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Editorial

Racism as a Social Determinant of Health in Brazil in the COVID-19 Pandemic and Beyond

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The World Health Organization (WHO) defines *disparity* as the unnecessary, avoidable, and unfair treatment of two groups based on identified differences.[1] *Racial disparities* refer to the different treatment of distinct subgroups of people based on differences without any scientifically proven biological reason.[2]

Growing evidence indicates that ethnic and racial disparities permeate health-related issues, and structural racism is key in determining population health.[3]

Racism is a system of domination of a racial group defined as inferior by dominant groups that use phenotypic characteristics to justify inequalities in access to resources and power.[4] Racism is structural insofar as the social structure is constructed racially hierarchical. And racism is cultural in that the values and cultural beliefs of the dominant racial group are used as the norms by which other groups are socially judged.[5] Institutional racism, in turn, refers to the maintenance of racial inequalities by institutional mechanisms. This type of racism acts diffusively, as it is implicit in the daily functioning of institutions and social organizations through discriminatory practices that disadvantage certain people from accessing services and opportunities according to their skin color.[6] Thus, cultural racism maintains structural racism and both constitute the root of racial inequalities in health.[4,5]

Health outcomes are directly impacted by the level of structural and institutional racism.[7] Racism is associated with worse physical and mental health outcomes, including increased depression, anxiety, and psychological stress based on the existence of racist beliefs and practices among health professionals about minority groups that influence their decision-making process and the care they provide.[8,9]

Differences based on skin color permeate several areas of health. For instance, Black people receive fewer prescriptions of analgesics in general, less palliative treatment for metastatic cancer, and lowered use of revascularization therapy to treat cerebrovascular accidents (CVA).[10–12] Overall, people of color have worse cardiovascular outcomes and experience longer waiting times for care at the emergency department.[13,14]

In Gynecology and Obstetrics, racial disparities are evident: Black women have the highest mortality rates and severe maternal morbidity, later onset and lack of prenatal care, are at higher risk of preeclampsia, prematurity, and postpartum hemorrhage, and report worse experiences during prenatal, delivery and postnatal care than other women.[15–21] Moreover, Black women have less access to contraceptive methods, receive more diagnoses of the human immunodeficiency virus (HIV) infection,[22] undergo fewer screening tests for cervical cancer, and have increased mortality rates from breast cancer[23] comparing to non-Black ones.[22–24]

In Brazil, the majority of the population is Black (*Negra*). The Brazilian Institute of Geography and Statistics (IBGE) conceptualizes Black as people who self-declare as Black (*Preta*) and Brown (*Parda*).[25] Despite their majority, racial disparities are perpetuated against the Black population.[26]

The COVID-19 pandemic exacerbated health inequalities.[27] The global public health emergency has imposed a new reality on health systems around the world and has accentuated inequalities in access to health services. Underdeveloped and developing countries were most affected by the effects of the pandemic, as existing socioeconomic inequalities affected the initial course of the disease and resulted in increased deaths from COVID-19, especially among the most vulnerable populations.[27–29]

In Brazil, infection and death rates from COVID-19 are uneven, with greater risk among Black people and those with low socioeconomic status.[30] Mortality from COVID-19 was higher among the Black population, and maternal mortality was twice as high among Black women compared to all other women in our country.[31,32]

The impact of the pandemic highlighted the existing racial disparities in health in Brazil.[33] An integrative review of Brazilian studies with population-based databases found that being Black was a risk factor independently associated

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with the severity of COVID-19. The authors concluded that the Black population suffered more than any other from the physical and economic impacts of COVID-19.[34]

Racial disparities are evident in our population and marked sociodemographic differences remain between Black and non-Black women. In this issue of RBGO, a retrospective multicenter Brazilian study carried out with pregnant and puerperal symptomatic women suspected of having COVID-19 showed that Black women were younger and had less education, a higher rate of unplanned pregnancy, and greater public health insurance coverage. In addition, the findings showed greater severity of infection among Black women, with a higher risk of severe acute respiratory syndrome, admission to the Intensive Care Unit, greater desaturation on admission, and higher maternal mortality in this group.[35]

Although the COVID-19 pandemic did not create these inequities, it reminded us of how structural racism is a driving force of the social determinants of health and highlighted the need for health professionals to change their approach and assistance, especially to discriminated populations. It means that all knowledge already produced about the health of the Black population should be appropriated by health professionals to deal more specifically with individuals, as well as call for greater production of knowledge about them. This is an important action to combat racism.

COVID-19 was not a democratic disease and further exposed the strong association between race, ethnicity, culture, socioeconomic status, and health outcomes.[36] Individual implicit prejudice and the profound impact of structural racism must be recognized and accepted before real progress can be made to reducing racial disparities in maternal mortality. To reduce the impacts of COVID-19 and other public health emergencies, it is urgent to adopt new models of care centered on women that consider racial disparities and overlapping vulnerabilities and develop public policies specifically aimed at the Black population while respecting their particularities.

Health inequalities are generated and maintained by social differences and unequal access to services, resources, and power.[1] Social determinants of health are non-medical conditions that involve the conditions in which people live, work, and grow and impact their risk factors and health outcomes.[37,38] These social determinants are responsible for health inequalities between countries and within the same country: generally, the worse the socioeconomic condition, the worse the health conditions.[1,37]

The United Nation's sustainable development goals (SDG) for the years 2015 to 2030 include combating social disparities, of which we highlight three: SDG3 refers to health and well-being for all, SDG5 strives for gender equality, and SDG10 focuses on reducing inequalities.[39] Indeed, the COVID-19 pandemic had a strong impact on the goals to be achieved during this period, a delay of decades in several sectors, such as the reduction of maternal mortality, a health indicator strongly linked to our specialty, obstetrical gynecology.[40]

Black women suffer from gender, social, and racial vulnerabilities that intersect and generate additive or multiplicative effects.[27] They also are under the impact of determinants produced by a historical movement, which built specific cultural ways of thinking about the Black population, as well as being vulnerable to the social conditions produced by an unequal society that affects their health.[41] The articulation of social determinants of difference was first thought by the Brazilian professor, philosopher, and author Lélia Gonzalez in the 80s, even before the intersectionality concept emerged.[42] Gonzalez relates the social makers of skin color, class, and gender in the racism construction and maintenance. The concept of intersectionality was then systematized by the American professor Kimberly Crenshaw as "the way in which racism, patriarchy, class oppression and other discriminatory systems create basic inequalities that structure the relative positions of women, races, ethnicities, classes, and others".[43] Crenshaw proposes the concept as a method of locating inequalities suffered by Black women from structural racism. In this sense, Black women aggregate the largest set of unfavorable conditions and are placed at the bottom of the social pyramid.[44]

Race is a social construction and researchers must consider the variable skin color within a historical context of discrimination as a complex variable that interferes with health outcomes not only due to genetic and biological factors but often due to social and economic factors.[45,46] Understanding racism and considering the existence of racial disparities in decision-making and the construction of public policies make it possible to reduce health inequalities.

Conflicts to Interest
None to declare.

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Prediction of Perinatal and Neurodevelopmental Outcomes in Newborns with a Birth Weight below the 3rd Percentile: Performance of Two International Curves – Prospective Cohort from a Brazilian City

Predição de resultados perinatais e de neurodesenvolvimento em recém-nascidos com peso ao nascer abaixo do percentil 3: Desempenho de duas curvas internacionais – coorte prospectiva de uma cidade brasileira

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Abstract

Objectives To evaluate the performance of Intergrowth-21 st (INT) and Fetal Medicine Foundation (FMF) curves in predicting perinatal and neurodevelopmental outcomes in newborns weighing below the 3rd percentile.

Methods Pregnant women with a single fetus aged less than 20 weeks from a general population in non-hospital health units were included. Their children were evaluated at birth and in the second or third years of life. Newborns (NB) had their weight percentiles calculated for both curves. Sensitivity, specificity, positive (PPV) and negative predictive value (NPV), and area under the ROC curve (ROC-AUC) for perinatal outcomes and neurodevelopmental delay were calculated using birth weight $<$ 3rd percentile as the cutoff.

Results A total of 967 children were evaluated. Gestational age at birth was 39.3 ($\pm$3.6) weeks and birth weight was 3,215.0 ($\pm$588.0) g. INT and FMF classified 19 (2.4%) and 49 (5.7%) newborns below the 3rd percentile, respectively. The prevalence of preterm birth, tracheal intubation $>$24 hours in the first three months of life,

Keywords
- fetal growth retardation
- birth weight
- neurodevelopmental disorders

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5th minute Apgar <7, admission to a neonatal care unit (NICU admission), cesarean section rate, and the neurodevelopmental delay was 9.3%, 3.3%, 1.3%, 5.9%, 38.9%, and 7.3% respectively. In general, the 3rd percentile of both curves showed low sensitivity and PPV and high specificity and NPV. The 3rd percentile of FMF showed superior sensitivity for preterm birth, NICU admission, and cesarean section rate. INT was more specific for all outcomes and presented a higher PPV for the neurodevelopmental delay. However, except for a slight difference in the prediction of preterm birth in favor of INT, the ROC curves showed no differences in the prediction of perinatal and neurodevelopmental outcomes.

Conclusion Birth weight below the 3rd percentile according to INT or FMF alone was insufficient for a good diagnostic performance of perinatal and neurodevelopmental outcomes. The analyzes performed could not show that one curve is better than the other in our population. INT may have an advantage in resource contingency scenarios as it discriminates fewer NB below the 3rd percentile without increasing adverse outcomes.

Resumo

Objetivos Avaliar o desempenho das curvas de Intergrowth-21 st (INT) e Fetal Medicine Foundation (FMF) na predição de resultados perinatais e de neurodesenvolvimento de recém-nascidos com peso abaixo do percentil 3.

Métodos Foram incluídas gestantes de feto único com idade inferior a 20 semanas de uma população geral em unidades de saúde não hospitalares. Seus filhos foram avaliados ao nascimento e no segundo ou terceiro anos de vida. Os recém-nascidos tiveram seus percentis de peso calculados para ambas as curvas. Sensibilidade, especificidade, valor preditivo positivo (VPP) e negativo (VPN) e área sob a curva ROC (ROC-AUC) foram calculados para desfechos perinatais e atraso de neurodesenvolvimento considerando o peso ao nascimento menor que o percentil 3 como ponto de corte.

Resultados Um total de 967 crianças foram avaliadas ao nascimento e no segundo ou terceiro anos de vida. A idade gestacional ao nascer foi de 39,3 (±3,6) semanas e o peso ao nascimento foi de 3.215,0 (±588,0) g. INT e FMF classificaram 19 (2,4%) e 49 (5,7%) recém-nascidos abaixo do percentil 3, respectivamente. A prevalência de parto pré-termo, intubação traqueal > 24 horas nos primeiros três meses de vida, Apgar de 5° minuto < 7, internação em unidade de terapia intensiva neonatal (internação em UTIN), taxa de cesariana e atraso de neurodesenvolvimento foi 9,3%, 3,3%, 1,3%, 5,9%, 38,9% e 7,3% respectivamente. Em geral, o percentil 3 de ambas as curvas apresentou baixa sensibilidade e VPP e alta especificidade e VPN. O percentil 3 de FMF mostrou sensibilidade superior para parto prematuro, internação em UTIN e taxa de cesariana. INT foi mais específico para todos os desfechos e apresentou maior VPP para o atraso do neurodesenvolvimento. Entretanto, exceto por uma pequena diferença na predição de parto pré-termo em favor de INT, as curvas ROC não mostraram diferenças na predição de resultados perinatais e de desenvolvimento neurológico.

Conclusão O peso ao nascer abaixo do percentil 3 segundo INT ou FMF isoladamente foi insuficiente para um bom desempenho diagnóstico de desfechos perinatais e de neurodesenvolvimento. As análises realizadas não puderam mostrar que uma curva é melhor que a outra em nossa população. INT pode ter vantagem em cenários de contingência de recursos, pois discrimina menos recém-nascidos abaixo do percentil 3 sem aumentar os desfechos adversos.

Palavras-chave
- retardo do crescimento fetal
- peso ao nascer
- transtornos do neurodesenvolvimento

Introduction

Fetal growth restriction is associated with adverse perinatal outcomes, neurodevelopmental delay, and the onset of chronic disease in adults.[1–3] Identification of fetuses and newborns (NB) with growth restriction could help improve these results by intensifying prenatal and postnatal care.[4,5]

Several estimated fetal and birth weight (BW) charts have been published worldwide, showing significant differences.[6–12] While some authors suggest that these differences are due to racial and geographic variations, others attribute them to socioeconomic inequalities, nutritional deficits, or methods used in the studies.[7,9,13,14]

One of the healthcare challenges in Brazil is to define which fetal and neonatal growth charts better discriminate children with growth restriction in the Brazilian population. It is unclear whether using North American or European curves could increase false positive diagnoses, as the cut-off points may be too high. Using references that underestimate diagnoses bears even more risk as it could deprive the most vulnerable pregnant women and their children of the necessary care, leading to an increase in the incidence of adverse outcomes.

Therefore, it should be understood that the random choice of a fetal or neonatal weight curve without an in-depth analysis of morbidity and mortality is not recommended. Choosing a particular reference over another is only justified if the reference can better identify the NB with the highest risk of morbidity and mortality without excess diagnoses.[15]

The objective of this study was to evaluate the performance of two international BW curves, Intergrowth-21 st (INT) and Fetal Medicine Foundation (FMF) in predicting perinatal and neurodevelopmental outcomes in newborns based on birth weight below the 3rd percentile in a Brazilian city. This is the first prospective Brazilian study to include neurodevelopmental outcomes in assessing of birth weight curves.

Methods

This prospective cohort evaluated children at birth and in the second or third years of life.

Data from a BRISA-RP cohort study were used.[16] The preliminary study assessed etiological factors of preterm birth and the consequences of perinatal factors on child health. The research ethics committee approved this study at the University Hospital where it was performed. Ribeirão Preto is located in south-eastern Brazil and has ~710,000 inhabitants. This is a prosperous country region regarding income, consumption, and longevity. Birth data were collected between April 2010 and December 2011, and the neurodevelopmental assessment data in the second or third years of life.

Recruitment of this cohort started during pregnancy. Pregnant women from a general population with a single fetus aged less than 20 weeks were sequentially recruited from selected primary care units in this city. These units are part of the public health system, are not linked to the University, and generally serve a low- and middle-income population. The first ultrasound determined the gestational age (GA) used in this study. All pregnant women recruited had already undergone a first-trimester ultrasound with gestational age was calculated using the crown-rump length. Furthermore, all pregnant women underwent a new ultrasound to confirm the GA by certified physicians from the research team before 24 weeks. At birth, all NB with BW greater than or equal to 500 g were potentially eligible. NB older than 42 weeks were excluded to reduce the risk of bias in an incorrect recording of gestational age, as it is unlikely that a pregnancy will exceed this limit spontaneously or on medical advice. NB with severe malformations were also excluded. All cohort participants were encouraged to bring their children between the second and third years of life for a neurodevelopment assessment using the Bayley Scales of Infant Development, III edition (BSID-III).[17] All patients gave their informed written consent to participate in the study.

Sociodemographic and clinical data were collected, including maternal age, body mass index, race, parity, education level, smoking, alcohol use, hypertension, and diabetes. Data from the newborns of the included women were collected in their respective maternity hospitals in the city on birth or the following day by the research team.

The predictor variable was BW below the 3rd percentile for GA. The 3rd percentile was chosen because there is a high perinatal morbidity and mortality risk below this thresholds.[18,19] Furthermore, fetal or birth weight below the 3rd percentile is considered an isolated criterion for fetal and neonatal growth restriction, according to the latest expert consensus.[20,21]

The perinatal outcomes were preterm birth, tracheal intubation for more than 24 hours in the first three months of life (Intubation), 5 minute Apgar <7, admission to a neonatal intensive care unit (NICU admission), and cesarean section rate. The long-term outcome variable was the risk of neurodevelopmental delay between the second and third years of life.

Percentiles of BW were obtained for each NB. INT (specific gender) and FMF calculators were used to predict BW.[22,23] These charts were chosen because both include fetal and neonatal charts and are the only ones whose calculators were found on official open access Web sites.

The INT standards were constructed from a prescriptive population of over 4,500 healthy pregnancies in a study of over 59,000 total pregnancies. The project involved 8 countries from 4 continents and included only highly selected women with optimal nutrition and low risk of pregnancy complications. Fetal anthropometric data were prospectively collected every 5 weeks starting at 14 weeks. The aim of that approach was to create charts that could be used worldwide.[9,24]

Nicolaides et al. (FMF) used a heterogeneous sample of unselected pregnant women, most of them being white women from the United Kingdom. Data were collected from two sources. The first comprised 5163 paired measurements of EFW and BW, and the second of 95,579 pregnancies with EFW obtained by routine fetal ultrasound biometry. In

this study, the authors proposed to consider that all babies of the same gestational age, even intrauterine babies, could be included for BW references. Thus, the construction of the curves considered that in a given population with a defined gestational age, the median fetal weight and the median birth weight are similar, with different degrees of deviations from the median for fetal weight and birth weight, depending on the gestational age.[10]

Maternal, gestational, and childbirth data were obtained by filling out previously prepared questionnaires with interview data and medical records.

Neurodevelopment was assessed by ten psychologists who received identical, simultaneous, and group training. Children were assessed in three domains: cognitive, language (receptive and expressive), and motor (gross and fine), with each domain including specific tests for each age. For each age group (13–24 months; 25–42 months), there is a corresponding starting point. The child's performance on each test item was scored 0 or 1. The points obtained in each domain were summed, and children were classified as competent, emerging, or at risk according to the cut-off points provided by the test. A score that resulted in a risk for any domains was considered positive for neurodevelopmental risk.

There was no interference from researchers in prenatal care, labor and delivery, and postnatal care of children. All NB of pregnant women with conditions potentially associated with fetal growth deviations such as hypertension, diabetes, smoking, and preterm deliveries were included in the analysis.

Statistical analysis was performed using the SAS System for Windows (Statistical Analysis System), version 9.2., SAS Institute Inc, 2002–2008, Cary, NC, USA. Comparisons of descriptive variables were performed using the generalized estimating equations (GEE analysis) (numerical variables). Sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of perinatal outcomes and risk of neurodevelopmental delay were estimated, with differences being determined by the McNemar test and GEE analysis considering a BW below the 3rd percentile as the cut-off point. The discriminatory ability of each curve was assessed using the AUC of the ROC curve. To be significant, were considered results with p-value <0.05 with a confidence interval of 95%.

Results

Participants

A total of 1417 pregnant women were recruited. Seventy-three dropouts were reported, and 17 NB were excluded (6 with major malformations, 3 without weight records, 2 weighing less than 500 g, and 6 with a gestational age of 42 weeks or more). The total number of children with no or incomplete neurodevelopmental tests was 360 (27.1%). The final number of cases for analysis was 967 (►**Fig. 1**).

Descriptive Data

The median age of pregnant women was 26.0 (±12.0) years. The majority (79.9%) were nuligest or secundigest, and 90.7%

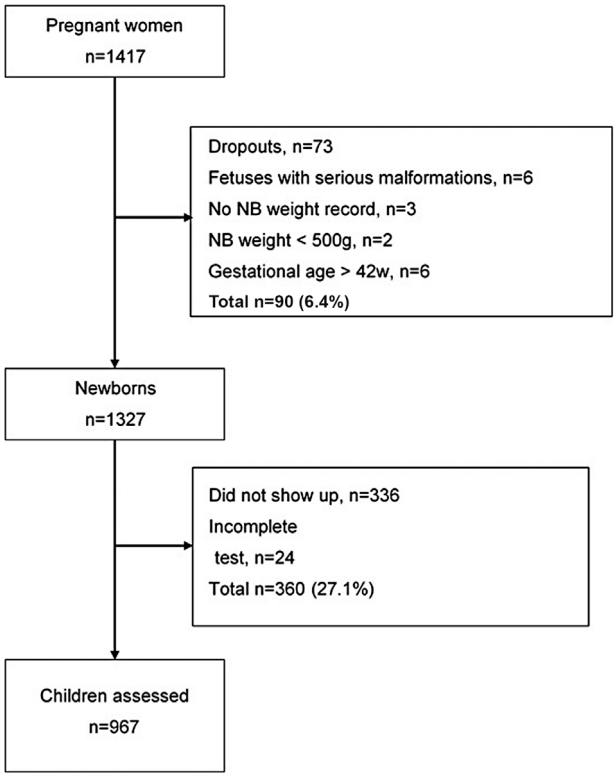

Fig. 1 Flowchart of the participants included in the study.

had full-term delivery. The median GA at birth, and the NB weight was 39.3 (±3.6) weeks, and 3,215.0 (±588.0) g respectively. The prevalence of hypertension was 15.4%, and smoking, 12.4%. The total prevalence of diabetes in the sample was 6.1%. In the INT and FMF groups, the diabetes rate was 10.5 and 4.1%, respectively. The overall prevalence of prematurity was 9.3%; however, among NB below the 3rd percentile, it was 46.2% for INT and 32.4% for FMF. For neurodevelopment, 741 children were evaluated between 13 and 24 months and 226 between 25 and 36 months (►**Table 1**). The prevalence of intubation, 5 minute Apgar <7, NICU admission, cesarean section and neurodevelopment delay was 3.3%, 1.3%, 5.9%, 38.9% and 7.3%, respectively (►**Table 2**).

Main Results

INT and FMF classified 19 (1.9%) and 49 (5.1%) NB below the 3rd percentile, respectively. As a rule, high specificity was observed, but low sensitivity and positive predictive value. Some results were statistically superior for FMF, such as sensitivity for preterm delivery, NICU admission, and cesarean, respectively 13.3% (95%CI 7.4–22.5) versus 6.7% (95%CI 2.7–15.5) ($p=.014$), 13.8% (95%CI 6.6–22.9) versus 3.5% (95% CI 0.6–13.0) ($p=.014$) and 6.7% (95%CI 4.4–9.8) versus 2.1% (95%CI 1.0–4.3) ($p<.001$). On the other hand, INT was superior in all outcomes when specificity was evaluated ($p<.001$). In addition, the NPV for neurodevelopment delay was 21.1% (95%CI 7.0–46.1) for INT versus 10.2% (95% CI 3.8–23.0) for FMF ($p=.005$) (►**Table 3**). However, analysis using

Table 1 Cohort demographic characteristics

	Total n = 967	INT NB weight $p < 3$ n = 19	FMF NB weight $p < 3$ n = 49	p-value[d]
Maternal age, years (IQR)	26.0 (12.0)	26.0 (12.0)	26.0 (12.0)	0.718
BMI, kg/m^2 (IQR)	26.5 (6.8)	27.8 (8.5)	27.0 (6.6)	0.218
Study US, weeks IQR)	22.9 (1.7)	23.1 (2.3)	22.9 (1.7)	0.919
Ethnicity				
- White (%)	510 (52.4)	11 (57.9)	27 (55.1)	0.756
- Non-white (%)	457 (47.3)	8 (42.1)	22 (44.9)	
Schooling				
- ≥12 years (%)	77 (8.0)	1 (5.3)	4 (8.2)	0.595
- <12 years (%)	890 (92.0)	18 (94.7)	45 (91.8)	
Marital status				
- Married or cohabiting (%)	778 (80.5)	14 (73.7)	37 (75.5)	0.810
- No partner (%)	189 (19.5)	5 (26.3)	12 (24.5)	
Parity				
- 0–1 (%)	773 (79.9)	16 (84.2)	43 (87.8)	0.515
- ≥2 (%)	194 (19.5)	3 (15.8)	6 (12.2)	
NB sex				
- Male (%)	474(49.0)	11 (57.9)	23 (46.9)	0.228
- Female (%)	493 (51.9)	8 (42.1)	26 (53.1)	
Hypertension[a] (%)	149 (15.4)	4 (21.1)	12 (24.5)	0.667
Diabetes[a] (%)	59 (6.1)	2 (10.5)	2 (4.1)	<0.001
Smoking[b] (%)	120 (12.4)	6 (31.6)	11 (22.5)	0.189
Alcohol[b] (%)	238 (24.6)	6 (31.6)	14 (28.6)	0.706
Delivery, weeks (IQR)	39.3 (3.6)	39.6 (4.6)	39.3 (3.4)	0.220
≥37 weeks	39.4 (1.7)[e]	40.0 (1.6)[g]	39.7 (1.4)[i]	
< 37 weeks	35.7 (2.4)[f]	35.9 (1.0)[h]	34.8 (2.3)[j]	
NB weight, g (IQR)	3215.0 (588.0)	2425.0 (660.0)	2455.0 (465.0)	0.464
≥37 weeks	3250.0 (570)[e]	2500.0 (135)[g]	2500.0 (295)[i]	
< 37 weeks	2645.0 (877.5)[f]	1842.5 (178.8)[h]	1735.0 (381.3)[j]	
Breastfeeding ≥1month (%)	863 (89.3)	18 (94.7)	41 (83.7)	0.187
Day care center (%)	469 (48.5)	4 (21.1)	12 (24.5)	0.667
Neurodevelop. Assessm[c], years (IQR)	1.9 (0.3)	1.8 (0.3)	1.8 (0.3)	0.428

Abbreviations: BMI, body mass index; FMF, Fetal Medicine Foundation; INT, Intergrowth-21st; IQR, interquartile interval; NB, newborn; p, percentile; US, ultrasound.

