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Editorial

About the Performance of Latin American Gynecology and Obstetrics Journals in the International Scenario

Marcos Felipe Silva de Sá[1]

[1] Editor-in-Chief – Revista Brasileira de Ginecologia e Obstetrícia – RBGO

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In this issue, RBGO publishes a Letter to Editor[1] in which the author refers to the fact that Latin American Gynecology and Obstetrics Journals occupy low positions in the international rank of journals in the specialty and have little impact on the international scientific scenario. In his diagnosis to justify the low number of Latin American journals ranked in Scimago Journal Rankings (SJR) and the low citation rates of their articles, the author states that better quality articles are sent to international journals and there is little research training during medical residency, hence the authors have scientific limitations for this.

In fact, Latin American authors prefer to send their articles to international journals because of their greater visibility and projection. In the Brazilian case, additional factors of very relevant weight contribute to the international dispersion of our publications to the detriment of national journals. Regarding the lack of training in research during medical residency, in most countries, medical residency constitutes a differential for the training of professors in medicine. However, to become a professor/researcher of medicine in Brazil, especially in public universities, after performing the medical residency, the professional must attend a Postgraduate Program since medical residency programs are focused on preparing the physician for professional practice, and developing research and writing scientific texts is not part of their scope.

Postgraduate programs have two levels: Master or Doctoral studies. These programs are offered by few universities given the degree of requirements for their accreditation, done by a regulatory government agency, the Coordination for the Improvement of Higher Education Personnel - CAPES. Only a small portion of physician graduates from medical residency choose training in teaching and research in the Postgraduate Program. They study under guidance of a qualified professor (advisor), and for conclusion, students must prepare and defend a Master's or Doctoral thesis. For illustrative purposes, in 2021, 4,862 medical residency programs in different specialties were offered by 809 hospital institutions in Brazil in which 53,776 residents were enrolled.[2,3] On the other hand, considering the surgical and clinical areas, Master and Doctoral Postgraduate Programs are offered by 273 university institutions, where around 4,581 students were enrolled in 2021 (1,904 master and 2,677 doctoral students), corresponding only to 8.5% of the number of physicians enrolled in medical residency programs in Brazil.[4]

Master and Doctoral Postgraduate Programs became a great source of medical research in Brazil, and their scientific production corresponds to an important aspect in the assessment of their quality performed periodically by CAPES. The quality of research is measured based on evaluation of journals where papers are published and the Impact Factor (IF) or the CiteScore of the journal are used as main criteria, establishing a ranking called the Qualis System.[5] In the development of Qualis, CAPES places Brazilian journals in direct competition with the main international journals, especially from the North America and Western Europe, which makes this dispute very unequal, with a clear disadvantage for Brazilian journals which end up stratified in the lowest percentiles of the classification. Evidently, this fact makes the publication in Brazilian journals uninteresting for the researchers, as these publications contribute nothing or little to the score in the evaluation of the Postgraduate Program. For these reasons, they are motivated to try to publish their theses in foreign journals with higher IF. In general, theses evidently are publications with better scientific quality and will have a greater chance of citations in the literature.

However, it has not been easy to publish in important international journals. They have very high demands for manuscript submissions, which implies high rejection rates, often even for well-qualified articles, as in many occasions, research can focus on an issue relevant to a particular community or country, but that may be irrelevant or

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uninteresting to readers of a foreign journal. In addition, it is important to mention the high fees in US dollars or euros charged by renowned international journals, resources often inaccessible to authors, which can lead them to give up publishing even the already accepted articles. After all, by Brazilian standards, the cost of a publication in some international journals may be the equivalent of developing the entire research project. In short, the end result of this whole context is the high percentage of good quality theses that end up not being published, which is a regrettable fact considering the investments made in research projects that will have their results abandoned in drawers of laboratories.

Despite all these difficulties, data presented in the charts of the Letter to Editor[1] show a Brazil with strong scientific production quantitatively and qualitatively, ahead of other countries in Latin America. Brazil currently occupies the 13th position in the world in scientific publications and our universities stand out in the international scenario. Brazil is recognized as one of the countries that produce the most PhDs in the world and certainly already has the stature to be included in the list together to the main developed countries in research. Therefore, it would be natural for Brazil to have its own journals with international competitiveness. Unfortunately, Brazilian journals have not been the receptacles of much of the qualified science produced here due to the veiled incentive of CAPES for publications in foreign journals. CAPES seems not to believe in the potential of Brazilian journals to become internationally competitive in the short or medium term. Nowadays, ~25–30% of articles published in RBGO, like in many others Brazilian journals, originate from authors from other countries, particularly in Latin America and Asia. So we must believe that we already have journals with international acceptance and potential to be competitive.

It is noteworthy that journals in the medical fields are maintained and financed by specialties societies themselves which are private and non-profit entities. The journals are edited as a result of the selfless work of their associates, who, in general, are professionals linked to universities and research institutions. They are the ones exercising functions of editors, reviewers, editorialists, etc., and almost all are teachers/advisors of Postgraduate Programs. All of them work voluntarily without any remuneration, trying to offer to Brazilian authors the opportunity to publish in journals of increasingly better quality and already with great international visibility. Therefore, it is difficult to understand how CAPES, which has on the advisors the support of the Postgraduate Programs, does not recognize these activities as an important part of the expression of national scientific production.

As a governmental Agency CAPES needs to make available competitive journals to internationally disseminate the significative Brazilian scientific production, especially those arising from the PPGs. It is necessary to create an opportunity to boost national journals and this has been a long-time request of Brazilian journals editors. The time has come for the Qualis System to be revised to become an instrument of a State policy to encourage Brazilian scientific literature. CAPES could establish the minimum quality criteria required for Brazilian journals based on international publishing standards and requiring them to be registered in the main international databases. Once they having fulfilled these requirements, each journal would have a established score designated on a scale attributed to Brazilian journals, without prejudice to the greater appreciation, in parallel, to international journals.

This way, the decision to publish papers in Brazil or abroad would be at researchers' free will, as they would always be contributing to increase the score of their respective Postgraduate Program. Everyone will have a gain: researchers (advisors and students), Postgraduate Programs, government funding agencies and Brazilian science as a whole, All this at zero cost to CAPES.

Therefore, dear readers, with regard to Brazilian journals, these are our explanations to answer the question: 'Latin America Obstetrics and Gynecology. What is up with the journals?'.[1] Although the question was addressed to Latin American Gynecology and Obstetrics Journals, in the case of Brazil, the explanations are valid for journals of all specialties.

Conflict of Interest
None declared.

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Estimate of Dietary Total Antioxidant Capacity of Pregnant Women and Associated Factors

Estimativa da capacidade antioxidante total da dieta de gestantes e fatores associados

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Abstract

Objective To investigate the dietary total antioxidant capacity (DTAC) of pregnant women, and associated factors.

Methods Cross-sectional study conducted with 785 pregnant adult women attended in primary health care centers of Ribeirão Preto, state of São Paulo, Brazil. Two 24-hour dietary recalls were obtained, and the usual intake was estimated through the Multiple Source Method. The DTAC was estimated using the ferric reducing antioxidant power assay. The relationship between the higher DTAC estimate ($\geq$ median of 4.3 mmol/day) and associated factors was investigated using adjusted logistic models with backward selection.

Results In total, 25% of the pregnant women were classified as overweight, and 32% as obese. The median (P25, P75) DTAC was 4.3 (3.3–5.6) mmol/day. Through adjusted logistic regression models with backward selection, a higher chance of DTAC estimates above the median among pregnant women aged $\geq$ 35 years old (2.01 [1.24–3.27]) was verified when compared with younger pregnant women. Women with prepregnancy overweight (0.63 [0.45–0.89]) and obesity (0.59 [0.40–0.88]) presented a lower chance of DTAC estimates above the median when compared with eutrophic pregnant women. A higher DTAC estimate was positively associated with the use of dietary supplements (1.39 [1.03–1.88]), and negatively associated with total dietary energy (0.59 [0.42–0.85]).

Conclusion The DTAC estimate over the median was associated with greater age, adequate body weight, use of dietary supplements, and lower energy intake.

Keywords
- total antioxidant capacity
- pregnant women
- diet
- antioxidants

Resumo

Objetivo Investigar a capacidade antioxidante total da dieta (CATd) de gestantes e os fatores associados.

Métodos Estudo transversal conduzido entre 785 gestantes adultas em acompanhamento de pré-natal em Unidades Básicas de Saúde de Ribeirão Preto, São Paulo, Brasil. Para a estimativa da dieta usual, 2 inquéritos recordatórios de 24 horas foram obtidos e ajustados empregando-se o Multiple Source Method. A CATd foi estimada com base no ensaio de potência de redução de ferro. Para investigar a relação entre a

Palavras-chave
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- gestantes
- dieta
- antioxidantes

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maior estimativa de CATd ($\geq$ mediana de 4,3 mmol/dia) e os fatores associados, foram empregados modelos de regressão logística ajustados em função backward.

Resultados No total, 25% das gestantes foram classificadas com sobrepeso e 32% com obesidade. A mediana (P25; P75) da CATd foi de 4,3 (3,3–5,6) mmol/dia. Em modelos de regressão logística ajustados em função backward, verificou-se maior chance da estimativa da CATd acima da mediana entre gestantes com idade $\geq$ 35 anos (2,01 [1,24–3,27]), quando comparadas às gestantes de menor idade. Mulheres com sobrepeso (0,63 [0,45–0,89]) e obesidade (0,59 [0,40; 0,88]) no período pré-gestacional apresentaram menor chance da estimativa da CATd acima da mediana, quando comparadas às eutróficas. A estimativa da CATd foi positivamente associada ao uso de suplementos dietéticos (1,39 [1,03–1,88]) e negativamente associada à energia total da dieta (0,59 [0,42–0,85]).

Conclusão A estimativa da CATd acima da mediana foi positivamente associada à maior idade, eutrofia, ao uso de suplementos dietéticos e à menor ingestão energética.

Introduction

Maternal nutrition during pregnancy has a great influence on birth outcomes and on the development of chronic diseases in adulthood.[1] Evidence suggests that adherence to healthy eating patterns composed of foods that are sources of antioxidants, such as fruits, legumes, and vegetables (FLVs), have a protective effect during pregnancy in relation to prematurity and low birth weight (LBW), promoting adequate childhood growth and development.[2]

Numerous vitamins and minerals with antioxidant properties are used to explain the pathway that connects maternal healthy eating behavior with fetal growth. Increased maternal intake of vitamin D supplements reduces the risk of small for gestational age (SGA) infants.[3] Furthermore, the adequate intake of zinc, magnesium, calcium, and vitamin D supplements is associated with a reduction in oxidative stress in pregnant women with gestational diabetes mellitus (GDM).[4]

Higher levels of reactive oxygen species are physiologically checked during pregnancy and may in fact be important for its organogenesis.[5] However, excessive production of free radicals associated with a low antioxidant defense can negatively impact the development of the placenta and, consequently, the health of the newborn.[5] To inhibit and/or reduce the damage caused by the action of free radicals, the human body has enzymatic and nonenzymatic antioxidant defense systems.[6]

The enzymatic defense system includes the enzymes superoxide dismutase, peroxidase, catalase, and glutathione-peroxidase. The activity of these enzymes depends on the participation of nonenzymatic cofactors, the diet being the main contributing factor for the regulation of the serum antioxidant status.[7]

Dietary antioxidants evaluated in isolation may not reflect the total antioxidant power of the diet, as this does not consider the additive or synergistic effects of the interaction between them. Therefore, the dietary total antioxidant capacity (DTAC) has been used to investigate the potential antioxidant effects of foods present in the diet, considering the synergy between them.[8] The DTAC is recognized as a potential marker of the quality of the usual diet and is positively correlated with the consumption of FLVs, and negatively correlated with the ingestion of fats.[9]

Evidence suggests that the DTAC is directly associated with a lower risk of all-cause mortality, cancer, and cardiovascular disease.[10] In a study conducted among pregnant women, it was found that women classified in the third tertile of the DTAC estimation had a 46% lower chance of premature births, regardless of confounding factors. In addition, at an intermediate level, the DTAC was associated with a 75% lower chance of LBW infants.[11]

Sociodemographic and lifestyle characteristics and the presence of morbidities influence food choices. Studies suggest that older pregnant women, who live with a partner, who perform paid work and have a higher level of education tend to adopt more diverse and healthier diets.[12] Conversely, it has been observed that younger pregnant women present greater adherence to the patterns of snacks (breads, cheese, sweets, and chocolate, among others).[13] However, we are unaware of the existence of studies that have investigated the factors associated with higher DTAC estimates in pregnant women.

The aim of the present study was to investigate the factors associated with higher DTAC estimates in pregnant women and to identify the main dietary sources of the DTAC.

Methods

This is a secondary analysis of a cross-sectional study conducted with 785 adult pregnant women attended at Primary Health Units of the Brazilian National Health System (SUS, in the Portuguese acronym) in the city of Ribeirão Preto, state of São Paulo, Brazil. Conducted between 2011 and 2012, the study aimed to investigate the association between the usual diet during pregnancy and GDM, as described in detail in the publication by Barbieiri et al.[14]

The pregnant women were invited to participate in the study when the oral glucose tolerance test (OGTT) was performed. A shift plan was established in five laboratories with the health department of the municipality. All interviews were conducted by previously trained nutritionists. The women that fulfilled the inclusion criteria and agreed to participate in the study were interviewed after signing the consent form.

Fasting blood samples, 1 and 2 hours after ingestion of a 75 g glucose overload, were obtained from all study participants. The glucose oxidase method was used to determine plasma glucose. The diagnosis of GDM was based on the 2014 World Health Organization (WHO) criteria.[15]

The sample size calculation was based on the primary outcome of the study, GDM. Considering a prevalence of 20% of GDM among adult women attended in the SUS, with an acceptable margin of error of 5%, a sample of 512 pregnant women was necessary.[16] Considering that, in logistic regression models, 10 cases are required for each exploratory variable, the sample was considered sufficient for the analysis of the present study.[17]

Women aged $\geq$ 20 years, with pregestational BMI $\geq$ 20kg/m^2 and screened for GDM from the 24th gestational week were included. Pregnant women diagnosed with previous type 1 or type 2 diabetes mellitus (DM), twin pregnancies, who reported use of drugs that altered blood glucose (such as glucocorticoids) and reported diseases that interfered with their habitual food consumption (chronic renal failure, acquired immunodeficiency syndrome or cancer) were excluded. In total, 1,446 women were invited to participate in the study, with 785 eventually included, as described in ►**Fig. 1**.

The estimation of the diet of the pregnant women was performed by means of 2 24-hour dietary recalls (24hR), following the "multiple-pass" methodology in 3 stages, between the 24th and 39th gestational weeks. The first 24hR was collected from all pregnant women on the day of the face-to-face interview.[18] The second 24hR was obtained from a subsample of 73% of the pregnant women through telephone contact, on nonconsecutive days, with at least 1 week between replications, regardless of the day of the week or season.

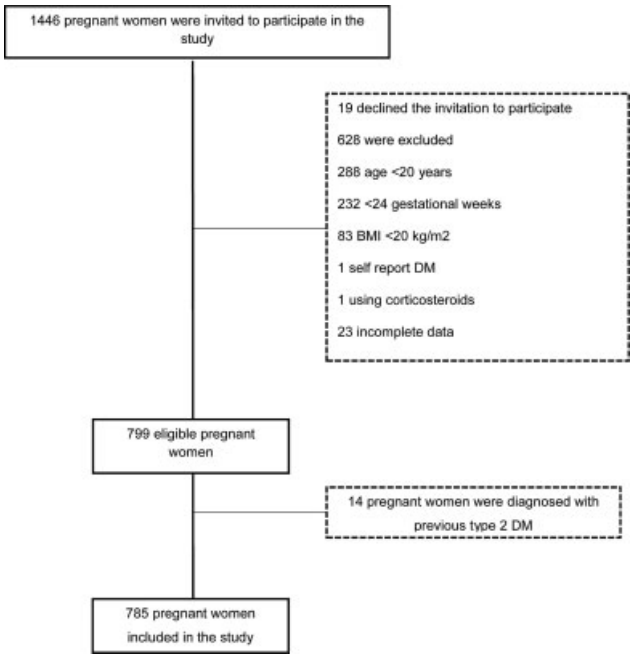

Fig. 1 Flowchart of the study.

For the estimation of dietary nutrients, the Brazilian Table of Chemical Composition of Food (TACO) was used with the NutWin® Program (Programa de Apoio à Nutrição. Version 1.5. São Paulo: Escola Paulista de Medicina; 2002).[19] The underreporting of energy intake was estimated using the method by Goldberg et al.[20], adopting a cutoff point of 1.35 for the ratio between the energy estimate and the basal metabolic rate.

The DTAC (in mmol/100 g), represented by the sum of the TAC of the food and the TAC determined in the supplements, was estimated using data from previous studies that established the total amount of antioxidant present in food and drink through the Ferric Reducing Antioxidant Power assay (FRAP).[8,21] For foods without TAC determination, the value of a similar food item or of the same botanical group was used: for chicory, endive and arugula, the spinach estimate was used. For red fruits, nectarines and cream, the TAC values of strawberry, peach and butter were used, respectively. For cooked foods that did not have certain TAC values, the value of the fresh food was used. To obtain the TAC value of homemade preparations, previously broken down into ingredients, the calculation of the TAC of each item of the recipe was performed. It was not possible to consider the TAC values of coconut water, salted cod, cane juice, flaxseed, maxixe, sardines, sova, and sushi, as the TAC has not been established for these foods.

The TAC of dietary supplements was estimated by multiplying the amount of antioxidant compound (mg or IU) present in the capsule by its TAC value (mmol/100 g). Of the antioxidant compounds present in the dietary supplements, it was not possible to estimate the TAC values of thiamine (B1), riboflavin (B2), nicotinamide (B3), pantothenic acid (B5), and biotin (B7), as the TAC has not been determined for these.

To estimate the usual DTAC, the Multiple Source Method (MSM) was used. This program was developed by the European Prospective Investigation in Cancer and Nutrition (EPIC) (https://msm.dife.de/).[22] The MSM estimates the usual intake of food and nutrients through the product of the probability of intake and the usual intake, corrected for variability. Correction for variability in intake eliminates the need for a large number of 24hR replications. The DTAC estimate was adjusted for the total dietary calories using the residual method.[23]

Information on age, self-reported skin color, education of the pregnant woman and of the head of the family, possession of items, occupation, marital status, parity, physical activity, smoking, consumption of alcoholic beverages, and use of dietary supplements was obtained by through a structured questionnaire. For the classification of the economic stratum, the Brazil Economic Classification Criterion was used, which defines the strata from A (highest level) to E (lowest level), based on the possession of items and on the educational level of the head of the family.[24]

Weight (kg) and height (m) measurements were obtained using a digital scale (TANITA model HS302 Arlington Heights, Illinois, 60005, USA) and a portable stadiometer (SANNY model ES2040 São Bernardo do Campo, São Paulo, 09628-060, Brazil), respectively. Gestational age was estimated from the date of the last menstrual period recorded on the card of the pregnant woman and was subsequently corrected through ultrasound. Pregestational weight was self-reported and corrected from recording on the card of the pregnant woman. The Institute of Medicine criteria were used to assess the adequacy of pregestational BMI (kg/m^2).[25]

Descriptive data were presented as mean ± standard deviation (SD) or median (P25, P75) for continuous variables, and *n* (%) for categorical variables. To investigate differences in maternal characteristics according to the DTAC tertiles, the chi-squared test (X^2) was used for the categorical variables and analysis of variance (ANOVA) or the Kruskal-Wallis tests for the continuous variables. The Spearman coefficient was used to investigate the correlation between the DTAC and the food and nutrient groups of the maternal diet.

The factors associated with the higher DTAC estimate ($\geq$ 4.3 mmol/day) were investigated in age-adjusted backward logistic regression models (20–25/25–30/30–35/$\geq$ 35 years old), self-reported skin color (white/not white), socioeconomic strata (A + B/C/D + E), living with a partner (yes/no), paid work (yes/no), pregestational BMI (kg/m2), current smoker (no/yes), physical activity ($<$ 150 minutes/$\geq$ 150 minutes of walking and/or physical exercises per week), education ($<$ 4/4–8/$\geq$ 9 years of study), parity ($<$ 1/$\geq$ 2 children), consumption of alcoholic beverages (yes/no), use of food supplement (yes/no), underreport of energy intake (yes/no), total dietary energy (kcal/day tertiles), and gestational trimester at the time of the interview ($2^{nd}/3^{rd}$). The associated factors investigated were determined through theoretical assumptions; however, the final models were established based on backward selection.

P values $<$.05 were considered significant. Statistical analyses were performed using the SPSS Statistics for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA).

The present article complies with the ethical principles contained in the Declaration of Helsinki. The study was approved by the Research Ethics Committee of the School Health Center of the Faculdade de Medicina de Ribeirão Preto (Auth. No. 014/2018-CEP/CSE - FMRP - USP).

Results

In total, 785 pregnant women were investigated. The mean (SD) age of the pregnant women was 28 (5) years old, and the education level varied between zero and 15 years of study. Among them, 25% were overweight and 32% were obese. The mean (SD) of the DTAC exclusively from the diet was 4.7 (2.4) mmol/day, with the mean considering the use of dietary supplements being 4.8 (2.5) mmol/day. The median (P25, P75) of the DTAC was 4.3 (3.3–5.6) mmol/day. Among the women classified in the third tertile of the DTAC, a greater proportion of self-reported white skin color presented a lower mean pregestational BMI when compared with the pregnant women with lower DTAC estimates (►**Table 1**).

A positive correlation was observed between the DTAC and the estimates of carbohydrates, fiber, vitamin A, vitamin E, folic acid, and the consumption of sugar, coffee and tea, beans, fruits, vegetables, dairy products, breads, and natural fruit juice. Conversely, there was a negative correlation between the DTAC and the consumption of snacks and sandwiches, soft drinks, and artificial juices (►**Table 2**).

The main food groups that contributed to the DTAC estimate were coffee and tea (24.12%), dairy products (21.34%), fruits, and natural fruit juices (20.37%) (►**Fig. 2**).

In the backward logistic regression models, it was found that pregnant women $\geq$ 35 years old were twice as likely to have an antioxidant intake above the median when compared with the younger pregnant women. The women that were overweight or obese in the pregestational period had a 37 and 41% lower likelihood of the DTAC estimate being above the median, respectively, when compared with the eutrophic pregnant women. Those that reported using dietary supplements during pregnancy had a 39% higher chance of ingesting DTAC above the median when compared with those who did not ingest them. There was also an inverse relationship between total dietary energy intake and the higher DTAC estimate. There was no significant association between the DTAC and the other factors investigated (►**Table 3**).

Discussion

Among the pregnant women investigated, women $\geq$ 35 years old, with pregestational BMI $<$ 25kg/m^2, and who reported using dietary supplements during pregnancy had a greater chance of ingesting antioxidants above the median DTAC ($\geq$ 4.3mmol/day). However, it was observed that pregnant women with higher energy intakes had less chance of ingesting antioxidants above the median DTAC ($\geq$ 4.3mmol/day).

The median DTAC observed among the pregnant women using the FRAP method was 4.3mmol/day, which is much lower than that reported in studies with adults in Spain (17mmoL/day) and France (13mmoL/day).[26,27] The findings of the present study agree with previous evidence that suggests a high prevalence of inadequate intake of nutrients with antioxidant properties by pregnant women in Brazil.[28] The discrepancy in DTAC values observed in the present study, when compared with data from other countries, can be partially explained by the low consumption of fruits and vegetables by the pregnant women in the sample. The mean daily consumption of fruits and vegetables observed was 87.30 g and 43.37 g, respectively, values well below those recommended by the WHO.[29]

In the present study, the coffee and tea groups (24.12%), dairy products (21.34%), and fruits and natural fruit juices (20.37%) were the ones that most contributed to the DTAC estimate of the usual diet of the pregnant women. Coffee stood out as the main DTAC source both due to its high antioxidant capacity and its high consumption, corroborating findings of other studies.[13,30] However, coffee

Table 1 Sociodemographic and lifestyle characteristics according to tertiles of the estimated dietary total antioxidant capacity of the pregnant women ($n = 785$)

	DTAC tertiles[a]			*p-value*[b]
	T1 ($n = 261$)	T2 ($n = 262$)	T3 ($n = 262$)	
Age (years old)	27 ± 5.2	28 ± 5.7	27.6 ± 5.51	0.07
White skin color self-reported	119 (45.6)	102 (38.9)	131 (50.0)	0.04
Education (years of study)				
< 4	8 (3.1)	9 (3.4)	10 (3.8)	0.13
4 to 8	67 (25.7)	84 (35.9)	94 (32.1)	
≥ 9	186 (71.3)	159 (60.7)	168 (64.1)	
Paid work	113 (43.3)	117 (44.8)	134 (51.1)	0.16
Socioeconomic stratum				
A + B	59 (22.6)	45 (17.2)	50 (19.1)	0.29
C	175 (67.0)	179 (68.3)	172 (65.6)	
D + E	27 (10.3)	38 (14.5)	40 (15.3)	
Living with partner	209 (80.1)	201 (76.7)	206 (78.6)	0.64
Parity (number of children)	1.11 ± 1.21	1.2 ± 1.29	1.2 ± 1.19	0.37
Pre-gestational body mass index (kg/m^2)	26.44 ± 5.6	25.86 ± 5.6	25.27 ± 4.5	0.02
Practice physical activity[c]	30 (0.0; 120.0)	45 (0.0; 140.0)	50 (0.0; 142.5)	0.14
Current smoker	24 (9.2)	22 (8.4)	25 (9.5)	0.44
Consumption of alcoholic beverages	68 (26.1)	70 (26.7)	59 (22.5)	0.50
Use of food supplement	153 (58.6)	170 (65.1)	176 (67.2)	0.10
Energy (kcal/day)	1981.55 ± 554.60	1956.60 ± 542.23	1926.25 ± 538.45	0.51
Energy underreport	136 (52.1)	109 (41.6)	124 (47.0)	0.06
Gestational trimester at interview				
Second	130 (49.8)	147 (56.1)	139 (53.1)	0.35
Third	131 (50.2)	115 (43.9)	123 (46.9)	

Values presented as mean ± SD or *n* (%) or median (P25; P75).
[a]DTAC, Dietary total antioxidant capacity. For the analysis, the DTAC adjusted for the total dietary calories, using the residual method, was considered. T, tertile. TAC (mmol/day) Mean (SD) minimum- maximum: T1 (2.8 [0.62], 0.3–3.6); T2 (4.4 [0.4], 3.6–5.2); T3 (6.9 [2.0], 5.2–21.84).
[b]$p < .05$ according to ANOVA test for the continuous variables with normal distribution, Kruskal-Wallis test for the continuous variables without normal distribution, and chi-squared test for the categorical variables.
[c]Minutes of walking or exercise/week

consumption during pregnancy should be moderate because caffeine is absorbed rapidly upon ingestion and passes the placental barrier leading to higher exposure for the fetus.[30] Observational studies suggest that excess intake of caffeine may be associated with negative birth results. In a meta-analysis of observational studies, there was a 3% increase in the risk of babies with low birth weight (LBW) for each additional 100 mg of caffeine consumed per day during pregnancy.[31]

The milk and dairy products group was the second group that most contributed to the determination of the DTAC of pregnant women. Despite the fact that milk is not a relevant source of TAC, a high consumption was verified in the study population. The group of fruits and natural fruit juices was the third that most contributed to the determination of DTAC. However, the mean consumption of fruit by the pregnant women was below that recommended by the WHO, contributing to a low mean intake of antioxidants.[29]

There was a positive correlation between sugar consumption and the DTAC. A possible explanation for this unexpected result is that sugar is commonly added to some of the DTAC source foods by the study population, such as coffee, tea, milk, and natural fruit juices.

The DTAC, in addition to measuring antioxidant intake, can be considered a potential marker of diet quality, allowing a comparison between our results and studies that assessed diet quality using dietary indices.[10] The data from the present study suggest a higher chance of estimating the DTAC above the median among eutrophic women, in agreement with previous evidence. In a study conducted by Laraia et al.,[32] the pregestational BMI was inversely associated with the quality of the diet of pregnant women, evaluated using the Diet Quality Index for Pregnancy (DQI-P).

A direct relationship between the age of the pregnant women and the DTAC was observed in the present study, corroborating studies that also found better quality diets in

Table 2 Characteristics of the diet according to the tertiles of the estimated dietary total antioxidant capacity of pregnant women ($n = 785$)

	DTAC tertiles[a]			
	Spearman correlation. (*r*)	T1 ($n = 261$)	T2 ($n = 262$)	T3 ($n = 262$)
Nutrients				
Carbohydrate (%TEV)	0.19[c]	53 (49; 58)	54 (51; 58)	56 (52; 59)
Protein (%TEV)	0.01	16 (14; 19)	16 (14; 18)	16 (14; 18)
Lipid (%TEV)	− 0.05	24 (21; 28)	24 (21; 27)	24 (21; 27)
Fiber/1000kcal	0.22[c]	11 (8; 13)	11 (9; 14)	12 (10; 14)
Vitamin A (mg)	0.14[c]	305 (219; 393)	346 (265; 468)	345 (262; 464)[b]
Vitamin B12 (mg)	0.06	4 (3; 6)	5 (3; 7)	5 (3; 6)
Vitamin C (mg)	0.32	30 (13; 89)	60 (22; 137)	102 (35; 197)[b]
Vitamin E (mg)	0.18[c]	4 (3; 5)	4 (3; 5)	4 (4; 6)[b]
Iron (mg)	0.05	63 (8; 69)	65 (9; 69)	65 (9; 69)
Zinc (mg)	0.00	10 (8; 12)	10 (8; 12)	10 (8; 12)
Selenium (mg)	− 0.23	82 (69; 95)	80 (69; 95)	77 (67; 99)
Folic Acid (µg)	0.23[c]	365 (302; 459)	399 (333; 490)	429 (344; 537)[b]
Foods				
Chocolate (g)	− 0.02	2 (1; 10)	2 (1; 21)	1 (1; 11)[b]
Sugar (g)	0.37[c]	2 (1; 5)	5 (2; 10)	9 (4;14)[b]
Rice (g)	− 0.04	218 (150; 301)	215 (159; 277)	201 (158; 267)
Coffee/Tea (ml)	0.49[c]	8 (4; 28)	29 (6; 666)	74 (28; 111)[b]
Beans (g)	0.09[c]	88 (52; 149)	110 (59; 149)	102 (71; 149)
Fruits (g)	0.31[c]	53 (31; 116)	87 (35; 160)	132 (57; 216)[b]
Snacks and sandwiches (g)	− 0.13[c]	11 (7; 42)	9 (6; 25)	9 (6; 13)[b]
Legumes (g)	0.16[c]	39 (24; 66)	47 (23; 78)	57 (30; 85)
Milk/Yogurt (ml)	0.28[c]	133 (38; 240)	199 (97; 277)	221 (133; 304)[b]
Eggs (g)	0.02	2 (2; 3)	2 (2; 3)	2 (2; 3)
Bread (g)	0.11[c]	49 (18; 55)	54 (31; 68)	54 (29; 68)[b]
Soda/Artificial Juice (ml)	− 0.21[c]	487 (230; 712)	357 (193; 580)	314 (154; 535)[b]
Natural Juice (ml)	0.16[c]	3 (2; 3)	3 (3; 2)	3 (2; 171)[b]
Root vegetables (g)	0.01	18 (11; 27)	17 (9; 39)	18 (10; 28)

[a]DTAC, Dietary total antioxidant capacity. For the analysis, the DTAC adjusted for the total dietary calories, using the residual method, was considered. TAC (mmol/day) Mean (SD) minimum - maximum: T1 (2.8 [0.62], 0.3–3.6); T2 (4.4 [0.4], 3.6–5.2); T3 (6.9 [2.0], 5.2–21.84).
[b]$p < .05$ according to the Kruskal-Wallis test (continuous variables without normal distribution).
[c]$p < .05$ according to Spearman Correlation test (*r*)

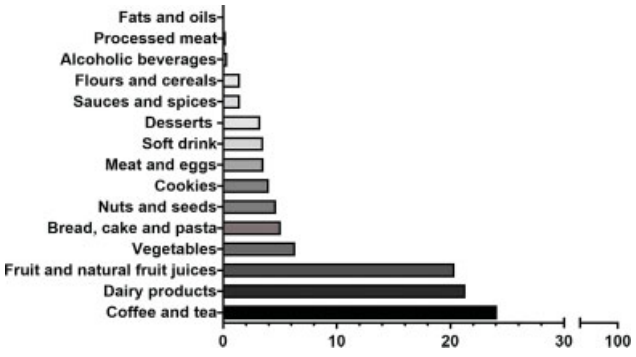

Fig. 2 Main dietary contributors to the DTAC intake of the pregnant women ($n = 785$).

older pregnant women.[13,33] One of these studies, conducted with Brazilian pregnant women, found that older women presented greater adherence to a "healthy" dietary pattern, composed of vegetables and legumes, fruits, and natural fruit juices.[14]

The mean (SD) of the TAC exclusively from the diet was 4.7 (2.4) mmol/day, with the mean considering the use of dietary supplements being 4.8 (2.5) mmol/day. There was a small variation in the DTAC when considering the use of a dietary supplement; however, this showed a direct relationship with the higher median of the DTAC. The combination of dietary sources rich in antioxidants and the use of supplements contributes to favorable health outcomes for the baby. However, further studies in other populations are needed. Pregnant

Table 3 Factors associated with the determination of the DTAC above the median (≥ 4.3 mmol/day) ($n = 785$)

	Total Antioxidant Capacity[a]					
	Unadjusted model			Adjusted model[b]		
	OR	95%CI	*p*-value	OR	95%CI1	*p-value*
Age (years old)			.03			0.02
20–25	1	–		1	–	
25–30	1.20	0.85–1.69		1.21	0.85–1.72	
30–35	1.12	0.75–1.65		1.16	0.77–1.73	
≥ 35	1.89	1.18–3.03		2.01	1.24–3.27	
Skin color self-reported			.24			
White	1	–				
Non-white	0.84	0.64–1.12				
Socioeconomic stratum			.11			
A + B	1	–				
C	1.06	0.74–1.52				
D + E	1.56	0.95–2.57				
Marital status			.61			
Married	1	–				
Single, widowed or separated	0.91	0.65–1.28				
Working			.61			
No	1	–				
Yes	1.08	0.81–1.42				
Pregestational body mass index			.01			0.003
< 25	1	–		1	–	
25–29	0.66	0.47–0.91		0.63	0.45–0.89	
≥ 30	0.66	0.45–0.98		0.59	0.40–0.88	
Current smoker			.89			
No	1	–				
Yes	1.03	0.63–1.68				
Practice physical activity			.73			
< 150 minutes	1	–				
≥ 150 minutes	1.06	0.76–1.49				
Education (years of study)			.13			
< 4	1	–				
4 to 8	0.86	0.39–1.91				
≥ 9	0.70	0.32–1.52				
Parity			.86			
≤ 1	1	–				
≥ 2	1.03	0.76–1.39				
Consumption of alcoholic beverages			.55			
No	1	–				
Yes	0.91	0.65–1.25				
Use of food supplement			.02			0.03
No	1	–		1	–	
Yes	0.71	0.53–0.95		1.39	1.03–1.88	
Energy underreport			.94			
No	1	–				
Yes	0.98	0.74–1.31				
Total dietary energy (kcal/d)[c]			.01			
T1	1	–		1	–	0.004
T2	0.64	0.46–0.91		0.62	0.44–0.89	
T3	0.64	0.45–0.90		0.59	0.42–0.85	
Gestational trimester at the interview			.56			
2nd	1	–				
3rd	0.92	0.69–1.22				

[a]DTAC Adjusted for total dietary calories, using the residual method. Median DTAC 4.3 mmol/day.

[b]Logistic regression model with age-adjusted backward function (20–25/25–30/30–35/≥ 35 years old), self-reported skin color (white/non-white), socioeconomic strata (A + B/C/D + E), living with partner (yes/no), paid work (yes/no), pre-pregnancy body mass index (kg/m^2), current smoker (no/yes), physical activity (< 150 minutes/≥ 150 minutes of walking and/or physical exercises/week), education (< 4/4–8/≥ 9 years of study), parity (< 1/≥ 2 children), consumption of alcoholic beverages (yes/no), use of food supplement (yes/no), underreport of energy intake (yes/no) total dietary energy (kcal/day tertiles) and gestational trimester at the time of the interview (second/third).

[c]Total dietary energy (kcal/d): T1: 644–1695 kcal/d; T2: 1696–2129 kcal/d; T3: 2130–4464 kcal/d.

women with lower energy intake were more likely to present DTAC estimates above the median. Evidence show that healthier diets are rich in foods with a high nutrient density and low energy density, as they are based on foods of plant origin. Consequently, they are rich in vitamins and minerals with antioxidant properties, as well as rich in fiber.[34]

The present study has some limitations, the main one being its cross-sectional design. The DTAC determination of the diet of the pregnant women was based mainly on an international database, in which the values may vary in relation to the food produced in Brazil, considering the differences in soil and climate. The underreporting of energy intake was estimated using the formula by Goldberg et al.[20], adopting a cutoff point $\leq$ 1.35.[20] The high proportion of underreporting of the diet among the participants in our study (47%) corroborates an investigation conducted among pregnant women in Ireland, in which the underreporting of energy intake was 42%, even adopting a cutoff $\leq$ 1.2.[35] It is important to note that the method by Goldberg et al.[20] may not be the best approach to estimate the underreporting of the energy intake during pregnancy, as it does not consider the practice of physical activity of the individual and presupposes the maintenance of body weight. In addition, the cutoff point of the BMI adopted as an inclusion criterion in the study was $\geq$ 20kg/m^2, not allowing the extrapolation of data for pregnant women with lower BMI values.

Among the strengths of the present study, its originality stands out. Furthermore, the data collection was performed by trained nutritionists, and the DTAC estimate was performed using 24hR adjusted through the MSM. Future studies are necessary to confirm the findings of the present study.

Conclusion

In conclusion, pregnant women $\geq$ 35 years old, eutrophic, using dietary supplements, and with lower energy intake had a greater likelihood of presenting DTAC estimates above the median. It should be highlighted that the DTAC of the evaluated pregnant women was the lowest value ever described in the literature, showing the importance of developing public policies that encourage adherence to the recommendations for the consumption of FLVs during the different life cycles.

Contributions

Carvalho M. R., Crivellenti L. C. and Sartorelli D. S. contributed to the design and planning of the study. Data collection was performed by Crivellenti L. C. and Sartorelli D. S.. The analysis and interpretation of the data was performed by Carvalho M. R. and Sartorelli D. S.. The first version of the manuscript was written by Carvalho M. R. and was revised by Crivellenti L. C. and Sartorelli D. S.. All authors approved the final version of the manuscript and are responsible for the content of the article.

Conflict of Interests

The authors have no conflict of interests to declare.

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Levels and Predictors of Anxiety and Depression in Turkish Pregnant Woman During the Covid-19 Pandemic

Níveis e preditores de ansiedade e depressão em gestantes turcas durante a pandemia de Covid-19

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Abstract

Objective In addition to being a medical phenomenon, pandemics affect the individual and society on several levels and lead to disruptions. In the pandemic process, different groups in the population, including pregnant women as a defenseless group, are subjected to psychological threat. The present study aimed to determine the levels of anxiety and depression and related factors in pregnant women during the the coronavirus disease 2019 (Covid-19) pandemic.

Methods The present cross-sectional study was conducted with 269 pregnant women through face-to-face interviews held in Istanbul, Turkey. Regarding the data collection tools, the Cronbach α reliability coefficient was of 0.90 for the Beck Anxiety Inventory, and of 0.85 for the Beck Depression Inventory.

Results Among the participating pregnant women, 30.5% had mild, 17.5% had moderate, and 5.9% had severe anxiety symptoms, whereas 35.3% had mild, 16.7% had moderate, and 2.2% had severe depression symptoms. We found that those who were concerned about their health had 5.36 times ($p = 0.04$) more risk of developing anxiety, and 4.82 times ($p = 0.01$) more risk of developing depression than those who were not concerned. Those who had a history of psychiatric disease had 3.92 times ($p = 0.02$) more risk of developing anxiety than those without it.

Conclusion We determined that about half of the pregnant women included in the study had some degree of anxiety and depression during the COVID-19 pandemic. The risk factors for anxiety and depression among the pregnant women were determined as smoking, concerns about health and getting infected with the coronavirus, history of psychiatric disease, and undergoing regular antenatal care.

Keywords
- Covid-19
- anxiety
- depression
- pregnant women

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Resumo

Objetivo Além de ser um fenômeno médico, as pandemias também afetam o indivíduo e a sociedade em vários níveis, e causam perturbações. No processo de pandemia, diferentes grupos da população, incluindo mulheres grávidas como um grupo indefeso, estão sujeitos a ameaças psicológicas. Este estudo teve como objetivo determinar os níveis de ansiedade e depressão e os fatores relacionados em mulheres grávidas durante a pandemia de doença do coronavírus 2019 (*coronavirus disease* 2019, Covid-19, em inglês).

Métodos Este estudo transversal foi realizado com 269 mulheres grávidas por meio de entrevistas pessoais em Istambul, Turquia. Com relação às ferramentas de coleta de dados, o coeficiente de confiabilidade alfa de Cronbach foi de 0,90 para a Escala de Ansiedade de Beck, e de 0,85 para a Escala de Depressão de Beck.

Resultados Entre as gestantes participantes, 30,5% apresentaram sintomas de ansiedade leves, 17,5%, moderados, e 5,9%, graves, ao passo que 35,3% apresentaram sintomas de depressão leves, 16,7%, moderados, e 2,2%, graves. Verificou-se que as participantes que se preocupavam com sua saúde tinham 5,36 vezes ($p = 0,04$) mais risco de desenvolver ansiedade e 4,82 vezes ($p = 0,01$) mais risco de desenvolver depressão do que aquelas que não se preocupavam. As pacientes que tinham histórico de doença psiquiátrica tinham 3,92 vezes ($p = 0,02$) mais risco de desenvolver ansiedade do que as que não tinham.

Conclusão Determinou-se que cerca de metade das gestantes incluídas no estudo tiveram algum nível de ansiedade e depressão durante a pandemia de Covid-19. Os fatores de risco para ansiedade e depressão nas gestantes foram determinados como tabagismo, preocupação com a saúde e infecção pelo coronavírus, histórico de doença psiquiátrica, e cuidados pré-natais regulares.

Palavras-chave

- Covid-19
- ansiedade
- depressão
- mulheres grávidas

Introduction

After reporting cases of pneumonia of unknown etiology in the city of Wuhan, Hubei province, China, on December 31st, 2019, on January 7th, 2020, the World Health Organization (WHO) declared the discovery of a novel coronavirus (2019-nCoV) that had not been determined in humans before. The virus, which causes a condition called coronavirus disease 2019 (Covid-19), then spread to the entire world rapidly, in what constituted a pandemic.[1] Although the virus was observed for the first time in China,[2] countries in Europe[3] and the United States[4] have been the most affected since, and the first case in Turkey was reported on March 11th, 2020. By August 9th, 2021, the total number of cases reported in Turkey was 5,895,841, while the number of deaths was 52,088.[5]

In addition to being a medical phenomenon, pandemics also affect the individual and society on several levels, and lead to disruptions. This is because people who experience panic and stress as the perception of the threat posed by the contagious disease increases display different behaviors than at other times. The way in which individuals and society manage and cope with the emotional and psychosocial effects of the uncertainty and crisis that emerge during the pandemic periods is important.[6] It is accepted as natural for people to display behaviors of protection and avoidance with the feelings of fear and panic while facing an unpredictable situation like an epidemic disease. The existing situation leads to health problems such as stress, anxiety, depressive symptoms, insomnia, denial, anger, and fear.[7] Pandemic-related questions without precise answers, such as when it will end and treatment/protection methods, and the constant exposure to an information flow regarding the pandemic and its effects and recommendations/bans, like social isolation and staying home as much as possible, may especially affect the mental health of the society in a negative way. It has been reported[8] that signs like anxiety, depression, fear, stress and sleep disorders are being observed more frequently during the Covid-19 pandemic in healthy individuals. At the same time, these symptoms are also common among Covid-19 patients.[9] In the pandemic process, different groups in the population, including pregnant women as a defenseless group, are subjected to psychological threat. In addition to the unknown nature of the virus, the lack of information about its transmission, reproduction, risk factors, mortality rates and maternal and fetal effects may pose a risk not only for the physical health but also for the mental health of individuals.[10]

While pregnancy is one of the most special situations that can be experienced by a woman throughout her life, transition to motherhood is a complex process in which physiological and psychological changes, as well as changes in sociality, take place, and several psychosocial factors are in interaction with

each other.[11–13] There are many factors that disrupt the mental health of the mother during pregnancy. These may include a history of previous depression, family history of depression, unwanted pregnancies, history of miscarriage and curettage, history of stillbirth, low socioeconomic status, anxiety related to the fetus, parenthood stress, and negative life experiences.[14–17] Mental health disorders are a cause of morbidity that is prevalently seen during pregnancy, and studies[18] have reported depression in 12% and anxiety disorders in 22% of pregnant women, especially in the second and third trimesters. Moreover, studies conducted in Canada[19] and Turkey[20] have revealed that pregnant women had higher levels of stress, anxiety and depression during the COVID-19 pandemic in comparison to before the pandemic. A study conducted among Iranian pregnant women by Effati-Daryani et al.[21] showed anxiety symptoms in 43.9% of the sample, and depression symptoms in 32.7%, at degrees varying from mild to highly severe. Consequently, considering the effects of mental disorders on maternal and fetal health, in order to determine and improve the psychological state of pregnant women and prevent complications, the most important responsibility of healthcare professionals is to provide psychological support and help in the recovery process. Therefore, the present study aimed to determine the levels of anxiety and depression and their related factors in pregnant women during the COVID-19 pandemic.

Methods

Design and Participants

The present is a cross-sectional study conducted to determine the levels of anxiety and depression levels of pregnant women and their associated factors during the COVID-19 pandemic.

The population of the study consisted of all pregnant women who visited the pregnancy polyclinics of three hospitals in the province of Istanbul, Turkey, between July 15th and September 15th, 2020 and volunteered to participate in the study. With a Type-I error rate of 0.05, ratios of 50% for the H_o hypothesis and 60% for the H_1 hypothesis, and a testing power of 99%, the minimum sample size needed for the study was calculated as 269 individuals.

Inclusion Criteria

Based on the objectives of the present study and a literature review, the inclusion criteria were as follows:

- Being in the first, second or third trimesters of pregnancy; and
- Being able to read and write in Turkish.

Exclusion Criteria

- Experiencing pregnancy complications;
- Getting diagnosed with Covid-19; and
- Being under psychiatric treatment.

Data Collection Tools

As the data collection instruments, we used a personal information form developed to determine the descriptive characteristics of the pregnant women and their risk factors that could be associated with anxiety and depression, the Beck Anxiety Inventory (BAI) to assess their anxiety symptoms, and the Beck Depression Inventory (BDI) to assess their depression symptoms.

Personal information form: Developed by the researchers and including twenty questions, this form asked for information on some sociodemographic characteristics of the pregnant women, their general health status and habits, obstetric characteristics, and psychosocial factors during the pandemic.

Beck Anxiety Inventory: Developed by Beck et al. (1988),[22] it measures the frequency of the anxiety symptoms experienced by the individual. Its validity and reliability study in Turkey was performed by Ulusoy et al. (1998).[23] It is a 4-point, 21-item Likert-type self-assessment scale in which each item is scored between 0 and 3. By adding the scores of all 21 items, scores in the range of 0 to 63 are obtained, and higher scores indicate higher levels of anxiety symptoms. The results of the BAI are: as 0 to 7 points – no anxiety symptoms; 8 to 15 points – mild anxiety; 16 to 25 points – moderate anxiety; and 25 to 63 points – severe anxiety. In the validity and reliability study by Ulusoy et al.,[23] the cutoff point of the scale was determined as 18. In the present study, the Cronbach alpha reliability coefficient of the BAI was determined as 0.90.

Beck Depression Inventory: Developed by Beck et al. (1961)[24] and adapted into the Turkish language by Hisli (1989),[25] the BDI consists of 21 items on depressive symptoms such as pessimism, sense of failure, self-dissatisfaction, guilt, irritability, fatigability, loss of appetite, indecisiveness, insomnia and social withdrawal. Each item contains 4 self-assessment statements and a 4-point Likert-type scoring system with scores ranging from 0 to 3 based on the severity of the depression. By adding the scores of all 21 items, scores in the range of 0 to 63 are obtained, and higher scores indicate higher levels of depressive symptoms. In the validity and reliability study conducted by Hisli,[25] the cut-off score of the scale was determined as 17. The results of the BDI are: 0 to 9 points – no depressive symptoms; 10 to 16 points – mild depressive symptoms; 17 to 29 points – moderate depressive symptoms; and 30 to 63 points – severe depressive symptoms.[25,26] In the present study, the Cronbach alpha reliability coefficient of the BDI was determined as 0.85.

Data Collection

The participants were informed verbally and in writing by the researchers about the objective and significance of the study. The pregnant women who agreed to participate and provided their written consent were directed to a private room where they would answer the forms in line with the rules enacted due to the pandemic. During data collection, it took each participant ~ 10 to 15 minutes to fill out the forms.

Ethical Considerations

To assess the ethical suitability of the study, an application was made to the Health Sciences Ethics Board at Bandırma Onyedi Eylül University, and approval was obtained under

number 2020/264. Additionally, written institutional permissions were received from the hospitals in order to conduct the study.

Data Analysis

The data were analyzed by using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, US) software, version23.0. The Kolmogorov-Smirnov test was used to examine if the variables conformed with a normal distribution. To examine the main effects of the sociodemographic data on the dependent variables of anxiety and depression, multivariate analysis of variance (MANOVA) was performed. Binary logistic regression analysis was used to determine the risk factors for anxiety and depression. The quantitative data are presented as mean and standard deviation values. The results were interpreted in a 95% confidence interval and a significance level of $p < 0.05$.

Results

The ages of the pregnant women in the sample varied from 20 to 45 years, and their mean age was of 31.74 ± 5.04 years. The mean gestational week was 24.50 ± 8.77, and 62.8% ($n = 169$) did not have any living children. The mean length of time they stayed home during the pandemic was of 56.93 ± 9.65 days (►**Table 1**).

We determined that, while 46.1% ($n = 124$) of the sample did not have anxiety, 30.5% ($n = 82$) had mild, 17.5% ($n = 47$) had moderate, and 5.9% ($n = 16$) had severe levels of anxiety symptoms. We observed that, while 45.7% ($n = 123$) of the participants did not have depressive symptoms, 35.3% ($n = 95$) had mild, 16.7% ($n = 45$) had moderate, and 2.2% ($n = 6$) had severe levels of depressive symptoms (►**Table 2**).

