3.43%) came from the "Alpha laboratory." This indicator remained within the acceptable limit (5%), with the exception of only the third cycle of the "Beta laboratory" (5.69%). In this regard, the results found in the present study were better than the results described in studies performed in Mato Grosso do Sul (11.4%), Goiânia (21.0%), and São Paulo (3.8%) and were surpassed only by studies performed in Paraná (1.8%).[17–20] This data may reflect the good technical quality of the team performing the cervix cytopathological exams in the Municipal Units of Primary Health Care, the continuing education and effectiveness of the External, Internal Quality Monitoring program in improving the quality of these exams.

The performance of each participating laboratory was assessed based on the agreement between observers (Kappa index) and the discordant test percentage estimated in the MEQ cycles. It was observed that the concordance between observers (monitored laboratory/UMEQ) of the "Beta laboratory" remained excellent in all cycles of the studied period. In the "Alpha laboratory" the agreement was good in the first two cycles of MEQ, becoming excellent in the following cycles. A progressive and significant improvement in agreement between the "Alpha laboratory" and UMEQ was observed over time.

In this study, the reviewers were aware of the initial report, which may have influenced the analyses.[8,21] The report was made from the records of the External Synthetic Monitoring Report presenting the results of 16 categories of cytopathological diagnosis of the cervix.[9]

The median K index of the MEQ cycles in the city of Rio de Janeiro in this study was 0.86, coming close to the K indexes of the states of Paraná (0,88)[20] São Paulo (0.80),[19] corroborating the quality warranty of the reliability of cervix cytopathological exams performed by the laboratories evaluated.[19,20]

The percentage of diagnostic disagreement in the reviewed examinations was 6.63, of which 5.38% required a change of conduct. Despite the low percentages,[20] educational interventions are necessary because of their clinical impact. They were found predominantly in the results of squamous and glandular atypia of undetermined significance, in which the interobserver variability is greater, there is greater difficulty in defining the diagnosis, increasing the chance of false-negative and false-positive results. In the case of glandular atypia, the clinical implications are very relevant, as it requires a specific clinical management and it is related to more serious diseases.[21]

The delay in the care delivery according to the defined recommendations was observed in a small percentage in both laboratories 0.15%.

The false-negative results of both laboratories predominated in the ASC-US category with low percentages,[18,19] especially in cases of greater clinical relevance (postconsensus diagnosis of HSIL or more severe lesion), tending to decrease with cycles. These results have a great impact on screening programs, which may result in loss of follow-up, delaying the early diagnosis of precursor lesions of cervical cancer.[10]

The false-positive results presented their highest percentages in the ASC-US category, and although they were low,[20] the "Beta laboratory" showed a tendency towards an increase in the incidence of false positives, while the "Alpha laboratory" showed a significant reduction. This reduction is important and necessary to avoid unnecessary diagnostic investigation, causing physical and emotional harm to women, undue occupation of places in specialized procedures, overloading and honoring health services.[22]

Diagnostic discordance leads to changes in clinical behavior that directly impact on quality of care and screening programs.

The results of false diagnoses are due to inadequate collection, technical failures in fixation, staining of the samples and errors in reading and interpretation of

cytomorphological criteria, being more frequent in the border diagnosis, which involves greater subjectivity (ASC-US, ASC- H, AGC).[10,22] To minimize these issues, the professionals who work in the primary care units carry out training and retraining; the monitored laboratories adopted measures to improve their infrastructure, internal quality control in all stages of the process (sampling, analysis and delivery of the final result), participation in the MEQ and meetings to discuss the discordant cases, contributing to the standardization of cytomorphological criteria, reducing interobserver variability. The UMEQ provided the monitored laboratories with a report with detailed pre and postanalytical evaluation data, CD images of discordant diagnoses, recommendations for improvements that should be implemented, and participated in the continuing education of professionals involved in the process.

Our results showed a good performance of the participating laboratories. However, there is a need to reduce the percentage of rejected samples, discordant results with change of conduct and false-positive results through the systematization of MEQ and continuing education.

One difficulty encountered in the management of MEQ was the lack of reports of experience regarding the way the second outcome was communicated to women with change of behavior, the strategy of calling and selecting the secondary referral units, ensuring reception and counseling. The understanding of the process by these women was fundamental, and not one case of non-acceptance or ethical questioning was registered.

Conclusion

The implementation of the MEQ has increased the efficiency of the process involved in cytopathological examinations of the cervix and consequently in the screening and early detection of cervical cancer. Our results revealed that this process was an important diagnostic improvement exercise, and its performance in a systematic way had a direct impact on the quality of the cytopathological exams performed by the participating laboratories. The continuing education of professionals, and the continuity of process monitoring were the main strategies that ensured the progressive improvement of the quality and reliability of these exams in the scope of the Unified National Health System (SUS, in the Portuguese acronym), contributing to the qualification of care in the line of care of cervical cancer in the city of Rio de Janeiro. Ethical and responsible behavior throughout the process, especially in the active pursuit of women to change behavior, was critical in the quality of care.

Contributors
Rocha V. S. O., Malfacini S. S., Gomes A. M. and Rocha C. R. M. declared to have contributed with the conception of the study, collection, and tabulation, critical review, drafting of the manuscript and final approval of the version to be published.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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Cervical Cancer Registered in Two Developed Regions from Brazil: Upper Limit of Reachable Results from Opportunistic Screening

Câncer de colo de útero registrado em duas regiões desenvolvidas do Brasil: limite superior de resultados alcançáveis a partir do rastreamento oportunístico

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Abstract

Objective The aim of this study was to assess the time trends and pattern of cervical cancer diagnosed in the period from 2001 to 2012 by means of an opportunistic screening program from two developed regions in Brazil.

Methods An observational study analyzing 3,364 cancer records ($n = 1{,}646$ from Campinas and $n = 1{,}718$ from Curitiba region) available in hospital-based cancer registries was done. An additional 1,836 records of CIN3/AIS from the region of Campinas was analyzed. The statistical analysis assessed the pooled data and the data by region considering the year of diagnosis, age-group, cancer stage, and histologic type. The Cochran-Armitage trend test was applied and *p-values* < 0.05 were considered significant.

Results The total annual cervical cancer registered from 2001 to 2012 showed a slight drop (273–244), with an age average of 49.5 y, 13 years over the average for CIN3/AIS (36.8 y). A total of 20.6% of the diagnoses (1.6% under 25 y) were done out of the official screening age-range. The biennial rate of diagnoses by age group for the region of Campinas showed an increase trend for the age groups under 25 y ($p = 0.007$) and 25 to 44 y ($p = 0.003$). Stage III was the most recorded for both regions, with an annual average of 43%, without any trend modification. There was an increasing trend for stage I diagnoses in the region of Campinas ($p = 0.033$). The proportion of glandular histologic types registered had an increased trend over time ($p = 0.002$), higher for the region of Campinas (21.1% versus 12.5% for the region of Curitiba).

Keywords
- cervical cancer
- cervical intraepithelial neoplasia
- preventive medicine
- public health
- epidemiology

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Conclusion The number, pattern and trends of cervical cancer cases registered had mild and slow modifications and reflect the limited effectivity of the opportunistic screening program, even in developed places.

Resumo

Objetivo Avaliar as tendências temporais e padrão de diagnóstico de câncer de colo de útero (CCU) através de programa de rastreamento oportunístico em duas regiões brasileiras desenvolvidas, no período de 2001 a 2012.

Métodos Estudo observacional com 3.364 registros de câncer ($n = 1.646$ da região de Campinas e $n = 1.718$ da região de Curitiba) obtidos de sistemas de registro hospitalar de câncer. Para a região de Campinas foram analisados 1.836 registros adicionais de CIN3/AIS. A análise estatística avaliou os dados agrupados e por região considerando o ano de diagnóstico, grupo etário, estágio de câncer e tipo histológico, e utilizou o teste de tendência Cochran-Armitage com valor $p < 0,05$.

Resultados O total anual de CCU registrado no período de 2001 a 2012 apresentou uma ligeira queda (273 para 244), com idade média de 49,5 anos, 13 a mais que a idade média (36,8 anos) para CIN3/AIS. O total de diagnósticos realizados fora da faixa etária oficial de rastreamento foi 20,6% (1,6% abaixo de 25 anos). Houve uma tendência de aumento de casos nas faixas etárias inferior a 25 anos ($p = 0,007$) e de 25 a 44 anos ($p = 0,003$) para a região de Campinas. Ambas as regiões apresentaram maior proporção diagnósticos de câncer em estágio III (43% em média), sem modificação de tendência. Houve tendência crescente para diagnóstico em estágio I na região de Campinas ($p = 0,033$) e da proporção de tipos histológicos glandulares em ambas regiões ($p = 0,002$), 21,1% para a região de Campinas e 12,5% para Curitiba.

Conclusão O número, o padrão e as tendências dos casos registrados de câncer de colo de útero apresentaram modificações pequenas e lentas ao longo do tempo, reflexo da efetividade limitada do programa de rastreio oportunista, mesmo em locais desenvolvidos.

Palavras-chave
- câncer de colo de útero
- neoplasia intraepitelial cervical
- medicina preventiva
- saúde pública
- epidemiologia

Introduction

Cervical cancer (CC) is a preventable neoplasia with known etiology and precursor lesions of slow evolution, able to be screened.[1] Screening in Brazil is based on cytology for women from 25 to 64 years old, and is performed every 3 years, after two consecutive negative annual tests, and is currently available for the entire country with different degrees of access, depending on the region.[2] The Brazilian screening program is considered opportunistic, with no control over the screened population, resulting in limited impact on the incidence and mortality from this type of cancer.[3] The official estimate is 16,340 new cases in 2016, one of the most prevalent types of cancer, but with great regional variability.[4,5]

Currently, an important amount of information about cancer available for the Brazilian population comes from the Hospital-Based Cancer Registries (HCRs) system, which started working in the late 1990s.[6] This information is considered consistent and being used by the Brazilian National Cancer Institute (INCA, in the Portuguese acronym) to audit and plan health care assistance.[6]

The cities of Campinas (São Paulo State [SP]) and Curitiba (Paraná State [PR]), located respectively in the Southeast and South of Brazil, administer two major metropolitan areas, with high human development indexes (HDIs) of 0.805 and 0.823, respectively.[7] The region of Campinas has 82 cities with 5.5 million people, and the region of Curitiba has 95 cities with a population of 5.1 million.[8,9] Both regions represent around 5% of the Brazilian population. Both main cities keep their cancer centers in hospitals where treatment is available and have had HCRs since 2000. Regions covered for both main cities have a well-developed network available for primary health care as part of the Brazilian Public Health System (SUS, in the Portuguese acronym), in which cytological screening of CC is available. Routinely, cases with suspicion of high-grade intraepithelial lesion or CC are referred to specialized centers, often regional.

Therefore, the aim of this study was to assess the time trends and pattern of CC diagnosed in the period from 2001 to 2012 at the comprehensive hospitals for cancer management of the regions of Campinas (SP) and Curitiba (PR), and evaluate the changes related to opportunistic screening in a scenario of socioeconomic development.

Methods

This was an observational study with information collected from HCRs of SUS Regional Hospitals related to CC management

between January 2001 and December 2012. Hospitals from cities of Campinas (SP) and Curitiba (PR) were considered.

We considered all records with the C53 disease classification code (CC) in the 10th revision of the International Classification of Diseases (ICD-10) and patients aged $\geq$ 15 years, totalizing 3,875 subjects. Histological types considered were squamous cell carcinoma (SCC), adenocarcinoma (AC) and adenosquamous carcinoma (ASC), in accordance with the International Classification of Diseases for Oncology (ICD-O).[10,11] The cases excluded were uncommon histological types less detectable by screening or secondary cancers ($n = 58$), and all cases arising from cities outside the official regions coverage for Campinas and Curitiba ($n = 453$).[8,9]

Therefore, 3,364 records were analyzed, 1,646 from Campinas and 1,718 from Curitiba. Additionally, we evaluated a series of 1,836 cervical intraepithelial neoplasia grade 3 (CIN3) or adenocarcinoma in situ (AIS) by age group, registered at same period, from regional hospital of Campinas region, as a reference to compare with cancer data.

Statistical Analysis

The longitudinal pattern rates of the diagnoses registered between 2001 and 2012 was analyzed according to period (biennial), age-group (up to 25 y, 25–64 y - the age range of official cytological screening program in Brazil, and more than 64 y), International Federation of Gynecology and Obstetrics (FIGO, in the Portuguese acronym) stage, and histologic type (World Health Organization [WHO] classification).[2,11,12] The Cochran-Armitage trend test was applied by region of care, and by aggregate data, using the SAS 9.2 program (SAS Institute Inc., Cary, NC, USA), and p values < 0.05 were considered significant.[13]

This study followed the regulatory standards of the National Health Council of Brazil and was approved by the local ethics committee of each institution (CAAE 38524914.1.0000.5404).

Results

The CC registries analyzed by region had similar proportions for almost all variables (year, age group, cancer stage, and histology), with some punctual differences observed in cancer stage and histological type (►**Table 1**).

The age group distribution of cancer showed a similar pattern in both regions, with a peak around 45 to 49 y. The age average for the total aggregate was 49.5 y (15–97), 13 years later than the 36.8 y age average for CIN3 or AIS (distribution peak around 30 years) available for the region of Campinas.

The total annual cases of cancer registered and the breakdown by region showed a slight drop during the period studied, from 273 cases in 2001 to 244 cases in 2012 (Years 2001–2012: Campinas 141–133 cases, Curitiba 132–111 cases). For the region of Campinas, the number of cases of CIN3 and AIS registered yearly over time was compared with the cancer registries and showed a trend towards increase (121 cases in 2001 and 177 cases in 2012, $p < 0.001$) (►**Fig. 1**, dotted line).