[a]Types of hypertension included chronic, gestational, or preeclampsia. Types of diabetes included: type 1, 2 our gestational; [b]Any amount of consumption; [c]Child's age at evaluation of neurodevelopment by Bayley III test; [d]Comparisons of categorical and numerical variables considering only newborns with <p3 in each curve, through GEE (Generalized Estimating Equations) analysis; [e]n = 877; [f]n = 90; [g]n = 13; [h]n = 6; [i]n = 37; [j]n = 12.

ROC curves did not show adequate performance in predicting perinatal and neurodevelopmental outcomes (►**Fig. 2**).

Discussion

For both curves evaluated, the cutoff point for birth weight below the **3rd percentile** alone did not prove to be a good predictor of adverse perinatal outcomes and risk of neurodevelopmental delay. FMF classified more than double NB with BW below the 3rd percentile. This increased the sensitivity but did not improve the other parameters.

The sample size was one of the limitations of the study because some outcomes such as intubation ($n = 32$), 5 minute Apgar score <7 ($n = 13$), and NICU admission ($n = 58$) had a low incidence, resulting in lower reliability of the results. Until birth, few cases were excluded or dropped out of the study ($n = 90$; 6.4%); however, many children did not attend the neurodevelopment test ($n = 360$; 27.1%). We were unable to investigate the reasons for the withdrawal of pregnant women and the absence of children. Data on the quality of management of fetal growth restriction pregnancies, perinatal deaths, the onset of diseases, and quality of infant

Table 2 Performance of birth weight below the 3rd percentile for perinatal, and infant neurodevelopment outcomes according to Intergrowth-21 st and fetal medicine foundation curves

		n (%)	Sensitivity% (95%CI)	p-value[a]	Specificity% (95%CI)	p-value[a]	PPV (95%CI)	p-value[b]	NPV (95% CI)	p-value[b]
Preterm birth n = 90 (9.3%)	INT	6 (31.6%)	6.7 (2.7–14.5)	0.014	98.5 (97.4–99.2)	<0.001	31.6 (13.6–56.5)	0.334	91.1 (89.1–92.8)	0.136
	FMF	12 (24.5%)	13.3 (7.4–22.5)		95.8 (94.2–97.0)		24.5 (13.8–39.2)			91.5 (89.5–93.2)
Intubation n = 32 (3.3%)	INT	2 (10.5%)	6.3 (1.1–22.2)	0.083	98.2 (97.0–98.9)	<0.001	10.5 (1.8–34.5)	0.952	96.8 (95.5–97.8)	0.217
	FMF	5 (10.2%)	15.6 (5.9–33.6)		95.3 (93.7–96.5)		10.2 (3.8–23.0)			97.1 (95.7–98.0)
5 minute Apgar <7 n = 13 (1.3%)	INT	0	0.0 (0.0–28.4)	0.317	98.0 (96.8–98.8)	<0.001	0.0 (0.0–20.9)	1.00	98.6 (97.6–99.2)	0.537
	FMF	1 (2.0%)	7.7 (0.4–37.9)		95.1 (93.4–96.3)		2.1 (0.1–12.5)			98.7 (97.7–99.3)
NICU admission n = 58 (5.9%)	INT	2 (10.5%)	3.5 (0.6–13.0)	0.014	98.1 (97.0–98.9)	<0.001	10.5 (1.8–34.5)	0.429	94.1 (92.4–95.5)	0.065
	FMF	8 (16.3%)	13.8 (6.6–25.9)		95.5 (93.9–96.7)		16.3 (7.8–30.2)			94.6 (92.8–95.9)
Cesarean n = 376 (38.9%)	INT	8 (42.1%)	2.1 (1.0–4.3)	<0.001	98.1 (96.6–99.0)	<0.001	42.1 (21.1–66.0)	0.327	61.2 (58.0–64.3)	0.060
	FMF	17 (34.7%)	6.7 (4.4–9.8)		95.9 (93.9–97.3)		51.0 (36.5–65.4)			61.8 (58.5–64.9)
Neurodevelopment n = 71 (7.3%)	INT	4 (21.1%)	5.6 (1.8–14.5)	0.317	98.3 (97.2–99.0)	<0.001	21.1 (7.0–46.1)	0.005	92.9 (91.1–94.4)	0.257
	FMF	5 (10.2%)	7.0 (2.6–16.4)		95.1 (93.4–96.4)		10.2 (3.8–23.0)			92.8 (90.9–94.4)

Abbreviations: FMF, Fetal Medicine Foundation ($n = 49$); INT, Intergrowth-21st ($n = 19$); Intubation, tracheal intubation for more than 24 hours in the first three months of life; Neurodevelopment, neurodevelopment delay (assessment in the second and third years of life by the BayleyIII test); NICU, neonatal intensive care unit; VPN, negative predictive value; VPP, positive predictive value.
[a]Mc Nemar test, [b]GEE (generalized estimating equations).

stimulation are scarce. The high number of absences may cause some bias in the results, as perinatal losses usually occur among those with the lowest weight percentile, which would probably influence the INT group more because it concentrates the smallest NBs. However, it is essential to remember that absences interfere in analyzing both patterns since the study group is the same.

It is important to note that this study only included newborns weighing below the 3rd percentile. We did not include the restricted fetuses because we did not have estimated fetal weight and Doppler data. Therefore, probably some NBs above the 3rd percentile but at risk were not included.

The prospective design add advantages to the study, as it was possible to obtain a sample of pregnant women of non-hospital origin and were still in the first half of pregnancy. Including pregnant women with complications such as hypertension and smoking was purposeful, as low birth weight can result from multiple maternal and gestational conditions. Thus, we intended to obtain a sample that well represented the general population with its proportion of healthy women and others with prevalent diseases during pregnancy.

The main strength of this study was the inclusion of neurodevelopmental outcomes, as the predictive capacity of perinatal outcomes is low.[25,26] Long-term results are essential to assess the role of gestational complications such as low birth weight in the onset of permanent neurological damage, which is difficult to assess in the neonatal period.[27] This is the first prospective Brazilian study to include neurodevelopmental outcomes in assessing birth weight curves.

We believe that the assessment of the curves made in this study was timely, as they represent two distinct types of population samples. One of them (INT) is based on intercontinental and multi-ethnic populations, including the Brazilian population, while the other (FMF) is predominantly based on the population of European women.[9,10]

Both curves were poor predictors of perinatal and neurodevelopmental outcomes, probably because these outcomes are influenced by multiple factors beyond the birth weight, such as prematurity, birth conditions, neonatal care, breastfeeding, and infant stimulation. This has already been demonstrated in other studies with fetal and neonatal patterns.[28,29] The most remarkable difference between the curves in this study was the highest cut-off point on the FMF graph. INT discriminated 19 NB below the 3rd percentile while FMF 49. In practice, we had more than twice as many newborns classified as having restricted growth according to the new consensus for one standard (FMF) compared with the other (INT). To exemplify, if we had a hypothetical 39-week NB weighing 2,580 g, this NB would be in the fifth (male chart) or seventh (female chart) percentiles of the INT, but by FMF references, it would be in the second percentile. This difference may seem insignificant, but it can place many additional newborns in the growth-restricted group in a population context. Changes in cutoff points could make any growth curve potentially suitable for any population. We

Table 3 Comparison of area under receptor operating characteristics curve for prediction of perinatal and infant neurodevelopmental outcomes between intergrowth-21 st and fetal medicine foundation using birth weight percentiles

	INT	FMF	p-value
	ROC curve AUC (95%CI)	ROC curve AUC (95%CI)	
Preterm birth	0.54 (0.47–0.60)	0.52 (0.45–0.59)	0.032
Intubation	0.57 (0.48–0.67)	0.60 (0.49–0.70)	0.090
5 minute Apgar <7	0,54 (0.39–0.70)	0.56 (0.39–0.73)	0.437
NICU admission	0.58 (0.50–0.66)	0.59 (0.51–0.67)	0.319
Cesarean	0.57 (0.53–0.60)	0.56 (0.53–0.60)	0.887
Neurodevelopment	0.52 (0.45–0.59)	0.52 (0.45–0.59)	0.453

Abbreviations: FMF, Fetal Medicine Foundation; INT, Intergrowth-21st; Intubation, tracheal intubation for more than 24 hours in the first three months of life; Neurodevelopment, neurodevelopment delay (assessment in the second and third years of life by the BayleyIII test); NICU, neonatal intensive care unit; ROC curve AUC, area under receptor operating characteristics curve.

could have tested other thresholds to define the one that best discriminates the children at the most significant risk in each pattern.[30] However, we did not do this because it would be of little practical use as most hospitals have their chosen fetal and neonatal growth reference charts and well-known thresholds such as the 3rd or 10th percentile. Some expected differences were found with the applied statistical tests due to differences in the cutoff points of the evaluated curves. Higher sensitivity for FMF and higher specificity for INT. However, the ROC curves, except for a small difference in the prediction of preterm birth in favor of INT, did not show consistent differences.

The birth weight of our sample was similar to that of other national studies. Barros et al. conducted a study in Pelotas, a city in southern Brazil, with a cohort of 4,558 newborns. Most pregnant women came from urban areas, and 61.7% were white. The BW was 3,149.6 g, slightly lower than in this study (3,215.0 g). However, the sample by Barros et al. included a higher proportion of pregnancies with complications such as smoking (27.5%), premature birth (15.3%), and

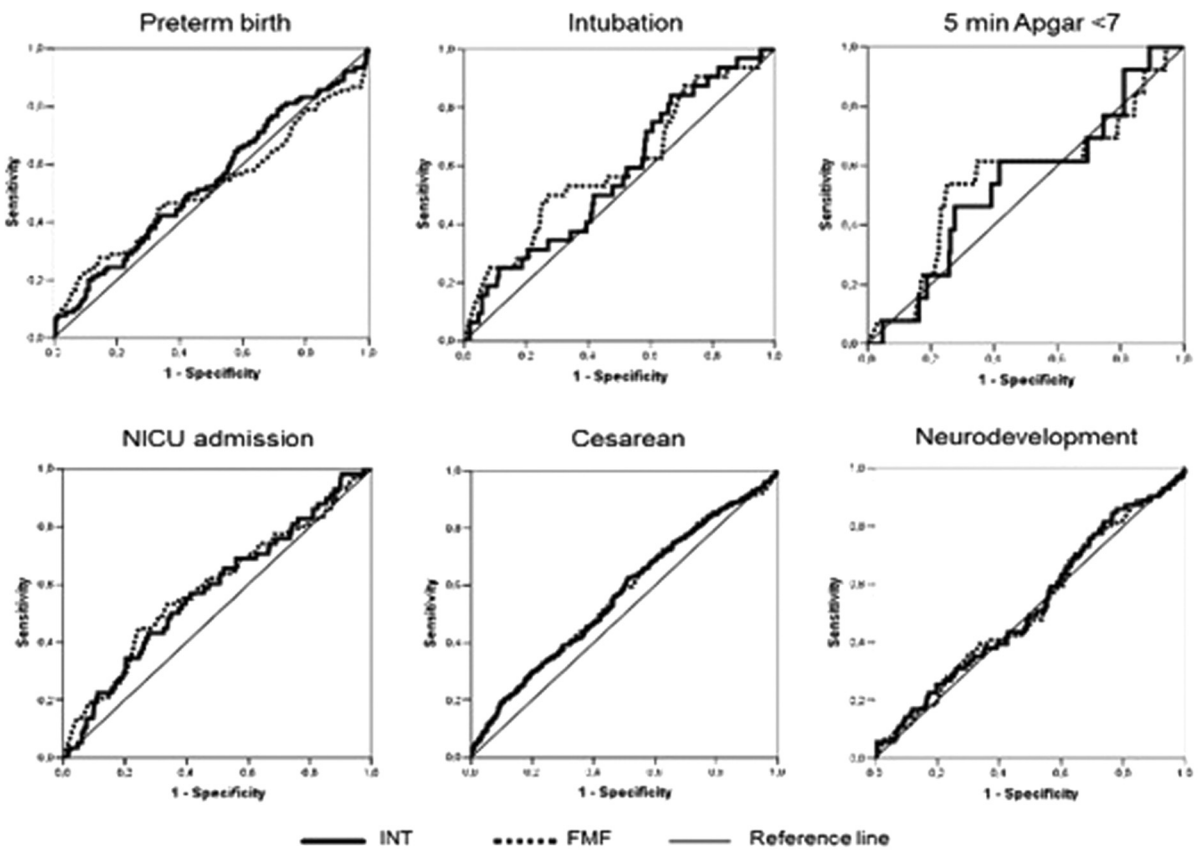

Fig. 2 Receiver operating characteristic curve of Intergrowth-21 st and Fetal Medicine Foundation to predict perinatal and infant neurodevelopmental outcomes using birth weight percentiles.

hypertension (23.7%).[31] Kiserud et al., similarly to the INT project, used a multinational sample that included a Brazilian city (Campinas; $n = 150$) to create EFW and BW standards for the World Health Organization.[7] Interestingly, the GA at the birth of the Brazilian sample was 39 weeks, similar to this study (39.3 weeks), and the BW was 3290.0 g, also similar to this study (3243.0 g) when growth-restricted NB are excluded.

The prevalence of premature births was 9.3%, lower than that found in the study by Passini et al. (12.3%).[32] The study cited above included 20 referral hospitals and more than 33,000 deliveries in Brazil. This difference can be explained by the characteristics of the samples obtained in each study. Our study recruited pregnant women in non-hospital units, while the study by Passini et al. included pregnant women from referral hospitals. Although some of the pregnant women in our study had complications during pregnancy, pregnant women coming from referral hospitals are more likely to have risk factors for preterm delivery, whether spontaneous, due to rupture of membranes, or therapeutic. In addition, the study by Passini et al. showed that Brazilian regions presented slightly different prevalences, with a lower prevalence for the Southeast region, where our study was performed.

Among the maternal diseases that can negatively affect fetal growth and bias the analyses, arterial hypertension had a slightly higher prevalence in this study (15.2%) compared with the general population.[20,33] We postulate that the recruitment may have been biased because the hypertensive pregnant woman seeks the health unit more frequently. The prevalence of smoking was similar to other studies.[34] The prevalence of diabetes was low in this study, despite the indistinct inclusion of type 1, 2, and gestational diabetes, probably due to underreporting and the use of old diagnostic criteria for gestational diabetes used at the time. The International Association of Diabetes in Pregnancy Study Group criteria, which are more sensitive, were adopted from 2015 onwards in our country. The statistical difference observed between the INT and FMF groups is probably due to the small number of diabetes diagnoses in these groups (the same 2 cases for both groups).

The INT and FMF curves were tested in different populations. Kajdy et al., in Poland, obtained a BW reference curve of 39,092 single births and compared their percentiles with 6 published charts, including the INT. In that study, the 50th percentile at 40 weeks was 3645.8 g and 3486.7 g for male and female NB, respectively. The authors obtained 3.2% of NB below the 3rd percentile by the local chart and only 0.6% by INT.[35] Anderson et al. obtained data from 53,484 NB in Auckland, New Zealand, and compared small-for-gestational-age (SGA) new-born outcomes between INT versus a customised standard using maternal characteristics of height, weight, parity, and ethnicity. The GA was 39.4 weeks, and the weight was 3433 g, with a higher weight associated with Pacific ethnicity (3585 g) and a lower weight associated with Indian ethnicity (3130 g). The incidence of SGA was 4.5% when INT was used and 11.6% when the customised standard was used. The authors concluded that customised curves identified more NB SGA at risk for perinatal morbidity and mortality than INT standards.[36] Francis et al. analyzed data from 1.25 million full-term pregnancies from 10 countries. INT was compared with a customised standard to determine stillbirth rates in SGA and large for gestational age (LGA) groups. Significant differences in SGA rates would be found between countries using INT. The most significant differences were observed between Sweden (10.7% for the customised standard and 3.1% for INT) and India (11.3% for the customised standard and 16.8% for INT). In Sweden ($n = 257{,}924$), the GA at birth was 40.8 weeks, and the BW was 3623.0 g, while in India ($n = 6436$) the GA at birth was 39.0 weeks, and the BW was 3055.5 g.[37]

Regarding FMF patterns, Duncan et al. compared the detection of SGA in preterm prelabor rupture of membranes by Hadlock versus the FMF charts. A sample of 106 patients from a university hospital in Tennessee with 84.9% African American was assessed. The cutoff point adopted was the 10th percentile. In this study, the FMF and Hadlock patterns discriminated respectively 48 (45%) and 22 (21%) of NB below the 10th percentile. Both patterns had similar accuracy in predicting SGA and were equally poor in predicting severe adverse neonatal outcomes. The FMF chart resulted in a 2-fold increase in positive cases, potentially increasing surveillance.[38]

Based on the studies cited above, it is evident that different populations can provide different proportions of NB below the 3rd or 10th percentile when using the same curve. Given its miscegenation, it is plausible that the INT provides standards more suited to the Brazilian population as the multiethnic sample is one of the main features of the INT standards. Compared with FMF, INT is less sensitive but appears safe as it does not increase adverse outcomes. This can be advantageous in resource contingency scenarios.

Conclusion

Although BW below the 3rd percentile is associated with adverse perinatal and neurodevelopmental outcomes, it was insufficient for a good diagnostic performance when evaluated alone. The analyses performed in this study could not show that one curve is unequivocally better than the other in our population. The apparent excess of newborns classified below the 3rd percentile by FMF may mean that it is not advisable to use references imported from countries of different racial composition, such as European countries or the United States. It is plausible that INT is more suitable for the Brazilian population due to its mixed racial composition. Further prospective studies are needed in Brazil to compare global standards, such as INT, with locally customized curves.

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

Conflicts to Interest

The authors inform that there are no conflicts of interest, whether political, economic, resources to carry out the research or intellectual property.

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A New Brazilian Device for Cervical Cancer Screening: Acceptability and Accuracy of Self-sampling

Um Novo Dispositivo Brasileiro para Diagnóstico de Câncer Cervical: Aceitabilidade e Precisão da Autoamostragem

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Abstract

Objective To evaluate the accuracy and patient acceptability toward self-sampling using a new device - SelfCervix® - for detecting HPV-DNA.

Methods A total of 73 women aged 25–65 who underwent regular cervical cancer screening from March to October 2016 were included. Women performed self-sampling followed by a physician-sampling, and the samples were analyzed for HPV-DNA. After that, patients were surveyed about their acceptability of self-sampling.

Results HPV-DNA detection rate of self-sampling presented high accuracy and was similar to physician-collection. Sixty-four (87.7%) patients answered the acceptability survey. Most patients (89%) considered the self-sampling comfortable, and 82.5% preferred self-sampling to physician-sampling. The reasons cited were time-saving and convenience. Fifty-one (79.7%) reported that they would recommend self-sampling.

Conclusion Self-sampling using the new Brazilian device SelfCervix® is not inferior in HPV-DNA detection rate compared with physician-collection, and patients are supportive of the method. Therefore, it might be an option to reach under-screened populations in Brazil.

Keywords
- uterine cervical neoplasms
- human papillomavirus
- cytology
- diagnostic screening programs
- early detection of cancer

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Resumo

Objetivo Avaliar a acurácia e aceitabilidade da auto-coleta utilizando um novo coletor - SelfCervix® - para a detecção de DNA de HPV.

Métodos Foram incluídas no estudo 73 mulheres com idade entre 25–65 anos que realizaram seu rastreamento regular do câncer de colo do útero entre Março e Outubro de 2016. Estas mulheres realizaram a auto-coleta, seguida de coleta profissional e as amostras foram analisadas para a presença de DNA de HPV. Após, elas responderam um questionário sobre a experiência da auto-coleta.

Resultados As taxas de detecção de DNA de HPV por auto-coleta foram altas e similares as da coleta profissional. Sessenta e quatro (87,7%) pacientes responderam o questionário de experiência. A maioria (89%) considerou a auto-coleta confortável, e 82,5% preferiram o método comparado a coleta profissional. As razões citadas foram economia de tempo e conveniência. Cinquenta e uma (79,7%) mulheres confirmaram que recomendariam a auto-coleta.

Conclusão Auto-coleta utilizando o novo coletor desenvolvido no Brasil não é inferior na detecção de DNA de HPV quando comparada a coleta profissional, e apresenta uma boa aceitabilidade pelas mulheres. Desta maneira, pode ser uma opção para alcançar populações que não realizam o rastreamento padrão.

Palavras-chave

- Neoplasias do colo de útero
- Papiloma vírus humano
- Programas de rastreamento
- Detecção precoce do câncer

Introduction

Cervical cancer is the fourth most common cancer in women worldwide and is responsible for ~311,000 deaths per year.[1] Despite highly preventable neoplasia, this tumor frequently occurs in women who do not participate in screening programs[2,3] Papanicolaou (Pap) test is Brazil's gold-standard method for cervical cancer screening and since the introduction of screening programs, the early diagnosis has decreased considerably the cervical cancer burden.[4] In Brazil, Pap testing-based cervical cancer screening programs are available for the population through the public health system, however, many women do not attend the programs and are not reached by them. Problems such as lack of knowledge, physician embarrassment, competing priorities, and access difficulties to the public health system are associated with not-attendance to screening programs.[5] Therefore, the adoption of alternative methods to complement the traditional screening already available is needed.

Persistent infection with high-risk Human Papillomavirus (mainly HPV types 16 and 18) is the etiologic cause of cervical cancer development.[6] This link between HPV infection and cervical cancer supported the introduction of HPV testing in screening programs.[7,8] The HPV testing presented high negative predictive results and is very sensitive for detecting patients at high risk of developing cervical cancer precursor lesions and cancer.[8–10]

Self-sampling of cervicovaginal specimens is feasible, can be done at a convenient location and time, is cost-effective, avoids the need for a professional-based sampling, and enhances women's empowerment for their health. The combination of self-sampling with HPV DNA testing has similar accuracy compared with professional-based collection,[11,12] can increase screening adherence in populations under-screened,[9,13,14] and is a promising strategy for expanding screening coverage.

We developed a Brazilian self-collector of cervicovaginal samples, SelfCervix®, to collect enough cells to perform HPV DNA testing, liquid-based cytology, and analysis of several sexually transmitted diseases. Our study aims to evaluate self-sampling acceptability and accuracy using the SelfCervix® for detecting HPV DNA in a Brazilian cohort.