►**Table 2** presents the comparison of the BAI and BDI scores based on the descriptive characteristics of the sample. Significant differences were found in the mean BAI scores in terms of concerns about health, status of planning the pregnancy, history of psychiatric disease, concerns of being infected with the coronavirus, presence of an individual older than 65 years of age at their residence, and regular follow-up status ($p < 0.05$). While the mean BAI score of the pregnant women who were concerned about health was of 12.7, the mean score of those who were not concerned was of 5.9 ($p < 0.00$). The mean BAI score of those with a planned pregnancy was of 9.9, and for those with an unplanned pregnancy, it was was 14.1 ($p = 0.02$). Regarding history of psychiatric disease, the mean BAI score was of 16.1 among those who had it, while that of those without such a history was of 10 ($p = 0.01$). Those who were concerned about getting infected with the coronavirus had a mean score of 12.3 on the BAI, whereas that of those who were not concerned was of 6.2 ($p = 0.00$). The mean BAI score of the participants who shared their residence with individuals over the age of 65 was of 13.3, while for those that did not, it was of 9.9 ($p = 0.02$). The mean BAI score of those who were continuing regular antenatal follow-ups was pf 9.5, while the mean score of those who delayed their follow-ups was of 16.2 ($p = 0.00$).

In the present study, there were significant differences in the BDI scores regarding the participants' smoking status, concerns about health, and history of psychiatric disease ($p < 0.05$). Among the participants, while the mean BDI score of those who were smoking was 14.4, the mean score of those who were not smoking was 10.1 ($p = 0.03$). The mean BDI score of those who were concerned about health was 12, and for those who were not concerned, it was 6.8. And the mean BDI score of those with a history of psychiatric disease was 15.5, and for those without such a history, 9.8 ($p = 0.00$).

►**Table 3** presents the logistic regression results for the risk factors affecting the anxiety and depression levels of the study participants. We found that those who were concerned about their health had 5.362 times ($p = 0.04$) more risk iof developing anxiety, and 4.818 times ($p = 0.01$)more risk of having depression than those who were not concerned. There was a significant difference between the participants whose pregnancies were planned and those whose pregnancies were unplanned in terms of the presence of anxiety ($p = 0.05$). Those who had a history of psychiatric disease had 3.924 times ($p = 0.02$) more risk of developing anxiety than those without such a history. There was a significant difference between the participants who delayed their regular antenatal follow-ups and those who continued their follow-ups in terms of the presence of anxiety ($p = 0.01$).

Discussion

The present study aimed to determine the levels of anxiety and depression and related factors in Turkish pregnant women during the COVID-19 pandemic. Our findings showed that 53.9% of the pregnant women had anxiety and 54.3% of them had depression symptoms at varying degrees, from mild to highly severe. Lebel et al. (2020),[27] in a study with a similar sample, found a rate of anxiety of 59%, amd a rate of depression of 37%. In China, Wu et al.[28] found a prevalence of depression ofs 34.2%. In a study[21] in Iran, the prevalence of anxiety was determined as 43.9%. In a study[29] in India, the authors stated that the general prevalence of moderate and severe depression was of 13.2% ($n = 66$), and the prevalence of moderate and severe anxiety disorder was of 9.8% ($n = 49$). These studies have emphasized that the levels of anxiety and depression have increased among pregnant women in comparison to before the pandemic. While similar rates have been reported in a limited number of studies conducted in different countries during the COVID-19 pandemic, it was striking that the anxiety and depression rates in our study were a bit higher.[30] Examining the studies in the literature, one can see that they were conducted at the beginning of the pandemic (February-March 2020), while ours was conducted 6 months after the pandemic had started. The extension of the pandemic and the uncertain nature of this time may have increased the levels of anxiety and depression. At the same time, these findings emphasize the need for urgent interventions to

Table 1 Descriptive Characteristics of the Participants and Mean BAI and BDI Scores

Characteristics ($n = 269$)	Mean ± SD		
Age (years)	31.74 ± 5.044		
Week of pregnancy	24.50 ± 8.77		
Stayed at home during the pandemic (days)	56.93 ± 9.65		
Level of schooling	n (%)	BAI: mean ± SD	BDI: mean ± SD
Primary school	21 (7.8)	10.2 ± 5.9	10.7 ± 6.7
High school	57 (21.2)	10.8 ± 9	10.5 ± 6.1
Bachelor's degree	191 (71)	10.7 ± 8.9	10.4 ± 7.2
Economic status			
Income lower than expenses	14 (5.2)	11.4 ± 5.9	12.1 ± 6.6
Income equal to expenses	214 (79.6)	10.6 ± 8.7	10.5 ± 7
Income higher than expenses	41 (15.2)	10.9 ± 9.6	9.3 ± 6.4
Occupation			
Employed	176 (65.4)	10.9 ± 8.8	10.1 ± 6.6
Unemployed	93 (34.6)	10.1 ± 8.5	11 ± 7.5
Smoking			
Yes	20 (7.4)	14.3 ± 9.1	14.4 ± 7.9
No	249 (92.6)	10.4 ± 8.6	10.1 ± 6.7
Regular physical activity			
Yes	97 (36.1)	10.4 ± 8.4	10.8 ± 6.6
No	172 (63.9)	10.8 ± 8.9	10.2 ± 7.1
Presence of social support			
Yes	203 (75.5)	10.5 ± 8.4	10.4 ± 6.9
No	66 (24.5)	11 ± 9.6	10.5 ± 7.1
Concerned about health			
Yes	188 (69.9)	12.7 ± 9.2	12 ± 7
No	81 (30.1)	5.9 ± 4.5	6.8 ± 5.3
Planned pregnancy			
Yes	222 (82.5)	9.9 ± 8.2	9.9 ± 6.9
No	47 (17.5)	14.1 ± 10	13 ± 6.2
Chronic disease			
Yes	20	11.1 ± 7	11.4 ± 6.3
No	249	10.6 ± 8.8	10.3 ± 7
History of psychiatric disease			
Yes	27 (10)	16.1 ± 8.7	15.5 ± 7.4
No	242 (90)	10 ± 8.5	9.8 ± 6.6
Concerned about infection by the coronavirus			
Yes	195 (72.5)	12.3 ± 9.2	11.2 ± 6.9
No	74 (27.5)	6.2 ± 5	8.3 ± 6.4
Measures taken during the pandemic			
Use of face mask	201 (74.7)	10.7 ± 9	10.5 ± 7.3
Use of face mask + gloves	49 (18.2)	9.7 ± 7.1	9.7 ± 5.9
Use of face mask + gloves + disinfectant	19 (7.1)	12.1 ± 8.9	11.2 ± 5.4
Following Covid-19 news			
Yes	254 (94.4)	10.6 ± 8.7	10.4 ± 7
No	15 (5.6)	12 ± 8.8	9.9 ± 5
Presence at home of an individual older than 65 years of age			
Yes	58 (21.6)	13.3 ± 8.5	10.5 ± 6.7
No	211 (78.4)	9.9 ± 8.6	10.4 ± 7
Receiving regular antenatal care			
Yes	222 (82.5)	9.5 ± 8	9.9 ± 6.6
No	7 (2.6)	15.4 ± 9.1	15.3 ± 8.4
I chose to delay	40 (14.9)	16.2 ± 10.2	12.2 ± 8

Abbreviations: Covid-19, coronavirus disease 2019; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; SD, standard deviation.

Table 2 MANOVA Results of the BAI and BDI Scores Based on The Descriptive Characteristics of the Sample

Characteristics ($n = 269$)	Scales	SS	df	MS	F	*p*-value	η^2
Level of schooling	BAI	29.31	2	14.65	0.25	0.78	0.00
	BDI	3.34	2	1.67	0.04	0.96	0.00
Economic status	BAI	36.50	2	18.25	0.32	0.73	0.00
	BDI	28.73	2	14.37	0.36	0.70	0.00
Employment status	BAI	11.63	1	11.63	0.20	0.65	0.00
	BDI	95.43	1	95.49	2.41	0.12	0.01
Smoking status	BAI	160.51	1	160.51	2.77	0.10	0.01
	BDI	174.04	1	174.04	4.39	0.03	0.01
Regular exercise	BAI	10.91	1	10.91	0.19	0.67	0.00
	BDI	16.11	1	16.11	0.41	0.52	0.00
Presence of social support	BAI	14.01	1	14.01	0.24	0.62	0.00
	BDI	4.62	1	4.62	0.12	0.73	0.00
Concern about health	BAI	794.87	1	794.87	13.73	< 0.00	0.05
	BDI	982.78	1	982.78	24.82	< 0.00	0.09
Planned pregnancy	BAI	306.20	1	306.20	5.29	0.02	0.02
	BDI	150.39	1	150.39	3.80	0.05	0.02
Chronic disease during pregnancy	BAI	28.79	1	28.79	0.50	0.48	0.00
	BDI	3.92	1	3.92	0.09	0.75	0.00
History of psychiatric disease	BAI	379.10	1	379.10	6.55	0.01	0.03
	BDI	441.02	1	441.02	11.14	0.00	0.04
Precautions taken during the pandemic	BAI	4.76	2	2.38	0.04	0.96	0.00
	BDI	4.25	2	2.18	0.05	0.95	0.00
Concerns of getting infected by the coronavirus	BAI	521.51	1	521.51	9.01	0.00	0.04
	BDI	17.98	1	17.98	0.45	0.50	0.00
Following Covid-19 news	BAI	30.59	1	30.59	0.53	0.46	0.00
	BDI	0.01	1	0.01	0.00	0.98	0.00
Presence at home of an individual older than 65 years of age	BAI	319.87	1	319.87	5.52	0.02	0.02
	BDI	16.12	1	16.12	0.41	0.52	0.00
Receiving regular antenatal care	BAI	813.50	2	406.75	7.03	0.00	0.05
	BDI	56.25	2	28.13	0.71	0.49	0.01

Abbreviations: η^2, partial eta-squared; Covid-19, coronavirus disease 2019; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; MANOVA, multivariate analysis of variance; MS, mean squares; SD, standard deviation; SS, sum of squares.

increase the state of psychological wellbeing during pregnancy.

According to the results of the logistic regression analysis, the variables of the pregnant women (experiencing concern about their health, having an unplanned pregnancy, presenting history of psychiatric disease, and not attending regular antenatal follow-ups) were determined as predictors of anxiety symptoms. As a predictor of depression symptoms, only the status of being concerned about health was determined. During the pandemic, various nationwide precautions are being taken to reduce the spread of the virus, including social distancing, curfews, and self-isolation. At the same time, following the announcement of the start of the second wave of the pandemic worldwide, the numbers of infections and deaths continued to increase fast. Considering all these factors, it is inevitable for pregnant women, who are considered a risk group, to have concerns about their health. Similar to our study, the study by Lebel et al. (2020)[27] conducted on pregnant women found that the fact that pregnant women had concerns about their health and that of their babies increased their anxiety levels. In similar studies[17,31–33] conducted before the pandemic, history of psychiatric disease, not receiving regular antenatal care, and unplanned pregnancies were identified as risk factors affecting the prevalence of anxiety and depression. In their study on a Turkish population in the pandemic period, Özdin and Bayrak Özdin[34] determined that the female gender and history of psychiatric disease were risk factors for anxiety and depression. This is why it was an expected finding that, during the pandemic, pregnant women had relatively high levels of anxiety and depression.

Table 3 Risk factors affecting Anxiety and Depression levels

Characteristics	Beck Anxiety Inventory		Beck Depression Inventory	
	OR (95%CI)*	*p*-value	OR (95%CI)**	*p*-value
Education level				
Primary school	0.212 (0.015–3.004)	0.25	0.215 (0.027–1.718)	0.15
High school	1.494 (0.551–4.053)	0.43	0.93 (0.356–2.43)	0.88
Income status				
Income lower than expenses	0.147 (0.009–2.284)	0.17	2.441 (0.312–19.111)	0.40
Income equal to expenses	0.485 (0.172–1.368)	0.17	1.471 (0.477–4.537)	0.50
Employment status (no)	0.994 (0.406–2.436)	0.99	0.465 (0.208–1.038)	0.06
Smoking (no)	3.121 (0.824–11.818)	0.09	2.706 (0.826–8.861)	0.10
Regular exercise (no)	0.826 (0.354–1.928)	0.66	0.947 (0.432–2.076)	0.89
Presence of social support (no)	1.026 (0.385–2.731)	0.96	1.094 (0.443–2.699)	0.85
Concern about health (no)	5.362 (1.092–26.33)	0.04	4.818 (1.451–15.999)	0.01
Planned pregnancy (no)	0.366 (0.134–0.996)	0.05	0.977 (0.361–2.64)	0.96
Chronic disease during pregnancy (no)	0.459 (0.099–2.127)	0.31	0.514 (0.12–2.199)	0.37
History of psychiatric disease (no)	3.924 (1.244–12.379)	0.02	2.692 (0.95–7.634)	0.06
Length of stay at home during the pandemic	1.004 (0.965–1.045)	0.83	1.013 (0.975–1.053)	0.52
Isolation precautions taken during the pandemic				
Use of mask	1.859 (0.416–8.316)	0.42	1.187 (0.277–5.084)	0.82
Use of mask and gloves	1.82 (0.322–10.271)	0.50	0.939 (0.171–5.153)	0.94
Concern about getting infected by the coronavirus (no)	6.064 (1.203–30.571)	0.03	0.947 (0.353–2.54)	0.91
Following Covid-19 news (no)	1.934 (0.304–12.295)	0.49	3.349 (0.337–33.256)	0.30
Presence at home of an individual older than 65 years of age (no)	2.319 (0.996–5.395)	0.05	1.614 (0.71–3.666)	0.25
Receiving regular antenatal care				
Yes	0.283 (0.109–0.734)	0.01	0.523 (0.2–1.367)	0.19
No	2.298 (0.225–23.448)	0.48	2.185 (0.328–14.553)	0.42

Abbreviations: 95%CI, 95% confidence interval; Covid-19, coronavirus disease 2019; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; OR, odds ratio.
Notes: *Cox & Snell R^2: 0.231; Nagelkerke R^2: 0.380; accuracy: 0.870. ** Cox & Snell R^2: 0.112; Nagelkerke R^2: 0.192; accuracy: 0.867; $p < 0.05$.

In the present study, we determined that the regular practice of exercise and the presence of social support were not among the risk factors affecting the levels of anxiety and depression among the pregnant women. This finding contradicts with that of similar studies that have shown that physical activity and social support are associated with reduced anxiety and depression symptoms.[35–37] However, Lebel et al. [27] did not find a relationship between increased physical activity and reduced anxiety either.[22] The rate of regular physical activity in the pregnant women in our sample was of 36.1%. It may be stated that isolation measures taken during the pandemic (curfew, social distancing etc.) have led to a limitation in physical activity, especially in metropolitan areas, where the pandemic is intensely experienced. Encouraging pregnant women to perform physicala activities while taking the necessary protective measures is one of the most important interventions among the strategies to cope with the symptoms of anxiety and depression.

Social support is an important determinant of physical and psychological wellbeing, especially during pregnancy, when individuals are taking on new responsibilities and roles. Supportive social relationships affect mental health directly by encouraging positive health behaviors, increasing positive emotions, strengthening emotional regulation, and indirectly reducing reactions to physical stress.[38] In the present study, the prevalence of social support was of 75.5%. In the traditional structure of the Turkish society, the belief that pregnant and postpartum women should not be left alone is prevalent. In general, during pregnancy, support is provided by the mothers or grandmothers of the pregnant women, who, since they are generally older than 65 years of age, are also in another risk group for Covid-19. For this reason, during the pandemic, for the fact that pregnant women may have to provide care for family members who live in the same residence as them may comprise an additional risk factor. Moreover, unlike similar studies, the fact that the present study was conducted during the pandemic shows how strong the effect of the pandemic was on the psychological health of the pregnant women, even in the presence of social support.

One of the limitations of the present study was that its cross-sectional design may not completely reflect the causality in the relationship between the sociodemographic variables and the levels of anxiety and depression. Another limitation was that it was conducted in the province of Istanbul, which concentrated ~ 60% of the cases of Covid-19 in Turkey. Therefore, the present study may not represent all pregnant women in Turkey. The small sample size is among the most important limitations of the study.

The Covid-19 pandemic was found to cause hemodynamic changes in the brain.[39] The present study mainly used self-reported questionnaires to measure psychiatric symptoms, and did not make clinical diagnoses. The gold standard to establish psychiatric diagnoses involves structured clinical interviews and functional neuroimaging.[40–42]

Conclusion

Anxiety and depression levels were present in about half of the pregnant women included in the present study. The risk factors to develop anxiety and depression were smoking, concerns about health and getting infected with the coronavirus, history of psychiatric disease, and sundergoing regular antenatal care. The present study also showed that pregnant women are vulnerable to changes in mental status during the pandemic, and special care should be taken to overcome the high levels of anxiety and depression brought about in this period of uncertainty and stress. Thus, we recommend that healthcare professionals perform psychosocial assessments in addition to physical examinations in antenatal follow-ups, and take precautions by determining the pregnant women under risk in the early period. Furthermore, health commissions should prepare national-level psychological crisis intervention guidelines. Vaccination is vital in the fight against Covid-19. We recommend the planning of a research on the perceptions of pregnant women against the Covid-19 vaccine and their willingness to get vaccinated.

Contributions
YAA, BAS, OO, and OD contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

Conflict of Interests
The authors have no conflict of interests to declare. Funding of this research were covered by the authors.

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Prevalence of Depression in Pregnant Women with Bariatric Surgery History and Associated Factors

Prevalência de depressão em gestantes com histórico de cirurgia bariátrica e fatores associados

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Abstract

Objective To analyze the prevalence and factors associated with depressive symptoms among Brazilian pregnant women with history of bariatric surgery (BS).

Methods This is a cohort study with 247 women who got pregnant after BS. Based on data collection via Google Form, the recruitment of participants occurred in Facebook groups for 13 months. All of them answered a form with Informed Consent, a general data protocol and the Brazilian version of the Depression, Anxiety and Stress Scale-21. Descriptive and inferential analysis were performed, and a binary logistic regression model was tested to predict the factors associated with depressive symptoms.

Results The prevalence of depressive symptoms was 32.8%, noted as being higher in the first (40.6%) and third (34.3%) gestational trimesters. Significative associations were found between depression and marital status ($p = 0.000$), planned pregnancy ($p = 0.001$), desired pregnancy ($p = 0.004$) and psychiatric history ($p = 0.000$). Women who were not married (odds ratio, OR = 3,38; $p = 0.002$) and had a psychiatric history (OR = 2.70; $p = 0.102$) had higher chances of showing depression symptoms; while planned and desired pregnancy showed as protective factors to the symptoms of depression.

Conclusion These findings highlight the importance of psychological assistance for pregnant women with history of BS, to prevent development of mental disorders and their outcomes for maternal-child health.

Keywords
- bariatric surgery
- pregnancy
- mental health
- depression
- perinatal care

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Resumo

Objetivo Analisar a prevalência e fatores associados à sintomatologia depressiva entre gestantes brasileiras com histórico de cirurgia bariátrica.

Métodos Trata-se de um estudo de coorte com 247 mulheres que engravidaram após uma Cirurgia Bariátrica. Baseado em coleta via Google Form o recrutamento das gestantes ocorreu em grupos do Facebook durante 13 meses. Todas responderam a um formulário com o Termo de Consentimento Livre e Esclarecido, um protocolo de dados gerais e a versão brasileira da Depression, Anxiety and Stress Scale-21. Análises, descritiva e inferencial foram realizadas, e um modelo de regressão logística binária foi testado para predizer os fatores associados à sintomatologia depressiva.

Resultados A prevalência da sintomatologia depressiva foi de 32,8%, sendo notada como maior no primeiro (40,6%) e terceiro (34,3%) trimestres gestacionais. Associações significativas foram encontradas entre sintomatologia depressiva e estado civil ($p = 0{,}000$), gestação planejada ($p = 0{,}001$), gestação desejada ($p = 0{,}004$) e histórico psiquiátrico ($p = 0{,}000$). Mulheres que não eram casadas (OR = 3,38; $p = 0{,}002$) e tinham um histórico psiquiátrico (OR = 2,70; $p = 0{,}102$) apresentaram mais chances de manifestarem sintomas de depressão; enquanto gestação planejada e desejada mostraram-se como fatores protetivos aos sintomas de depressão.

Conclusão Os achados ressaltam a importância do acompanhamento psicológico para gestantes com histórico de cirurgia bariátrica para prevenção do desenvolvimento de transtornos mentais e seus desfechos para a saúde materno-infantil.

Descritores

- cirurgia bariátrica
- gravidez
- saúde mental
- depressão
- assistência perinatal

Introduction

Obesity is a chronic disease which involves genetic, metabolic, behavioral, environmental, cultural, and psychological factors. It is characterized by excess body fat due to energy imbalance for a long period, either by an excessive fat consumption, or by sedentarism or lack of physical activity.[1] The most recent data of Brazilian's Ministry of Health show that 55.7% of the Brazilian population is overweight, in other words, closer to obesity.[2] The rise in obesity in Brazil is justified by the behavioral, social, and dietary transformation of its population. According to Garcia,[3] the urbanization and industrialization binomial is a predominant factor in the way that people eat, since demand for bad and practical eating, as well as fast foods have increased. This demand makes space for higher consumption of invariable foods, without "real food" that can be found as fast food.

Bariatric surgery (BS) has been embraced as an effective option as a preventive and therapeutic intervention to obesity treatment and its related diseases, such as infertility.[4,5] In accordance with the 424/2013[4] decree of Ministry of Health and the new Brazilian Guidelines of Obesity (2016),[5] BS candidates must show a body-mass index (BMI) higher than 40 kg/m^2 or 35 kg/m^2, be associated with one or more serious comorbidities caused by obesity, and have attempted, unsuccessfully, non-surgical techniques for losing weight in a prior period of at least two years.[4,5] The greatest benefit of this surgery procedure is the reduction of comorbidities, although it emphasizes gains with regard to self-esteem, sexuality and social interaction among patients.[6]

In addition to the search for better health conditions, women who underwent BS can also have the urge to conform with a cultural parameter of slimness, in other words, a female physical ideal. However, the fast physical, nutritional, and psychosocial changes which occur after BS, aside from the newest silhouette (excessive or suddenly thin) may cause psychological disorders, such as depression, anxiety, alcoholism, bulimia, and anorexia, as well as other compulsive behaviors/disorders like compulsive gambling, shopping, and hypersexuality.[6,7]

Moreover, it stands out that 80% of the patients who answered the survey were obese women between 18 and 45-years-old.[8,9] In this population, ovarian polycystic syndrome and infertility are usually found, causing more difficulty to become pregnant.[9] Studies reveal the weight loss resulting from BS has a positive impact to female fertility, with better obstetric prognosis and reduction of obstetric complications associated with overweight, such as gestational diabetes, hypertension, preeclampsia, thromboembolism, fetal macrosomia, urinary infection, prematurity, intrauterine fetal death, anesthetic, and surgical complications.[9,10] Nevertheless, women who did BS must be warned about the minimum time to become pregnant after surgery, with the aim to wait for weight stabilization due to deficiency of vitamin, mineral, and protein absorption resulting from digestive physiology changes.[6,9] This time varies from 12 to 18 months, and it corresponds to a minimum hiatus for a post-BS pregnancy with less maternal-fetal risks.[6,9,11]

Therefore, the risks arising from physical, psychological, and metabolic alterations caused by BS add up to a high vulnerability to mental disorders during the pregnancy-puerperal cycle, especially on the first and third trimesters of pregnancy, and on 30 days postpartum (puerperium).[12,13] During gestation, this can be explained by issues and fears

related to the adjustment period to pregnancy and the proximity to childbirth.[13,14] Besides that, the challenges of the physical and mental transformations related to gestation result in greater emotional ambivalence that must require the women's mental effort to take on a new role as mothers,[15] which can be harder to women with BS history because of the adaptations in physical and mental levels that result from the surgery.

Despite the emphasis given to puerperal psychological disorders such as postpartum depression, mental disorders during pregnancy are not uncommon and have high prevalence, similar to the puerperal period.[16] Depressive episodes are the most frequent during gestation[12,17] and may negatively impact pre- and postnatal care.[12] Depressive mood or anhedonia is one of main symptoms of depression during pregnancy, albeit alterations in sleep and appetite, irritability, loss of libido, psychomotor retardation, and suicidal ideation are also observed and may cause psychosocial impacts on women.[12] Thus, some of these manifestations such as fatigue, alterations in sleeping, appetite, and libido patterns may cause misdiagnosis of depression on pregnancy.

Studies reveal that prevalence rates of depression during pregnancy in developing countries, such as Brazil, are around 20%.[12,17–20] Among risk factors associated with depression during pregnancy the biggest factor seems to be a history of psychiatric conditions, especially depression.[12,20] Added to that, sociodemographic factors related to poverty, such as unemployment, low income, education, and unwanted pregnancy; and other factors like alcohol dependence and substance abuse, besides lack of social and emotional support are also predictors of depression during pregnancy.[14,18–20] It is necessary to stress that the presence of untreated depression during pregnancy can lead to fetal-maternal and obstetric risks like the increase of abortion rates, placenta abnormalities, hemorrhage, prematurity, fetal pain, low selfcare, low weight of the newborn, preeclampsia, and low adherence to prenatal monitoring.[12,16,21] Hence, depression during pregnancy can lead to a higher risk of postnatal depression, has an impact on the mother-child binomial, may compromise the fetal-maternal and mother-child relationship, as well as the child's psychosocial development.[18,22,23]

Thus, the early assessment and treatment of depression symptoms during pregnancy is fundamental to reduce negative outcomes to maternal health, fetal development, labor, and the child's health.[12,16] Regarding women who underwent BS, there might be higher risks related to psychological disorders in the face of difficulties of adaptation to physical and mental changes resulted from surgery. The purpose of this research is analyze the prevalence of depressive symptomatology in Brazilian pregnant women with history of BS, and study factors associated with depression incidence, as well as predictive factors of depression in this type of pregnancy.

Methods

This is a quantitative cohort comprised of 247 pregnant women from different Brazilian regions, which fulfilled the following criteria: age equal or superior to 18 years old, pregnant at the moment of the survey, and who underwent BS before getting pregnant. Women who, despite having a history of BS, answered the survey after childbirth were excluded.

The project was approved by the Comitê de Ética em Pesquisa da Maternidade Escola da UFRJ (CAEE: 65713417.9.0000.5275) before the beginning of data collection, which occurred for 13 months, from October 2017 to November 2018. The study was announced on Facebook groups predominantly formed by women who underwent BS and got pregnant or wanted to get pregnant, for example: Pregnancy after Bariatric Surgery, Gestation after Bariatric Surgery and Being a Mother after Bariatric Surgery. After the research was authorized and the researcher was included by group administrators, the participants were invited to the study through a link with access to a survey elaborated in Google Forms. The survey began with an Informed Consent Form (ICF), which was a necessary condition for the participant to proceed and answer the following data collection tools: 1) general data protocol for socio demographic, psychosocial and clinical data collection (physical and mental health); 2) Brazilian version of the Depression, Anxiety and Stress Scale (DASS-21)[24] to rate the occurrence of depressive symptomatology detected, with a cutoff point of ≥ 14, which would correspond to moderate levels of the disorder for DASS-21.

All social demographic, psychosocial and clinical data (mental and physical health) were processed and analyzed in terms of frequency of occurrence of information collected by the General Data Protocol. Depressive symptomatology data were rated according to DASS-21 scale's instructions. Analyses, inferential and descriptive, were conducted by using Statistical Package for Social Science (SPSS, IBM Corp. Armonk, NY, USA) version 20.0. The Chi-Squared Test was adopted to investigate sociodemographic (marital status, education, labor activity, and familiar income), psychosocial (planned pregnancy, desired pregnancy, emotional support, financial support, and history of obesity) and clinical factors, as well as both physical health (gestational age and time of BS) and mental health (compulsive behaviors and history of psychiatric disorders) associated with depressive symptomatology, assuming p-values ≤ 0.05 as statistically significant. Finally, a binary logistic regression model was tested to detect predictive factors of depressive symptomatology in pregnant women with history of BS, controlling the following statistically significant variables ($p \leq 0.05$): marital status, planned pregnancy, desired pregnancy, and history of psychiatry disorders.

Finally, it is necessary to emphasize that the variables of history of obesity and compulsive behaviors show as missing because they were inserted after the beginning of data collection. Therefore, these two variables were collected only in 71 participants.

Results

As can be observed on ►**Table 1**, the sample was mostly from married women (84.6%; n = 209), white women (64.8%; n = 160), between the age of 30 to 34-years-old (38.5%; n = 95), followed by women from 25 to 29-years-old

(28.3%; n = 70). More than a half of them had uncompleted or completed college (68.9%; n = 124). Moreover, 74.5% (n = 184) had labor activities, with monthly incomes centered in the group of 2 to 4 minimum wage (43.7%; n = 108), followed by remunerations between 4 to 10 minimum wage (33.2%; n = 82). In the most part, participants lived in the Southeast of Brazil (53.4%; n = 132), and 79.1% (n = 188) of them did prenatal in the private health care system.

Table 1 Participants' sociodemographic data (n = 247)

Variables	Category	n	%
Marital status	Single	33	13.4
	Married	209	84.6
	Divorced	5	2.0
Total		247	100
Race/Ethnics	Yellow	3	1.2
	White	160	64.8
	Mixed race (parda)	61	24.7
	Black	14	5.7
	No answer	9	3.6
Total		247	100
Age group	20 to 24 years	18	7.3
	30 to 34 years	95	38.5
	35 to 39 years	54	21.9
	40 to 44 years	10	4
Total		247	100
Education	Incomplete elementary school	1	0.4
	Complete elementary school	2	0.8
	Incomplete middle school	8	3.2
	Complete college	116	47.0
Total		247	100
Labor Activity	Yes	184	74.5
	No	63	25.5
Total		247	100
Family income	No income	7	2.8
	To 2 minimum wage	32	13.0
	From 2 to 4 minimum wage	108	43.7
	From 4 to 10 minimum wage	82	33.2
	From 10 to 20 minimum wage	13	5.3
	More than 20 minimum wage	5	2.0
Total		247	100
Brazilian region	North	2	0.8
	Northeast	33	13.4
	Center-West	16	6.5
	Southeast	132	53.4
	South	64	25.9
Total		247	100
Prenatal assistance	Public institution	50	20.2
	Private institution	188	76.1
	No monitoring	9	3.6
Total		247	100

In relation to psychosocial data, though half of the women (51%; n = 126) declared unplanned pregnancy, it is understood that gestation was predominantly desired by them (86.6%; n = 214). Nonetheless, 56.3% (n = 139) denied having financial and/or emotional support, 37.7% (n = 93) reported having emotional support, and 3.2% (n = 8) both supports. Most of the women declared being obese since childhood (42.3%; n = 30), followed by adolescence (36.6%; n = 26).

Clinical data of mental and physical health are described in ►**Table 2**. It is noted that 25.9% (n = 64) were found in the first gestational trimester, 34% (n = 84) in the second trimester, and 40.1% (n = 99) in the third trimester. Most participants declared being pregnant after 18 months of BS (63.6%; n = 157) by Gastric Bypass technique (87.4%; n = 216), and are still on medical follow-up (47.4%; n = 117). Most of them (78.9%) reported having some disease before pregnancy, with clinical pathologies such as systemic arterial hypertension, anemia, hypothyroidism, diabetes, musculoskeletal disorders, and hepatic steatosis in more than half of them (53.4%; n = 132); followed by history of psychiatric disorders, such as depression and anxiety/panic attack (12.1%; n = 30), or both (13.4%; n = 33).

Based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[25] diagnostic criteria: 39.4% (n = 28) of the women declared having compulsive behaviors during pregnancy, with 32.4% (n = 23) being eating compulsions such as bulimia nervosa (11.3%; n = 8), anorexia nervosa (2.8%; n = 2), and binge eating disorder (18.3%; n = 13).

The estimated prevalence of gestational depressive symptomatology of women with history of BS on this survey was of 32.8% (M = 11.4; DP = 11.5; AV = 0–42), with a cutoff point of ≥ 14, which is considered moderate depressive symptomatology level by DASS-21.

On ►**Table 3** were presented the Chi-Squared Test results used to test relations among depressive symptomatology in pregnant women and sociodemographic, psychosocial, and clinical variables. Variables such as marital status ($p = 0.000$), planned pregnancy ($p = 0.001$), wanted pregnancy ($p = 0.004$), and history of psychiatric disorders ($p = 0.000$) showed statistically significant association with depressive symptoms ($p \leq 0.05$). Then, unmarried women, who did not plan or want the pregnancy, and had a history of psychiatric disorders (depression, anxiety, and/or panic attack) had high depressive symptomatology scores identified by DASS-21. Other variables such as education, income, social and emotional support, gestational age, labor activity, history of obesity, time of BS before getting pregnant, gestational trimester, and compulsive behaviors do not show a statistically significant association with depressive scores.

The result of binary logistic regression was significative: X^2 (5) = 276.759; $p < 0.001$; R^2 Nagelkerke = 0.188, and confirmed that variables like marital status and history of psychiatric disorders were predictors of depressive symptomatology's occurrence in the pregnant women with history of BS participants in this survey. As noted in ►**Table 4**, single

Table 2 Clinical data about participants' physical and mental health (n = 247)

Indicators of clinical health	Frequency	%
Gestational age		
1 to 13 weeks (1st Trimester)	64	25.9
14 to 26 weeks (2nd Trimester)	84	34.0
27 to 40 weeks (3rd Trimester)	99	40.1
Total	247	100
Time of BS		
Less than 6 months	7	2.8
6 to 11 months and 30 days	28	11.3
12 to 17 months and 30 days	55	22.3
18 months to 23 months and 30 days	35	14.2
More than 24 months	122	49.4
Total	247	100
Type of BS		
Gastric bypass	216	87.4
Vertical gastrectomy	31	12.6
Total	247	100
Time of medical supervisor after BS		
Less than 6 months	25	10.1
6 months to 1 years	52	21.1
1 year to 2 years	53	21.5
Still on supervisor	117	47.4
Total	247	100
Diseases before pregnancy		
Clinical pathologies	132	53.4
History of psychiatric disorders	30	12.1
Both	33	13.4
None	52	21.1
Total	247	100
Compulsive behaviors		
Bulimia nervosa	8	11.3
Anorexia nervosa	2	2.8
Binge eating disorder	13	18.3
Alcohol use disorder	2	2.8
Disorder related to substance abuse (sedatives, hypnotics, anxiolytics or drugs)	1	1.4
Other compulsions (sex, gambling, physical exercise, shopping etc.)	2	2.8
No	43	60.6
Total	71	100
Didn't answer	176	0

Abbreviations: BS, bariatric surgery.

women with history of BS proved to be three times (OR = 3.38; 95% CI = 1.586–7.221; $p = 0.002$) more likely to develop depressive symptoms, when compared to married women. Similarly, pregnant women with history of psychiatric disorders showed a more than double chance (OR = 2.70; 95% CI = 1.438–5.081; $p = 0.102$) to develop these symptoms.

In contrast, planned pregnancy ($p = 0.102$) and desired pregnancy ($p = 0.438$), do not perform as significance predictions to depression occurrence in this population. On the contrary, planned pregnancy (β = - 0.530; OR = 0.59) and desired pregnancy (β = –0.592; OR= 0.55) may represent protection factors to this population, since in these cases participants had nearly 40% (41 and 45%, respectively) less probability of having depressive symptoms.

Discussion

In order to investigate the prevalence and related factors to depressive symptomatology in pregnant women with history of BS, this study shows scientific evidence about the importance of examining depressive symptoms in this population. In accordance with the expected results, women who underwent BS are more likely to have mental disorders during the pregnancy-puerperal cycle, especially in the first and third trimesters of pregnancy. Our results confirmed that the prevalence of depressive symptomatology (32.8%) among pregnant women who underwent BS is higher than in low-risk pregnant women, which is around 20%.[12,17,18,20] Marital status, planned and desired pregnancy, and history of psychiatric disorders are factors that must be considered in prenatal monitoring of this population because they are significantly related to depressive symptoms.

Moreover, it should be noted that this study would be done on newly released Endocrine Technological Disorders Unit in Pregnancy (Unidade de Transtornos Endócrino-Metabólicos na Gestação – UTEM) at the Maternity School of Federal University of Rio de Janeiro, a public service reference center to perinatal health essential care in Rio de Janeiro, Brazil. However, participants' recruitment to the survey in this unit was not possible, bearing in mind the low demand for this service. It must be observed that the adherence of the pregnant population with BS history to public services specialized in gestational health was not frequent. In Rio de Janeiro, in addition to UTEM, only the Public Servants Federal Hospital of the State (Hospital Federal dos Servidores do Estado) offers public prenatal monitoring oriented to post-bariatric pregnant women. In other words, the women who did their prenatal on those services, which mostly focused on low-risk and typical pregnancies, did not receive the necessary care oriented to their characteristics.

Although public health policies in Brazil assure BS indication in cases of severe obesity, like class III,[26] to be adopted, an as a procedure to infertility treatment among women,[27] it was observed that a large part of them sough care in private institutions, where it is not always possible to guarantee a multiprofessional, specialized service, capable of caring for and reducing risks in a pregnancy post-BS. It should also be stressed that UTEM is a unit which aims to create a multiprofessional model of prenatal service to the pregnant population with different types of endocrine metabolic disorders, such as obesity, diabetes, and history of BS. The specialized service to this type of pregnancy is important, due to the

Table 3 Data of the relation among depressive symptomatology and participants' sociodemographic, psychosocial and clinical variables (n = 247)

Variables	No depressive symptoms		With depressive symptomatology		
	n	%	n	%	*P*-value
Marital status					0.000*
Unmarried	16	41	23	16	
Married	150	72.1	58	150	
Education					0.062
Completed and uncompleted elementary school	3	100	0	0	
Completed and uncompleted high school	56	75.7	18	24.3	
Completed and uncompleted college	107	66	55	34	
Family income					0.096
No income	4	57.1	3	42.9	
Up to 2 minimum wage	17	53.1	15	46.9	
From 2 to 4 minimum wage	79	73.1	29	26.9	
From 4 to 10 minimum wage	52	63.4	30	36.6	
From 10 to 20 minimum wage	10	76.9	3	23.1	
More than 20 minimum wage	4	80	1	20	
Labor activity					0.177
Yes	150	71.1	58	28.9	
No	16	41	23	59	
Planned pregnancy					0.001**
Yes	96	77.4	28	96	
No	70	56.9	53	70	
Desired pregnancy					0.004*
Yes	151	70.6	63	29.4	
No	15	45.5	18	54.5	
Emotional support					0.605
Yes	66	65.3	35	34.7	
No	100	68.5	46	31.5	
Financial support					0.238
Yes	8	53.3	7	46.7	
No	158	68.1	74	31.9	
History of obesity					0.974
Obese since childhood	21	70	9	30	
Obese as of adolescence	18	69.2	8	30.8	
Obese as of adulthood	10	66.7	5	33.3	
Gestational age					0.122
1st Trimester	38	59.4	26	40.6	
2nd Trimester	63	75	21	25	
3rd Trimester	65	65.7	34	34.3	
History of psychiatric disorders					0.000*
Yes	31	49.2	32	50.8	
No	45	86.5	7	13.5	
Compulsive behaviors					0.197
Eating disorder	11	52.4	10	47.6	
Disorder related to use of some substance	2	66.7	1	33.3	
Other compulsions	1	50	1	50	
No	35	77.8	10	22.2	

Notes: (%) frequency; *$p \leq 0{,}05$; **with $p \leq 0{,}001$ being statistically significant.

Table 4 Predictive factors of depressive symptomatology in participants (n = 247)

Variables	β	OR	95% CI	*P*-value
Marital status	1.219	3.38	1.586–7,221	0.002**
Planned pregnancy	-0.530	0.59	0.312–1,111	0.102
Wanted pregnancy	-0.592	0.55	0.234–1,305	0.438
History of psychiatry disorder	0.994	2.70	1.438–5,081	0.002**

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio. Notes: *$p \leq 0{,}05$; **with $p \leq 0{,}001$ being statistically significant.

demand for attention directed to the related risk factors related to gestation after BS, whose impacts to the mother-child binomial are unquestionable. Studies reveal that these risks have different negative results for the mother, such as nutrient deficiency,[28] that may cause anemia, malnutrition, and intestinal obstruction.[28] And for fetal development, it is observed a higher incidence of congenital anomalies, such as neural tube defect and intrauterine growth restriction,[29] and the consequences to the child's health in their development, such as premature birth and low birth weight.[29]

Due to the struggle to gather face-to-face data from UTEM patients, the survey's data collection happened, exclusively, in an online environment. This can, for instance, explain the participants' high level of education. Therefore, the participants were recruited in Facebook groups related to women who got pregnant and/or wanted to get pregnant after BS. In these groups they share their experiences before, during, and after gestation. In this virtual context, we observed that pregnant women seem to adopt various methods to deal with difficulties related to maternity, creating support networks and closer ties with other women in these groups. According to Frossard and Dias,[30] internet groups facilitate communication among peers and enable the gathering, organization, and circulation of information about people's needs, and focus on respective demands. In the groups where the survey was made, a huge circulation of information about various aspects involving a gestation after BS was noted. In the vast majority, the information was practical in nature, without a scientific accuracy and without any commitment to medical discourse. Still, it was possible to note that the participants, for the most part, followed medical advice because they kept up medical monitoring (79.1%) and got pregnant after 18 months of BS (63.3%), which is the minimum period recommended for a low-risk pregnancy[6,9,11] after BS by surgical technique gastric bypass (87.4%), which is, according to Santo et al.,[9] the golden pattern to this type of obesity treatment.

Since the research's proposal was to recognize indicators of mental health, more specifically of mood disorders, in pregnant women after BS, we chose to call it "depressive symptomatology" and not "depression", as depression is a psychopathological disorder which demands wider psychiatric and psychodiagnostic assessments. Likewise, DASS-21 is a scale with good psychometric properties to depression symptoms' measurement in Brazilian population.[24] Although this scale is not validated for use in the pregnant population yet, some cautions were adopted to minimize this limitation of the instrument. To identify pregnant women with depressive symptomatology, higher cutoff points were chosen. Different from cutoff < 9, that indicates there are no depression symptoms in the population in general, the chosen cutoff point was ≥ 14, which would indicate the presence of moderate symptoms in the patients. Here, we clarify that this decision was adopted after doing analyses using two cutoff points: ≥ 10, which identifies mild symptoms, and ≥ 14, for moderate symptoms. the first cutoff found a prevalence of 46.9%, which is higher than the prevalence of depression among low-risk pregnant women (20%).[12,17,18,20] Therefore, the cutoff ≥ 14 would be more indicated to investigate the presence of depression symptoms in the population observed, even without a support of DASS-21's psychometric study of sensitivity and specificity for use in pregnant women.

Thus, it is important to discuss how the prevalence of 32.8% depressive symptomatology in pregnant women after BS was higher when compared to that in low-risk pregnant women.[12,17,18] Depression symptoms were more frequent in the first (40.6%) and third trimesters (34.3%), which reinforces the need for policies focused on pregnancy health in the most critical moments during gestation, either by issues related to pregnancy adaptation or to the fear of childbirth.[13,14] This response reinforces the idea that gestation is, indeed, a difficult and vulnerable time in a woman's life which can lead to psychiatric disorders[12,13] particularly associated with physical, hormonal, mental, and social changes, specific from this period.[8,16]

Regarding the support system, although most of the participants were married (84.6%), 56.3% denied having any type of financial and/or emotional support. Our data indicates that single women with history of BS showed three times more chances (OR = 3.38; 95% CI = 1.586–7.221; $p = 0.002$) to manifest depressive symptoms, when compared with married women, which highlights the importance of support systems (emotional and social) to face the issues and insecurities that the pregnancy-puerperal period can bring.

Likewise, the presence of psychiatric history (anxiety, panic attack, and depression) found in 25.5% of the participants must be considered, since psychiatric disorders previous to pregnancy may have obstetric, neonatal, and puerperal impacts. The increase of abortion rates,[12,16,18] hemorrage,[12,16,18] low birth weight,[12,16,18] and the consequences to psychosocial child development,[12,16,18] are examples of negative outcomes to the mother-child binomial related with these disorders during the pregnancy-puerperal cycle. Moreover, psychiatric backgrounds may result in a lesser adherence to prenatal care,[12,16,18] with difficulties for the woman to adopt self-care habits,[16,18] impacts to the quality of the maternal-fetal

relationship during pregnancy, and the mother-child relationship on puerperium, especially for its association with postnatal depression.[12,16,18] Ratified these risks, we verified that the participants with psychiatric backgrounds demonstrate double chances (OR = 2.70; 95% CI = 1.438–5.081) of manifesting depression symptoms on gestation after BS.

These findings deserve attention because 39.4% of the participants also report compulsive behaviors, especially disorders related to eating, such as binge eating disorder (18.3%), bulimia nervosa (11.3%), and anorexia nervosa (2.8%). Studies suggest these behaviors are common in patients with history of BS[6,7,29,31,32] and may indicate the destination of voracity, despair, and eating impulse[31,32] in these pregnant women. Paradoxically, these behaviors were not related to depressive symptomatology in the participants of this study. Although BS has weight loss as objective, as well as mental and physical health improvement, the presence and/or conservation of compulsive behaviors in pregnant women seem to work as a strategy to relieve their anguish, with effects on mood responses such as depression during pregnancy. We may assume that compulsive behaviors involved in this period can be moderators of the anxiety typical during pregnancy, and high prevalence of depressive symptomatology during pregnancy after BS.

Despite the improvement of metabolic and reproductive functioning after the surgery procedure,[5,9,11] the decision to do a BS does not seem to be a determinant to the intent of getting pregnant, as there was no significative difference between the women who planned (49%) and those who did not (51%) their pregnancies. Nevertheless, most of them (86.6%) affirmed that the gestation was desired. It should be reinforced that neither planned pregnancy ($\beta = -0.53$; OR = 0.58; $p = 0.102$) nor desired pregnancy ($\beta = -0.59$; OR = 0.55; $p = 0{,}438$) were predictive factors for depressive symptoms. On the contrary, these factors appear as protectives to the occurrence of depression symptoms for this population, since women who planned and wanted to get pregnant had around 40% (41 and 44% respectively) less chances to manifest those symptoms. This suggests that pregnancy planning and willingness are protective factors to the mental health of pregnant people with a history of BS.

Most of the women affirmed that they were obese since childhood (42.3%) or adolescence (36.6%). Although there is no significative association with depression indicators, we may infer that, despite weight gain before pregnancy, the pressure for a perfect body reduces during gestation due to the expected physical transformations[28] and, possibly, there is a sort of social tolerance for the pregnant body to be a nonstandard body imposed by thinness culture. In spite of that, although gestational age is not associated significantly with depression symptoms, these symptoms were more frequent in pregnant women in the first (40.6%; n = 26) and third trimesters (34.3%; n = 34). It seems to indicate that, as literature has already considered, there is a variation between risks for mental disorders during the pregnancy-puerperal cycle,[12,13] when the second trimester is a moment of emotional stability. Presumably, the difficulties during the adaptation to physical, mental, and social transformations, typical from pregnancy after BS, may result in a higher emotional ambivalence that require women's mental efforts to take a new role as mother.[15] And, still, it seems that due to the physical transformations during gestational trimesters, with the changes of a pregnant body and the alterations of body image, women are more vulnerable to the manifestation of depressive symptomatology, even if it is not significantly related to history of obesity.

Finally, some limitations of this study must be indicated. First, while online collection via Facebook groups enabled this research and expanded its reach, by recruiting participants from different parts of Brazil, the lack of face-to-face meetings between researcher and participants may have caused difficulties to clarify doubts about the survey. Although this strategy of online survey is becoming more disseminated, especially during the Coronavirus pandemic, this type of data collection precludes capture of nuances which face-to-face collection of data may generate, although the participants might feel more comfortable answering the study online. A second important limitation involves the DASS-21 scale used to identify participants with depression symptoms. We reinforce that although it might be a limitation to this study, the choice of DASS-21 was due to it being an easy instrument of application and analysis, besides having a user-friendly language, mainly by collecting data in a virtual environment. For this reason, the studies suggest we use more tools with the purpose of expanding scientific knowledge and the recognition of risk factors and protection related to this type of gestation.

In conclusion, the evaluation of possible mental disorders during pregnancy with history of BS is fundamental, since identifying the risk factors and protections associated with these cases would allow the medical staff to plan specific and preventive interventions for the negative outcomes that this condition imposes. The discoveries in this study ratify the importance of early tracking, diagnostic, and treatment to reduce the impact of perinatal mental disorders, both for the mother and child's health.[12,20]

Conclusion

Therefore, we concluded that the prevalence of depressive symptomatology in pregnant women with BS is higher than what was found in low-risk pregnancies, proving the psychological control of these women is related to prenatal factors, since this condition may show impacts to the mother-child binomial with short, medium and long-term outcomes. Some factors, such as marital status, planned pregnancy, desired pregnancy, and psychiatric history must be observed by the professionals involved. Henceforth, it is necessary to emphasize that planned and desired pregnancies seem to succeed as protection factors to depressive symptomatology, even if these topics were poorly studied into the perinatal psychology field. Considering obstetric mental disorders, serious consequences to fetal-maternal health, and the underdiagnosis of these disorders in this period, the results of this research indicate the importance of psychological support to pregnant women who underwent BS. Moreover, the training of multiprofessional teams is fundamental for the early recognition and strategic orientation for pregnant women with some symptoms of those disorders, for the sake of a better psychodiagnostic assessment

and appropriate treatment, minimizing the negative impacts on obstetric and neonatal care. This study highlights the importance of new studies about depression in pregnancy, so that they can subsidize clinical eye development, sensitive and wide, which is oriented to subjective questions from pregnant women with BS, bearing in mind a total attention to perinatal health care of these women and their families.

Contributors

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

Conflict of Interests:

The authors have no conflict of interests to declare.

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Analysis of the Correlation/Agreement of Maternal–fetal Doppler Parameters in Normal and Growth-Restricted Fetuses

Análise da correlação/concordância dos parâmetros Doppler materno-fetal em fetos normais e com restrição do crescimento

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Abstract

Objective To assess the degree of correlation/agreement of maternal–fetal Doppler parameters between normal and growth-restricted fetuses (fetal growth restriction [FGR]).

Methods The present observational and retrospective study included 274 singleton pregnancies. The following maternal–fetal Doppler parameters were assessed: uterine artery (UAt), umbilical artery (UA), middle cerebral artery (MCA), cerebroplacental ratio (CPR), and umbilical–cerebral ratio (U/C). The assessment of FGR was based on the Figueiras and Gratacós[9] criteria. Spearman correlation coefficients were estimated to assess the correlation between resistance (RI) and pulsatility (PI) indices of Doppler parameters. The agreement between two Doppler parameters was assessed by the Kappa coefficient.

Results In total, 502 Doppler examinations were included, and FGR was observed in 19 out of 274 fetuses. A strong correlation was observed between RI and PI of UAt, UA, and MCA in all of the samples ($p < 0.001$). Of the 502 Doppler examinations, there was agreement between U/C and CPR percentiles for 480 (95.6%) and disagreement for 22 (4.4%), with Kappa coefficient of 0.26, thereby corresponding to weak agreement. Of the 68 cases with estimated fetal weight $\leq 9^{th}$ percentile (small for gestational age [SGA]), there was agreement between U/C > 1.0 and CPR $< 5^{th}$ percentile in 61 (88.4%) and disagreement in 7 (5.8%) with Kappa coefficient of 0.49, thereby corresponding to moderate agreement.