Table 1 Distribution of cervical cancer cases registered by region according to some parameters

Parameter	Campinas	Curitiba	Total aggregate
	n (%)	n (%)	n (%)
Year			
2001–2002	319 (19.4)	289 (16.8)	608 (18.1)
2003–2004	264 (16.0)	316 (18.4)	580 (17.2)
2005–2006	271 (16.5)	292 (17.0)	563 (16.7)
2007–2008	292 (17.7)	266 (15.5)	558 (16.6)
2009–2010	240 (14.6)	285 (16.6)	525 (15.6)
2011–2012	260 (15.8)	270(15.7)	530 (15.8)
Age group (year)[a]			
< 25	25 (1.5)	29 (1.7)	54 (1.6)
25–44	537 (32.6)	679 (39.5)	1,216 (36.2)
45–64	712 (43.3)	743 (43.3)	1,455 (43.3)
> 64	372 (22.6)	266 (15.5)	638 (19.0)
Stage (FIGO)			
I	585 (36.1)	415 (31.6)	1,000 (34.1)
II	171 (10.5)	308 (23.5)	479 (16.3)
III	751 (46.3)	521 (39.7)	1,272 (43.3)
IV	115 (7.1)	69 (5.3)	184 (6.3)
Missing information	24	405	429
Histologic type			
Squamous cell	1,299 (78.9)	1,502 (87.4)	2,801 (83.3)
Adenocarcinoma	277 (16.8)	198 (11.5)	475 (14.1)
Adenosquamous	70 (4.3)	18 (1.0)	88 (2.6)
Total	1,646 (100.0)	1,718 (100.0)	3,364 (100.0)

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.
[a]1 case missed for Curitiba region.

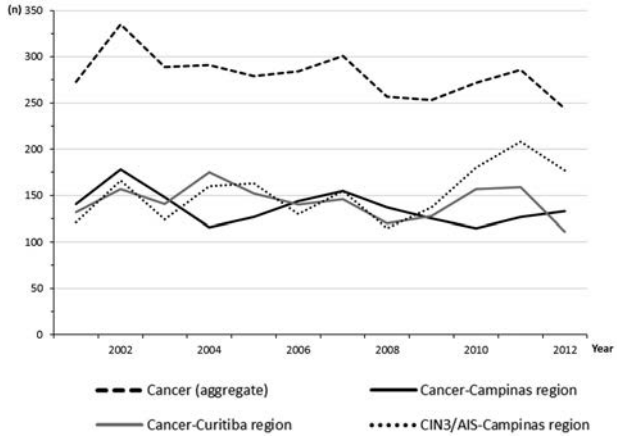

Fig. 1 Number of women with cervical cancer and cervical intraepithelial neoplasia grade 3 (CIN3) or adenocarcinoma in situ (AIS) registered yearly, total (aggregate) and by region.

The trend in detection of cancer by age group in the region of Campinas showed an increase in the number of cases at ages under 25 years ($n = 2$ or 0.6% in 2001–2002 to $n = 8$ or 3.1% in 2011–2012, $p = 0.007$) and 25 to 44 years ($n = 91$ or 28.5% to $n = 103$ or 39.6%, $p = 0.003$). There was a decreasing trend for diagnoses in the age group 45 to 64 years (from $n = 143$, or 44.8%, to $n = 96$, or 36.9%, $p = 0.008$) and maintained trend in age 65 years or more ($n = 83$, or 26.0%, to $n = 53$, or 20.4%, $p = 0.306$) (►**Fig. 2A-B**). While the same pattern was observed for the aggregate data, the region of Curitiba showed no significant changes in trend during the period studied (►**Fig. 2C**).

There was 13% rate of missing information about cancer clinic stage for the region of Curitiba. Stage III was the most recorded for both regions, without any modification trend over the period evaluated, with an annual average of 43% (37–55) (►**Table 1** and ►**Fig. 3A**). For the region of Campinas, a significant increasing trend of proportion for stage I at diagnosis was observed, with 32% ($n = 99$) in 2001 to 2002 and 40% ($n = 103$) in 2011 to 2012 ($p = 0.033$) (►**Fig. 3A**), and the absolute numbers for stages II-IV were $n = 208$ in 2001 to 2002 and $n = 157$ in 2011 to 2012.

The histological types distribution over time showed a similar pattern for both regions, with significant trend to increase diagnoses of glandular cancer (adenocarcinoma [AC] or atypical squamous cell [ASC]) and decreasing squamous cell carcinoma (SCC). The proportion of glandular cancer changed from 15.0 (in 2001–2002) to 21.1% (for 2011–2012) ($p = 0.002$), more evident in the region of Campinas (from 21.6%–26.2%) than in Curitiba (from 7.6%–16.3%) (►**Fig. 3B**).

Discussion

The annual rate of diagnoses of CC registered in the referral hospitals from two developed Brazilian regions showed a slight drop in the period from 2001 to 2012. Most cases of cancer recorded were in the age group 45 to 64 years and at stage III. There were increasing trends in proportion of diagnoses below 45 years and cancer with glandular histology. In the region of Campinas, we observed an increasing trend of cancer diagnosed in stage I compared with stages II to IV.

Screening programs with periodic cytology aim to detect precursor lesions and reduce the incidence of cancer and mortality rates. After their implementation and with maintenance over time, the number of cancer cases may decrease gradually, depending on the level of organization. The initial effect expected is diagnosis in advance, with detection of neoplasia in younger women and at early stages, and then, increasing diagnosis of CIN3. After this, a greater impact on histological type SCC compared with AC should be observed.[14,15]

In this study, there was a small and slow decline in the number of cancer cases registered, although it was consistent and in both regions. This pattern is similar to previously reported results of cytological screening and mortality in Brazil.[5,16]

Another factor related to the positive impact of screening on CC observed in these regions is the opposite pattern of CIN3 or AIS records, available for the region of Campinas, with significant upward trend in diagnostics, one of the main goals of screening programs.[14,15]

The region of Curitiba showed no significant changes by age group, and the changes observed at total aggregate data

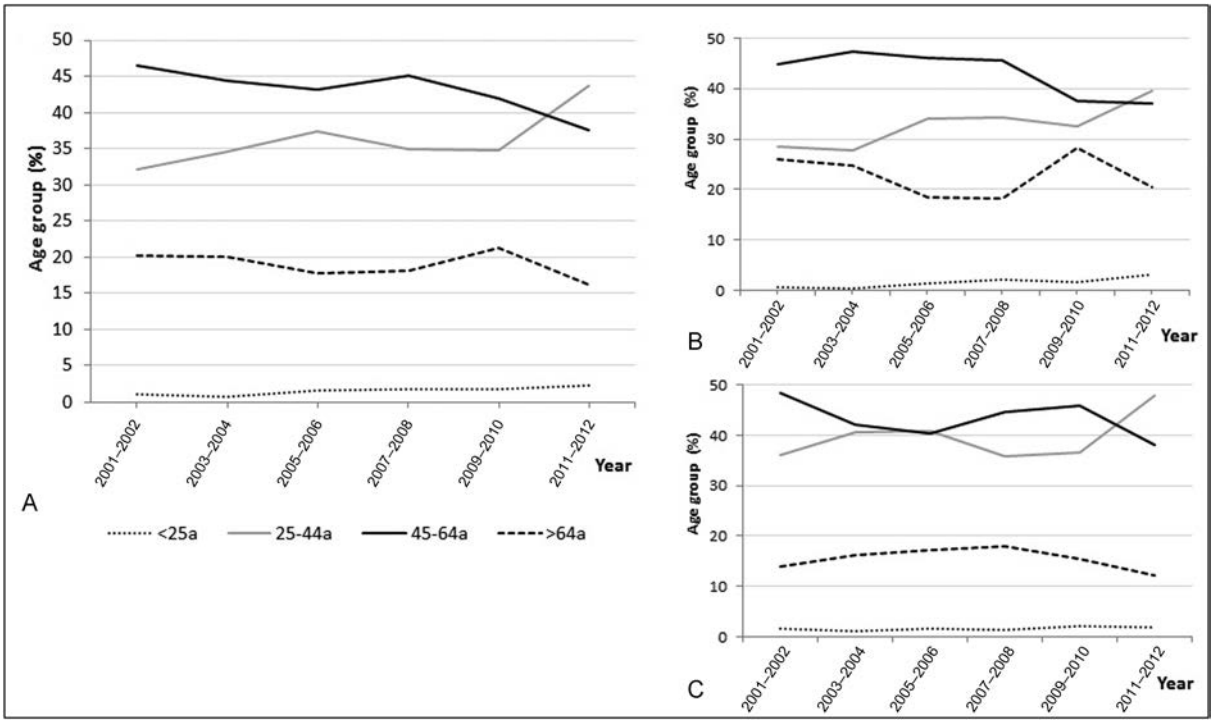

Fig. 2 Biennial percentage distribution of cervical cancer registered between 2001 and 2012, by age-group and region (A = Total aggregate; B = Campinas; C = Curitiba).

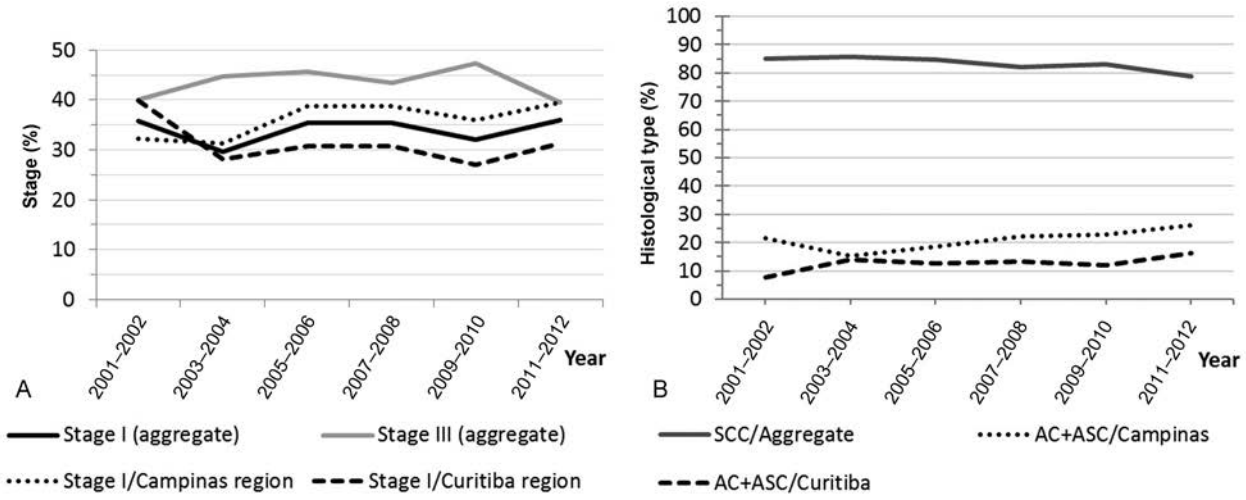

Fig. 3 Biennial percentage distribution of cervical cancer registered in the period from 2001 to 2012 by (**A**) cancer stage according to the International Federation of Gynecology and Obstetrics (FIGO, in the Portuguese acronym), (**B**) histological type (SCC: Squamous cell carcinoma; AC: adenocarcinoma; ASC: adenosquamous carcinoma) and region.

were due to changes from the region of Campinas. The region of Campinas showed a significant trend for increased diagnoses in those patients younger than 45 years and decreased cases between 46 and 64 years, demonstrating a possible anticipation of diagnosis. On the other hand, both regions exhibited 19 to 22% of cases of cancer registered after 64 years of age, which is the upper age limit for the Brazilian Screening Program and with no trend changes, maybe indicating lower effectivity (or coverage) of the screening program at earlier ages. In general, almost all women who had cervical cancer after 64 years-old had not performed a standard screening before. Brazilian guidelines advise 2 to 3 negative pap tests in the past 10 years to stop the screening.

Comparing both regions, the trend for CC registered below 25 years observed in Campinas region draws attention. In Brazil, the routine screening begins at age 25, and a report based on regional data from the state of São Paulo referring to the period from 2000 to 2009, stated that only 1% of all CC cases was recorded below 25 years.[2] Besides, the biennial number of CC cases under 25 years is low, our study indicates that this number tends to increase over time, especially in the region of Campinas. Maybe it reflects the cultural and behavioral characteristics. A published study with Brazilian adolescents and young adult women, including both cities of Campinas and Curitiba, showed a high prevalence of high-risk HPV infection.[17] Our findings add information for a possible revision in the Brazilian program regarding the age to start the screening, as it has already happened in other countries, such as USA, England, Germany, Denmark and Sweden.[18,19]

Regarding the cancer stage, there was a high percentage of cases in stage III, around 40% for both regions, a pattern consistent with lack of screening effectivity.[20] Only the region of Campinas showed an increasing trend for diagnoses in stage I, compatible with a certain anticipation of diagnosis.

Historically, the epidemiology about histological type of CC trend to change overtime as consequence of cervical sampling technique, that are more representative of ectocervix than endocervix, resulting in a greater impact on detection of squamous premalignant lesions compared with glandular neoplasia.[14,15] Similarly, our results indicate progressive changes for both regions in the proportion of glandular epithelium cancers (AC or ASC) over time. Campinas region that changed glandular histology from 22 to 26% in the period from 2001 to 2012, a proportion considered high and found in countries after decades of effective screening.[14,15]

Although this study presents some limitations, such as lack of information about tumor stage in 23% of the cases registered in the region of Curitiba, the information analyzed can be considered as an adequate representation of the women assisted by the SUS. Another point to clarify is the coverage of the SUS assistance and the representativeness of the data evaluated. The regions studied have had an important economic development and up to 50% of their populations has had access to private health care assistance for some periods. Nevertheless, there are few services out of the SUS to care for women with CC, and the hospitals studied remain as the main reference centers until now. The HCR from each hospital has dedicated professionals and record information from 100% of the assisted cases, indicating that the data analyzed here have significant power to provide consistent and useful information to support future action. Further studies are essential to confirm our findings.