Methods

Women aged 25–65 years who underwent previous Pap testing for cervical cancer screening at USP Clinic Hospital (São Paulo, SP, Brazil), USP University Hospital (São Paulo, SP, Brazil), and Citoclin (Porto Alegre, RS, Brazil) from March to October 2016 were invited to participate in the study. Pregnant women, women who have not yet started the sexual activity, or those who underwent chemotherapy or radiotherapy for cervical cancer were not eligible for the study. Patients presented the following results in the previous Pap testing: no histology alteration in one (1.6%) sample, cervicitis in 13 samples (20.2%), atypia in one (1.6%) sample, Cervical intraepithelial neoplasia I (CINI) in 13 (20.2%) samples, CIN2/CIN3 in 31 (48.4%) samples, adenocarcinoma in two (3.2%) samples, condyloma/warts in one (1.6%) sample, and squamous metaplasia in two (3.2%) samples. From 9 patients, the histology information was missing due to insufficient samples to perform the test.

Women who provided informed consent performed self-sampling followed by a physician-sampling with a vaginal swab. Before the physician-sampling, the SelfCervix® and verbal instructions explaining how to carry out the cervical self-sampling were provided to each patient by the physician. The SelfCervix® comprises a plunger with a soft

material in the distal portion. After inserting the device into the vagina, women depressed the plunger, and through rotational movements, the device collected the cells from the cervicovaginal area. Once collected, the material was placed in a tube containing PreservCyt® (Hologic, MA, USA) medium. The material obtained was used for carrying out HPV-DNA tests and liquid-based cytology when the HPV-DNA was positive.

After the self-sampling using SelfCervix®, the physician collected cervical smears with a vaginal swab, and the patient underwent a standard professional exam. The sample was placed in a tube containing PreservCyt® (Hologic, MA, USA) medium for carrying out HPV-DNA test and liquid-based cytology. Our study's gold-standard analysis of cervical samples was the HPV-DNA detection rate by physician-based sampling. The samples were classified according to the International Federation for Cervical Pathology and colposcopy 2011.[15]

The HPV-DNA test was performed using the hybrid capture technique II Qiagen (Gaithersburg, USA). Oncogenic probes were used to identify HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. For HPV-DNA-positive women, liquid-based cytology was performed on the same cervical sample.

When the cytology was positive for any cervical abnormality (diagnosis of atypical cells of undetermined significance or more (ASCUS+)), the woman was referred for colposcopy and classified according to Bethesda classification: CIN 1 corresponds to low-grade squamous intraepithelial neoplasia and CIN 2 and 3 to high-grade squamous intraepithelial neoplasia.

The HPV-DNA testing, liquid-based cytology, and colposcopy were analyzed at the Gynecological Oncology Research Institute (IPOG) laboratory based in São Paulo.

The participants were invited to complete the acceptability of vaginal self-sampling survey following the self and physician-sampling. The survey consisted of 15 questions regarding sexual activity, prior experience with Pap testing, tolerability of both methods, preferences for self or physician-sampling, reasons for preferring one approach, and if they will indicate the self-sampling for other women.

Continuous variables were presented as mean and standard deviation and frequency and percentage for categorical variables. The comparison between self-sampling and physician collection samples was analyzed using the Kappa index. Value 0 was considered poor agreement, between 0 - 0.2 reasonable agreement, 0.2–0.4 agreement, 0.4–0.6 moderate agreement, 0.6–0.8 substantial agreement, and above 0.8 excellent agreement. Fischer's exact test and chi-square were used to assess the relationship between each technique and colposcopy and biopsy results. The SPSS version 19.0 (IBM Inc, Chicago, IL) was used. A p-value < 0.05 was considered significant with a 95% confidence interval.

This study was performed according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) ethical guidelines and was approved by the ethics committee of the USP University Hospital under the number CAAE 56311616.6.0000.0076 (approval date: 24 June 2016) and USP Clinic Hospital CAEE 38719314.2.0000.0068 (approval date: 11 April 2017). All patients signed the informed consent form to participate in the study.

Results

A total of 73 women from 3 different institutions were included in our study. Twenty-two (30.1%) women underwent cervical sample collection at Citoclin, 17 (23.3%) at the University Hospital of São Paulo (HU), and 34 (46.6%) at Clinic Hospital of São Paulo (HC). The median age of the patients was 33 years.

The detection rate of HPV-DNA in self-collected and physician-collected samples was 64.4% and 71.2%, respectively ($p = 0.1$) (►**Fig. 1**).

Discrepancies in HPV-DNA detection between self and physician-collected samples occurred in 9 (12.3%) cases. Of these samples, 7 were positive for HPV-DNA as determined in the physician-sampling and the other 2 samples corresponded to cases classified as negative for HPV-DNA in physician-sampling and positive in self-sampling. All HPV-DNA-positive samples in physician and self-sampling were referred to liquid-based cytology. In the discordant results, the physician-sampling was the gold-standard for liquid-based cytology. If the sample was positive for HPV in physician-sampling and negative in self-sampling, only the physician-sampling was referred to liquid-based cytology; and if the sample was HPV negative in physician-sampling but positive in self-sampling, both samples were referred to liquid-based cytology. "These results are summarized in ►**table 1**.

In our study self-sampling presented 87% accuracy, 86% sensibility, and 84% efficiency for HPV-DNA detection. For HPV-DNA-positive women, liquid-based cytology was performed on the same cervical sample to analyze cellular alterations and also presented 87% accuracy. The HPV-DNA detection rate of the samples collected by the physician was used as the gold standard for comparisons (►**Table 2**).

Of 73 patients, 64 (87.7%) answered the survey. The mean age was 35 (18–65) years old. Approximately half of the patients, 31 (48.4%) started sexual activity between 18 and 20 years, and 38 (59.3%) did not use a condom in sexual

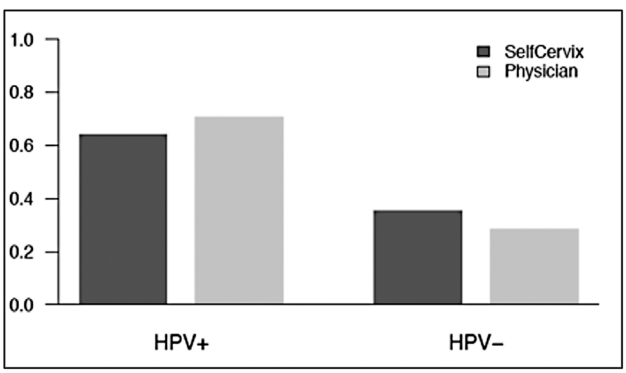

Fig. 1 The detection rate of HPV-DNA in cervical samples collected by self-sampling and physician-sampling.

Table 1 Characteristics of discordant results in samples collected by self-sampling and physician-sampling

		Physician-sampling		Self-sampling	
Age	Histology	HPV	Liquid-based cytology	HPV	Liquid-based cytology
30	Cervicitis	+	Inflammation	−	Not performed
32	CIN2/CIN3	+	ASCUS	−	Not performed
36	CIN2/CIN3	+	ASCUS	−	Not performed
45	Cervicitis	+	ASCUS	−	Not performed
35	CIN2/CIN3	+	Low grade	−	Not performed
27	CIN2/CIN3	+	High grade	−	Not performed
24	Missing data	+	High grade	−	Not performed
22	Cervicitis	−	Inflammation	+	Inflammation
23	Cervicitis	−	Inflammation	+	Inflammation

Abbreviations: ASCUS, Atypical squamous cells of undetermined significance; CIN, Cervical intraepithelial neoplasia; HPV, Human Papillomavirus.

relationships. All the patients underwent prior Pap testing at least once in life, 71.4% perform the screening annually, and 22.2% every three years. Fifty-seven patients (89%) considered self-sampling tolerable/painless, and 29 (45.3%) reported self-sampling was more comfortable to use than physician-sampling. The majority (82.5%) preferred self-sampling to physician-sampling, and the reasons cited were convenience (54.7%) and time-saving (30%). Most patients (79.7%) reported that they would recommend self-sampling to other women.

Discussion

To our knowledge, this is the first Brazilian self-collector product, SelfCervix® (ANVISA registry 80525329009), that allows the analysis of HPV and liquid-based cytology with a unique collection.

HPV testing as a primary screening method for cervical lesions and cancer is approved in different countries, including the USA, England, and the Netherlands.[16–18] HPV-based cervical cancer screening increased by 90% the detection of CIN3+ and, due to the high negative predictive value, is considered superior to cytology.[16,19,20] A population-based study with 1.160,981 women from rural China demonstrated the efficiency of HPV testing in detecting CIN2+ lesions and supports the introduction of HPV testing in primary screening in China.[21] The benefit of HPV DNA testing for cervical cancer screening is still debatable regarding the detection of adenocarcinomas. HPV testing is less sensitive for adenocarcinoma precursors compared with squamous cancer precursors.[22,23] However, since none of the available screening options, cytology and HPV testing, are able to detect all cervical cancer, the HPV testing is presenting better results for the detection of overall cervical carcinoma and precursors.[16,23,24] In a preliminary analysis, a study conducted in 2017 in Indaiatuba city (SP, Brazil) evidenced increased coverage, high adhesion to follow-up, few unsatisfactory samples, and a high referral for colposcopy using DNA-HPV testing as a primary screening program compared with cytology.[25,26] In population-based data from Brazil, cervical cancer screening with HPV testing was also cost-effective compared with cytology.[27] Indeed, screening every 4 years using HPV testing presented a lower cost.[28] Current study showed a probability lower than 1% of CIN2+ detection ten years after a negative HPV test and suggested that the interval of HPV testing could be prolonged in selected women.[29] Despite that, until now in Brazil the gold-standard method for cervical cancer screening is the Papanicolaou (Pap) test, and HPV DNA testing is available on public health system only for sexual disease diagnosis.

Table 2 Efficacy of self-sampling for HPV-DNA detection compared with physician-sampling physician-collection (gold-standard)

	HPV
Sensibility	0.86
NPV	0.95
PPV	0.73
Specificity	0.90
Accuracy	0.87
Efficiency	0.84

In the present study, we demonstrated that self-sampling of cervicovaginal samples using the SelfCervix® presented high accuracy, sensibility, and good specificity to detect HPV-DNA and cellular alterations in liquid-based cytology for positive HPV-DNA samples. Corroborating our findings, previous studies presented similar HPV-DNA detection accuracy on self and physician-based sampling, good acceptability, and preference for self-sampling in populations under-screened and women attending routine cervical screening.[9,13,30–33] Lorenzi and colleagues evaluated the acceptability of cervicovaginal self-sampling in a cross-sectional study with 116 women from two university hospitals in Brazil. The authors demonstrated that most women

preferred self-sampling to the collection by a healthcare professional due to the possibility of choosing the place and the best time to perform the sampling.[34] Castle and colleagues showed a preference for under-screened Brazilian women to perform self-sampling. The authors suggested that self-sampling combined with HPV-DNA testing could improve screening coverage in Brazil and reach women who do not have access to the Pap testing.[9] Torres and colleagues also showed that cervicovaginal self-collection with detection of cervical malignancy using HPV 16 and 18 E6 oncoproteins is feasible and expanded screening coverage in women from a remote geographic location in Amazonas (Brazil).[14] In Argentina, the self-collection with HPV testing increased 4-fold the cervical screening coverage through a community of health workers.[13] The increased coverage makes HPV testing with self-collection most cost-effective than traditional screening methods in low and middle-income countries.[32] Future studies using SelfCervix® in HPV-based cervical cancer screening in a large cohort must verify the acceptability, coverage, and cost-effectiveness.

We observed an HPV detection concordance of 87.7% between the SelfCervix® and physician-based sampling. In accordance, previous authors showed over 90% of HPV detection concordance between self and clinician-collected samples.[12,35,36] Nine women presented discordant results in HPV-DNA testing: in the self-sampling, two samples were positive, and seven were negative, contrary to professional-sampling findings. It is interesting to highlight that the patients with discordant results were younger, with a median age of 29.5 years and none of the patients aged > 45 years presented disagreement in HPV results with the different collection types. The patient's age and HPV testing are important factors to be considered when evaluating HPV self-sampling.

We compared the results of a meta-analysis already published in the literature with the results of a Pap testing collected by a health professional to our findings of HPV-DNA detection rate by the SelfCervix® device. The Selfcervix® presented a sensitivity of 86% to detect HPV-DNA compared with the meta-analysis results that demonstrated 59% sensitivity of the Pap testing for cervical cancer screening strategy. The two methodologies showed a similar specificity (90% versus 94%).[37] When comparing data already published from other cervical collectors[34] to the SelfCervix®, we observed that SelfCervix® presented a tendency of higher sensibility (86% versus 74%) and similar specificity (90% versus 92%) in HPV detection. The studies evaluating other cervical collectors used HC2 assay to detect HPV-DNA (16,18,31,33,35,39,45,51,52,56,68,69 and 68) and swab, spatula/Cytobrush, cervix broom brush, and Digene sampler for cervicovaginal sampling.[37]

We also performed a survey with the participants to evaluate women's perception of the use of self-sampling. They reported a preference for self-sampling compared with physician-sampling, considering convenience the most important perceived benefit, and almost 80% would recommend it. Nine women did not answer the survey claiming a lack of time. These findings follow previous literature showing positive feedback from women and good acceptability of self-sampling.[9,34,38,39] A literature review including articles from low-and middle-income countries showed that most patients considered HPV self-sampling easy to perform, painless and preferred compared with physician-sampling. The most reported benefits were the convenience of screening from home, time-saving and less embarrassment.[38] Highly acceptability of HPV self-sampling, regardless of age and country of residence, and a preference for home-based self-sampling was also evidenced in a systematic review comprising 72 studies published between 2002 and 2018.[39] Lorenzi and colleagues evaluated the acceptability of self-sampling in a cross-sectional study involving 116 Brazilian women. The authors showed that most participants considered self-sampling easy to collect cervicovaginal samples and preferred self-sampling over physician-collection. Corroborating our results, the participants also reported the convenience of choosing the place and time for sampling as the main benefit.[34]

Our study presented limitations, including the sample size, the possible difference in the professional-sampling and cytology evaluation from the 3 different institutions, and the use of professional-sampling as the gold-standard methodology instead of anatomo-pathological analysis.

Conclusion

The self-collector of cervicovaginal samples, SelfCervix®, demonstrated high performance in HPV-DNA detection and patient acceptability in a Brazilian cohort. The SelfCervix® is not inferior in the detection of HPV compared with physician-collection. We suggest that the use of SelfCervix® in combination with HPV testing might be an option to reach under-screened populations and increase the coverage of cervical cancer screening in Brazil.

Contributions

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

Conflicts to Interest

The authors have no conflict of interest to declare.

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Effect of Combined Training on Body Image, Body Composition and Functional Capacity in Patients with Breast Cancer: Controlled Clinical Trial

Efeito do treinamento combinado na imagem corporal, composição corporal e capacidade funcional em pacientes com câncer de mama: ensaio clínico controlado

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Abstract

Objective: Evaluate the effect of combined training on body image (BI), body composition and functional capacity in patients with breast cancer. As also the relationship of BI with body composition and functional capacity.

Methods: This was a Controlled Clinical Trial study, this study including 26 patients with breast cancer (30 to 59 years). The training group (n = 13) underwent 12 weeks of training, including three 60-min sessions of aerobic exercise and resistance training, and two sessions of flexibility training per week; each flexibility exercise lasted 20s. The Control Group (n = 13) received only the standard hospital treatment. Participants were evaluated at baseline and after 12 weeks. BI (primary outcomes) was assessed using the Body Image After Breast Cancer Questionnaire; Body composition was estimated with the indicators: Body mass index; Weight, Waist hip Ratio; Waist height ratio; Conicity index; Reciprocal ponderal index; Percentage of fat; Circumference of the abdomen and waist; Functional capacity by cardiorespiratory fitness (cycle ergometer) and strength (manual dynamometer). The statistic was performed in the Biostatistics and Stata 14.0 (α = 5%).

Keywords
- Breast neoplasms
- Health
- Exercise
- Women

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Results: The patients in the training group showed a reduction in the limitation dimension ($p = 0.036$) on BI, However, an increase in waist circumference was observed in both groups. In addition an increase in VO2max ($p < 0.001$) and strength in the right ($p = 0.005$) and left arms ($p = 0.033$).

Conclusion: Combined training demonstrates to be an effective and non-pharmacological strategy to patients with breast cancer, with improvement on BI and functional capacity, changing related variables negatively when there is no physical training.

Resumo

Objetivo: Avaliar o efeito do treinamento combinado na imagem corporal (IB), composição corporal e capacidade funcional em pacientes com câncer de mama. Assim como a relação do IB com a composição corporal e capacidade funcional.

Métodos: Este foi um estudo de Ensaio Clínico Controlado, este estudo incluiu 26 pacientes com câncer de mama (30 a 59 anos). O grupo de treinamento ($n = 13$) foi submetido a 12 semanas de treinamento, incluindo três sessões de 60 min de exercício aeróbio e treinamento de resistência, e duas sessões de treinamento de flexibilidade por semana; cada exercício de flexibilidade durou 20s. O Grupo Controle ($n = 13$) recebeu apenas o tratamento hospitalar padrão. Os participantes foram avaliados no início e após 12 semanas. O IB (desfechos primários) foi avaliado por meio do Body Image After Breast Cancer Questionnaire; A composição corporal foi estimada com os indicadores: índice de massa corporal; Peso, relação cintura-quadril; Relação da altura da cintura; Índice de conicidade; Índice ponderal recíproco; Porcentagem de gordura; Circunferência do abdômen e cintura; Capacidade funcional por aptidão cardiorrespiratória (cicloergômetro) e força (dinamômetro manual). A estatística foi realizada na Bioestatística e no Stata 14.0 ($\alpha = 5\%$).

Resultados: Os pacientes do grupo de treinamento apresentaram redução da dimensão da limitação ($p = 0{,}036$) no IB, porém, foi observado aumento da circunferência da cintura em ambos os grupos. Além disso, um aumento do VO2máx ($p < 0{,}001$) e da força nos braços direito ($p = 0{,}005$) e esquerdo ($p = 0{,}033$).

Conclusão: O treinamento combinado demonstra ser uma estratégia eficaz e não farmacológica para pacientes com câncer de mama, com melhora do IB e da capacidade funcional, alterando variáveis relacionadas negativamente quando não há treinamento físico.

Palavras-chave
- Neoplasias da mama
- Saúde
- Exercício
- Mulheres

Introduction

At least 16% of the world's population died of cancer in 2015, with breast cancer being the most frequent in women, especially in underdeveloped countries.[1] The disease and its treatment can generate important changes in body appearance and functionality. Changes in appearance include alopecia, surgical scars, breast removal, rashes etc.[2,3] Mastectomy can lead to emotional, social, postural, and sexual alterations. It can also cause lesions in muscles, lymphedema, and a decrease or loss in the range of motion. Furthermore, patients on antineoplastic therapy may present reduced strength and cardiopulmonary capacity.[4]

Body composition is considered a worrying factor, since treatment may imply a weight gain of 71.43%.[5] Excess weight and obesity are a poor prognosis, due to increases in tumors, the positivity of estrogen and progesterone receptors, risk of distant metastasis, and mortality.[6]

There has been an expansion in the clinical and investigative interest in oncology since 2012,[7] when Supportive Care in Cancer highlighted the importance of assessing body image (BI) in cancer patients. BI is a multidimensional construct, and it is necessary to consider the subjective experiences of the disease,[3] as well as the symbolic value attributed to specific body segments, such as the breast, for the woman.[7]

Thus, in the elaboration of BI, the social and cultural influence derived from interpersonal experiences should be considered, allied to several elements of the appearance and body functionality.[8] Therefore, women with breast cancer are vulnerable to adverse impacts on their BI[9,10] which in turn can generate various consequences such as anxiety, depression, mutilation, and low self-esteem.[11]

Physical training methods, both strength and aerobic, have been used as safe and well tolerated interventions in cancer patients.[12–14] Studies have shown a decrease in body fat, and improvements in cardiopulmonary function,

strength,[12,13] and BI[15,16] after interventions with physical activity. However, although interventions with combined training (CT), aerobic and resistance training in the same session, are widely used,[17–19] the available information is still insipid.[13] Little is known about the influence of combined training (underwent 12 weeks of training, including three 60-min sessions of aerobic exercise and resistance training, and two sessions of flexibility training per week; each flexibility exercise lasted 20 s and was performed in sets of three repetitions) on BI, on functional and body composition parameters in this population.

In addition, the investigation of parameters in the construction of BI, appearance and function, with elements of body composition and functional capacity in patients with breast cancer, since suffer adverse effects in cancer treatment. Thus, the present study aims to evaluate the influence of CT on the BI, body composition and functional capacity of patients with breast cancer, as also the relationship of BI with body composition and functional capacity.

Methods

Study Design

Controlled Clinical Trial study, intervention training combined (aerobic, resistance and flexibility training) the 12 weeks in patients with breast cancer.

Participants

Thirty-one women (30 to 59 years old) selected in the Hospital participated in the study, through standardized invitations given at routine meetings at the institution. The inclusion criteria were: 1)Not having performed physical training for at least 6 months, 2)Being on treatment (chemotherapy and hormone therapy, radiotherapy) or monitoring of breast neoplasms, 3)No diagnosis of mental disorders or psychological disorders, 4)Able to communicate verbally, 5)No motor restrictions, 6)Not pregnant or lactating, 7) Performing all evaluations, 8)Having previous medical release. To remain in the physical training group, it was necessary to not be absent from more than three consecutive sessions.

Patients were contacted and invited to participate in this study by telephone, through invitations issued at regularly-scheduled meetings with HCAB patients, and by referral from oncologists, mastologists, physiatrists, physical therapists, psychologists and pain management specialists. Patients who showed interest received a complete explanation of the study.

Groups were divided 1:1, they were randomly with sweepstakes, assigned to groups into the Training Group (TG), with 15 patients who performed CT for 12 weeks together with conventional hospital treatment, and the Control Group (CG) with 16 patients who only underwent conventional hospital treatment (chemotherapy and hormone therapy, radiotherapy) for 12 weeks. The physical evaluations were performed blindly by the evaluator, who was only informed of the day and time of evaluations. The sample size was calculated using statistical G-power 3.1, with power 0.8 and level of significance 0.05, which showed that twelve participants were needed.

Participants were informed about the objectives of the study and written informed consent was obtained. The study had approval from the Research Ethics Committee of the Federal University of Maranhão, protocol number 20665713.2.0000.5087 and Trial Registration: NCT03061773.

Assessments of both the TG and the CG were conducted at the study's outset to establish a baseline, and at the end of 12 weeks, corresponding to the length of the combined training intervention. The team was trained in the application of each survey and test procedure, and the researchers were blinded with regards to the physical assessments, only being informed of the day and time of the assessments.

Intervention

The CT program consisted of aerobic, resistance, and flexibility exercises lasting 12 weeks, with 3 sessions per week of aerobic and resistance training in the same session (supervised by trainers specialized in physical exercise) and intercalate 2 sessions per week of flexibility training. Each aerobic and resistance training session lasted 60 minutes, following the order: 30 minutes on cycle ergometer, hip flexion and extension, shoulder development, Swiss ball squatting, French triceps, and curved paddling.

The aerobic training was controlled by the training heart rate.[20–26] In the cardiorespiratory test, the ramp protocol adapted.[27] was used on a cycle ergometer (ERGO FIT brand, model ERGO 167-FITC CYCLE). Blood pressure was measured with conventional mercury column apparatus (BD®), heart rate (Polar FT2) and subjective perception of exertion using the Borg scale (Inforfisic Mark) in the final 15 seconds of the stages. Before and after the cardiorespiratory test, the patients remained seated at rest to verify the subjective perception of exertion, blood pressure, and heart rate. The test was performed after a 72-hour interval of familiarization. subjective perception of exertion was used to verify the individualized intensity of training (7 to 20), with the patients verbally encouraged to reach maximum fatigue.