Keywords
- fetal growth restriction
- doppler
- cerebroplacental ratio
- agreement
- correlation

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Conclusion Strong correlation was observed among RI and PI UAt, UA, and MCA Doppler examinations in the present study; however, weak agreement was observed between U/C and CPR in the normal and FGR fetuses. In SGA, U/C and CPR demonstrated moderate agreement.

Resumo

Objetivo Avaliar o grau de correlação/concordância dos parâmetros Doppler materno-fetal entre fetos normais e com restrição do crescimento (restrição de crescimento fetal [RCF]).

Métodos O presente estudo observacional e retrospectivo incluiu 274 gestações únicas. Os seguintes parâmetros Doppler materno-fetal foram avaliados: artéria uterina (AUt), artéria umbilical (AU), artéria cerebral média (ACM), razão cérebro-placentária (RCP) e razão umbilical-cerebral (U/C). A avaliação da RCF baseou-se nos critérios de Figueiras e Gratacós.[9] Os coeficientes de correlação de Spearman foram estimados para avaliar a correlação entre os índices de resistência (IR) e pulsatilidade (IP) dos parâmetros Doppler. A concordância entre dois parâmetros do Doppler foi avaliada pelo coeficiente Kappa.

Resultados No total, 502 exames Doppler foram incluídos e RCF foi observado em 19 de 274 fetos. Observou-se forte correlação entre IR e IP da AUt, AU e ACM em todas as amostras ($p < 0{,}001$). Dos 502 exames Doppler, houve concordância entre os percentis U/C e RCP para 480 (95,6%) e discordância para 22 (4,4%), com coeficiente Kappa de 0,26, correspondendo a concordância fraca. Dos 68 casos com peso fetal estimado $\leq 9^{\circ}$ (pequeno para a idade gestacional [PIG]), houve concordância entre U/C > 1,0 e RC$p < 5^{o}$ percentil em 61 (88,4%) e discordância em 7 (5,8%) com coeficiente Kappa de 0,49, correspondendo a concordância moderada.

Conclusão Forte correlação foi observada entre o IR e IP dos exames Doppler AUt, AU e ACM no presente estudo; entretanto, fraca concordância foi observada entre U/C e RCP em fetos normais e com RCF. Nos PIG, U/C e RCP demonstraram concordância moderada.

Palavras-chave
- restrição do crescimento fetal
- doppler
- relação cérebro-placentária
- concordância
- correlação

Introduction

Fetal growth restriction (FGR) occurs when the conceptual product does not reach its intrauterine growth and development potential. However, in the clinical practice, FGR is difficult to define, and, to date, there is no gold standard method for its diagnosis.[1] Fetal growth restriction can be secondary to numerous conditions that include congenital malformations, chromosomal disorders, and intrauterine infections; however, most cases of FGR occur as a consequence of placental insufficiency that can lead to fetal hypoxia.[2]

One of the first investigations regarding the clinical importance of FGR was performed by Lubchenco et al.,[3] who determined the fetal weight in relation to gestational age at the time of delivery. This analysis resulted in an increase in perinatal morbidity and mortality in newborns weighing $< 10^{th}$ percentile for gestational age. However, the definition of FGR using only the estimated fetal weight (EFW) $< 10^{th}$ percentile would also encompass fetuses small for gestational age (SGA), and a distinction between restricted (those at high risk of perinatal complications) and SGA fetuses is necessary.[4]

The society of Maternal-Fetal Medicine states that the prenatal detection of FGR can improve the perinatal outcome through appropriate fetal monitoring and optimization of the time of delivery.[5] Doppler has become an essential tool in the diagnosis and management of FGR. Some Doppler indices can be used to evaluate the waveform of both maternal and fetal vessels: resistance index (RI), represented by the systole-diastole/integral mean velocity of the spectral area, and the pulsatility index (PI), represented by the systole-diastole/systole. When RI is used, the Doppler waveform is represented only on a scale of 0 to 1 and has been reported to have a linear relationship with gestational age. In comparison, it is believed that the use of the PI allows continuous waveform analysis over a more extensive range of waveform patterns in addition to having a quadratic relationship with gestational age.[6]

The Doppler assessment in FGR is based on the assessment of fetal well-being by examining the compensatory signs triggered by hypoxemia in the fetal circulation.[7] In the PORTO study, regardless of EFW or abdominal circumference (AC), the strongest and most significant association with adverse perinatal outcomes in the low-risk population was

found when umbilical artery (UA) Doppler was altered. The authors suggest that EFW $< 3^{rd}$ percentile or the combination of EFW $< 10^{th}$ percentile with abnormal UA Doppler represent an increased risk of any adverse perinatal outcome or admission to the neonatal intensive care unit (ICU) compared with EFW or AC $< 10^{th}$ percentile but with normal UA Doppler.[8]

In the last decade, other factors that could help differentiate between SGA and FGR have been investigated; when altered, these parameters were associated with adverse perinatal outcomes. Estimated fetal weight or AC $< 3^{rd}$ percentile, uterine artery (UtA) Doppler $> 95^{th}$ percentile, middle cerebral artery (MCA) Doppler $< 5^{th}$ percentile, and alteration in cerebroplacental ratio (CPR) were associated with adverse perinatal outcomes in low-weight fetuses. In the current FGR concept, UA Doppler should no longer be used as a single standard to determine diagnosis and prognosis. According to the criteria of Figueiras and Gratacós[9] FGR can be defined through the EFW $< 3^{rd}$ percentile or the EFW between the 3^{rd} and 10^{th} percentile associated with altered maternal-fetal Doppler parameters.

Currently, the FGR is divided into early- and late-onset, with a cutoff of 32 weeks of pregnancy. However, this division does not represent only the gestational age at the diagnosis, but two entities with different natural histories and distinct biochemical, histological, and clinical characteristics.[7]

In this context, we decided to investigate the behavior of maternal-fetal Doppler parameters and the CRP in fetuses with FGR and to evaluate the degree of agreement/correlation of maternal-fetal Doppler parameters between normal and FGR fetuses.

Methods

The present observational and retrospective study was conducted in a private clinic of fetal medicine and at the Department of Gynecology and Obstetrics of the Universidade Federal do Paraná (UFPR, in the Portuguese acronym), Curitiba, state of Paraná, Brazil, between July 2017 and May 2019. The present study was approved by the Ethics Committee of UFPR, and consent form was not necessary as it was a retrospective study.

In total, 502 obstetrical ultrasound examinations with maternal-fetal Doppler parameters of 274 pregnant women were analyzed in the present study. The criteria of Figueiras and Gratacós were considered to evaluate the occurrence of FGR.[9] The sample inclusion criteria were singleton pregnancies from 24 weeks, considered to be at low risk or with FGR. The gestational age was determined by the last menstrual period and confirmed by ultrasound examination performed until $13 + 6$ weeks of gestation using the crown-rump length.

The ultrasound examinations were performed by 10 doctors specialized in fetal medicine, who used the Voluson 730 PRO (General Electric Healthcare Zipf, Austria) and Accuvix V10 (Samsung-Medison, Seoul, South Korea) apparatus.

Data were collected regarding the gestational age at ultrasound examination, EFW with its percentile in the respective ultrasound examination, fetal abnormalities observed on the obstetric ultrasound examinations, and findings from the Doppler examination. Calculations were made to assess the respective percentiles of the RI and PI observed in the UtA, UA, MCA, and CPR with the Fetal ID calculator, v.2017 found on the Fetal Medicine Web site of Barcelona (https://medicinafetalbarcelona.org/calc). The CPR was obtained by dividing the PI of the MCA by the PI of the UA. Additionally, the umbilical-cerebral ratio (U/C) was obtained by dividing the RI of the UA by the RI of the MCA.

To assess the occurrence of FGR, the following criteria, according to Figueiras and Gratacós,[9] were considered: EFW $< 3^{rd}$ or between the 3^{rd} and 9^{th} percentiles according to the table by Hadlock et al.[10] Additionally, the criteria also included at least 1 of the following conditions: UAt Doppler $> 95^{th}$, UA Doppler $> 95^{th}$, MCA Doppler $< 5^{th}$, and CPR $< 5^{th}$ percentile. The U/C was considered altered if it was > 1.0.[11]

The sample size was calculated to estimate the percentage of FGR. Considering an estimate of 6.8% for this percentage (Figueras et al.),[12] a sample of 271 fetuses would be sufficient to estimate this parameter with a margin of error of 3% and 95% confidence interval (CI).

The results of quantitative variables were described by means, standard deviations (SDs), medians, and ranges. Categorical variables were described by frequencies and percentages. A 95% CI was presented for determining the percentage of FGR. Spearman correlation coefficients were estimated to assess the correlation between PI and RI of maternal-fetal Doppler parameters. The agreement between two Doppler parameters was assessed by estimating the Kappa coefficient. The values of $p < 0.05$ indicated statistical significance. The data were analyzed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

The present analysis was based on the data from 274 pregnant women who underwent Doppler examinations between 1 and 7 times from 24 weeks of gestation; moreover, 136 (49.6%) pregnant women underwent Doppler examination only 1 time. In total, 502 Doppler examinations were included in the study, and FGR was observed in 19 of 274 fetuses, with 4 early-onset (< 32 weeks) and 15 late-onset cases of FGR (≥ 32 weeks). Hence, it was estimated that the percentage of FGR was equal to 6.9% with a 95%CI (3.9–9.9%). Of the 274 pregnant women, 11 (4%) had any EFW $< 3^{rd}$ percentile, 28 (10.2%) had any EFW assessment between the 3^{rd} and 9^{th} percentiles, and 235 (85.8%) had EFW $\geq 10^{th}$ percentile. ►**Table 1** shows the descriptive analysis of all the maternal-fetal Doppler parameters.

►**Table 2** shows the correlation between RI and PI of UtA, UA, and MCA of all Doppler examinations. According to the Spearman correlation coefficient, there was an expressive and significant correlation between the Doppler parameters ($p < 0.001$) (►**Fig. 1**).

The CPR percentile was normal in 476 of 502 (94.8%) and altered in 26 of 502 (5.2%) examinations. In contrast, U/C was normal in 498 of 502 (99.2%) and altered in 4 (0.8%)

Table 1 Descriptive analysis of maternal–fetal Doppler parameters

Doppler parameter	GA (weeks)	*n*	Mean	Median	Minimum	Maximum	Standard deviation
RI Right UAt	≤ 28	51	0.51	0.49	0.22	1.71	0.20
	28.1–32	112	0.49	0.48	0.23	0.85	0.10
	32.1–36	178	0.47	0.46	0.27	0.81	0.10
	> 36	161	0.45	0.44	0.08	0.77	0.10
PI Right UAt	≤ 28	51	0.77	0.73	0.28	2.17	0.30
	28.1–32	112	0.77	0.71	0.27	2.37	0.31
	32.1–36	178	0.71	0.67	0.34	1.71	0.24
	> 36	161	0.67	0.63	0.32	1.77	0.20
RI Left UAt	≤ 28	51	0.52	0.52	0.35	0.89	0.10
	28.1–32	112	0.49	0.48	0.30	0.74	0.09
	32.1–36	178	0.47	0.47	0.17	0.76	0.09
	> 36	161	0,45	0.44	0.24	0.78	0.09
PI Left UAt	≤ 28	51	0.80	0.77	0.45	1.65	0.22
	28.1–32	112	0.75	0.70	0.36	1.79	0.23
	32.1–36	178	0.71	0.68	0.24	1.90	0.23
	> 36	161	0.67	0.61	0.30	1.70	0.21
PI UA	≤ 28	51	1.14	1.14	0.57	1.89	0.20
	28.1–32	112	1.01	1.02	0.61	1.67	0.19
	32.1–36	178	0.90	0.89	0.55	1.48	0.17
	> 36	161	0.85	0.84	0.45	1.22	0.15
Percentile UA	≤ 28	51	45.69	46.00	3.00	99.00	20.41
	28.1–32	112	46.16	46.00	5.00	98.00	20.34
	32.1–36	178	43.92	41.00	8.00	96.00	20.06
	> 36	161	41.82	40.00	6.00	84.00	17.85
RI UA	≤28	51	0.70	0.70	0.45	0.88	0.07
	28.1–32	112	0.64	0.65	0.45	0.83	0.07
	32.1–36	178	0.59	0.60	0.43	0.79	0.07
	> 36	161	0.57	0.57	0.38	0.73	0.06
PI MCA	≤28	51	2.21	2.22	1.43	3.09	0.45
	28.1–32	112	2.17	2.13	0.86	3.65	0.51
	32.1–36	178	1.93	1.88	0.73	4.30	0.47
	>36	161	1,60	1.51	0.84	2.60	0.33
RI MCA	≤ 28	51	0.89	0.88	0.74	1.00	0.08
	28.1–32	112	0.88	0.87	0.57	1.06	0.08
	32.1–36	178	0.83	0.83	0.62	1.04	0.07
	> 36	161	0.77	0.76	0.55	1.00	0.07
CPR	≤ 28	51	1.98	1.93	1.21	3.45	0.50
	28.1–32	112	2.20	2.15	0.51	4.15	0.60
	32.1–36	178	2.20	2.16	0.69	3.98	0.58
	> 36	161	1.94	1.87	1.15	5.04	0.56
Percentile CPR	≤28	51	50.37	56.00	4.00	99.00	30.98
	28.1–32	112	53.04	51.50	1.00	99.00	31.08
	32.1–36	178	52.86	53.00	1.00	99.00	30.04
	> 36	161	43.07	38.00	3.00	99.00	30.07
U/C	≤ 28	51	0.79	0.80	0.58	0.99	0.10
	28.1–32	112	0.74	0.73	0.45	1.46	0.11
	32.1–36	178	0.72	0.71	0.51	1.08	0.10
	> 36	161	0.74	0.75	0.46	0.95	0.10
Percentile MCA	≤ 28	51	59.47	67.00	4.00	99.00	31.72
	28.1–32	112	56.79	60.00	1.00	99.00	32.66
	32.1–36	178	52.30	53.50	1.00	99.00	30.11
	> 36	161	48.09	46.00	1.00	99.00	29.16

Abbreviation: CPR, cerebroplacental ratio; GA, gestational age; MCA, middle cerebral artery; PI, pulsatility index; RI, resistance index; U/C, umbilical–cerebral ratio; UA, umbilical artery; UAt, uterine artery.

Table 2 Correlation between maternal–fetal Doppler parameters

Variables	*n*	Spearman's correlation coefficient	*p-value*
RI Right UAt versus PI Right UAt	502	0.97	< 0.001
RI Left UAt versus PI Left UAt	502	0.97	< 0.001
RI UA versus PI UA	502	0.97	< 0.001
RI MCA versus PI MCA	502	0.96	< 0.001

Abbreviations: MCA, middle cerebral artery; PI, pulsatility index; RI, resistance index; UA, umbilical artery; UAt, uterine artery.

Table 3 Description of the percentile of cerebroplacental ratio by the percentile of umbilical–cerebral ratio

Percentile CPR	U/C		Total
	Normal (≤ 1)	Altered (> 1)	
Normal ($\geq 5^{th}$)	476	0	476
	94.8%	0.0%	94.8%
Altered ($< 5^{th}$)	22	4	26
	4.4%	0.8%	5.2%
Total	498	4	502

Abbreviations: CPR, cerebroplacental ratio; U/C, umbilical–cerebral ratio.

examinations. Of the 502 Doppler examinations, there was an agreement between U/C and CPR percentiles in 480 (95.6%) and disagreement in 22 (4.4%) examinations (►**Table 3**). In all the cases of disagreement, U/C was normal, and the CPR percentile was altered. The estimated Kappa coefficient of agreement was 0.26 with 95%CI (0.05–0.46), thereby corresponding to a weak agreement.

Of the 68 cases with EFW $\leq 9^{th}$ percentile (SGA), there was an agreement between U/C > 1.0 and CPR $< 5^{th}$ percentile for 61 (88.4%) and disagreement in 7 (5.8%) Doppler examinations. In all cases of disagreement, the U/C > 1.0 was "no" and the CPR $< 5^{th}$ percentile was "yes" (►**Table 4**). The estimated Kappa coefficient of agreement was 0.49 with 95%CI (0.13–0.85), thereby corresponding to a moderate agreement.

Discussion

Although FGR is one of the greatest challenges in obstetrics, there is still no treatment that can reverse placental insufficiency. In this context, the management of these patients is of fundamental importance. Additionally, Doppler examination is crucial in assessing the fetal well-being and deciding the

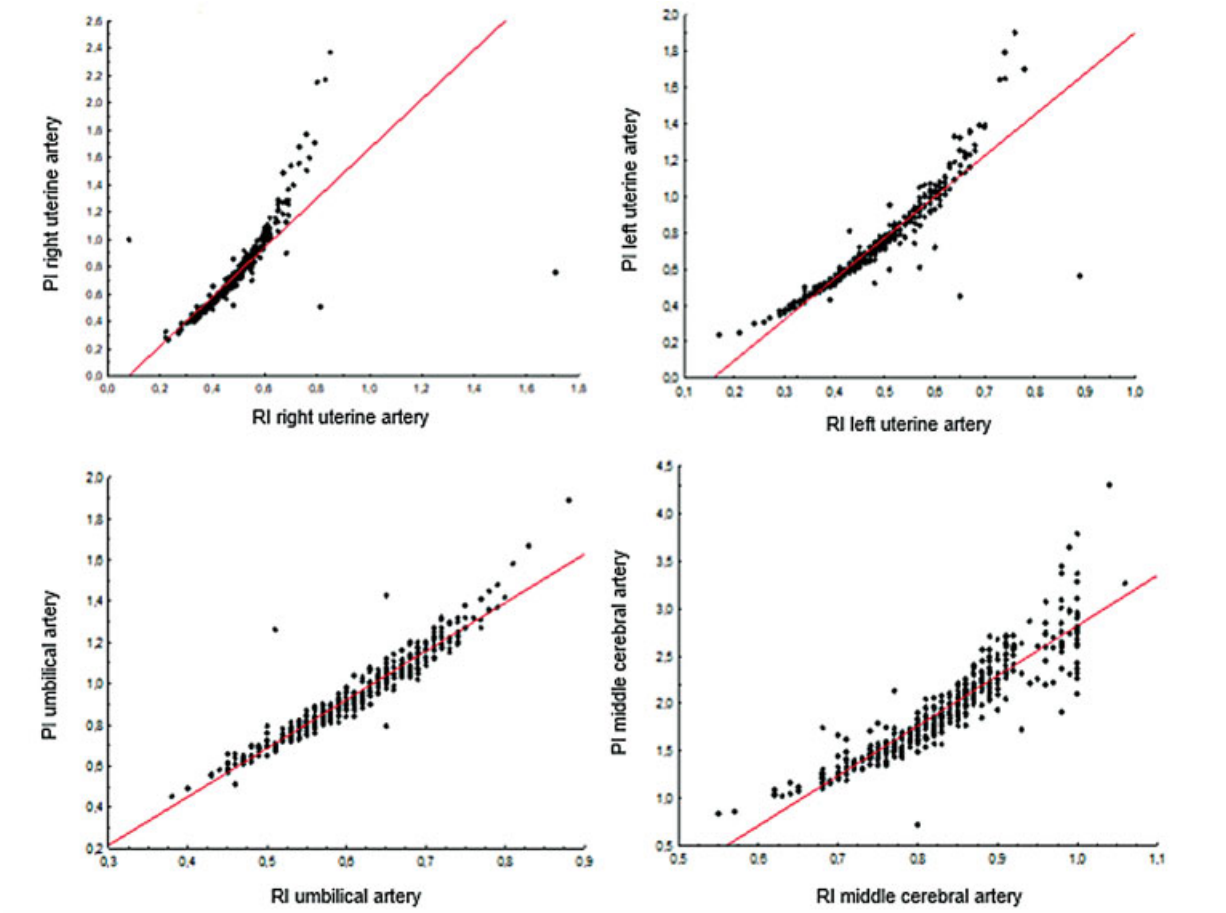

Fig. 1 Correlation between resistance (RI) and pulsatility (PI) indices of maternal–fetal Doppler parameters.

Table 4 Analysis of agreement between CPR (< 5th) and U/C (> 1.0) in fetuses with estimated weight ≤ 9th percentile

CPR (< 5th)	U/C (> 1.0)		Total
	No	Yes	
No	57	0	52
	89.1%	0.0%	
Yes	7	4	16
	10.9%	100%	
Total	64	4	68

Abbreviations: CPR, cerebroplacental ratio; U/C, umbilical–cerebral ratio.

moment of delivery while examining the risks of prematurity with the risks of fetal death.

It is important to perform fetal Doppler examination with the correct technique. Similarly, its interpretation is also important along with the knowledge of the most appropriate Doppler parameter (PI or RI) to attest the fetal vitality. In our study, we obtained an excellent correlation between the PI and RI of UA, MCA, and UtA; hence, both PI and RI can be used in the follow-up of FGR. This result is consistent with studies in the literature such as the one by Khanduri et al.,[13] who concluded that both the PI and the RI of the UA have a similar accuracy for the diagnosis of FGR. Another study, conducted by Rani et al.,[14] showed that the PI and RI of both UA and MCA had a similar accuracy to predict adverse perinatal outcomes in pre-eclampsia.

Also corroborating with our study, Cnossen et al.[15] conducted a systematic review with meta-analysis demonstrating that, in the 2nd trimester, both the PI and RI of the UtA present a similar performance for the prediction of FGR (positive likelihood ratio for RI = 2.4 and for PI = 2.3) in the high-risk pregnant women.

Cerebroplacental ratio is a new Doppler tool that has recently been gaining prominence in the monitoring of FGR, so much so that it has been included in the recent classification of expert consensus based on the Delphi method to assist in the diagnosis of late-onset FGR.[14] Cerebroplacental ratio has been shown to be more sensitive to hypoxia than its individual components and demonstrates a better correlation with adverse perinatal outcomes in SGA or FGR. Triunfo et al.[16] showed that CPR improves the prediction of adverse perinatal outcomes compared with only the EFW in low-risk pregnancies at 37 weeks. Morales-Roselló et al.[17] evaluated 891 fetuses between 34 and 41 weeks and concluded that CPR was the parameter that best predicted adverse perinatal outcomes at the end of pregnancy.

There are some references for the use of this Doppler tool, and two of them were studied: the CPR, which is the ratio of the PI of the MCA divided by the PI of the UA, and the U/C, which is the ratio of the RI of the UA divided by the PI of the MCA. The data from our study showed that, for FGR cases, there was only a moderate correlation between the two parameters (kappa = 0.49) and that the use of PI would be more accurate. However, in the literature, the multicentric study PORTO[6] and the study of To et al.[11] showed that it would be possible to use both the PI and RI. The PORTO study[6] compared the CPR performed with PI and RI values to predict the adverse perinatal outcomes, and To et al.[11] compared the CPR to assess the need for an operative delivery. In both studies, the authors obtained a good correlation between the use of PI and RI. A possible explanation for this difference in our results in the relationship to previous studies may be the smaller number of FGR cases in our sample. Additionally, another possible bias was that a fixed value was used for the normality value for the U/C, whereas a reference curve variable according to the gestational age was used for CPR.

Although Doppler examination plays a very important role in FGR and can identify placental insufficiency and fetal cardiovascular adaptation, hypoxia does not yet exist as a universal concept in which an index or a reference should be used. Hence, further studies are necessary to standardize the conduct and, consequently, improve the perinatal outcomes.[18]

The small number cases of FGR ($n = 19$, 4 early- and 15 late-onset) is a limitation of the present study. Early- and late-onset FGR are two completely different entities; however, the main purpose of the present study was assessing the correlation/agreement of maternal-fetal Doppler parameters in normal and FGR fetuses. The approach to assess the maternal-fetal vessels during the Doppler examinations was the same for both early- and late-FGR as well as normal fetuses.

Conclusion

In summary, we observed a strong correlation between RI and PI UAt, UA, and MCA Doppler; however, a weak agreement was observed between U/C and CPR in normal and FGR fetuses. In SGA fetuses, the agreement between U/C and CPR was moderate.

Contributions

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

Conflict of Interests

The authors have no conflict of interests to declare.

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Expression of Endothelin-1 and Endothelial Nitric Oxide Synthase in Normal and Preeclamptic Placentae

Expressão de endotelina-1 e de óxido nítrico sintase endotelial em placentas normais e pré-eclâmpticas

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Abstract

Objective To investigate the expression of endothelin-1 (ET-1) and endothelial nitric oxide (NO) synthase (eNOS) in normal and preeclamptic (PE) placentae.

Methods The present cross-sectional analytical study was performed in normal and PE primigravidae ($n = 10$ in each group) who were admitted to the North Okkalapa General and Teaching Hospital from February 2019 to February 2020. Serum samples were collected immediately before delivery, and placental tissues were collected immediately after emergency or elective cesarean section. The expression of placental eNOS was measured by western blot, and the levels of ET-1 in placental tissue homogenates and in the serum were measured by enzyme-linked immunosorbent assay (ELISA).

Results The PE group had significantly higher serum levels of ET-1 (median: 116.56 pg/mL; IQR: 89.14–159.62 pg/mL) than the normal group (median: 60.02 pg/mL; IQR: 50.89–94.37 pg/mL) ($p < 0.05$). However, statistically significant differences were not observed in the levels of ET-1 in placental tissue homogenates between normal and PE placentae (median: 0.007 pg/µg of total protein; IQR: 0.002–0.0123 pg/µg of total protein; and median: 0.005 pg/µg of total protein; IQR: 0.003–0.016 pg/µg of total protein respectively). The median and IQR values of relative placental eNOS expression were significantly higher in the PE group than in the normal group ($p < 0.05$). The serum levels of ET-1 level were not significantly correlated with placental ET-1 expression, and neither there was a significant correlation between placental ET-1 and eNOS expression in any of the groups.

Conclusion The serum levels of ET-1 were significantly higher in PE pregnant women compared with normal pregnant women, while the ET-1 levels of placental tissue homogenates were not significantly different. Serum ET-1 rather than placental ET-1 might play a major role in the pathogenesis of PE.

Keywords
- endothelial nitric oxide synthase
- endothelin-1
- placenta
- preeclampsia

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Resumo

Objetivo Investigar a expressão da endotelina-1 (ET-1) e da óxido nítrico sintase endotelial (*endothelial nitric oxide synthase*, eNOS, em inglês) em placentas normais e com pré-eclâmpsia (PE).

Métodos Este estudo transversal e analítico foi realizado em primigestas normais e com PE ($n = 10$ em cada grupo) internadas no Hospital Geral e das Clínicas de North Okkalapa entre fevereiro de 2019 e fevereiro de 2020. Amostras de soro foram coletadas imediatamente antes do parto, e os tecidos placentários foram coletados imediatamente após cesariana de emergência ou eletiva. A expressão da eNOS da placenta foi medida por *western blot*, e os níveis de ET-1 nos homogenatos de tecidos placentários ET-1 e no soro foram medidos por ensaio de imunoabsorção enzimática.

Resultados O grupo com PE apresentou níveis séricos de ET-1 significativamente mais altos (mediana: 116,56 pg/mL; IIQ: 89,14–159,62 pg/mL) do que o grupo normal (mediana: 60,02 pg/mL; IIQ: 50,89–94,37 pg/mL) ($p < 0,05$). No entanto, não foi observada diferença significativa no nível ET-1 dos homogenatos de tecidos placentários entre placentas normais e com PE (mediana: 0,007 pg/µg de proteína total; IIQ: 0,002–0,0123 pg/µg de proteína total; e mediana: 0,005 pg/µg de proteína total; IIQ: 0,003–0,016 pg/µg de proteína total, respectivamente). Os valores da mediana e do IIQ da expressão relativa da eNOS placentária foram significativamente maiores no grupo com PE do que no grupo normal ($p < 0,05$). O nível sérico de ET-1 não estava significativamente correlacionado com a expressão placentária de ET-1, e tampouco houve correlação significativa entre as expressões placentária de ET-1 e de eNOS em nenhum dos grupos.

Conclusão Os níveis séricos de ET-1 foram significativamente maiores em gestantes com PE em comparação com gestantes normais, ao passo que os níveis de ET-1 dos homogenatos de tecidos placentários não foram significativamente diferentes. A ET-1 sérica, em vez da ET-1 placentária, pode desempenhar um papel importante na patogênese da EP.

Palavras-chave

- óxido nítrico sintase endotelial
- endotelina-1
- placenta
- pré-eclâmpsia

Introduction

The central organ in the pathogenesis of preeclampsia (PE) is the placenta, and the only definitive cure is delivery. Abnormal placentation and endothelial dysfunction play a key role in the pathological changes in PE. Nitric oxide (NO) and endothelin-1 (ET-1) are natural counterparts in vascular function, and an imbalance between these two mediators is a characteristic of endothelial dysfunction and is important in the progression of PE.[1]

Nitric oxide is synthesized from L-arginine, and it is catalyzed by a key enzyme called endothelial nitric oxide synthase (eNOS),[2] and studies have investigated the association between the expression of placental eNOS and PE. In an in vitro study, Baker et al.[3] observed that eNOS activity was significantly increased in endothelial cells exposed to the plasma of preeclamptic women. Likewise, Smith-Jackson et al.[4] observed a significant increase in the mRNA expression of placental eNOS in preeclamptic pregnant women compared with normal pregnant women. However, Wang et al.[5] observed a significant reduction of eNOS expression in cultured endothelial cells from preeclamptic pregnant women compared with normal pregnant women. Accordingly, these associations are still controversial, and will remain the subject of active investigation.

Evidence from clinical studies suggest that serum ET-1 is a final common pathway in the pathophysiology of PE[6–10] which indicates the positive correlation between the level of circulating ET-1 and the severity of disease symptoms.[11] However, there are still controversial findings concerning the level of placental ET-1 in normal pregnant women and those with PE. Studies have found that the levels of tissue endothelin in placental tissues were higher,[12,13] lower,[14] or not significantly different[8,15,16] in preeclamptic pregnant women compared with normal pregnant women.

In the vessels, NO inhibits the bioavailability of ET-1 under physiological conditions.[1] When NO is diminished, it cannot inhibit the activity of ET-1. Consequently, unmitigated ET-1 regulates itself through a negative-feedback mechanism by stimulating eNOS to increase the production of NO.[17,18] Thus, balance between eNOS and ET-1 in the pathophysiology of PE became an area of interest. However, there are still controversial reports and limited information regarding role of placental tissue ET-1 and eNOS expression in PE. The present study evaluated the expression of ET-1 and eNOS in normal and preeclamptic placentae. Moreover, there was still doubt

whether the increased serum level of ET-1 found in PE was related to placental ET-1. The present study evaluated the serum levels of ET-1 as well as the expression of ET-1 and eNOS in normal and preeclamptic placentae.

Methods

A cross-sectional study was performed in singleton pregnancies of women with and without PE ($n = 10$ in each group) who were admitted to the North Okkalapa General and Teaching Hospital from February 2019 to February 2020. Individuals with a new onset of hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg) on or after the 20th week of gestation were categorized as having PE by obstetricians.[19] Normal pregnancy is defined as uncomplicated normotensive singleton term pregnancy from 37 to 40 completed weeks. Pregnant women with diabetes mellitus, liver or renal disease, cardiovascular disease or primary hypertension, infectious diseases (such as malaria, AIDS, and hepatitis B and C), and cases of multiple pregnancy were excluded.

Participation in the study was voluntary. The selection of subjects was based on their availability and willingness to participate. A thorough explanation about the study was provided to all patients, and written informed consent was taken. History taking and the physical examination were performed according to a pro forma. Blood pressure and proteinuria were measured in each visit throughout the pregnancy. An estimation of proteinuria was performed using the dipstick method in spot urine (urine dipstick reading $\geq 1+$ [a concentration of 30 mg/dl][19] (Urocolor™10 SD Inc, Korea). Personal data and detailed clinical history were also reviewed from previous records. The study was approved by the Ethics Review Committee of University of Medicine 2, Yangon.

Sample collection was performed on the day of delivery. About 5 ml of venous blood from the antecubital vein were collected under aseptic conditions 1 to 2 hours before delivery. Then, the blood was placed into a serum separator tube and allowed to coagulate at room temperature and centrifuged at $\sim$ 3,000 rpm for 20 minutes. Then, the serum was promptly separated into aliquots and stored at -80°C until the assessment of the levels of ET-1 by enzyme-linked immunosorbent assay (ELISA).

Placental tissues were collected from normal and preeclamptic women who underwent emergency or elective cesarean section immediately after delivery. Placental tissue samples (measuring $\sim 1.5 \times 1.5 \times 0.5$ cm) were cut from the maternal side of placenta $\sim$ 1.5 cm away from margin and 1.5 cm away from insertion of the umbilical cord in sterile conditions. The samples were immediately placed into a 15-ml centrifuge tube and then transported on ice to the Common Research Laboratory at University of Medicine 2, Yangon. The placental tissues were rinsed with phosphate buffer saline (PBS) three times to remove as many blood clots as possible and stored at -80°C until the analysis the expression of ET-1 and eNOS by western blot.

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was used to separate target proteins. Approximately 0.01 g of placental tissue for each sample was homogenized with 250 µL of homogenizing buffer (radioimmunoprecipitation assay [RIPA] buffer: 0.5 M of ethylenediaminetetraacetic acid [EDTA] [solution]: halt protease and phosphatase inhibitor cocktail [100:1:1]) twice for 20 seconds. Then, the samples were centrifuged at 5,000 rpm for 20 minutes in a centrifuge refrigerated at 4°C to separate the supernatant and palette. A lithium dodecyl sulfate (LDS) sample buffer (Invitrogen, Waltham, MA, United States) with 8 M of dithiothreitol (DTT) (20:1) was prepared and mixed with tissue lysate (1:3 ratio). The samples were boiled in digital dry bath at 100°C for 5 minutes and stored at -80°C. The total protein concentration of 20 µg/well for each sample was loaded in 12.5% SDS-PAGE, and a 30-mA current was applied for protein separation. For membrane transfer, a semidry transfer system (ATTA, Japan) and an invitrolon 0.45 µm polyvinylidene fluoride (PVDF) membrane (Invitrogen) were used for membrane blotting at 200 mA for 60 minutes. Then, the membrane was blocked to prevent non-specific binding with 3% skimmed milk. The primary antibody solution was prepared by mixing 3% skimmed milk dissolved in 1X tris-buffer saline 1X-TBS) and anti-ET-1/anti-eNOS antibody (Invitrogen) in a dilution of 1:1,000 and stored at 4°C overnight for antigen-antibody reaction. After overnight incubation, the membrane was rinsed with 1X-TBS with Tween 20 (1X-TBST) 4 times on a mechanical shaker (twice for 5 minutes, and twice again for 10 minutes). The secondary antibody solution (3% skimmed milk dissolved in 1X-TBST and anti-rabbit immunoglobulin G (IgG)/anti-mouse IgG [Invitrogen]) was prepared in a dilution of 1:10,000 and incubated with the membrane for 1 hour at room temperature. After that, the membrane was once more rinsed with 1X-TBST 4 times. Then, it was rinsed twice with the 1X-TBS solution. The detection of protein band was performed with the Pierce ECL Plus Western Blotting substrate solutions A and B (in a 40:1 ratio) (Thermo Fisher Scientific, Waltham, MA, United States) and incubated for 1 minute. The protein band was detected by the X-ray cassette in the dark. The relative expression of placental eNOS was determined by the western blot method, and the intensity of the protein band was calculated using the ImageJ software (National Institutes of Health, USA). The values were expressed relative to age-matched controls (fold change value > 1.0 indicates an increase in abundant relative to the control).

For the assessment of the levels of ET-1 in the placental tissue, placental tissues that had already been rinsed were mixed with PBS (1 g of placental tissue + 9 mL of PBS) and homogenized (twice for 20 s) in an ice bath. Then, the placental tissue lysates were centrifuged at 5,000 rpm for 20 minutes in a refrigerated centrifuge, and the resulting supernatants were collected in separated aliquots and stored at -80°C until being analyzed by ELISA. The levels of ET-1 in the serum and placental tissue were determined using an ET-1 ELISA kit (MBS761947, MyBiosource, San Diego, CA, United States).

Data was analyzed using the Statistical Package for the Spcial Sciences (SPSS for Windows, SPSS Inc., Chicago, IL,

Table 1 General characteristics of the study subjects

	Normal pregnancy ($n = 10$) (mean ± standard deviation)	Preeclampsia ($n = 10$) (mean ± standard deviation)	*p*-value
Maternal age (years)	28 ± 4.3	28.5 ± 5.7	Not significant
Systolic blood pressure (mmHg)	114 ± 5.2	156 ± 13.5	< 0.01
Diastolic blood pressure (mmHg)	73 ± 4.8	100 ± 14.1	< 0.01
Gestational age at birth (weeks)	39 ± 1	36 ± 2	< 0.05
Fetal birth weight (grams)	3,070 ± 312.8	2,720 ± 644.4	Not significant

United States) software, version 16.0. The variables pertaining to the outcomes were expressed as medians and interquartile ranges (IQRs) and computed by non-parametric tests. The comparison of the ET-1levels in the serum and in the placenta, and the placental eNOS expression between normal and preeclamptic pregnant women was performed using the Mann-Whitney U test. The correlation studies were performed using the Spearman correlation coefficient. Values of $p < 0.05$ were considered statistically significant.

Results

The general characteristics of participants of the present study are presented in ►**Table 1**.

The PE group had significantly higher sereum levels of ET-1 than the normal group (median: 116.56 pg/mL; IQR: 89.14–159.62 pg/mL; and median: 60.02 pg/mL; IQR: 50.89–94.37 pg/mL; $n = 10$; $p < 0.05$) (►**Fig. 1**), but there was no significant difference regarding the ET-1 levels in the placental tissue between normal (median: 0.007 pg/µg of total protein ; IQR: 0.002–0.0123 pg/µg of total protein) and preeclamptic placentae (median: 0.005 pg/µg of total protein; IQR: 0.003–0.016 pg/µg of total protein) (►**Fig. 2**). The expression of eNOS in the placental tissue was significantly higher in preeclamptic placentae than in normal placentae (median: 1.728; IQR: 1.229–2.042; and median: 0.945; IQR: 0.48–1.11 respectively; $p < 0.05$) (►**Figs. 3** and **4**). There was no significant correlation between the placental and serum ET-1 levels of both study groups (►**Table 2**). Neither there was a

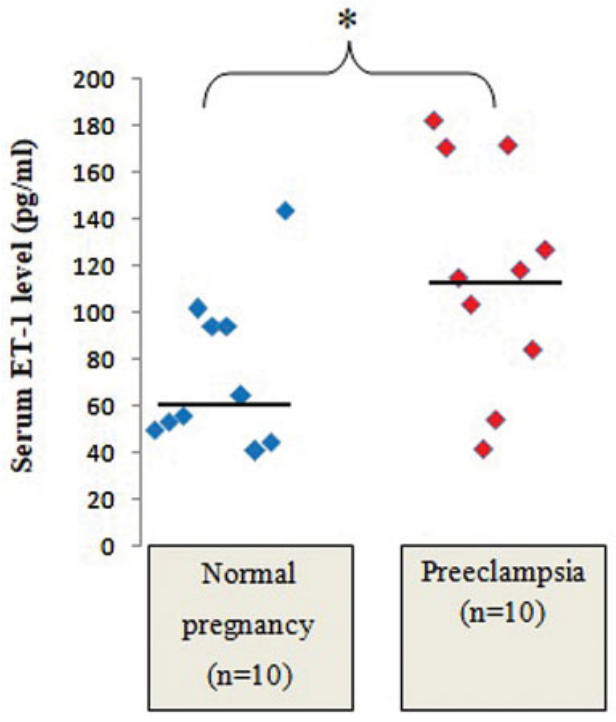

Fig. 1 Comparison of serum ET-1 levels between normal and preeclamptic pregnant women. Abbreviation: NS, not significant. Notes: statistical test: Mann-Whitney U Test; the solid line indicates the median value.

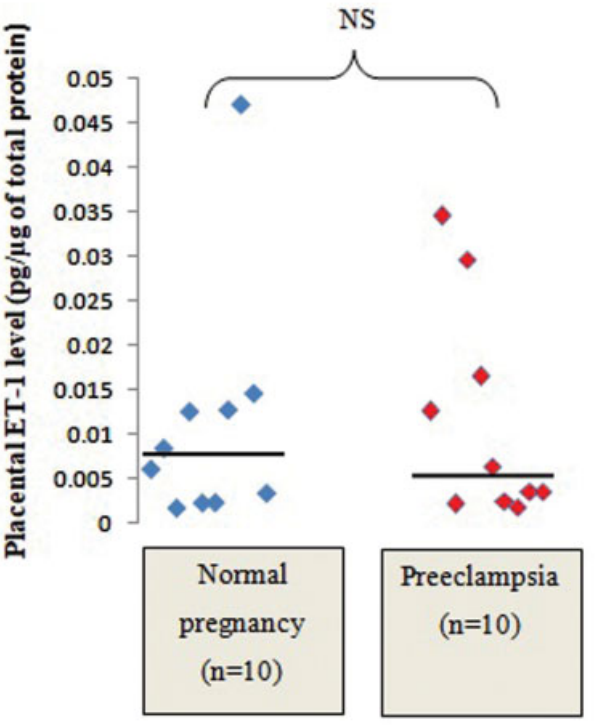

Fig. 2 Comparison of placental ET-1 levels between normal and preeclamptic placentae. Abbreviations: N, normal pregnancy; PE, preeclampsia.

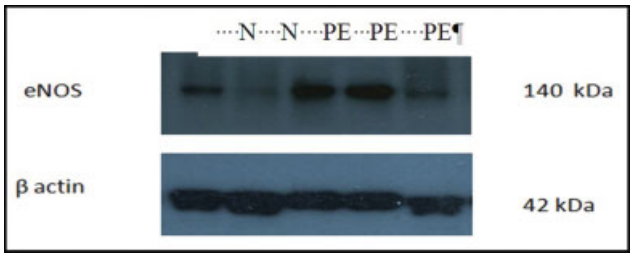

Fig. 3 Placental eNOS expression in normal and preeclamptic placentae. Notes:* statistical significance ($p < 0.05$); statistical test: Mann-Whitney U Test.

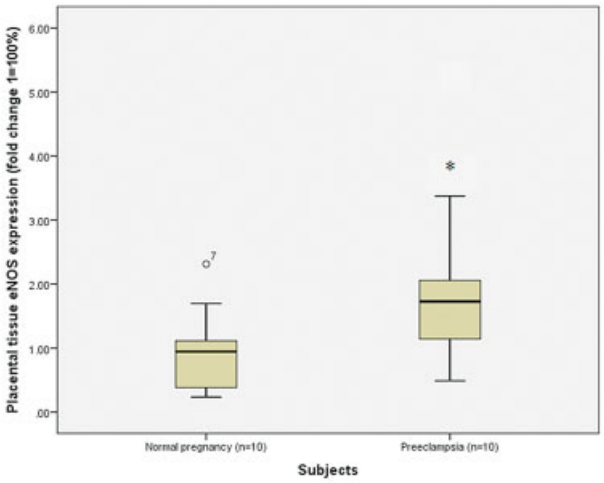

Fig. 4 Comparison of placental eNOS expression between normal and preeclamptic placentae. Notes: * statistical significance ($p < 0.05$); statistical test: Mann-Whitney U Test; the solid line indicates the median value.

significant correlation between the ET-1 levels in the placental tissue and eNOS expression in both study groups (►**Table 2**).

Discussion

In the present study, we selected preeclamptic women and age-matched controls since aging is likely to have an effect on NO synthesis and activity.[20] Hence, there was no significant difference in maternal age in the whole sample. The mean gestational age at birth of the PE group (36 ± 2 weeks) was significantly lower than that of the normal group (39 ± 1 weeks) ($p < 0.05$), since birth is the definite treatment to relieve the symptoms of PE. Even though eNOS expression and the level of NO increase with gestation until third trimester and return to prepregnancy levels postpartum,[21] the plasma levels of nitrite and nitrate are independent of the duration of gestation during the third trimester of pregnancy.[6] In the present study, all the pregnant women were in their third trimester, so it was unlikely to affect the NO level. The mean fetal birth weight of the PE group (2720 ± 644.4 g) was lower than that of the normal group (3070 ± 312.8 g) but without statistical significance.

In a normal healthy pregnancy, cytotrophoblasts originated from the fetus migrate and invade the maternal spiral arteries, undergoing a transformation into an endothelial-like cell. This remodeling converts the normally low-capacitance, high-resistance maternal spiral vessels into high-capacitance, low-resistance vessels. In the preeclamptic placenta, due to the failure to remodel, insufficient blood flow to the uteroplacental unit results in poor placentation.[22] This poor placentation causes repeated periods of placental hypoxia and reperfusion injury, resulting in endothelial damage. On the other hand, hypoxia increases the production of ROS, leading to oxidative stress.[23] Consequently, vascular endothelial damage and oxidative stress in the placenta increase the production of placental factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), inflammatory cytokines (tumor necrosis factor alpha, TNF-α), and agonistic autoantibodies to the angiotensin II type-1 receptor (AT1-AA).[24,25] These placental factors enter the maternal circulation and cause generalized maternal vascular endothelial dysfunction, leading to increased production of vasoconstrictors (ET-1).[9] Moreover, it was also noted that ET-1 was positively correlated with anti-angiogenic factors (sFlt-1and sEng) released by the placenta.[9,26]

Another important mechanism is the inflammatory and autoimmune responses to placenta ischemia. The production of the agonistic autoantibodies to the AT1-AA seems to be causally related to placental ischemia through the induction of TNF-α.[27,28] Consequently, angiotensin II stimulates ET-1 expression.[29] Consistent with the previous studies,[8,9,26] the present study also showed that the serum levels of ET-1 were significantly higher in the PE group than in the normal group. Since serum ET-1 and the severity of PE symptoms are related,[11] the assessment of the serum levels of ET-1 could be considered an additional investigation in PE patients.

The present study determined placental levels of ET-1 in the maternal surface of placental tissue homogenates from normal and preeclamptic pregnant women by ELISA. The ET-1 levels in the placental tissue were very low in both study groups. There was no significant difference in tissue ET-1 concentrations between normal (median: 0.007 pg/μg of total protein; IQR: 0.002–0.0123 pg/μg of total protein) and preeclamptic placentae (median: 0.005 pg/μg of total

Table 2 Correlation between the placental and serum levels of endothelin-1 (ET-1) of the study sample ($n = 20$)

Correlation between	ρ (rho) value	*p*-value
Placental ET-1 and serum ET-1 levels in normal and preeclamptic pregnant women	−0.3	0.19
Expression of placental ET-1 and placental eNOS in normal and preeclamptic pregnant women	0.28	0.23

Note: Statistical test: Spearman correlation coefficient.

protein; IQR: 0.003–0.016 pg/μg of total protein). Consistent with the findings of present study, there is much evidence of no significant differences in preproendothelin-1 mRNA gene expression by northern-blot analysis,[15,16] generation of ET-1 precursor by specific radioimmunoassay analysis,[14] and mature ET-1 by ELISA[8] between normal and preeclamptic placentae.

Contrary to the result of present study, some studies have reported that placental ET-1 expression was significantly higher in preeclamptic placentae than in normal placentae,[12,13] whereas other studies have reported that ET-1 mRNA expression was significantly lower in preeclamptic placentae than in normal placentae.[14] In these studies, placental ET-1 mRNA expression was determined by northern-blot analysis,[12] real-time polymerase chain reaction (RT-PCR)[14] and western blot.[13] In a study by Irtegun et al.[13] using the western blot method, the placental ET-1 expression in normal pregnancies was not at a detectable level, but preeclamptic placental ET-1 expression was high enough to detect. Likewise, in the present study, tissue ET-1 expression was too low to be detected by the western blot method in both normal and preeclamptic placentae. However, it could be detected by ELISA in the present study. Taking into consideration both the present and previous studies, discrepancies between methods of analysis might yield controversial findings. It is important to consider the methodology used to detect and interpret ET-1 levels to establish the diagnosis and severity of the disease.

In the present study, placental ET-1 level was not significantly different between normal and preeclamptic placentae, while serum ET-1 level was significantly higher in preeclamptic pregnant women compared with normal pregnant women. In agreement with this finding, Bernardi et al.[8] demonstrated that there was a significant difference in serum ET-1 levels but not placental ET-1 levels between normal and preeclamptic pregnant women. In the present study, the placental ET-1 level was not correlated with the serum ET-1level in any of the subjects, a finding also observed by Bernardi et al.[8] According to the findings of the present study together with those of the study by Bernardi et al.,[8] it can be assumed that serum ET-1 rather than placental ET-1 plays a role in the pathogenesis of PE. A significantly high level of serum ET-1 in PE might be produced from the maternal vascular endothelium rather than the placenta. It can be suggested that targeting serum ET-1 could be used to determine an accurate value for the diagnosis and prognosis of PE, but this has to be validated before any implementation in the clinical practice.

In the present study, the relative eNOS expression was significantly higher in preeclamptic placentae than in normal placentae ($p < 0.05$). In line with this finding, Myatt et al.[30] showed increased immunostaining for eNOS in stem villous cells of the fetoplacental unit in PE pregnancies compared with control pregnancies. Likewise, Napolitano et al.[12] found a significantly high level of eNOS mRNA expression in trophoblastic cells of preeclamptic placentae compared with the trophoblastic cells of normal placentae. In an in vitro study, Baker et al.,[3] investigated NO production and eNOS activity in the endothelial cell line from a bovine coronary microvessel, and they reported that NO production and eNOS activity were significantly higher in endothelial cells exposed to plasma from the preeclamptic women than in endothelial cells exposed to plasma from normal pregnant women.[3] They concluded that there might be a factor or factors in preeclamptic plasma which induced NO production and eNOS activity in endothelial cells.

A vasoconstrictor, when its levels are increased, ET-1 regulates itself through a negative feedback mechanism, acting on ET-1 receptor B (ET_B1) in maternal vascular endothelial cells to activate eNOS to increase the production of NO, a vasodilator.[17,18] Taking into account all of these findings and those of Baker et al.,[3] one can be assume that increased eNOS expression in the placental tissue of preeclamptic placenta in the present study might be due to exposure of maternal serum containing ET-1.

Contrary to the result of present study, other studies[31,32] found no significant difference in eNOS immunostaining in syncytiotrophoblasts from preeclamptic placentae compared with normal placentae. Another in vitro study, conducted by Wang et al.,[5] determined eNOS expression in endothelial cells isolated from normal and preeclamptic pregnancies, and reported that a significant reduction in eNOS expression was also noted in preeclamptic placentae. The underlying reason for the reduced eNOS expression might be the increased oxidative stress in PE. Increased levels of free radicals (reactive oxygen species, ROS) cause oxidation of tetrahydrobiopterin (BH_4, which is required for eNOS coupling) to trihydrobiopterin (BH_3), consequently resulting in eNOS uncoupling.