In summary, both regions exhibited positive changes, some of them remarkable, perhaps as result of the strong commitment to control this cancer observed in the health care system of these regions. Still, the results are modest but encouraging and reflect the lack of organization of these programs. While the Brazilian Ministry of Health states that the country has a national organized screening program and shows numbers of cytology performed annually sufficient to cover 90% of the target population of the program, the reality is different. There is a high proportion of cytologies performed outside the target age group and at shorter intervals, usually annual intervals,

resulting in a real coverage not exceeding 30%, as reported by Freitas et al,[21] for the region of Campinas in 2003. Most of the cytologies performed have no impact on this type of cancer, and this is reflected in the results presented in this study, typical of opportunistic programs.

It should be evident that additional efforts are needed and must be directed to correct what is missing so far: an individual population registration system for preventive health actions that can be fed and checked continuously. After that, the next step would be just the surveillance and effective communication with women who deviate from the planned screening protocol. The positive cases would call for the reassessment of other steps, including quality control of laboratories that perform cytology exams.[3,22]

Based on the Brazilian history in this field, it may take a few decades for an effective action to take place and, unfortunately, thousands of women will succumb to this preventable disease, since the current program is not able to detect most of the cases at curable stage. In the near future, the time will come to screen vaccinated women, and a positive and impactful effect on the incidence of CC will require an organized program, with individual registries and an adequate quality control of the various steps involved, or conversely, the potential of the vaccination program that Brazil is doing maybe also be put at risk.

Our data exhibited the limitations of an opportunistic screening, notably a stagnation of the impact over time to decrease the number of cancer cases and mortality, while maintaining a high proportion of diagnosis in advanced stages. In this study, there was a maintenance trend for diagnoses in stage III, around 40% for the 2 regions, confirming the limitation of the local programs, although an increased trend for cancer detection in stage I has been observed in the region of Campinas.

Conclusion

The cases of CC registered for both regions had mild and slow positive modifications, more evident in the region of Campinas, with an increased number of cases of CIN3 or AIS, trend for more diagnoses in younger patients, those in stage I, and cases of glandular neoplasia. The results observed are modest and can be considered as an indicator of the reachable upper limit of effectiveness expected by an opportunistic screening program. Additional efforts should be directed to organize the program, and further studies are essential to confirm our findings.

Contributions

Teixeira J. C., Maestri C. A., Machado HC, Zeferino L. C. and Carvalho N. S. contributed with the project and interpretation of data, writing of the article, critical review of the intellectual content and final approval of the version to be published.

Conflicts of Interest

The authors have no conflicts of interest regarding this manuscript.

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Breastfeeding and the Benefits of Lactation for Women's Health

Aleitamento materno e seus benefícios para a saúde da mulher

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Abstract

The offer of the maternal breast to the baby is an unquestionable right of mothers and their children, and all efforts should be made to promote, follow and maintain exclusive breastfeeding for up to 6 months and supplement it until the child completes 2 years of age. Many publications are available in the literature about the qualities of breast milk, its benefits and health repercussions, stimulating the practice of breastfeeding and supporting campaigns for its implementation. However, although it is widely known that breastfeeding is an important step in the reproductive process of women and its practice offers benefits to both mother and child, most of the available information highlights the benefits of breast milk for children, while mention of the effects of breastfeeding on the health of the mother is usually neglected. Thus, the objective of the present study is to highlight the multiple benefits of breastfeeding for the physical and emotional health of the nursing mother. The authors consulted articles published in the databases PubMed, Virtual Health Library and Web of Science using the keywords breastfeeding, breast milk, lactation and maternal health.

Keywords
- breastfeeding
- breast milk
- postpartum period

Resumo

A oferta do seio materno às crianças é um direito inquestionável das mães e de seus filhos, e todos os esforços devem ser feitos no sentido de promover, acompanhar e manter o aleitamento materno exclusivo até os 6 meses e complementado até que a criança complete 2 anos de idade. A literatura apresenta incontáveis publicações acerca das qualidades do leite materno, seus benefícios e repercussões para a saúde, estimulando a prática do aleitamento materno e embasando campanhas. Porém, mesmo sendo de conhecimento geral que a amamentação é uma importante etapa no processo reprodutivo da mulher e que sua prática oferece benefícios para mãe e filho, a grande maioria das informações destacam os benefícios que o leite materno oferece às crianças, esquecendo-se de mencionar todas as repercussões que o aleitamento materno traz para a saúde da mãe. Assim, o objetivo deste artigo é destacar os inúmeros benefícios que o aleitamento materno proporciona à saúde física e emocional da lactante. Para tanto, os autores consultaram artigos publicados nas bases de dados PubMed, Biblioteca Virtual de Saúde e *Web of Science* utilizando as palavras-chave aleitamento materno, leite materno, lactação e saúde materna.

Palavras-Chave
- aleitamento materno
- leite materno
- período pós-parto

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Introduction

The offer of the mother's breast to her baby is a biologically and ethically unquestionable right of both mother and child and is of fundamental importance for the survival and quality of life of the nursing baby during its first years of life. Today, the benefits of breastfeeding are considered not to be limited to the duration of the practice, but to extend until adult life, with repercussions on the long-term quality of life.[1] Many publications are available in the literature about the qualities of breast milk, its benefits and health repercussions, stimulating the practice of breastfeeding and supporting campaigns such as the World Week of Breastfeeding. Even though it is widely known that breastfeeding is an important stage in the reproductive process of women and that its practice is beneficial for both mother and child, it can be seen that the information provided during prenatal care, puericulture practices or public health campaigns is directed at the benefits of breastfeeding for babies, while mention of all the effects of breastfeeding on the health of the mother is neglected.[2]

Lactation is a differential characteristic of mammals and both the synthesis and secretion of milk are complex biochemical and neuroendocrine processes that involve the sensitive terminals of the areole and the nipple and are under hormonal control. Thus, lactation is the direct and natural result of pregnancy and birth, like an integral part of reproductive process that benefits both mother and child simultaneously.[3] The interaction of all of these factors will culminate with the production of milk and will definitely cause changes in the maternal organism by also favoring good physical and emotional health conditions for the nursing mother extending into her future life.[4,5]

Benefits for the Mother

Breastfeeding (BF) seems to be related to good physical and emotional health for the mother during the puerperium, the lactation period and all her future life. Epidemiological studies have demonstrated that, compared with women who did not breastfeed, lactating women reported seeking for medical care less often, a lower frequency of respiratory, cardiocirculatory and gastrointestinal diseases, as well as fewer symptoms related to emotional problems.[6,7] On this basis, it is possible to emphasize the benefits of breastfeeding for the lactating mother, as described in ►**Table 1**.

Table 1 Benefits of breastfeeding for the mother's health

Immediate	Long-term
Uterine involution Reduced bleeding Reduced infection Lactational amenorrhea Reduced adiposity and weight Reduced postpartum depression Reduced stress and anxiety Improved body image	Reduced: cancer (breast, ovarian, endometrium) endometriosis, diabetes, osteoporosis, blood pressure and cardiovascular diseases, metabolic syndrome, rheumatoid arthritis, Alzheimer disease and multiple sclerosis

1. Uterine involution and reduced bleeding

Early suckling of the areal-mammillary region is one of the most important stimuli for the production of oxytocin, which is also responsible for uterine contraction, accelerating the return of the organ to its normal size and reducing the possibility of the occurrence of postpartum hemorrhage and anemia. High levels of oxytocin can increase the pain threshold, reducing maternal discomfort and thus contributing to an increased feeling of love for the baby.[8]

2. Lactational amenorrhea

During the lactation period, both progesterone and estrogen are suppressed, with the occurrence of a period of infertility. While the mother exclusively breastfeeds, her protection against pregnancy can reach 96% during the first 6 months, thus ensuring spacing between pregnancies.[9,10] To this end, the mother also must not have menstruated and should maintain exclusive breastfeeding on demand for at least eight times a day. Breastfeeding amenorrhea may be explained by the inhibition of ovarian activity resulting from high prolactin levels that lead to inhibition of the gonadotropin hormone and to the interruption of ovulation.[11] It has been estimated that, after the return of the menstrual cycles, the probability of conception is reduced by 7.4% for each additional month of breastfeeding.[12]

3. Weight and body image

During pregnancy, the body of a woman accumulates a weight of $\sim$ 3 kg of fat that will be utilized throughout the first 6 months of breastfeeding, since this process consumes $\sim$ 2,100 kj/day.[13] On this basis, there will be a more rapid weight loss and the return to pregestational conditions, with an average monthly reduction of 450 g in the maternal weight,[14] since the released oxytocin also exerts its lipolytic and anorexigenic effects. A lower body mass index has been detected among mothers who breastfed for a period of 6–12 months, and those who exclusively breastfed were leaner than those who breastfed on a partial basis at the end of the first semester of life of the baby.[15,16] A study conducted on 314 Mexican mothers revealed that those who exclusively breastfed for at least 3 months underwent a weight reduction of 4.1 kg compared with those who did not breastfeed.[17] This observation confirmed the weight reducing capacity of breastfeeding, which provides a sensation of greater self-esteem and satisfaction with their body image among lactating women, reducing the possible occurrence of negative emotional factors that might interfere with milk production and with the practice of breastfeeding.

4. Postpartum depression

The birth of a child is usually a source of happiness and pleasure for the family. However, it is known that $\sim$ 13% of all puerperae may develop signs and symptoms of depression within a period of 12 weeks after delivery.[18] Among these women, oxytocin levels have been found to be lower than those of the other new mothers. Recent studies have shown that oxytocin is a fundamental element for the stimulation of

the bond between mother and child, triggering positive effects such as vocalization with the baby, looking into its eyes, encouraging touch and caresses. Mothers have reported that they feel calmer, less aggressive and stressed, in a better mood and more interested in socializing since the first postpartum days.[19]

Breastfeeding may also act on a mechanism of regulation of daytime cortisol secretion, with a stable concentration of the hormone possibly reducing the risk of postpartum depression.[20] Recent studies have demonstrated that women who do not start or maintain BF have a higher risk of depression during the postpartum preriod.[21–23] There is an inverse association between these phenomena due to the hormonal and psychological conditions that occur during the first 6–8 weeks of puerperium, since the lactogenic hormone, oxytocin and prolactin can have anxiolytic effects. This attenuates stress via neuroendocrine responses, since BF is associated with reduced adrenocorticotrophic hormone (ACTH) and cortisol levels. Suckling at the maternal breast preceded by skin to skin contact triggers this process and the longer the duration of this contact, the lower the cortisol levels.[24]

5. Maternal stress

Several factors can be identified as sources of stress for the puerpera. The physical task of baby care together with other household activities, the few hours of sleep, changes in body image, reduced sexual activity and the emotional pressure of trying to be a good mother and to fulfill all the expectations represent an overload that is often incompatible with the personality and ability of a women to carry out her role as a mother. In this situation, BF may act by reducing stress levels because of its effect on the reduction of cortisol and ACTH levels, consequently reducing the levels of anxiety.[25] In addition, the strengthening of the mother-child bond is a potent stimulus for BF maintenance for the longest possible time, closing a virtuous cycle that tends to benefit both mother and child.