The load progressions were performed every 4 weeks, respecting the biological individuality in the cardiorespiratory capacity test and maximal repetitions to predict the initial load.[28] The initial intensity of the aerobic training was 50 to 60% of the training heart rate, ending with 80 to 90% of the training heart rate. The load of the resistance training started with the weight of the body itself or 1kg in dumbbells and shin guards, and moderate intensity in the elastic band. In the fifth week, there was an increase to 1kg and strong intensity in the elastic band, remaining until the twelfth week.

The resistance training protocol included 3 sets for each exercise with 12 repetitions and a one-minute interval between sets and repetitions. The speed of execution of each movement was three seconds in the concentric phase and three seconds in the eccentric phase.[29] The exercises were alternated by segment, prioritizing the large muscle groups. The loads were by means of shin guards, dumbbells, elastic bands, and the weight of the body itself.

The resistance training load was verified by means of the maximal repetition test, with 12 repetitions and a 72-hour interval of familiarization.[30] Patients who exceeded 12 repetitions were given a 5-minute interval before performing the 12 repetitions with a new load. The flexibility training was active, without pain, where each exercise lasted 20 seconds in 3 series.[28] Participants were instructed to perform ten stretches.

Primary Outcomes Measures

Body Image

BI was assessed using the Body Image After Breast Cancer Questionnaire,[20] a specific instrument for patients with breast cancer. This tool was validated for the Brazilian female audience.[3] It consists of 44 questions organized in 6 dimensions: 1)Vulnerability (V), 2)Transparency (T), 3) Body Stigma (BS), 4)Concerns about the Arm (CA), 5) Body Concerns (BC), and 6)Limitations (L). The answers are given on a *Likert* scale of agreement (1 to 5). The scores vary according to the scale and surgery; the higher the score, the more compromised the BI.[3,21] For the questions that presented negative scores, a value of 6 is inserted for the calculations of the dimensions.

Secondary Outcomes Measures

Body Composition

Anthropometric measurements were taken on a mechanical scale (Fillizola®, São Paulo, Brazil) to the nearest 0.1 kg, on a fixed stadiometer (Sanny®, São Paulo, Brazil) to the nearest 0.1 cm and with a measuring tape (Sanny®, São Paulo, Brazil) to the nearest 0.1 cm respectively.[22] The weight was measured with the women without moving with the weight distributed equally between the feet in the center of the platform of the electronic scale, the participants.[22] Height was measured with the participants in the Frankfurt plan and stared at the horizon.[22] The circumference and skinfold measurements were verified with the participants standing and relaxed muscles.[22]

Body composition was verified through the following indicators: 2)Weight[22]; 1)Body Mass Index (BMI)[23]; 3)Waist Hip Ratio[24]; 4)Waist Height Ratio[24]; 5)Conicity Index[24]; 6) Reciprocal Ponderal Index[25]; 7)Percentage of Fat[23]; 8)Circumference of the abdomen, waist (WC), hip, and right and left thighs[22]; 9)Fat-free mass.[22]

Functional Capacity

The static force was evaluated by grip strength using a hand held dynamometer (Jamar Sammons Preston) scale from 0 to 100 kilograms. Guidance was provided to press the equipment with maximum force, without flexing the elbow or changing the posture.[22] The participants were seated with the adducted shoulder and turned in a neutral way, elbow flexed at 90° and forearm and wrist in a neutral position.[31] Three attempts were allowed on both sides (alternately) and select the best result.[22] The maximum oxygen volume (VO2max) was measured using the estimated submaximal cycle ergometer test[23] based on the final power in a protocol of 15 Watts per minute, using the formula for women.

Statistical Analysis

Data normality was checked using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The comparisons of the baseline variables between groups were analyzed using the Student t test for independent samples when parametric statistics were observed. If the data presented non-parametric distribution, the Mann-Whitney and dichotomous variables χ^2 and Fisher's Exact test were used.

The differences between the CT and control groups were analyzed by two-way repeated measures of ANOVA (group x time). When a significant interaction was observed, a Bonferroni post hoc test was conducted. For all measured variables the estimated sphericity was verified according to Mauchly's W test and the Greenhouse–Geisser correction when necessary. The partial eta-squared was classified according to Cohen.[32] The correlation was verified through the tests: Pearson and Spearman, with classifications.[33] The data were analyzed using the Biostatistics and Stata 14.0, significance was set at $p < 0.05$.

Results

Twenty-six patients (13 TG and 13 CG) completed the study (►**Figure 1**). The patients presented homogeneity between the groups (►**Table 1**). Regarding the clinical aspects, only one patient in the TG had a bilateral mastectomy and patients of neither group performed breast reconstructions.

BI of the patients who performed CT presented a reduction for the L dimension ($p = 0.036$). In the concern with the body dimension was a tendency for TG reduction ($\Delta = 5.23$, $p = 0.183$). In the transparency dimension, the groups presented differences ($p = 0.009$). In the analysis of body composition, a change was observed after 12 weeks for WC ($p = 0.034$), fat-free mass ($p = 0.032$) and circumference of the right thigh ($p = 0.049$). Strength presented changes after 12 weeks, for both the right arm ($p = 0.005$) and observed left arm ($p = 0.033$). The detected increased right arm strength for the TG ($p = < 0.001$). In the VO2max there was also changes after 12 weeks ($p = < 0.001$) (►**Table 2**).

At the baseline period, the CG demonstrated a strong negative correlation between WC and all BI dimensions. After 12 weeks, the fat percentage was still correlated strongly and positively with the BC ($p = 0.016$). The muscle strength of the right arm was negatively and moderately correlated in the basal period with the L ($p = 0.042$) and after 12 weeks it remained negative, but strong, for the L ($p = 0.002$) and moderate for the CA(0.019) and T ($p = 0.035$) (►**Table 3**).

The concern with the arm dimension in the CG presented a positive and strong correlation with the waist hip ratio ($p = 0.011$) and fat-free mass ($p = 0.011$), and negative correlation with the volume of oxygen ($p = 0.018$) in the basal period. On the other hand, body composition variables, specifically the BMI ($p = 0.027$), weight ($p = 0.021$), waist

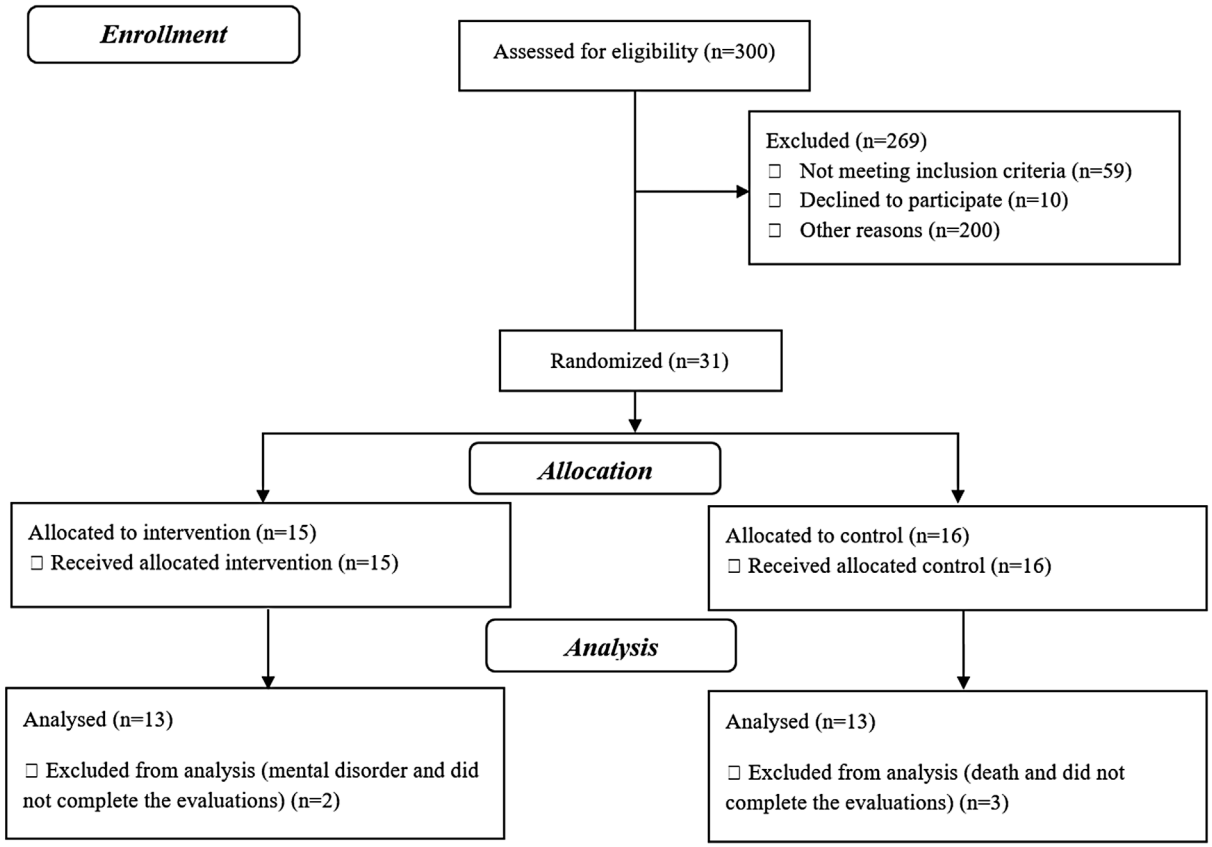

Fig. 1 Consort flowchart.

hip ratio ($p = 0.018$), WC ($p = 0.026$), and fat-free mass ($p = 0.011$) were negatively correlated with V (►**Table 3**).

Discussion

The main findings of this research were: 1)CT favored positive changes in BI; 2)Variables related to appearance were correlated with the vulnerability dimension in TG; 3)Variables related to body appearance and function were directly related to BI in the CG; 4)CT promoted improvements in functional capacity (FC), but not in body composition in TG women.

Statement of Main Finding

The central axis of this research is the investigation of BI changes. This was analyzed from the theoretical model with six dimensions[20] and validated for Brazilian women with breast cancer.[3] Three dimensions demonstrated sensitivity to CT: L, BC, and T. After the intervention, the TG demonstrated a reduction in the perception of functional limitations of the body, such as movement restrictions and oncologic fatigue. Arab et al.[13] in one of the few studies in this scope performed in Brazil, presented similar results, although applied only resistance training over 12 weeks. The authors attribute the improvement to the higher physical competence acquired for the performance of motor tasks. Unlike our data, did not find training effects in the other dimensions.[13] It is possible that this difference is associated with the specificity of the intervention given.

Concern with the body is a striking feature in women with breast cancer,[34] is accentuated either through the chemotherapy or mastectomy process.[35] As we hypothesized, the TG showed a tendency to reduce BC, that is, with their general appearance, including concern about the gain or loss of weight. Previous studies have demonstrated similar results after both strength training[16] and aerobic training,[14] in which improvements in the perception of body appearance and lower concern with weight were detected, respectively.

Concern with appearance is related to the alterations promoted by the disease and treatment, which may be less or more visible.[20] Issues relating to concern with how obvious the disease were denominated transparency by the authors. This variable was different between the groups so that women who did not receive the intervention with the CT presented higher scores in this dimension. We did not find similar studies that addressed this point, which limits our discussion. However, a qualitative research with Latina women with breast cancer, identified that the acceptance of changes in appearance is considered a central axis in BI.[9] The authors encourage the development of intervention strategies that favor the acceptance of appearance during and after treatment. Our results suggest that CT may be of potential assistance. This becomes more consistent when we observe the gross scores of all analyzed dimensions and find

Table 1 Characteristics of patients with breast cancer

Variables	Training group	Control group	p-value
Antopométricas[a]			
Age (years)	46.9 ± 7.4	51.8 ± 12.5	0.303
Height (m)	1.5 ± 0.1	1.5 ± 0.1	0.962
Weight (kg)	58.2 ± 9.7	63.2 ± 11.4	0.200
Employed[b]			
Yes	4(30.77%)	0	0.057
No	9(69.23%)	13(100%)	
Marital Status[b]			
Single	7(53.85%)	6(46.15%)	0.848
Married	6(46.15%)	7(53.85%)	
Time since most recent physical training[b]			
3 to 12 months	4(30.77)	0	0.057
> 12 months	9(69.23)	13(100)	
Clinical Period[b]			
Observation	6(46.15%)	2(15.38%)	0.343
Chemotherapy and Hormone Therapy	5(38.46%)	8(61.54%)	
Radiation Therapy	2(15.38%)	3(23.08%)	
Type of Tumor[b]			
Invasive Ductal Carcinoma	13 (100%)	11(84.62%)	0.220
Fuso-cellular or Epithelial Carcinoma	0	2(15.38%)	
Typo of Surgery[b]			
Conservative	3(23.08)	2(15.38)	0.500
Mastectomy	10 (76.92)	11(84.62)	
Mastectomy + Reconstruction	0	0	

[a]Student T-Test; [b]Fisher's Exact; [d]Chi-squared test; * $p < 0.05$; Expressed values: mean ± standard deviation. absolute frequency (relative frequency).

that, although there is no statistical significance, there is an increase in the CG and reduction in the TG, indicating a tendency to reduce BI impairment with the practice of CT.[3]

Discuss Essential Differences in Comparison to Other Studies

Next question was to identify whether improvements in BI could be attributed to changes in appearance and/and functionality as a result of CT. This hypothesis was partially rejected because the TG did not present a significant correlation between BI and FC. On the other hand, the body composition, BMI, weight, waist hip ratio waist hip ratio, WC, and fat-free mass variables, although not presenting significant changes in our sample, were negatively correlated with BI, specifically with the vulnerability dimension, in the basal period, assuming statistical significance after the intervention. This fact leads us to reflect that the body experience with the CT may have directed the attention of these women to their body measurements, however, differently to women without breast cancer, since the literature indicates that BMI, waist hip ratio, WC, and fat-free mass are predictors of negative changes in BI, such as body dissatisfaction.[34,36] In our study, the opposite occurred, the higher these scores, the lower the feeling of invasion of the body by the disease, which may have consequently caused a lower sensation of vulnerability.

Unlike our results did not identify any variable of body composition and/or function capable of mediating the effect of training on the improvements found in BI.[14,16] On the other hand, the positive effect on FC, identified here and in the studies above, is pointed out by the authors as a factor that influences BI, although indirectly. Speck et al.[16] explain that muscular strength provides benefits to the general quality of life and this, in turn, mediates the intervention in the perception of the body. Pinto et al.[14] concluded that the improvement found in patient's self-assessment of their physical condition is consistent with the increase in VO2max, thus indicating a refinement of the patient about her physical condition.

In contrast to the TG, the BI of the women who were not submitted to the intervention was influenced, over time, as much by the variables related to appearance as by body functionality. WC, a variable commonly associated positively with female body dissatisfaction,[34] precisely because it delineates female body forms, manifested itself in an opposite way for all dimensions of BI. Thus, the smaller this variable, the greater the perception of functional limitations,

Table 2 Body image, body composition and functional capacity of patients with breast cancer undergoing combined training

Variables	TG (n = 13)		CG (n = 13)					
	Base	12 weeks	Base	12 weeks	Time	Group	Interaction	Eta-squared
Body image								
Body stigma	32.5 ± 10.6	33.1 ± 7.7	36.1 ± 12.4	35.6 ± 14.3	0.981	0.478	0.759	0.00
Limitations	16.2 ± 4.8	11.2 ± 2.9*	13.9 ± 6.7	14.9 ± 5.7	0.036	0.704	0.003	0.20
Concerns about the arm	8.7 ± 3.9	9.8 ± 4.1	8.2 ± 3.2	9.8 ± 3.8	0.251	0.773	0.816	0.05
Body concerns	17.9 ± 7.0	12.7 ± 3.8	14.3 ± 6.0	15.9 ± 6.8	0.183	0.906	0.019	0.10
Transparency	14.7 ± 5.0	12.1 ± 3.3	17.8 ± 5.2	18.0 ± 5.9	0.295	0.009	0.214	0.04
Vulnerability	24.2 ± 9.1	19.4 ± 4.2	21.9 ± 9.6	22.7 ± 8.4	0.198	0.870	0.071	0.10
Body composition								
Body mass index (Kg/m^2)	24.6 ± 3.7	24.6 ± 2.9	26.8 ± 4.0	26.8 ± 3.9	0.864	0.135	0.947	0.00
Weight (kg)	58.2 ± 9.7	58.9 ± 9.2	63.2 ± 11.4	63.4 ± 10.9	0.224	0.257	0.479	0.10
Waist hip ratio (cm/cm)	0.8 ± 0.0	0.8 ± 0.0	0.8 ± 0.1	0.8 ± 0.1	0.112	0.086	0.702	0.10
Waist height ratio (cm/cm)	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.1	0.5 ± 0.1	0.259	0.071	0.689	0.05
Conicity index (m/kg/m)	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.2	1.3 ± 0.7	0.121	0.075	0.457	0.10
Reciprocal ponderal index (cm/kg)	39.8 ± 2.0	39.9 ± 1.6	38.7 ± 2.0	38.7 ± 1.8	0.845	0.112	0.860	0.00
Percentage of fat (%)	28.5 ± 5.6	27.4 ± 5.6	28.5 ± 5.6	27.4 ± 5.6	0.124	1.000	1.000	0.10
Circumference of the abdômen (cm)	87.1 ± 7.2	88.2 ± 8.0	92.2 ± 8.8	92.7 ± 9.4	0.191	0.148	0.626	0.10
Circumference of the waist (cm)	77.3 ± 6.5	78.8 ± 6.7	82.7 ± 8.9	83.3 ± 8.4	0.034	0.110	0.336	0.20
Circumference of the hip (cm)	96.9 ± 8.2	97.5 ± 6.7	100.0 ± 9.6	99.9 ± 8.3	0.655	0.408	0.553	0.01
Circumference of the right thigh (cm)	56.2 ± 6.6	53.7 ± 7.1	50.9 ± 3.9	51.9 ± 5.1	0.417	0.102	0.049	0.03
Circumference of the left thigh (cm)	54.5 ± 9.1	52.8 ± 7.2	50.4 ± 4.1	51.8 ± 5.5	0.897	0.298	0.173	0.00
Fat-free mass (Kg)	41.3 ± 4.8	42.4 ± 3.9	45.0 ± 7.6	45.8 ± 7.5	0.032	0.147	0.781	0.20
Functional capacity								
Strength of the right arm (Kgf)	20.2 ± 6.1	25.7 ± 5.5*	21.4 ± 7.4	20.5 ± 7.1	0.005	0.420	<0.001	0.30
Strength of the left arm (Kgf)	20.2 ± 6.2	23.4 ± 5.3	22.8 ± 6.9	22.2 ± 6.8	0.033	0.765	0.004	0.20
Maximum oxygen volume (ml^{-1}kg^{-1}min^{-1})	16.9 ± 2.0	20.7 ± 2.6#	11.9 ± 3.0	14.9 ± 3.0	<0.001	<0.001	0.243	0.51

*Difference in the TG after 12 weeks of training; #Difference between groups; TG: Training Group; CG: Control Group; Time: time referring to the intervention period; Interaction: Referring to the interaction between time and group.

the concern with the arm and with the body, accentuating the feelings of vulnerability, visibility of the disease (transparency), and BS.

The percentage of fat, also considered a predictor of body dissatisfaction in women,[34] especially for the lean body ideal,[36] maintained this characteristic for the CG, in proportion to the BS, BC, T, and V. This may be due to the gradual and complex process of acceptance of changes in appearance from disease and treatment, requiring women to learn and deal with these changes.[9]

Functional capacity also presented an influence on CG BI. The CG showed a negative correlation between arm muscle strength and the limitations and transparency dimensions in all phases. Concerns with the arm were positively related (although not significant at baseline) to muscle strength, assuming statistical significance, but negative, after 12 weeks. The opposite occurred between CA and VO2max,[37] whits the hypothesized that women with breast cancer feel empowered psychologically as they become more physically effective. Although we cannot state that the benefits of CT positively and directly impacted BI in the TG, the authors' idea applies in our results, since we observed that impairments in FC were negatively associated with CG BI.

The TG may have benefited from body experiences in the intervention, thus impacting dimensions which, although not evaluated herein, are indicated in the specific literature as linked to this process: cognitive, affective, and behavioral.[8] Interventions with physical exercise can provide the sensation of regaining control of the body itself, which may translate into a greater sense of self-efficacy in other areas of life.[37] Thus, it is possible to infer that CT promotes subjective experiences that go beyond body appearance and function, although indirectly influencing it.