Placental ET-1 mRNA expression is upregulated in early-onset PE (gestational week [GW] $\leq$34) and downregulated in late-onset PE (GW $>$ 34) compared with age-matched normal pregnancies. However, the mRNA changes were not found at the protein level in all subjects in a study by Dieber-Rotheneder et al.[14] In the present study, all preeclamptic participants had late-onset PE, and the ET-1 protein level was not significantly different between normal and preeclamptic pregnancies. There might be a complex regulation of the endothelin system, and further molecular studies will be needed.

Under normal physiological conditions, serum NO and ET-1 are natural counterparts in vasculature function and may remain in a delicate balance.[1] It has been reported that NO antagonizes the ET-1 pathway via several mechanisms, including expression,[33] release,[34] receptor interactions, and second-messenger signaling systems[35] in the vasculature. On the other hand, ET-1 acts on the ET_B1 located on the vascular endothelium to stimulate eNOS, resulting in increased NO production.[17,18] Accordingly, in the pathophysiological condition of diminished NO bioavailability, like in PE, a compensatory increase in NO can be induced by ET-1 via stimulation of eNOS. In support of this concept, a previous study conducted by Napolitano et al.[12] reported that exogenous ET-1 upregulated eNOS mRNA expression in cultured trophoblastic cells in both preeclamptic and normal trophoblast cell cultures. However, the present study showed no

significant correlation between placental eNOS expression and placental ET-1 level or serum ET-1 in both normal and preeclamptic women. In the present study, we found no relationship between ET-1 levels in the placental tissue and eNOS expression, and this might be due to ROS as a product of oxidative stress, which might play an important role in eNOS uncoupling. Another reason might be the relative small sample size for the correlation analysis.

Conclusion

The serum levels of ET-1 in preeclamptic pregnant women were significantly higher than those of normal pregnant women. Since exposure of maternal serum containing ET-1 to placental vascular endothelial cells stimulates eNOS expression through ET_B1 on placental vascular endothelial cell, the relative eNOS expression was significantly higher in preeclamptic placentae than in normal placentae. The levels of ET-1 in placental tissue were very low and not significantly different between the study groups. Moreover, the placental ET-1 level was not significantly correlated with the serum ET-1 level in normal and preeclamptic pregnant women. We conclude that serum ET-1 rather than placental ET-1 may play a more important role in the pathogenesis of PE.

Contributors

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

Conflict to Interests

The authors have no conflict of interests to declare.

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Prevalence of Premenstrual Syndrome and Associated Factors Among Academics of a University in Midwest Brazil

Prevalência de síndrome pré-menstrual e fatores associados entre acadêmicas de uma Universidade no Centro-Oeste do Brasil

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Abstract

Objective To investigate the prevalence of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) in university students, the factors associated with PMS, the most prevalent symptoms, and the interference of symptoms in academic, family, social, and work activities.

Methods This cross-sectional study included 1,115 university students aged ≥ 18 years from the University of Rio Verde, Goiás. Premenstrual syndrome and PMDD were identified using the Premenstrual Symptoms Screening Tool. Associations with sociodemographic, behavioral, reproductive, nutritional, and health factors were investigated using the Poisson regression.

Results The prevalence of PMS was 46.9% (95% confidence interval [CI] 44.0–49.8), and of PMDD, 11.1% (95% CI 9.3–13.0). The most prevalent symptoms were physical, such as breast tenderness, bloating, e weight gain (73%); followed by psychological ones such as overeating/food cravings, tearful/more sensitive to rejection (> 60%). More than 30% of the patients reported that the symptoms interfered in a moderate-to-severe way in their social and academic activities. After adjusted analysis, PMS was more prevalent in those who were attending the 1st/2nd semester of college (prevalence ratio [PR] 1.44; 95% CI 1.14–1.80), those who consumed alcohol in the last 30 days (PR 1.23; 95% CI 1.04–1.47), and those who had depression (PR 1.49; 95% CI 1.30–1.71).

Keywords
- premenstrual syndrome
- premenstrual dysphoric disorder
- cross-sectional studies
- risk factors
- students

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Conclusion Almost half of the university students had PMS and ~ 11%, PMDD. Physical symptoms were the most common and interfered in a moderate-to-severe way in various aspects of life. Attending the first semesters, consuming alcohol, and having depression were risk factors for PMS. The identification of risk factors for PMS is essential to prevent symptoms and reduce the impact of the syndrome.

Resumo

Objetivo Investigar a prevalência de síndrome pré-menstrual (SPM) e do transtorno disfórico pré-menstrual (TDPM) em alunas universitárias, os fatores associados à SPM, os sintomas mais prevalentes e a interferência dos sintomas nas atividades acadêmicas, familiares, sociais e de trabalho.

Métodos Este estudo transversal incluiu 1.115 estudantes universitárias ≥ 18 anos da Universidade de Rio Verde, Goiás. Síndrome pré-menstrual e TDPM foram identificados por meio do *Premenstrual Symptoms Screening Tool*. As associações com fatores sociodemográficos, comportamentais, reprodutivos, nutricionais e de saúde foram investigadas utilizando-se a regressão de Poisson.

Resultados A prevalência de SPM foi de 46,9% (intervalo de confiança [IC] de 95% 44,0–49,8) e de TDPM, 11,1% (IC 95% 9,3–13,0). Os sintomas mais prevalentes foram físicos, como sensibilidade mamária, distensão abdominal e ganho de peso (73%); seguidos por psicológicos, como comer demais/desejos por comida, chorar/mais sensível à rejeição (> 60%). Mais de 30% relataram que os sintomas interferiam de forma moderada a grave em suas atividades sociais e acadêmicas. Após análise ajustada, a SPM foi mais prevalente naquelas que estava cursando o 1°/2° semestre da faculdade (razão de prevalência [RP] 1,44; IC 95% 1,14–1,80), as que haviam consumido álcool nos últimos 30 dias (RP 1,23; IC 95% 1,04–1,47), e as que tinha depressão (RP 1,49; IC 95% 1,30–1,71).

Conclusão Quase metade das universitárias tinha SPM e cerca de 11%, TDPM. Os sintomas físicos foram os mais comuns e interferiram de forma moderada a grave em vários aspectos da vida. Frequentar os primeiros semestres, consumir álcool e ter depressão foram fatores de risco para SPM. A identificação dos fatores de risco para a SPM é essencial para prevenir os sintomas e reduzir o impacto da síndrome.

Palavras-chave
- síndrome pré-menstrual
- transtorno disfórico pré-menstrual
- estudos transversais
- fatores de risco
- estudantes

Introduction

Premenstrual syndrome (PMS) is characterized by a set of physical and psychological symptoms, which start 1 to 2 weeks before menstruation, subside with the onset of menstrual flow, and are cyclical and recurrent. In addition to premenstrual tension, PMS can be severe enough to impact some aspects of a woman's life.[1]

The etiology of PMS remains unknown, but the source of symptoms is associated with the susceptibility of some women to normal hormonal changes that occur during the menstrual cycle. Premenstrual symptoms often improve with the use of ovulation inhibitors during pregnancy and after menopause, which provides strong evidence of their relationship with cyclic ovarian function. In addition, the stabilization of neurotransmitters, such as serotonin, and changes in the effect of gamma-aminobutyric acid (GABA) through the use of antidepressant or anxiolytic drugs can improve the symptoms of PMS. Therefore, it appears that these neurotransmitters play an important role in the development of premenstrual symptoms.[2]

The main symptoms observed in women with PMS are increased breast size and sensitivity, swelling, weight gain, headache, acne, anxiety, irritability, depression, mood swings, and changes in appetite. The intensity of symptoms varies among women. Many women have mild symptoms in their reproductive years, such as breast engorgement and edema, but do not perceive these symptoms as distressing or debilitating. However, other women may have intense and disabling symptoms, which may lead to the more severe form of PMS, that is, premenstrual dysphoric disorder (PMDD),[3,4] which is characterized by significant and debilitating psychiatric symptoms that can lead to disruptions in relationships, work, or social activities at levels similar to those of severe depression.[5]

Confirming the diagnosis of PMS is important to differentiate it from other diseases, determine its prevalence, and define an effective treatment.[5] There are no definitive and universally accepted diagnostic criteria for PMS. Some criteria are comprehensive, based on the presence of only one symptom, and others are restrictive, taking into account the interference of symptoms in daily activities.[6] The existing

criteria recognize a wide range of symptoms related to the syndrome, their severity, and their temporal pattern in parallel with the menstrual cycle, allowing the differentiation of clinically significant PMS from normal changes in the menstrual cycle.[6,7] Interviews, questionnaires, and self-assessment scales based on the criteria have been established for the diagnosis of PMS and PMDD.[8]

In the available literature, variations in prevalence can be found. A review study found that the prevalence of physiological premenstrual symptoms varied between 50 and 85% , PMS varied between 30 and 40%, and PMDD varied between 3 and 8%. The absence of diagnostic consensus, differences in the interpretation of symptoms to define PMS, and the different populations investigated justify, at least in part, the inconsistencies in the prevalence of PMS between the studies of the review.[2]

Some sociodemographic, reproductive, and behavioral characteristics are associated with the occurrence of PMS. Studies have shown that the prevalence of premenstrual symptoms is high in younger, black, and obese women; those with unhealthy eating habits; those who consume alcohol; and those who smoke.[3,9–13] On the contrary, the use of hormonal contraceptives and the practice of regular physical activities reduce the probability of occurrence of PMS.[14,15] Some studies have shown a direct association of socioeconomic level and education with PMS, while others showed an inverse association.[3,13,14]

Regarding the impact of PMS symptoms, the literature shows that it can be severe enough to interfere with the relationships and daily activities of women of reproductive age.[16,17] These symptoms can also impair women's professional or academic performance and have economic consequences owing to increased absenteeism.[17]

Therefore, the present study aimed to investigate the prevalence of PMS and PMDD in university students, the factors associated with PMS, the most prevalent symptoms, and the interference of symptoms in academic, family, social, and work activities.

Methods

This was a cross-sectional university-based study performed with students of courses in the area of health from a university in the Midwest Brazil. The study is part of a larger project that evaluated the epidemiological profile of university students in the health field at Universidade de Rio Verde, Goiás, in 2018. The larger study included all university students (men and women) aged $\geq$ 18 years, from the courses of nursing, dentistry, medicine, physiotherapy, pharmacy, and physical education, from three campuses, who were attending the university from November 2018 and who agreed to participate in the research. The present study included female university students aged $\geq$ 18 years. University students who did not menstruate (due to health problems, use of continuous contraceptives, menopause, pregnancy, or breast-feeding) and those with irregular menstrual cycles (intervals shorter than 21 days or longer than 35 days, according to literature at the time of the study) were excluded because the instrument used to measure PMS has not been validated for this population.[3,11,18,19]

To achieve the objectives of this study, the sample size was calculated adopting 40% prevalence for PMS and 16% for PMDD, with a margin of error of 3 percentage points, and a 95% confidence level,[20] resulting in a size of sample of 557 university students. The sample size was inflated by 25% to account for potential losses and refusals (10%) and to maintain statistical power after adjusting for confounding factors (15%). Thus, the sample size obtained allowed the detection of prevalence ratios 1.3 or higher, with a 95% confidence interval, with statistical power of 80%.

The fieldwork was performed by a trained field team, who approached the students on campuses. After receiving explanation of the nature of the study and having granted informed consent, the participants filled out a standardized, self-administered, and pretested questionnaire in a pilot study.

The study outcome was the prevalence of PMS and PMDD, measured by the Premenstrual Symptoms Screening Tool (PSST), which was validated for the Brazilian population.[18,19] The PSST consists of two domains: the first one comprises the 14 physical and psychological manifestations that reflect the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, while the 2nd domain consists of 5 items that assess the functional impact of premenstrual symptoms. Each item is classified according to severity as "absent," "mild," "moderate," or "severe." The symptoms included were as follows: 1) anger/irritability, 2) anxiety/tension, 3) tearful/sensitive to rejection, 4) depressed/hopeless mood, 5) lack of interest in activities at work, 6) lack of interest in homework, 7) lack of interest in social activities, 8) difficulty concentrating, 9) fatigue/lack of energy, 10) overeating/food cravings, 11) insomnia, 12) hypersomnia (too much sleep), 13) feeling overwhelmed or out of control, and 14) physical symptoms (breast tenderness, headaches, joint/muscle pain, bloating, weight gain). The second domain included the impact of these symptoms on A) work/college efficiency or productivity, B) relationships with coworkers/colleagues, C) relationships with family, D) social life activities, and E) home responsibilities. In items A and B, the words "college" and "colleagues" were added to suit the reality of the population studied. To confirm the presence of PMS, the following criteria were established: the presence of 1) at least 5 symptoms (1–14), rated as moderate or severe; 2) at least 1 of the first 4 symptoms (1–4), rated as moderate or severe, and 3) at least 1 item from A to E, rated as moderate or severe. For PMDD, the following criteria were established: the presence of 1) at least 5 symptoms (1–14) rated as moderate or severe, 2) at least 1 of the first 4 symptoms (1–4) rated as severe, 3) and at least 1 item from A to E, rated as severe.[18,19]

The sociodemographic characteristics assessed were age (18–20, 20.1–22.0, 22.1–24.0, or $>$ 24 years), self-reported skin color (white or non-white), course period (1st–2nd, 3rd–4th, 5th–6th, 7th–8th, or $\geq$ 9th), and economic class (categorized using the Economic Classification Criterion of the Brazilian Association of Research Companies: A, B, C, D or E

and recategorized later in A, B, C–E).[21] This classification criterion estimates the buying power of individuals and families including the possession of household items and the education level of the householder. The behavioral variables measured were smoking status (non-smoker: never smoked or smoked for less than a month; former smoker: stopped smoking; smoker: smokes for more than a month), alcohol consumption in the last 30 days (no: no cup or dose in the last 30 days/yes: at least one cup or dose in the last 30 days; one dose is equivalent to a can of beer or a glass of wine or a dose of cachaça or whiskey or others), physical activity (no: when they engaged in physical activities < 150 minutes per week, or yes: when they engaged in physical activities for ≥ 150 minutes per week),[22] and eating habits (unhealthy: consumption of vegetables and fruits < 5 times/week, or healthy: ≥ 5 times/week).[23] Reproductive variables included the use of hormonal contraceptives (do not use; use of one method; use of two or more methods, e.g., oral/injectable contraceptives/other methods, such as vaginal rings, implants, patches, and hormonal intrauterine device [IUD]), and age at menarche (≥ 12 years, or < 12 years). Nutritional status was assessed according to body mass index (BMI [kg/m^2]) and classified as normal weight (BMI $< 25\,kg/m^2$), overweight (BMI $\geq 25\,kg/m^2$ and $< 30\,kg/m^2$), and obesity (BMI $\geq 30\,kg/m^2$).[24] The health variables evaluated were medical diagnosis of hyperthyroidism or hypothyroidism (no/yes) and depression (no/yes), referred by the university students.

Data were compiled in the EpiData 3.1 software, by the double-data entry method, followed by comparison of entries and consistency analysis. The Stata 13.0 software (StataCorp LP, College Station, TX, USA) was used to describe the study population, the premenstrual symptoms investigated in the two PSST domains, and to calculate the prevalence of PMS and PMDD. The hierarchical approach[25] and Poisson regression[26] with variance were used for multivariate analysis. Socioeconomic variables were considered distal (level 1) determinants, behavioral and reproductive variables as intermediate (level 2) determinants, and nutritional and health variables as proximal (level 3) determinants. The effect of each variable on the sample was calculated by means of prevalence ratios and their respective 95% confidence intervals. All exposures (sociodemographic, behavioral, reproductive, nutritional, and health variables) under study were considered to be potential confounding factors. Variables with $p < 0.20$ on crude and adjusted analysis were carried forward to the multivariate model as potential confounders, and the significance level adopted was 5%.

This study was approved by the Research Ethics Committee at Universidade do Vale do Rio dos Sinos (UNISINOS), Protocol 2.892.764, which hosted the study's coordination, and Universidade de Rio Verde, Protocol 2.905.704, which hosted the study's data collection, in accordance with the National Health Council Resolution 466/12. All participants signed a consent form, guaranteeing confidentiality of information and the right to withdraw participation at any time.

Results

In total, 1,596 university students were considered eligible. Of these, 481 met the exclusion criteria; thus, 1,115 university students were analyzed. The most prevalent characteristics found among university students were age range between 20.1 and 22 years (mean age 22.5 ± 3.4 years), white skin color, attending the $3^{rd}/4^{th}$ semester of college, and economic class B. Regarding behavioral characteristics, 62.7% were physically active, less than half had healthy eating habits (43.9%), more than 90% did not smoke, and 74% had consumed alcohol in the last 30 days. About two-thirds of the group used hormonal contraceptives, and more than 70% had menarche at age ≥ 12 years. Approximately 15% had BMI $> 25\,kg/m^2$, 7.9% had hypothyroidism or hyperthyroidism, and 20.6% were diagnosed with depression (►**Table 1**).

The prevalences of PMS and PMDD were 46.9% (95% CI, 44.0–49.8) and 11.1% (95% CI, 9.3–13.0), respectively, according to the PSST criteria. The physical symptoms (breast tenderness, headaches, joint/muscle pain, bloating, weight gain) were present in 73% of university students, and the most prevalent psychological symptoms were overeating/food cravings, tearfulness/sensitivity to rejection, anxiety/tension, and anger/irritability; in more than 60% of the cases in moderate or severe way. In more than 30%, these symptoms interfered with their efficiency and productivity at work/college, relationships with colleagues, family relationships, activities, and social life, in moderate-to-severe ways. Difficulty concentrating and feeling under pressure or severely out of control were reported by $\sim 8.5\%$ and 8.4% of the students, respectively (►**Table 2**).

The prevalence of PMS was higher in students who attended 1^{st} and 2^{nd} course periods (54.6%), had unhealthy eating habits (49.6%), were smokers (62.2%), and who consumed alcohol in the last month (49.4%). It was also prevalent in those who used one or more hormonal contraception methods (43.7% and 59.6%, respectively) and in those with depression (65%) (►**Table 3**).

After adjusting for confounding factors, being in the first periods of the academic course (PR 1.44, 95% CI 1.14–1.80), alcohol consumption (PR 1.23, 95% CI 1.04–1.47), and medical diagnosis of depression (PR 1.49, 95% CI 1.30–1.71) remained associated with PMS. (►**Table 4**). The use of hormonal contraceptives and PMS did not maintain a direct linear association after adjustment. However, women who reported using 2 or more hormonal contraceptives were 22% more likely to have PMS compared with those who reported not using hormonal contraceptives (PR 1.22; 95% CI 1.02–1.46).

Discussion

The present study found a high and consistent prevalence of PMS among university students in the health field. The main complaints reported were physical (sensitive breasts, headache, muscle, or joint pain, swelling, and weight gain) and psychological symptoms (overeating/food cravings,

Table 1 Sociodemographic, behavioral, reproductive, nutritional, and health characteristics of students from a university in Midwest Brazil, 2018 ($n = 1{,}115$)

Variables	n	%
Total	1,115	100
Age (years)		
18–20	212	19.0
20.1–22	386	34.6
22.1–24	294	26.4
> 24	223	20.0
Skin color		
White	653	58.6
Non-white	462	41.4
Course period (semester) ($n = 1{,}114$ - uninformed: 1)		
$\geq 9^{th}$	163	14.6
7^{th} and 8^{th}	219	19.7
5^{th} and 6^{th}	241	21.6
3^{rd} and 4^{th}	262	23.5
1^{st} and 2^{nd}	229	20.6
Economic class* ($n = 1{,}076$ - uninformed: 39)		
A (high)	448	41.6
B	496	46.1
C–E (low)	132	12.3
Practice of physical activity** ($n = 1{,}084$ - uninformed: 31)		
No	404	37.3
Yes	680	62.7
Eating habits*** ($n = 1{,}114$ - uninformed: 1)		
Unhealthy	625	56.1
Healthy	489	43.9
Smoking status ($n = 1{,}093$ - uninformed: 22)		
Non-smoker	1,003	91.8
Former smoker	45	4.1
Smoker	45	4.1
Alcohol consumption (in the last month) ($n = 1{,}114$ - uninformed: 1)		
No	290	26.0
Yes	824	74.0
Use of hormonal contraceptives ($n = 969$ - uninformed: 146)		
Do not use	336	34.7
1	487	50.3
≥ 2	146	15.1
Menarche ($n = 1{,}106$ - uninformed: 9)		
≥ 12 years	780	70.5
< 12 years	326	29.5
Nutritional status ($n = 1{,}095$ - uninformed: 20)		
Normal	924	84.4
Overweight	135	12.3
Obesity	36	3.3
Hyperthyroidism/ Hypothyroidism**** ($n = 1{,}098$ - uninformed: 17)		
No	1,011	92.1
Yes	87	7.9
Depression**** ($n = 1{,}081$ - uninformed: 34)		
No	858	79.4
Yes	223	20.6

*ABEP, Economic Classification Criterion of the Brazilian Association of Research Companies.
**Practicing some physical activity for at least 150 minute/week.
***Healthy eating habits considered: consumption of fruits and vegetables ≥ 5 days/week.
****Diagnosed by a doctor, as reported by the university student.

tearfulness/sensitivity to rejection, anxiety/tension, and anger/irritability). These symptoms interfered in moderate-to-severe ways in the academic, family, and social activities of this population. After adjustment, the highest PMS probability occurred for university students who were attending the first periods of the course, who had consumed alcoholic beverages in the last 30 days, and who were diagnosed with depression.

The prevalence of PMS (46.9%) identified in the present study is consistent with that in the literature. One systematic review identified a combined prevalence of PMS of 47.8% (95% CI 32.6–62.9,),[20] which was similar to the value found in our study. In this review of 17 articles, the lowest prevalence reported was in France, at 12% (95% CI 11–13),[27] and the highest in Iran, at 98% (95% CI 97–100).[28] The reviewed studies used different methodologies, populations, assessment tools, and outcome categorization instruments, which may explain the wide difference in the prevalence rates. The prevalence of PMDD (11.1%) was lower than that reported in a study conducted in the Northeast of Brazil, with health professionals and university students (16.5%).[19]

In relation to symptoms, the most prevalent ones found in this study were physical symptoms (tender breasts, headache, muscle, or joint pain, swelling, and weight gain), followed by desire for overeating/food cravings, tearfulness/sensitivity to rejection, anxiety/tension, and anger/irritability, which is consistent with the literature. A prospective, observational study involving 60 university students from Centro Universitário São Camilo, in São Paulo, with a mean age of 24.6 ± 4.7 years, identified the following main symptoms of PMS: irritability (76.6%), swelling (65%), and anxiety (58.3%).[4] A cross-sectional population study performed in Pelotas, RS, with 1,395 women aged between 15 and 49 years found the following main premenstrual symptoms: irritability, abdominal discomfort, nervousness,

Table 2 Frequency of responses on premenstrual symptoms addressed in the domains of the premenstrual symptoms screening tool in students from a university in Midwest Brazil, 2018 ($n = 1,115$)

	Absent n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Premenstrual symptoms				
Anger/irritability	120 (10.8)	304 (27.3)	492 (44.1)	199 (17.9)
Anxiety/tension	120 (10.8)	302 (27.1)	488 (43.8)	205 (18.4)
Tearful/more sensitive to rejection	114 (10.2)	235 (21.1)	471 (42.2)	295 (26.5)
Depressed mood/hopelessness	267 (24.0)	321 (28.8)	345 (30.9)	182 (16.3)
Lack of interest in activities at work	322 (28.9)	340 (30.5)	329 (29.5)	124 (11.1)
Lack of interest in homework	307 (27.5)	333 (29.9)	333 (29.9)	142 (12.7)
Lack of interest in social activities	313 (28.1)	368 (33.0)	312 (28.0)	122 (10.9)
Difficulty concentrating	418 (37.5)	322 (28.9)	278 (24.9)	97 (8.7)
Fatigue/lack of energy	271 (24.3)	331 (29.7)	381 (34.2)	132 (11.8)
Overeating/food cravings	90 (8.1)	239 (21.4)	438 (39.3)	348 (31.2)
Insomnia	584 (52.4)	274 (24.6)	193 (17.3)	64 (5.7)
Hypersomnia	422 (37.9)	291 (26.1)	268 (24.0)	134 (12.0)
Feeling overwhelmed	457 (41.0)	275 (24.7)	289 (25.9)	94 (8.4)
Physical symptoms: breast tenderness, headaches, joint/ muscle pain, bloating, weight gain.	86 (7.7)	220 (19.7)	439 (39.4)	370 (33.2)
Interferes with				
Work/college efficiency or productivity	278 (24.9)	438 (39.3)	346 (31.0)	53 (4.8)
Relationships with coworkers/colleagues	257 (23.1)	425 (38.1)	359 (32.2)	74 (6.6)
Relationships with family	233 (20.9)	422 (37.9)	376 (33.7)	84 (7.5)
Social life activities	248 (22.2)	450 (40.4)	349 (31.3)	68 (6.1)
Home responsibilities	366 (32.8)	442 (39.6)	250 (22.4)	57 (5.1)

headache, tiredness, and mastalgia, all with a prevalence $> 50\%$,[3] data similar to that found in this study.

Upon analyzing the associated factors, a high prevalence of PMS was found among university students in the initial periods of the course compared with those attending the final semesters. The association between lower educational levels and PMS has been described previously. In a population study performed in the United Kingdom, an inverse linear association was found in which the lowest level of education was associated with a high occurrence of PMS.[14] However, a Brazilian study identified a high prevalence of PMS in women with higher education.[2] It is worth mentioning that in the present study, the schooling indicator evaluated was the period of the course, since the population was composed only of university students. We found that university students from the first periods (1st and 2nd semesters) are susceptible to premenstrual symptoms in the same way that they are to depression and anxiety disorders. The higher probability of depressive symptoms and anxiety in freshmen than in university students in the last semesters has been reported in previous study.[29] Sex steroids and their receptors are abundant in the brain; they regulate emotions and behaviors and modulate the secretion of serotonin, which is implicated in the etiology of PMS.[30] As the first semesters are adaptation periods, these university students could be susceptible to these changes.

In relation to behavioral variables, an association was also found between alcohol consumption and PMS, which has already been evidenced. In a systematic review, 19 studies were evaluated, and it was found that alcohol consumption was associated with a 50% increase in the likelihood of developing PMS (odds ratio [OR] = 1.45; 95% CI 1.17–1.79).[12] Alcohol consumption can change the levels of sex steroid hormones and gonadotropin during the menstrual cycle, which may increase the risk of PMS occurrence, since the etiology of this syndrome is linked to fluctuations of these sex hormones during the menstrual cycle.[31] In addition, alcohol intake may increase the risk of PMS through its effect on serotonin and GABA activity, since these neurotransmitters are involved in the etiology of PMS.[12]

Regarding the morbidities assessed, depression was associated with PMS after adjusting for possible confounding factors. This finding is consistent with another study that shows that university students with depressive symptoms are more likely to have symptoms of PMS and its most severe form, PMDD, which has already been classified as a depressive disorder.[32] In addition, it has already been shown that women with PMS have a higher risk of depression than those without PMS.[33] Although there is a clear association between depressive disorders and PMS in the literature, it is not yet clear whether these conditions predispose one to PMS or whether PMS increases the likelihood of these disorders.[30]

Table 3 Prevalence and crude Poisson regression of premenstrual syndrome in relation to sociodemographic, behavioral, reproductive, nutritional, and health variables of students from a university in Midwest Brazil, 2018 ($n = 1{,}115$)

Variables	Prevalence of PMS	PR (95% CI)	*p*-value
	n (%)		
Age (years)			0.325[a]
18–20	102 (48.2)	1	
20.1–22	186 (48.2)	1.00 (0.84–1.19)	
22.1–24	137 (46.6)	0.97 (0.80–1.17)	
> 24	98 (44.0)	0.92 (0.74–1.12)	
Skin color			0.518[b]
White	301 (46.1)	1	
Non-white	272 (48.1)	1.04 (0.92–1.18)	
Course period (semester)			0.001[a]
≥ 9th	62 (38.0)	1	
7th and 8th	99 (45.2)	1.19 (0.93–1.52)	
5th and 6th	107 (44.4)	1.17 (0.92–1.49)	
3rd and 4th	129 (49.2)	1.30 (1.03–1.63)	
1st and 2nd	125 (54.6)	1.44 (1.14–1.80)	
Economic class			0.999[a]
A (high)	207 (46.2)	1	
B	238 (48.0)	1.04 (0.91–1.19)	
C–E (low)	59 (44.7)	0.97 (0.78–1.20)	
Practice of physical activity*			0.869[b]
No	191 (47.3)	1	
Yes	325 (47.8)	1.01 (0.93–1.41)	
Eating habits**			0.047[b]
Unhealthy	310 (49.6)	1	
Healthy	213 (43.6)	0.88 (0.77–0.99)	
Smoking status			0.018[b]
Non-smoker	458 (45.7)	1	
Former smoker	25 (55.6)	1.22 (0.93–1.59)	
Smoker	28 (62.2)	1.36 (1.07–1.73)	
Alcohol consumption (in the last month)			0.008[b]
No	116 (40.0)	1	
Yes	407 (49.4)	1.23 (1.06–1.44)	
Use of hormonal contraceptives			0.036[a]
Do not use	153 (45.8)	1	
1	213 (43.7)	0.95 (0.82–1.11)	
≥ 2	87 (59.6)	1.30 (1.09–1.55)	
Menarche			0.064[b]
≥ 12 years	353 (45.3)	1	
< 12 years	167 (51.2)	1.13 (0.99–1.29)	
Nutritional status			0.062[a]
Normal	422 (45.7)	1	
Overweight	75 (55.6)	1.22 (1.03–1.44)	
Obesity	18 (50.0)	1.09 (0.78–1.53)	
Hyperthyroidism/ Hypothyroidism***			0.206[b]
No	467 (46.2)	1	
Yes	46 (52.9)	1.14 (0.93–1.41)	
Depression****			< 0.001[b]
No	354 (41.3)	1	
Yes	145 (65.0)	1.58 (1.39–1.79)	

Abbreviations: 95% CI, 95% confidence interval; PR, prevalence ratio.
*Practiced some physical activity for at least 150 minute/week.
**Healthy eating habits considered: consumption of fruits and vegetables ≥ 5 days/week.
***Diagnosed by a doctor, as reported by the university student.
[a]Wald test, *p*-value for linear trend.
[b]Wald test, *p*-value for heterogeneity.

Longitudinal studies are necessary to understand this relationship.

Contrary to what would be expected in relation to the use of hormonal contraceptive, there was no dose-response effect between the categories of this variable and PMS, through adequate statistical test. However, it was observed that women who reported using 2 or more hormonal contraceptives showed 22% more probability of having PMS than those who did not, even after adjustment for confounding factors. As there is no knowledge of a medical recommendation for the use of an overlap of hormonal contraceptive methods, a possible explanation for the association found for this category would be that women who present premenstrual symptoms replace hormonal methods more frequently during life, in search of a pharmacotherapy that fulfills the contraceptive function and reduces the premenstrual symptoms. Thus, it cannot be said that the use of a combination of hormonal contraceptives occurred, but that the woman experienced the use of more than one hormonal method.

In the present study, no association was found between smoking, eating habits, physical activity, and PMS, which was also demonstrated by other authors.[14,34] University students with healthy eating habits were less likely to have PMS, but after adjustment, this association showed a borderline *p*-value. Smoking was associated with PMS only in the crude analysis, probably because of the low prevalence of university smokers (4%), which gave little power to this analysis.

One of the main limitations of this study was its cross-sectional design since the association between PMS and some associated factors, such as depression, may have been affected by reverse causality as exposure and outcome were measured at the same time. Another limitation was the use of an instrument with retrospective information. There is evidence that data collected prospectively show a prevalence

Table 4 Adjusted Poisson regression for premenstrual syndrome in relation to sociodemographic, behavioral, reproductive, and health variables of students at a university in Midwest Brazil, 2018 ($n = 1{,}115$)

Level	Variables	PR (95% CI)	*p*-value
1	Course period (semester)		0.001[a]
	$\geq 9^{th}$	1	
	7^{th} and 8^{th}	1.19 (0.93–1.52)	
	5^{th} and 6^{th}	1.17 (0.92–1.49)	
	3^{rd} and 4^{th}	1.30 (1.03–1.63)	
	1^{st} and 2^{nd}	1.44 (1.14–1.80)	
2	Eating habits*		0.058[b]
	Unhealthy	1	
	Healthy	0.88 (0.76–1.00)	
	Alcohol consumption (last 30 days)		0.018[b]
	No	1	
	Yes	1.23 (1.04–1.47)	
	Use of hormonal contraceptives		0.115[a]
	No		
	1	0.94 (0.80–1.10)	
	2 or +	1.22 (1.02–1.46)	
	Menarche		0.094[b]
	$\geq$ 12 years	1	
	$<$ 12 years	1.13 (0.98–1.30)	
3	Depression**		$<$ 0.001[b]
	No	1	
	Yes	1.49 (1.30–1.71)	

Abbreviations: 95% CI: 95% confidence interval; PR, prevalence ratio.
Each variable was adjusted to the others at the same or previous level in a hierarchical model of causality. Only variables associated with the outcome at $p < 0.20$ in the unadjusted model were subsequently entered and retained in the final multivariate-adjusted model.
*Healthy eating habits considered: consumption of fruits and vegetables $\geq$ 5 days/week.
**Diagnosed by a doctor, as reported by the student.
[a]Wald test, *p*-value for linear trend.
[b]Wald test, *p*-value for heterogeneity.

different from that of data obtained retrospectively.[8] However, PSST has been used in other studies and is considered a quick and easy-to-use assessment tool, which is valid for the screening of PMS/PMDD in Brazilian women.[18,19] Furthermore, all university students who did not menstruate but could still report the presence of premenstrual symptoms were excluded. However, this strategy sought to avoid memory bias inherent to studies that use recall. Finally, university students with a medical diagnosis of depression were not excluded. The exclusion of depressed subjects is indicated when using this type of instrument to distinguish the underlying psychiatric disorders that could be exacerbated in the premenstrual period.[32] However, the non-exclusion in our study allowed us to determine the independent association between depression and PMS in university students.

This study has several strengths. First, this is one of the few Brazilian studies that, in addition to determining the prevalence of PMS and PMDD in a population of young university students, evaluated the association of PMS with sociodemographic, reproductive, behavioral, nutritional, and health variables. Thus, this study expands the knowledge on PMS and the associated factors in Brazilian university students. Second, the significant sample size added power to the investigated associations. Third, the rigorous application of the methodology, using a validated instrument for the diagnosis of PMS, and controlling possible confounding factors, made it possible to analyze the independent effects of the variables.

Conclusion

In conclusion, the study identified that almost half of the university students had PMS, and $\sim$ 11% had PMDD. Physical symptoms were more prevalent than psychological ones. These symptoms interfered in a moderate-to-severe manner in their social and academic activities. The university students who were at the beginning of the course, who consumed alcohol as well as those who had a diagnosis of depression had a higher prevalence of premenstrual symptoms; therefore, this population should be better monitored. The identification of risk factors for PMS is essential to prevent symptoms and reduce the impact of the syndrome. However, longitudinal studies are necessary to better elucidate the associations described here.

Contributors

Dias-da-Costa J. S., Patussi M. P., and Paniz V. M. V. contributed to the conception and design of the study, review of the analysis, critical review, and final approval of the manuscript. Rezende A. P. R., Alvarenga F. R., and Ramos R. contributed to the study design, collection, and data analysis and interpretation as well as to writing the draft versions of the manuscripts. Franken D. L. contributed to the data analysis and interpretation as well as to writing the draft versions of the manuscripts. All the authors have approved the final version and are responsible for all aspects of this work, including guaranteeing its accuracy and integrity.

Conflict of Interests

The authors have no conflict of interests to declare.

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Adrenal Androgen Predictive Effects on Clinical and Metabolic Abnormalities of Polycystic Ovary Syndrome

Efeitos preditivos dos androgênios adrenais nas anormalidades clínicas e metabólicas da síndrome dos ovários policísticos

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Abstract

Objective To examine the possible effects of adrenal prohormones in the prediction of clinical and metabolic abnormalities in women with polycystic ovary syndrome (PCOS).

Methods The present study enrolled 299 normal cycling non-PCOS, 156 normoandrogenemic, and 474 hyperandrogenemic women with PCOS. Baseline characteristics were compared using a chi-squared test or analysis of variance (ANOVA) as appropriate. The roles of adrenal prohormones and their ratios with total testosterone in predicting co-occurring morbidities in women PCOS were evaluated using univariate and multivariate logistic regression analyses.

Results Adrenal hyperandrogenism per dehydroepiandrosterone sulfate (DHEAS) levels were found in 32% of women with PCOS. In non-PCOS women, dehydroepiandrosterone (DHEA) and its sulfate had no predictive role concerning clinical, anthropometric, and metabolic parameters. In PCOS women, mainly in the hyperandrogenemic group, DHEA showed to be a significant predictor against most anthropometric-metabolic index abnormalities (odds ratio [OR] = 0.36–0.97; $p < 0.05$), and an increase in triglycerides (TG) levels (OR = 0.76; $p = 0.006$). Dehydroepiandrosterone sulfate presented a few predictive effects regarding PCOS-associated disorders. In controls, DHEAS predicted against the increase in estimated average glucose (OR= 0.38; $p = 0.036$). In the normoandrogenic group, it predicted against elevation in the waist/hip ratio (WHR) (OR= 0.59; $p = 0.042$), and in hyperandrogenemic PCOS women, it predicted against abnormality in the conicity index (CI) (OR = 0.31; $p = 0.028$).

Keywords
- polycystic ovary syndrome
- hyperandrogenism
- obesity
- hyperinsulinemia
- metabolism

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Conclusion Dehydroepiandrosterone was shown to be a better predictor of abnormal anthropometric and biochemical parameters in women with PCOS than DHEAS. Thus, regarding adrenal prohormones, DHEA measurement, instead of DHEAS, should be preferred in PCOS management. The effects of androgen prohormones on the prediction of PCOS abnormalities are weak.

Resumo

Objetivo Examinar os possíveis efeitos dos pró-hormônios adrenais na predição de alterações clínicas e metabólicas em mulheres com síndrome dos ovários policísticos (SOP).
Métodos O presente estudo envolveu 299 mulheres com ciclos menstruais regulares e 630 mulheres com SOP, sendo 156 normoandrogenêmicas e 474 hiperandrogenêmicas. As variáveis incluídas como objeto do estudo foram comparadas entre os grupos usando o teste de qui-quadrado ou análise de variância (ANOVA, na sigla em inglês). Os impactos dos pró-hormônios adrenais e suas razões com a testosterona total na predição de comorbidades em mulheres com SOP foram determinados por regressão logística univariada e multivariada.
Resultados Hiperandrogenismo adrenal foi encontrado em 32% das mulheres com SOP. Nos controles, a dehidroepiandrosterona e seu sulfato (DHEAS) não mostraram significância na predição das alterações clínicas, antropométricas e metabólicas. Em mulheres com SOP, principalmente no grupo de mulheres com hiperandrogenemia, a dehidroepiandrosterona (DHEA) mostrou ser um preditor significante da maioria das anormalidades nos índices antropométrico-metabólicos (odds ratio [OR] = 0,36–0,97; $p < 0,05$) e aumento nos níveis de triglicerídeos (TG) (OR = 0,76; $p = 0,006$). A DHEAS apresentou ter pouco valor na predição dos distúrbios associados à SOP; nas mulheres com androgênios elevados, restringiu-se à predição da elevação do índice de conicidade (IC) (OR = 0,31; $p = 0,028$).
Conclusão A DHEA mostrou ser um melhor preditor na identificação das alterações dos parâmetros antropométricos e bioquímicos em mulheres com SOP do que o seu sulfato. Assim, em relação aos pró-hormônios adrenais, a dosagem de DHEA, em vez de DHEAS, parece ser mais útil no manejo da SOP. O papel dos pró-hormônios adrenais na predição de anormalidades antropométricas e metabólicas da SOP é limitado.

Palavras-chave
- síndrome dos ovários policísticos
- hiperandrogenismo
- obesidade
- hiperinsulinemia
- metabolismo

Introduction

Polycystic ovary syndrome (PCOS) is found in up to 20% of women of reproductive age.[1] Since 1990, PCOS has been defined by the presence of oligoanovulation, clinical or biochemical hyperandrogenism, and/or polycystic ovary morphology (PCOM).[2–4] The main characteristic of PCOS appears to be hyperandrogenism because PCOS women with high levels of androgens have increased risk for the development of central obesity, dysfunctional adipocyte, impaired fasting glucose (IFG), glucose intolerance (GI), insulin resistance (IR), dyslipidemia, metabolic syndrome (MS), low-grade chronic inflammation, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and, in the end, cardiovascular disease (CVD).[5–10] All these harmful co-occurring conditions, to a certain extent, are associated with hyperandrogenemia.[11–14]

Strong androgens, such as testosterone (T), direct macrophages toward adipocytes, induce adipocyte hypertrophy, promote visceral obesity, decrease adipocyte sensitivity to insulin, and decrease adipocyte glucose uptake.[15–19] Conversely, it appears that the adrenal prohormones dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) have a beneficial effect by inhibiting the proliferation and differentiation of subcutaneous adipocyte and adipogenesis in omental adipocyte and enhancing adipocyte glucose uptake.[20–22] Furthermore, DHEA seems to exert antiglucocorticoid action on preadipocyte proliferation and differentiation, and DHEAS stimulates lipolysis.[23,24]

Different effects of adrenal prohormones on the development of harmful subphenotypes in PCOS, when compared with the effects of testosterone and free testosterone index, have been reported.[25,26] The present study expands and amplifies the initial findings by examining separately women with PCOS who were classified as normoandrogenemic (NA-PCOS) and hyperandrogenemic (HA-PCOS) and comparing them with non-PCOS normal-weight controls. Therefore, the present study proposed to examine the possible beneficial effects of adrenal prohormones in preventing clinical abnormalities in women with PCOS. The secondary objective

was to verify the influence of adrenal products on carbohydrate and lipid metabolism biomarkers.

Methods

Subjects, Design, Eligibility Criterion

The present cross-sectional study enrolled 630 women with PCOS, aged 27.6 ± 5.4 years old, and 299 normal cycling nonobese controls, aged 29.9 ± 4.8 years old ($p < 0.001$), in whom DHEA and DHEAS were measured; all of them were attended at the outpatient clinic of the Instituto Tropical de Medicina Reprodutiva and at the Hospital Universitário Julio Muller, Cuiabá, state of Mato Grosso, Brazil, between 2003 and 2019. Women with PCOS were further divided into 156 (24.8%) NA-PCOS and 474 (75.2%) HA-PCOS. These subjects were enrolled from a previously described large sample of women with PCOS.[27] Every patient gave full-informed written consent by signing a form approved by the local Ethics in Research Committee (decision No.093/FCM/03). Late-onset adrenal enzyme deficiencies were excluded as follows: 21-hydroxylase (17-hydroxyprogesterone [17-OHP4] levels ≤ 15 nmol/L), 3β-hydroxysteroid dehydrogenase (3β-HSD) (17-hydroxypregnenolone [17-OHPE] ≤ 13.5 nmol/L), and 11-hydroxylase (compound S ≤ 23 nmol/L). Hypothyroidism was excluded by thyroid-stimulating hormone (TSH) level ≤ 4.2 µUI/mL, free thyroxin (FT4) ≤ 9.0 pmol/L, and hyperprolactinemia by prolactin (PRL) ≤ 1.1 pmol/L.[9,28] Women with PCOS who had used sex steroids, insulin-sensitizing, or dipeptidyl peptidase-4 inhibitors over the previous 6 months or those who did not fulfill the Rotterdam criteria were excluded.

Definitions

Polycystic ovary syndrome was diagnosed using the Rotterdam criteria, after exclusion of other hyperandrogenic conditions.[28] The normal menstrual cycle was defined by a menstrual interval of between 24 and 35 days; amenorrhea was defined by the absence of a menstrual period for ≥ 90 days.[29] Frequent menses were defined as an interval < 24 days or as > 4 menstrual episodes in 90 days, and infrequent menses were defined as a menstrual cycle ≥ 35 days or as ≤ 8 menstrual periods in the previous year.[30]

Because of inconsistent results due to ethnicity and inter-rater evaluation, clinical hyperandrogenism was registered as a dichotomous variable according to the complaints of the patient and the presence or lack of hirsutism in the upper lip, chin, chest, upper or lower back, upper or lower abdomen, upper arms, and thighs in the medical examination.[31–33] Biochemical hyperandrogenism was defined by at least 1 of the following criteria: total T ≥ 1.75 nmol/L, free testosterone (FT) ≥ 0.032 pmol/L, DHEAS ≥ 6.6 µmol/L, androstenedione (A4) ≥ 9.4 nmol/L, DHEA ≥34 nmol/L, and free androgen index (FAI) ≥ 5.2%. All these cutoff values were ≥ 90th percentile of 425 normal cycling, normal weight, non-PCOS women.[33]

Impaired fasting glucose (IFG) was defined by fasting plasma glucose concentration > 100 mg/dL (5.5 mmol/L) or < 126 mg/dL (7.0 mmol/L). Glucose intolerance (GI) was defined by a glucose concentration ≥ 7.8 nmol/L at 120 minutes after the ingestion of dextrose. Insulin resistance (IR) was defined by fasting insulin levels > 90 pmol/L and/or a HOMA-IR value ≥ 2.6.[33] Type 2 diabetes mellitus (T2DM) was defined as fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or glucose ≥ 200 mg/dL (11.1 mmol/L) at 120 minutes after the ingestion of dextrose.[34]

Ultrasound Evaluation

Ovarian morphology was examined by ultrasonography using a vaginal transducer with a frequency of between 5 and 8 MHz (Toshiba Xario SSA-660A, Toshiba Medical do Brazil LTDA, Taboão da Serra, SP, Brazil or Voluson E8, GE Health Care, Bedford, United Kingdom). Antral follicle count ≥ 20 follicles in at least 1 ovary and ovarian volume ≥ 10 cm3 were the reference for assuming PCOM. The ovarian volume was calculated by the ellipsoid formula: $\pi/6 \times D1 \times D2 \times D3$, where D1, D2, and D3 were taken as the maximum diameters.[29]

Clinical and Anthropometric Parameters

All data were registered in a template used in both institutions; however, in some participants, a few observations completely at random were not recorded. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with the study participants in a sitting position after at least 5 minutes of resting. Height was measured using a harpenden stadiometer (Holtain Ltd., Crymych, Dyfed, UK). Body weight was acquired using an electronic scale, and the waist circumference (WC) was measured as the narrowest measuring midway point between the lower rib margin and the iliac crest, and the hip was measured at the widest circumference at the greater trochanters. Body mass index (BMI) was calculated from the ratio between weight and height squared, despite the limitations of indirect measurement. Lean body mass (LBM) was calculated using the James[35] equation. Fat mass (FM) was calculated as body weight minus LBM. Body shape index (BSI) was calculated according to the formula: WC(cm) / [$BMI^{2/3}$ x height $(cm)^{1/2}$],[36] and the waist circumference triglyceride index (WTI) was calculated as the product of WC (cm) multiplied by TG (mmol/L).[37] The conicity index (CI) was calculated by the equation: WC(cm) / 10.109 × square root of BW(kg) / higher(m).[38] The VAI was calculated using the equation: WC / [36.58 + (1.89 x BMI)] x (TG / 0.81) x (1.52 / HDL-C),[39] and the lipid accumulation product (LAP) was calculated as (WC (cm)-58) x (TG9mmol)), as established for women.[40]

Biochemical Measurements

A glucose oxidase technique (Beckman Glucose Analyses, Fullerton, CA, USA) was used to measure fasting glucose. For the oral glucose tolerance test (OGTT), blood samples were collected at 0, 30, 60, 90, 120, and 180 minutes after the ingestion of 75 g of dextrose for the measurement of plasma glucose and insulin levels.[41] Glycated hemoglobin was measured using the turbidimetric assay (Wiener Laboratories, Rosario, Argentina). The estimated average glucose (eAG, mmol/L) was calculated using the equation eAG= 1.5944

multiplied by glycated hemoglobin minus 2.5944.[42] Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and basal insulin release (β-cell function, HOMA % B) were calculated using the free HOMA 2 calculator software (Diabetes Trials Unit, Oxford, UK).[43] Triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC) were measured after a 12-hour overnight fast using an enzymatic assay (Wiener Laboratories, Rosario, Argentina). Low-density lipoprotein cholesterol (LDL-C) was calculated as TC – (HDL-C + TG/5).[44]

Hormone Measurements

Without the requirement of any resting period, blood samples were taken by cubital venipuncture between 7:30 and 10:00 AM, after 10 to 12 hours of fasting, between the 3rd and 5th days of spontaneous menstruation or, in the case of infrequent menses or amenorrhea, on any day regardless of the time elapsed since the last menstrual period; in this case, the progesterone (P4) level was used to certify that samples were collected in the follicular phase and the results were validated whenever the P4 level was < 6.3 nmol/L.[45,46] Thyroid-stimulating hormone, estradiol (E2), PRL, SHBG, total T, DHEA, and FT4 were measured with an electrochemiluminescence assay (Elecsys 1010, Roche Diagnostics GmbH, Mannheim, Germany). Serum P4, A4, DHEAS, cortisol (F), and insulin were measured using a chemiluminescence assay (Advia Centaur, Siemens Healthcare Diagnostics, UK or Siemens Medical Solution Diagnostics, Los Angeles, CA, USA). Free testosterone concentrations were measured using an ELISA kit (GenWay Biotech Inc., San Diego, CA, USA). 17-hydroxyprogesterone levels were verified using a coat-a-count radioimmunoassay (Siemens Health Care Diagnostics Inc., Los Angeles CA, USA). The precision of these hormone measurements was verified in a recent publication.[33] The FAI was calculated as T (nmol/L divided by SHBG (nmol/L) $\times$ 100, and index of hyperandrogenism (IHA) was estimated as fifth root FAI x A4 X DHEA x DHEAS.[46]

Statistical Analysis

The original data of each variable were initially submitted to the Grubs test to avoid interference of outliers. Distributions of all variables were examined using the Shapiro–Wilk test. Data with asymmetric distribution are presented as numbers and percentages (n%), and data with symmetric distribution are shown as mean ($\bar{x}$) and standard deviation (SD). Proportions were compared using the chi-squared test or the Fisher exact test when appropriate. Comparisons of Gaussian variables were performed using one-way analysis of variance (ANOVA). Univariate logistic regression was applied to examine the relationship between anthropometric and metabolic parameters as dependent variables and DHEA, DHEAS, DHEA/T ratio, and DHEAS/T ratios as independent variables. The strength of independent variables in predicting anthropometric and metabolic abnormalities were controlled by age and BMI and given as odds ratio (OR) and 95% confidence interval (CI). The Kruskal-Wallis test, followed by the Bonferroni post-hoc test, was used in univariate logistic regression. For all univariate logistic regression analyses, the 90th percentile of dependent variables, taken from 425 normal-weight non-PCOS controls, was used as a cutoff.[9] The explained variation in the criterion variable was given by Cox and Snell R^2 and Nagelkerke R^2 values. Multivariate forward stepwise logistic regression was done including DHEA, DHEAS, DHEA/T, and DHEAS/T as significant independent variables in the models. Age and BMI were also included to control for confounders. The fit of the logistic regression models was evaluated using the Hosmer–Lemeshow goodness-of-fit test. Receiver operating characteristic (ROC) analysis curves were calculated using DHEA, DHEAS, DHEA/T, and DHEAS/T as independent variables, and significant anthropometric and metabolic variables were used as dependent variables. All tests were two-sided, and p-values < 0.05 were considered statistically significant. All statistical procedures were performed using SPSS Statistics for Windows, version 17 (SPSS Inc, Chicago, IL, USA).