6. Adiposity

The visceral or intra-abdominal fatty tissue accumulated by a woman during pregnancy is metabolically more active than the fat deposited in other areas and is related to cardiocirculatory diseases. However, these deposits can be mobilized during the lactation period, a process that continues to occur in parallel to BF, reducing the maternal weight and risk of type 2 diabetes mellitus.[11,26]

7. Breast cancer

Mammary neoplasia is the most common gynecological cancer, quite prevalent after the fourth decade of life, although it can also occur before 40 years of age at frequencies ranging from 17–36%.[27] Several studies have pointed out the benefits of BF time and its consequent protective effect against the risk of breast cancer, since the reduction of estrogen levels during the lactation period reduces the rates of cell proliferation and differentiation. Tissue exfoliation and epithelial apoptosis at the end of the BF period may contribute to the reduction of the probability of cells with mutation arising in mammary tissues.[28–30] It is estimated that the risk of breast cancer can be reduced by more than 4% for each year of BF.[27,31–33] According to UNICEF, a 16% increase in the proportion of mothers who breastfeed for 6 months can reduce the expected prevalence of breast cancer by 1.6% per year.[34]

8. Ovarian cancer

Cancer of the ovarian epithelium is one of the neoplasias that most affect women and is usually diagnosed late, with a consequent reduction of survival prognosis. Some theories have indicated that its causes may be related to cell proliferation and uninterrupted ovulation traumas. On the other hand, the suppression of gonadotropins (luteinizing hormone in particular), the low concentration of estrogens and the consequent anovulation and amenorrhea caused by BF have been considered to be protective factors.[35,36] The relative risk of developing ovarian cancer is estimated to be reduced by 2% for each month of BF.[37] Meta-analysis studies have observed an inverse relationship between these events and have reported that protection is greater when the time of BF is longer than 10 months.[38,39] An analysis of prospective cohort and case-control studies has shown that women who have never breastfed had a probability of more than 30% of developing cancer of the ovarian epithelium.[35,40] In addition to offering a lower risk of development of ovarian cancer among lactating women, BF can also increase the life-expectancy of women who have already developed the disease.[41]

9. Cancer of the endometrium

Over the last few years, several epidemiological studies have pointed out some relationship between cancer of the endometrium and BF and have shown that long periods of BF are associated with a reduced risk of this type of neoplasia.[42–44]

10. Endometriosis

Endometriosis is a common gynecological disease that affects more than 10% of reproductive-aged women. Common symptoms include dysmenorrhea, dyspareunia and infertility, and women who suffer from this chronic condition may experience a wide variety of symptoms, ranging from mild pain to extremely debilitating disease.[45] According to Farland et al,[45] the duration of total and exclusive BF was significantly associated with a decreased risk of endometriosis. For every additional 3 months of total BF per pregnancy, women experienced an 8% lower risk of endometriosis, and women who breastfed for $\geq$ 36 months in total across their reproductive lifetime had a 40% reduced risk of endometriosis compared with women who never breastfed.[46]

11. Diabetes

The prevalence of type 2 diabetes mellitus has been increasing all over the world in parallel with the dietary changes, sedentarism and obesity that affect large part of the population. In this respect, it is opportune to emphasize an important action of oxytocin, which is a reduction of insulin

resistance. Meta-analysis studies have detected a statistically significant inverse association between BF duration and risk of type 2 diabetes.[47,48] An important review study conducted by Perrine et al[48] detected an inverse and dose-dependent association between BF and type 2 diabetes, with a reduction of 4–12% of the risk of developing type 2 diabetes with each additional year of lactation. In contrast, among women who never breastfed, the risk was 50% higher compared with those who breastfed even for short periods of time ranging from 1–3 months.[49,50]

12. Osteoporosis

Breastfeeding can contribute to the reduction of the risk of osteoporosis in future life since it has been demonstrated that lactating women have a bone mass with higher mineral density. Although the organism of women loses calcium during the BF period (with the production of 800 ml/day milk a woman can transfer as much as 200 mg calcium daily, which are recovered after weaning and with the return of menstruation), there are compensatory mechanisms that increase the intestinal and renal absorption of calcium and its mobilization from the bones, thus reestablishing bone mineral density.[51–53] During the lactation period there is a 4–7% bone loss, especially in the lumbar spine and femoral head, which is reversed about 1 year after weaning.[54] The protective effect of this mechanism of bone demineralization is directly proportional to the duration of BF.[55]

13. Blood pressure

Studies correlating BF with blood pressure have detected lower levels of both systolic and diastolic pressure among nursing mothers during the BF period, with the observation of a long-lasting dose–response effect, even though this effect may not persist until old age.[56–61]

14. Cardiovascular diseases

Vascular changes, such as atherosclerotic plaque, increased wall thickness and reduced arterial lumen, increase the risk of cardiovascular diseases, a fact that has raised the interest of some investigators in the study of a possible association between lactation and these vascular changes.[50] Women who breastfeed for long periods of time, 7–12 months after the first delivery, have a 28% lower risk to develop vascular diseases compared with women who never breastfed.[50,62] These findings are also associated with the weight loss and metabolic work to which the maternal organism is submitted for the daily production of milk, which may persist even after weaning, contributing to a beneficial effect on the maternal organism. Women with a total BF time of more than 2 years had a 23% lower probability of developing coronary diseases than women who never breastfed.[28] An inverse association has also been described between BF duration and atherosclerosis, after other confounding factors, such as smoking and obesity, are excluded, as determined by the thickness of carotid artery walls.[62]

15. Metabolic syndrome

Metabolic syndrome (MS) is the result of several changes that include central obesity, arterial hypertension, dyslipidemia and insulin resistance, which, when associated, involve severe complications and high mortality rates. It is known that women who breastfeed for prolonged periods of time have a lower risk of the incidence of MS, after other factors, such as body mass index and parity, for example, are adjusted. One of the most important mechanisms involved in this occurrence is the reduced insulin resistance provided by BF, since a 12% reduction in the risk of MS development has been observed for each year of lactation.[28,63,64]

16. Rheumatoid arthritis

A recent meta-analysis study by Chen et al[65] demonstrated that BF is associated with a lower risk of the onset of rheumatoid arthritis among nursing women, whether or not the duration of BF is longer than 12 months.

17. Alzheimer disease

Fox et al[66] studied a cohort of elderly English women and observed that the risk of developing Alzheimer disease was lower among those who had breastfed, possibly owing to the hormonal effects of estrogens on brain receptors and of insulin sensitivity triggered by BF.

18. Multiple sclerosis

Multiple sclerosis is a chronic autoimmune disease with a susceptibility and disease course that are influenced by reproductive factors, affects predominantly women during their childbearing years and the risk relapses is significantly diminished during pregnancy and exclusive BF. Among women who had live births, a cumulative duration of BF for $\geq$ 15 months was associated with a reduced risk of multiple sclerosis compared with 0–4 months of breastfeeding.[67]

Conclusion

The benefits of BF for children have been known and reported for a long time, although the prevalence of this practice and the dissemination of its benefits for the nursing mother have been found not to be satisfactory in various parts of the world. Despite that great knowledge, relatively little progress has been made in improving BF outcomes, such as early initiation and exclusive breastfeeding for 6 months.[3]

Due to its individual and collective importance, the access to BF protection and support has also been framed as a human right with issues of social justice and equity becoming superlative.[68] Lactation plays an important role in maternal recovery from pregnancy, and can determine multiple aspects of maternal health in later life.[69] Therefore, informing pregnant women of the maternal health effects of lactation would strengthen their intentions to breastfeed. However, it is necessary to respect the wishes and rights of the mother, who must have autonomy to decide how to feed her child. The mother, in consultation with other family members, should be the one who decides how the child is to be fed, and in making this decision, the mother must be supported and aided by family, employers, health professionals and society.[3] It is also the duty of health professionals to identify the knowledge, previous experience and social

and family context of women since the prenatal period to promote educational actions directed at the introduction and maintenance of BF when she so decides.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Guidelines for HPV-DNA Testing for Cervical Cancer Screening in Brazil

Recomendações para o uso de testes de DNA-HPV no rastreamento do câncer do colo útero no Brasil

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Abstract

Evidence-based clinical guidelines ensure best practice protocols are available in health care. There is a widespread use of human papillomavirus deoxyribonucleic acid (HPV-DNA) tests in Brazil, regardless of the lack of official guidelines. On behalf of the Brazilian Association for the Lower Genital Tract Pathology and Colposcopy (ABPTGIC, in the Portuguese acronym), a team of reviewers searched for published evidence and developed a set of recommendations for the use of HPV-DNA tests in cervical cancer screening in Brazil. The product of this process was debated and consensus was sought by the participants. One concern of the authors was the inclusion of these tests in the assessment of women with cytologic atypia and women treated for cervical intraepithelial neoplasia (CIN). Testing for HPV is recommended in an organized screening scenario to identify women with precursor lesions or asymptomatic cervical cancer older than 30 years of age, and it can be performed every 5 years. It also has value after the cytology showing atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSILs) as a triage test for colposcopy, in the investigation of other cytological alterations when no abnormal findings are observed at colposcopy, seeking to exclude disease, or, further, after treatment of high-grade cervical intraepithelial neoplasia, to rule out residual disease.

Keywords
- screening
- cervical neoplasms
- DNA-HPV probes
- cervical intraepithelial neoplasia
- cytology

Resumo

O uso de diretrizes clínicas baseadas em evidências visa assegurar as melhores práticas na área de cuidado à saúde. O uso de testes de ácido desoxirribonucleico de papilomavírus

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humano (DNA-HPV) vem crescendo e se disseminando sem que existam recomendações de uso no cenário brasileiro. Em nome da Associação Brasileira de Patologia do Trato Genital Inferior e Colposcopia (ABPTGIC), grupos de revisores pesquisaram evidências e formularam recomendações para o uso dos testes de DNA-HPV no rastreamento do câncer do colo do útero, no seguimento de mulheres com atipias citológicas, e após tratamento de neoplasia intraepitelial cervical (NIC). O produto desse processo foi debatido e foi buscado consenso entre participantes. Os testes de DNA-HPV são recomendados num cenário de rastreamento organizado para identificação de mulheres portadoras de lesões precursoras ou câncer assintomático com mais de 30 anos e podem ser realizados a cada 5 anos. Também têm valor após a citologia mostrando células escamosas atípicas de significado indeterminado (ASC-US) ou lesão intraepitelial escamosa de baixo grau (LSIL) como teste de triagem para colposcopia, na investigação de outras alterações citológicas quando não são observados achados anormais à colposcopia, buscando excluir doença, ou, ainda, no seguimento após tratamento das neoplasias intraepiteliais de alto grau, para exclusão de doença residual.

Palavras-chave
- rastreamento
- neoplasias do colo do útero
- sondas de DNA de HPV
- neoplasia intraepitelial cervical
- citologia

Introduction

The present article is a result of the review and update process of the Brazilian Guidelines for Cervical Cancer Screening,[1] published in 2016. Human papillomavirus deoxyribonucleic acid (HPV-DNA) tests had already been widely used in Brazil for years, without specific national guidelines, and these recommendations aimed to fill this gap.

Thus, the workgroup that revised and updated the current Brazilian guidelines prepared the present document on behalf of the Brazilian Association for the Lower Genital Tract Pathology and Colposcopy (ABPTGIC, in the Portuguese acronym). This document does not represent the position of the Brazilian Ministry of Health on the use of DNA-HPV detection tests, and it should be emphasized that this text does not replace the existing recommendations, which are based on technologies widely recognized and available to the Brazilian population.

The aim of these recommendations is to guide practitioners working in scenarios in where the test is available, so they can use it according to the best practice and in the light of the best evidence.

The process of building these recommendations was described in the Brazilian Guidelines for Cervical Cancer Screening - 2nd edition, revised, expanded and updated.[1]

Technical Considerations

By "HPV-DNA test," we mean any test for the detection of oncogenic HPV-DNA in biological specimens obtained by a cervical smear or brushing. The detection of non-oncogenic HPV types is not clinically relevant in this setting.

Generally, the use of HPV-DNA tests in cervical cancer screening is beneficial because it is more sensitive, identifying more women with precursor lesions and cancer than the conventional Pap smear. On the other hand, because of its lower specificity, more women may be unnecessarily referred for colposcopy, which leads to an increase in costs and unwanted morbidity.

One advantage of HPV-DNA tests following an abnormal Pap smear is their high negative predictive value. When oncogenic HPV-DNA is undetectable, the occurrence of precursor lesions or cervical cancer is very unlikely.

Methods

In summary, from February 2013 to August 2014, almost 40 experts got together to update the previously published recommendations[2] based on the best available evidence. Among these experts were prominent gynecologists with known experience in the subject, as well as representatives of institutions involved in cervical cancer screening and the follow-up of abnormal screening tests, who share the authorship of this paper. The remaining participants of the revision and consensus process are listed in the Acknowledgments. The review leaders were selected by a panel of specialists leaded by the ABPTGIC. Each review leader invited other specialists from other parts of the country, considering their work in the specific area of interest. Each review group reviewed one main topic, searching for the best evidence in original articles or secondary information sources, submitting their summary and updated recommendations to the whole group. The result of the work of each group was discussed in videoconferences and, at the end of this process, the final text was discussed in a special meeting in Rio de Janeiro.

The following text presents, in each topic, evidence that supports the use of the HPV-DNA tests in each individual scenario. The evidence from the literature was classified as high, moderate or low, according to the risk of bias (►**Table 1**).

The summary of evidences is followed by specific recommendations that resulted in the experts' consensus. Each recommendation is followed by a capital letter in parentheses, meaning its strength, based on the degree of certainty from the best scientific evidence and judgment of the participants (►**Table 2**). In ►**Table 3** we list the most relevant recommendations.

Table 1 Level of certainty

Certainty Level*	Description
High	The available evidence usually includes consistent results from well-designed and well-conducted studies among the representative populations to which they apply. These studies assess the effects of the preventive practice on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to establish the effects of the preventive practice on health outcomes, but confidence is limited by factors such as: • The number, size or quality of the individual studies • Inconsistency in the findings across individual studies • Limited generalizability of the findings to the routine practice • Lack of consistency in the chain of evidence As more information becomes available, the magnitude or direction of the observed effect may change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. The evidence is insufficient because of: • The limited number or size of the studies • Important flaws in the studies' designs or methods • Inconsistency in the findings across individual studies • Gaps in the chain of evidence • Findings not generalizable to the routine practice • Lack of information on important health outcomes More information can allow estimates of the effects on health outcomes.

*The United States Preventive Services Task Force (USPSTF) attributes a level of certainty based on the general nature of the evidence available to assess the net benefit of a preventive practice.[3]

Table 2 Strength of recommendation

Grade	Definition*	Recommendations for practice
A	The practice is recommended. There is high certainty that the net benefit is substantial.	Offer or provide the practice.
B	The practice is recommended. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide the practice.
C	The practice is not routinely recommended. There may be considerations that support the practice at an individual level. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The practice is not recommended. There is moderate or high certainty that the practice has no net benefit, or that the damages outweigh the benefits.	Discourage the use of this practice.
I	The current evidence is insufficient to assess the balance between its benefits and harms. The evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the introductory text containing evidence obtained in the literature review that supports this recommendation. If the practice is offered, the patients should understand that there is uncertainty in the balance between benefits and harms.