Discussion of Secondary Outcomes

However, in the current study, there were no positive changes in body mass, percentage of fat, BMI, or other anthropometric indices in either group. It is worth noting that, despite this, the maintenance of these variables already indicates good maintenance, since the disease and its treatment promote negative changes in body composition.[5]

Table 3 Correlation between body image, body composition and functional capacity of patients with breast cancer undergoing combined training

Variables	TG				CG			
	Base		12 weeks		Base		12 weeks	
Corporal Stigma Dimension	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**
Body mass index (Kg/m^2)	0.03	0.925	0.17	0.581	0.54	0.057	0.20	0.519
Weight (kg)	-0.04	0.897	-0.05	0.867	0.48	0.101	0.16	0.612
Waist hip ratio (cm/cm)	0.24	0.431	0.13	0.676	-0.05	0.865	0.15	0.627
Percentage of fat (%)	-0.22	0.469	-0.06	0.857	0.59	0.035[b]	0.35	0.235
Circumference of the waist (cm)	0.03	0.915	0.02	0.954	-0.66	0.014[a]	0.20	0.509
Fat-free mass (Kg)	0.14	0.649	0.01	1.000	0.21	0.489	-0.02	0.954
Strength of the right arm (Kgf)	-0.31	0.309	-0.09	0.780	0.31	0.307	-0.17	0.580
Strength of the left arm (Kgf)	-0.34	0.261	-0.14	0.655	0.40	0.181	-0.06	0.851
Maximum oxygen volume (ml^{-1}kg^{-1}min^{-1})	0.20	0.509	0.14	0.648	-0.49	0.091	0.09	0.782
Limitations Dimension								
Body mass index (Kg/m^2)	0.16	0.610	-0.442	0.131	0.01	0.998	0.01	0.991
Weight (kg)	0.24	0.431	-0.291	0.335	0.03	0.928	0.19	0.536
Waist hip ratio (cm/cm)	-0.02	0.938	-0.459	0.115	-0.15	0.616	0.04	0.891
Percentage of fat (%)	-0.09	0.768	-0.268	0.377	0.52	0.066	0.33	0.270
Circumference of the waist (cm)	0.16	0.608	-0.385	0.194	-0.66	0.014[a]	-0.37	0.210
Fat-free mass (Kg)	0.33	0.266	-0.239	0.431	-0.22	0.477	0.03	0.926
Strength of the right arm (Kgf)	-0.41	0.167	-0.233	0.444	-0.57	0.042[b]	-0.78	0.002[a]
Strength of the left arm (Kgf)	-0.10	0.739	-0.048	0.877	-0.03	0.900	-0.50	0.080
Maximum oxygen volume (ml^{-1}kg^{-1}min^{-1})	0.20	0.509	0.370	0.214	-0.27	0.372	0.06	0.845
Concerns about the Arm Dimension								
Body mass index (Kg/m^2)	-0.27	0.369	0.11	0.722	0.50	0.083	0.09	0.766
Weight (kg)	-0.24	0.426	0.10	0.733	0.47	0.106	0.16	0.604
Waist hip ratio (cm/cm)	0.08	0.799	-0.15	0.633	0.68	0.011[a]	0.11	0.728
Percentage of fat (%)	-0.43	0.145	0.14	0.648	-0.33	0.264	0.14	0.653
Circumference of the waist (cm)	-0.27	0.378	0.12	0.699	-0.66	0.014[a]	-0.37	0.210
Fat-free mass (Kg)	-0.05	0.868	0.07	0.831	0.67	0.011[a]	0.09	0.759
Strength of the right arm (Kgf)	-0.33	0.265	0.20	0.510	0.06	0.844	-0.64	0.019[a]
Strength of the left arm (Kgf)	-0.24	0.432	0.08	0.801	0.09	0.781	-0.41	0.159
Maximum oxygen volume (ml^{-1}kg^{-1}min^{-1})	0.20	0.509	0.28	0.361	-0.64	0.018[a]	-0.16	0.600
Body Concerns Dimension								
Body mass index (Kg/m^2)	-0.10	0.739	0.01	0.964	0.27	0.373	0.01	0.964
Weight (kg)	-0.10	0.741	0.14	0.638	0.37	0.218	0.13	0.678
Waist hip ratio (cm/cm)	0.38	0.198	0.18	0.554	-0.04	0.897	-0.09	0.765
Percentage of fat (%)	-0.37	0.216	0.05	0.868	0.65	0.016[a]	0.65	0.016[a]
Circumference of the waist (cm)	-0.03	0.927	0.10	0.751	-0.66	0.014[a]	-0.37	0.210
Fat-free mass (Kg)	0.14	0.649	0.17	0.586	0.08	0.790	-0.18	0.563
Strength of the right arm (Kgf)	-0.20	0.509	-0.47	0.106	-0.29	0.337	-0.25	0.420
Strength of the left arm (Kgf)	-0.20	0.522	-0.21	0.482	-0.03	0.931	-0.22	0.473
Maximum oxygen volume (ml^{-1}kg^{-1}min^{-1})	0.20	0.509	0.28	0.361	-0.37	0.220	0.25	0.246
Transparency Dimension								
Body mass index (Kg/m^2)	0.10	0.757	0.37	0.211	0.27	0.364	-0.06	0.834
Weight (kg)	-0.08	0.789	0.28	0.360	0.27	0.371	0.04	0.889

(*Continued*)

Table 3 (*Continued*)

Variables	TG				CG			
	Base		12 weeks		Base		12 weeks	
Corporal Stigma Dimension	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**
Waist hip ratio (cm/cm)	0.31	0.302	-0.24	0.434	-0.10	0.745	0.05	0.866
Percentage of fat (%)	0.07	0.828	0.45	0.126	0.78	0.002[a]	0.14	0.647
Circumference of the waist (cm)	0.03	0.920	0.18	0.563	-0.66	0.014[a]	-0.37	0.210
Fat-free mass (Kg)	-0.15	0.624	0.10	0.754	-0.08	0.786	-0.03	0.922
Strength of the right arm (Kgf)	0.02	0.953	0.45	0.125	-0.17	0.574	-0.59	0.035[b]
Strength of the left arm (Kgf)	0.01	0.996	0.26	0.392	0.08	0.795	-0.35	0.242
Maximum oxygen volume ($ml^{-1}kg^{-1}min^{-1}$)	0.20	0.509	0.28	0.361	-0.30	0.328	0.05	0.869
Vulnerability Dimension								
Body mass index (Kg/m^2)	-0.29	0.341	-0.61	0.027[a]	0.22	0.463	0.20	0.519
Weight (kg)	-0.37	0.216	-0.63	0.021[a]	0.28	0.362	0.31	0.302
Waist hip ratio (cm/cm)	0.18	0.564	-0.64	0.018[a]	0.06	0.851	-0.01	0.963
Percentage of fat (%)	-0.33	0.275	-0.41	0.169	0.57	0.042[b]	0.38	0.197
Circumference of the waist (cm)	-0.24	0.428	-0.61	0.026[a]	-0.66	0.014[a]	-0.37	0.210
Fat-free mass (Kg)	-0.26	0.383	-0.68	0.011[a]	0.01	0.981	0.12	0.696
Strength of the right arm (Kgf)	-0.43	0.139	-0.20	0.510	-0.38	0.199	-0.54	0.058
Strength of the left arm (Kgf)	-0.43	0.141	-0.12	0.689	0.16	0.598	-0.24	0.434
Maximum oxygen volume ($ml^{-1}kg^{-1}min^{-1}$)	-0.46	0.119	0.28	0.361	-0.55	0.053	0.21	0.496

[a]Strong and significant correlation (r:0.6 the 0.8); [b]Moderate and significant correlation (r:0.4 the 0.6); TG: Training Group; CG: Control Group.

Similar results were found in women with breast cancer submitted to strength training,[15] aerobic[14] and combined protocols.[17] On the other hand had a reduction in fat percentage after intervention with CT.[18] This difference may be attributed to the superiority in the intervention time (24 weeks) and method of analysis (bioimpedance), performed by the researchers. However, the multi-frequency electrical bioimpedance analysis method indicates greater precision when performed in a segmental way, due to the morphological variation in the tissues.[38]

On the other hand, there was an interaction between time and group for the right thigh and changes in fat-free mass and WC after 12 weeks. Despite the maintenance of these variables, promoting health through physical training, there was an increase in the WC of both groups, which shows a negative trend and can be attributed to the cancer treatment. There is a large incidence of high WC in patients with breast cancer, which is linked to cardiovascular risk; these authors suggest that this population requires adherence to a nutritional program.[39,40] However, the study by Kim et al.[41] demonstrated a reduction in WC after a 12-week CT intervention, this difference may be due to the stage of the treatment, since all the patients were survivors of breast cancer. Further studies are needed to define the type of intervention effects in the reduction of visceral fat in patients in the treatment of breast cancer.

The effect of CT was confirmed by increased arm muscle strength and improvements in VO2max. These results corroborate studies in the literature which submitted women with breast cancer to protocols composed of aerobic and strength exercises and found similar results.[17–19] CT prevents the physical deconditioning inherent in cancer treatment.[19] These variables enhance the perception of this population of improvements in their quality of life.[15] CT promotes greater adherence to physical activity, due to the diversification of exercises.[18]

Strengths and Weakness of the Study

We recognize some methodological limitations of this research. The high exclusion of participants may negatively impact the results of randomized clinical trials, biasing the research. Also, the history of physical exercise of non-eligible patients was not investigated, information that may be useful for understanding some results.

Although we analyzed important variables in the elaboration of the BI of this population, such as the type of surgery,[2,11] a relevant point in this context is breast reconstruction since it is known that women undergoing reconstruction are less dissatisfied with their bodies.[35] Accordingly, we recommend new studies that compare women with and without breast reconstruction and analyze the relationship of BI with body composition and FC.

Clinical Implications

Thus, the data obtained here have theoretical and practical implications refers to the need to broaden the understanding of BI adaptations as a function of specific physical changes in breast cancer, using a specific tool and theoretical axis

that considers BI as a multidimensional and independent construct.

We believe that this information could help in the delineation of facilitating factors, mediators, and protectors of BI in the treatment process, allowing the elaboration of adequate interventions. Practical implications involve the use of this information in interventions that deal directly with the body, making them more assertive and efficient.

Conclusion

CT was shown to be a useful strategy capable of promoting improvements in the FC and BI of women with breast cancer. The effect of combined training may imply improvements in these variables that are negatively related in cancer patients who do not undergo physical training. Thus, we recommend the combined training use together with conventional treatment.

Contributions

1. Substantial contributions to conception and design, data collection or analysis, and interpretation of data (Andréa Dias Reis, Jurema Gonçalves Lopes Castro Filha, Evelyn Feitosa Rodrigues, Isadora Pinheiro Laranjeira, Bianca Trovello Ramallo, Fabrício Eduardo Rossi, Ismael Forte Freitas Júnior e João Batista Santos Garcia); 2. Writing of the article or critical review of the intellectual content (Andréa Dias Reis, Paula Tâmara Vieira Teixeira Pereira, Marcela Rodrigues de Castro e João Batista Santos Garcia); and 3. Final approval of the version to be published (Andréa Dias Reis, Marcela Rodrigues de Castro, Fabrício Eduardo Rossi e João Batista Santos Garcia).

Conflicts to Interest:

The authors have no conflict of interest to declare.

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Brazilian Black Women are at Higher Risk for COVID-19 Complications: An Analysis of REBRACO, a National Cohort

Mulheres negras brasileiras correm maior risco de complicações da COVID-19: uma análise do REBRACO, uma coorte nacional

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Abstract

Objective To evaluate the impact of the race (Black versus non-Black) on maternal and perinatal outcomes of pregnant women with COVID-19 in Brazil.

Methods This is a subanalysis of REBRACO, a Brazilian multicenter cohort study designed to evaluate the impact of COVID-19 on pregnant women. From February 2020 until February 2021, 15 maternity hospitals in Brazil collected data on women with respiratory symptoms. We selected all women with a positive test for COVID-19; then, we divided them into two groups: Black and non-Black women. Finally, we compared, between groups, sociodemographic, maternal, and perinatal outcomes. We obtained the frequency of events in each group and compared them using X2 test; p-values < 0.05 were considered significant. We also estimated the odds ratio (OR) and confidence intervals (CI).

Results 729 symptomatic women were included in the study; of those, 285 were positive for COVID-19, 120 (42.1%) were Black, and 165 (57.9%) were non-Black. Black women had worse education ($p = 0.037$). The timing of access to the health system was similar between both groups, with 26.3% being included with seven or more days of symptoms. Severe acute respiratory syndrome (OR 2.22 CI 1.17–4.21), intensive care unit admission (OR 2.00 CI 1.07–3.74), and desaturation at admission (OR 3.72 CI 1.41–9.84) were more likely to occur among Black women. Maternal death was higher among Black women (7.8% vs. 2.6%, $p = 0.048$). Perinatal outcomes were similar between both groups.

Conclusion Brazilian Black women were more likely to die due to the consequences of COVID-19.

Keywords

- COVID-19
- Obstetrics
- Racial disparities
- Black women

Resumo

Objetivo Avaliar o impacto da raça (negra versus não negra) nos desfechos maternos e perinatais de gestantes com COVID-19 no Brasil.

Métodos Esta é uma subanálise da REBRACO, um estudo de coorte multicêntrico brasileiro desenhado para avaliar o impacto da COVID-19 em mulheres grávidas. De fevereiro de 2020 a fevereiro de 2021, 15 maternidades do Brasil coletaram dados de mulheres com sintomas respiratórios. Selecionamos todas as mulheres com teste positivo para COVID-19; em seguida, as dividimos em dois grupos: mulheres negras e não negras. Finalmente, comparamos, entre os grupos, os resultados sociodemográficos, maternos e perinatais. Obtivemos a frequência dos eventos em cada grupo e comparamos usando o teste X2; Valores de $p < 0,05$ foram considerados significativos. Também estimamos o odds ratio (OR) e os intervalos de confiança (IC).

Resultados 729 mulheres sintomáticas foram incluídas no estudo; desses, 285 foram positivos para COVID-19, 120 (42,1%) eram negros e 165 (57,9%) não eram negros. As mulheres negras apresentaram pior escolaridade ($p = 0,037$). O tempo de acesso ao sistema de saúde foi semelhante entre os dois grupos, com 26,3% incluídos com sete ou mais dias de sintomas. Síndrome respiratória aguda grave (OR 2,22 CI 1,17–4,21), admissão em unidade de terapia intensiva (OR 2,00 CI 1,07–3,74) e dessaturação na admissão (OR 3,72 CI 1,41–9,84) foram mais prováveis de ocorrer entre mulheres negras. A mortalidade materna foi maior entre as negras (7,8% vs. 2,6%, $p = 0,048$). Os resultados perinatais foram semelhantes entre os dois grupos.

Conclusão Mulheres negras brasileiras tiveram maior probabilidade de morrer devido às consequências da COVID-19.

Palavras-chave

- COVID-19
- Obstetrícia
- Disparidades raciais
- Mulheres negras

Introduction

During pregnancy, COVID-19 has been associated with worse maternal and perinatal outcomes, such as a higher likelihood of admission to the Intensive Care Unit (ICU), requiring invasive ventilation, increased risk of preterm birth, pre-eclampsia, indication for C-sections, more significant admission to the neonatal ICU, and maternal death.[1]

In Brazil, one of the countries that have arguably suffered the most from the pandemic, disparities according to skin color have also affected maternal mortality - with maternal deaths being twice as frequent in Black women compared to White women.[2] The consequences of the pandemic have thus exposed underlying healthcare delays and highlighted the vulnerability of the system's diverse and multi-racial population.[3]

Brazil is known for its racial plurality but is also marked by structural and cultural racism.[4] According to the Brazilian Institute of Geography and Statistics (IBGE),[5] the Brazilian population is primarily Black (56.3%). Nevertheless, racism and racial disparities are perpetuated. It is known that structural racism is central to determining population health and there is increasing evidence of ethnic and racial disparities pervading health issues.[6] Concerning maternal health, Black women have the highest mortality and severe maternal morbidity rates in addition to delayed (or lack of) prenatal care, inappropriate health assistance, and worse experiences during pregnancy, childbirth, and postpartum.[7,8]

The Brazilian network of COVID-19 during pregnancy initiative (REBRACO) is a multicenter cohort study aimed at evaluating the clinical and epidemiological characteristics of SARS-CoV-2 infection and its associated outcomes during pregnancy and postpartum in Brazil.[9] This analysis aimed to understand the impact of race on maternal and perinatal outcomes of Brazilian women with COVID-19.

Methods

This is a secondary analysis of REBRACO (Brazilian Network of COVID-19 and Obstetrics, in the Portuguese acronym). REBRACO was a multicenter prospective cohort conducted from February 2020 until February 2021 that included 15 Brazilian maternity hospitals.

Methodological aspects and main findings of REBRACO have previously been published elsewhere.[9–11] Briefly, during the data collection period, all women with suspected SARS-CoV-2 infection attended at any center of those participating in REBRACO were invited to participate in the study after signing informed consent. Suspected SARS-CoV2 infection was considered when women presented any of the following signs and symptoms: fever, cough, nasal congestion, runny nose, dyspnea, chest pain, chills, diarrhea, vomiting, nausea, wheezing, dizziness, fatigue, myalgia, arthralgia, headache, sore throat, hyposmia/anosmia, ageusia, desaturation/oxygen saturation <95%, loss of consciousness, confusion, seizure, cyanosis, rash, skin ulcer, difficulty in swallowing, dehydration, inappetence, intercostal retraction, pain abdominal pain, conjunctivitis, lymphadenopathy, contractions, reduced fetal movements, vaginal bleeding and inability to walk. Participants were tested for SARS-CoV-2 infection according to the local availability of testing.

For this analysis, we selected all women with a positive test for SARS-CoV-2 and for whom data regarding racial status was available. We considered the IBGE criteria for skin color classification for the racial status analysis.[12] The IBGE classifies the Brazilian population into five categories based on skin color by asking individuals to self-identify as either White, Black, "Pardo" (brown), Yellow (East Asian), or Indigenous.[12] In Brazil, ethnicity is particularly complex due to great miscegenation, and the term "Pardo" thus represents a diverse range of ethnic-mixed backgrounds.[12] The IBGE categorizes Black people in Brazil as all people who identify as Black and Pardo. So, in this study, the category "Black woman" referred to women who self-declared as Black or "Pardo". In contrast, the category "non-Black woman" corresponds to the other three IBGE skin color categories (i.e., White, Yellow, and Indigenous).[12]

The following characteristics were evaluated in the current study: sociodemographic (age, education, marital status, pre-gestational BMI, region), obstetric characteristics (multiple pregnancy, parity, planned or unplanned pregnancy, pregnancy or postpartum period, type of prenatal insurance), and previous maternal comorbidities (alcohol use, asthma, chronic kidney disease, diabetes, HIV infection, hypertension, and smoking). For descriptive purposes, the North and Northeast Brazilian regions were grouped. This information was collected at enrolment.

After the clinical presentation of a suspected case of COVID-19, we followed the women until delivery if pregnant or until resolution of the COVID-19 suspected case if postpartum at admission. Data related to the suspicious symptomatic COVID-19 infection, characteristics of the management and resolution of the suspected infection, pregnancy, and maternal and perinatal outcomes were collected through a review of medical records, telephone interviews with the women, and in-person interviews.

Medical chart data were registered in the online RedCap® platform (an encrypted database where all the participating investigators could insert and update confidential patient information). Research collaborators had hierarchical and clustered access to the system; data was properly anonymized and personal, and contact information was kept confidential. The STROBE Statement (Strengthening the Reporting of Observational Studies in Epidemiology) was followed.[13]

For statistical analysis, women were divided into Black and Non-Black women. For bivariate analysis, we performed Chi-square or Fisher's exact tests (according to the number of subjects). A p-value < 0.05 was considered statistically significant. We also obtained the Odds ratio (OR), and respective 95% confidence intervals (CI) were calculated for conditions relating to care provision and outcomes according to skin color. We performed statistical analysis with the software EpiInfo 7.2.5.0 (Center for Disease Control, Atlanta, 2011).

The REBRACO study followed the Declaration of Helsinki amended in Hong Kong in 1964, and it was approved by the Institutional Review Board (IRB) of the coordinating center and by each participating center (Research Ethics Committee of the School Medical Science, Letters of Approval numbers 4.047.168, 4.179.679, and 4.083.988). All women invited to participate received detailed information about the study, the follow-up, and the data and sample collections, when applicable. Participating women signed written informed consent documents before being enrolled. Regarding the

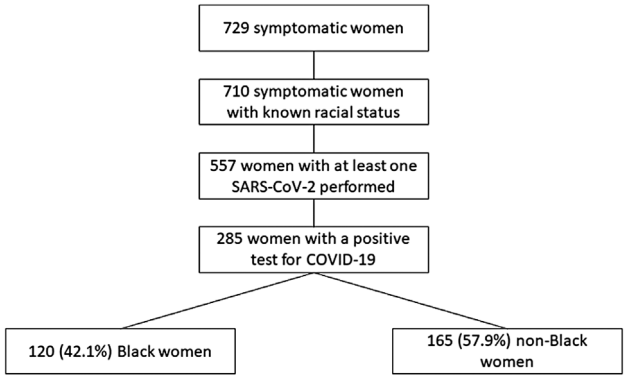

Fig. 1 Flowchart of women included in this analysis.

underage patients, written informed consent was obtained from their guardians before enrollment and after receiving complete information about the study.

Results

A total of 729 women were included in the REBRACO cohort; of those, data regarding racial status was available for 710 women (301 (42.4%) Black women and 409 (57.6%) non-Black women). Of those, 557 underwent COVID-19 testing, according to each center's protocol. Two hundred eighty-five (285) women were positive for SARS-CoV-2 infection and were included in this analysis. Among those women, 120 (42.1%) were Black, and 165 (57.9%) were non-Black. ►**Figure 1** presents the inclusion flowchart for this analysis.

►**Table 1** presents the sociodemographic and obstetrical characteristics of included women in this analysis. The majority of women included in both groups came from the Southeast region of Brazil, which is the largest in the country. Among Black women, the second most important region was North/Northeast. In contrast, in the other group, the second most important region was the South, expressing a national difference in racial distribution of the population (p-value <0.01). Black women had low educational levels (27.4% vs. 41.3%, p-value $= 0.037$). Another critical difference among both groups was regarding the source of payment for antenatal care: exclusive public funding occurred for 75.5% of Black women and 63.8% of non-Black women (p-value $= 0.044$).

►**Table 2** shows some delays associated with care among women with COVID-19. Inclusion in the study after seven or

Table 1 Sociodemographic and obstetrical characteristics of COVID-19 symptomatic women classified according to skin colour

Variable	Black	Non-Black	P-value
N	**120 (42.1)**	**165 (57.9)**	
Region			<0.01
North/Northeast	39 (32.5)	4 (2.4)	
Southeast	75 (62.5)	108 (65.5)	
South	6 (5.0)	53 (32.1)	
Marital Status			0.58
With partner	75 (64.1)	109 (67.3)	
Without partner	42 (35.9)	53 (32.7)	
Schooling			0.037
Secondary or less	74 (73.3)	82 (60.3)	
College or more	27 (26.7)	54 (39.7)	
Obesity	20 (27.4)	52 (41.3)	0.049
Health insurance of antenatal care			0.044
Public	80 (75.5)	102 (63.8)	
Private	26 (24.5)	58 (36.2)	
Parity			0.027
First pregnancy	50 (42.4)	49 (29.7)	
Two or more	68 (57.6)	116 (70.3)	
Unplanned pregnancy	46 (46.0)	94 (63.5)	>0.01
Pre-existing hypertension	9 (7.5)	16 (9.7)	0.517
Pre-existing diabetes	3 (2.5)	3 (1.8)	0.692
Asthma	12 (10.0)	9 (5.5)	0.147
Chronic kidney disease	1 (0.8)	0 (0)	0.240
Smoking	2 (1.7)	0 (0)	0.09

Table 2 Risk estimates for delays associated with care among women with COVID-19, according to race background

	Black	Non-Black	Odds ratio (Confidence interval)	p-value
Multiple testing	23 (19.3)	32 (19.6)	0.981 (0.540–1.782)	0.949
$\geq$ 7 days with symptoms at enrolment	29 (25.7)	46 (29.7)	0.818 (0.474–1.411)	0.470
Difficulty in self-perception of illness	17 (14.8)	22 (13.8)	1.088 (0.549–2.156)	0.809
Difficulty in health services access	2 (1.8)	4 (2.5)	0.688 (0.124–3.819)	0.667

more days of symptoms was considered a proxy for the delay to start care, and 29 (25.7%) Black women and 46 (29.7%) non-Black women had delays according to this criterion. Also, 17 (14.8%) and 22 (13.8%) women in the groups expressed difficulty in self-perception of illness; however, few reported difficulties accessing health services. Rates of delays were similar among both groups.

Black women had a higher frequency of adverse maternal outcomes, according to the results presented in ►**Table 3**. Black women were more likely to be admitted with desaturation (OR 3.723, CI 1.408–9.844) and severe acute respiratory syndrome (OR 2.216, CI 1.166–4.211). The association of these conditions increased the intensive care unit admission among those women (OR 1.998, CI 1.067–3.743). Occurrence of maternal death was significantly higher among Black women: 9 (7.8%) deaths in this group, compared to 4 (2.6%) (p-value 0.048) in the other group.

We observed a high frequency of preterm delivery in our sample (32.5% and 29.2%, Black and non-Black women, respectively); however, it was similar between both groups; it probably impacted the frequency of neonatal intensive care unit admission (28.4% and 26.1%). The majority of women included in this analysis underwent cesarean section. These data is presented in ►**Table 4**.

Discussion

Our study compared maternal and perinatal outcomes of women included in the REBRACO study, a Brazilian national cohort of women with COVID-19. Our results showed that, despite having similar sociodemographic characteristics, Black women were more likely to present SARS, desaturation, and need for ICU admission. The frequency of death among Black women was higher when compared to non-Black women.