Results

Comparisons of age, ethnicity, clinical, and hormone parameters among groups are shown in ►**Table 1**. Most PCOS patients were Caucasians, 72.4% NA-PCOS and 70.6% HA-PCOS ($p = 0.603$). African descendants were 9.6 and 12.7% NA-PCOS and HA-PCOS, respectively ($p = 0.307$). Women of other ethnicities were also similar in NA-PCOS and HA-PCOS (18.0 versus 16.0%, respectively, $p = 0.711$). Among controls, the distribution of these ethnicities was different from that of the PCOS groups: 89.3% were Caucasians, 60.0% were African descendants, and 4.7% were of other races ($p < 0.05$ for all comparisons). Comparisons of anthropometric, anthropometric-metabolic indexes, and metabolic characteristics of normal cycling controls, NA-PCOS, and HA-PCOS women are shown in ►**Supplementary Table S1** (available online only).

The Predictive Role of DHEA in Clinical, Anthropometric, and Metabolic Parameters

In non-PCOS controls, DHEA had no significant predictive role but tended to predict an increase in SBP (OR = 2.47; $p = 0.054$; area under the curve [AUC] = 0.705; $p < 0.001$), and a decrease in eAG (OR = 0.69; $p = 0.051$; AUC = 0.700; $p = 0.006$) without reaching statistical significance. In NA-PCOS (►**Table 2**), DHEA levels predicted elevation in body weight (OR = 2.58; $p = 0.039$), fasting glucose (OR = 4.36; $p = 0.021$), and against increase in HOMA %B (OR = 0.58; 0.029). In HA-PCOS, ►**Table 3**, DHEA significantly predicted against the increase in most anthropometric-metabolic indexes (OR = 0.36–0.97). Regarding biochemical markers, DHEA levels predicted against elevation of TG concentrations (OR = 0.76; $p = 0.006$).

The Predictive Role of DHEAS in Clinical, Anthropometric, and Metabolic Parameters

In non-PCOS controls, DHEAS was not associated with any abnormality in anthropometric or anthropometric-metabolic index. Regarding metabolic parameters, DHEAS predicted against increase in eAG (OR = 0.38; $p = 0.036$; AUC = 0.706;

Table 1 Comparisons of baseline clinical characteristics of normoandrogenemic, hyperandrogenemic, women with polycystic ovary syndrome, and normal cycling controls

Variables	Non-PCOS	NA-PCOS	HA-PCOS
Age (years old)	**29.9 ± 4.8[a]**	**29.0 ± 5.2[a]**	**27.0 ± 5.5[b]**
Ethnicity (n,%)*			
Caucasian	267 (89.3)[a]	113 (72.4)[b]	335 (70.6)[b],**
African descendent	18 (6.0)[a]	15 (9.6)[a]	60 (12.7)[b]
Other	14 (4.7)[a]	28 (18.0)[b]	79 (16.7)[b]
Blood pressure ($\bar{x} \pm$ SD)***			
SBP (mmHg)	113.1 ± 9.5[a]	116.6 ± 72.1[b]	120.0 ± 12.4[b]
DBP (mmHg)	71.4 ± 9.0[a]	74.6 ± 9.3[b]	76.2 ± 9.3[b]
Clinical signs (n,%)*			
Acne	12 (4.0)[a]	70 (44.9)[b]	217 (45.7)[b]
Hirsutism	7 (2.3)[a]	72 (46.2)[b]	224 (47.3)[b]
Acanthosis	2 (0.7)[a]	27 (17.3)[b]	95 (20.0)[b]
Striae	0 (0.0)[a]	19 (12.2)[b]	70 (14.7)[b]
Galactorrhea	0 (0.0)[a]	2 (1.3)[b]	6 (1.3)[b]
Metabolic disorders*			
IFG	8 (2.6)[a]	8 (5.1)[b]	62 (13.1)[c]
GI	11 (3.7)[a]	16 (6.9)[b]	78 (26.3)[c]
T2DM	10 (3.3)[NS]	5 (5.0)[NS]	18 (6.0)[NS]
Hormones*			
DHEAS > 34nmol/l	32 (10.7)[a]	8 (5.1)[a]	32 (6.8)[a]
DHEAS > 6.6µl/l	29 (9.7)[a]	1 (0.6)[a]	144 (31.8)[b]
T > 1.75 mmol/l	30 (10.0)[a]	11 (7.1)[a]	328 (70.4)[b]
FAI > 5.2	12 (4.0)[a]	19 (12.2)[b]	260 (61.3)[c]

Abbreviations: DBP, diastolic blood pressure; DHEAS, dehydroepiandrosterone sulfate; DM, diabetes mellitus; FAI, free androgen index; GI, glucose intolerance; HA-PCOS, hyperandrogenemic polycystic ovary syndrome; IFG, impaired fasting glucose; NA-PCOS, normoandrogenemic polycystic ovary syndrome; SBP, systolic blood pressure; T, testosterone.

*Comparisons using chi-squared or Fisher tests as appropriate.

**Equal subscript letter denotes proportions that do not differ significantly from each other at the level of 0.05; otherwise, different letters indicate $p < 0.05$ between proportions or means ± standard deviation. NS= not significant.

***Comparisons using one-way analysis of variance.

$p = 0.001$). In NA-PCOS women, DHEAS only predicted against increase in WHR (OR = 0.59; $p = 0.042$; AUC = 0.757; $p = 0.002$). In HA-PCOS, DHEAS concentrations predicted against elevation in the CI (OR = 0.31; $p = 0.028$; AUC = 0.740; $p < 0.001$) (►**Table 3**).

The Predictive Role of DHEA/total Testosterone Ratio in Clinical, Anthropometric, and Metabolic Parameters

The DHEA/total testosterone ratio (DHEA/T) was a good predictor against increase in WHR (OR = 0.44; $p = 0.015$; AUC = 0.662; $p < 0.001$) in the control group. In NA-PCOS women, the DHEA/T ratio tended to predict against increase in BW (OR = 0.95; $p = 0.071$; AUC = 0.974; $p < 0.001$), and decrease in C-pep levels (OR = 0.68; $p = 0.070$; AUC = 0.805; $p < 0.001$). This ratio predicted increase in fasting glucose (OR = 2.65; $p = 0.018$; AUC = 0.915; $p < 0.001$). In HA-PCOS women (►**Table 4**), the DHEA/T ratio predicted against increase in WTI (OR = 0.70; $p = 0.003$), CI (OR = 0.79; $p = 0.036$), BSI (OR = 0.77; $p = 0.046$), VAI (OR = 0.76; $p = 0.039$), and LAP (OR = 0.76; $p = 0.032$). However, with statistical significance, the DHEA/T ratio predicted against increase in TC (OR = 0.76; $p = 0.033$), in VLDL-C (OR = 0.90; $p = 0.049$), and in TG (OR = 0.72; $p = 0.006$).

The Predictive Role of DHEAS/Total Testosterone Ratio in Clinical, Anthropometric, and Metabolic Parameters

In non-PCOS controls (►**Table 5**), the DHEAS/T ratio predicted only against the increase in WHR (OR = 0.44; $p = 0.015$; AUC = 0.663; $p < 0.001$). In NA-PCOS, the DHEAS/T ratio did not predict any biomarker of anthropometric or metabolic abnormalities. In the HA-PCOS group, the DHEAS/T ratio predicted against increase in CI (OR = 0.29; $p = 0.007$; AUC = 0.738; $p < 0.001$), and in TC (OR = 0.37; $p = 0.041$; AUC = 0.655; $p = 0.001$). Without reaching statistical significance, this ratio also tended to predict against increase in VLDL-C (OR = 0.87; $p = 0.084$; AUC = 0.570;

Table 2 Age and body mass index controlled univariate logistic regression between clinical, anthropometric, anthropometric-metabolic indexes, and metabolic biomarkers as dependent variables, and dehydroepiandrosterone as the independent variable in normoandrogenemic women with polycystic ovary syndrome

Variable	B	Wald	Sig	Exp B (Lower-Upper)	AUC	*p-value*
SBP (mmHg)	−0.424	1.761	0.184	0.655 (0.350–1.224)	0.842	< 0.001
DBP (mmHg)	−0.222	0.286	0.593	0.801 (0.355–1.808)	0.757	0.006
BW (kg)	0.950	4.247	0.039	2.584 (1.048–6.372)	0.976	< 0.001
WC (cm)	−0.206	0.385	0.535	0.814 (0.424–1.560)	0.957	< 0.001
WHR (ratio)	−0.295	0.627	0.429	0.745 (0.359–1.545)	0.697	0.019
FM (kg)	0.592	1.033	0.309	1.808 (0.577–5.667)	0.991	< 0.001
FM (%)	0.640	1.286	0.257	1.826 (0.628–5.726)	0.989	< 0.001
FM/LBM (ratio)	0.172	0.163	0.686	1.194 (0.505–2.824)	0.980	< 0.001
WTI	−0.107	0.169	0.681	0.898 (0.835–1.499)	0.789	< 0.001
CI (%,pg/ml, nmol/L)	−0.262	1.089	0.297	0.770 (0.471–1.258)	0.748	< 0.001
BSI	−0204	1.043	0.307	0.816 (0.552–1.206)	0.600	0.041
VAI	0.242	0.689	0.407	1.274(0.719–2.257)	0.734	< 0.001
LAP (cm, mmol/L)	−0.424	2.008	0.157	0.654 (0.364–1.177)	0.885	< 0.001
Go (mmol/L)	1.473	5.321	0.021	4.363 (1.248–15.257)	0.924	< 0.001
Io (pmol/L)	−0.069	3.742	0.053	0.9336 (0.820–1.001)	0.838	< 0.001
C-pep (pmol/L)	−0.455	3.182	0.074	0.635 (0.385–1.046)	0.780	< 0.001
HOMA-IR	0.095	0.089	0.766	1.100 (0.582–1.063)	0.784	< 0.001
HOMA %B	−0.544	4.740	0.029	0.581 (0.356–0.947)	0.739	< 0.001
eAG (mmol/L)	−0.075	0.089	0.765	0.928 (0.567–1.518)	0.638	0.027
TC (mmol/L)	0.010	0.001	0.971	1.010 (0.576–1.771)	0.554	0.293
HDL-C (mmol/L)	−0.025	0.793	0.373	0.975 (0.922–1.031)	0.700	< 0.001
LDL-C (mmol/L)	−0.135	0.255	0.613	0.874 (0.519–1.473)	0.552	0.431
VLDL-C (mmol/L)	0.009	0.054	0.816	1.009 (0.937–1.086)	0.732	< 0.001
TG (mmol/L)	0.025	0.567	0.452	1.026 (0.960–1.096)	0.722	< 0.001
DM	−0.072	0.517	0.472	0.931 (0.765–1.132)	0.868	0.006
IG	0.019	0.134	0.714	1.019 (0.920–1.129)	0.820	< 0.001

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BW, body weight; WC, waist circumference; WHR, waist-hip ratio; FM, fat mass; LBM, lean body mass; WTI, waist circumference-triglyceride index; CI, conicity index; BSI, body shape index; VAI; visceral adiposity index; LAP, lipid accumulation product; Go, fasting glucose; Io, fasting insulin; C-pep, C-peptide; HOMA-IR,homeostatic assessment model of insulin resistance; HOMA%B, homeostatic model assessment of β-cell function; eAG, average glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; TG, triglyceride; DM, diabete mellitus; IG, intolerance glucose.

$p < 0.001$), and in WTI (OR = 0.64; $p = 0.067$; AUC = 0.719; $p < 0.001$).

Multivariate Logistic Regression Analysis

Multivariate logistic regression models, consistent with univariate regression, retained the predictive role of the DHEAS/T ratio against increase in WHR (OR = 0.44; $p = 0.016$) and of DHEAS against increase in eAG (OR = 0.36; $p = 0.029$) in the non-PCOS control group. In NA-PCOS women, the results of the univariate regression were maintained after multiple regression. Thus, DHEA maintained the predictive role favoring increase in BW (OR = 2.60; $p = 0.019$). In these women, DHEA also predicted against the increase in HOMA %B (OR = 0.34; $p = 0.039$). The DHEA/T ratio favors an increase in fasting glucose (OR = 2.60; $p = 0.019$). In HA-PCOS, DHEA maintained prediction against the increase in VAI (OR = 0.74; $p = 0.006$) and in TG (OR = 0.74; $p = 0.002$). The DHEAS/T ratio predicted against the increase in TC (OR = 0.30; $p = 0.005$); nevertheless, the DHEAS/T ratio favors an increase in CI (OR = 1.54; $p = 0.004$). The DHEA/T ratio predicted against an increase in WTI (OR = 0.70; $p = 0.004$) and in LAP (OR = 0.76; $p = 0.038$).

Discussion

Many studies have investigated the role of adrenal androgens in PCOS. There have been attempts to translate basic knowledge into the clinical practice. The present study evaluated the strength of adrenal androgens in predicting blood pressure, anthropometric, and metabolic abnormalities in women with PCOS, after separating PCOS women with normal from high androgens in the blood. The impact of DHEA, DHEAS, and the ratios of these prohormones and total testosterone were considered because between ~ 70 and

Table 3 Age and body mass index controlled univariate logistic regression between clinical, anthropometric, anthropometric-metabolic indexes, and metabolic biomarkers as dependent variables, and dehydroepiandrosterone as the independent variable in hyperandrogenemic women with polycystic ovary syndrome

Variable	B	Wald	Sig	Exp B (Lower-Upper)	AUC	*p-value*
SBP (mmHg)	0.059	0.327	0.567	1.061 (0.866–1.300)	0.773	< 0.001
DBP (mmHg)	−0.098	0.559	0.455	0.907 (0.702–1.171)	0.751	< 0.001
BW (kg)	0.003	0.001	0.978	1.003 (0.794–1.268)	0.947	< 0.001
WC (cm)	−1.072	2.968	0.085	0.342 (1.101–1.159)	0.957	< 0.001
WHR	−0.189	2.429	0.119	0.828 (0.652–1.050)	0.730	< 0.001
FM (kg)	0.103	0.461	0.497	1.108 (0.824–1.491)	0.987	< 0.001
FM (%)	0.013	0.008	0.929	1.013 (0.767–1.336)	0.977	< 0.001
FM/LBM (ratio)	−0.005	0.001	0.976	0.995 (0.711–1.392)	0.986	< 0.001
WTI (WC/TG)	−0.227	5.256	0.022	0.797 (0.656–0.968)	0.803	< 0.001
CI (%,pg/ml, nmol/L)	−0.841	0.3178	0.049	0.451 (0.187–0.996)	0.742	< 0.001
BSI	−0.274	11.388	0.001	0.761 (0.649–0.892)	0.601	< 0.001
VAI	−0.999	4.204	0.040	0.369 (0.142–0.957)	0.726	< 0.001
LAP (cm, mmol/L)	−0.024	3.971	0.046	0.976 (0.954–1.000)	0.886	< 0.001
Go (mmol/L)	0.676	1.302	0.254	1.966 (0.616–6.282)	0.708	< 0.001
Io (pmol/L)	0.175	0.161	0.688	1.192 (0.506–2.084)	0.785	< 0.001
C-pep (nmol/L)	−0.138	1.815	0.178	0.871 (0.713–1.065)	0.832	< 0.001
HOMA-IR	0.065	0.017	0.897	1.067 (0.397–2.866)	0.774	< 0.001
HOMA %B	0.133	0.098	0.755	1.143 (0.495–2.638)	0.701	< 0.001
eAG (mmol/L)	−0.022	0.055	0.814	0.978 (0.812–1.178)	0.699	< 0.001
TC (mmol/L)	0.145	0.096	0.752	1.156 (0.461–2.898)	0.630	< 0.001
HDL-C (mmol/L)	0.442	1.094	0.296	1.556 (0.679–3.565)	0.688	< 0.001
LDL-C (mmol/L)	0.084	0.035	0.852	0.919 (0.378–2.233)	0.602	0.002
VLDL-C (mmol/L)	−0.074	0.492	0.483	0.928 (0.755–1.142)	0.698	< 0.001
TG (mmol/L)	−0.270	0.748	0.006	0.763 (0.629–0.926)	0.740	< 0.001
DM	−0.212	0.836	0.361	0.809 (0.513–1.278)	0.812	< 0.001
IG	0.175	2.265	0.132	1.192 (0.948–1498)	0.732	< 0.001

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BW, body weight; WC, waist circumference; WHR, waist-hip ratio; FM, fat mass; LBM, lean body mass; WTI, waist circumference-triglyceride index; CI, conicity index; BSI, body shape index; VAI; visceral adiposity index; LAP, lipid accumulation product; Go, fasting glucose; Io, fasting insulin; C-pep, C-peptide; HOMA-IR,homeostatic assessment model of insulin resistance; HOMA%B, homeostatic model assessment of β-cell function; eAG, average glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; TG, triglyceride; DM, diabete mellitus; IG, intolerance glucose.

95% of DHEA and DHEAS molecules have the adrenal gland as a primary source.[26] Either in a combination of various androgens or in the elevation of at least one androgen, biochemical hyperandrogenism is found in > 70% of women with PCOS.[46,47] Higher androgens of the adrenal source are reported in between 20 and 30% of PCOS women.[48,49] Insulin resistance is a common comorbidity of hyperandrogenemic PCOS through decreased insulin-like growth factor 1 (IGF-BP) leading to increased free insulin-like growth factor 1 (IGF-1), which stimulates ovarian androgen production.[50] The role of insulin resistance in the adrenal function of PCOS women is unclear.[51] Conversely, the cross-talk between adrenal androgens and insulin acting in women with PCOS is of clinical relevance. Furthermore, while insulin is higher in obesity, cortisol (F), DHEA, and DHEAS appear to be lower.[52]

The incidence of 75% of biochemical hyperandrogenism in women with PCOS in the present study is in agreement with other studies.[53–55] As shown in ►**Table 1**, the slightly higher SBP and DBP levels in PCOS than in controls, observed mainly in the hyperandrogenemic group, found in the present study, also endorse previous findings.[56–58] In the same way, a higher prevalence of glucose intolerance in women with PCOS has been extensively found.[7,13,45,59,60] The finding that, in NA-PCOS, DHEA was negatively correlated with body weight, fasting glucose, and β-cell activity, indicates a protective role of DHEA against adiposity and insulin resistance. In previous studies, DHEA has been shown to inhibit the proliferation and differentiation of adipocytes in the subcutaneous adipose tissue compartment (SAT) and to increase adipocyte glucose uptake in this location.[21,61] Additionally, DHEA appears to inhibit adipogenesis in omental adipocytes through an increase in resistin production.[20,62] Dehydroepiandrosterone also increases insulin signaling to its secretion and protects against omental adipogenesis.[63]

Table 4 Age and body mass controlled univariate logistic regression between clinical, anthropometric, and anthropometric-metabolic indexes as dependent variables, and dehydrotestosterone/testosterone ratio as the independent variable in hyperandrogenic women with polycystic ovary syndrome

Variable	B	Wald	Sig	Exp B (Lower-Upper)	AUC	*p-value*
SBP (mmHg)	0.279	0.387	0.568	1.323 (0.508–3.441)	0.773	< 0.001
DBP (mmHg)	0.130	0.048	0.826	1.138 (0.357–3.627)	0.742	< 0.001
BW (kg)	0.058	0.009	0.924	1.060 (0.320–3.500)	0.947	< 0.001
WC (cm)	−0.146	0.954	0.329	0.864 (0.645–1.158)	0.957	< 0.001
WHR (ratio)	−0.195	1.779	0.182	0.823 (0.618–1.096)	0.722	< 0.001
FM (kg)	0.013	0.005	0.944	1.013 (0.709–1.447)	0.987	< 0.001
FM (%)	0.342	0.225	0.636	1.408 (0.342–5.792)	0.978	< 0.001
WTI (ratio)	−0.355	8.615	0.003	0.701 (0.553–0.889)	0.809	< 0.001
CI (%, pg/ml, nmol/L)	−0.227	4.406	0.036	0.797 (0.645–0.985)	0.739	< 0.001
BSI (ratio)	−0.252	3.988	0.046	0.777 (0.607–0.995)	0.888	< 0.001
VAI	−0.267	4.276	0.039	0.766 (0.594–0.986)	0.723	< 0.001
LAP (cm, mmol/L)	−0.275	4.624	0.032	0.760 (0.591–0.976)	0.888	< 0.001
Go (mmol/L)	−0.032	1.773	0.183	0.968 (0.923–1.015)	0.703	< 0.001
Io (pmol/L)	−0.014	0.016	0.898	0.987 (0.803–1.273)	0.783	< 0.001
HOMA-IR	−0.492	0.946	0.331	0.611 (0.227–1.648)	0.775	< 0.001
HOMA %B	0.387	0.800	0.371	1.472 (0.632–3.437)	0.694	< 0.001
C-pep (nmol/L)	−0.028	2.464	0.116	0.972 (0.938–1.007)	0.838	< 0.001
eAG (mmol/L)	−0.561	1.544	0.214	0.571 (0.235–1.303)	0.719	< 0.001
TC (mmol/L)	−0.216	4.168	0.033	0.766 (0.600–0.962)	0.652	< 0.001
HDL-C (mmol/L)	−0.046	0.204	0.652	0.955 (0.783–1.166)	0.689	< 0.001
VLDL-C (mmol/L)	−0.040	3.888	0.049	0.961 (0.923–1.000)	0.705	< 0.001
TG (mmol/L)	−0.738	7.629	0.006	0.720 (0.920–0.909)	0.740	< 0.001
LDL-C (mmol/L)	−0.115	1.007	0.316	0.891 (0.711–1.116)	0.611	< 0.001
DM	−0.091	2.495	0.114	0.913 (0.815–1.022)	0.849	< 0.001
IG	−0.059	0.010	0.918	0.943 (0.306–2.909)	0.735	< 0.001

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BW, body weight; WC, waist circumference; WHR, waist-hip ratio; FM, fat mass; WTI, waist circumference-triglyceride index; CI, conicity index; BSI, body shape index; VAI; visceral adiposity index; LAP, lipid accumulation product; Go, fasting glucose; Io, fasting insulin; HOMA-IR, homeostatic assessment model of insulin resistance; HOMA%B, homeostatic model assessment of β-cell function; C-pep, C-peptide; eAG, average glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; DM, diabete mellitus; IG, intolerance glucose.

Furthermore, DHEA suppresses the activity and expression of glucose-6-phosphate and of phosphoenol carboxykinase, decreasing gluconeogenesis and increasing glucose uptake in the adipocyte and hepatocyte.[64] Clinical biomarkers of central adiposity were not correlated with DHEA concentrations in the present study in normoandrogenemic women with PCOS.

On the other hand, in HA-PCOS women, DHEA was negatively correlated with various anthropometric-metabolic indexes and TG abnormalities. Thus, the present study supports the knowledge of the beneficial role of DHEA levels in women with PCOS, at least in those with high androgen levels.[18,65] Both in vitro and in vivo studies have shown a protective role of DHEA in the cardiovascular system.[66] Furthermore, lower levels of DHEA are associated with increased body fat accumulation.[67] In contrast, high levels of DHEA are associated with lower BMI,[68] lower body fat accumulation, and lower risk of T2DM.[69,70] An antiatherogenic effect of DHEA through inhibition of fibroblast growth, improvement of lipid profile, and decrease of platelet aggregation has also been shown.[71] It is worthy of note that lower levels of DHEA are found in hyperinsulinemic status due to its diminished synthesis or increased metabolic clearance. Additionally, high levels of glucose and insulin might impair DHEA synthesis in the adrenal gland.[72]

In PCOS, as a whole group, high levels of DHEAS have been found in between 18 and 72%.[25,59,73,74] The high levels of DHEAS have also been associated with a favorable metabolic and cardiovascular profile.[74–78] DHEAS opposes T action concerning the risk of obesity, and IR.[25] High levels of DHEAS are associated with lower BMI[68] when compound with controls and its levels decrease after weight loss after bariatric surgery.[79] Dehydroepiandrosterone sulfate levels have been negatively correlated with WC, WHR, LDL-C, and TG concentrations, adjusted for the confounding effects of age and BMI.[74,78] Furthermore, DHEAS levels were

Table 5 Final models of multivariate logistic regression analysis between anthropometric, anthropometric-metabolic, and metabolic indexes it is dependent variables and androgens as independent variables in non-polycystic ovary syndrome controls and women with polycystic ovary syndrome

Dependent variables	Retained independent variables	B	Wald	P	Exp B (Lower-Upper)	AUC	*p-value*
Non-PCOS							
WHR (ratio)	DHEAS/T	−0.8113	5.857	0.016	0.444(0.230–0.857)	0.663	< 0.001
eAG (mmol/L)	DHEAS	−1.881	4.848	0.028	0.152(0.145–0.903)	0.704	0.001
NA-PCOS							
BW (kg)	DHEA	0.979	4.360	0.037	2.662(1.062–6.672)	0.977	< 0.001
Go (mmol/L)	DHEA/T	0.957	5.498	0.019	2.605(1.170–5.800)	0.906	< 0.001
HOMA %B	DHEA	−0.543	4.277	0.039	0.581(0.348–0.972)	0.739	< 0.001
HA-PCOS							
WTI (ratio)	DHEA/T	−0.350	8.263	0.004	0.705(0.555–0.895)	0.809	< 0.001
CI (%, pg/ml, nmol/L)	DHEAS/T	0.434	8.405	0.004	1.544(1.151–2.071)	0.759	< 0.001
VAI	DHEA	−0.299	7.511	0.006	0.741(0.599–1.136)	0.719	< 0.001
LAP (cm, mmol/L)	DHEA/T	−0.265	4.291	0.038	0.767(0.597–0.986)	0.888	< 0.001
TC (mmol/L)	DHEAS/T	−1.189	8.037	0.005	0.305(0.134–0.693)	0.666	< 0.001
TG (mmol/L)	DHEA	−0.300	9.380	0.002	0.741(0.611–0.897)	0.739	< 0.001

Abbreviations: Non-PCOS, not polycystic ovary syndrome; WHR, waist-hip ratio; eAG, average glucose; NA-PCOS, normoandrogenemic polycystic ovary syndrome; BW, body weight; Go, fasting glucose; HOMA%B, homeostatic model assessment of β-cell function; HA-PCOSβ hyperandrogenemic polycystic ovary syndrome; WTI, waist circumference-triglyceride index; CI, conicity index; VAI; visceral adiposity index; LAP, lipid accumulation product; TC, total cholesterol; TG, triglyceride.

negatively correlated with carotid intima-media thickness[75] and improved endothelial function.[80] The predictive value of DHEAS against abnormalities in WHR and in the CI of women with PCOS seen in the present study supports its beneficial effect on predicting anthropometric and metabolic derangements.[25,74,81,82]

The DHEA/T ratio was reported to be strongly associated with insulin sensitivity.[63] However, there is an inconsistent correlation between the DHEAS/T ratio, insulin levels, and insulin receptor binding.[83] In the clinical practice, this ratio has been used for the prediction and early diagnosis of metabolic syndrome and it appears to antagonize the effect of T in women with PCOS, which is associated with a favorable metabolic profile.[25,84] Furthermore, this ratio has been negatively correlated with lower BMI, lower WC, lower WHR, lower TG, lower LDL-C, and higher HDL-C, insulin levels, and HOMA-IR.[76–78] It also appears that the DHEA/T ratio improves lipid metabolism.[84–88] The present study supports the knowledge that the DHEA/T ratio predicts various abnormalities in anthropometric-metabolic indexes in PCOS women with biochemical hyperandrogenism and against the increase in fasting glucose despite normal androgens in the blood. Nevertheless, the predictive effect of DHEAS/T against anthropometric and metabolic abnormalities in PCOS is limited.

A few limitations must be considered in the analysis of the present study. The cross-sectional design does not allow to determine causal effects; instead, it provides associations or predictions. The assays used may have some imprecision, but they have presented a good correlation with the gold-standard high-performance liquid chromatography-tandem mass spectrometry assays.[89,90] The sample size, a clear definition for normoandrogenemic and hyperandrogenemic groups of women with PCOS, and their analysis in separate are the principal strengths of the present study.

Conclusion

Dehydroepiandrosterone has been demonstrated to be a better predictor of abnormal anthropometric and biochemical parameters in women with PCOS than DHEAS, particularly in hyperandrogenemic women. The DHEA/T ratio has also shown increased prediction to predict against increase in anthropometric and metabolic parameters in PCOS. Dehydroepiandrosterone measurement seems to be preferred in PCOS management. In general, in the clinical practice, it must be highlighted that the predictive and protective effects of both adrenal hormones DHEA and DHEAS are mild or weak.

Contributions

Medeiros S. F.: design, data description, statistical analysis, and writing of the manuscript; Medeiros M. A. S.: data search, revision of the manuscript; Barbosa B. B.: data search, data analysis, revision of the manuscript; Medeiros A. K. L. W. Y.: data search, revision of the manuscript. Yamamoto M. M. W.: data search, revision of the manuscript. All authors approved the final version of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Immediate Postpartum Copper IUD: A Comparative Analysis between Profiles of Women who Accept and who Refuse it

DIU de cobre imediatamente pós-parto: Uma análise comparativa entre os perfis das mulheres que aceitam e recusam o método

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Abstract

Objective To analyze the profiles of women who accepted and who refused the insertion of the copper intrauterine device (IUD) postpartum and to learn the motivations related to the refusal of the method.

Methods Cross-sectional study with 299 pregnant women. The women were informed about the possibility of inserting a copper IUD postpartum and were questioned about their interest in adopting or not this contraceptive. All participants answered a questionnaire with information relevant to the proposals of the present study. The sample size was limited to the number of devices available for the present study.

Results A total of 560 women were invited to join the present study and 299 accepted. Out of the 299 women included in the present study, 175 accepted the copper IUD and 124 refused. As the number of pregnancies increased, the IUD acceptance rate raised ($p = 0.002$), especially between the groups with 1 and with $\geq$ 4 pregnancies ($p = 0.013$). Regarding the desire to have more children, the women who planned to have more children were more likely to refuse the method than the ones who did not ($p < 0{,}001$).

Conclusion Women with multiple pregnancies and desire to not have more children were more likely to accept the copper IUD. The profile of those who refused was first pregnancy and desire to have more children. Among the three most frequent reasons reported for copper IUD rejection, two responses stood out: no specific justification and desire to have more children.

Keywords

- intrauterine devices
- contraception
- postpartum period
- family planning services
- copper intrauterine device

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Resumo

Objetivo Analisar o perfil das mulheres que aceitaram e recusaram a inserção do dispositivo intrauterino (DIU) de cobre no pós-parto imediato e conhecer as motivações relacionadas à recusa ao método.

Métodos Estudo transversal com 299 gestantes, as quais foram informadas sobre a possibilidade de inserir o DIU de cobre imediatamente após o parto e questionadas sobre o interesse em adotar ou não este contraceptivo. Todas as participantes responderam a um questionário com informações pertinentes às propostas do presente estudo. O tamanho da amostra foi limitado ao número de dispositivos disponíveis para o presente estudo.

Resultados Um total de 560 mulheres foram convidadas a participar do estudo, dentre as quais 299 aceitaram. Das 299 participantes, 175 aceitaram o DIU e 124 recusaram. Conforme aumentou o número de gestações, maior foi a taxa de aceitação do DIU ($p = 0{,}002$), principalmente quando comparados os grupos de mulheres com 1 e ≥ 4 gestações ($p = 0{,}013$). Quanto ao desejo de ter mais filhos, as mulheres que planejavam ter mais filhos tiveram maior chance de recusar o dispositivo do que as que não planejavam ($p < 0{,}001$).

Conclusão Mulheres com múltiplas gestações e sem desejo de ter mais filhos apresentaram maior probabilidade de aceitar o DIU. O perfil das que recusaram foi primeira gravidez e desejo de ter mais filhos. Dentre os três motivos mais frequentes de rejeição do DIU relatados, duas respostas se destacaram: a falta de justificativa específica e o desejo de ter mais filhos.

Palavras-chave

- dispositivos intrauterinos
- anticoncepção
- período pós-parto
- planejamento familiar
- dispositivo intrauterino de cobre

Introduction

The intrauterine device (IUD) is a safe, reversible, and effective contraceptive method, associated with few side effects.[1,2] It is also one of the most used in the world, with a very high percentage of success, with < 1 pregnancy for every 100 women in the 1st year of use.[1]

Women who want to start contraception in the immediate postpartum period can benefit from the insertion of an IUD to reduce the risks of an unplanned pregnancy and of an undesired short interval between births.[3,4] The IUD is an interesting method for women with difficulty in accessing health services, especially those in situations of social vulnerability and who end up adopting less effective methods.[5,6]

In addition, other convenient aspects for inserting the device during this period are the safety of the breastfeeding mother, of the newborn, and the absence of detriment to breastfeeding.[2]

Differently from the rest of the world, where 13,9% of women in childbearing age use this method, in Brazil, the IUD is still an underused contraceptive, used by only 3% of women.[7,8] Considering these data, the Municipal Health Department of São Paulo included copper IUDs and hormonal implants in the list of essential drugs.[9]

In this context, in 2018, the Obstetrics and Gynecology Department of the Santa Casa de São Paulo implemented the project "Long-term reversible contraception – LARC – in the immediate postpartum period", with the objective of making this method available and contributing to family planning.

Considering the scarcity of Brazilian studies about acceptance and reasons to refusal of postplacental placement of copper IUD and the high rates of unplanned pregnancies, the objectives of the present study were to analyze the profiles of the women who accepted and who refused the insertion of copper IUDs postpartum and to learn the reasons of refusal, when the offer to insert the IUD was declined.

Methods

The present cross-sectional study was developed from June 8 to October 8, 2018. During this period, pregnant women admitted to the L&D room of the Santa Casa de São Paulo for childbirth assistance were asked soon upon arriving on the hospital if they had interest in inserting a copper IUD postpartum (within 10 minutes postplacental) and if they would like to take part in the present study.[10]

During the study period, 560 pregnant women were admitted to the maternity ward of the Santa Casa de São Paulo for childbirth assistance, and 299 of them accepted to be included in the present study.

The sample size was limited to the number of devices available for the present study (299); therefore, the power of the test was not calculated.

After signing the consent form, all participants answered a questionnaire with relevant information to the proposals of the study and authorized the use of data from their medical records for research. This questionnaire included information on age, marital status, number of pregnancies (number of deliveries, abortions, ectopic pregnancy), number of

antenatal consultations, existence of comorbidities or of obstetric complications, previously used contraceptive methods, desire to have more children and, in those who refused to insert a copper IUD, the reason for rejection. The current type of childbirth data was gathered from the medical records.

The exclusion criteria included patients admitted with abortion (defined as termination of pregnancy before 20 weeks or fetal weight < 500 g) and ectopic pregnancy (extrauterine pregnancy), in addition to those who declined to participate in the study.[11,12]

The descriptive and comparative analysis of the collected data was made by the Statistics Department of Santa Casa de Sao Paulo School of Medical Sciences using SPSS for Windows version 13.0 (SPSS Inc., Chicago, IL, USA) and Epi Info 3.4.1. The statistical analysis included the calculation of the summary measures such as mean, standard deviation (SD), and minimum and maximum values for continuous variables. Categorical variables were presented as frequency and percentage.

The two groups (women that accepted and women that refused the copper IUD insertion) were compared and, to check if they differed, the t-student test or the Mann-Whitney test for the continuous variables was applied. For categorical variables, the chi-squared test or the Fisher exact test were applied. In all analyzes, the significance level of 5% was adopted.

All participants were informed about the benefits, risks, contraindications, and main adverse effects of the contraceptive offered and accepted to participate voluntarily in the research. The study was approved by the Research Ethics Committee of the Santa Casa de São Paulo.

All devices (TCu 380A IUD, lot 151171, FURP) were offered with no additional cost.

Results

From the 560 pregnant women who were admitted to the maternity ward of the Hospital da Santa Casa de São Paulo during the study period, 299 (53.4%) accepted to participate in the research and 261 (46.6%) refused. From this group of 299 participants, 175 (58.5%) accepted the insertion of the copper IUD and 124 (41.5%) refused it. Considering all 560 participants, the overall acceptance was 31,25%. The age variation ranged from 15 to 43 years old. The average age of the participants who accepted was 27.9 years old (SD $\pm$ 7.2), and that of those who refused the insertion of the copper IUD postpartum was 28.2 years old (SD $\pm$ 5.7). Using the t-Student test, a result with no statistic value was obtained ($p = 0.768$). Therefore, there was no evidence that age increases copper IUD acceptance or rejection. The complete analysis is shown in ►**Table 1**.

Marital status and type of childbirth did not influence the decision to insert the copper IUD postpartum ($p = 0.550$ and 0.257, respectively). Considering the number of pregnancies, it was observed that the higher the number of pregnancies, the higher the copper IUD insertion rate. The result of $p = 0.002$ in the test revealed the statistical difference between the primiparous participants and those with ≥ 4 pregnancies (►**Fig. 1**). This means that multiparity was a factor that increased IUD acceptance in the immediate postpartum period.

On the other hand, the number of antenatal visits, previous comorbidities of the pregnant woman, and use of other contraceptives did not show statistical differences between the groups that accepted and refused the copper IUD in the immediate postpartum period; therefore, these factors did not impact the decision. The present study revealed that for 265 of the 299 participants, the most known and used contraceptive methods were pills (44.2%), condoms (19.2%), other methods (10.6%), and 26.0% of women did not use any method. The rest of the women did not answer this question. The type of contraceptive method used prior to the current pregnancy did not influence the option for the insertion of the IUD in the immediate postpartum period. In contrast, the lack of desire to have more children resulted in greater acceptance of the copper IUD postpartum than in those who intended to have other pregnancies or were in doubt (►**Fig. 2**).

A total of 124 women did not adhere to the method, 106 of whom explained their reason and 18 did not respond (14.5%). Among the 106 women who expressed the reason for rejection, 41 (38.7%) had no specific reason, 25 (23.6%) preferred another contraceptive method, 17 (16%) intended to have more children, 9 (8.5%) had medical contraindications to IUDs, 5 (4.7%) had language barriers, and 9 (8.5%) revealed other reasons.

Discussion

Actions in the family planning field in Brazil still face many challenges. Despite the existence of several contraceptive methods, unplanned pregnancies and a short period between two pregnancies are still very frequent and expose the lack of effective policies for a significant portion of the population.[13]

It is a fact that $> 55.4\%$ of Brazilian women who had children did not plan their pregnancy, according to a survey by the National School of Public Health of the Fundação Oswaldo Cruz, which heard 24,000 women between 2011 and 2012.[13]

For many women, the hospitalization period for childbirth assistance is the only opportunity for some health system contact, especially in regions where there is still limited access to medical services. Research shows that, on this occasion, patients are more motivated to address the issue of contraception, with the IUD being one of the options that appears, due to its safety, convenience, and few contraindications.[13–15]

An initiative from the Municipal Health Department of São Paulo to meet this demand was the implementation of the Long-Acting Reversible Contraceptives (LARC) Project in the immediate postpartum and postabortion periods in public service maternity hospitals.[9] Long-acting reversible contraceptives are defined as those that last ≥ 3 years and are represented by subdermal implant and IUD (levonorgestrel intrauterine system and copper IUD).[16]

Table 1 Summary of the results from the analyzed data

Characteristics	Accepted IUD $n = 175$	Refused IUD $n = 124$	*p-value* (chi-squared test)
Marital status – *n* (%)			0.550
Married/Stable union	87 (56.9)	66 (43.1)	
Single	88 (60.3)	58 (39.7)	
Type of childbirth – *n* (%)			0.257
Natural childbirth	117 (60.9)	75 (39.1)	
C-section	58 (54.2)	49 (45.8)	
Number of pregnancies – *n* (%)			0.013
1	47 (49.5)	48 (50.5)	
2	48 (53.9)	41 (46.1)	
3	37 (64.9)	20 (35.1)	
≥ 4	43 (74.1)	15 (25.9)	
Number of antenatal consultations – *n* (%)			0.835
Without consultations	9 (64.3)	5 (35.7)	
< 5	17 (63.0)	10 (37.0)	
≥ 5	148 (58.5)	105 (41.5)	
No information	1 (20.0)	4 (80.0)	
Comorbidities – *n* (%)			0.831
Yes	53 (59.6)	36 (40.4)	
No	117 (58.2)	84 (41.8)	
No information	5 (55.6)	4 (44.4)	
Previous contraceptive method – *n* (%)			0.594
Yes	116 (59.2)	80 (40.8)	
No	33 (47.8)	36 (52.2)	
No information	26 (76.4)	8 (23.6)	
Desire for more children – *n* (%)			< 0.001
Yes	16 (31.4)	35 (68.6)*	
No	94 (71.8)	37 (28.2)*	
Does not know	45 (48.9)	47 (51.1)	
No information	20 (80.0)	5 (20.0)	

Abbreviation: IUD, intrauterine device.

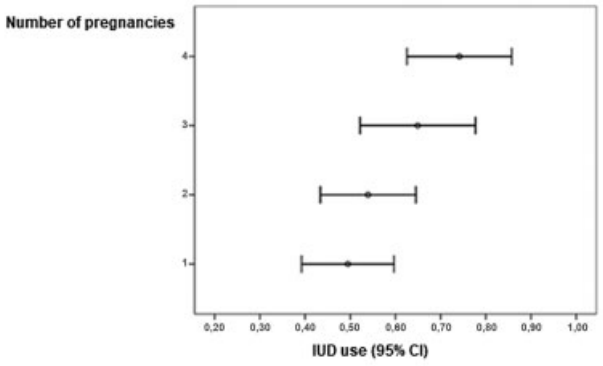

Fig. 1 Confidence intervals for copper IUD acceptance in the immediate postpartum period in 299 participants and number of pregnancies.

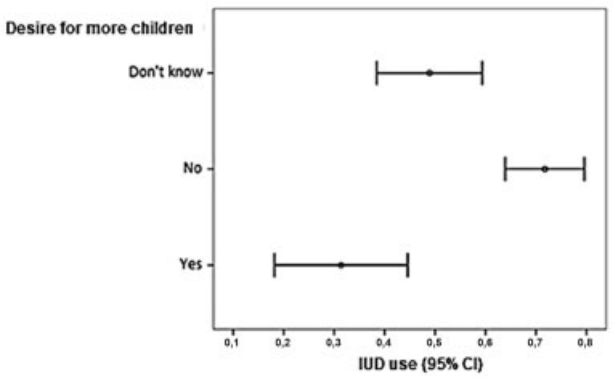

Fig. 2 Error bar diagram of desire to have more children and acceptance of the IUD.

Within this context, since 2018, our institution started offering and making available the copper IUD to pregnant women admitted to the obstetric center, most of them for childbirth assistance. In the case of the T380A copper IUD used in the project, the contraceptive effect lasts for 10 years. It produces an inflammatory, cytotoxic reaction, which is spermicidal, determining endometrial changes, which compromise the quality and viability of sperm. These effects are local and do not interfere with lactation.[17]

Unlike short-acting reversible contraceptive methods (administered orally, intramuscularly, vaginally or by transdermal routes), copper IUDs unite high efficacy (both in perfect use and in typical use) and the highest rates of satisfaction and continuity among users.[8,17] A Brazilian study about insertion of IUDs during cesarean section in women without prenatal contraceptive counseling demonstrated that, after 6 weeks, the rate of IUD permanence was 90%, proving it to be an efficient contraception strategy for women, especially those in a situation of social vulnerability. Moreover, the same study found no difference between the expulsion rate during the first 6 weeks and in the period between 6 weeks and 6 months.[18]

In addition, the immediate postpartum period portrays an opportune moment to start contraception with a LARC, mainly considering that the rates of missed postpartum consultations are high (10 to 40%), which delays contraceptive guidelines, and the low average time of exclusive breastfeeding in Brazilian puerperal women, of only 50 to 60 days, consequently with early return to fertility.[5,19]

In our research, more women accepted the copper IUD postpartum than refused it. However, it is important to remember that 560 women were invited to join the study and that 261 did not want to participate. This nonacceptance may have been a prior intention of not using the proposed method.

From the 299 women who accepted to join the study, 175 (58.5%) participants opted for the insertion of the copper IUD postpartum, and there was greater acceptance of the method by women with a higher number of pregnancies. In contrast, Tang et al.[20] reported that older and multiparous women showed less interest in inserting the IUD postpartum when compared with younger and primiparous women - the justification in his study was the preference for tubal ligation in that group.

It is interesting to note that women who wanted to have more children were more likely to refuse the copper IUD, while those who did not want more children were more willing to accept the device (►**Fig. 2**). We raised the hypothesis of the existence of a misunderstanding about reversibility and the possibility of withdrawing the method when requested, considering that the third most frequent cause of copper IUD refusal was "I want to have more children." In agreement with our results, Tang et al.[20] reported that a greater interest in the insertion of the IUD postpartum occurred among women who did not wish to have any more children.

Factors such as age, marital status, number of antenatal visits, type of delivery, comorbidities or obstetric complications, and previous use of contraceptive methods did not impact the acceptance or the refusal of the copper IUD postpartum in our study.

In the literature, there is no consensus regarding age. Makins et al. studied the age range and IUD postpartum acceptance in India, Nepal, Sri Lanka, and Tanzania. They observed that, in India, older women were more likely to accept the device, while the same did not happen in the other three countries.[21]

Regarding marital status, in some countries, such as Ethiopia and India, there is information that when husbands are against the use of IUDs, there are higher refusal rates among married women.[2,22] In our research, marital status had no statistical significance, but the desire of the husbands was not asked in the questionnaire.

For Gonie et al.,[2] the chance of accepting the insertion of the IUD was greater among women who attended more antenatal consultations. In our study, the number of consultations did not interfere with adherence to the method; however, we do not know whether the topic of contraception was addressed during antenatal care or not.

The presence of previous or acquired comorbidities during pregnancy did not prove to be relevant to the decision to insert the IUD immediately after birth. No other studies that correlated these factors were found.

Even though the type of delivery has not shown an association with the desire to the postplacental IUD placement and it was neither pointed out as a reason for rejection of the method, Hochmuller et al.[23] revealed that the type of delivery was a significant predictor for IUD expulsion. Vaginal delivery was 4-fold more likely to be associated with IUD expulsion inserted in the puerperal period than cesarean section.[23] Laporte et al.[24] also found that the odds of IUD expulsion were higher among women with vaginal compared with cesarean delivery.

Hubacher et al.,[25] who described similar findings to those of our study, found no relationship between previous use of a particular contraceptive method and adoption of a long-term method after birth.

The three most frequent reasons reported by the participants who refused the copper IUD placement were: no specific reason, preference for another method, and desire to have more children. Our results were different from those described in the Ethiopian study by Gonie et al.[2] In the study performed on the African continent, the three most relevant factors for the refusal of the IUD in the immediate postpartum period were fear of complications, religious beliefs, and refusal of the husband. These factors were not directly questioned to our patients, but they could make up some of the reasons that were not expressed. Possibly, the lack of knowledge about the LARC Project and the moment (immediately after admission to the Obstetric Center) when the IUD was offered may have interfered in this response.

The idea of the ineffectiveness of postpartum IUD was the main reason for rejection in the study by Chacko et al.,[26] in which women, consequently, opted for another method. In our study, the second major reason for refusal was the

preference for another method; however, none of our patients mentioned the uselessness of the device.

It is worth mentioning that the desire to have more children was the third most frequent cause of refusal in our research, perhaps indicating the belief in the myth that the IUD is a method of permanent contraception, when in fact it is a long-lasting, reversible method that can be removed when desired.[27]

Considering all the aspects analyzed, some suggestions to improve adherence to contraception methods would be: training of professionals in Basic Health Units, inclusion of the theme "family planning" in the scope of consultations during antenatal care, and dissemination of the IUD opportunity in the immediate postpartum period.

With these adjustments, the pregnant woman and her partner could research, learn, and reflect more calmly on their contraceptive options and clarify doubts about the different methods, including the copper IUD, especially aspects related to effectiveness, complications such as chronic pain, and reversibility of the method.

We believe that the improvement of the integration and of the alignment of work between the maternity teams and multidisciplinary groups in the Basic Health Units can contribute to more consolidated and assertive decisions by our pregnant women.

The Hospital Central da Santa Casa de São Paulo, since it is a tertiary center, receives referrals from several Basic Primary Health Care Units and serves pregnant women with very different levels of knowledge about the use of the copper IUD, especially immediately after birth. For this reason, we cannot say that the results obtained are extendable to the population as a whole.

The sample size was not calculated with a previous statistical analysis, it was limited to the number of devices available for the study (299) and, therefore, the power of the test was also not calculated. Consequently, the results obtained may not even be extrapolated to the population studied.

The refusal to participate in the study may have occurred due to the prior intentions the pregnant woman of not wanting the method offered, which was not considered in the study.

The IUD was offered after admission to the L&D room and the pregnant women were in different stages of labor, which is as aspect that was not considered in our study and could have influenced the decision.

Conclusion

Women with multiple pregnancies and desire to not have more children were more likely to accept the copper IUD. The profile of those who refused was first pregnancy and desire to have more children. Among the three most frequently reported reasons for copper IUD rejection, two responses stood out: no specific justification, and desire to have more children. This highlighted the importance and the need to improve previous educational actions on contraception and clarifications on the mechanisms of action and reversibility of this method.

Contributions

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

Conflict of interests

The authors have no conflict of interests to declare.

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Protective Effects of Platelet-rich plasma for in vitro Fertilization of Rats with Ovarian Failure Induced by Cyclophosphamide

Efeitos protetores do plasma rico em plaquetas para fertilização in vitro de ratos com falência ovariana induzida por ciclofosfamida

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Abstract

Objective Premature ovarian insufficiency (POI) contributes significantly to female infertility. Cyclophosphamide (CYC has adverse effects on folliculogenesis. Platelet-rich plasma (PRP) is an autologous product rich in many growth factors. We evaluated the protective effect of PRP on in vitro fertilization in female rats with CYC-induced ovarian damage.

Methods Twenty-eight adult female Sprague-Dawley rats were randomly divided into four groups. Group 1 (control-sodium chloride 0.9%; 1 mL/kg, single-dose intraperitoneal [IP] injection); group 2 (CYC), 75 mg/kg, single-dose IP injection and sodium chloride 0.9% (1 mL/kg, single-dose IP injection); group 3 CYC plus PRP, CYC (75 mg/kg, single-dose and PRP (200 µl, single-dose) IP injection); and group 4 (PRP, 200 µl, single-dose IP injection).