*The United States Preventive Services Task Force (USPSTF) defines certainty as the "likelihood that the USPSTF's assessment of the net benefit of a preventive practice is correct." The net benefit is defined as the benefit minus the practice injury when implemented in a general population.[2]

HPV-DNA Test Use in Cervical Cancer Screening

The occurrence of false-negative and unsatisfactory cytology tests prompted the development of new technologies that improve screening quality.[4] In addition, the evidence of a causal relationship between oncogenic HPV infection and cervical cancer and its precursor lesions led to the development of HPV-DNA detection techniques to prevent and identify these lesions.[5]

There is currently scientific evidence supporting HPV-DNA tests as the primary screening method for women aged 30 years or older. Screening for HPV-DNA has a high sensitivity, and anticipates the diagnosis of cervical intraepithelial neoplasia (CIN) II and III even when the screening is performed in a 5-year interval. This technique is better than regular cervical cytology in the diagnosis of glandular lesions (adenocarcinoma) (evidence level: high).[6] Staff training is fast, laboratory

Table 3 Most relevant recommendations for the use of the HPV-DNA test in cervical cancer screening and after an abnormal cytology

The HPV-DNA test can be the primary screening method as an alternative to cytology in women aged 30 years or older. When negative, the test should be repeated every 5 years.
When the HPV-DNA test is positive for oncogenic HPV, triage with cytology is recommended. If genotyping is available and if it is positive for HPV types 16 or 18, the woman may be referred for colposcopy.
Women aged 30 years or older with ASC-US can perform the HPV-DNA test as an alternative to a new cytology after 6 months.
Women 30 years of age or older with LSIL can perform the HPV-DNA test to select those who should be referred for colposcopy.
In women with ASC-H or HSIL and normal colposcopy, a negative HPV-DNA test will virtually rule out precursor lesions or invasive disease.
In women with AGC or AIS and normal colposcopy, a negative HPV-DNA test means a low probability of cervical disease, demanding investigation of the endometrium and other pelvic organs.
The HPV-DNA test may be used at follow-up after the treatment of CIN II/III and AIS to exclude residual or recurrent lesions, and it is recommended between 6 and 12 months after the treatment.

Abbreviations: ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; AGC, atypical glandular cells; AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HPV-DNA, human papillomavirus deoxyribonucleic acid; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

results are reproducible, and it qualifies for self-sample HPV-DNA-based screening (evidence level: high).[7]

The main limitation of HPV-DNA-based tests is their low specificity (positive results when there is no lesion – a common finding in women under 30 years of age) (evidence level: high).[8] To avoid an excessive number of women unnecessarily referred to colposcopy because they were screened with a positive HPV result, triage methods are necessary. One option is the cytology triage of HPV-DNA-positive cases, referring only women who tested positive for HPV-DNA and whose cytology test was abnormal (evidence level: high).[9] This strategy has proven to be more sensitive and to have the same specificity as cytology alone in a Swedish randomized clinical trial, which was part of the national population-based screening program (evidence level: high).[10]

Screening for HPV-DNA has a greater operational advantage if performed using a sample that would also allow a cytology triage, and this is the case of the liquid medium. Therefore, if the HPV-DNA test is positive, the cytology test can be performed in the same sample, and a new sample collection is not necessary, thus saving time and resources.

Human papillomavirus types 16 and 18 (genotyping) in women with a positive HPV-DNA test and a negative cytology have shown favorable results for the selection of women with a higher probability of having CIN II or higher type (CIN II +). Prospective studies with a large number of women support the immediate referral of patients with positive HPV-DNA types 16 and 18 to colposcopy, regardless of the use of cytology as triage (evidence level: high).[11–13]

In summary, screening with HPV-DNA-based tests may be advantageous in women aged 30 years or older, followed by a triage with cytology, provided that only those with cytological atypia are referred for colposcopy. This is true for an organized screening scenario, that is, one in which there is a control of who should be screened at the recommended time intervals. There are only a few municipalities with organized cervical cancer screening programs in Brazil. There is no suitable control of the women who carry out their screening or how often they do it. Thus, there are no tools to ensure that the interval between screening tests will be effectively widened with the adoption of an HPV-DNA test, nor that women missed by this screening program will be identified. Furthermore, in most Brazilian municipalities, the cost-effectiveness improvement of HPV-DNA testing is not warranted. Given this background, the use of this technology in each and every municipality of Brazil can only be recommended once their screening program is organized and operational.

Recommendations

Testing based on HPV-DNA as an alternative to cytology in cervical cancer screening should be performed every 5 years in women aged 30 years or older, and may be extended up to when the patients are 64 years of age (B). Testing for HPV-DNA is unacceptable before the age of 30 (D). When an HPV-DNA test is positive for oncogenic types, a cytology exam should be performed, preferably using the same sample, since no further sampling would be necessary. Therefore, the recommended medium for HPV-DNA test collection is the same as for liquid-based cytology (B).

If an HPV-DNA test is positive for oncogenic types and the cytology shows any atypia (ASC-US or worse), the woman should be referred for colposcopy (A). Instead, if the cytology is negative, the woman should repeat the HPV-DNA test after 12 months (A). If the HPV-DNA result remains positive for oncogenic types, the woman should be referred for colposcopy (A). If the sample is negative for oncogenic HPV on the first or second sampling opportunity after a negative cytology, a new cytology exam must be performed after three years (A). If HPV-DNA genotyping is available and is positive for HPV types 16 or 18, the woman should be directly referred for colposcopy, bypassing the cytology test (A). If an HPV-DNA test (with or without genotyping) is negative, it should be repeated in 5 years (A). Any therapeutic procedure

performed because of a positive HPV-DNA test is unacceptable (D). Women between the ages of 25 and 29 should keep performing cytology tests (A). Women aged 65 years or older who tested negative for HPV-DNA may discontinue screening (B). ►**Fig. 1** summarizes the recommendations for the use of HPV-DNA tests in cervical cancer screening.

Use of HPV-DNA Tests in the Follow-up of Women with Abnormal Cytology Results

Atypical Squamous Cells

Atypical Squamous Cells of Undetermined Significance (ASC-US), Possibly Non-neoplastic

The cytology diagnosis of atypical squamous cells of undetermined significance (ASC-US) does not mean, in most cases, the presence of a precursor lesion or cancer. However, identifying which women with this diagnosis are more likely to have one of these lesions has led to several screening recommendations for colposcopy referral.

As mentioned in the Brazilian Guidelines for Cervical Cancer Screening,[1] there is a similarity among management recommendations for woman with ASC-US in France,[14] the United Kingdom,[15] and Australia and New Zealand.[16] In these countries, a repeat cytology test is recommended after 6 to 12 months. The American Society for Colposcopy and Cervical Pathology (ASCCP) states that using the oncogenic HPV-DNA test for women aged over 25 with ASC-US cytology is preferable to cytology. This same guideline states that this test is acceptable in 21- to 24-year-old women with ASC-US, but repeat cytology is preferable in this age range.[17] The guidelines published in Korea[18] and Argentina[19] follow ASCCP recommendations and

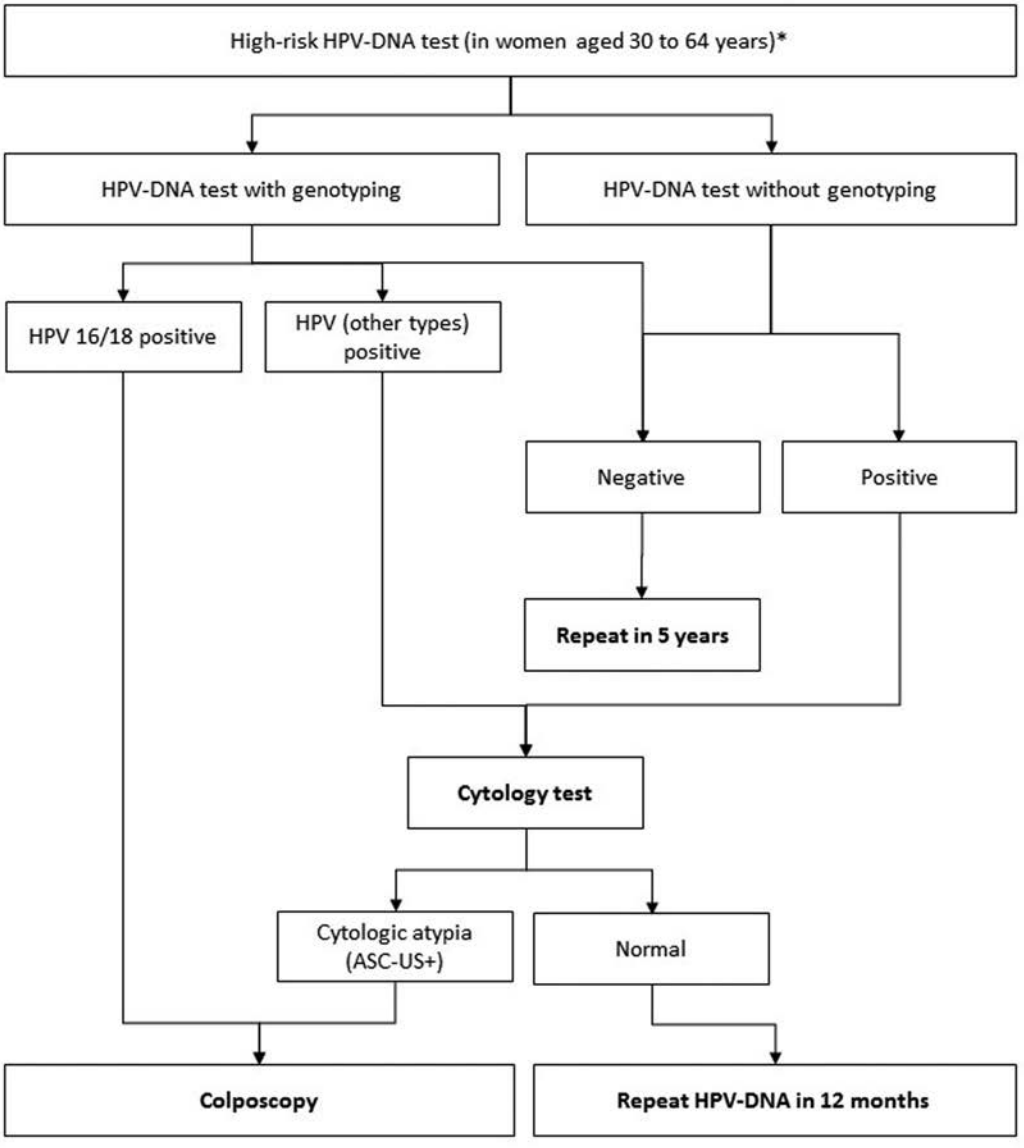

Fig. 1 Recommendations for HPV-DNA testing in cervical cancer screening in women aged 30 to 64 years.*

endorse the use of oncogenic HPV-DNA testing in women with ASC-US cytology.

Recommendations

Women with ASC-US cytology can perform the HPV-DNA test alternatively to a new cytology test within 6 months. If the test is positive for oncogenic types, the woman should be referred for colposcopy (A).

The HPV-DNA test can also be used to outline the follow-up of women with ASC-US cytology aged 30 years or older after a negative colposcopy. If the test is positive, the woman should be followed in the primary care unit in the same way as the others. She should undergo a new cytology test every 6 months (for women aged 30 years or more) or annually (for younger women) (I) until 2 consecutive negative test results are achieved, then she should return to triennial cytological screening, unless a different cytology result occurs (A). If the HPV-DNA test is negative for oncogenic types, this woman may return to triennial screening (A).

Atypical Squamous Cells, Cannot Exclude High Squamous Grade Intraepithelial Lesion (ASC-H)

Differently from the diagnosis of ASC-US, in the presence of atypical squamous cells, cannot exclude high squamous grade intraepithelial lesion (ASC-H), the probability of a precursor lesion or cancer is significantly higher. Of all current recommendations, the most favored is referral to colposcopy.

However, in many cases, colposcopy cannot ensure there is no lesion, and a negative oncogenic HPV-DNA test virtually ensures its absence (evidence level: moderate).[20]

Recommendations

When available, the HPV-DNA test may also be used in women with an ASC-H cytology who have a type-III transformation zone (TZ) and no abnormal colposcopy findings (B). If there is no oncogenic HPV, this woman may return to triennial cytology screening (I). If there are abnormal findings, this woman should continue to undergo the investigation of the endocervical canal as recommended by the Brazilian Guidelines for Cervical Cancer Screening (I). If the presence of a precursor or invasive lesion is not proven, the HPV-DNA test may also be used at the follow-up. In this case, it should be performed within 6 months of the initial cytology test (A). If there is no oncogenic HPV, this woman can go back to triennial screening (A). If oncogenic HPV is present, this woman should be referred for colposcopy to ensure there are no precursor lesions (I).

In postmenopausal women with an ASC-H cytology test, the HPV-DNA test may also be used, avoiding topical estrogens before a new colposcopy, as indicated in the Brazilian Guidelines (I). If there is no oncogenic HPV, this woman may return to triennial cytological screening (I). If positive for oncogenic HPV, she should be followed as recommended in the Brazilian Guidelines for Cervical Cancer Screening: continuation of the investigation, preferably with estrogen preparation (I).

Atypical Glandular Cells (AGC)

Atypical Glandular Cells of Undetermined Significance, Possibly Non-neoplastic or Atypical Glandular Cells in Which High-grade Intraepithelial Lesions Cannot Be Ruled Out

Atypical glandular cells are another challenge. The prevalence of precursor lesions and invasive disease in women with this cytological diagnosis is higher than in women with ASC-US. In addition, most glandular lesions are in the endocervical canal, which is often a colposcopic challenge, with less specific colposcopic findings than those of squamous lesions.