The results obtained after analyzing the sociodemographic characteristics were not surprising as a previous study, using data from the Brazilian population, reported similar findings. In that 2017 Brazilian study, having included 23 532 postpartum national women from 266 hospitals, it could be seen that the North and Northeast regions were more concentrated with Black women and showed a higher proportion of adolescent pregnancies.[14] In addition, Black women presented with less education and higher public insurance than non-Black women. Similarly, a previous national population survey showed higher unplanned pregnancy rates and greater use of public health services among Black women than White women.[15] Such findings reinforce how racial disparities are still very present in our population and illustrate how these marked sociodemographic differences may influence access to health services and the quality of care provided, supporting racial inequities in health.[16]

Studies carried out in other countries have also pointed to socioeconomic differences between different racial groups as determinants of health. A cross-sectional analysis of survey data (between 2015 and 2017) from 107 921 women in 40 North American states showed lower rates of insurance among all categories of racial-ethnic minority women when compared to White, non-Hispanic women.[17]

In our study, there was no significant difference between the skin color groups regarding the performance of multiple tests, readmission rate, delay in identifying those who were ill, or difficulty in reaching the health service. Nevertheless, Black women presented with more significant desaturation at admission when compared to non-Black women. Another Brazilian study (including 669 maternal SARS-CoV-2 cases) reported that Black women were more likely to be admitted with low O2 saturation at admission.[18] This factor may also be associated with the greater severity of adverse maternal outcomes detected in our analysis since low oxygen

Table 3 Risk estimates for adverse maternal outcomes in COVID-19 positive women classified according to skin colour

	Black	Non-Black	Odds ratio (Confidence interval)	p-value
SARS	27 (22.5)	19 (11.6)	2.216 (1.166–4.211)	0.014
ICU admission	27 (22.7)	21 (12.8)	1.998 (1.067–3.743)	0.029
Intubation	9 (8.1)	9 (6.7)	1.225 (0.469–3.201)	0.678
Pronation	9 (8.2)	5 (3.7)	2.299 (0.747–7.07)	0.137
Maternal Death	9 (7.8)	4 (2.6)	3.175 (0.953–10.580)	0.048
Desaturation	16 (13.7)	6 (4.1)	3.723 (1.408–9.844)	$<$0.01

Table 4 Risk estimates for gestational and perinatal outcomes in confirmed COVID-19 women classified according to skin colour

	Black	Non-Black	Odds ratio (Confidence interval)	p-value
Fetal Death	2 (2.5)	1 (0.9)	2.897 (0.258–32.510)	0.367
Preterm delivery	26 (32.5)	33 (29.2)	1.167 (0.628–2.168)	0.624
Preeclampsia	10 (12.8)	11 (9.7)	1.364 (0.549–3.387)	0.503
Cesarean section	50 (62.5)	76 (66.1)	0.855 (0.472–1.550)	0.606
Small for gestational age	20 (29.0)	22 (22.4)	1.410 (0.697–2.851)	0.338
Large for gestational age	7 (12.5)	12 (13.6)	0.905 (0.333–2.457)	0.844
5th-minute Apgar < 7	4 (5.3)	5 (4.5)	1.189 (0.309–4.578)	0.801
NICU admission	21 (28.4)	29 (26.1)	1.120 (0.579–2.166)	0.735
Neonatal death	4 (5.5)	3 (2.7)	2.068 (0.449–9.522)	0.342

saturation at admission is associated with a higher risk for severe disease.[19]

Black people, with the highest rates of perceived discrimination are generally associated with poorer health outcomes and even worse maternal outcomes.[5,7,20] Individuals who have reported any perceived medical setting discriminations in a medical setting have a higher frequency of reporting poor quality of care (e.g., not being allowed to partake in decision-making or not having enough time with the physician). Another effect among individuals who feel discriminated against may be the consequent underutilization of health services.[20] Therefore, it is possible that Black women avoid seeking health assistance because of perceived discrimination and subsequently obtain more severe clinical features.

Previous studies have shown Black skin color as a risk factor for worse adverse maternal outcomes (including maternal death) in women with COVID-19 infection.[1–3] In a cross-sectional study including 12,566 pregnant and postpartum women, Black women with any comorbidity had a 2-fold mortality rate when infected with SARS-CoV-2 as opposed to White women.[2] Another observational study of COVID-19 patients (not limited to obstetrics) showed that hospital admitted Mixed skin color (Pardo) Brazilians had a 1·45 higher risk of mortality, while Black Brazilians had a 1·32 higher risk of death.[3]

Maternal death was 3-fold higher among Black women in our study. Still, when pregnant women (compared to non-pregnant women) have an increased risk for severe illness associated with COVID-19, the non-White skin color potentially adds additional clinical risk.[1,2] Historically, higher rates of severe maternal morbidity and mortality could be seen among Black women (compared to non-Black women), indicating that racial disparities are present in maternal mortality.[6] The COVID-19 pandemic has also exacerbated these inequalities.[21] Data on maternal mortality in Brazil due to COVID-19 have highlighted the inadequate monitoring of obstetric complications.[22] According to a cross-sectional observational study of COVID-19 hospital mortality using data from the SIVEP-Gripe with not only obstetrics patients, *Pardo* Brazilians admitted to hospital had 1.45 higher risk of mortality and Black Brazilian 1.32 higher risk of death than White ones.[3] Data from the Brazilian Official Acute Respiratory Syndrome Surveillance System (ARDS-SS), including 9563 pregnant and postpartum women with acute respiratory distress syndrome (ARDS), showed that 3·8% died with a confirmed diagnosis of COVID-19.[23] In our study, there were 13 maternal deaths representing 4.7% of the confirmed SARS-CoV-2 infected patients.

We did not find any significant differences in our study regarding preterm births. This was contrasting to previous literature where, in a retrospective cohort study with 162 pregnant and SARS-CoV-2 infected women, the preterm delivery rate was higher among Black women.[24]

COVID-19 does not seem to be a democratic disease and has further exposed the strong association between race, ethnicity, culture, socioeconomic status, and health outcomes.[25] For example, despite being a middle-income country where the majority of the population is Black, the structural racism of Brazil (rooted in historical oppression and embedded in dominant cultures and social institutions that, in turn, led to poorer socioeconomic conditions) disproportionally made them the most vulnerable to COVID-19.[3]

While this study has limitations, such as not being representative of the whole country and some regions being underrepresented, it provides some insight into well-documented data regarding the referral maternity hospitals involved in the care of pregnant and postpartum women that have tested positive for COVID-19.

Black women were already disproportionally affected before the pandemic, with the reasons for health system disparity being the same, i.e., implicit bias and structural racism.[26] Healthcare professionals might fail to recognize the effect of implicit bias in their practices, and this failure can potentially affect how obstetricians/gynecologists counsel patients.[13] It is, therefore, essential to broaden the debate and raise awareness of this issue, allowing for identifying and confronting practices that potentially result in verified inequities. Individual implicit bias and the profound impact of structural racism must be acknowledged and accepted before real progress can be made in reducing racial disparities in maternal mortality. However, it remains difficult to talk about racial health disparities in a country marked by structural racism. By helping shed some light on the health

system-related discrimination and detrimental effects of SARS-CoV-2 on the Black population, this study hopes to expand the debate on racism in Brazil.

Conclusion

Brazilian pregnant or postpartum Black women with COVID-19 were more likely to present desaturation, SARS, and ICU admission; maternal deaths were significantly higher among them compared to non-Black women. Urgent measures are needed to reduce racial disparities in pregnancy outcomes and discuss the causes of these disparities.

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.

Conflicts to Interest

The authors have no conflicts of interest to declare.

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Existence of SARS-Cov-2 in the Peritoneal Fluid

Existência de SARS-Cov-2 no líquido peritoneal

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Abstract

Objective To determine the existence of SARS-CoV-2 in the peritoneal fluid to assess the risk of exposure through surgical smoke and aerosolization threatening healthcare workers during abdominal surgery.

Background SARS-CoV-2 is a respiratory virus and possible ways of viral transmission are respiratory droplets, close contact, and fecal-oral route. Surgeries pose risk for healthcare workers due to the close contact with patients. Aerosolized particles may be inhaled via the leaked CO_2 during laparoscopic procedures and surgical smoke produced by electrocautery.

Methods All the data of 8 patients, who were tested positive for COVID–19, were collected between August 31, 2020 and April 30, 2021. Recorded clinicopathologic data included age, symptoms, radiological and laboratory findings, antiviral treatment before surgery, type of surgery and existence of the virus in the peritoneal fluid. Nasopharyngeal swab RT-PCR was used for the diagnosis. COVID–19 existence in the peritoneal fluid was determined by RT-PCR test as well.

Results All 8 COVID–19 positive patients were pregnant, and surgeries were cesarean sections. 1 of the 8 patients was febrile during surgery. Also only 1 patient had pulmonary radiological findings specifically indicating COVID-19 infection. Laboratory findings were as follows: 4 of 8 had lymphopenia and all had elevated D-dimer levels. Peritoneal and amniotic fluid samples of all patients were negative for SARS-CoV-2.

Conclusion SARS-CoV-2 exposure due to aerosolization or surgical fumes does not seem to be likely, provided the necessary precautions are taken.

Keywords
- SARS-CoV-2
- peritoneal fluid
- surgical smoke
- amniotic fluid
- COVID-19

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Resumo

Objetivo Determinar a existência de SARS-CoV-2 no fluido peritoneal para avaliar o risco de exposição através da fumaça cirúrgica e aerossolização que ameaçam os profissionais de saúde durante a cirurgia abdominal.

Contexto O SARS-CoV-2 é um vírus respiratório e as possíveis formas de transmissão viral são gotículas respiratórias, contato próximo e rota fecal-oral. As cirurgias representam risco para os profissionais de saúde devido ao contato próximo com os pacientes. As partículas aerossolizadas podem ser inaladas através do CO2 vazado durante os procedimentos laparoscópicos e a fumaça cirúrgica produzida pela eletrocauterização.

Métodos Todos os dados de 8 pacientes, que foram testados positivos para COVID-19, foram coletados entre 31 de agosto de 2020 e 30 de abril de 2021. Dados clinicopatológicos registrados incluíam idade, sintomas, achados radiológicos e laboratoriais, tratamento antiviral antes da cirurgia, tipo de cirurgia e existência do vírus no fluido peritoneal. O diagnóstico foi feito através do swab nasofaríngeo RT-PCR. A existência de COVID-19 no fluido peritoneal foi determinada pelo teste de RT-PCR também.

Resultados Todas as 8 pacientes positivas para COVID-19 estavam grávidas, e as cirurgias eram cesarianas. 1 das 8 pacientes estava com febre durante a cirurgia. Também apenas 1 paciente tinha achados radiológicos pulmonares especificamente indicando infecção por COVID-19. Os achados laboratoriais foram os seguintes: 4 de 8 tinham linfopenia e todas apresentavam níveis elevados de D-dímero. Amostras de fluido peritoneal e líquido amniótico de todas as pacientes foram negativas para SARS-CoV-2.

Conclusão A exposição ao SARS-CoV-2 devido à aerossolização ou fumaças cirúrgicas não parece ser provável, desde que sejam tomadas as precauções necessárias.

Palavras-chave

- SARS-CoV-2
- fluido peritoneal
- fumaça cirúrgica
- líquido amniótico
- COVID-19

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak was declared as a pandemic by the World Health Organization (WHO) on January 30, 2020.[1] The disease initially appeared in China and spread to many other countries rapidly. Human to human transmission was demonstrated shortly after the outbreak and the virus infected millions of people around the world in the following months. Early reports showed the mortality rate as 2.3% in China while as %1.6 in other countries.[2]

SARS-CoV-2 is a respiratory virus and possible ways of viral transmission are respiratory droplets, close contact, and fecal-oral route.[3] Operating rooms (OR) are among risky places in situations like viral outbreaks because patients and healthcare workers are often in close contact. National and international surgical guidelines still evolve to protect healthcare workers from the risks posed by their colleagues and patients.

Inhalation of aerosolized particles is considered as a risk factor for transmission of SARS-CoV-2.[4,5] Surgical smoke due to electrocautery or the leaked CO2 that is used during laparoscopy may be inhaled in the OR. Mintz et al. claimed that laparoscopy should be used if the procedure is more suitable for the patient. They also stated that more evidence – based research is needed to determine the safety of laparoscopy.[5] Viral load of the peritoneal fluid seems to be the main factor that increases the risk of transmission through inhalation of leaked laparoscopic gases and smoke due to electrocautery.

This study was designed to evaluate patients, who were tested positive for COVID-19 and underwent obstetrical surgery, regarding the presence of viral genome in the peritoneal cavity.

Methods

All women, who underwent surgery and had positive COVID-19 test results, at Dokuz Eylul University Hospital Department of Obstetrics and Gynecology between August 31,2020 and April 30, 2021 were included in the study. The diagnosis was determined with nasopharyngeal swab test. A positive test was defined as a positive result for SARS-CoV-2 with reverse transcriptase – polymerase chain reaction (RT-PCR) assay. Ethical approval for the study was obtained from the local ethics committee of Dokuz Eylul University Hospital (No:2021/04–41). Written informed consent forms were obtained from all participants.

The study was designed as a prospective study. The hospital electronic patient database provided epidemiological, clinical, laboratory and radiological data of the patients.

Table 1 Characteristics of the patients

Case No.	Nasal swab for Covid-19	Age (year)	Parity	Gestational age (week)	Birth Weight (g)
1	+	26	0	39	3115
2	+	27	0	40	3348
3	+	30	1	37	3400
4	+	33	2	38	3600
5	+	30	1	39	3217
6	+	27	0	39	3300
7	+	26	2	39	3320
8	+	27	1	40	2960
Mean ± SD		28 ± 2			3282 ± 191

Nasopharyngeal swab specimens were tested for SARS-CoV-2 at the microbiology laboratory of the same institution. The test was conducted by using virus mini kit (EZ1 Virus Mini Kit v2.0, Germany), followed by RT-PCR according to WHO guidelines.

Birth weight and gestational age at the delivery were recorded. Amniotic fluid samples were collected in addition to peritoneal irrigation fluid for the pregnant patients during the cesarean section (C/S). Peritoneal cavity was irrigated with 10 mL of saline solution and then the irrigation fluid was aspirated for testing. Peritoneal washing aspirate was also used by other researchers.[6,7] The peritoneal fluid sample was obtained before hysterotomy to prevent contamination. Testing for COVID-19 was performed 24/7 in the institution and therefore specimens were transferred to the laboratory momentarily in sterile vials provided by the laboratory. All biological samples were tested for SARS-CoV-2 with the same kit that was used for the nasopharyngeal specimens followed by RT-PCR according to WHO guidelines.

All analyses were performed by using IBM SPSS Statistics Version 25. Only descriptive statistics were calculated and given. Mean ± standard deviation was used to present the data.

This study was performed in consensus with our universitýs ethics guidelines. The ethics committee approval was obtained for this study (No:2021/04–41).

Results

The mean age of patients was 28 ± 2 years. All patients, who underwent surgery when they were tested positive for COVID-19, were pregnant and all surgeries were cesarean sections. 3 of 8 (37.5%) patient were in their first pregnancy. All patients were at term during birth and only one of them was symptomatic while the other 7 were clinically asymptomatic. The symptomatic patient's body temperature was 39C during admission. This patient was operated 4 days after the onset of fever. Due to pregnancy, ionizing radiation was avoided and no patient had radiological imaging except obstetrical ultrasonography preoperatively. However, computerized tomography (CT) scanning was performed on one patient after birth (case 6). Ground – glass opacities and patchy lung consolidations were detected in the CT scan. None of the patients received antiviral medication preoperatively (►**Tables 1** and **2**).

Blood samples from all patients were tested within 24 hours before surgery. Complete blood count, serum c – reactive protein (CRP), alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine concentrations and plasma d – dimer concentrations were recorded. Lymphopenia was detected in 4 of 8 patients and plasma d – dimer concentration was high in all 8 patients as laboratory findings related with COVID – 19 infection (►**Table 3**).

Table 2 Clinicopathologic data of the patients

Case No.	Fever	Cough	Dyspnea	Radiological finding	Time between symptoms and delivery (day)	Antiviral treatment before delivery	Covid-19 test in amniotic fluid	Covid-19 test in peritoneal fluid
1	–	–	+	–	4	–	–	–
2	–	–	- -	0	–		–	–
3	–	–	- -	0	–		–	–
4	–	–	- -	0	–		–	–
5	–	–	- -	0	–		–	–
6	-	-	- +	0	-		-	-
7	-	-	- -	0	-		-	-
8	-	-	- -	0	-		-	-

Table 3 Laboratory findings of the patients

Case No.	Leukocyte (x10^9 cells/L)	Lymhpcyte (x10^9 cells/L)	Neutrophile (x10^9 cells/L)	Platelet (x10^9 cells/L)	C-reactive protein (mg/L)	Aspartate transaminase (IU/L)	Alanine transaminase (IU/L)	Urea (mmol/L)	Creatinine (µmol/L)	D-dimer (µg/ml)
1	*9.1*	1.1*	7.3*	272	70.4*	45*	44	7	0.6	3.2*
2	15.7*	1.7	12.8*	329	4.7	22	10	6.8	0.52	1.8*
3	4.2	1.1*	2.8	144	11.6*	29	12	3.3	0.53	5.9*
4	10.8*	1.8	8.5*	280	18.8*	15	10	6.7	0.36	1.5*
5	9	0.9*	7.8*	308	18.4*	21	9	5.3	0.36	8.1*
6	8	1.7	5.7	326	16.4*	27	23	4.2	0.38	2.4*
7	3.7	1*	2.4	255	63*	14	6	6.6	0.36	4*
8	14.2*	2.3	10.9*	162	50.2*	26	9	9	0.39	0.8*
Median (P25–P75)	9 (5.1 -13.3)	1.4 (1–1.7)	7.5 (3.5–10.3)	276 (185–321)	18.6 (12.8–59.8)	24 (16.5–28.5)	10 (9–20.2)	6.6 (4.4–6.9)	0.3 (0.3–0.5)	2.8 (1.5-5.4)

Cesarean sections were performed in an isolated operating room. The average birth weight was 3282 ± 191 g. Peritoneal irrigation fluid and amniotic fluid samples were tested for SARS-CoV-2 and all samples were determined to be negative.

Discussion

There is limited data regarding intraoperative aerosolization of SARS-CoV-2 at the moment. Many medical institutions have different protocols for urgent and elective surgeries. Our institution requires all patients, who are planned to be operated, to be tested for COVID-19 preoperatively both for elective and urgent procedures. Exceptionally urgent procedures may commence before the test result is obtained. The patients in the study were all cases of cesarean section. Since it was possible to postpone other gynecological procedures at least until the patient's test becomes negative, only obstetrical procedures were performed while the patient had active infection.

Personal protective equipments (PPE) should be used by all healthcare staff, who may be in contact with COVID – 19 positive patients, including surgeons, nurses, anesthesiologists and other personnel. Current knowledge is that SARS-CoV-2 is a respiratory virus and possible ways of viral transmission are respiratory droplets, close contact, and fecal-oral route.[8–11] Airborne transmission has been Although airborne transmission may be considered as an unlikely way for viral transmission, past experiences on the SARS-CoV outbreak shows us aerosol-generating procedures such as tracheal intubation can have the possibility to spread the disease.[12,13] However, there is limited data regarding the management of procedures that can result in aerosolization of Covid-19.

There are several studies that investigated the viral existence in the peritoneal fluid.[7,14] According to our research, there is only one study that demonstrated viral genome in the peritoneal fluid while other studies did not.[15] Absence of the virus may be due to the size of the virus and the pores of the peritoneal membrane. Peritoneal membrane has pores with a maximum diameter of 20–40 nm, in contrast with the diameter of the virus, which is ~125 nm.[16] SARS-CoV-2 was not detected in the peritoneal fluid according to a case report that investigates SARS-CoV-2 existence in the peritoneal cavity of a non-perforated appendicitis patient.[7] The variation of test methods can play a crucial role in the test results. 20% or even more false negative rates were declared according to the methods of the tests.[17]

There are several studies evaluating the viral presence of hepatitis B virus (HBV), human papillomavirus (HPV), and human immunodeficiency virus (HIV) in surgical smoke. All these viruses were detected in the surgical smoke.[18–22] On the other hand, during earlier viral outbreaks, the transmission of other coronaviruses such as SARS-CoV and MERS-CoV through surgical smoke or laparoscopic gas was never confirmed.[23] Limited controversial data regarding the existence of SARS-CoV-2 in the peritoneal fluid, does not seem to create grave concerns for laparoscopic surgery or using

electrocautery while operating on COVID-19 positive patients. Surgery of COVID-19 patients should be performed by staff with required PPE and the operating rooms should be managed according to current COVID-19 guidelines. Further studies are needed to investigate the viral presence in the peritoneal fluid to establish more reliable protocols.

Most of the patients were asymptomatic and this may be considered as a limitation, since severe cases concomitantly might have higher viral load and a higher probability of viral presence in the peritoneal fluid. Nevertheless, in the light of our findings, laparoscopic surgery or electrocautery usage should not be avoided due to COVID-19 when indicated and performed under required safety precautions. Our data will contribute to the literature and eventually also help to improve the surgical guidelines for COVID-19 patients.

Conclusion

SARS-CoV-2 was not detected in the peritoneal fluids or amniotic fluids of all 8 patients with positive nasopharyngeal test results. Apparently, C/S is not a laparoscopic technique and does not provide an ideal example to assess the risks of laparoscopic surgeries. However, the key point is the virus presence in the peritoneal fluid. Although our study is helpful to understand the risk of aerosolization of SARS-CoV-2 during laparoscopy and electrocautery usage, further studies are needed in the field of surgical safety during the COVID-19 pandemic.

Contributions

OI: conception and design, analysis and interpretation of data, statistical analysis MEO: acquisition of data, drafting of manuscript OA: acquisition of data, technical support BE: analysis and interpretation of data HTT: drafting of the manuscript OED: critical revision of the manuscript for important intellectual CP: supervision

Conficts to Interest

The authors have no conflict of interest to declare.

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Clinical Simulation in the Training of Obstetrics and Gynecology Resident from the Perspective of Medical Residency Programs

A Simulação Clínica na Formação do Residente em Obstetrícia e Ginecologia na Perspectiva do Programa de Residência Médica

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Abstract

Objective This study analyzes the role of clinical simulation in internal medical residency programs (IMRP) in Obstetrics and Gynecology (OB/GYN), attributed by the supervisors, in the training of residents in the city of São Paulo (SP).

Methods Cross-sectional descriptive, qualitative, and exploratory approach. Semi-structured interviews were performed with ten supervisors of Medical Residency programs in Obstetrics and Gynecology. Interviews were analyzed by means of content analysis under the thematic modality, starting with the core *the role of clinical simulation in Obstetrics and Gynecology Medical Residency Programs.*

Results Supervisors view Clinical simulation as: a complementary tool for the teaching and learning process, a possibility of a safe teaching and learning environment, an opportunity to learn from mistakes, a support for professional practice committed to patient safety, a learning scenario for teamwork, a scenario for reflection on the work process in Obstetrics and Gynecology, a scenario for evaluative processes in the medical residency. Still according to supervisors, Clinical Simulation favors decision-making and encourages the resident participation in activities.

Conclusion Supervisors recognize Clinical Simulation as a powerful pedagogical tool in the learning process of resident doctors in Obstetrics and Gynecology Residency Programs.

Keywords
- simulation training
- internship and residency
- obstetrics and gynecology department hospital
- health human resource training
- patient safety

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Resumo

Objetivo O presente estudo analisa o papel da Simulação Clínica em programas de Residência Médica (PRM) de Obstetrícia e Ginecologia, atribuído pelos supervisores, na formação do residente no município de São Paulo (SP).

Métodos Abordagem qualitativa, transversal, de natureza exploratória e descritiva. Foram realizadas entrevistas semiestruturadas com dez supervisores de programas de Residência Médica de Obstetrícia e Ginecologia. Para análise das entrevistas foi realizada análise de conteúdo na modalidade temática partindo do seguinte núcleo: o papel da simulação clínica nos Programas de Residência Médica de Obstetrícia e Ginecologia.

Resultados A Simulação Clínica, na visão dos supervisores, emerge como: ferramenta complementar para o processo de ensino e aprendizagem; possibilidade de um ambiente de ensino e aprendizagem seguro; possibilidade de aprendizagem a partir do erro; suporte para prática profissional comprometida com a segurança do paciente; cenário de aprendizagem para o trabalho de equipe; cenário de reflexão sobre o processo de trabalho em Obstetrícia e Ginecologia; favorecimento na tomada de decisão; cenários de processos avaliativos na residência; e, por fim, estímulo à participação dos residentes nas atividades.