Results In the comparisons in terms of M1 and M2 oocytes, it was observed that the CYC group presented a significantly lower amount than the control, CYC/PRP, and PRP groups. (for M1, $p = 0.000$, $p = 0.029$, $p = 0.025$; for M2, $p = 0.009$, $p = 0.004$, $p = 0.000$, respectively). The number of fertilized oocytes and two-celled good quality embryos was found to be statistically significant between the CYC and control groups, CYC + PRP and PRP groups ($p = 0.009$, $p = 0.001$, $p = 0.000$ for oocytes, respectively. For embryos; $p = 0.016$, $p = 0.002$, $p = 0.000$).

Keywords
- ovary
- premature ovarian insufficiency
- cyclophosphamide
- in vitro fertilization
- platelet-rich plasma

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Conclusion Platelet-rich plasma can protect the ovarian function against damage caused by CYC, and, in addition, it improves oocyte count and the development of embryos as a result of oocyte stimulation during the IVF procedure.

Resumo

Objetivo A insuficiência ovariana prematura (POI) contribui significativamente para a infertilidade feminina. A ciclofosfamida (CYC) tem efeitos adversos na foliculogênese. O plasma rico em plaquetas (PRP) é um produto autólogo rico em muitos fatores de crescimento. Avaliamos o efeito protetor do PRP na fertilização in vitro em ratas com lesão ovariana induzida por CYC.

Métodos Vinte e oito ratas Sprague-Dawley adultas foram divididas aleatoriamente em quatro grupos. Grupo 1 (controle - cloreto de sódio 0,9%; 1 mL/kg, injeção intraperitoneal [IP] em dose única); grupo 2 (CYC), 75 mg/kg, injeção IP de dose única e cloreto de sódio 0,9% (1 mL/kg, injeção ip de dose única); grupo 3 CYC + PRP, CYC (75 mg/kg, dose única e PRP (200 µl, dose única) injeção IP); e grupo 4 (PRP, 200 µl, injeção IP de dose única).

Resultados Nas comparações em termos de ovócitos M1 e M2, observou-se que o grupo CYC apresentou uma quantidade significativamente menor que os grupos controle, CYC/PRP, e PRP. (Para M1, $p = 0{,}000$, $p = 0{,}029$, $p = 0{,}025$; para M2, $p = 0{,}009$, $p = 0{,}004$, $p = 0{,}000$, respectivamente). O número de oócitos fertilizados e embriões bicelulares de boa qualidade foi considerado estatisticamente significativo entre os grupos CYC e controle, CYC + PRP e grupos PRP ($p = 0{,}009$, $p = 0{,}001$, $p = 0{,}000$ para oócitos, respectivamente. Para embriões, $p = 0{,}016$, $p = 0{,}002$, $p = 0{,}000$).

Conclusão O PRP pode proteger a função ovariana contra os danos causados pelo CYC e, além disso, proporciona melhora na contagem de oócitos e no desenvolvimento de embriões como resultado da estimulação ovariana durante o procedimento de fertilização in vitro.

Palavras-chave
- ovário
- insuficiência ovariana prematura
- ciclofosfamida
- fertilização in vitro
- plasma rico em plaquetas

Introduction

While ovarian reserve is defined as the number of follicles/oocytes present in the ovaries, premature ovarian insufficiency (POI) is defined as a decrease in ovarian functions and oocyte reserve before the age of 40.[1] The prevalence of POI is estimated to be around 1 to 3% among women when the general population is evaluated.[2] Most POIs are classified as idiopathic.[3] However, the pathophysiology of POI is thought to be related to genetic factors, radiotherapy, and chemotherapy factors, autoimmune disorders, and infections.[3] Premature ovarian insufficiency results in premature loss of ovarian function, major health problems, and infertility, especially as a result of the decreased number of oocytes in the ovaries due to accelerated atresia. In case of sufficient residual ovarian reserve, in vitro fertilization (IVF) with autologous oocytes obtained by ovarian stimulation is an effective treatment for women with POI.[4]

Platelet-rich plasma (PRP) is an autologous product rich in many growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β, and vascular endothelial growth factor (VEGF).[5,6] Growth factors in PRP stimulate chemotaxis, proliferation, and differentiation of stem cells and angiogenesis in a way that accelerates tissue repair.[7,8] Platelet-rich plasma, which is an inexpensive product compared with many other agents, has many advantages, such as being easy to obtain and having an antimicrobial effect as well as being an autologous product.[9]

Alkylating chemotherapy agents such as cyclophosphamide (CYC), which are highly gonad-toxic, cause a decrease in ovarian function and have detrimental effects on the female reproductive organs.[10] These effects of CYC are primarily due to the inhibition of DNA synthesis and function and induction of DNA damage. Cyclophosphamide has been shown to reduce primitive follicles, oocytes, and granulosa cells on eggs by inducing apoptosis, inhibiting angiogenesis, thus causing ovarian atrophy.[11]

Pathological changes in CYC-generated POI patterns are similar to clinical observations in POI patients, and these pathological changes in the POI model can be reversed with drugs.[12]

Growth factors such as VEGF, EGF, PDGF, and TGF-have been shown to have protective effects on ovarian damage.[6,13–15] Platelet-rich plasma has been found to have a predominant positive effect on ovarian cortex volume, antral follicle number and antral follicle diameter on ovarian damage caused by CYC.[12,16]

There are various medical treatments, such as immunomodulating therapies, apoptotic inhibitors, antioxidant therapies, IVF, and embryo transfer using donor oocytes to restore impaired ovarian function and/or restore fertility in women with POI.[17] Women with POI require significantly higher doses of exogenous gonadotropin to initiate folliculogenesis compared with patient groups with normal ovarian reserve.[4] They commonly have a poor response to stimulation, with only four or fewer follicles available for oocyte retrieval.[4] It seems that not every approach applied to remedy this situation can be created as effective or guaranteed for successful management.[4] The protective and curative effect of PRP at the level of folliculogenesis in CYC-induced ovarian damage has been shown in previous studies.[12,16] A recent study has shown that intraovarian injection of autologous PRP has improved IVF results in women with primary ovarian insufficiency.[18] The aim of this study is to investigate the protective effect of PRP on in vitro fertilization in female rats with CYC-induced ovarian damage.

Methods

The study was conducted in Sakarya University's SÜDETAM laboratory under the authority of Sakarya University's experimental animal ethics committee on 04/11/2020 under decision No.62. Applications for all research animals were performed according to the "The European Commission Directive 86/609/ECC guideline" protocol. Twenty-eight adult female Sprague-Dawley rats (weight 200–250 g; age 65–75 days) were provided by the Sakarya University Animal Reproduction Center and housed in groups with ad libitum food and water in the Animal Laboratory of Sakarya University. The holding room was maintained at room temperature of 22 ± 2°C with humid conditions (45–55%) and a 12-hour light/day cycle.

The rats were randomly divided into four different experimental (Exp.) groups:

Group I (control group) received sodium chloride 0.9% (1 mL/kg, single dose) intraperitoneal (IP) injection on the 1st, 8th, and 15th days.

Group II (CYC group) received cyclophosphamide (CYC) (75 mg/kg, single dose) IP injection on the 1st, 8th, and 15th, days.

Group III (CYC + PRP group) received CYC (75 mg/kg, single dose) and PRP (200 µl, single dose) IP injection on the 1st, 8th, and 15th days.

Group IV (PRP only group) received PRP (200 µl, single dose) IP injection on the 1st, 8th, and 15th days.

The stage of the estrous cycle of the rats was determined by performing daily vaginal smears after acclimation. Rats determined to have at least 3 consecutive 4-day estrous cycles were prepared for in vitro fertilization (IVF). All the rats were subjected to the IVF protocol to create hyperstimulation. On the day the stimulation was completed, female rats were sacrificed, and their oocytes were collected.

Human tubal fluid (HTF) medium (Cat. No. 90166, Irvine Scientific, Santa Ana, CA, USA) was used for sperm preincubation, fertilization, and embryo transfer. For sperm preincubation, a 200 mL droplet was used. For oocyte collection and IVF, a 100 mL volume droplet was used. Embryos were washed by passing through four such droplets. Each droplet was placed on a 35-mm culture dish (Nunc, Cat. No.63754, Denmark), covered with liquid paraffin oil (Cat. No. 9305, Irvine Scientific), and kept at 37°C under 5% CO2 in humidified air overnight.

The ovaries were stimulated through the IP route for both ovaries in the female rats. For the first injection, we used an IP injection of 150 to 300 internal units (IUs)/kg of pregnant mare serum gonadotropin (PMSG) (Chronogest/PMSG, Intervet, Istanbul, Turkey), followed $\sim$ 48 hour later by 150 to 300 IUs/kg of human chorionic gonadotropin (hCG; Gonatropin, Chorulon Intervet, Istanbul, Turkey). At 17 to 19 hours after hCG administration, 15 IUs of PMSG were administered.[19] All the rats were weighed and anesthetized by an intramuscular administration of 50 mg/kg ketamine hydrochloric acid (Ketalar; Eczacibasi Warner-Lambert Ilac Sanayi, Levent, Istanbul, Turkey) and 7 mg/kg xylazine hydrochloric acid (Rompun, Bayer Sisli, Istanbul, Turkey). After immobilizing the rats on a standard surgery board, blood samples were collected to measure the level of serum anti-Mullerian hormone (AMH). The aseptic technique was used to make a ventral midline incision to expose the reproductive organs, and the oviducts were removed. In this manner, the oocytes were collected from removed ovaries. To incubate the oocytes, HTF medium with the addition of 4 mg/ml of human serum albumin (HSA) was cultured for 1 day before being placed in an incubator at 37°C and 5% CO_2. Culture drops were prepared as group cultures on the culture dish under mineral oil. Fertilization, 2 washes, and culture drops were prepared in 500 µl, 150 µl, and 150 µl amounts, respectively. The oocytes and capacious sperm (approximate concentration 1×106 ml-1) were transferred to the fertilization drops. Then, fertilization was checked, and the fertilized oocytes were washed and transferred to culture drops, and the resulting embryos were monitored up to the blastocyst stage.[20]

Before the oocyte collection, a mixture of 75 mg/kg of ketamine (Ketasol, Richter Pharma, Austria) and 10 mg/kg of xylazine (Basilazin, Bavet, Turkey) was applied intraperitoneally to a male rat, and then the rat was euthanized. Following the euthanasia procedure, the male reproductive system was surgically opened from the abdomen, and the left and right epididymis were separated from the testicles and transferred to HTF medium containing 1 ml of HTF (Cat. No. 90168, Irvine Scientific, USA) and 4 mg/ml of bovine serum albumin (BSA). The epididymis was carefully peeled off using forceps, and the sperm were transferred into petri dishes and incubated at 37°C for 30 minutes before in vitro fertilization.[21]

Approximately 6.5 hours after insemination, the oocytes were washed 3 times with HTF medium and cultured as above. At 7 to 8 hours after insemination, the oocytes were checked for sperm penetration or pronuclear formation under an inverted microscope to identify any polyspermic fertilization or parthenogenetic embryos ($\sim$ 6.5% of the total). After culturing for a further 20 hours, the numbers

of 2-cell stage embryos were counted; these were defined as fertilized embryos.

Eight mature male Sprague-Dawley rats were used to prepare PRP. Blood samples were taken from these rats by heart puncture from the right ventricle under anesthesia and taken into test tubes containing 3.2% sodium citrate (Merck, Darmstadt, Germany) at the rate of 9/1 blood/citrate. After the blood samples were centrifuged at 400 × for 10 minutes, the upper part of the plasma containing the platelets and buffy coat was transferred to another tube and centrifuged again at 800 × g for 10 minutes. This tube contained platelet deposits and some red blood cells (an erythrocyte-platelet cluster). By removing the upper ⅔ of the supernatant containing platelet-poor plasma, the remaining layer (lower ⅓) was accepted as PRP. The final fraction, containing 2.4 × 106 platelets/ml, was ~ 3.9 times larger than the blood platelet count (570,000 platelets/µl). We used fresh PRP per administration.

Anti-Mullerian hormone was quantitatively estimated in rat serum samples using enzyme-linked immunosorbent assay (ELISA) kits (MyBioSource, Rat AMH ELISA Kit Catalog No: MBS2509909, San Diego, California, USA).

Statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 24.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to evaluate the normal distribution of the data. For the comparison of more than two variables, one-way analysis of variance (ANOVA) was used for normally distributed data and the Kruskal-Wallis test was used for data that did not show normal distribution. To determine which group was different from the others, the Tukey honestly significant difference (HSD) test was used for variables with homogeneous variances, and the Tamhane T2 test for non-homogeneous variables. The results are given as mean ± standard error (SE). The statistical evaluation was considered significant when $p < 0.05$ for each test.

Results

The oocytes were classified as germinal vesicle (GV), metaphase I (M1), and metaphase II (M2). To compare the meiotic progression during oocyte maturation in different systems, the average time that each stage of nuclear progression takes was calculated. This method was previously described by Sirard et al.[22] As a result of the statistical evaluation made in the light of this situation, it was seen that only cyclophosphamide (CYC) application decreased the average number of M1 and M2, increased the number of GVs, and PRP application prevented this effect of CYC (►**Fig. 1**). In the comparisons in terms of M1 and M2 numbers, it was observed that the CYC group presented a significantly lower number than the control, CYC/PRP, and PRP groups (for M1, respectively: $p = 0.000$, $p = 0.029$, $p = 0.025$; for M2, respectively: $p = 0.009$, $p = 0.004$, $p = 0.000$). In the evaluation made in terms of the GVs number, it was observed that the GVs number increased in the CYC group, and the PRP application decreased the GVs number. In the comparisons between groups, the GV value in the CYC group was significantly

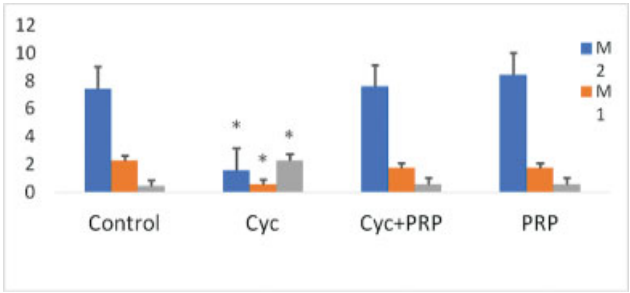

Fig. 1 Comparison of the mean of metaphase I (M1), metaphase II (M2) oocytes and germinal vesicles (GVs) in experimental groups. Abbreviations: Control, control group; CYC, cyclophosphamide administered group; CYC + PRP, cyclophosphamide and platelet rich plasma applied group; PRP, platelet-rich plasma applied group. * $p < 0.05$ compared with the control, CYC + PRP, and PRP groups. Values are given as mean and standard error.

higher compared with the control, CYC + PRP, and PRP groups ($p = 0.001$, $p = 0.003$, $p = 0.003$, respectively). When the CYC + PRP group was compared with the control and PRP groups, there was no significant difference in terms of MI, MII, GV, and oocyte count ($p > 0.05$). The average number of oocytes, fertilized oocytes and two-celled good quality embryos belonging to the groups are presented in ►**Fig. 2**. The mean oocyte count was statistically significantly lower in the CYC group compared with the control, CYC + PRP, and PRP groups ($p = 0.000$ for each). When the CYC + PRP group and the control and PRP groups were compared in terms of mean oocyte count, there was no statistically significant difference between the groups ($p > 0.05$). The mean number of fertilized oocytes and two-celled good quality embryos was the lowest in the CYC group, while it was highest in the PRP only group. In the comparison between the groups, the number of fertilized oocytes and two-celled good quality embryos was found to be statistically significant between the CYC group and control, CYC + PRP, and PRP groups ($p = 0.009$, $p = 0.001$,

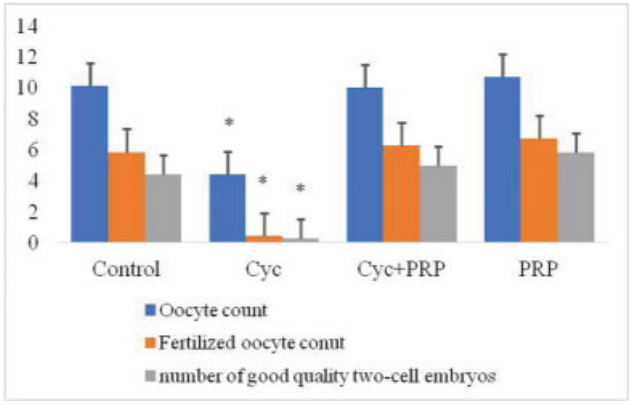

Fig. 2 Comparison of the mean numbers of total oocytes, fertilized oocytes, and two-celled good quality embryos in the experimental groups. Abbreviations: Control, control group; CYC, cyclophosphamide administered group; CYC + PRP, cyclophosphamide and PRP applied group; PRP, platelet-rich plasma applied group. * $p < 0.05$ compared with control, CYC + PRP, and PRP group. Values are given as mean and standard error.

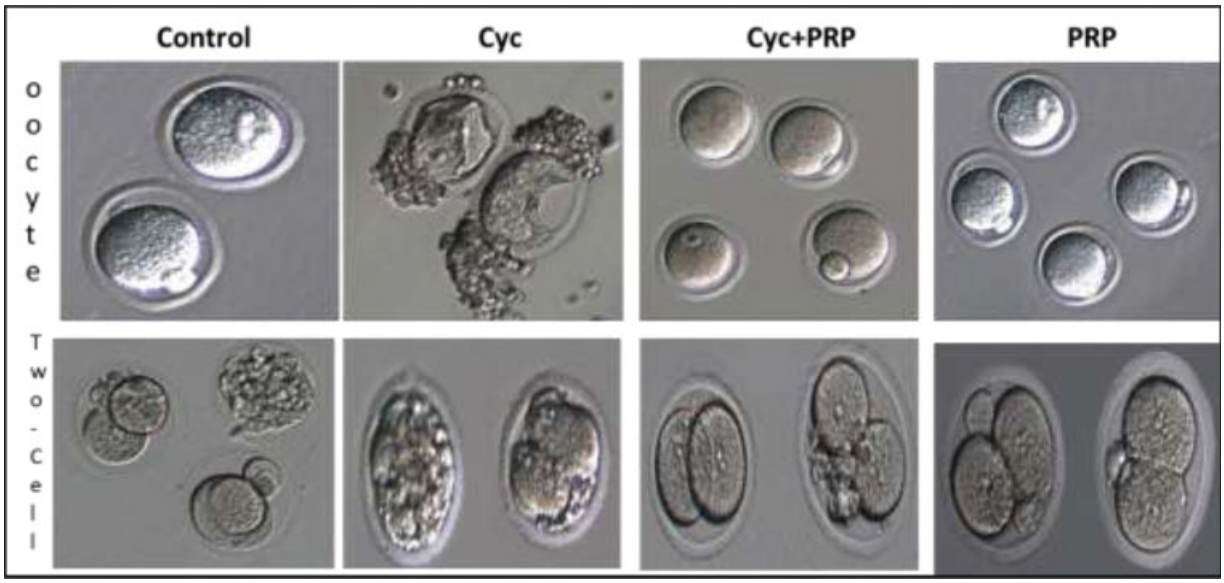

Fig. 3 Oocyte and two-cell embryo images of control, CYC, CYC + PRP and PRP groups, 200X magnification in inverted microscope. There are two M2 oocytes belonging to the control group, 3 M2 and 1 GV oocyte in the CYC + PRP group and 4 M2 oocytes in the PRP group. In the CYC group, there are 2 GV oocytes whose ooplasms are severely damaged. In the CYC group, the quality of the 2-cell embryo is very poor, with a high rate of fragmentation. While two-cell embryos with equal blastomeres are seen in the CYC + PRP and PRP groups, embryos with a very small amount of fragmentation are seen in the CYC + PRP group. Although embryos with equal blastomeres were seen in the CYC + PRP and PRP groups, embryos with a small amount of fragmentation were seen in the CYC + PRP group. Abbreviations: Control, control group; CYC, cyclophosphamide administered group; CYC + PRP, cyclophosphamide and platelet-rich plasma applied group; PRP, platelet-rich plasma applied group; GV, germinal vesicle; MII, metaphase II.

$p = 0.000$ for fertilized oocytes, respectively. for the number of good quality embryos; $p = 0.016$, $p = 0.002$, $p = 0.000$).

Two-celled embryos were obtained by culturing oocytes after IVF. In the CYC group, the quality of the two-celled embryo was very poor, a high rate of fragmentation was seen. Although embryos with equal blastomeres were seen in the CYC + PRP and PRP groups, embryos with a small amount of fragmentation were seen in the CYC + PRP group. This effect was thought to be due to CYC. In the control group, embryos with equal blastomeres were generally seen, however, it was seen in embryos with fragmentation (►**Fig. 3**).

When the AMH concentrations in the study groups were examined, it was found that it was the highest in the PRP group, while it was the lowest in the CYC group (►**Fig. 4**). It was observed that there was a statistically significant difference between the CYC and CYC + PRP groups when compared with the control group ($p = 0.000$).

Discussion

For ovarian failure, the presence of ovarian atrophy, follicle reduction, and sex hormonal diminution are used.[23] Looking at society, ovarian failure (POI) is one of the most important diseases that cause infertility in women and threaten women's health. The early detection and treatment of ovarian dysfunctions continues to be an important research and clinical area of interest in gynecology. Infertile patients with aging ovaries - sometimes called the approaching POI, their numbers are increasing day by day and constitute a significant proportion of patients applying for IVF/ART. Current approaches to effective management of patients diagnosed with POI offer a wide range of options. Although egg donation (ED) is still the most successful and final treatment for POI patients, the vast majority of these infertile women are reluctant to consent to ED upon initial diagnostic interview and demand alternative solutions using their own autologous eggs, despite the low chance of success.[24] Many researchers have investigated the use of stem cell transplantation, including human menstrual blood stem cells, fat-derived stem cells, human endometrial mesenchymal stem cells, Platelet-rich plasma (PRP), as a cell therapy to reverse ovarian damage caused by chemotherapy.[12,16,25,26] PRP has

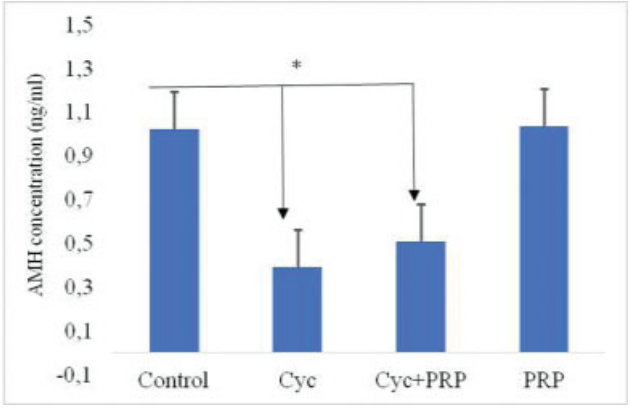

Fig. 4 Comparison of experimental groups serum anti-Mullerian hormone (AMH) concentrations. Abbreviations: Control, control group; CYC, cyclophosphamide administered group; CYC + PRP, cyclophosphamide and PRP applied group; PRP, platelet-rich plasma applied group. $p < 0.05$, compared with the control group. Values are given as mean and standard error.

been defined as a blood plasma fraction with a platelet concentration 4 to 5 times higher than the normal level, and its beneficial effect on tissue regeneration, angiogenesis activation, inflammation control and anabolism has already been demonstrated in many medical fields.[27] The main components of PRP that contribute to tissue healing and regeneration, anabolism increase, differentiation and proliferation, angiogenesis activation, inflammation control can be listed as hormones, macrophages, neutrophils, cytokines and various growth factors.[28,29] Therefore, the use of PRP is considered a justified and potentially successful opportunity to increase the fertility outcome in POI patients where the main problem is ovarian failure.

A POI model induced by cyclophosphamide (CYC) was used in the present study. Cyc is an alkylating agent which induce ovarian failure in animal models.[30] It has been shown in previous studies that CYC disrupts the ultrastructure of granulosa cells and induces apoptosis and autophagy and eventually causes ovarian failure.[30,31] Cyc has been shown to reduce ovarian weight and volume, reduce the number of different follicles and sex hormone levels, and increase atretic follicles.[12] In their study of agents that prevent chemotherapy-induced ovarian damage, Roness et al.[32] noted that AS-101, AMH, imatinib, sphingosine-1-phosphate, granulocyte colony stimulating factor, bortezomib, and multi-drug resistance gene-1 were effective in preventing chemotherapy-induced ovarian damage.[32] Different mechanisms of action associated with different protective agents have been shown to be effective, including inhibition of follicle activation, anti-apoptosis effects, vascular effects, and gene upregulation.[32] When this protective effect is evaluated in terms of PRP, there are studies showing the success of PRP.[12,16] These studies were generally performed on ovarian tissue and were performed on oocytes obtained at the stage of folliculogenesis.

Growth factors play an important role in improving the structure and function of the ovaries, and different growth factors such as VEGF, EGF, PDGF, and TGF-b have been shown to have protective effects on ovarian damage.[13,14,33] Platelet-rich plasma has a protective effect against ovarian damage caused by CYC, as it has high amounts of these factors in its structure. This efficiency has been demonstrated in previous studies.[12,16] This protective feature of PRP in POI patients is to protect follicle development and oocyte number during folliculogenesis. Except for the protective effects of PRP on the ovary, there are many studies on the effects of PRP on the endometrium.[34] It has been shown that intrauterine PRP treatment supports endometrial growth and improves assisted reproductive outcome in patients with thin endometrium.[35] In humans, PRP used in autologous ovarian transplantation to improve the vascularization and quality of the implant has been shown to increase transplant success resulting in live birth.[36] There is no study on the effectiveness of PRP for POI patients who have serious difficulties in IVF applications. Human studies on the subject in the literature are only at the level of case reports.[37,38]

As a result of our study, it is seen that the addition of PRP treatment in the group where POI was created with CYC positively affected the results of subsequent IVF. This positive effect is valid for both the number of oocytes obtained by ovulation stimulation and the number of embryos on day 2 obtained after fertilization. When the day-2 embryos obtained were evaluated in terms of their quality, it was noted that there is a significant difference in the PRP applied group compared with the untreated group. This may be due to the fact that the PRP treatment could probably enrich the dysfunctional ovarian tissues with essential factors for neoangiogenesis, leading to tissue regeneration and reactivation. Although the effect of PRP on regenerative and repair processes in somatic tissues remains largely uncertain, growth factors contained in PRP content may have many critical roles in the ovaries through physiologically local effects such as cell growth, proliferation, differentiation, chemotaxis, angiogenesis, and formation. These growth factors control the release of the extracellular matrix and even other growth factors in close proximity to the release sites.[39] Platelet-rich plasma can accelerate this process while supporting the self-repair of ovaries, follicles after chemotherapy, which already have the potential to repair itself.[40]

When the control group and the PRP-only group were compared, the number of oocytes obtained in the group receiving PRP and the number of embryos on day 2 were higher, but this result was not found to be statistically significant. This situation makes us think that PRP does not have a significant effect in conditions with normal ovarian function and reserve. It seems, the beneficial effect of PRP is only applied on damaged ovaries, and it has no effect on the normal structure for IVF cycles.

Anti-Mullerian hormone, a powerful marker of ovarian reserve, is a member of the transforming growth factor superfamily produced by the granulosa cells of the antral follicles in the ovary.[41] Considering the AMH levels, there was an increase in the PRP-CYC group compared with the CYC group. However, the AMH levels following PRP treatment corresponded to the expected lower AMH levels in a POI case, although an improvement in overall reproductive potential was observed. Although the PRP-CYC group had a low AMH level that could be diagnosed with POI compared with the control group, this decrease is not as extreme as in the group without PRP treatment, and it is not at a low level that will allow more oocytes and embryos to be obtained as a result of IVF. This suggested that PRP could improve ovarian reserve by protecting ovarian granulosa cells. This evidence demonstrated the protective effects of PRP from CYC damage to the ovarian follicles.

Conclusion

The present study evaluated the number and quality of oocytes obtained after ovarian stimulation and the number and quality of embryos obtained on the second day after fertilization. Our study showed that PRP can protect the ovarian function against damage induced by CYC, but it provides an improvement in the number of oocytes and developing embryos as a result of the oocyte stimulation performed during the subsequent IVF procedure. However,

investigating the implantation results of these embryos, and evaluating the ongoing pregnancy results will be a good target for future studies.

Contributions

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

Conflict of Interests

The authors have no conflict of interests to declare.

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Habits of Genital Hygiene and Sexual Activity among Women with Bacterial Vaginosis and/or Vulvovaginal Candidiasis

Hábitos de higiene genital e atividade sexual entre mulheres com vaginose bacteriana e/ou candidíase vulvovaginal

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Abstract

Objective To evaluate genital hygiene among women with and without bacterial vaginosis (BV) and/or vulvovaginal candidiasis (VVC).

Methods A cross-sectional study of reproductive-aged women who underwent gynecological and laboratory tests and fulfilled a genital hygiene questionnaire.

Results This study evaluated 166 healthy controls and 141 women diagnosed with either BV (n = 72), VVC (n = 61), or both (n = 8). The use of intimate soap and moist wipes after urination was more frequent among healthy women ($p = 0.042$ and 0.032, respectively). Compared to controls, bactericidal soap was more used by women with BV ($p = 0.05$).

Conclusion Some hygiene habits were associated to BV and/or VVC. Clinical trials should address this important issue in women's health.

Keywords
- bacterial vaginosis
- candida albicans
- hygiene
- sexual behavior
- disbiosis

Resumo

Objetivo Avaliar a higiene genital de mulheres com e sem vaginose bacteriana (VB) e/ou candidíase vulvovaginal (CVV).

Métodos Estudo transversal com mulheres em idade reprodutiva submetidas a exames ginecológicos e laboratoriais e preenchimento de questionário de higiene genital.

Resultados Este estudo avaliou 166 controles saudáveis e 141 mulheres com diagnóstico de VB (n = 72), VVC (n = 61) ou ambas (n = 8). O uso de sabonete íntimo e lenços umedecidos após a micção foram hábitos mais frequentes entre mulheres

Palavras-chave
- vaginose bacteriana
- candida albicans
- higiene
- comportamento sexual
- disbiose

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saudáveis ($p = 0,042$ e 0,032, respectivamente). Em comparação com os controles, o sabonete bactericida foi mais usado por mulheres com VB ($p = 0,05$).
Conclusão Alguns hábitos de higiene foram associados à VB e/ou VVC. Os ensaios clínicos devem abordar esta questão importante na saúde da mulher.

Introduction

Vulvovaginal candidiasis (VVC) and bacterial vaginosis (BV) are among the most prevalent conditions seen by medical doctors assisting women with several vulvovaginal symptoms. The prevalence of VVC and BV may vary in function of endogenous and exogenous factors, leading to the development of one or both of these conditions in 60% of women in reproductive age.[1,2] However, many of the women suffering with vulvovaginal disorders (VDs) do not match the well-known risk factors.[3]

Bacterial vaginosis, which is the most frequently cited cause of vaginal discharge and malodor, is associated with an increased risk of sexually transmitted disease (human papillomavirus [HPV], human immunodeficiency virus [HIV], pelvic inflammatory disease [PID]) and a number of other adverse reproductive outcomes.[4] An increased vaginal pH and the replacement of vaginal lactobacilli by *Gardnerella vaginalis* and anaerobic gram-negative rods characterizes this VD.[5] Vulvovaginal candidiasis is an extremely common infection in women of childbearing age of all strata of society, the second most common cause of vaginitis in the United States and the most common cause in Europe, and it has a high negative impact over women's comfort and well-being.[6]

Some genital hygiene behaviors and/or sexual practices might represent potential mechanisms for facilitating the installation of one of these conditions. Certain vulvar cleansing agents and vaginal douching may affect the vulvovaginal ecology through alteration of pH or bactericidal effects on the normal lactobacilli and, so, predispose to BV.[7] Feminine hygiene products (such as women's blades, sprays, showers, yeast creams, and pubic hair removal oils) are extensively used worldwide, even though they could modify the genital environment; however, unfortunately, this is still poorly studied. Even if feminine hygiene products are not causative of VD, the use of these products could cause symptoms that mimic VD, such as discharge or irritation, or may mask symptoms of vulvar and vaginal infections, misleading the diagnosis and treatment.

The literature suggests that receptive oral sex could introduce abnormal flora or lactobacilli phages into the vagina, or that a salivary mediator could cause alteration in the vaginal flora and favor VVC installation.[8,9] Therefore, the goal of the present study was to describe the genital hygiene and sexual habits among reproductive-aged women and to look for possible associations between the diagnosis of VD and those practices.

Methods

This is a cross-sectional study of reproductive-aged women attended at Hospital da Mulher Professor Doctor José Aristodemo Pinotti-CAISM-UNICAMP. The period of data collection was between February, 2013 and May, 2014, after approval of the institutional ethics committee (CAAE: 04945812.5.0000.5404). In the first step of patient selection, the main researcher checked on charts of patients who were in the waiting room. The inclusion (to be in reproductive age [considered from 18–45 years old] and to have preserved ovaries function) and exclusion criteria (diagnose of sexual transmitted diseases, genital hygiene orientation received previously in our services, previous gynecological cancer, diagnose of diabetes or other immunosuppressive disease, cognitive difficulties, antibiotic or vaginal medication use in the 15 days prior to selection) were accessed in order to appoint eligible participants. In total, 360 patients were selected and invited to participate in the study. One hundred and ninety cases were elected at the family planning and 170 cases at the genital infection outpatient clinics. All women who fulfilled the inclusion criteria and signed the informed consent form were enrolled in the study. They answered questions about sociodemographic and gynecological characteristics and fulfilled a self-reported standardized questionnaire containing habits of genital hygiene, sexual activity, and related care. They were guided to a gynecological examining room where signals of vaginal disorders were searched, and vaginal sampling for clinical and microbiological diagnosis of BV and/or VVC were collected. Infections such as HIV, hepatitis B and C, and syphilis were excluded by serology, HPV by oncologic colpocytology and *Neisseria gonorrhoeae* by culture in Thayer-Martin medium. In case of clinical suspicion of infection by *Chlamydia trachomatis,* patients were excluded. There were no cases of clinical genital herpes infection. In order to compound the healthy group, all cases presenting vaginal microflora missing *Lactobacilli* or presenting more than 10 leucocytes per immersion oil field (x 1,000) or with severe cytolysis in the microscopy were excluded.

Questionnaire

Because there is no validated questionnaire for genital hygiene and daily care available in the scientific literature so far, some researchers in this field developed specific questions in order to understand these important habits among women. However, the questionnaires used in the consulted literature[7,9–12] not only are not validated, but also lack valuable information such as frequency of genital washing, technique used to have pubic hair removed, among others that might be relevant to this research. The developed tool's structure is divided into the following 6 main domains:

1. Genital cleansing and washing; 2. Sexual activity and related care; 3. Genital hair removal aspects; 4. Tattooing and piercing; 5. Pad, tampon, and other products used during menstruation, and 6. Type and fabric of most used clothing and underwear. The domains add up to 60 questions that can be answered categorically (eg: yes or no, never, sometimes, frequently or always, or by checking directly the product used on the query care). Before beginning data collection, the tool was tested in a pilot study and adjusted as necessity was pointed out either by patients or professionals who analyzed the questionnaire' answers. In addition, Cronbach's alpha coefficients were calculated to assess the internal consistency of the questionnaire. Only the questions scored with an almost perfect agreement level (> 0.80) were used in the analysis of the present study, in order to assure an adequate test-retest reliability to assess the genital hygiene and sexual behavior of women with and without vulvovaginal diagnosis. This study analyzed questions of the domains 1, 2, and 3 (genital cleansing and washing, sexual activity and related care, and genital hair removal aspects). The variables regarding *genital cleansing and washing* were time away from home, baths per day, frequency of genital hygiene a day, products used in genitalia, posturinary method of hygiene, postevacuation method of hygiene, and vaginal douching. The variables of *sexual activity and related care* were frequency of intercourse per week, habits of having more than one intercourse a day, oral sex, anal sex in the last 30 days, use of lubricant, erogenous substance or sex toys use, vaginal douching after sex, genital cleansing method used before and after intercourse. The variables of *genital hair removal aspects* were frequency, area, and method of genital hair removal and products used before, during, and after hair removal. All variables were comparatively studied both on groups with and without VVC and/or BV.

Technique

In a gynecological examination, the vaginal pH was determined using a pH indicator paper (colorimetric pH strips; Merck Laboratories, Germany), which was placed for 1 minute on the right side of vaginal wall. Then, vaginal material was collected from the left side of the vaginal wall using two swabs, one designed for smear slide examination under optic microscopy, and a Whiff test, which was considered positive when it released a bad odor after the addition of potassium hydroxide and the other to smear into a Sabouraud agar culture media. The BV diagnosis was performed analyzing the vaginal content smears slides (gram-stained) under oil immersion objective (1,000x magnification) and graded as per the Nugent criteria.[10] Specifically for this study, the diagnosis of BV and VVC were very rigorous, being considered positive only when all three criteria (Nugent score, pH, and Whiff test) were positive. The diagnosis of VVC was positive for women who presented: 1 - symptoms and/or signs of vaginitis, that is, vaginal discharge (described as thin or thick like cottage cheese, with no particular odor), itch or discomfort, external dysuria, and vulvovaginal erythema, 2 - spores, hyphae, or yeast buds identified on microscopic analysis, and 3 - fungal positive culture in Agar Saboureaud medium, read after 36 to 48 hours and until 80 hours of incubation at 25 to 30 degrees Celsius.[11] Women without CVV and/or BV were those who did not fit into the earlier diagnosis and with a vaginal content smear without present inflammation. Women with some symptoms, such as vaginal discharge, sporadic burning or itching, or other clinical symptoms without any laboratory positive tests were included in the control group. Microbiologists performed all laboratory assessments.

Statistical Analysis

The sample size calculation was based on the prevalence of some genital hygiene habits of women with and without bacterial vaginosis, observed in a previous study.[12] Common variables examined, such as *front to back cleaning of genital area,* presented a 37.3% of prevalence for *never* and 22.9% for *always* among women with BV, and *frequency of vaginal intercourse (less than 7 times per week)* was prevalent on 39% of women as *never* and 22.6% as *always*. Adjusting for the design effect and considering a significance level of 5% and test power of 80%, the sample sizes calculated for the 2 questions were respectively of $n = 256$ and $n = 248$. Therefore, the sample should have enrolled at least $n = 256$ subjects, for there should be half in each group (128 of women with and 128 without VVC and/or BV). The obtained data were analyzed using the SAS version 9.2 SAS Institute Inc, 2002–2008, (SAS Institute, Cary, NC, USA), and the chi-squared^2 and Fisher tests assessed the significance of associations between categorical variables. Demographic and gynecological categorical data are showed as frequency and percentage, and numerical variables are showed by mean $\pm$ standard deviation. The categorical variables on genital care and habits were compared between the groups using the chi-squared or Fisher exact test. The significance level was considered $p < 0.05$. The numerical data were compared using the Mann-Whitney test, because of non-normal distribution of data. Both uni and multivariated logistic regressions were used to evaluate the association between the presence of VD and genital hygiene and care habits, and the confidence interval for odds ratio was 95%.

Results

Twenty-nine out of 360 eligible women (18 from family planning and 11 from genital infections disease outpatient clinics) declined to participate in the study. Of the 331 who volunteered, 10 were excluded from the sample because they presented an associated sexual transmitted disease and 14 that did not fulfill the absence or presence of diagnosis of BV or VVC only, as proposed in this study. Then, 307 participants composed the sample, divided into two major groups: health controls, without any vulvovaginal symptoms ($n = 166$–54.07%) and women with either VVC and/or BV (total of 141–45.93%), BV ($n = 72$), VVC ($n = 61$), and BV + VVC ($n = 8$) (►**Figure 1**).

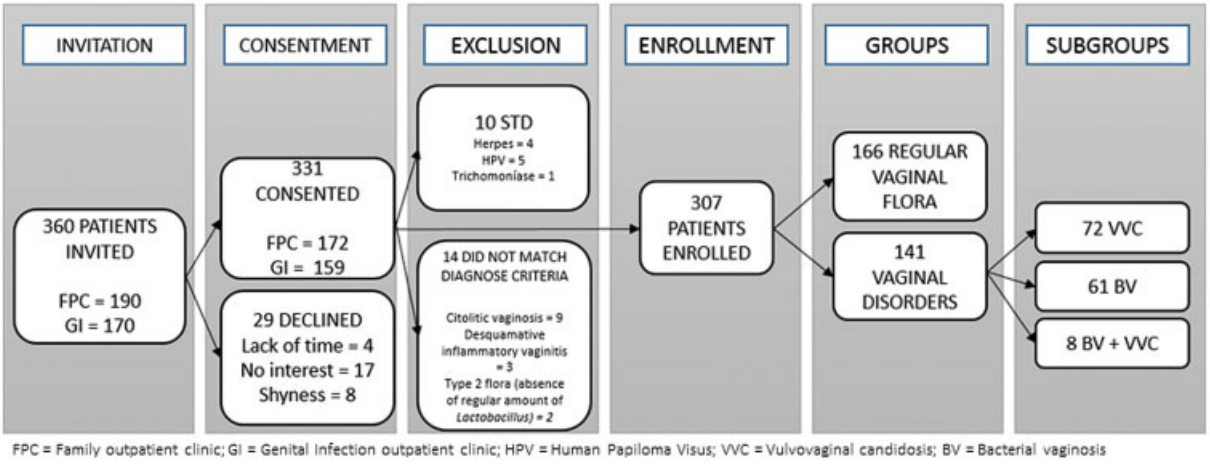

Fig. 1. Sampling flow chart.

The participants were young (33 ± 6.9 years old), with a health weight (body mass index of 22.2 ± 5.5), had 10.2 (± 3.3) years of schooling and one pregnancy. Having no sex partner on last 6 months was reported by 8.5% of women, 83.7% had a steady partner and 7.8% had an eventual partner. Those characteristics did not differ when total of participants were divided according to positive or negative diagnosis for VVC and/or BV. Contraceptive methods, menstrual cycle and smoking habit were also similar between the two groups (►**Table 1**). There were no statistical differences between the studied groups when clinically symptomatic women with negative laboratory results included in control group (regular vaginal flora) were isolated from statistical analysis ($p > 0.05$).

There was a significant association between presence of VVC and/or BV and the use of bactericidal soap for daily genital hygiene ($p < 0.001$, OR = 5.47, IC 95% OR = 2.17–13.8). In contrast, intimate soap (liquid and slightly acid soap) use for daily hygiene and moist wipes use for hygiene after urination were significantly more common among women

Table 1 Demographic, gynecological and behavioral characteristics of women with and without (controls) VVC and/or bacterial vaginosis

	Total	Controls	VVC/BV	*p*-value*
Variables	**(n = 307)**	**(n = 166)**	**(n = 141)**	
AGE ± SD	33.1 ± 6.9	33.6 ± 6.7	32.6 ± 7.0	0.22
BMI ± SD	22.1 ± 5.5	22.3 ± 5.3	22.8 ± 5.7	0.39
SCHOOLING(YS) ± SD	10.2 ± 3.3	10.4 ± 3.3	10 ± 3.3	0.30
PREGNANCIES ± SD	1.8 ± 1.1	1.8 ± 1.1	1.8 ± 1.2	0.87
SEXUAL PARTNER (SP)				0.91
NO PARTNER	26 (8.5%)	14 (8.4%)	12 (8.5%)	
STEADY PARTNER	257 (83.7%)	140 (84.3%)	117 (83%)	
EVENTUAL PARTNER	24 (7.8%)	12 (7.2%)	12 (8.5%)	
WHITE RACE	162 (52.8%)	87 (52.4%)	75 (53.2%)	0.89
CATHOLIC RELIGION	158 (51.4%)	78 (46.9%)	80 (56.7%)	0.08
CONTRACEPTIVE METHODS 0.31				
NOTHING OR DEFINITIVE	14 (4.6%)	7 (4.2%)	7 (5%)	
BLOCKAGE	21 (6.8%)	13 (7.8%)	8 (5.7%)	
HORMONAL	195 (63.5%)	111 (66.9%)	84 (59.6%)	
IUS - LNG OR CU	77 (25.1%)	35 (21.1%)	42 (29.8%)	
SMOKING	33 (10.7%)	13 (7.8%)	20 (14.2%)	0.07
MENSTRUAL CYCLE +	194 (63.2%)	92 (55.4%)	102 (72.3%)	0.47

Abbreviations: BMI, body mass index; Cu, copper bearing; IUS, intrauterine system; LNG, levonorgestrel; NV, negative vulvovaginitis diagnostic; PV, positive vulvovaginitis diagnostic; SD, standard deviation; VV, vulvovaginitis.
*Chi-square Test, SP for 6 month or more.

without VVC and/or BV ($p = 0.04$, OR = 0.67, IC 95% OR = 0.75–0.98 and $p = 0.01$, OR = 0.24, IC 95% OR = 0.05–0.52, respectively). Mean time away from home, number of baths per day, frequency of genital hygiene, vaginal douching or genital hygiene performed after sexual intercourse did not differ between women with and without VVC and/or BV. Anal hygiene was practiced in the wrong way (from back to front) by 6.6% of the VD-negative group and 11.3% of the VD-positive group, although it was not statistically significant (►**Table 2**). There were no statistically significant differences for these variables when the group of women without vaginal disorders was compared with BV and VVC groups alone.

Anal sex practiced on the 30 days preceding the interview was reported by 30.2% of women in the VD group, and in 8.8% in the group without VD ($p < 0.0001$, OR = 4.34 IC 95% OR = 2.21-8.55). Comparing the groups of women with BV and/or VVC to those without VD, it was observed that both anal sex ($p < 0.001$, O.R = 2.33 IC 95% OR = 1.08–5.05) and use of sex toys ($p < 0.03$, OR = 2.33, IC 95% OR = 1.08–5.05) correlated to the presence of bacterial vaginosis. Among the 51 women reporting anal sex in the last 30 days and the 31 reporting the use of sex toys, only 2 (6.45%) of the first and 2 of the second (4%) groups used condoms regularly. Frequency of sexual intercourse, oral sex practice and lubricant use were statistically similar between groups (►**Table 3**).

The great majority of the participants (95%) reported to have genital hairs removed, with no significant statistical difference between groups. The characteristics of this habit, such as reason for epilation, method, frequency, area of epilation, and products used before and after having genital hair removed were similar among the different groups ($p > 0.05$). Although also similar between groups, the opinion of the 61% of the participants about the influence of hair removal to genital health were highly reported as *probably harmful*, and most of those who removed their genital hairs reported an associated vulvar irritation increase because of this practice (71% of women without VD and 78% of women with VD). The results showed that independent of the technique or area of genital hair removal, this practice did not relate to the presence of genital infections.

Discussion

Our results showed that bactericidal soap, habit of having anal sex, and using sex toys during intercourse were related to a higher prevalence of VVC and/or BV, while other variables, such as genital hair removal, oral sex, use of lubricants, frequency of sexual intercourse, or other hygiene habits did not show such association. In comparison to other studies with similar objectives,[7,9,12] this study investigated many variables for the first time. Probably because the studied population lives in a tropical weather country, this explains why most of women are used to bathing twice per day. However, less than 15% of them had the habit of washing the genitalia other than when bathing, and the common, bar-shaped soap was the most used cleanser to do daily genital hygiene. However, these findings agree to another study[13] investigating the skin care regimen of 121 pregnant volunteers who reported to take more than one bath a day and to use common bar soap to do genital hygiene.

On the other hand, Volochtchuk et al.[14] evaluated the pH of 42 different forms of soap and found that most bar-shaped soaps had a pH between 9 and 10, while liquid soap had a pH lower than 8. Gfatter et al.[15] underlines that an alkaline pH is the main factor to provoke irritation and skin dehydration as well as to eliminate local protection. In fact, genital hygiene with intimate soap (liquid and with slight acidity), the second most commonly used product for this purpose, was more frequently reported by women without VVC and/or BV ($p < 0.05$). Schmid and Korting[16] suggested that the lower pH helps to maintain the physiological acid coat of the skin, thus preventing the installation of pathogens. Nevertheless, it is important to highlight that when compared with healthy ones, women with VVC and/or BV used bactericidal soap more frequently. The probable explanation is that the sterilization of vaginal flora that this product causes, including its protective microorganisms, which, once eradicated, offer no dispute for nutrients or substrate, leading to rainless growth of harmful bacteria, and, therefore, to the increase in vulvar and vaginal infections.

Some previous studies indicate more frequent habits of vaginal douching among women with vaginal infections.[17,18] We investigated vaginal douching in two situations: as a daily habit and after sexual intercourse. In the first case, 24% of women answered to do it as a habit and 31% reported to do it only after intercourse. Nevertheless, we found the same rates for both with and without VVC and/or BV groups. Other Brazilian studies report rates from 20 to 40% and do not support the association between vaginal douching and genital infections.[19–21]

Despite our population having been selected from a low-income public hospital, the average of 10 years of schooling might explain the avoidance of back-to-front handling of disposable toilet paper after evacuation in 6.6% of the VD-negative group and in 11.3% in the VD-negative group. This data was similar to the one found by Cesar et al.[20] when investigating pregnant women, who found rates between 9 and 11%. The low prevalence of women performing back-to-front wiping found in this study probably explains the lack of correlation between this variable and the presence of VD. Disposable toilet paper was the prevalent mode of hygiene posturination and postdefecation. Our findings showed much lower rates for washing after toilet use (10–26%) than those found in a study that enrolled American women, who seemed to have the habit to wash their genitalia with water and soap after urination and defecation in 50 to 66% of the time.[22] Interestingly, we found a statistically significant difference for the use of moist wipes after urination pointing it as a more frequent habit of women without genital infections ($p < 0.05$). This finding agrees with literature, which sustains the use of moist wipe as safe and beneficial to genital health.[23] Because of its moist characteristic, these wipes might be more efficient at promoting genital hygiene than regular disposable toilet paper.