Considering the limitations of cytology and colposcopy in such situations, the HPV-DNA test may provide additional information to the investigation. The presence of oncogenic HPV-DNA also showed association with invasive or precursor glandular disease (evidence level: high).[21] The probability that an intraepithelial lesion may reach 40% when oncogenic HPV types are present, compared with 4% when absent, points to a possible use of this test in the investigation of these women (evidence level: high).[22]

Recommendations

In women with an AGC cytology, and in situations in which the colposcopy cannot ensure the absence of glandular disease, a negative oncogenic HPV-DNA test will virtually rule out precursor or malignant disease of the cervix (A).

Low-grade Squamous Intraepithelial Lesion (LSIL)

This cytology result implies a low probability of cancer or a precursor lesion. In order to identify women at a greater risk of developing these diseases and to define the need to refer them for colposcopy, the use of HPV-DNA tests was proposed. In this situation, HPV-DNA tests have a significantly higher sensitivity, but significantly lower specificity, when compared with repeat cytology (evidence level: high).[23] The low specificity of HPV-DNA tests is due to the high HPV prevalence in women with LSIL (76.9%) (evidence level: high),[24] which would imply the referral of most women for colposcopy, compromising the cost-effectiveness strategy. However, a positive HPV-DNA test is determined by the prevalence of HPV infection, which in turn is age-dependent. More recent studies have shown that several HPV-DNA tests have increased specificity with increasing age, in addition to high sensitivity, for the detection of CIN II + in women with LSIL (evidence level: high).[25,26] Scientific evidence suggests that HPV-DNA tests may be useful for the triage of older women with LSIL. However, because of the lack of stratified data, we don't have enough evidence to recommend the best moment to use it in this situation (evidence level: high).[27]

A meta-analysis of studies on the performance of HPV-DNA test as a triage for the colposcopy of women with LSIL cytology published in 2013 concluded that these tests may have a greater ability to detect cases of NIC II +. However, their use should be weighed against the costs of the testing and the colposcopy, in addition to the adherence to follow-up. Furthermore, they point out that DNA-HPV tests are certainly useless in young women with LSIL, that more studies are needed to

define their usefulness in the triage of older women (in the US it is recommended for postmenopausal women), and that higher cut-off points might be used to consider the test positive (evidence level: high).[22]

In the follow-up after colposcopy, if there are no abnormal findings, or when the result is compatible with CIN I or a less severe type, the sensitivity of the biannual cytology control and the 12-month HPV-DNA test for CIN II+ detection was similar (89% and 92% respectively). However, the referral rates for new colposcopy were different (64% for cytology and 55% for HPV-DNA), pointing to a higher cost-effectiveness of the HPV-DNA test (evidence level: high).[26]

Recommendations

Where HPV-DNA testing is available, it may be used in women with LSIL cytology who are aged 30 years or older for referral for colposcopy. If the HPV-DNA test is negative for oncogenic types, the woman should return to triennial cytology screening (I). If the HPV-DNA test is positive for oncogenic types, the woman should be referred for colposcopy (I). In addition, after the first colposcopy, in the follow-up of the women with no abnormal findings or after the histology diagnosis of CIN I, a 12-month HPV-DNA test may be used (A) as an option. When oncogenic types are present, the follow-up should be continued as aforementioned (A). Negative cases should go back to the triennial cytology screening routine (A).

High-grade Squamous Intraepithelial Lesion (HSIL)

The use of HPV-DNA tests is of no value for the colposcopy referral of women after this cytology result. However, in view of the high prevalence of oncogenic HPV types in precursor lesions (evidence level: high),[20] it can be useful in situations in which the colposcopy cannot rule out disease.

Recommendations

In cases of high-grade squamous intraepithelial lesion (HSIL) cytology, the HPV-DNA test, when available, may be used only if there are normal or low-grade colposcopy findings. If no oncogenic types are present, precursor or invasive disease is virtually excluded, and the woman can return to triennial cytology screening (A).

Adenocarcinoma in situ (AIS) and Invasive Adenocarcinoma

These cytology results are a challenge for colposcopy. These lesions are usually located inside the endocervical canal and are not easily recognized, even by experts. Occasionally, the disease may come from the endometrium or other pelvic organs.

As a result, there usually are no abnormal findings at the colposcopy, and that requires an excisional diagnostic procedure, as well as investigation of the endometrium and other pelvic organs in women aged 35 years or older, or below that age if there is any abnormal bleeding.[1]

A negative oncogenic HPV-DNA test may be useful in identifying women at a higher risk of having endometrial disease, especially those over 50 years of age (evidence level: moderate).[28]

Recommendations

Where available, HPV testing may be used in the initial investigation of women with a cytology result of adenocarcinoma in situ (AIS) or invasive adenocarcinoma. If negative, this will mean a lower probability of having cervical disease, and that will endorse the evaluation of the endometrium as well as of other pelvic organs in women aged 35 years or older and in those with abnormal bleeding under 35 years of age (I).

Use of the HPV-DNA Test in the Follow-up of Women Treated for Cervical Cancer Precursor Lesions

After Treatment of CIN II/III

Long-term follow-up studies indicate that women treated for CIN II/III are at a higher risk of developing cervical cancer for at least 10 years, and perhaps up to 20 years after treatment, when compared with the general population (evidence level: high).[29]

The ideal follow-up for the detection of residual or recurrent disease appears to be cytology associated with colposcopy, but current data suggests that the HPV-DNA test identifies disease earlier, with greater sensitivity and specificity, than the cytology follow-up (evidence level: moderate).[30]

Several studies have reported the elimination or persistence of HPV infections after the treatment of high-grade squamous intraepithelial cervical lesions. These reports vary, and they sometimes show conflicting results. One study reported that out of 49 women treated with large loop excision of the transformation zone (LLETZ), only 6 (12.2%) persisted with viral infection 3 months after the treatment (evidence level: moderate).[28] Another study identified that at 31 months of follow-up after a high-grade lesion treatment, the HPV-DNA test was still positive in 19.6% of the patients, and no longer detectable in 80.4% of the women (evidence level: moderate).[31] Another study showed that 94% of women with a positive HPV-DNA test before treatment had cleared the infection in 12 months (evidence level: moderate).[32]

Brazilian studies showed that most patients undergoing excisional treatment for high-grade lesions were negative for HPV-DNA six months after the procedure (evidence level: moderate).[33]

Recommendations

The HPV-DNA test may be used for follow-up after NIC II/III treatment to exclude residual or recurrent lesions. In this case, it should be performed between 6 and 12 months after the treatment (A). If cleared from oncogenic types, the woman may return to triennial cytological screening (A).

After Treatment of Adenocarcinoma in situ

The HPV-DNA test can also be useful after a conservative treatment for AIS (when the uterus is maintained) because, if negative, it indicates that the patients have a lower risk of persistence and relapse (evidence level: moderate).[34]

Recommendations

The HPV-DNA test may be used at follow-up after a conservative AIS treatment (when the uterus is maintained) to exclude residual or recurrent lesion. In this case, it should be

performed 6 to 12 months after the treatment (A). If the oncogenic HPV-DNA test is negative, the woman may return to triennial cytological screening (A).

Conflicts of Interest

The authors have none to declare.

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Vulvar Hemangioma: Case Report

Hemangioma vulvar: Relato de caso

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Abstract

Hemangioma is a benign neoplasm that may affect the vulva, and it can cause functional or emotional disability. This article reports the case of a 52-year-old female patient with a history of a genital ulcer for the past 3 years and who had undergone various treatments with creams and ointments. The patient was biopsied and diagnosed with vulvar hemangioma and was subsequently submitted to surgical excision of the lesion. We emphasize the importance of following the steps of the differential diagnosis and proceeding with a surgical approach only if necessary.

Keywords

- ulcer
- vulvar neoplasms
- hemangioma
- biopsy

Resumo

O hemangioma é uma neoplasia benigna que pode afetar a vulva e pode causar incapacidade funcional ou emocional. Este artigo relata o caso de uma paciente de 52 anos com história de úlcera genital nos últimos 3 anos, submetida a diversos tratamentos com cremes e pomadas. A paciente foi biopsiada e diagnosticada com hemangioma vulvar e subsequentemente submetida a excisão cirúrgica da lesão. Ressaltamos a importância de seguir as etapas do diagnóstico diferencial e proceder a uma abordagem cirúrgica somente se necessário.

Palavras-chave

- úlcera
- neoplasias vulvares
- hemangioma
- biópsia

Introduction

Hemangiomas are proliferative soft-tumor lesions marked by increased cell turnover. They are the product of a derangement in angiogenesis that allows for the unsuppressed proliferation of vascular elements. These tumors usually appear after birth, grow rapidly and involute over the years.[1] A total of 60% of hemangiomas are situated in the cervicofacial region.[2] The remaining section can occur at various locations in the body, including the vulva. However, vascular tumors are rarely found in the female genital tract.[3] In fact, the female genital tract is an unusual location for hemangiomas, they are seldom found in this site.[3–5] Therefore, there are very few reports on the condition on the literature.[4]

Although rare, we must be aware of the diagnosis of hemangiomas in the inferior female genital tract, as they might be a reason for a gynecologic consultation[3] and can cause functional or emotional disability.[4] We report here a rare case of a vulvar hemangioma that presented as a genital ulcer causing functional impairment and bleeding.

Case Report

The patient is a 52-year-old female , married, self-employed, non-smoker, with prediabetes, dyslipidemia and premenopausal, with no use of hormonal contraception. The patient reported a genital lesion for the past 3 years and the use of various treatments involving creams and ointments, even though there was no diagnosis associated with dyspareunia

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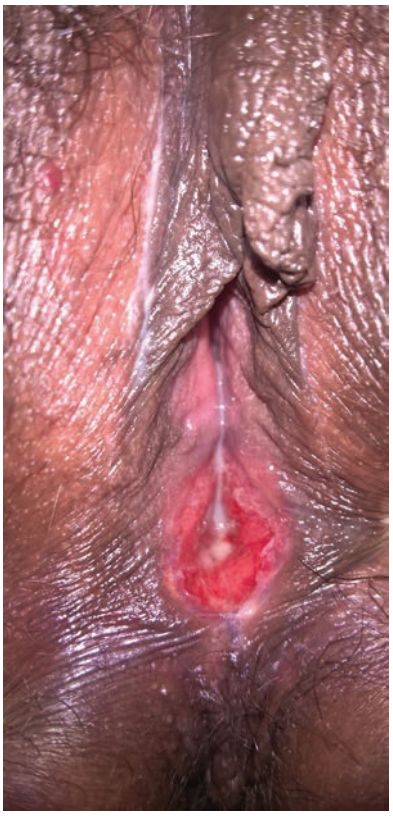

Fig. 1 Examination of the vulva with a lesion between the vaginal vestibule and the perineal region.

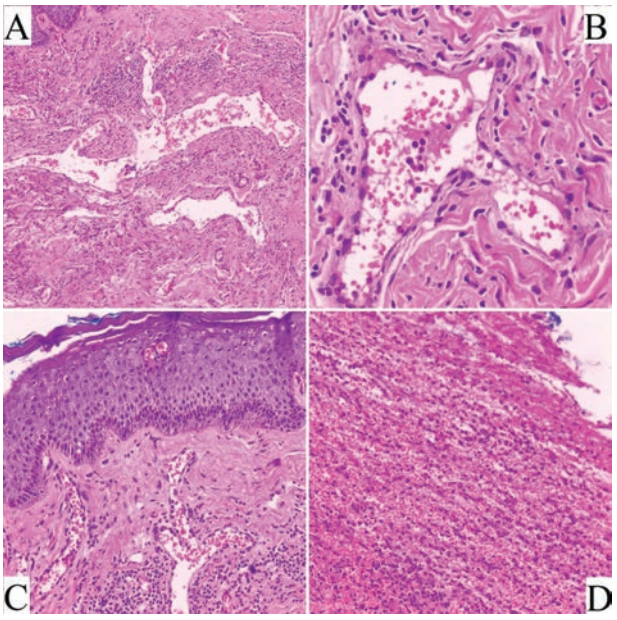

Fig. 2 This figure shows a proliferation of tortuous vessels in the submucosa, with variation in size. (A) Detail of a tortuous vessel and its endothelial lining formed by a single layer of some flattened cells. Some more swollen, without nuclear atypia. (400x magnification). (B) Some of them are larger and full of erythrocytes, while others are smaller and located in the periphery. (400x magnification). (C) Field of observation demonstrating the superficiality of these tortuousvessels and their close relation to the mucosa (stratified squamous epithelium). (200x magnification). (D) Nude area (without epithelial lining) composed of acute inflammatory cells (polymorphonucleated), chronic (lymphocytes and plasma cells) and erythrocytes, characterizing ulcerated lesion. (100x magnification). All using hematoxylin-eosin staining.

and intermittent bleeding. Physical examination revealed a solitary vulvar ulcer (►**Fig. 1**). The cervix had no abnormalities according to the colposcopy. No abnormalities were present in the routine blood tests and examinations of the patient. Initially, the investigation began by discarding all possible infectious causes of genital ulcers, such as syphilis, herpes and chancroid, which all proved to be negative.

There was suspicion of a manifestation of Behcet disease; therefore, we initiated the treatment with systemic corticosteroids. The first response was partial, the patient presented a decrease in the itching and burning sensations, but the bleeding did not cease. Furthermore, the pathergy test result was negative. Due to the patient complaints of pain and sexual dysfunction, it was decided to conduct a surgical excision of the lesion. The biopsy examination showed a proliferation of tortuous vessels in the submucosa (►**Fig. 2**) and thus, the pathological diagnosis was reported as a hemangioma.