Conclusão Os supervisores reconhecem a Simulação Clínica como uma ferramenta pedagógica potente no aprendizado dos médicos residentes em Obstetrícia e Ginecologia.

Palavras-chave

- treinamento por simulação
- internato e residência
- unidade hospitalar de ginecologia e obstetrícia
- capacitação de recursos humanos em saúde
- segurança do paciente

Introduction

Historically, traditional methodology based on Cartesian thought has guided the education of health professionals, marked by a fragmented and reductionist approach. The search for technical efficiency and for specialized knowledge has led to the emergence of several changes within the educational institutions as well as on the educational propositions. Such changes have equally produced effects in the teaching and learning dynamic, in which the lecturer performs as a content transmitter while the student just plays the role of a spectator. A system that remained unaltered for the past 100 years, notwithstanding the important changes in healthcare.[1]

Lately, there has been a change from the traditional Halstedian training model – "see one, do one, teach one" – to a more contemporary model of Based in Competence Medical Education – BCME. A Medical Education founded on competencies becomes popular all over the world as a new approach in education and evaluation of the novice physician.[2–4]

The Entrustable Professional Activity – EPA – a concept brought about by Ten Cate and Scheele, 2007–emerges within that context to fill in the gap between competence-guided education and the clinical praxis.[5] In clinical practice the competences are intertwined in a complex way so that they are less explicit and measurable. A reliable professional activity is one that may be entrusted to a person once that person has achieved the necessary competence. The EPAs represent the professional's daily activity, which means they are observable, measurable entities that can be the focus of evaluation.[6]

Therefore, thinking that teaching-and-learning process within a perspective of construction of knowledge – in which resident and professor take effective participation – implies vertically substituting both the memorizing-of-information process and the fragmented transfer of knowledge by a praxis that gathers knowledge through an interdisciplinary posture. In that regard, one values the adoption of methods that encourage students to effectively participate throughout the process. The simulation method is among those known as active methodologies.[7]

Medical simulation may be an ancient art. However, it is a young science that has just held a position at higher education institutions.[8] Simulation uses technology and has tools like simulators, and yet these last ones do not encompass the meaning of simulation despite of being part of it.[9]

Simulation also favors the development of competencies related to clinical procedure pertaining to the professional praxis. It also goes beyond the technical and technological aspects to reach the development of analysis, synthesis, and the decision-making process. In the United States, Canada, and Europe, several higher education institutions have simulation centers where that methodology is explored and widespread.

In Brazil, it is possible to notice a greater adhesion to simulation from private and public institutions, as well as an increasing tendency to build simulation centers. However, the high costs demanded to build facilities, to acquire simulators, and to hire skilled personnel seem to hinder that expansion. Notwithstanding those factors, simulation has become popular in the medical field as a complementary means to the traditional training in patients, by improving the abilities while favoring doing "the real thing" in a safe learning environment.

While pondering the national scenario regarding the use of Clinical Simulation within the medical postgraduation courses, a worry emerged concerning the way that tool is employed throughout the Medical Residency Programs, specially those of Obstetrics and Gynecology. The primary assumption was that Clinical Simulation is comprehended by supervisors of the Medical Residency Programs of Obstetrics and Gynecology as an effective pedagogical tool in the residents learning process, though not very used. Therefore, the purpose of this study was to analyze the role given by the program supervisors to the Clinical Simulation applied to the training of residents in Obstetrics and Gynecology in the city of São Paulo.

Methods

A cross-sectional descriptive, qualitative, and exploratory study was conducted. The research took place in the city of São Paulo by interviewing 10 program supervisors among 18 who were present at data collection time. The physicians interviewed supervise a total of 358 residents, 72% of the total number of trainees in Gynecology and Obstetrics in the city of São Paulo. As of the seventh interview, a saturation point of data collection was noticed once information reoccurred. However, it was decided to continue interviewing up to the tenth interview aiming to gather a diversity of institutional features.

First section of data collection used a questionnaire composed of closed questions to characterize the survey participants. The second section consisted of an interview intended to apprehend the role supervisors ascribed to clinical simulation.

Data analysis of the literal transcription of the semi-structured interviews was performed and the results were analyzed by means of a three-stage content analysis namely pre-analysis, exploring the material, and treatment of results. Pre-analysis involved a fluctuating reading of all transcripted material obtained from the interviews, which allowed a better comprehension of the context as well as assimilation of impressions and trends that were found.[10] A session of repeated reading of material was followed by the identification of Context Units (CU), that was guided by the core theme *The role of simulation in OG Residency.* CU are understood as broader and more contextualized parts of all that was said related to that theme, and that was considered essential to the necessary analysis and interpretation of texts to be deciphered.[11] Based on the CUs one could get to the Register Units (RU) as "the smaller part of content whose occurrence is registered according to the categories found.[11]"

A categorization process followed the defining of UC and UR. Categorization process is understood as "a classification operation of constituent elements of a set by differentiation, followed by an analogy-based regrouping according to defined criteria.[11]" To get to the categories and subcategories the semantic process was applied by grouping the RUs interpretations. Both categories and subcategories came forth from what was said by the interviewees.[11]

Results and Discussion

OG Residency Programs of diverse natures were included, such as those from universities, and from nonprofit hospitals owned by federal, municipal or state public administration, as well as from philanthropic hospitals. Each participant received an interviewee's code that ranged between 1 and 10 to assure anonymity. Among the institutions, six are public and four are philanthropic. As for the number of vacant posts accredited at the Medical Residency National Committee (MRNC), the average was 12 vacant posts per year (six at minimum and 20 at maximum). All participant institutions either hold their own medical internship program or provide a training field to another institution's internship. Characterization is presented on ►**Table 1**.

As for the supervisors' profiles, most of them were male doctors, aged between 40 and 50, with an academic title, as one can see on ►**Table 2**.

As initial findings all supervisors considered that Clinical Simulation plays a relevant role in Obstetrics and Gynecology Medical Residency Programs, according to what is said in the following transcript:

Personally, I consider Realistic Simulation very important... quite inexorable, a matter of time to evolve to that point [E6]. As for the acquisition of abilities, some research indicate that simulation could be superior to traditional medical.[12] Those professionals who work as OG educators must study simulation and certainly embody it in their students and residents educational processes.[8] In the United States the use of simulation is among the criteria set to accredit Medical Residency Programs, which corroborates the importance of extensively using it to improve performance of specialists during their technical procedures.[13] Analysis of interviews identified 58 context unities and 78 register unities. Among the register unities, 9 categories and 11 subcategories emerged, according to ►**Chart 1**.

Table 1 Characterization of the Institutions which participated in the research

Characteristics	n	%
Administrative Category		
Public	6	60
- Federal	1	10
- State	4	40
- Municipal	1	10
Philanthropic	4	40
Academic Organization		
University	5	50
Nonprofit Hospital	5	50
Number of accredited OG MR vacant posts Vacant posts / year (Mean)	12	
Medical Internship		
Yes	10	100

Table 2 Characterization of Supervisors who participated in the research

Characteristics	n	%
Age (years)		
< 39	1	10
40–49	6	60
50–59	2	20
> 60	1	10
Gender		
Male	7	70
Female	3	30
Time undertaking their duties (years)		
< 1 year	2	20
1 a 5 years	4	40
5 a 10 years	3	30
> 10 years	1	10
Academic title		
Specialist	4	40
Master	1	10
Doctor	5	50

Simulation appears as a **teaching and learning process complementary tool** in OG Residency, able to assist in the resident professional development. In the last decades, OG international and national societies have encouraged the use of Simulation as a complementary tool in the teaching and learning process. In 2007 the American College of Obstetricians and Gynecologists (ACOG) acknowledged simulation as a valuable educational element in undergraduate and graduate studies. Simulation-based methods offer medical students the opportunity to obtain key qualities at the working place, such as confidence, knowledge, skills, and the appropriate behavior able to offer a high-quality service to the patient within a safe learning environment.[14,15]

Among the highlighted options, supervisors emphasized *that simulation may homogenize teaching and learning opportunities*. Thereby, the use of simulation seems to be significant, specially nowadays when health services make changes in health care while reduce length of hospital stay, which limits bedside learning opportunities. Such circumstance entails curtailment of occasions when residents could be in touch with risky situations and procedures.[16]

The possibility of training rare procedures was also emphasized by supervisors. Simulation may protect against unnecessary exposure to a variety of situations, which represents an increasing need due to limited clinical training opportunities.[11]

Chart 1 Core theme categories and subcategories: the role of simulation in obstetrics and gynecology medical residency programs

Category	Subcategory
Teaching and learning process complementary tool	Teaching and learning opportunities homogeneity possibility
	Less common procedures training possibility
	Unlimited repetition of procedures
	Residents self-confidence training
Safe teaching and learning environment possibility	
Learning from error possibility	Improving performance by repeating the undergone experience
Support for professional practice committed to patient safety	
Teamwork learning scenario	
Reflection scenario on the Obstetrics and Gynecology working process	Discussion about multidisciplinary care/assistance protocols
	Preparation for safer professional practices aiming at reducing judicial risk
Decision-making support	
Residency appraisal process scenario	Recruitment process scenario for admission at medical residency
	Possibility to appraise multiple skills expected from health professionals during Medical Residency Programs
	Possibility for Interactive feedback
Encouraging residents participation in the Medical Residency Programs activities	Practical performance improvement

Supervisors also emphasized *the possibility of unlimited repetitions of procedures*. Simulations may also allow deliberated practice, which could be defined as the engagement of students in repeating the abilities thoroughly, focusing on progressive exercises and informative feedback.[17]

Deliberated practice is essential in cases whose procedures are so rarely performed that few professionals could actually master the necessary abilities without having practice and feedback at a non-clinical environment. Such rare procedures have usually been associated with high-risk situations, which lead to medical errors. Deliberated practice performs a main role in preparing professionals for critical events,[18] besides being regarded as a most powerful indicator of the specialist's performance when compared with experience and academic aptitude.[19]

Supervisors also emphasized *the residents' self-confidence training*, as it allows greater confidence in their abilities. Humes et al report that resident doctors felt more confident about their abilities after performing a vaginal hysterectomy training in a uterus model by using a sponge and a PVC pipe.[20]

According to the interviewees, the possibility to have a safe teaching and learning environment offers calm conditions to the residents as they do not feel pushed to be perfect at performing or even not to make errors. The possibility to ensure a protected environment in which residents may perform tasks, detect errors, and correct them without producing adverse consequences, and where instructors may find the opportunity to connect better with their apprentices and techniques, is one of the elements which contributes to effectiveness in simulation.[21]

In this context, the possibility of learning form errors minimizes the trouble of dealing with that matter in real practice before the patients. It helps *improving performance by experience repetition* until attaining the goal. To Maslovitz, simulated training allows thus identifying and correcting common clinical errors made during emergencies.[22]

Supervisors understand that clinical simulation provides support to a professional practice that is committed to patient safeness. Evidence shows that obstetricians have improved their technical and communication abilities by practicing. In that sense, programs, which concern patient safety, must incorporate Obstetrics and Gynecology simulation.[23]

Sustained and increasing focus on medical error reduction and on patient safeness, as well as the need to offer a safe, ethical, and student-centered training lead to a model, which incorporates Simulation-based Education.[18]

The role of simulation has also been described as a scenario for teamwork in which it is emphasized its application in multidisciplinary training as well as in Permanent Education.

Training patterns for quick response in obstetrics emergencies are useful to improve team performance and bring better results to patients.[24] A systematic review on simulation-based training evaluation determined that teamwork became more efficient not just due to advancement of scientific knowledge, but also due to improvement in both communication skills and obstetrics emergency management.[25]

Simulation-based education proved itself as a Scenario for reflection about OG work process. It is important to highlight that failure to communicate in teamwork contributes to most obstetrics sentinel events. Labor pains and labor itself are critical moments when emergencies occur.

The American College of Obstetricians and Gynecologists – ACOG (2014) states that the care provided in emergency cases is enhanced by protocols that have standardized interventions and that promote on-the-job training. Team may learn and practice the necessary interventions while improve efficiency and reduce errors.[26]

Within this context, simulation may be used to *discuss multidisciplinary protocols of assistance*. As an example, a pilot study using simulation identified ~20 flaws in the safe application of a new intraoperative radiotherapy procedure before testing it out in patients. Such procedure included radiation safety, teamwork, team communication, and problems with both equipment and supply.[27] Thus, simulation was a scenario for the creation and discussion of a patient safeness protocol whenever innovation is brought to clinical environment.

Due to the increasing of lawsuits against medical practitioner's performance, supervisors stated that *preparation for safer professional practice reduces the risk of taking practitioners to court.*

According to a report by the General Council of Medicine from São Paulo (2006), professional obstetricians and gynecologists are sixth in the ranking of lawsuits. The main for these concerns the procedures related to labor assistance. Patients are usually awake when unpredictable emergencies that risk their lives occur, which makes teaching more difficult during these moments. Even experienced professionals could be surprised by both unexpected situations and rare complications that may happen during labor assistance. On account of that, medical schools and Medical Residency Programs are encouraged to develop strategies so as to avoid exposing patients to teaching under such conditions when simulation stands out as a training opportunity for students and residents.[8]

Simulation highlights and enhances the role of favoring the decision-making process so as to provide the increment of professional attitudes.

A study on simulation being applied to evaluate teamwork training in decision-making process via simulation demonstrated a time reduction of 33 to 21 minutes from the indication of cesarean section to the moment of surgical incision.[28]

Another role Clinical Simulation performs is that of becoming a scenario for evaluative processes in residency, by expanding the items to be evaluated within the competencies expected from professionals.

During the interviews, supervisors mentioned 3 evaluation strategies using simulation in Residency. A *scenario for the selective process enrollment* appears as a possibility. Clinical simulations allows a better evaluation of candidates as it enables a better observation of their technical abilities,

in addition to their professionalism, communication, and critical thought.[29]

The second strategy mentioned by the supervisors refers to the *possibility of evaluating multiple competencies expected from health professionals during Medical Residency Programs*. Simulation was thus mentioned in summative assessment as the internship completion and as the conclusion of a stage in the residency program. Although knowing about the use of simulation in evaluation, just a supervisor mentioned the OSCE model of evaluation as a preparation for the specialist diploma in Obstetrics and Gynecology. The third strategy referred by the supervisors was the *possibility of interactive feedback*, which provides an immediate and constructive response to the resident. To students, feedback represents a moment of effective learning.[30] In research done with simulation educators, Rall, Manser and Howard (2000) emphasized that debriefing is the most important part of training via simulation. One of interviewees called it "the heart and soul" of simulation-based training.[31]

In conclusion, there is unanimity among supervisors as to acknowledge that simulation represents an encouragement to resident participation in Medical Residency Programs activities. They highlight resident improvement in performance while doing their practical activities. Some studies have assessed the efficacy of simulated training in student confidence, examination skills and in communication. In 2015, Smith and collaborators published a systematic review with a data meta-analysis in which a comparison between teaching pelvic examination through simulation and through traditional methods was made. The authors concluded there is an improvement in the student competence concerning pelvic examination performance, as well as in their communication abilities when the simulation method is used.[32]

Conclusion

Based on the data found in this study, OG Clinical Simulation in Residency:

- Complements the teaching and learning process, allows homogeneity of opportunities, enables less-common procedures training, a deliberate and sustainable practice as well as the resident self-confidence training.
- Provides a safe teaching and learning environment.
- Encourages trial-and-error learning which enables improvement in performance by repeating the experience.
- Favors professional practice committed to patient safeness.
- Enhances teamwork as it favors its knowledge and the development of communication abilities. Furthermore, enhances emergency managing performance.
- Encourages reflection about work process, which brings the opportunity for discussion on multidisciplinary assistance protocols, prepares for safer professional practice and reduces the risk of law suits.
- Favors the decision making process, especially in emergency situations.
- Increases evaluative processes in residency, which allows the analysis of the multiple competences expected to be found in health professionals during the Obstetrics and Gynecology Medical Residency Programs.
- Favors interactive feedback and the resulting improvement of the resident, as well as of the professor and preceptor.
- Encourages participation of residents in the activities of the Obstetrics and Gynecology Medical Residency Programs, resulting in enhancement of practical performance. Clinical Simulation is thus acknowledged as a powerful tool to be used in the residents teaching and learning process.

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

Conflicts to Interest
None to declare.

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Pituitary Apoplexy in Pregnancy: What do We Know?

Apoplexia hipofisária na gravidez: o que sabemos?

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Abstract

Pituitary apoplexy refers to a rare clinical syndrome consisting of signs and symptoms that occur due to rapid expansion of the contents of the *sella turcica*. It can occur spontaneously or associated with pituitary tumors. It can have a broad clinical spectrum, but usually presents with severe headache, visual impairment and hypopituitarism. Sudden onset of symptoms associated to imagiologic confirmation makes the diagnosis. Surgical treatment is advised when there is important compression of the optic tract. We present a case report and a review of the literature on pituitary apoplexy in pregnancy. The cases were reviewed to obtain information on maternal characteristics, clinical presentation, diagnostic studies, therapeutic modalities and maternal and fetal outcomes. Our review found 36 cases of pituitary apoplexy in pregnancy. Most of the cases occurred in the second trimester of pregnancy and headache was the most frequent symptom at presentation. Surgical therapy was required in more than half of the patients. In what respect maternal and fetal outcomes, there were 3 cases of preterm delivery and one case of maternal death. Our clinical case and literature review reinforces the importance of an early diagnosis to avoid potential adverse consequences.

Keywords

- pituitary apoplexy
- endocrinology in pregnancy

Introduction

Pituitary apoplexy refers to a rare clinical syndrome consisting of signs and symptoms that occur due to rapid expansion of the contents of the *sella turcica*, due to hemorrhagic or ischemic events. It can occur spontaneously or associated with pituitary tumors. In many cases, pituitary apoplexy is the initial presentation of an adenoma. The etiology is multifactorial, but several precipitating factors have been described, including pregnancy.[1–7]

The clinical spectrum goes from asymptomatic or mild symptoms to a life-threatening situation, to both the mother and the fetus, particularly when associated with corticotropin deficiency and adrenal insufficiency. The diagnosis is made through the identification of the clinical syndrome associated with *sella turcica* imaging. Magnetic resonance imaging (MRI) is the most sensitive method to confirm the diagnosis by revealing a pituitary tumor with hemorrhagic and/or necrotic components.[4,6]

The treatment of choice is conservative, but surgery might be required when there are important visual disturbances due to optic tract compression.[4,7]

These study aims to report a case of a woman presenting with pituitary apoplexy during pregnancy who was treated

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Chart 1 Summary of available literature on pituitary apoplexy during pregnancy

Author [reference]	Age (years)	Clinical presentation	GA	Pituitary imaging (MRI or CT)	Treatment (GA)	Evolution	Delivery
Prior lesion: Prolactinoma							
Tandon et al.[37]	27	Headache, Visual defects	36WG	MRI: suprasellar, hemorrhagic mass with optic chiasm compression	Endoscopic endonasal transsphenoidal resection (36WG)	Resolution	C-section at term
Castro et al.[26] -Case 2	32	Headache, nausea vomiting	28WG	MRI: intrapituitary hemorrhage	Steroids	Improvement	C-section at term
Prior lesion: Macroprolactinoma							
Freeman et al.[8]	22	Headaches, diaphoresis, Visual defects, DI	32WG	MRI: pituitary hemorrhage, with optic chiasm compression and without neurohypophysis visualization	BCP stopped when pregnancy was diagnosed Transsphenoidal evacuation	Resolution	Delivery at term
Parihar et al.[34]	22	Headache, vomiting, vision loss	20WG	Pituitary apoplexy and compression over optic nerve and chiasm	BCP stopped when pregnancy was diagnosed Transsphenoidal decompression, removal of hematoma	Resolution	Delivery at term
Grand'Maison S et al.[15] -Case 2	30	Headache	20WG	MRI: pituitary mass with acute bleeding	Continued CBG (initiated before pregnancy)	Resolution	Vaginal delivery at term
Jemel M et al.[20] -Case 2	35	Severe headache, nausea, vomiting deterioration of the visual field	22WG	MRI: a pituitary mass of compatible with a pituitary adenoma in apoplexy	CBG initiated before pregnancy Microsurgical transsphenoidal		Delivery at term
Oguz et al.[31]	26	Headache, nausea, visual defects, left temporal deficit	22WG	MRI: macroadenoma with hemorrhage and optic chiasm compression	CBG Transsphenoidal surgery	Improvement	C-section at term
Witek et al.[38]	25	Headaches, dizziness, Visual defects	14WG	MRI: tumor enlargement with optic chiasm displacement and focal hemorrhage	BCP stopped when pregnancy was diagnosed Restarted BCP Transsphenoidal adenomectomy (20WG)	Improvement	C-section at term
Gondim et al.[13]	29	Headache, visual defects	30WG	MRI: Macroadenoma with inside hemorrhage	Continued BCP (initiated before pregnancy) Mini-invasive pituitary surgery (32WG)		Delivery at term
Janssen et al.[19]	27	Headache, visual defects	10WG	MRI: tumor growth, suprasellar extension and optic chiasm compression. Liquefaction within the tumor, indicating apoplexy	BCP stopped when pregnancy was diagnosed Restarted BCP	Resolution	Vaginal delivery at term

Chart 1 (*Continued*)

Author [reference]	Age (years)	Clinical presentation	GA	Pituitary imaging (MRI or CT)	Treatment (GA)	Evolution	Delivery
Hayes et al.[17]	41	Visual defects	18WG	MRI: pituitary hemorrhage with a significant increase in the size of the tumor	CBG stopped when pregnancy was diagnosed Stereotactic endoscopic transsphenoidal excision (2nd trimester)		Vaginal delivery at term
Couture et al.[6]	37	Headache, Nausea, Visual defects	16WG	MRI: sellar mass with suprasellar extension and contact with the optic chiasm, compatible with hemorrhage in a pituitary tumor	BCP switched to CBG when pregnancy was diagnosed	Resolution	C-section at term
Prior lesion: GHoma							
Lunardi et al.[24]	21	Headache, Visual defects	24WG	CT: intrasellar space-occupying lesion with a marked suprasellar extension.	Transsphenoidal approach	Resolution; DI development	Normal delivery at term
Atmaca et al.[3]	33	Headache, Visual defects	33WG	MRI: Pituitary apoplexy	Transsphenoidal resection during labor		C-section at term
Prior lesion: ACTHoma (Nelson syndrome)							
Gheorghiu et al.[12]	33	Headache, nausea	22WG	MRI: intrasellar mass suggesting pituitary apoplexy		DI development	Delivery at term
Prior lesion: Adenoma							
Ohtsubo et al.[32]	29	Headache, vomiting, Visual defects	24WG	CT and MRI: pituitary adenoma with hematoma	Transsphenoidal approach (32WG)		Delivery at term
Prior lesion: Macroadenoma							
Iuliano et al.[18]	28	Headache, edema of the right optic disk	29WG	MRI: pituitary macroadenoma with hemorrhage and compression of the right optic nerve	BCP Transnasal approach (29WG)	Resolution	Delivery at term
Unknown prior lesion							
Murao et al. [30]	35	Nausea, vomiting	39WG	MRI: pituitary apoplexy			
Kita et al.[21]	26	Visual defects	26WG	MRI: pituitary mass with a fluid level component displacing the optic chiasm	Endonasal endoscopic surgery (27WG)	Improvement; DI development	Delivery at term

(*Continued*)

Chart 1 (*Continued*)