Table 2 Daily habits and products used in genital hygiene by volunteers with and without vulvovaginal disorders

Variables	Total	VD-negative (n = 166)	VD-positive (n = 141)	*p*-value	OR	CI 95% OR
TIME AWAY FROM HOME				0.42*	1.2	0.7–1.82
≤ 5H	109 (35.5)	61 (36.8)	48 (34)			
6H–9H	107 (34.8)	55 (33.1)	52 (36.9)			
≥ 10H	91 (26.6)	50 (30.1)	41 (29.1)			
BODY BATHS PER DAY				0.58*	1.36	0.76–2.92
≤ ONE		36 (21.7)	24 (17)			
TWO		110 (66.3)	100 (70.9)			
≥THREE		20 (12.1)	17 (12.1)			
FREQUENCY OF FG HYGIENE				0.47*	1.49	0.68–3.22
≤ ONE		24 (14.5)	14 (9.9)			
TWO		97 (58.4)	88 (62.4)			
≥THREE		45 (27.1)	39 (27.7)			
FG HYGIENE PRODUCTS						
NOTHING		1 (0.6)	1 (0.7)	1**	—	
BACTERIAL SOAP		6 (3.6)	24 (17)	< 0.0001*	5.47	2.17–13.81
COMMON SOAP		100 (60.2)	80 (56.7)	0.62*	—	
INTIMATE SOAP		59 (35.5)	35 (24.8)	0.04*	0.67	0.75–0.98
BODY LOTION		10 (6)	13 (9.2)	0.89*	—	
OTHERS		6 (3.6)	8 (5.7)	0.38*	—	
POST URINARY HYGIENE						0.05–0.52
USE OF DBP		139 (83.7)	123 (87.2)	0.32	—	
WASHES WITH SOAP		18 (10.8)	14 (9.9)	0.47	—	
USES MOIST WIPES		18 (10.8)	6 (4.3)	0.01	0.24	
OTHER		2 (1.2)	1 (0.7)	0.56	—	
NOTHING		0 (0)	2 (1.4)	–	—	
POST EVACUATION HYGIENE					0.94	0.6–1.7
FB DBP USE		148 (89.2)	119 (84.4)	0.41		
BF DBP USE		11 (6.6)	16 (11.3)	0.52		
WASH WITH WATER		43 (25.9)	37 (26.2)	0.54		
SOAP		21 (12.7)	24 (17)	0.48		
NOTHING		1 (0.6)	2 (1.4)	0.80		
VAGINAL DOUCHING					0.92	0.4–2.11
NEVER		112 (67.5)	96 (68.1)	0.26		
SOMETIMES		14 (8.4)	11 (7.8)	0.54		
ALWAYS		40 (24.1)	34 (24.1)	0.48		
FG HYGIENE BEFORE SI					1.25	0.75–2.07
NO		41 (27.7)	41 (32.5)	1.00		
YES		107 (72.3)	85 (67.5)	0.11		
FG HYGIENE AFTER SI					1.3	0.59–2.86
NO		13 (8.8)	14 (11.1)	0.84		
YES		135 (91.2)	112 (88.9)	0.14		

Abbreviations: Bact., bactericide; BF, back to front; CI, confidence interval; DBP, disposable bathroom paper; FB, front to back; FG, female genital; Min., minute; NV, negative diagnostic of vulvovaginitis; OR , odds ratio confidence interval of 95% for risk of vaginal disorder; PV, positive diagnostic of vulvovaginitis; SI, sexual intercourse; VC, vulvovaginal candidiasis; VC, vaginal disease; VV, vulvovaginitis.
Observation: Inconsistence in numbers might occur due to a number of volunteers who did not have sexual intercourse in the last 6 months and were not included in related questions and women who could use more than hygiene products or way of cleaning themselves.
Chi-squared test* and Fisher** exact test were used for p value.

Table 3 Sexual habits of women with and without vulvovaginal disorders

	VD-negative	VD- positive	*p*-value	OR	CI 95% OR
Variables	**(n = 166)/n (%)**	**(n = 141)/n (%)**			
SI PER WEEK,			0.49*	1.55	0.61–3.95
NO SI (#)	18 (10.8)	15 (10.6)			
< ONCE	39 (23.5)	35 (24.8)			
1–3 TIMES	92 (55.4)	69 (48.9)			
≥ 4	17 (10.2)	22 (15.6)			
+ 1 SI/ DAY			0.8*	1.3	0.59–2.93
NEVER	99 (66.9)	81 (64.3)			
SOMETIMES	36 (24.3)	31 (24.6)			
FREQUENTLY	13 (8.8)	14 (11.1)			
ORAL SEX (receptive)			0.9*	1.08	0.52–2.26
NEVER	84 (54.5)	67 (51.9)			
SOMETIMES	52 (33.8)	46 (35.7)			
FREQUENTLY	18 (11.7)	16 (12.4)			
ANAL SEX (IN THE PREVIOUS 30 DAYS)			< 0.0001*	4.34	2.21–8.5
NO	135 (91.2)	88 (69.8)			
YES	13 (8.8)	38 (30.2)			
USE OF LUBRICANT			0.8*	1.0	
NO	118 (79.7)	99 (78.6)			
YES	30 (20.3)	27 (21.4)			
EROGENOUS SUBSTANCE OR SEX TOYS USE			0.03*	2.33	1.1–5
NO	137 (92.6)	106 (84.1)			
YES	11 (7.4)	20 (15.9)			
DOUCHING AFTER SI			0.78*	1.0	0.58–1.8
NEVER	101 (60.8)	88 (62.4)			
SOMETIMES	14 (8.4)	9 (6.4)			
FREQUENTLY	51 (30.7)	44 (31.2)			

Abbreviations: BV, bacterial vaginosis; CI, confidence interval; ns, *p*-value not significant; OR, odds ratio; SI, sexual intercourse; VC, vaginal candidiasis; VD, vulvovaginal disorders;.
(*) Chi-squared and (**) Fisher test, (#) for more than 6 months.

Sexual practice differed between women with and without infections in the modalities anal sex in the previous 30 days to the date of data collection and use of sex toys during intercourse. Both were more practiced by women with BV ($p < 0.0001$ and $p = 0.03$, respectively). Although there was a relatively high reporting of anal sex, no one reported being paid for sex. This is probably an underestimated prevalence in the literature as anal sex is yet a taboo, and, perhaps, the fact of using a self-reported survey contributed to the increased numbers of such a reporting. In addition, there is a possibility of women with vulvovaginitis having had opted for anal penetration because their vaginas were sore. Thus, this data agrees with the findings of Rosa and Rumel[24] that pointed statistical significance for the relation between anal sex and clinically diagnosed VVC and/or BV. It is known, however, that the anal region is colonized by bacteria that, once transmitted to the genital region, can be quite harmful to its environment. Although our study did not investigate whether those women had the habit of anal sex before or after (or even alternating) having vaginal penetration, gynecologists should educate their patients about changing the condom used to anal sex before having vaginal penetration, or not going from anal to vaginal penetration afterwards. The anal sex data presented in this paper (30.2% in the VD-positive group versus 8.8% in the VD-negative group) is similar to the one from the American women population between 15 and 44 years, reported by Chandra et al.[25] in 2013.

Investigation about the use of sex toys is as scarce in the medical literature, as the physiopathology knowledge of its role over the disturbance of vaginal homeostasis and reliability of its potential disturbance. A study conducted in

China with homosexual women found use of sex toys in 13.4% of the time, but half of the time they did not use a condom protecting it. Although our population have declared their selves as heterosexual, the frequency of sex toys use is similar to the one found in this study (11.3%).[26] The literature[8,9] has suggested that oral sex can play an important role in sexually transmitted diseases, and Saini et al.[9] concluded, in their study, that "oral sex is a mode of transmission for genital pathogens". However, our results showed equal prevalence in oral sex (both giver and receptor) for women with and without VD.

There were no statistically significant differences in terms of habit, frequency, or method of genital hair removal among the studied groups. However, most women in this study declared to associate vulvar irritation with removal of genital hair. Even though it can present no harm to vaginal health, this symptom can often mimic VD symptoms, which might confound the patient or even mislead the diagnosis and treatment. In addition, it is important that women opt for hair removal practices that promote as little discomfort as possible.

The limitation in this study includes the fact that the variables of genital care were self-reported and obtained through a questionnaire not yet validated in the medical literature, which may have led to under reporting and misclassification of some behaviors. However, the inclusion of a great number of women and the accuracy applied in the methodology for vaginal disorders diagnose might have balanced any inconsistency. Further studies containing the patient's correct diagnosis in conjunction with hygiene and genital care habits and associated complaints would be valuable to guide future orientation improving the prevention and treatment of vaginal disturbances.

Conclusion

The results suggest that some hygiene habits and the absence of others were associated with the presence of VVC and/or BV. It is not clear, though, if female genital hygiene can be the cause or consequence of such VDs. Controlled trials are needed to clarify the influence of hygiene and sexual habits on the vulvovaginal environment.

Contributions

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

Conflict of Interests

The authors have no conflict of interests to declare.

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Colposcopic Findings and Diagnosis in Low-Income Brazilian Women with ASC-H pap Smear Results

Achados colposcópicos e diagnóstico em mulheres brasileiras de baixa renda com resultado de exame citopatológico ASC-H

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Abstract

Objective To determine the accuracy of colposcopy findings in diagnosing cervical intraepithelial neoplasia (CIN) in women with an atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H) pap smear result and analyze whether the prevalence of HSIL and cancer correlates with sociodemographic risk factors and specific colposcopic findings.

Methods Colposcopic findings and sociodemographic risk factors were analyzed as possible predictors of a CIN 2 or worse diagnosis in women with an ASC-H pap smear result.

Results Accuracy of the colposcopic impression was 92%, sensitivity was 91.6%, and specificity was 93.1%, with a positive predictive value of 96.4% and negative predictive value of 84.3%. Diagnosis of CIN 2 or worse was more frequent in patients with a previous history of cervical dysplasia and pre-menopausal patients. Identification of major colposcopic findings, dense acetowhite epithelium, coarse mosaicism, and punctuation correlated significantly with CIN 2 or worse.

Conclusion Colposcopy performed by an experienced examiner can accurately differentiate patients with CIN 1 or less from patients with CIN 2 or worse. Diagnosis of CIN 2 or worse was more frequent in patients with a previous history of cervical dysplasia and pre-menopausal patients. The degree of acetowhite changes was the best colposcopic feature to predict CIN2 or worse.

Keywords
- colposcopy
- cervical intraepithelial neoplasia
- cervical cancer
- ASC-H
- cervix uteri

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Resumo

Objetivo Determinar a acurácia dos achados colposcópicos no diagnóstico das neoplasias intraepiteliais cervicais (NIC) em mulheres com resultado de exame citopatológico de células escamosas atípicas de significado indeterminado não podendo excluir lesão intraepitelial de alto grau (ASC-H) e analisar a correlação entre a prevalência de HSIL ou câncer com fatores de risco sociodemográficos e achados colposcópicos específicos.

Métodos Os achados colposcópicos, e os fatores de risco sociodemográficos foram analisados como possíveis preditores de diagnóstico NIC 2 ou mais grave em mulheres com resultado de exame citopatológico ASC-H.

Resultados A acurácia da impressão colposcópica foi de 92%, sensibilidade foi 91,6%, e a especificidade foi de 93,1%, com um valor preditivo de 96,4% e valor preditivo negativo de 84,3%. O diagnóstico de NIC 2 ou mais grave foi mais frequente em pacientes com história pregressa de displasia cervical e nas que não estavam na pós menopausa. A identificação de achados colposcópicos maiores, epitélio acetobranco denso, mosaico e pontilhados grosseiros se correlacionaram positivamente com o diagnóstico NIC 2 ou mais grave.

Conclusão A colposcopia realizada por um examinador experiente pode diferenciar com acurácia pacientes com NIC 1 ou menos grave de pacientes com NIC 2 ou mais grave. O diagnóstico de NIC 2 ou mais grave foi mais frequente em pacientes com história pregressa de displasia cervical e pacientes que estavam na pré menopausa. A densidade da acetorreação foi o melhor preditor colposcópico para NIC 2 ou mais grave.

Palavras-chave

- colposcopia
- neoplasia intraepithelial cervical
- câncer de colo uterino
- células escamosas atípicas do colo do útero
- colo do útero

Introduction

The cytological diagnosis of atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H) is a relatively new cytological classification for atypical squamous cells formally introduced with the 2001 Bethesda system.[1] Because of the high incidence of clinically significant lesions noted on subsequent follow-up, it has been suggested that patients with an ASC-H pap smear result be observed closely and referred for colposcopic examination.[2,3]

The management of a cervical cytological lesion depends on the severity of the lesion and its inherent underlying or future risk of high-grade cervical intraepithelial neoplasia (CIN) or cancer.[3] A low-grade squamous intraepithelial lesion (LSIL) often regresses spontaneously, especially in young women, whereas a high-grade squamous intraepithelial lesion (HSIL) is more likely to persist or even progress to more severe lesions.[4,5] Therefore, HSIL diagnosis and treatment is the main goal of cervical cancer screening and prevention programs. The aim of the colposcopic examination is to correctly identify patients at high risk of developing cervical cancer and refer them for excisional or destructive treatment. Interpreting colposcopic epithelial patterns and subsequently selecting the site for biopsy is a subjective procedure that correlates strongly with the skill and experience of the colposcopist.[6] The number of biopsies, type of human papilloma virus (HPV), the size of the lesion, and its severity are potential factors that may influence the accuracy of colposcopy.[7–9] The sensitivity of colposcopy ranges from 64 to 99% and the specificity from 30 to 93%.[10]

This study aimed to investigate the diagnostic performance of colposcopy performed by a highly experienced examiner using the International Federation for Cervical Pathology and Colposcopy (IFCPC) nomenclature in a low-income Brazilian population with an ASC-H pap smear result.[11] This study also aimed to analyze whether the prevalence of HSIL and cancer correlates with sociodemographic risk factors and specific colposcopic findings. We believe this knowledge can potentially help develop clinical protocols for selecting cases for a "see and treat" approach in the ASC-H cytological category.

Methods

This study was conducted in the city of Curitiba at the Clinics Hospital of the University of Paraná, a Brazilian institution responsible for patients requiring a higher level of health care.

Between July 2009 and August 2016, all women with cytological diagnosis of atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H) or high-grade squamous intraepithelial lesion (HSIL) referred to the Lower Genital Tract Disease and Colposcopy specialized service, were analyzed.

Colposcopic examinations performed by the same highly experienced colposcopist (with 30 years of experience performing over 4,000 colposcopies/year) were selected. Biopsies were taken from the area with the worst colposcopic impression according to the standard practice.

After approval from the local ethical committee colposcopic findings were collected from medical records and colposcopic impressions were classified according to the International Federation for Cervical Pathology and Colposcopy (IFCPC) criteria as either negative, Grade 1 (minor), or Grade 2 (major).[11]

The sociodemographic risk factors for cervical cancer collected from medical records were age, parity, menopausal status, lifetime number of sexual partners, tobacco smoking, co-infection with HIV or other sexually transmitted infection, and previous medical history of cervical dysplasia.

The same staff pathologist blindly reviewed all cytology results using the same criteria used in daily practice. The reviewed cases were classified in accordance with the 2001 Bethesda System and the Brazilian Nomenclature for Cytopathological Reports.[12] Blinded to the previous cytology results, a second staff pathologist reviewed the remaining discordant cases. The final diagnosis was then defined by agreement with either the original diagnosis or the first staff pathologist, resulting in the diagnosis of ASC-H cases or HSIL cases. When agreement could not be reached the most severe diagnosis was used.

Histological diagnosis of a biopsy obtained by large loop excision of the transformation zone (LLETZ) or cold knife conization was considered the gold standard for diagnosis of CIN 2 or worse.

A diagnosis of CIN 1 or less was defined as a negative colpocytological result 6 and 12 months after the initial colposcopy. When a negative result was not achieved at follow-up, and a second abnormal pap smear result was obtained, the patient was then referred for LLETZ or cold knife conization and this histological diagnosis was considered the "gold standard".

The inclusion criteria were: 1) aged 21 years and older, 2) not pregnant, 3) no recent treatment for cervical intraepithelial neoplasia, 4) no history of total hysterectomy, and 5) no history of radiotherapy treatment for invasive cervical carcinoma. The exclusion criteria were 1) colposcopic examination at another clinic, 2) no records of colposcopic examination, 3) inadequate colposcopy, 4) slides inadequate for cytology review panel.

We examined the accuracy of colposcopy findings for the prediction of two main diagnostic endpoints, CIN 1 or less (low risk of developing cervical cancer) and CIN 2 or worse (high risk of developing cervical cancer) in women with an ASC-H pap smear result.

Data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 software (IBM Corp., Armonk, NY, USA). Results are presented as means, standard deviations, medians (with ranges), numbers, or frequencies, as appropriate. A Chi-squared or Fisher exact test was used to univariately identify factors related to the presence of the diagnostic endpoints. A multivariate analysis of factors predicting these endpoints was estimated using binary logistic regression featuring Hosmer-Lemeshow goodness-of-fit testing. All p-values < 0.05 were considered statistically significant.

Results

During the study period, 18,046 women were screened for cervical neoplasia with conventional cytology. Abnormal cervical cytology prevalence was 14.6%, of which 159 women with an ASC-H pap smear result and 258 with a HSIL finding were referred to the lower genital tract disease and colposcopy specialized service. After cytological panel review was complete 106 cases with an ASC-H result were selected for further analysis, *kappa* values for interobserver agreement between pathologists was 0,49 (moderate agreement) (►**Fig. 1**).

In terms of sociodemographic characteristics, the study population showed a high prevalence of tobacco smoking, HIV infection, and a previous history of HSIL treatment (►**Table 1**).

After initial assessment, 65 patients with major colposcopic impressions were identified. In 60 cases, the histological assessment was compatible with HSIL or cancer. A total of 19 patients with major colposcopic impressions were referred to LLETZ without prior histologic diagnosis (see and treat" approach). In 18 cases, histological assessment of the LLETZ specimens confirmed the presence of HSIL and one patient was lost to follow-up before undergoing LLETZ treatment (►**Table 2**).

Twelve patients had minor colposcopic impressions, and only two (18.2%) had a final diagnosis of CIN 2 or worse.

Table 1 Demographic and clinical characteristics of the study population

Characteristic	n	(%)
Age		
Median	36	N/A
Range	21 to 84	N/A
Lifetime number of sexual partners		
Median	2	N/A
Range	1 to 30	N/A
Menopause		
Yes	23	(21.7%)
No	83	(78.3%)
Tobacco smoking		
Yes	36	(34.0%)
No	70	(66.0%)
Coinfection with others sexually transmitted agents and HIV		
Yes	17	(16.0%)
No	85	(80.2%)
HIV	4	(38%)
Previous history of HSIL		
Yes	21	(19.8%)
No	85	(80.2%)

Abbreviations: HIV, human immunodeficiency virus; HSIL, high-grade squamous intraepithelial lesion.

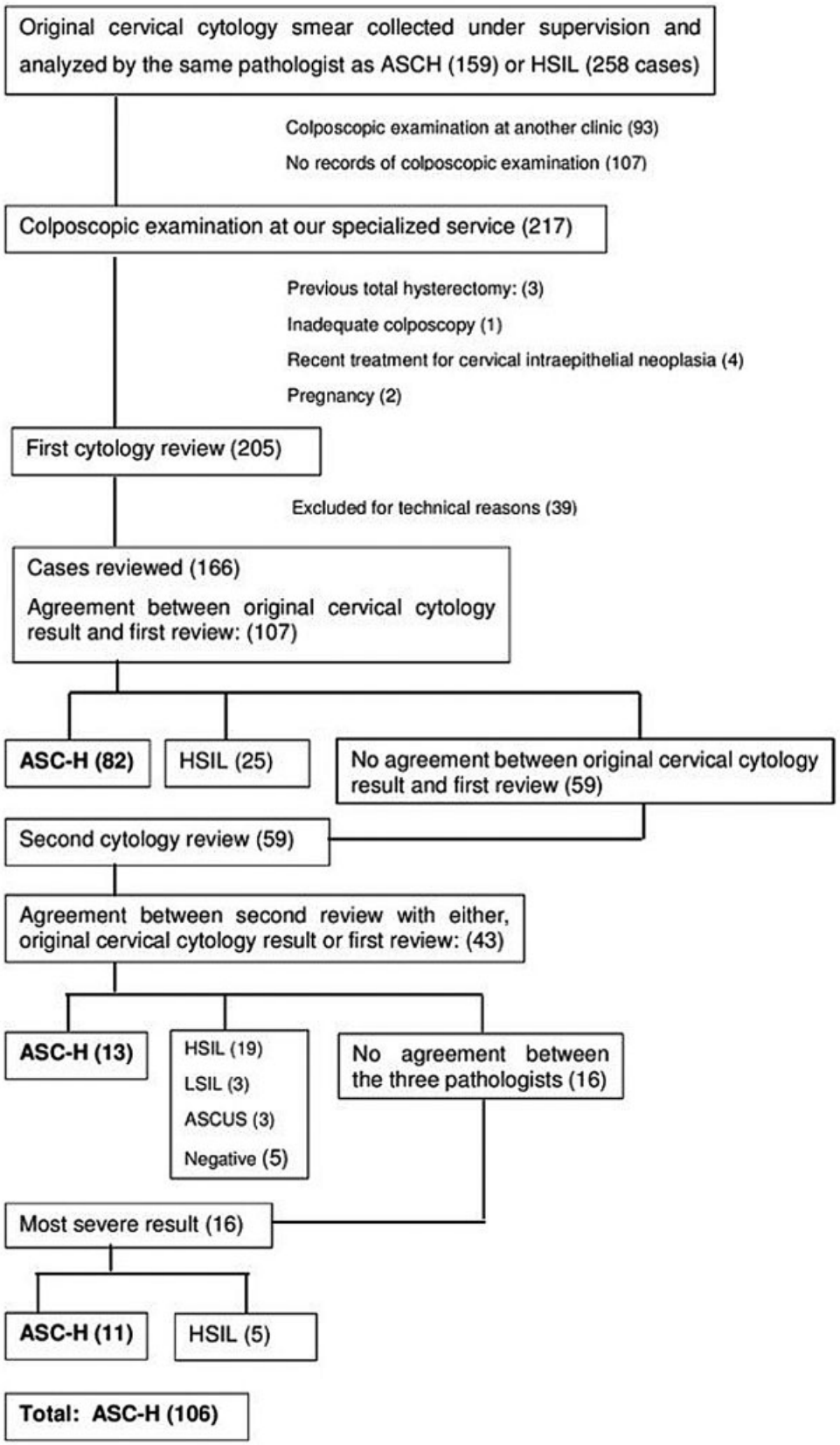

Fig. 1 Case selection and peer review of cervical smears.

Table 2 Colposcopic impression and clinical and histopathologic outcome

	CIN 1 or less			CIN 2 or worse		Non-attendance	*P*-value[†]
Colposcopic Impression/Transformation Zone	Negative Clinical follow-up	LLETZ histopathologic results					
		Negative	CIN 1	CIN2/3	Cancer		
Major (grade 2) (n = 65)	0 (0.0)	2 (3.1)	2 (3.1)	53 (82.2)	7 (10.9)	1	< 0.001*
TZ1 (n = 36)	0 (0.0)	1 (2.8)	1 (2.8)	31 (88.6)	2 (5.7)	1	
TZ2 (n = 14)	0 (0.0)	1 (7.1)	0 (0.0)	12 (85.7)	1 (7.1)	0	
TZ3 (n = 15)	0 (0.0)	0 (0.0)	1 (6.6)	10 (66.6)	4 (26.6)	0	
Minor (Grade 1) (n = 12)	6 (54.5)	0 (0.0)	3 (27.3)	2 (18.2)	0 (0.0)	1	< 0.001*
TZ1 (n = 9)	5 (62.5)	0 (0.0)	2 (25.0)	1 (12.5)	0 (0.0)	1	
TZ2 (n = 1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0	
TZ3 (n = 2)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0	
Negative (n = 29)	18 (66.7)	4 (14.8)	2 (7.4)	2 (7.4)	1 (3.7)	2	
TZ1 (n = 6)	6 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	
TZ2 (n = 4)	2 (66.6)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1	
TZ3 (n = 29)	10 (55.5)	4 (22.2)	1 (5.5)	2 (11.1)	1 (5.5)	1	
Total (n = 106)	24 (23.5)	6 (5.9)	7 (6.9)	57 (55.9)	8 (7.8)	4	

Abbreviations: CIN, cervical intraepithelial neoplasia; LLETZ, large loop excision of the transformation zone; TZ, transformation zone.
Data are presented as number (percentage) unless stated otherwise.
Non-attendance was not included in the calculation of proportions of histological results.
[†]comparing the incidence of CIN2/3and cancer between the groups with minor or negative versus major colposcopic impression. n, number of women in each category.
*statistically significant.

One was lost to follow-up. Negative colposcopic findings occurred in 29 cases and three (10.3%) of them had a final diagnosis of CIN 2 or worse. All of these cases had a type 3 transformation zone. Two cases were lost to follow-up (►**Table 2**).

A CIN 1 or less endpoint occurred in 37 (34.9%) patients and a CIN 2 or worse endpoint occurred in 65 (61.3%) patients. The non-attendance rate was 3.7%. Excluding non-attenders, the rate of HSIL diagnosis was 55.9% and the rate of invasive carcinoma diagnosis was 7.8%.

In this study, the sensitivity, specificity, and the positive and negative predictive values of colposcopy were determined to be 91.6% (95% CI, 81.6–97.2), 93.1% (95% CI, 77.2–99.1), 96.4% (95% CI, 87.8–99.0), and 84.3% (95% CI, 69.9–92.6), respectively. The overall accuracy of colposcopic impressions was 92%.

We applied the chi-square test in order to establish the correlation between the colposcopic impression result and the two main diagnostic endpoints. The colposcopic impression was statistically relevant with a p-value of < 0.001 for the detection of CIN 1 or less and CIN 2 or worse (►**Table 2**).

Univariate analysis showed a statistical correlation between all major findings and the CIN 2 or worse endpoint, and between minor findings and the CIN 1 or less endpoint (►**Table 3**). Interestingly, a transformation zone (TZ) type 3 finding seemed to be a statistically significant protective factor, whereas a smaller lesion size was not (►**Table 3**).

Multivariate analysis showed that once dense acetowhite changes were present, there was a 63.7% odds ratio in favor of a CIN 2 or worse endpoint compared to CIN 1 or less. Although not statistically significant, only pre-menopausal status and a previous history of HSIL showed a tendency towards prediction of the two diagnostic endpoints (►**Table 4**).

Discussion

Given the higher complexity of the cases attending our hospital, it was not surprising that the rate of ASC-H in our laboratory was 0.88%, which is much higher than the average of 0.2% previously reported.[2]

A pap smear result indicating atypical squamous cells that cannot exclude HSIL (ASC-H) may reflect a mixture of true HSIL and its mimics. These definitions leave some room for individual interpretation, as shown by Confortini et al.,[13] who reported the lowest degree of agreement for the ASC-H category (specific $k = 0.38$) after a peer review of 63,754 smears. Therefore, the panel review of cytology results in this study aimed to reduce selection bias, what we consider a strength in our study. Interobserver agreement between pathologists in our study was considered moderate ($k = 0.49$), similar to previously reported by Confortini et al.[13]

In our study population, 63.7% of patients had a histologic diagnosis of CIN 2 or worse. Some authors have reported that

Table 3 Univariate analysis of colposcopic findings and main endpoints

Colposcopic findings	ENDPOINTS		*P*-value	Odds ratio
	CIN 1 or less	CIN 2 or worse		
Transformation zone				
Types 1 and 2	18 (48.6%)	48 (73.8%)	0.011*	2.98 (1.27–6.96)
Type 3	19 (51.4%)	17 (26.2%)		
Number of cervical quadrants covered by the lesion				
0, 1, and 2	25 (67.5%)	49 (75.3%)	0.396	0.68 (0.27–1.65)
3 and 4	12 (32.4%)	16 (24.6%)		
Acetowhite changes				
Fine and absent	33 (89.2%)	8 (12.3%)	< 0.001*	58.78 (16.5–210.2)
Dense	4 (10.8%)	57 (87.7%)		
Punctation				
Dense	1 (2.7%)	22 (33.8%)	0.005*	18.42 (2.36–143.4)
Fine and absent	36 (97.3%)	43 (66.1%)		
Mosaicism				
Dense	1 (2.7%)	18 (28.1%)	0.011*	14.08 (1.79–110.5)
Fine and absent	36 (97.3%)	46 (71.9%)		

*Statistically significant; CIN, cervical intraepithelial neoplasia.

approximately half (32–90%) of women with an ASC-H cytology result will have less than a HSIL diagnosis on their cervical biopsy sample.[14,15] Recently, a meta-analysis pooled over 4,000 ASC-H cases and estimated the prevalence of histopathological diagnosis of CIN 2 or worse to be 34% (CI 95%, 28–40) with a range of 13–66%.[16] The literature generally reports that the incidence of invasive disease in patients with an ASC-H result is rare (range 1–3%).[17,18] Our invasive carcinoma incidence (7.8%) was similar to the study of Nogara et al.[19] that reported a 7.9% incidence of invasive carcinoma. A higher prevalence of invasive carcinoma in an ASC-H population, such as the 9.3% prevalence of invasive carcinoma found in a study that only included patients with histological samples, is usually associated with different selection criteria.[20] The relatively high incidence of invasive disease in our study supported our classification of this population as "high-risk".

Future analysis is essential to estimate the benefits of a "see and treat" approach in an ASC-H population. In our study, a "see and treat" approach was applied in 18 selected cases and overtreatment did not occur. This practice is an attractive option, as clinical and laboratory resources would be used more efficiently, and the possibility of non-compliance with follow-up visits for further treatment is also avoided. However, we cannot ignore the issue of overtreatment or potential morbidity of LLETZ in patients who may not require treatment.[21]

The high incidence of invasive disease was probably a consequence of the high prevalence of sociodemographic risk factors. The proportion of tobacco smokers was 34% in our study population, whilst the national data shows that only about 15% of Brazilian women are regular smokers.[22] Another risk factor was the higher prevalence of seropositivity for HIV, found in 3.8% of patients, which is much higher than the 0.4 to 0.7% estimated by population-based data in Brazil.[23] There is no population data available on the prevalence of previous history of HSIL treatment in Brazil, but we considered 19.8% higher than expected. The mean age at the time of ASC-H cytology diagnosis was 38.7 years (median: 36 years), and this was similar to that previously reported by other studies such as Bonvicino et al.[24] (35.6 years) and Nogara et al.[19] (32.4 years).

Louro et al.[17] stated that patients 40 years or older were less likely to have a clinically significant lesion detected on subsequent histologic follow-up than patients younger than 40 years. In our findings, patients with a CIN 2 or worse endpoint were older than those presenting with CIN 1 or less. Although estrogen deficiency may lead to cytological changes that mimic HSIL, previous studies involving age group analyses have shown a higher prevalence of pre-invasive lesions in younger populations.[17,25] Univariate analysis of sociodemographic risk factors showed a borderline correlation between being pre-menopausal and a CIN 2 or worse endpoint with a *p*-value of 0.072. There is some evidence that the prevalence of CIN 2 or worse in ASC-H populations is lower after menopause.[17,25] Almost 20% (n = 21) of the study population reported a previous history of HSIL treatment 2 years or more before ASC-H cytology and metachronous lesions occurred in 11 (47.6%) cases. Several studies have demonstrated that women who had a previous diagnosis of a high-grade cervical lesion or invasive cervical cancer had an increased risk

Table 4 Univariate analysis of risk factors

	ENDPOINTS				*P*-value
	CIN 1 or less		CIN 2 or worse		
Menopause					
No	25	67.6%	54	83.1%	0.072
Yes	12	32.4%	11	16.9%	
Tobacco smoking					
No	27	73.0%	41	63.1%	0.308
Yes	10	27.0%	24	36.9%	
Coinfection with other sexually transmitted agents and HIV					
No	31	83.8%	52	80.0%	0.999
Yes	5	13.5%	10	15.4%	
HIV	1	2.7%	3	4.6%	
Previous history of HSIL					
No	26	70.3%	55	84.6%	0.085
Yes	11	29.7%	10	15.4%	
Age					
Average	41.54	SD 13.34	37.06	SD 12.42	0.091
Minimal	21		21		
First quartile	32		28		
Median	40		34		
Third quartile	50		43		
Maximal	74		84		
Lifetime sexual partners					
Average	3.92	SD 4.62	2.42	SD 2.42	0.817
Minimal	1		1		
First quartile	2		3		
Median	2		2.5		
Third quartile	3		4		
Maximal	20		10		

of developing metachronous lesions within the lower genital tract compared to women in the general population.[26,27] Despite this, our findings showed only a trend ($p = 0.085$) towards a relationship between a previous history of HSIL and a CIN 2 or worse endpoint.

The borderline correlations in our study analysis may be the consequence of our limited sample size. Perhaps, in larger populations, these sociodemographic factors would have been more representative as risk factors. A TZ type 3 finding behaved as a protective factor in our study population, and this was probably a consequence of its frequent association with older and postmenopausal patients. In those cases, the ASC-H result was most likely associated with atrophy changes rather than CIN 2 or worse lesions.

The colposcopic impression findings were statistically relevant in the detection of the two diagnoses of CIN 1 or less and CIN 2 or worse. Its sensitivity, specificity, and positive and negative predictive values showed an expressively high performance, close to the high confidence interval margins previously reported.[10,28,29]

The chi-square test showed that grade 2 (major) colposcopic impression findings correlated significantly with a CIN 2 or worse endpoint, and the Hosmer Lemeshow test confirmed this correlation to be 92%.

Interpreting colposcopic epithelial patterns and subsequently selecting the site for biopsy is a subjective procedure that is strongly correlated with the skill and experience of the colposcopist.[6] We believe that the good predictive performance of colposcopy in our study was influenced by the extensive experience of the colposcopist. The high prevalence of HSIL in the study population may have also contributed to colposcopy performance, as it has been reported that colposcopy is better at detecting more severe lesions.[10]

Our findings show that the degree of acetowhite change was the main colposcopic feature that predicted CIN. This was also previously reported by Shaw et al.,[30] who found that

after evaluating the individual variables of colposcopic findings, the degree of acetowhite change was the only feature significantly associated with cervical intraepithelial neoplasia after multivariate analysis.

Conclusion

In an ASC-H population, there is a high rate of severe underlying disease, and colposcopy performed by a highly experienced examiner using IFCPC terminology can produce excellent predictive performance to differentiate patients with CIN 1 or less and patients with CIN 2 or worse. Diagnosis of CIN 2 or worse was more frequent in patients with a previous history of cervical dysplasia and pre-menopausal patients. The degree of acetowhite changes was the best colposcopic feature to predict CIN2 or worse.

Contributions

C. F. MAFFINI: Data collection from medical records, data analysis and manuscript writing. L. M. COLLAÇO: Cytological panel review execution. A. P. M. SEBASTIÃO: Cytological panel review execution. R. M. ZANINE: Colposcopic impression findings, conceived and planned the study design and supervised the project execution.

Conflict of Interests

The authors have no conflict of interests to declare.

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Transcutaneous Nerve Electrostimulation (TENS) in Pain Relief During Labor: A Scope Review

Eletroestimulação nervosa transcutânea (TENS) no alívio da dor durante o trabalho de parto: Uma revisão de escopo

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Abstract

Objective To map health evidence on the effectiveness of transcutaneous nerve electrostimulation (TENS) therapy in pain relief during delivery.

Methods This is a scoping review in the PubMed, LILACS, Cochrane, VHL, PEDRO, and SciELO databases, through the descriptors *electric stimulation, transcutaneous* and *labor, obstetric* and their synonyms.

Results A total of 263 studies were identified, of which 54 duplicates were excluded. After sorting by titles and abstracts, there were 24 articles for reading, remaining 6. The six studies evaluated the reduction of pain through the visual analogue scale (VAS).

Conclusion The findings indicate that the use of TENS as a nonpharmacological strategy for pain relief in labor has positive results.

Keywords

- transcutaneous nervous electrical stimulation
- labor pain
- birth work

Resumo

Objetivo Mapear evidências em saúde sobre a eficácia da terapia por estimulação elétrica nervosa transcutânea (TENS, na sigla em inglês) no alívio da dor durante o parto.

Métodos Trata-se de uma revisão de escopo nas bases de dados PubMed, LILACS, Cochrane, VHL, PEDRO e SciELO, através dos descritores *estimulação eléctrica, transcutânea* e *trabalho, obstetrícia* e os seus sinônimos.

Resultados Foram identificados 263 estudos, dos quais 54 duplicados foram excluídos. Após a classificação por títulos e resumos, 24 artigos foram selecionados para leitura, restando 6. Os seis estudos avaliaram a redução da dor através da escala visual analógica (EVA).

Conclusão Os resultados indicam que a utilização de TENS como estratégia não farmacológica para o alívio da dor no parto tem resultados positivos.

Palavras-chave

- estimulação eléctrica nervosa transcutânea
- dores de parto
- trabalho de parto

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Introduction

Pain during labor is one of the most intense types of pain. This pain is a complex, subjective, and multidimensional phenomenon, which can vary from one person to another, being a physiological response to the sensory stimuli generated mainly by uterine contraction.[1–3] Women who experience high levels of pain during childbirth are at an increased risk of complications.[2]

In order to minimize the discomfort of pain during childbirth, humanized obstetric care should be provided with access by the parturient to pharmacological and non-pharmacological resources for pain relief in this process.[3]

Alternative nonpharmacological methods are recommended by the World Health Organization (WHO) for the care of normal delivery, classifying them as "behaviors that are clearly useful and that should be encouraged".[4]

Although there is a wide range of alternative options, there is still a preference among medical professionals to use in labor anesthetic drugs for pain relief that can cause undesirable effects, such as halting the progression of childbirth and fetal depression. This attitude seems to be contrary to the current expectations of society, which demand safe techniques that guarantee the reduction of labor pain, allowing them to participate actively throughout the work, without any unfavorable repercussions for the mother and the newborn.[4,5]

In this perspective, complementary therapy practices have been used both in the public and in the private health network in order to provide assistance in labor, being a strategy for reducing pain, stress, and cesarean rates, reflecting in the quality of obstetric care provided.[6]

Alternative methods of pain control provide women with the opportunity to have a positive view of the special moment that is the arrival of the child, increasing satisfaction with their experience in labor. Among the nonpharmacological methods of pain relief in childbirth is the application of transcutaneous nerve electrostimulation (TENS).[2,3]

Transcutaneous nerve electrostimulation is a noninvasive, safe physical therapy resource offered to parturients by the physiotherapist during labor.[7,8] The technique basically consists of administering low-voltage electrical impulses or stimuli through electrodes placed on the skin to reduce the painful sensation of labor, delaying or avoiding the need to use pharmacological methods.[6]

A preliminary survey, carried out in 2009 in the Cochrane Database of Systematic Reviews, revealed that TENS does not seem to have any impact (positive or negative) in reducing pain caused by labor due to the evidence being often obtained with weak and inconsistent methods.[9]

Considering the importance of nonpharmacological methods for a successful experience in labor and the need to evaluate the effectiveness of alternative methods, the present work aims to carry out a systematic search strategy (scoping review) in the main databases, over the past 10 years, to map new health evidence regarding the effectiveness of TENS therapy in pain relief during labor.

Methods

A scoping review is a secondary study with the objective of mapping the literature, clarifying the main concepts on the question formulated and presenting the types of evidence that may support the practice on the subject.[10,11]

This review addressed the following research question: what is the available scientific evidence on the effectiveness of transcutaneous nerve electrical stimulation (TENS) as a non-pharmacological therapy for pain relief during labor? The question and the main elements of the search for this study were elaborated from the PCC (Population, Concept and Context) strategy[11]. In this research, the following definitions were used: P - pregnant women, C - TENS and C - labor.

The search was performed electronically in the PubMed, Latin American and Caribbean Center Health Sciences Literature (LILACS), Cochrane, Virtual Health Library (VHL), PEDRO, and SciELO databases by means of the descriptors and their synonyms, according to the Health Sciences Descriptors (-DeCS/Mesh) with the combination by means of the Boolean terms AND and OR. The search was performed in July 2021 and the descriptors *electric stimulation, transcutaneous* and *labor, obstetric* were used, as well as their synonyms.

Clinical trials that addressed the TENS intervention with pain relief during labor as an outcome published in the last 10 years (covering the period from 2011 to 2021) in Portuguese, English, and Spanish were included,

The exclusion criteria were articles that did not focus on the use of TENS during labor to relieve pain, that examined the use of TENS for pain relief after cesarean section, that analyzed the effects of TENS on the strength of uterine contractions during induction of labor, that were performed for methodological reasons, that were not clinical trials, and those which we did not obtain access to the full text.

Results

A total of 264 studies were identified. Of this total, 54 duplicate articles were excluded, resulting in 209 articles for analysis. After sorting by titles and abstracts according to the eligibility criteria, 24 articles were left to be read in full text, with 19 articles excluded at this stage. Finally, six articles were selected and included for answering the guiding questions of the present scoping review (►**Figure 1**). The entire selection process of the articles was carried out through the site https://www.covidence.org.

Among the studies included, 2 (33,33%) were published in 2010, 1 (16,66%) in 2016, 1 (16,66%) in 2017, 1 (16,66%) in 2018, and 1 (16,66%), the most current to be included, was published in 2021.

The 2 studies published in 2010 carried out nonrandomized controlled clinical trials evaluating the effect of TENS on pain relief in labor, dividing the participants into 2 groups, 1 group receiving TENS as an intervention and the other being a control group.[12,13] The first study evaluated 20 parturients and found that 80% of pregnant women who used TENS felt strong pain relief during labor.[12] The second investigated 305 women and found that there was 68% of pain relief during

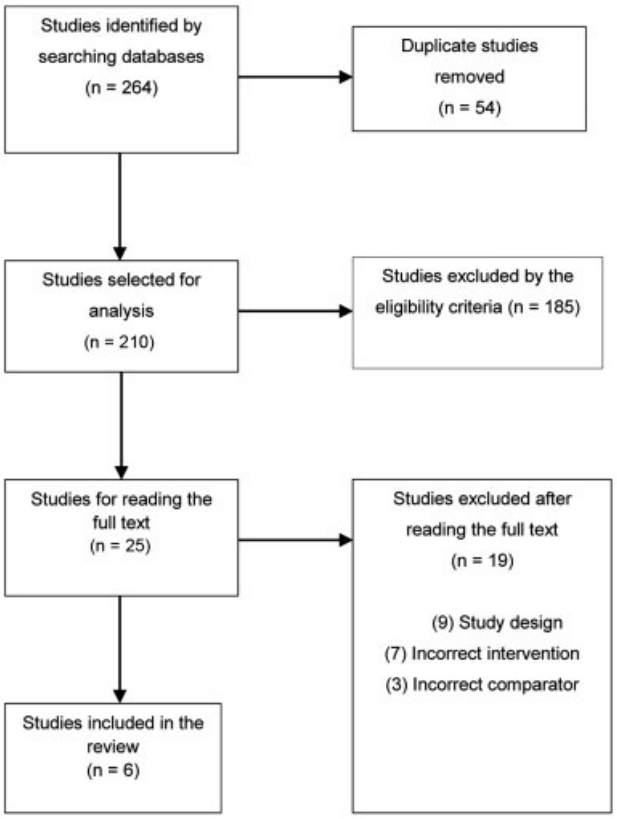

Fig. 1 Flowchart of electronic search and inclusion of articles.

labor in the group treated with TENS.[13] Both studies evaluated pain reduction using the visual analogue scale (VAS).

In 2016, a randomized clinical trial, blinded and with blind allocation, with 46 parturients was carried out. It was divided into an experimental group, with the application of TENS, and a control group, in which physical therapists guided and answered questions from parturients, in addition to routine obstetric care.[14] After the interventions in both groups, another investigator evaluated the pain through the VAS. Transcutaneous nerve electrostimulation reduced pain in the experimental group, decreasing an average of 11 mm (standard deviation [SD] = 18) until the end of the intervention. Through the VAS, 69% of the control group and 70% of the experimental group classified pain as 37 before the intervention. After the intervention, 34% of the experimental group classified pain as 37, as opposed to 83% of the control group, showing a significant reduction in pain during labor (RR: 0.42; 95% confidence interval [CI]: 0.23–0.76).

In the 2017 randomized, nonblind clinical trial, 90 nulliparous women were included and divided into the following groups: intervention (TENS activated), placebo (TENS deactivated), and control (TENS not used), each group consisting of 30 participants. One hour after the intervention, pain intensity was significantly lower in the experimental group compared with the placebo and control groups. The mean pain intensities assessed by the VAS 1 hour after the intervention were 6.4 (SD = 2.14), 8.4 (SD = 1.38), and 8.2 (SD = 1.6), for the experimental, placebo, and control groups, respectively.[15]

The 2018 study conducted a randomized, double-blind, placebo-controlled clinical trial looking at the effect of different doses of TENS for pain relief during labor.[2] In this study, 63 women were recruited, divided into active TENS 1 ($n = 21$), active TENS 2 ($n = 21$), and placebo ($n = 21$) groups. The active TENS 2 group obtained the best performance in pain reduction, with clinically relevant results in the VAS (-2.9; 95%CI: - 4.1– - 1.6; $p < 0.001$). There was more satisfaction in the active TENS groups than in the placebo group. The analysis between the groups highlighted a significant decrease in pain, measured on the VAS, in the active TENS 2 group compared with the TENS 1 group and also compared with the placebo group.

The most recent study, from 2021,[16] conducted a single-blinded randomized clinical trial with 326 low-risk pregnant women who anticipated spontaneous vaginal delivery. The experimental group had 161 participants and the control group had 165 participants. The VAS was used for pain assessment, and high-tech TENS was used at 30, 60, and 120 minutes and from 2 to 24 hours after delivery. The experimental group had statistically significantly lower mean VAS scores at different times and the experimental group showed statistically significant shorter duration of the active phase of labor than the control group. The authors concluded that the use of TENS had satisfactory results both for reducing pain and for shortening the active phase of labor.

►**Tables 1** and **2** present the articles according to authors, year of publication, main objectives, intervention, main results, and conclusions.

Discussion

In the present scoping review, the results of the six studies were favorable regarding the use of TENS in pain relief during labor. The articles included in the present review are described below, outlining the main outcome, which is pain relief.

Most studies (75%) included in an integrative review conducted by Mafetoni et al.[17] in which they applied TENS for pain relief during labor demonstrated increased pain reduction responses compared with the placebo group, corroborating the findings of the present study.

In the open and randomized clinical trial conducted by Orange et al.[5] that evaluated 22 women in labor, it was found that the application of TENS in the early stages of labor delays the need for additional analgesic techniques, confirming the findings of the present scoping review.

The main advantage of using TENS in labor would be the absence of the need to use drugs or the shorter time of exposure of the mother and fetus to drugs used for pain relief, which could reduce the incidence of undesirable effects, such as halting the progression of childbirth and fetal depression.[5]

Knobel et al.[18] conducted a controlled, randomized and triple-blind (neither the parturients, the health team, nor

Table 1 Description of the articles included in the scoping review

Authors and year	Objective	Intervention	Results	Conclusions
Abreu et al. (2010)[12]	To evaluate the effectiveness of TENS in pain relief during labor.	Experimental group: Application of TENS by means of a pair of electrodes at the level of the T10-L1 vertebrae and another pair at the level of S2-S4. Control group: TENS with subliminal stimulus.	TENS provided pain relief in 80% of the cases, assessed by the VAS. There were no cases of pain relief in the control group.	TENS is effective in relieving pain during labor.
Peng et al. (2010)[13]	To investigate the effectiveness of TENS to reduce pain in labor when applied to four specific acupuncture points.	Experimental group: Application of TENS in four specific acupuncture points (LI4, PC6, BL19, and BL21). Control group: without any intervention.	There was 68% of pain relief during labor in the group treated with TENS, measured by the VAS	The application of TENS to acupuncture points LI4, PC6, BL19, and BL21 is an effective, noninvasive method for pain control during labor.
Santana et al. (2016)[14]	To assess whether TENS relieves pain or changes its location in the first phase of labor and whether TENS delays the request for neuraxial analgesia.	Experimental group: Application of TENS by means of a pair of electrodes at the level of the T10-L1 vertebrae and another pair at the level of S2-S4. Control group: physiotherapist for guidance and answer questions.	TENS reduced pain in the experimental group, assessed by the VAS, but did not change its location or distribution. Pharmacological analgesia was postponed for 5 hours after TENS intervention, compared with the control group.	TENS significantly reduces pain in labor and postpones the need for pharmacological analgesia.
Shahoei et al. (2017)[15]	To investigate the effect of TENS on labor pain among nulliparous women.	Experimental group: Application of TENS by means of a pair of electrodes at the level of the T10-L1 vertebrae and another pair at the level of S2-S4. Placebo group: TENS off (no electrical stimulus). Control group: no TENS, just routine care and guidance.	TENS provided a significant reduction in pain during labor and also 4 hours later, assessed by the VAS. TENS had no placebo effect.	TENS reduces pain during labor and 4 hours afterwards.
Báez-Suárez et al. (2018)[2]	To investigate the effect of pain relief by applying TENS in labor.	Experimental group: Application of TENS by means of a pair of electrodes at the level of the T10-L1 vertebrae and another pair at the level of S2-S4. Placebo group: TENS off (no electrical stimulus).	TENS provided a greater degree of pain relief in the active TENS group than in the placebo TENS group.	TENS is a safe and effective nonpharmacological option for pain relief during labor.
Njogu et al. (2021)[16]	To determine the effects of TENS therapy in the first stage of labor.	Experimental group: Application of TENS by means of a pair of electrodes at the level of the T10-L1 vertebrae and S2-S4, in addition to a pair in each arm. Control group: routine obstetric care.	The experimental group had lower mean pain scale scores than the control group and shorter duration of the active phase of labor.	TENS can be used as a nonpharmacological therapy to reduce pain and shorten the active phase of labor.

Abbreviation: TENS, transcutaneous nerve electrical stimulation; VAS, visual analogue scale.

Table 2 Characteristics of the studies included in the present review

Authors	Participants	Age range	Study methodology	Blinding	Subject allocation	Eligibility criteria
Abreu et al. (2010)[12]	20	18–26	Nonrandomized controlled trial	No	Numeration of medical records (medical records with even endings were allocated to the TENS group, and those with odd endings to the control group)	Parturients between 18 and 30 years old; term pregnancy; active stage of labor; single viable fetus in cephalic presentation.
Peng et al. (2010)[13]	305	24–30	Nonrandomized controlled trial	No	Pregnant women who requested analgesia were enrolled in the TENS group and others were assigned to the control group	Pregnant women who dismissed epidural analgesia; term pregnancy; primiparous with singleton; fetal cephalic presentation; active stage of labor; have no obstetric complications.
Santana et al. (2016)[14]	46	18–21	Randomized controlled trial	Evaluator	Computer-generated random assignment list	Primiparous women do not have obstetric complications; term pregnancy; single fetus in cephalic position; spontaneous onset of labor; no use of oxytocin or other medications from hospital admission until randomization.
Shahoei et al. (2017)[15]	90	16–36	Randomized controlled trial	No		Primiparous; single fetus in cephalic position; pregnancy age of 38-42 weeks; active phase of labor; intact membranes.
Báez-Suárez et al. (2018)[2]	63	22–35	Randomized controlled trial	Double-blind	Computerized random number generator	Age $>$ 18 years old; women with a low-risk pregnancy; 37–42 weeks gestation age; single fetus.
Njogu et al. (2021)[16]	326	18–29	Randomized controlled trial	Evaluator	Computer-generated list	37–42 weeks gestation age; primipara and multipara with no complications; active stage of labor; single viable fetus in cephalic presentation.