Discussion

The patient presented a hemangioma, which was clinically manifested as a bleeding ulcer. In fact, the hemangioma can manifest as an ulceration and bleed, both occurring most often in younger patients.[5] Vulvar hemangiomas can cause functional and emotional disability,[4] pain, cosmetic problems, and sexual dysfunction,[5] the last three of which were complaints from our patient. For this reason, it is important to diagnose it correctly and to treat it adequately.

In this case, the first manifestation was a red, painful and persistent lesion followed by an ulcer complicated by life-threatening hemorrhage that was not responsive to conventional treatments and which showed no signs of involution for more than 3 years. Despite the negative evidence, over this time, an appropriated gynecological exam had been realized as well as the syndromic management, which is recommended by the Brazilian Ministry of Health. However, no final diagnostic was obtained, and no satisfactory results were observed.

The syndromic management of genital ulcers is recommended as an initial treatment, given the number of differential diagnoses and the practical difficulties in establishing a clear-cut etiologic diagnosis. It is prudent for healthcare providers to initially consider every female genital ulcer as a sexually transmitted disease (STD), which are: syphilis, chancroid, lymphogranuloma venereum, donovanosis and genital herpes.[6]

Therefore, our approach was to initially screen the patient for STDs; these all proved to be negative, which excluded these diseases from our differential diagnoses. Even with proper laboratory analysis, no pathogen is found in up to 25% of the patients with genital ulcers.[7]

Continuing the investigation of the etiology of the ulcer, we considered that it could be caused by a non-sexually transmitted disease,[6] such as Behcet disease.[8] Considering the possibility of this vasculitis, we performed a systemic

corticosteroid treatment. However, there was no complete regression of symptoms. Subsequently, the biopsy of an ulcer, which did not respond to initial therapy, was the recommended course of action.[6,9] Therefore, with the biopsy of the patient's ulcer, it was possible to reach a definite diagnosis of vulvar hemangioma (►**Fig. 2**).

As most hemangiomas present spontaneous involution, treatment may be reserved for lesions that present complications, such as functional impairment, pain, ulceration, and bleeding, as the ones presented by our patient; however, there are others, like unusually rapid growth, infection, and cosmetic concerns.[2] In our case, the discomfort of our patient with her symptoms and her sexual dysfunction led to our decision to treat her.

The initial approach in our case was a conservative treatment with systemic corticosteroids to minimize the inflammatory process, as we assumed we were dealing with a manifestation of Behcet disease. Fortunately, these medications are effective in inducing rapid involution in massive hemangiomas. The success rate varies from 30 to 90%.[2] The therapy was based on daily doses of Prednisone 20 mg. The patient responded partially with a significant improvement in the itching and burning symptoms. However, the ulcer did not involute as expected, and she was still suffering from bleeding and dyspareunia.

It is important to highlight that during this period, the biopsy was suggested and refused by the patient, who accepted it only upon knowledge that it could be a malignant neoplasm.

The surgical excision of hemangiomas of the female genitalia is reserved for symptomatic lesions refractory to medical management.[10] The procedure was performed for a curative purpose, to exclude malignancy and to obtain a definite diagnosis. A circular excision and purse-string closure are considered the best surgical approach for hemangiomas.[11] The resection of the lesion and reconstruction of the minor labia eliminated the symptoms and provided the cosmetic improvement required by the patient. A definite diagnosis of hemangioma was reached after pathological examination of the lesion. The proliferation of large vessels full of erythrocytes in the submucosa, involving the dermis are pathognomonic of hemangioma and excluded the possibility of being an ordinary inflammatory process (►**Fig. 2-A**). A second surgical approach was necessary in this case because of a residual vulvar lesion. The biopsy and histological examination of this tissue were compatible with a Bartholin cyst

Vulvar hemangioma is an extremely rare pathology in adults; however, infantile hemangioma is one of the most common benign soft-tissue tumors in infants. The treatment of infantile hemangiomas has been changing from surgical incision to the use of oral corticosteroids, cryosurgery, laser, radiation, propranolol, and anticancer drugs vincristine and bleomycin.[12–14]

More recent reports also suggest alternative modalities for the treatment of this disease, such as the use of curcumin, indicating that the effectiveness of curcumin in hemangioma may be associated with its potent antiproliferative and apoptotic activities in hemangioma endothelial cells.[15]

Conclusion

To conclude, this case represents a rare situation of a vulvar hemangioma that presented as a genital ulcer, associated with psychological and physical dysfunction for the patient. The symptoms of itching, pain and sexual impairment were significant, and the delay in the diagnosis and resolution of the problem were a source of distress for the patient and her husband. We emphasize the importance of following the steps of the differential diagnosis and proceeding with a surgical approach only if necessary.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Febrile Neutropenia following Parvovirus B19 Infection and Cross Anti-Kell Reaction to *E. Coli* in Pregnancy

Infeção por parvovírus B19 causando neutropenia febril e reação cruzada anti-Kell com E. coli na gravidez

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Abstract

Parvovirus B19 has tropism for red line blood cells, causing immune hydrops during pregnancy. A positive anti-Kell Coombs reaction usually happens during pregnancy when there is production of antibodies that target Kell antigens, but cross reactions to other antigens may occur. A 24-year-old Gypsy primigravida, 0 Rhesus positive, presented with persistent isolated hyperthermia for 2 weeks and a positive indirect Coombs test result with anti-Kell antibodies at routine tests. She had a 19-week live fetus. The blood tests revealed bicytopenia with iron deficiency anemia, leucopoenia with neutropenia, and elevated C-reactive protein. She was medicated with imipenem, and had a slow clinical recovery. Blood, urine and sputum samples were taken to perform cultures and to exclude other systemic infections. *Escherichia coli* was isolated in the urine, which most probably caused a transient cross anti-Kell reaction. *Haemophilus influenza* in the sputum and seroconversion to parvovirus B19 was confirmed, causing unusual deficits in the white cells, culminating in febrile neutropenia. Despite the patient's lack of compliance to the medical care, both maternal and fetal/neonatal outcomes were good. This a rare case report of 2 rare phenomena, a cross anti-Kell reaction to *E. coli* and parvovirus B19 infection with tropism for white cells causing febrile neutropenia, both events occurring simultaneously during pregnancy.

Keywords

- coombs test
- escherichia coli
- kell-active proteins
- parvovirus antenatal infection
- pregnancy complications
- infections

Resumo

O parvovírus B19 tem tropismo para as células sanguíneas da linha vermelha, causando hidropsia imune durante a gravidez. O teste Coombs anti-Kell positivo ocorre durante a gravidez quando há produção de anticorpos contra os antígenos de Kell, mas pode haver reações cruzadas para outros antígenos. Uma grávida primigesta de etnia cigana, de 24 anos, 0 Rhesus positivo, recorreu ao hospital às 19 semanas de gestação por hipertermia isolada persistente por 2 semanas e um teste Coombs indireto positivo por anticorpos anti-Kell em testes de rotina da gravidez. O estudo analítico revelou

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Palavras-chave
- teste coombs
- escherichia coli
- proteínas kell-ativas
- infeção antenatal por parvovírus
- complicações na gravidez
- infecções

bicitopenia com anemia ferropênica, leucopenia com neutropenia, e elevação da proteína C-reativa. A paciente foi medicada com imipenem, e teve uma recuperação clínica lenta. Foram colhidas amostras de sangue, urina e expectoração para culturas bacterianas. Na urina, foi isolada *Escherichia coli*, o que provavelmente causou a reação anti-Kell cruzada transitória. Na expectoração, foi isolada *Haemophilus influenza*, e foi confirmada seroconversão para o parvovírus B19, que causou um déficit incomum na linhagem sanguínea branca, culminando com neutropenia febril. Apesar da má adesão aos cuidados médicos, os desfechos materno e fetal/neonatal foram bons. Este é um caso de 2 fenômenos raros, uma reação cruzada anti-Kell à infecção por *E. coli*, e parvovírus B19 com tropismo para células brancas causando neutropenia febril, ambos ocorrendo simultaneamente durante a gravidez.

Introduction

Pregnancy is a physiological state of immunosuppression. This raises the risk of asymptomatic colonizations or clinical infections. Concerning infections during pregnancy, there is a general trend to overvalue their teratogenic effect, especially regarding infections caused by toxoplasma, other viruses (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus and herpes (TORCH) agents, and sometimes the potential harm to the mother is underestimated.[1] As immune-compromised patients, pregnant women are not only prone to contracting more infections, but also more severe infections, with challenging differential diagnoses (including the physiological changes that occur during pregnancy), and that are usually harder to treat, requiring inpatient care and intravenous medication more frequently.

Parvovirus B19 is a frequent and highly infectious virus during childhood, and is the cause of the fifth disease, also called erythema infectiosum or "slapped cheek syndrome", because of the characteristic facial rash. In healthy adults, it may cause a self-limited febrile illness with mild unspecific symptoms such as hyperthermia, arthralgia or erythema.[2] This fact may make it hard to suspect if there is no history of contact with affected people. The disease may be diagnosed with serologic tests (demonstrating seroconversion) or a polymerase chain reaction (PCR) test for viral DNA.[3] The virus has tropism for erythrocytes, so it may cause transient aplasia of the red line.[4] The affection of white cells and platelets is quite rare.[5,6] There is no specific treatment, as is the case for most temporary viral diseases.[7] The infection by parvovirus B19 is also a well-known potentially teratogenic infection if acquired during pregnancy, especially before the 20th week of gestation, and thus the importance of the diagnosis during pregnancy. The most common effect is hidropsia fetalis due to severe fetal anemia caused by the virus' tropism for the erythrocytes. Parvovirus B19 infection may also cause fetal myocarditis due to infection of the myocytes, which are attracted by the P antigen expressed on the fetal cardiac cells, leading to cardiac failure, abortion and/or fetal death.[8–10] The obstetric ultrasound is of upmost value to evaluate fetal morphology, presence of fetal edema, amniotic fluid index (AFI), and middle cerebral artery systolic peak velocity, which, if above 1.5 multiples of the median (MoM), may be an indirect sign of fetal anemia. This may be confirmed by culdocentesis.[2]

Pregnancy itself may induce changes in the blood cell count, a slight tendency to mild anemia, thrombocytopenia and leukocytosis, which are considered physiological changes.[11] Although more uncommon, other findings in blood tests during pregnancy are those concerning the indirect Coombs test, revealing some degree of cross reaction to fetal red cell antigens. The most common reaction (in the absence of prophylaxis) is in the Rhesus (Rh) antigens in Rh negative mothers. Minor antigens are common and less concerning, such as the Kell antigen.[12] Kell antigen is highly immunogenic, but more than 90% of the population is Kell-negative; therefore Kell is not as usually associated with incompatibility as Rhesus. As for other immunogenic reactions, there may be cross reactions to similar antigens. There are some old studies that report that some microorganisms (gram-negative bacteria) may contain antigens similar to or cross-reactive with human blood group antigens. Some subtypes of *Escherichia coli* may produce soluble substances with A-like and K-like blood group activity; however, little has been described in the literature about this phenomenon so far.[13,14]

Case Description

A 24-year-old pregnant gypsy woman came to our emergency department with persistent hyperthermia during the previous 2 weeks (around 39°C).

She was at the 19th week of her 1st gestation, estimated by the 1st ultrasound scan, which was performed at 16 weeks. This pregnancy had been poorly monitored because of the patient's lack of compliance. She had no medical history of any other surgical pathologic background, and no history of transfusion of blood components. She was immune to toxoplasmosis and rubella, and her blood type was 0 Rh positive.

The patient presented with hyperthermia persisting for 2 weeks. She had been previously medicated by her general practitioner (GP) with paracetamol 1 g per os, with temporary symptomatic relief. She reported her youngest nephew

(whom she usually took care of) had had varicella zoster primary infection (chickenpox) three weeks before, but she didn't know if she had had this infection before, and she hadn't been medicated with immunoglobulin. The patient didn't have any other signs or symptoms, including those concerning the respiratory, digestive or urinary tracts, or any cutaneous erythema. She also had the result of her routine pregnancy blood tests performed during this 2-week period, which showed a positive indirect Coombs test with anti-Kell antibodies (the titter was 1:32).

Upon admission, she had 38°C of body (auricular) temperature, 110/58 mm Hg of blood pressure, 112 bpm of cardiac frequency, 16 breaths per minute, and 98% of peripheral blood O2 saturation. She had normal mucosa coloration, and underwent cardiac and pulmonary auscultations, as well as an abdominal examination. There were no signs of edema. There were no abnormal cutaneous findings. The patient refused the gynecological examination.

The obstetric ultrasound scan revealed the patient had a 19-week live fetus, with no abnormal morphologic findings and normal AFI.

Maternal blood tests revealed bicytopenia with iron deficiency anemia (hemoglobin [Hgb]: 9.1 g/dL; mean corpuscular hemoglobin: 26.8%; mean corpuscular volume: 79 fL; iron: 34 ug/dL; and transferrin saturation [TSAT]: 10%), leukopenia (1700/uL) with neutropenia (200/uL, 13.6%), and elevated C-reactive protein (CRP: 163 mg/L). Blood, urine and sputum samples were taken to perform cultures and to exclude infection by: the hepatitis B virus (HBV) or the hepatitis C virus (HCV), the human immunodeficiency virus (HIV), cytomegalovirus (CMV), the Epstein-Barr virus (EBV), parvovirus B19, brucellosis, tuberculosis and syphilis. The Coombs test was repeated.

With the presumptive diagnosis of febrile neutropenia of unknown etiology, the patient was admitted to our high-risk pregnancy ward in isolation for treatment and further investigation. Empiric treatment with intravenous imipenem (500 mg each 12 hours) was started.

During the first days, the patient maintained the hyperthermia despite the antibiotic therapy, and her white blood cell count had only a slight improvement, despite the descending CRP. She was then submitted to a bone marrow biopsy.

The results of the study performed were negative for HBV, HCV, HIV, CMV, EBV, brucellosis infections, as well as for the diseases diagnosed by the Venereal Disease Research Laboratory (VDRL) test. The blood culture was negative, but the urine culture was positive for *E. coli*, and the sputum culture was positive for *H. influenza*; these last two cultures were sensitive to β-lactam antibiotics. The bone marrow biopsy revealed abnormal maturation of the granulocytes, with excessive stage III cells. The parvovirus B19 antibody blood test was positive for immunoglobulin M (IgM) and immunoglobulin G (IgG) (available only after discharge). The indirect Coombs test confirmed the previous findings (Ccee Kell-positive). The male progenitor was summoned to be tested for Kell antigen, but he never showed up.

Ten days later, the patient demanded to be discharged, against medical advice. The patient was clinically better, asymptomatic and apyretic. The blood tests revealed an improvement in the cell count and inflammatory parameters (Hgb: 9.5 g/dL, leukocytes: 1,800/uL, neutrophils: 500/uL, 29%; and CRP: 14.8 mg/L) (►**Table 1**). The obstetric ultrasound revealed that the amniotic fluid was normal, and that the peak systolic velocity of the middle cerebral artery was also normal. The patient was referred to our outpatient clinic to undergo a two-week interval obstetric ultrasound and frequent internal medicine and obstetric surveillance. She only came to one appointment of internal medicine at 22 weeks, 2 of obstetrics at 24 and 28 weeks, and 1 obstetric ultrasound scan at 30 weeks. During all of this period, the patient was asymptomatic, and the entire blood sample tests were normal, except the anti-Kell titters in the indirect Coombs test, which were 1/16 at 23 and 27 weeks. The routine pregnancy serum and urine analyses were normal. The obstetric ultrasound at 30 weeks revealed that there were no morphologic abnormalities: the fetus was in a cephalic presentation, with a growth percentile of 57, deepest fluid pocket of 3.4 cm (AFI of 11.5), and normal blood flow parameters at the umbilical and middle cerebral arteries. The

Table 1 Evolution of maternal serum analysis results throughout pregnancy

	19w4d (Admission)	19w6d	20w0d	20w3d	20w5d	21w0d (Discharge)	23w3d	27w5d	37w5d (Labor)
Hemoglobin (g/dL)	9.1	10.4	8.5	9.6	10.0	9.5	10.0	10.5	10.4
Hematocrit (%)	27	32.1	25.7	29.1	29.9	28.6	29.9	32.3	33.1
Leukocytes (x10^3/uL)	1.7	2.1	2.2	1.9	1.9	1.8	3.0	6.0	6.5
Neutrophils (x10^3/uL) [%]	0.2 [14]	0.4 [17]	0.4 [19]	0.4 [23]	0.4 [19]	0.5 [29]	1.5 [51]	4.5 [75]	4.6 [70.2]
Platelets (x10^3/uL)	249	269	256	274	263	252	254	225	205
C-reactive protein (mg/L)	163	147	84	23	14.1	14.8	–	–	14.5
Indirect Coombs test (titter)		Anti-Kell (1/32)					Anti-Kell (1/16)	Anti-Kell (1/16)	Negative

fetal echocardiography was also normal. From then on, the patient missed all of the medical appointments.

At 37 weeks and 4 days of gestation, the patient was readmitted to our hospital with premature rupture of membranes. Upon admission and postpartum, the blood cell count was normal, and the indirect Coombs test result was negative. She had an uncomplicated vaginal delivery. The female newborn weighed 2,780 g at birth, with Apgar scores of 9 and 10 at the 1st and 5th minutes of life respectively, with no visible abnormalities, and the first days of life examinations were normal, with the newborn requiring no special medical intervention. The analysis of the newborn at birth revealed normal levels of leucocytes (20.6×10^3/uL [normal range: 5–21]); normal total and direct bilirubin; and negative CRP. The patient was Kell-negative, and the direct Coombs test was negative as well. Both mother and child were discharged 48 hours after the delivery, according to hospital protocol. The patient never returned to the scheduled medical appointments since then, so we lost track of her and her child.

Discussion

Pregnancy is a well-known physiological state of immunosuppression. This fact allows the pregnant woman to tolerate antigens in her own body that otherwise would be strange to her immune system, thus avoiding the rejection of fetal antigens. On the other hand, as a consequence, pregnant women are more prone to infectious diseases. The result may only be asymptomatic colonization by microorganisms, and the most common types of colonization are vaginal candidosis and asymptomatic bacteriuria, but they may also result in severe infections, such as septicemia of various origins. Some infections may endanger the health of the mother, of the fetus, or of both of them. Our patient presented with persistent hyperthermia, with no other symptoms or physical findings suggesting any infectious origin. The blood study upon admission revealed iron deficiency anemia (which is common among pregnant women), leukopenia with neutropenia, and elevated CRP, so the patient was admitted to our inpatient ward with the diagnosis of febrile neutropenia, in isolation, and was medicated with a broad spectrum antibiotic (imipenem). Blood, Urine and sputum specimens were collected to search for points of infection. Serum analyses were preformed to exclude all major causes of hyperthermia and/or neutropenia. As initially there was no clinical improvement and there was still no explanation for the facts, a bone marrow biopsy was performed.

The studied revealed *H. influenza* in the sputum, and *E. coli* in the urine. Both agents were sensitive to imipenem. This could be part of the explanation for the febrile condition, but it wouldn't explain the neutropenia.

Blood tests revealed seroconversion to parvovirus B19 (IgG and IgM positive). Parvovirus B19 is the cause of infectious erythema. The patient had no cutaneous signs, but, in adults, this disease may have milder presentations. Hyperthermia is one of the other signs of parvovirosis. The patient also reported having contact with her nephew, who had chickenpox 3 weeks before, but the child had not been examined by a doctor, and there were no clinical data confirming this infection, so it is possible that he had a "slapped cheek" erythema caused by parvovirus B19, and infected his aunt afterwards. Parvovirus B19 has tropism for erythrocytes, and aplasia of the red line is common, especially in groups already suffering from anemia, including iron deficiency anemia, which was the case of our patient. However, there are few reports of bicytopenia or pancytopenia caused by parvovirus. Our patient had leukopenia with neutropenia, which (although rare) has already been described in the literature in healthy adults. There is a possibility that this immunosuppression, along with the pregnancy, may have led to the respiratory and urinary infections.

Parvovirus B19 is also a well-known potentially teratogenic infection, especially if acquired before 20 weeks of gestation. Our patient was in a limit age, considering this cutoff point, when the infection was acquired. Due to lack of compliance, the patient was only submitted to 2 obstetric ultrasounds, at 19 and 30 weeks, and none of them revealed fetal malformations, amniotic fluid changes, or signs of anemia, including middle cerebral artery systolic peak velocity. The Coombs test was only negative at delivery, but, as a serologic reaction, the result may remain positive for weeks after exposure to the antigen.

We had no opportunity to type the male progenitor for Kell, which would rule out the possibility of immune reaction if the father was negative. We opted not to type the fetus because there was no evidence of fetal anemia and so we could avoid an invasive procedure.

Unfortunately, it was not possible to correctly follow-up our patient and her child due to lack of compliance to the medical appointments, but, according to the facts we have, the pregnancy and the well-being of the mother and the fetus were not affected by these events. In the end, the newborn was Kell-negative, so the only explanation we have for the positive indirect Coombs test result is the urine colonization by *E. coli*, which, according to the literature, may explain the transient positive Coombs test.

Conclusion

Pregnancy is a physiological state of immunosuppression that may lead to atypical manifestations of different infectious diseases. Parvovirus B19 is a potentially teratogenic infection, but the possible harm to the mother must never be neglected. It has tropism for red line blood cells, but, in rare cases, it may affect the white line instead, which may be serious in immune-compromised groups such as pregnant women. Some infectious agents such as *E. coli* may be a cause of cross reaction to fetal blood antigens such as the Kell antigen, resulting in a false-positive indirect Coombs test.

Conflicts of Interest

The authors have no conflicts of interest to report.

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Instructions to Authors

Scope and policy

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

Manuscripts evaluation

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

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- Authorization of copyright transfer signed by all authors (scanned and attached as supplementary document) **Model;**
- In accordance with chapter XII.2 of Res. CNS 466/2012, in Brazil, research involving human subjects needs to inform the registration number referring to the Certificate of Ethical Assessment (CAAE) or the approval number of the research (CEP/CONEP) in the Ethics Committee. International manuscripts must present local ethical documentation to proceed with the submission process;
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The Brazilian Journal of Gynecology and Obstetrics publishes the following categories of manuscripts:

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

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

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

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

Editorial, only at the publisher's invitation.

Title

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

Abstract

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

Informational abstract of structured type of original articles

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

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

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

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

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

Informational abstract of structured type of systematic review articles

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

Objective: Declare the main purpose of the article.

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

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

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

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

Conclusions: Indicate the main conclusions and their clinical usefulness.

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

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

Keywords

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

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

Introduction

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

Methods

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

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

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

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

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

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

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

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

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

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

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

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

Script for statistical review of original scientific papers

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

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

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

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

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

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

Abstract: Does the abstract contain the proper article synthesis?

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

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

IMPORTANT!

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

Randomized clinical trial:

http://www.consort-statement.org/downloads/consort-statement

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

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

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

Results

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

ATTENTION!

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

Discussion

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

Conclusion

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

References

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

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Please check the American Medical Association (AMA) Citation Style to format your references.

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

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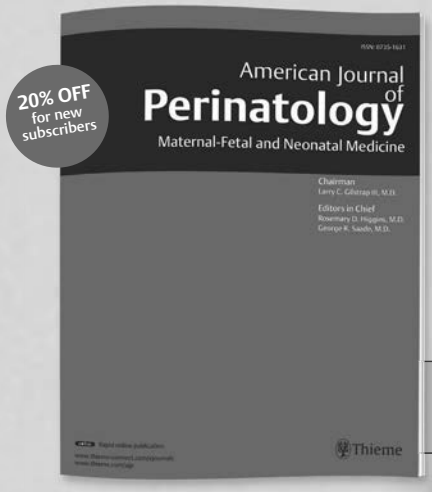

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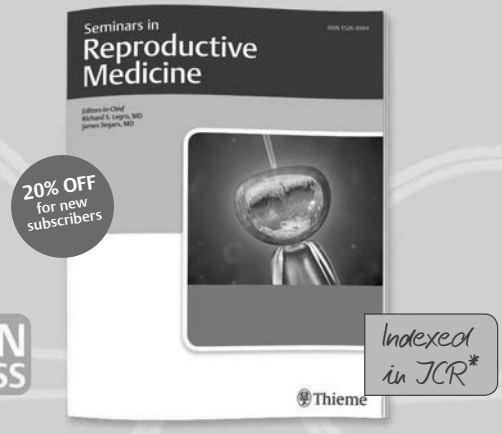

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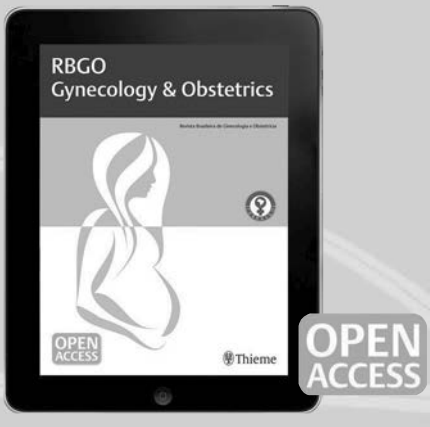

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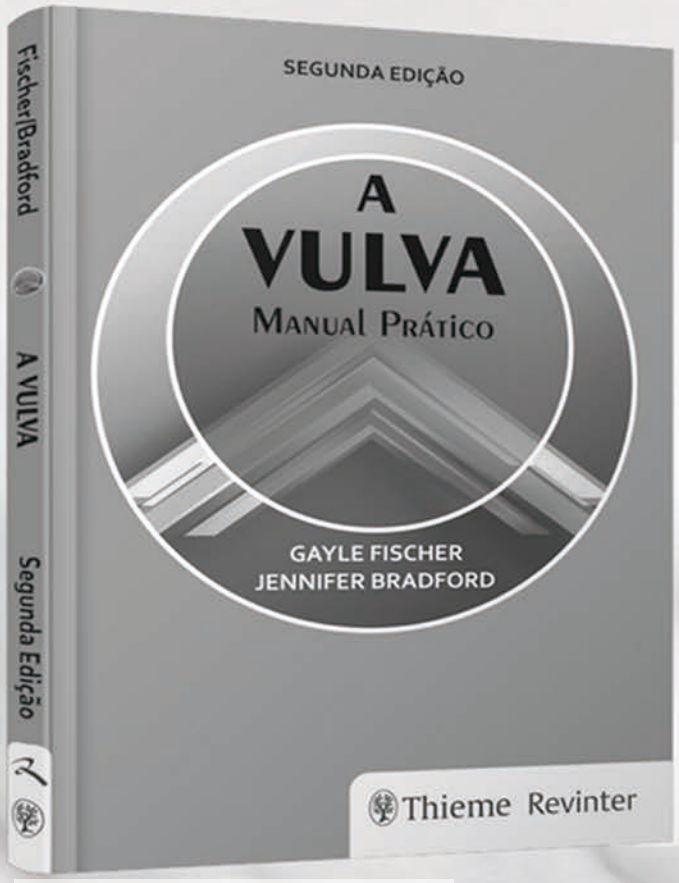

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