Abbreviation: TENS, transcutaneous nerve electrical stimulation.

the researcher knew which group each participant belonged to) with 60 parturients, using TENS to relieve pain during labor. They concluded that there was significant pain relief in more than half of the women who received real stimulation than in those who received placebo stimulation.[18]

Angelo et al.[19] carried out a systematic review on the effects of physical therapy resources applied to patients suffering from pain during labor. They found a variety of methods, such as massage therapy, TENS, ball exercises, immersion bath, breathing exercises, acupuncture, ambulation, mobility, and shower. They concluded that, in their majority, nonpharmacological methods contributed in a beneficial way to reducing the pain of the parturient.[19]

However, the systematic review by Dowswell et al.,[9] in which 17 studies were analyzed involving 1,466 women, concluded that there is no strong evidence that women who received TENS had reduced pain in childbirth compared with control groups. These findings differ from the results of the present scoping review.[9]

In line with the findings of Dowswell et al.,[9] the systematic review by Mello et al.[1] confirms that there was no statistically significant difference between groups in pain relief during labor (combined RR = 1.09; 95%CI = 0.72–1.65), which indicates limitations in the evidence that TENS reduces pain during labor.[1,9]

It is observed that, over the years, clinical trials developed to evaluate the effectiveness of TENS in reducing pain during labor have limitations in terms of methodological rigor. The controlled clinical trial of Abreu et al.[12] identified by the present review, used the criteria of numbering medical records for the allocation of participants, presenting a high risk of selection bias and of being able to interfere in the results. It is known that it is extremely important to ensure adequate randomization and confidentiality in the allocation of patients, which is the best way to minimize selection bias and to ensure more robust evidence.

The clinical trial by Njogu et al.[16] used a simple random assignment technique in a 1:1 ratio with researcher blinded to one group; the workers and researchers in the gynecology and obstetrics department knew the treatment group, and only the statisticians analyzed the blinded data. However, the study has limitations that may compromise the reliability of the results, such as simple blinding and inclusion of primiparous and multiparous women without specifying the proportionality of distribution in the groups.[16]

There is also weakness in relation to blinding clinical trials, where only the studies of Santana et al.,[14] Báez-Suárez et al.,[2] and Njogu et al.[16] performed some kind of blinding, which compromises the power of evidence in these studies.[2,14,16–19]

Despite the mentioned limitations, it is worth highlighting the importance of the studies carried out to evaluate the effectiveness of nonpharmacological methods that are encouraged by the WHO because they are strategies used in labor to increase tolerance to pain and to reduce undesirable effects related to drug therapy, and should be further explored with a deeper analysis of the context in which they were developed.

Conclusion

After an updated, transparent, and thorough search, and the analysis of the studies with the best levels of evidence, the findings of the present scoping review indicate that the use of TENS as a nonpharmacological strategy for pain relief in labor has positive results compared with the placebo intervention group, and it is possible to observe its effects even hours after its use; however, most studies still present inadequate methodological rigor, presenting a risk of bias regarding the evaluation of the effectiveness of the therapy. Another point is the method used for pain assessment in the studies, because pain is a personal experience, which makes it difficult to define and measure it. The perception of pain is individual, subjective, and influenced by the intensity and duration of exposure, the physical and emotional condition of the woman, her previous experiences, cultural and environmental factors, and several aspects can change the assessment of pain and influence the results of the studies. Therefore, for a better evaluation of the effects of this therapy, it is suggested the design of triple-blinded randomized clinical trials with confidentiality of allocation, showing clarity in the parameters used, with an appropriate selection of participants in order to reduce the differences related to experiences with pain in labor, and associated with other scales for pain assessment in order to measure more reliably the relief of pain in parturients. The present scoping review allowed mapping the scientific evidence available in the last 10 years that describe the action of TENS as a nonpharmacological therapy for pain relief during labor. New, more elaborate studies regarding the method and that may compare TENS with other nonpharmacological pain control therapies that have proven results are suggested.

Conflict of Interests

The authors declare that there is no conflict of interest.

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Effects of the COVID-19 Pandemic on Gynecological Health: An Integrative Review

Efeitos da pandemia de COVID-19 na saúde ginecológica: Uma revisão integrativa

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Abstract

Objective To analyze the existing scientific literature to find out if the coronavirus disease 2019 (COVID-19) pandemic has an effect on gynecological health.

Search Strategy We performed an integrative review of articles published between April 2020 and April 2021 on the PubMed, SciELO, and LILACS databases, using *COVID-19* and the following relevant terms: *Menstrual change*; *Ovarian function*; *Violence against women*; *Contraception*; *HPV*; *Mental health*; and *Urogynecology*.

Selection Criteria Among the eligible studies found, editorials and primary research articles, which describe the dynamics between severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection (the cause of the COVID-19 pandemic) and gynecological health, were included.

Data Collection and Analysis Through qualitative synthesis, data were extracted from the included publications and from guidelines of national and international societies of gynecology.

Main Results The 34 publications included in the present study showed that some factors of the SARS-CoV-2 infection, and, consequently, the COVID-19 pandemic, might be associated with menstrual abnormalities, effects on contraception, alterations in steroid hormones, changes in urogynecological care, effects on women's mental health, and negative impact on violence against women.

Conclusion The COVID-19 pandemic has significantly impacted the health of women. The scientific community encourages the development of recommendations for specialized care for women and strategies to prevent and respond to violence during and after the COVID-19 pandemic.

Keywords

- COVID-19 pandemic
- menstrual change
- ovarian function
- SARS-CoV-2
- violence against women
- contraception
- urogynecology

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Resumo

Objetivo Analisar a literatura científica existente para saber se a pandemia de doença do coronavírus 2019 (*coronavirus disease 2019*, COVID-19, em inglês) afeta a saúde ginecológica.

Estratégia de Pesquisa Realizou-se revisão integrativa de artigos publicados entre abril de 2020 e abril de 2021 nas bases de dados PubMed, SciELO e LILACS, utilizando *COVID-19* e os seguintes termos: *Menstrual change*; *Ovarian function*; *Violence against women*; *Contraception*; *HPV*; *Mental health*; e *Urogynecology*.

Critério de Seleção Entre os estudos elegíveis encontrados, foram incluídos editoriais e artigos de pesquisa que descrevem a dinâmica entre a infecção por coronavírus da síndrome respiratória aguda grave (*severe acute respiratory syndrome coronavirus*, SARS-CoV-2, em inglês), a causa da pandemia de COVID-19, e a saúde ginecológica.

Coleta e Análise de Dados Por meio de síntese qualitativa, os dados foram extraídos das publicações incluídas e de diretrizes de sociedades nacionais e internacionais de ginecologia.

Resultados Principais As 34 publicações incluídas no estudo mostraram que alguns fatores da infecção por SARS-CoV-2, e, consequentemente, da pandemia de COVID-19, podem estar associados a alterações menstruais, influências na contracepção, alterações em hormônios esteroides, adaptações na assistência uroginecológica, influência na saúde mental da mulher, e impacto negativo na violência contra a mulher.

Conclusão A pandemia de COVID-19 teve um impacto significativo na saúde das mulheres. A comunidade científica incentiva o desenvolvimento de recomendações para o atendimento especializado a mulheres, e estratégias para prevenir e combater a violência durante e após a pandemia de COVID-19.

Palavras-chave

- pandemia de COVID-19
- alteração menstrual
- função ovariana
- SARS-CoV-2
- violência contra as mulheres
- contracepção
- uroginecologia

Introduction

The world is currently in the second year of the coronavuirus disease 2019 (COVID-19) pandemic. Globally, infections by severe acute respiratory syndrome coronavirus (SARS-CoV-2) are continuously rising, with an increasing death toll. Worldwide, the public health response to the pandemic was the imposition of restrictions to minimize the spread of the virus, prevent health system overload, and counter the deficit of personal protective equipment.[1]

Although in most cases the symptoms are mild or absent, SARS-CoV-2 infection can lead to serious acute respiratory disease and multiorgan failure. The research community responded to this new disease with a high level of transparency and data sharing, to better understand its origin, pathophysiology, epidemiology and clinical manifestations, with the ultimate goal of developing vaccines, mitigation strategies, as well as potential therapies.[1]

Many studies have been performed with different approaches to try to understand the impact of COVID-19 on the maternofetal binomial. Evidence about COVID-19 and pregnancy has been increasing rapidly since December 2019. However, few studies have raised concerns specifically about gynecology.

The pandemic has significantly impacted gynecological health, causing great mental and physical anguish and huge implications on the overall health of females.[1–5] The aim of the present review is to summarize the current knowledge on the COVID-19 pandemic in gynecology, including what is known about the potential impact of the disease not only on menstrual abnormalities or steroid hormones, but also on reproduction assistance, fertility care, urogynecological assistance, and the dynamics of interpersonal relationships, including, unfortunately, violence against women.

Methods

The authors performed an integrative review of articles published between April 2020 and April 2021 on the PubMed, SciELO, and LILACS databases, using *COVID-19* and the following relevant terms: *Menstrual change*; *Ovarian function*; *Violence against women*; *Contraception*; *HPV*; *Mental health*; and *Urogynecology*. The present study is a narrative review of the literature available on the coronavirus so far, focusing on gynecological outcomes and strategies, aiming to gather information to safely approach women with suspected or confirmed COVID-19. There were no restrictions regarding language.

Among the eligible studies found, the authors included editorials and primary research articles which describe the dynamics between the SARS-CoV-2 infection (the cause of the COVID-19 pandemic) and gynecological health. Through qualitative synthesis, data were extracted from the included publications and from guidelines of national and international societies of gynecology.

Results

►**Table 1** shows relevant outcomes regarding women's health during the COVID-19 pandemic according to the

Table 1 Main findings on women's health disorders and issues associated to the COVID-19 pandemic

Author(s)	Women's health subarea	Disorder/issue	Main findings/ recommendations
Godin[3] Sharma et al.[4] Sánchez et al.[5] UN Women[6]	Women's mental and physical health	Violence against women	Support care for crisis management/ enlargement of judicial service and health care
UN Women[6]	Women's mental health	Family disruptions	Effects on family dynamics/counseling
Phelan et al.[7]	Endocrine Gynecology	Menstrual change	Worsening premenstrual symptoms; menstrual volume changes/counseling and treatment availability
Li et al.[8]	Women's mental health	Sexual health	Reduced libido/changes in partner relationships/counseling
Mauvais-Jarvis et al.[9] Al-Lami et al.[10] Cattaneo et al.[11] Cagnacci et al.[12] Cagnacci and Xholli[13] Yi et al.[14]	Endocrine Gynecology	Menopause	Changes in the immune response and risk of venous thromboembolism/hormonal therapy should be discontinued
Cagnacci et al.[12] Ramírez et al.[15] Fruzzetti et al.[16] Pires et al.[17]	Endocrine Gynecology	Contraception	Risk of venous thromboembolism in users of contraception during the COVID-19 pandemic/contraception availability and changes in selected prescriptions if necessary
Gemzell-Danielsson et al.[18] Council of Europe[19] United Nations[20] Brunson[21] Sawhill and Guyot[22] Makins et al.[23] Mantha et al.[24]	Endocrine Gynecology	Reproduction	Difficulties in the access to contraception and increase in unintended pregnancies/contraception availability and encouragement of the use of LARCs.
Ciavattini et al.[25,26] ASCCP[27] BSCCP[28] ACOG[29] Arbyn et al.[30]	Oncological Gynecology	HPV and cancer prevention	Maintenance or postponement of vaccination, screening programs and treatment for cervical cancer according to the flexibility of each country's restrictions.
Dvash et al.[31]	Emergency women's care	Decrease in emergency room arrivals	Strategies to recognize and improve assistance for this secondary impact of the pandemic
Grimes et al.[32] Ferreira et al.[33]	Urogynecology	Pelvic floor disorders	Telephysiotherapy and conservative management

Abbreviations: ACOG, American College of Obstetrics and Gynecology; ASCCP, American Society for Colposcopy and Cervical Pathology; BSCCP, British Society for Colposcopy and Cervical Pathology; COVID-19, coronavirus disease 2019; HPV,human papillomavirus; LARCs, long-acting reversible contraceptives; UN Women, United Nations Entity for Gender Equality and the Empowerment of Women.

available evidence-based studies, as well as the recommendations made by the authors of the most relevant published studies on COVID-19 and women's disorders.

Discussion

After the World Health Organization (WHO) characterized the COVID-19 outbreak as a pandemic on March 11, 2020, governments and authorities around the world introduced or intensified restrictive social distancing measures to reduce the spread of the infection. These measures have impacted family dynamics through their effects on income, interpersonal bonds, well-being, and mental health.[6]

Violence against women and girls is a human rights violation, and remains a major threat during health emergencies and epidemics. During the COVID-19 pandemic, unfortunately, there has been a remarkable increase in cases of domestic violence against women, with reports from countries such as China, the United Kingdom, the United States, France, Cyprus, Argentina, and Singapore,[3] which has alerted several organizations, researchers, and civil society representatives.[5,6] There have also been reports of sexual exploitation, with landlords physically exploiting female tenants in exchange for cheaper accommodations. The factor attributable to this rise could be the daylong stay at home and the failure to escape an abusive partner, social isolation, the absence of coordination among health, social, and

judicial services, and the lack of support care for crisis management.[3,4]

Another change that greatly impacts women's health during the pandemic can be observed in their menstrual cycles. It is known that periods of stress and psychological distress, like the current pandemic, can affect women's menstrual cycles. The long-term health implications of this are yet to be determined, and future studies should address it. In September 2020, in Dublin, Ireland, Phelan et al.[7] conducted a study in which 1,031 women of reproductive age were invited to complete an anonymous digital survey via social media. A total of 441 (46%) respondents reported changes in their menstrual cycle, 483 (53%) reported worsening premenstrual symptoms, and 467 (45%) reported reduced libido since the beginning of the pandemic.[7]

In a retrospective, cross-sectional study,[2] blood samples from the early follicular phase were tested for sex hormones and anti-Müllerian hormone. Disease severity appears to correlate with greater menstrual changes. Patients with comorbidities such as diabetes, liver disease and malignant tumors, as well as severe cases of confirmed COVID-19 (34% versus 8% of mild or asymptomatic cases) had greater alterations in the menstrual cycle, mainly prolonged cycles or a decrease in volume.[2] However, the average sex hormone concentrations and ovarian reserve did not change significantly in women of child-bearing age with COVID-19. From a biological standpoint, it is plausibe that a suppression in the function of the ovaries causes hormonal changes responsible for menstrual disorders in these patients affected by the severe form of COVID-19.[2]

Another study[8] assessed the impact of COVID-19 on partner relationships and sexual and reproductive health in China. From a total of 967 participants, 22% reported a decrease in sexual desire; 41% experienced a decrease in the frequency of sexual intercourse; 30% reported an increase in the frequency of masturbation; and 31% reported a deterioration in partner relationships during the pandemic. Besides that, outpatient services in general gynecology, human reproduction, low-risk prenatal care, family planning, and even access to contraceptives may have been disrupted during the COVID-19 pandemic.[8]

According to the data observed so far, it seems that females may show a greater protective response against severe cases of COVID 19 than males. The more favorable immune response may be due to the influence of sex steroids (estrogen, progesterone and androgens) on the patient's immunomodulation and anti-inflammatory response.[9] In addition, the scientific community has already described situations in which the presence of female steroid hormones may provide some advantage over male steroid hormones in the immune response to infectious diseases or aggravations of diseases such as those that are cardiovascular. The same immune response favored by estrogens, progesterone and androgens seems to have occurred in severe cases of COVID-19, which was not maintained in postmenopausal women exposed to COVID-19.[10]

If, on the one hand, natural female hormones can hinder the mortality of women by severe COVID-19, on the other hand, exogenous estrogens can increase clotting factors and the risk of thromboembolic events, with a potential consequent increase in mortality, in postmenopausal hormonal therapy users. Hospitalized patients with severe COVID-19 have an activated coagulation demonstrated by high levels of D-dimers (fibrin degradation products), which, in combination with hormonal therapies in postmenopausal women, can favor the development of thromboembolic events. These and other findings even motivated the administration of anticoagulants such as heparin in many protocols for these cases of high levels of D-dimer, in an attempt to reduce mortality, both in men and women.[11,12]

In view of these findings, there is a recommendation to suspend hormonal therapies in peri- and postmenopausal women with COVID-19 infection.[12–15] It is advisable to inform the patient that irregular bleeding may occur with the discontinuation of the hormonal therapy. Shifting from oral to transdermal estrogens (patch, gel, spray) may be considered, but the management of each case should be individualized.[12] When restarting the therapy, due to the lower risk of thromboembolic events, transdermal estrogens should be preferred.[12]

The same clinical reasoning can be applied to combined hormonal contraceptives. The use of contraceptive methods that contain only progestogens (oral, intrauterine devices, and implants) is not associated with an increased risk of venous thromboembolism.[12,15] It is recommended that, for users of hormonal therapy or combined oral hormonal contraception who suffer from mild cases of COVID-19 and wish to maintain the use of hormones, is it possible to do so, and, based on the risk factors for venous thromboembolism, and individualizing the management of the cases, the prophylactic use of heparin must be suggested.[15,16] However, low molecular weight heparin should not be used indiscriminately, but under medical supervision, aiming to reduce the risk of venous thromboembolism.[15,16]

In addition, in COVID-19 patients with mild symptoms and without severe risk factors, it is also wise to replace combined oral hormonal contraception by contraception containing progestogen alone. Regarding hormonal therapy, when oral, it is recommended to be replaced by transdermal.[16] It is up to gynecologists, like other health professionals, to provide guidance on general measures to prevent the pandemic, including social isolation, use of masks, and hygiene habits such as washing hands with soap and water or using alcohol gel regularly. Gynecologists should also be mindful of recommendations for hormonal therapy and contraception for their patients, whether during or after the pandemic.[17]

The pandemic can affect gynecological health not only directly through the SARS-CoV-2 infection, but also through the indirect impact in terms of access to assistance or changes in the dynamics of relationships. Difficulty in accessing health systems during the pandemic has also impacted basic family planning rights. The pandemic may have negatively impacted the basic access to contraceptive care, one of the universal women's health services that minimize gender inequality and grant female autonomy. The secondary impact of the

pandemic was observed not only in the difficulty in accessing family planning assistance, but also in effects on the production and transportation of contraceptive products, with the consequent unavailability of state-of-the-art contraceptives, favoring unplanned pregnancies.[1,4,18]

In this context, the recommendation of long-acting reversible contraceptives (LARCs) also provides positive social assistance, without the need to go frequently to pharmacies or public centers to get contraceptive, that was evident in the pandemic. By using LARCS, women have less need to access the outpatient family planning system, which, during the pandemic, favored greater health protection and lower economic impact for both the patient and the health system, with possible redistribution of funds to areas related to the fight against COVID-19.[18,19]

Therefore, gynecologoical societies, by encouraging access to LARCs, aligned themselves with the pandemic isolation scenario. Unlike short-acting methods such as oral contraceptive pills, LARCS provide effective contraception for years after a single intervention that can mitigate concerns regarding access to and availability of contraceptive services.[18,19] In the context of the COVID-19 pandemic, the therapeutic benefits of LARCs provide an option for treating women with conditions such as heavy menstrual bleeding without an organic cause or dysmenorrhea that minimizes exposure to the hospital environment and reduces lengthy waits for surgical appointments.[18,19]

In the field of Oncological Gynecology, the scientific community recognized the high level of concern with outpatient care during the COVID-19 pandemic. Cancer prevention and early diagnosis are basic pillars of gynecological care; unfortunately, they had to be postponed or suspended during the peak of the COVID-19 health crisis due to changes in the structures of medical institutions. In relation to cervical cancer, which fortunately presents an evolution that is not very rapid evolution, several societies supported the momentary postponement of follow-ups at the height of the pandemic, without affecting the safety of the disease's evolution. These recommendations should to be applied at the discretion of the services, with respect to the regionality and individuality of each case. But overall, societies such as the European Federation for Colposcopy (EFC) and the European Society of Gynecological Oncology (ESGO), have advised that human papillomavirus (HPV) vaccination, screening, colposcopy and outpatient lower genital tract surgery programs, as well as follow-up, should be rescheduled to a safer moment of the health crisis, without effectively compromising the safety of these measures.[25,26] Cervical cancer screening and HPV vaccination may continue in countries with no cases or sporadic cases of COVID-19, and should be delayed in countries with clusters of cases and/or community transmission of COVID-19 to minimize the progression of the pandemic.[25]

In addition, according to the EFC and ESGO, in case of suspension of elective diagnostic and therapeutic procedures, the timing of the management of abnormal histopathological results in cervical biopsies is dictated by the risk of progression of preinvasive lesions. Those patients may need a subsequent diagnostic procedure or outpatient surgical treatment (such as cervical, vaginal, or vulvar excision) or a complete assessment to plan the staging and treatment for invasive cancer.[25] Patients with a histopathologic diagnosis of invasive disease from cervical, vaginal, or vulvar biopsy should be contacted within two weeks. Additionally, patients with symptoms suggestive of lower genital tract cancers should also be evaluated within two weeks. A histopathological diagnosis of a low-grade intraepithelial lesion from a cervical, vaginal, or vulvar biopsy/excision enables physicians to postpone the contact up to 12 months.[25]

Another relevant consequence of the pandemic was the decrease in the search for assistance in gynecology emergency rooms. The reduced flow of patients seeking urgent care in gynecology may have screened cases that are really relevant for care, with real need, but, on the other hand, it may have decreased assistance in really urgent cases such as hemorrhagic, infectious acute abdomen, pelvic inflammatory disease, among other situations of emergency care.[31,32] An example of this contingency of emergency care in gynecology was evidenced in a retrospective cohort study that assessed the impact of the COVID-19 pandemic on the diagnosis, treatment, and complications of women who presented with tubal ectopic pregnancy.[31] The authors found a higher rate of ruptured ectopic pregnancy, with ultrasonographic evaluation of more cases of high volume of fluid in the abdomen during the COVID-19 pandemic than before (53% versus 17%; $p = 0.01$).[31] Evidence may have pointed to this change in behavior in seeking assistance in gynecology emergency rooms, but data are still very limited.

Likewise, the management of female pelvic floor disorders such as pelvic organ prolapse and urinary incontinence was a challenge due to the COVID-19 pandemic. Multidisciplinary care in urogynecology with pelvic physiotherapy in outpatient or surgical care had to be readapted and urogynecologists faced challenges to safely continue their work, considering the adoption of social distancing measures during the pandemic. Some guidelines have already been published by urogynecology associations; however, the recommendations should be applied at the discretion of the governments of each country, and according to each moment of the health crisis and each individual case.[32,33] General measures, behavioral therapies, medical and physiotherapy guidelines added to the conservative treatment were valuable as first-line treatments, often virtual. Certain situations required different treatments in the virtual environment, while others required a personal visit, despite the risks of COVID-19 transmission. Even after the climax of the health crisis, with the possibility of returning to surgical treatments, the multidisciplinary conservative approach is recommended as the first line of treatment to continue care in this area even during and after the COVID-19 pandemic, with the perspective of improving the quality of life of these patients.[32,33]

In summary, women's health and the COVID-19 pandemic are extremely linked; however, the impact of the pandemic on assistance and public health strategies is not yet clear. The strength of the study is a review focused on gynecology. Due

to the nobility of the materno-fetal binomial, most of the articles published on an urgent basis during the pandemic were directed to maternofetal care. The gynecological patient deserves attention with a collection of studies specifically aimed at health care, not only Obstetrics but also in Gynecology, for non-pregnant women associated with the pandemic.

A limitation of the study is the non-systematic methodology. The authors believe that the limitation of the non-systematized methodology does not detract from the study because the objective was to shed light on women's health care during and after the pandemic. Unfortunately, due to the scarcity of randomized studies on COVID-19 and women's health, far from establishing guidelines, the authors only suggest a possible way of assisting women during and after this moment of health challenge. Besides that, the academic articles report the need to think about strategies during and after the pandemic, given the probability that the vulnerable conditions of women will continue, mainly related to violence. As the WHO Director General has stated in his COVID-19 press briefings, "No one will be safe unless everyone is safe".[34]

Conclusion

This virus has reminded us that we are all inexorably linked in our common humanity. So far, in a way that is not yet fully clear, the COVID-19 pandemic affects gynecological health. The provision of effective women's health care strategies around the world will result in a healthier future for all. In addition, humanization and empathy in gynecological care, as in any other field, are always welcome, especially in times like those of a pandemic. Gynecological measures and guidelines are encouraged to safeguard the sexual and reproductive health of young people during this pandemic. Moving forward, it seems reasonable to hope that, with further developments and ongoing initiatives, access to LARCs will become a possibility for women across the globe even during the pandemic and after it. The authors suggest continuous strong reforms, policies, and measures such as telemedicine, hotlines, and online counseling forums, to counter the social disturbances related to women's health. Finally, based on the multiple tasks of women in society, the authors wish to rephrase the wise statement made by the WHO Director General as "No one will be safe unless every *woman* is safe".

Conflict of Interests

The authors have no conflict of interests to declare.

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Latin American Obstetrics and Gynecology. What is Up with the Journals?

Obstetrícia e Ginecologia da América Latina. O que está acontecendo com os journals?

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Dear Editor,

The Scimago Journal and Country Rank[1] measures and classifies the journals and country scientific indicators from the information contained in the Scopus database.[1,2] This portal uses several indicators such as the SJR, defined as "a measure of the impact, influence, or prestige of the journal. It expresses the average number of weighted citations received in the selected year by the documents published in the journal in the 3 previous years", and the H-index, "the number of articles of the journal (h) that have received at least h citations over the whole period".[1]

The rank of Obstetrics and Gynecology journals from Latin America and their settings are shown in the tables. The first in the SJR rank is the "Jornal Brasileiro de Reprodução Assistida" from Brazil, placed 8,257 in the rank of 25,232 world journal titles on "all subject areas" and 86 of 181 Obstetrics and Gynecology world journals (it is the only journal in Latin America classified in the Q2 SJR Quartile), followed by the "Revista Brasileira de Ginecologia e Obstetrícia" (Q3), 11,399 in the whole rank and 104 in the Obstetrics and Gynecology world journals, but the first in the H-index within this group in Latin America in the year 2020.

Latin American Obstetrics and Gynecology journals classified in the Scimago Journal Rankings are few, and those included are not much cited. Several reasons contribute to this situation, such as that the best quality articles are often sent to international journals, the scarce training in research during residency in these countries, the limitations of the authors and journals for the publication of articles in English to find better visibility, and the difficulty in financing the journals, which in some cases have led to the suspension of some issues or even of the journal itself or to compromise editorial independence when they need to be financed by the pharmaceutical industry.[3] However, the preservation and strengthening of these journals are important for Latin America because they serve as a means of dissemination for its researchers, and, occasionally, they focus on issues of local or regional importance. Obstetrics and Gynecology journals in Latin America should seek to improve the quality, visibility, and access of their publications to try to generate a greater number of citations (►**Charts 1** to **5** are available as ►**Supplementary material**).[1]

Conflict of Interests

The authors have no conflict of interests to declare.

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FEBRASGO POSITION STATEMENT

Perioperative management in gynecological surgery based on the ERAS program

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The National Specialized Commissions on Ginecologic Endoscopy, Endometriosis and Oncological Gynecology of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) endorse this document. The content production is based on scientific studies on a thematic proposal and the findings presented contribute to clinical practice.

Key points

- The Enhanced Recovery After Surgery (ERAS) program is based on perioperative medical optimization, including pre-admission counseling, pain relief, carbohydrate intake, thromboembolism prophylaxis, standard anesthetic protocol, optimized intraoperative fluid administration, recovery of normal gastrointestinal function and early mobilization.
- The main objectives of the ERAS program are to reduce the length of hospital stay after surgery and accelerate the return of patients to normal daily activities without increasing complications, hospital readmission rates and cost.
- The ERAS program has been adopted in several surgical specialties and is associated with faster and safer recovery, better quality of life and patient satisfaction.
- The process of implementing this program involves a multidisciplinary team and all units dealing with the surgical patient.
- Postoperative adverse events, venous thromboembolism is an example, are associated with longer hospital stay and higher mortality rates. Furthermore, factors such as postoperative pain and resumption of bowel function continue to be barriers to early discharge and return to daily activities.
- The program provides safe, high-quality perioperative care and should become standard practice for all women undergoing elective gynecological surgery.

Recommendations

- Pre-admission counseling with information about the surgical procedure, anesthesia and postoperative care should be provided.
- Light meals can be taken up to six hours before surgery and clear liquids can be given up to two hours before surgery.
- Oral carbohydrates should be given two to three hours before induction of anesthesia.
- Bowel preparation should not be routinely performed.
- Perioperative thromboembolic prophylaxis should include dual-modality prophylaxis (heparin, pneumatic compression, and/or compression stockings) depending on the indication in each case.
- Intraoperative fluid overload should be avoided by adopting goal-directed therapy.
- Hypothermia should be avoided with intraoperative use of thermal blankets, circulating-water garments and warming of intravenous (IV) fluids.
- The use of drains, tubes and catheters should be avoided. If indispensable, their use should be limited to the shortest duration needed.
- Incisional infiltration with liposomal bupivacaine or bupivacaine should be incorporated into all ERAS protocols as a component of multimodal analgesia.
- Postoperatively, patients can drink immediately after surgery. Intravenous fluids should be discontinued when patients demonstrate ability to maintain oral hydration with at least 500 mL of oral fluid intake.
- Early mobilization and feeding should be encouraged.
- Multimodal opioid-sparing analgesia is recommended postoperatively, with greater emphasis on non-opioid drugs such as nonsteroidal anti-inflammatory drugs, acetaminophen, gabapentin, and dexamethasone.
- Multimodal approach to prevention and treatment of postoperative nausea and vomiting should be considered, with intraoperative use of at least two agents from different classes of antiemetics.

Clinical context

The Enhanced Recovery After Surgery (ERAS – https://erassociety.org/) program represents a paradigm shift in conventional perioperative care, replacing, when necessary, some traditional practices with evidence-based practices and achieving better surgical quality, clinical improvements and lower costs to the health system. The program is based on perioperative optimization, including preoperative counseling, pain relief, carbohydrate intake, thromboembolism prophylaxis, standard anesthetic protocol, optimized fluid administration, recovery of normal gastrointestinal function, and early mobilization.[1]

The ERAS program has been adopted in several surgical specialties and institutions around the world and was associated with a reduction in the average length of hospital stay and complication rates, in addition to a faster and safer recovery and improvement in quality of life and patient satisfaction.[1] An essential aspect for the implementation of an ERAS program is a multimodal and multidisciplinary approach.[2] The process of implementing this program involves a team composed of surgeons, anesthetists, an ERAS coordinator, nurses, nutritionists and physiotherapists of units that care for surgical patients.[3] Adherence to the program is crucial and the continuous auditing of the care process allows the team to have a comprehensive view of the patient's results (Chart 1).[4]

Chart 1. Principles of the ERAS program

Enhanced Recovery After Surgery (ERAS) Program		
What does it promote?	**Why should it be implemented?**	**What is necessary for implementation?**
- Minimization of the stress response of the operation, controlling perioperative physiology - Surgical medical optimization: preoperative counseling, pain relief, carbohydrate intake, thromboembolism prophylaxis, standard anesthetic protocol, optimized intraoperative fluid administration, recovery of normal gastrointestinal function and early mobilization	- Shorter hospital stay - No increase in rates of readmissions and/or reoperations and/or complications - Faster and safer patient recovery - Better quality of life and patient satisfaction - Reduction of general healthcare costs	- Program Coordinator - Involvement of all units that deal with the surgical patient - Multidisciplinary team working with the patient - Multimodal approach to solving problems that delay recovery and cause complications - Evidence-based scientific approach to care protocols - Change in management through interactive and continuous audits - Minimally invasive surgery whenever possible

Source: Adapted from Silva Filho AL, Santiago AE, Derchain SF, Carvalho JP. Enhanced Recovery After Surgery (ERAS): new concepts in the perioperative management of gynecologic surgery. Rev Bras Ginecol Obstet. 2018;40(8):433-6. doi: 10.1055/s-0038-1668581.[4]

The main objectives of the ERAS program are to reduce the length of hospital stay after surgery and accelerate the return of patients to normal daily activities without increasing complications, hospital readmission rates or cost.[2] To this end, the ERAS program focuses mainly on minimizing the stress response of the operation, maintaining homeostasis, preventing catabolism with consequent loss of protein and muscle strength, in addition to minimizing cell dysfunction.[5]

What are the reasons for adopting the ERAS program in gynecological surgery?

Although most data are extrapolated from colorectal surgery, studies comparing the ERAS program to conventional practices in general gynecological surgery show positive results after implementation of the ERAS program, with a significant reduction in length of hospital stay, without an increase in readmission rates and complications in patients undergoing the practices recommended in the program.[1]

Although most studies related to the ERAS program in gynecology have focused on open surgery, there is growing evidence of safety and feasibility for patients undergoing minimally invasive surgery, including intestinal procedures.[6] A publication by the Royal College of Obstetricians and Gynecologists reviewed the key elements of the ERAS program and suggested that it provides safe, high-quality perioperative care and should become standard practice for all women undergoing elective gynecological surgery.[7]

Special focus is given to patients with gynecological cancer, since returning to the basal physiological level or close to it is essential for them, because it allows the performance of planned adjuvant therapies without delay, resulting in better oncological outcomes.[2] Non-randomized clinical trials involving patients with malignant gynecological neoplasms and the implementation of an ERAS program showed acceptable pain control, reduced hospital stay, adequate patient satisfaction and substantial cost reduction, with no difference in postoperative complications or mortality compared to conventional perioperative care.[8] This suggests the feasibility and safety of implementing the ERAS program in oncological gynecology, with benefits for patients undergoing major abdominal surgery.[4]

What to do before admission?

Pre-admission counseling is recommended with the aim to define expectations about surgical and anesthetic procedures and provide information about a care plan for the postoperative period. Preoperative education and psychological preparation can reduce anxiety and increase patient satisfaction, which can improve recovery and facilitate early discharge.[5]

Health professionals and the nursing staff should identify the patient's expectations regarding hospitalization and show the benefits of early postoperative mobilization and feeding, postoperative pain control goals and length of hospital stay.[1] Guidelines such as the suspension of tobacco and alcohol use, which should occur four weeks before surgery, must be provided during this period. The offer of nutritional support also begins at this moment.[9]

What is the evidence on preoperative fasting and diet release after surgery?

Surgical stress after major surgery induces a marked and well-defined postoperative metabolic response. Using preoperative oral carbohydrates and avoiding prolonged preoperative fasting attenuates these postoperative responses.[5] Several randomized controlled trials have reported that clear fluids can be safely administered up to two hours and a light meal can be administered up to six hours before elective procedures that require general anesthesia (Chart 2).[1,5,10]

Chart 2. ERAS protocol: preoperative recommendations

Fasting: light meal up to six hours before and ingestion of clear liquids up to two hours before elective procedures that require general or regional anesthesia, or sedation/analgesia
Carbohydrate drinks*
Bowel preparation: routine use is not recommended in gynecological surgery
Preemptive analgesia: preoperative use of gabapentin, oral or intravenous cyclooxygenase 2 (COX-2) inhibitors (eg celecoxib) and oral or intravenous paracetamol
If higher risk of venous thromboembolism: dual mechanical prophylaxis (stockings and pneumatic compression) and chemoprophylaxis with low molecular weight heparin or unfractionated heparin

Source: Adapted from Kalogera E, Dowdy SC. Enhanced recovery pathway in gynecologic surgery: improving outcomes through evidence-based medicine. Obstet Gynecol Clin North Am. 2016;43(3):551-73. doi: 10.1016/j.ogc.2016.04.006.[1] Nelson G, Bakkum-Gamez J, Kalogera E, Glaser G, Altman A, Meyer LA, et al. Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery After Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer. 2019;29(4):651-68. doi: 10.1136/ijgc-2019-000356.[5] Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Task Force on preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration. Anesthesiology. 2017;126(3):376-93. doi: 10.1097/ALN.0000000000001452[10]
* Attention to patients with delayed gastric emptying or gastrointestinal motility disorders – insufficient data for safety.

As for preoperative administration of oral carbohydrates two to three hours before induction of anesthesia, most protocols use a preoperative drink containing 50 g of carbohydrates.[5,11] In randomized controlled trials, oral carbohydrates have shown a better preoperative wellbeing, reduction of postoperative insulin resistance, decreased protein breakdown, maintenance of lean body mass and muscle strength, and provision of beneficial cardiac effects.[11,12]

However, oral fluids, including oral carbohydrates, may not be safely administered in patients with delayed gastric emptying or gastrointestinal motility disorders, as well as in patients undergoing emergency surgery.[5] Although obese and diabetic patients have been included in recent studies with oral carbohydrates and no problems with regard to safety have been reported, the studies are insufficient to allow a general recommendation.[5,13]

Maintaining an adequate nutritional status in the postoperative period leads to improvements in the return of intestinal activity, shorter length of hospital stay and lower rates of complications (for example, worse wound healing, anastomotic leaks or pulmonary complications).[5,14] Early feeding is considered the resumption of fluid and solid intake within 24 hours after surgery. According to the ERAS protocol, the patient is normally allowed to drink fluids upon recovery from anesthesia and is encouraged to resume the regular diet upon arrival in the room. Fundamental to the ERAS concept, oral ingestion is neither forced nor prohibited but encouraged, that is, the patient dictates the amount and type of oral ingestion.[1]

There are currently no definitive guidelines for surgical patients regarding protein requirements, but a postoperative high-protein diet may reduce complications, and immunologic nutrition and arginine supplementation have shown promising results over regimens of heterogeneous nutrition.[5,15,16]

Should bowel preparation be performed?

Preoperative bowel preparation has traditionally been used to decrease postoperative infectious morbidity, including anastomotic leak after bowel surgery. Although this benefit has yet to be unequivocally proven, in addition to patient dissatisfaction, its use has been associated with preoperative dehydration and electrolyte abnormalities that can hamper postoperative recovery. Quality data from studies in colorectal surgery have shown that mechanical preparation alone does not reduce postoperative morbidity and should be abandoned.[5] More data are needed to guide the use of bowel preparation in elective rectal resections below the peritoneal reflection.[17]

Bowel preparation with oral antibiotics may decrease infection rates in colorectal surgery, but high-quality evidence to support its use in gynecology is lacking.[1] Data from randomized clinical trials on the use of bowel preparation in gynecological surgery are limited to patients undergoing minimally invasive gy-

necological surgery. These studies conclusively showed that its use is not associated with better intraoperative visualization, ease of bowel handling or performance of procedures.[17-19]

Surgeons who recommend bowel preparation should limit its use to patients with a colon resection planned. In such cases, the use of oral antibiotics alone should be considered or combined with mechanical bowel preparation.[5]

How to prevent thromboembolic complications?

Perioperative thromboembolic prophylaxis should include dual-modality prophylaxis and commence before induction of anesthesia.[20] The effectiveness of mechanical prophylaxis is equivalent to that of heparin alone and leads to a greater reduction in the risk of venous thromboembolism (VTE) when combined with heparin in gynecological cancer patients. Graduated compression stockings, when properly adjusted, also appear to decrease the rate of deep venous thrombosis in hospitalized patients, especially when combined with another method of prophylaxis for VTE.[5] The presence of malignancy, high body mass index, advanced age, pelvic surgery, extrapelvic disease, histology, use of preoperative corticosteroids, undergoing chemotherapy, immobility, and a hypercoagulable state have been identified as independent risk factors for VTE and are common among women undergoing gynecological surgery, especially for cancer.[21] All gynecological cancer patients undergoing major surgery lasting more than 30 minutes should receive dual mechanical VTE prophylaxis and chemoprophylaxis with low molecular weight heparin or unfractionated heparin, and dual prophylaxis should continue throughout the hospital stay. These patients meet the American College of Chest Physicians (ACCP) high-risk criteria and, for this reason, prolonged chemoprophylaxis for 28 days is recommended.[20,21]

How to maintain normothermia?

In the ERAS protocol, patient warming techniques are used since the preoperative period in order to minimize the initial drop in core temperature during anesthetic induction. These techniques, which include the intraoperative use of thermal blankets, circulating-water garment and warming of IV fluids, have shown to be effective in preventing hypothermia and should be continued throughout the surgery and in the post-anesthesia care unit.[22] Intraoperatively, continuous monitoring of core body temperature is essential to guide the management of these devices and prevent extreme body temperatures, including hypothermia and hyperthermia (Chart 3).[1,5]

Chart 3. ERAS protocol: intraoperative recommendations

Short-acting anesthetics: continuous infusion of propofol/short-acting opioid analgesics/total IV anesthesia with propofol/regional anesthesia with or without concomitant general anesthesia
Thermal blankets and IV fluid heating: continuous monitoring of core body temperature
Maintain euvolemia - goal-directed therapy: minimize the use of crystalloids and increase the use of colloids in the case of hypotension, although in the case of euvolemia, consider the use of vasopressors instead of liberal administration of crystalloids
Prevention of postoperative nausea and vomiting - intraoperative use of at least two antiemetic agents of different classes: 5HT3 antagonists (ondansetron), NK-1 antagonists (aprepitant), corticosteroids (dexamethasone), antihistamines (dimenhydrinate), anticholinergics (scopolamine), butyrophenones (haloperidol) and phenothiazines (chlorpromazine)
Limited use of drains, tubes and catheters. If indispensable, their use must be for the shortest time required

Source: Adapted from Kalogera E, Dowdy SC. Enhanced recovery pathway in gynecologic surgery: improving outcomes through evidence-based medicine. Obstet Gynecol Clin North Am. 2016;43(3):551-73. doi: 10.1016/j.ogc.2016.04.006.[1] Nelson G, Bakkum-Gamez J, Kalogera E, Glaser G, Altman A, Meyer LA, et al. Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery After Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer. 2019;29(4):651-68. doi: 10.1136/ijgc-2019-000356.[5]

Adequate control of body temperature is critical, because intraoperative body temperature below 36°C can lead to adverse intraoperative and postoperative outcomes, including coagulopathy, with higher risk of bleeding, impaired drug metabolism and oxygen transport, increased peripheral oxygen uptake, cardiac morbidity, and higher risk of surgical site infections.[23]

How to proceed with drains, tubes and probes?

The ERAS protocol recommends the limited use of drains, tubes and catheters, but if they are indispensable, the use should be limited to the shortest duration required.[1] Selective use or no use of nasogastric tube (NGT) was associated with earlier return of bowel function, less pulmonary complications, a trend toward shorter hospital length of stay, and no change in rates of anastomotic leak or other postoperative complications compared with routine NGT use.[5,9] In addition, the use of routine NGT has been associated with higher rates of postoperative pneumonia, atelectasis, and fever.[1]

As for peritoneal drains, they should be considered in the ERAS protocol when there is a greater likelihood of postoperative pelvic collections, concerns about bleeding despite meticulous hemostasis, or very low intestinal resections without concomitant temporary intestinal deviation.[24] With the exception of intestinal anastomoses below the peritoneal reflection, where there may be a potential benefit in prophylactic drainage for a short

period postoperatively, data do not support the routine use of prophylactic drainage after bowel resection.[1]

Postoperatively, the recommendation is to remove urinary catheters within 24 hours after surgery, with some advocating removing them even earlier.[1] Studies have shown that patients who had the urinary catheter removed within the first few 24 hours after surgery showed less time to urinate spontaneously, with greater volume of urine and less need for re-catheterization for urinary retention, in addition to a shorter hospital stay.[25] When considering the intermediate removal (six hours after surgery), this seems superior to immediate removal (at the end of surgery) in terms of less frequent need for re-catheterization, and superior to late removal (within 24 hours postoperatively) in terms of less frequent urinary tract infections, earlier walking and shorter hospital stay.[26]

What is the recommended standard of anesthesia care?

Advances in anesthetic drugs and the expansion of outpatient care allowed the application of some of the principles of outpatient surgery to major surgery in order to mitigate the negative effects of surgical stress and pain, reduce side effects related to anesthetics and accelerate recovery.[1] Propofol has become the standard drug for induction of general anesthesia due to its rapid onset, favorable antiemetic profile, and rapid recovery. General anesthesia can be maintained with inhalation anesthesia or total IV anesthesia.[5] Short-acting inhalation agents such as sevoflurane or continuous infusion of propofol are recommended to allow rapid awakening from anesthesia, which is safely performed when these techniques are combined intraoperatively with short-acting opioid analgesics. Total IV anesthesia with propofol has been associated with fewer postoperative side effects and, specifically with a decrease in postoperative nausea and vomiting (PONV).[5,27]

Regional anesthesia with or without concomitant general anesthesia has been associated with rapid awakening and decreased systemic opioid need.[5] Regional analgesic techniques include neuraxial anesthesia (eg, epidural, spinal), peripheral nerve blocks, and surgical wound infiltration.[28] Incisional infiltration with liposomal bupivacaine or bupivacaine has no systemic side effects when used properly and should be incorporated into all ERAS protocols as a component of multimodal analgesia.[1]

How to manage fluid administration?

Maintaining euvolemia is one of the principles of the ERAS program.[1] Fluid overload can lead to electrolyte abnormalities, peripheral soft tissue edema that impairs mobility, small bowel edema that contributes to the delay in the return of bowel function, and pulmonary congestion that leads to increased pulmonary morbidity. Hypovolemia, in turn, can result in decreased cardiac output, affecting the supply of oxygen to tissues, with consequent damage to organs.[29]

To achieve intraoperative euvolemia, the ERAS protocol recommends avoiding intraoperative fluid overload, minimizing crystalloids and increasing the use of colloids. If a patient is hypotensive but at the same time euvolemic (which can occur after epidural anesthesia), the use of vasopressor rather than liberal administration of crystalloids is encouraged.[1] With this aim, some ERAS protocols have begun to adopt goal-directed therapy, a term used to describe the use of hemodynamic parameters such as stroke volume, cardiac output, peripheral vascular resistance, or similar parameters to guide the use of IV fluids and inotropic therapy.[30]

Postoperatively, patients can drink fluids immediately after surgery, and IV fluids are stopped when they are able to maintain oral hydration (usually after they have ingested at least 500 mL of oral fluids).[1] Even in the immediate postoperative period, the rate of IV fluid administration is kept to a minimum, no more than 1.2 mL/kg, often much lower. In ERAS protocols, IV fluids are rarely needed beyond 12 to 24 hours postoperatively.[7,9] Balanced crystalloids (ringer lactate), which are solutions with an electrolyte concentration similar to that of plasma, are preferable to 0.9% saline solution for the prevention of hyperchloremic acidosis.[1]

How to optimize pain, nausea and vomiting control?

In the ERAS protocol, pain management begins before the incision. This theory is based on the concept of preemptive analgesia, in which analgesics block the activation of pain receptors before they are activated by the presence of noxious stimuli, resulting in superior pain control and decreased need for analgesics. A multimodal approach that incorporates the preoperative use of gabapentin, oral or IV cyclooxygenase 2 (COX-2) inhibitors (celecoxib or parecoxib), and oral or IV paracetamol has been associated with reduced postoperative opioid use, therefore, it is commonly used in ERAS protocols.[1]

The use of opioids has traditionally been associated with increased PONV, compromised bowel function, delayed mobilization due to mental sensory changes, and increased pulmonary morbidity due to respiratory drive depression, in addition to a higher risk of dependence, leading to associated financial and social costs.[1] For these reasons, postoperative opioid-sparing multimodal analgesia is also recommended, with greater emphasis on non-opioid drugs such as non-steroidal anti-inflammatory drugs, acetaminophen, gabapentin and dexamethasone. The effectiveness of this approach is based on the synergistic action of two or more analgesics with different action mechanisms.[5]

In addition to opioid-sparing analgesia, the ERAS protocol also adopts a multimodal approach for the preventive treatment of PONV, which includes intraoperative use of at least two agents from different classes of antiemetics. These classes of antiemetic drugs include 5HT3 antagonists, NK-1 antagonists, corticosteroids, antihistamines, anticholinergics, butyrophenones, and phenothiazines. Additional strategies to decrease PONV include the use of propofol infusion and less use of opioids.[31]

Why encourage early mobilization?

Early mobilization is a vital component of the ERAS protocol, as it protects against muscle and physical conditioning loss by avoiding prolonged bed rest and immobility. As a result, it helps to reduce pulmonary and venous thromboembolic complications, improves insulin resistance, and helps to reduce hospital stay.[1] In addition, early ambulation contributes to the return of bowel function, decreasing postoperative ileus rates.[5]

How to prevent postoperative ileus?

The return of bowel function is usually the last milestone reached before hospital discharge after a laparotomy. Among the factors influencing the return of bowel function are the use of opioids, the balance of venous fluids, the extent of peritoneal disease in the case of cancer patients, the complexity of surgery, the need for blood transfusion and postoperative abdominopelvic complications.[32]

The implementation of minimally invasive surgery reduces the rate of postoperative ileus, but not all patients are candidates for this surgical approach. Among patients who need laparotomy, interventions that stimulate the enteric nervous system and reduce the use of opioids, such as early feeding, coffee consumption and chewing gum have shown to be effective in reducing the time for the return of bowel function in some studies. Although the use of chewing gum is safe and inexpensive, a large, recent, well-conducted randomized trial has shown no benefit. The consumption of coffee in the postoperative period has shown to reduce from 30% to 10% the rate of postoperative ileus in women undergoing gynecological cancer surgery. Furthermore, measures such as early ambulation and modal analgesia have shown a two to five times decrease of the rate of postoperative ileus.[5,33]

The ERAS protocol also considers the possibility of using laxatives in order to accelerate the return of gastrointestinal function, since an earlier time for the first evacuation was observed when bowel stimulation with oral osmotic laxatives was performed within six hours after abdominal hysterectomy, with no change in pain and PONV scores.[1,34] As for prokinetics, there is little or no evidence to support their use for the purpose of preventing postoperative ileus (Chart 4).[1,5]

Chart 4. ERAS protocol: postoperative recommendations

Resumption of oral intake of liquids and solids within 24 hours after surgery: Encourage fluid intake when the patient recovers from anesthesia Consider high-protein diets
Early mobilization
Removal of the urinary catheter within 24 hours after surgery
Opioid-sparing multimodal pharmacological system for pain (two or more drugs) and regional analgesia: Combination of non-steroidal anti-inflammatory drugs (NSAIDs) with paracetamol Thoracic epidural analgesia, transverse abdominal blocks, wound infiltration with local anesthetic and intraperitoneal local anesthetic
If increased risk of venous thromboembolism: dual mechanical prophylaxis (stockings and pneumatic compression) and chemoprophylaxis with low molecular weight heparin or unfractionated heparin Extended chemoprophylaxis (28 days postoperative) for patients who meet high-risk criteria
Euvolemia: Discontinue IV fluids when patient can maintain oral hydration (at least 500 mL of oral fluids) In the immediate postoperative period, IV fluids should be maintained at a minimum not exceeding 1.2 mL/kg

Final considerations

The principles of the ERAS protocol are applicable to all surgical specialties, and constant innovation must be the keynote to allow for the improvement of processes. The implementation of the ERAS program represents a paradigm shift in the perioperative management of surgical patients and is a multidisciplinary evidence-based approach. The program is clinically effective and impacts patient outcomes, providing a safe, high-quality approach and cost-effective perioperative care. In addition, a successful program can lead to faster and safer recovery and better quality of life and patient satisfaction. Therefore, the ERAS program should become standard practice for all women undergoing elective gynecological surgery.

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Conclusions: Indicate the main conclusions and their clinical usefulness.

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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

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

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

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

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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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*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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