Author [reference]	Age (years)	Clinical presentation	GA	Pituitary imaging (MRI or CT)	Treatment (GA)	Evolution	Delivery
Krull et al.[2]	28	Headache, DI	7WG	MRI: pituitary apoplexy			
Piantanida et al.[35]	27	Headache, Visual defects	35WG	MRI: sellar mass with suprasellar extension, with optic chiasm compression, deviation of the pituitary stalk, and with recent bleeding	Endonasal endoscopic transsphenoidal surgery. (postpartum)	Resolution	C-section at 35WG
Fujimaki et al.[9]	23	Headache, Visual defects	24WG	MRI: large mass occupying the pituitary fossa and suprasellar cistern	Surgery was performed 1 month postpartum	Improvement	C-section at 34WG
De Heide et al.[7]	26	Headache nausea, vomiting, Visual defects, DI	23WG	MRI: pituitary tumor with hemorrhage		Improvement	Delivery at term
Bamfo et al.[4]	31	Vomiting, Visual defects, Unilateral ptosis	10WG	Hemorrhage into a preexisting solid or cystic lesion, with extension into the left cavernous sinus and optic chiasm compression			C-section at term
Lee et al.[23]	26	Headache, visual defects, low TSH and FSH and high T4, prolactin and somatomedin C	24WG	MRI: mass arising from the pituitary fossa and extending into the suprasellar cistern compressing the optic chiasm	Transsphenoidal surgery	Resolution	Vaginal delivery at term
Grand'Maison S et al.[15] -Case 1	33	Headache, Visual defects, dizziness, neck stiffness	39WG	MRI/CT: sellar central hemorrhagic infarction and pituitary hyperplasia in contact with the optic chiasm			Labor induction at term
Abraham RR et al.[1]	32	Visual Defects decreased right V1-V2 facial	23WG	MRI: enlargement of the pituitary with hemorrhage and optic nerve compression	Emergent endoscopic endonasal surgery (23WG)		
Jemel M et al.[20] -Case 1	32	Headache, Visual defects	37WG	MRI: sellar central hemorrhagic infarction and pituitary hyperplasia, compatible with sub- acute pituitary apoplexy	None		Labor induction at term
Jemel M et al.[20] -Case 3	30	Headache, Visual defects	24WG	MRI: bleeding within a macroadenoma	Endoscopic transsphenoidal ressection (24WG)	Improvement	Delivery at term
Castro et al.[26] -Case 1	27	Headache, Visual defects	24WG	MRI: pituitary hemorrhage, with optic tract compression	Transsphenoidal partial excision of pituitary gland	Resolution; DI development	C-section at term

Chart 1 (*Continued*)

Author [reference]	Age (years)	Clinical presentation	GA	Pituitary imaging (MRI or CT)	Treatment (GA)	Evolution	Delivery
Mathur et al.[25]	34	Headache, neurological deficits, reversible vasoconstriction syndrome and stroke	Puer- perium	MRI: Pituitary apoplexy was diagnosed based on a pituitary hemorrhage	Steroids Nimodipine plus lamotrigine for seizure prophylaxis	Resolution	Emergent c- section
Okafor et al.[33]	30	Headache, vomiting. protrusion of the right eye	24WG	CT scan: pituitary tumor with pressure effects, occluding the anterior horn of the left lateral ventricle. The other ventricles were dilated	BCP	Hypertension with encephalopathy, cardiac arrest and death	Emergent C- section at 34 + 5WG
Chan et al.[5]	28	Headache, Visual defect, hypogonadism, low TSH and high serum prolactin	38WG	MRI: pituitary tumor, with hemorrhage and hypophysis and optic chiasm compression	Steroids Transsphenoidal surgery 2 days after delivery	Improvement	Forceps at term
Galvão et al.[10] - Case 1	30	Consciousness loss, Headache, Visual defects	28WG	MRI: macroprolactinoma, with sellar and suprasellar hemorrhage	None	Resolution	C-section at term
Galvão et al.[10] -Case 2	25	Headache, Visual defects		MRI: pituitary apoplexy	Transsphenoidal adenomectomy (2nd trimester)	Development of Hypothyroidism and DI	C-section at term
Cokmez et al.[16]	26	Headache, vomiting, Visual defects	24 WG	MRI: macroadenoma and bleeding	Steroids Tumor excision was performed with craniotomy	Improvement	C-section at term

Abbreviations: BCP, Bromocriptine; CBG, Cabergoline; CT, computed tomography; DI, Diabetes insipidus; GA, Gestational age; MRI, Magnetic resonance imaging; WG, weeks of gestation.

with conservative management and also to present a review of the literature on this subject.

Methods

We report a case of pituitary apoplexy during pregnancy and present a review of the published cases in the literature on this subject. To identify these cases, we performed a research using PubMed/MEDLINE, using the MeSH terms "pituitary apoplexy" and "pregnancy." We included all studies published until January 2021. Our search was limited to studies published as full-text articles in English or in Portuguese. All the articles without pituitary imaging were excluded. Written informed consent was obtained from the patient described in our case report. The selected cases were reviewed to obtain information on maternal characteristics, clinical presentation, diagnostic studies, therapeutic modalities and maternal and fetal outcomes. The collected data was analyzed and summarized in a table along with the author's name and respective reference (►**Chart 1**).[1–37]

Case Report

A 36-year-old women, 30 weeks pregnant was admitted to the emergency service with severe holocranial headache, blurred vision, photophobia and vomiting for the last 4 days. In the day before she had been discharged from another hospital with the diagnosis of migraine. She had type 1 Diabetes Mellitus for 18 years, without known micro or macrovascular complications. She was on insulin (detemir and lispro), acetylsalicylic acid, folic acid, ferrous sulfate and potassium iodine. At admission, physical examination, blood pressure and neurologic examination were normal. Hemoglobin, platelets, renal and hepatic function were in the normal range and *sFLT-1 /PLGF* ratio was negative (<38), excluding pre-eclampsia as the cause of this clinical picture. Brain MRI was suggestive of pituitary apoplexy with compression and swelling of the optic tract:

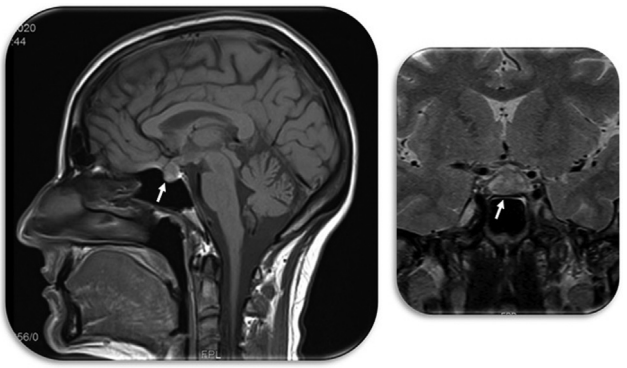

Fig. 1 MRI showing pituitary apoplexy and arrows indicating the pituitary gland.

"Enlarged pituitary gland 12 mm in height, with heterogeneous sign. There is an evident suprasellar extension and shaping of the optic chiasm." (►**Fig. 1**) After neuro-ophthalmological examination, optic chiasm compression was excluded and surgery was postponed. Blood levels of ACTH, FT4, TSH and cortisol were unremarkable. She was started on intravenous hydrocortisone 100 mg every 8 hours, with progressive improvement of symptoms. At 35 weeks of gestation, an urgent c-section was performed because of a non-reassuring fetal heart rate tracing (►**Fig. 1**) associated with absence fetal movements. A baby girl was born with 4080 g and an apgar index of 7/9. She was asymptomatic on discharge (►**Fig. 2**). In the post-partum period she remained clinically stable, asymptomatic and she was diagnosed with a non-functioning macroadenoma. She suspended corticotherapy without relapse.

Discussion

Pituitary apoplexy is a rare event and far less frequent in pregnancy. In the absence of more robust studies, the experience provided by case reports establishes an important guidance for managing these patients. The estimated

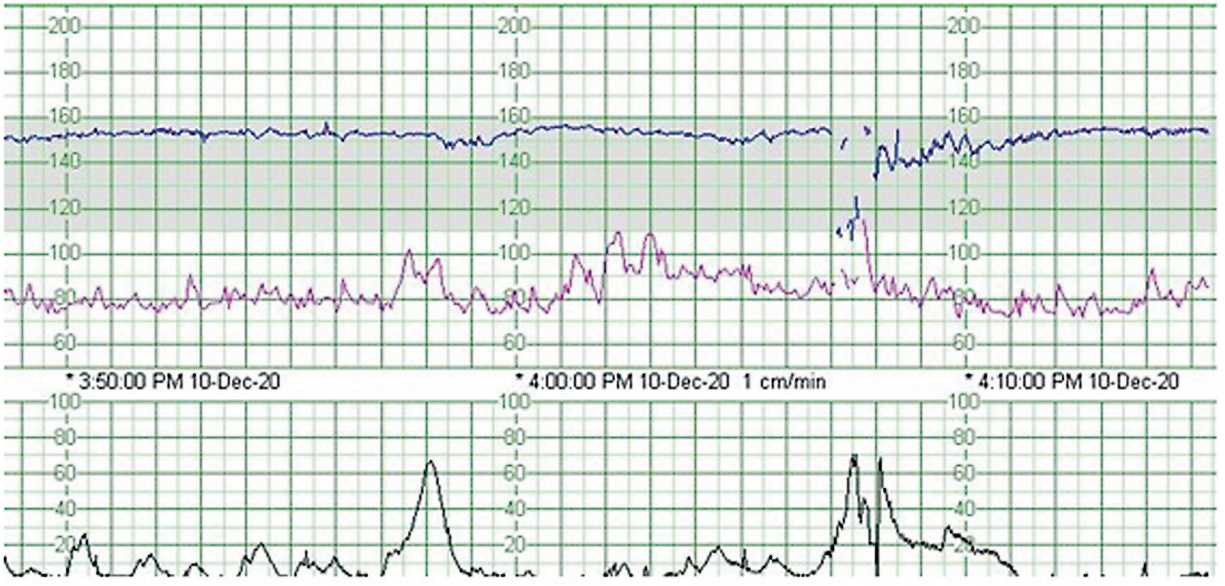

Fig. 2 Non-reassuring fetal heart rate tracing on CTG.

prevalence of pituitary apoplexy is 1:10000 pregnancies at term, with a mean gestational age of diagnose of 24 weeks' gestation and 10% of cases occurring in puerperium. In many cases, as in our case report, it constitutes the first presentation of a pituitary tumor, especially macroadenomas as they tend to be more hemorrhagic.[3,14,15]

Pituitary apoplexy can occur spontaneously or associated with pituitary tumors. The etiology is multifactorial, but several precipitating factors have been described: pregnancy (as in our clinical case), hemorrhagic disturbances, anticoagulation therapy, hypertension, diabetes mellitus, radiation or head trauma, cerebral aneurysm, major surgery, especially coronary artery bypass grafting, estrogen therapy, lumbar punction, upper respiratory tract infection, endocrine stimulation tests, initiation, or withdrawal of dopaminergic therapy.[1,4–7]

The typical presentation of pituitary apoplexy is the one described in our case, with sudden onset of severe bilateral headache, visual disturbances, nausea and vomiting and secondary symptoms to the involvement of cranial nerves (the oculomotor is the most frequently affected). The absence of classic symptoms can delay the diagnosis. In ~80% of the cases, patients will develop deficiency of one or more anterior pituitary hormones, depending on the percentage of pituitary tissue destroyed. Gonadotrophins are the most affected, followed by ACTH and TSH and less frequently prolactin. In this case, gonadotrophins are difficult to value since they are physiologically braked in pregnancy.[1–4]

Acute secondary adrenal insufficiency is seen in approximately two-thirds of patients with pituitary tumor apoplexy and it's the major source of mortality associated with the condition, requiring prompt corticosteroid replacement in anticipation.

The diagnosis is done in the presence of the clinical syndrome associated with *sella turcica* imaging. Magnetic resonance (MRI) is the most sensitive method to confirm the diagnosis and usually reveals a pituitary tumor with hemorrhagic and/or necrotic components.[4,6]

In the pregnancy context the treatment of choice is conservative. Medical therapy includes corticotherapy, dopamine agonists, such as cabergoline and bromocriptine and reposition of hormonal deficits. Surgery might be required during pregnancy, when there are important visual disturbances due to compression, endocrinal hypersecretion (especially Cushing disease) or for life-threatening apoplexy.[4,7,14]

As a result of a literature research on Pubmed we found 36 case reports. From their analysis, we found that the average age of the pregnant women was 29 years old (±4 years), with an average gestational age of 25 weeks (±8 weeks) at diagnose. Most cases occurred in the second trimester. Regarding previously diagnosed lesions, it was present in 47% of patients. There were 7 cases of macroadenomas, 4 cases of microadenomas and 6 cases of adenomas without size specification. Therefore, pituitary apoplexy during pregnancy can be the first manifestation of an unrecognized pituitary adenoma in a large portion of this series. Headache was the most frequent symptom, being present in 86% of cases. Corticotherapy was used in 11% of cases and surgery was required in 61%. Most deliveries were uneventful. C-section was the mode of delivery in 15 cases, there were 6 cases of vaginal delivery and the route of delivery was unknown in 48% of the cases. There were 3 cases of preterm delivery and 28 term deliveries. There was one case of maternal death.

Conclusion

We consider our case report an example of successful management with conservative therapy, since our patient had sustained remission of symptoms without surgery and has already suspended medical treatment without relapse. We would like to reinforce that a precocious diagnosis is essential to a timely approach, avoiding the morbimortality potentially related to this condition.

Conflicts to Interest

The authos have no conflicts of interest to declare.

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Mental Health Disorders in Circumcised Reproductive-age Women, Legal Dimensions and Prevention Strategies: A Narrative Review

Distúrbios de saúde mental em mulheres circuncidadas em idade reprodutiva, dimensões legais e estratégias de prevenção: uma revisão narrativa

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Abstract

Objective: Female genital mutilation/cutting (FGM/C) can affect women's lives through various physical, psychological, social and even sexual mechanisms. According to the World Health Organization guidelines for managing the health effects of FGM/C, further research into its psychological effects and preventative measures is required. In this study, a comprehensive review of the mental health consequences of circumcised women of reproductive age has been conducted with a special focus on providing preventive solutions.

Methods: A comprehensive search of the Web of Science, PubMed(MEDLINE), Proquest ,Scopus and Google scholar was carried outfrom 2000 to 2022. The second stage of search was conducted in grey literature. To facilitate a systematic approach to search the literature, the PECO framework, was adopted.

Results: The result of this narrative review study showed that, the most common mental health disorder in reproductive age circumcised women were depression, anxiety and post-traumatic stress disorder. Some studies found a significant relationship between parents' education level and circumcised girls, so that parents of the circumcised women had a low level of education. Two studies considered religious beliefs, tradition, cleanness, sexual desire control and virginity as the reasons for FGM/C.

Conclusion: All forms of FGM/C may be harmful to one's health. Women, who have undergone widespread forms of circumcision, are more likely to develop mental disorders. As the psychosocial effects of circumcision can affect the sexual experience of circumcised women, addressing this issue, emphasizing its legal aspects, and providing preventative solutions can improve physical, mental, social, and even sexual health in circumcised women.

Keywords

- Circumcisions
- Female
- Infibulation
- Clitoridectomy
- Genital mutilation
- Mental health
- Depression

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Introduction

According to the World Health Organization, female genital mutilation involves partial or total removal of the external genitalia for no medical reason, which falls into four categories: Type I: the clitoris (clitoridectomy) and / or the prepuce are removed in part or completely. Type II: the clitoris and the labia minora are removed in part or completely, with or without removal of the labia majora. Type III: the vaginal orifice is narrowed with formation of a covering seal by cutting and positioning the labia minora and / or the labia majora, with or without excision of the clitoris (infibulation). Type IV: it includes all other procedures that are harmful to the female genitalia (pricking, pulling, piercing, incising, scraping, and cauterization).[1] Female genital mutilation/cutting (FGM/C) is usually performed for cultural, religious or other nonmedical reasons,[2] and it is more common in girls aged 4-10.[3,4] Although it is not clear how many women and girls undergo FGM/C worldwide, the United Nations Children's Fund estimates, that there are currently about 200 million circumcised women and girls living in 30 countries.[5] Despite the legal ban, children and women are still circumcised in 30 African countries and several countries in Asia and the Middle East.[6] The number of circumcised girls and women is increasing in Western countries due to migration.[7] Although there are no accurate statistics on FGM/C in Iran, studies show that this custom exists in some provinces, and it is common in some rural areas of southern Iran.[8]

Low level of education and illiteracy, younger age, lack of knowledge about FGM/C, positive family history of FGM/C,[8,9] prevention of premarital sex, and promotion of marriage are among the common causes of FGM/C worldwide. Some communities considered female circumcision to be necessary for the transition to adulthood, and it has become a part of their cultural history and custom.[1] They also use religious interpretations to justify female circumcision, despite the fact that the Qur'an and the Bible do not support it.[10] Some ethnic groups also believe that the clitoris makes men impotent or even kills them during sex, or that the clitoris inhibits men's ability to erect.[11]

Female circumcision, in addition to human rights violations, may have multiple immediate (severe bleeding, severe pain, fever, infection, shock, and even death) and long-term consequences (urinary and genital problems, sexual problems, delivery problems, reoperation and mental disorders), and it is a serious threat to their health.[1,8] Studies suggest that anxiety disorders, somatization, phobia, low self-esteem,[12] post-traumatic stress disorder,[13] affective disorders,[14] depression,[15] and memory disorders[16] are more common in circumcised women and girls.

Given the negative effects of female genital mutilation, there is now a political, national and international will to eradicate it. As the United Nations has set the eradication of FGM /C as one of its goals for sustainable development in 2030.[17] The Istanbul Convention, adopted by the Council of Europe Committee of Ministers, also recognized FGM/C as a form of gender-based violence.[18] According to the World Health Organization guidelines for managing the health effects of FGM/C, further research into its psychological effects and preventative measures is required.[19] Despite the obvious clinical and social evidence, little research into its psychological effects has been done.

The current review study aimed to examine mental health consequences of circumcision among women of reproductive age, provide preventive strategies and legal aspects of female circumcision.

Methods

Narrative studies are considered a valuable research method in the following cases: Developing approaches to solving clinical problems, providing a voice to clients and nurses, informing social authorities and addressing diversity via understanding.[20] In addition, a narrative study is appropriate when there is limited literature for meta-analysis of the subject under study.[21] The research question in this narrative review was as follow: What are the most common psychological consequences of circumcision in women of reproductive age? Due to the relatively limited number of articles, narrative analysis was used to answer the questions.

Search Strategy

A comprehensive search was conducted between February 1 and March 1, 2021. The search was updated in February 2022, and studies conducted on the psychological effects of circumcision on women of reproductive age were identified. Pubmed, Scopus, Proquest, Web of science, and Google scholar were searched. The grey literature was used in the second stage of the search. In this review, Population, Exposure, Comparison and Outcomes (PECO) approach has been used to develop eligibility criteria, where: Population = circumcised women of reproductive age (15-45 years); Exposure = genital circumcision; Outcome = any type of psychological or mental disorder (Stress, Depression, Post-traumatic Stress, Anxiety). We did not include comparison component in search strategy. Approach was used to generate groups of medical subject heading (MeSH) keywords. In addition, we gained access to some keywords by reviewing related articles and consulting with experts. These keywords ["psychological disorder", "Mental disorder", "Psychiatric illness", "Psychiatric disease", "Mental illness", "Psychiatric disorder", "Mental Health", Stress, Depression, "Post traumatic Stress", Anxiety, "Genital mutilation" Clitorectomy, Infibulation, "Female genital cutting", "Female Genital mutilation", Circumcision] were searched and Boolean operators "OR", "AND", and "NOT" were used to include, restrict, and eliminate search terms. Finally, the reference list of all articles was searched for additional related studies.

Inclusion Criteria

All studies, which were conducted on the psychological effects of circumcision on women of reproductive age from 2000 to 2022, were included without language restrictions.

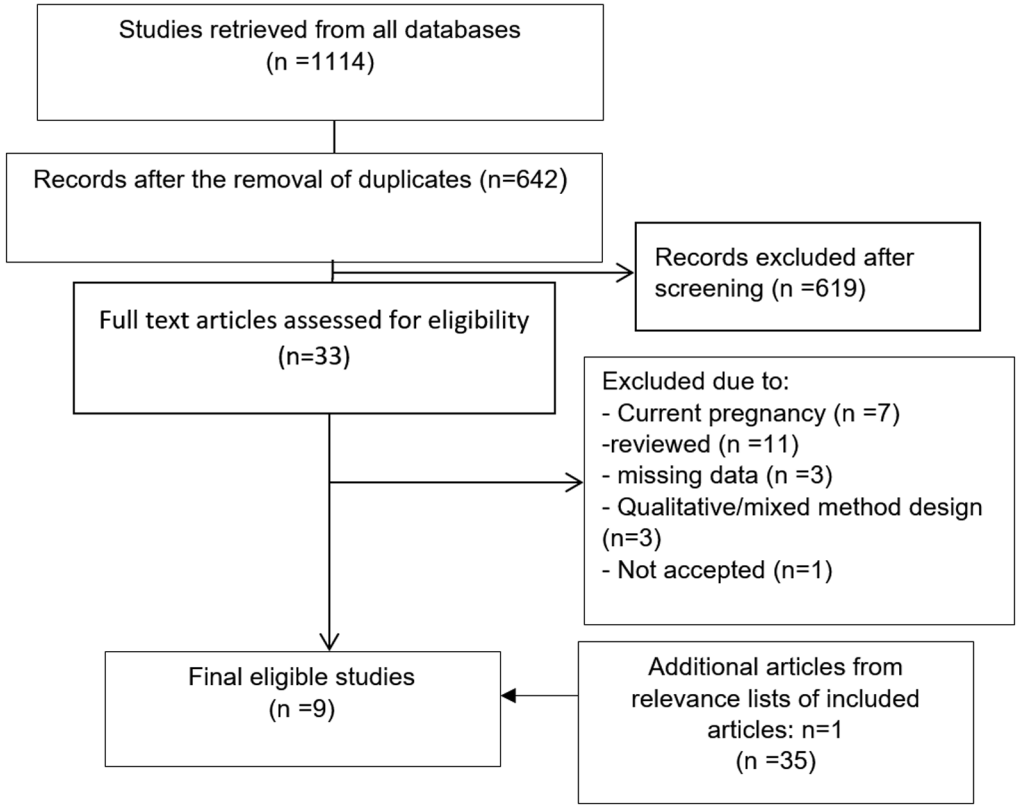

Fig. 1 Search flow diagram.

Exclusion Criteria

Studies conducted on circumcised female children or women over the age of 49 were excluded. Case reports, qualitative, methodological, mixed-method, clinical trial and review studies, studies with missing data were also excluded. By using the inclusion and exclusion criteria, 9 articles were finally included in the study and all authors agreed on the inclusion of these 9 articles.

Selection Process

In total, 1114 studies were extracted, which were independently evaluated by two authors (FA and MP). Duplicates were automatically removed. Then, the titles and abstracts of the remaining 642 studies were assessed and 619 more articles were excluded. Evaluating the full texts of the remaining 33 articles resulted in the exclusion of 25 ineligible articles and confirmed 9 papers as eligible (►**Figure 1**). Any cases of disagreement between authors were resolved through consensus.

Data Extraction

Two authors (FA and MP) and a third independent reviewer (MA) reviewed the titles and abstracts of the studies. The extracted data included study characteristics (Author (year), country, Study design, Sample size, Age (year), Mean age at FGM/C, assessment tool(s), Mental health outcomes investigated, Prevalence of mental outcome (%) and a summary of relevant findings).

Quality Assessment

The attachment of quantitative studies to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was evaluated as a measurement tool of their quality.[22] The STROBE guidelines were created to help the author for ensuring high-quality presentation of the conducted observational study.[23] Studies were classified as high, medium, and low quality if they adhered to all seven items, six items, and two or more items of the STROBE, respectively.

Results

Study Characteristics

►**Chart 1** shows the characteristics of the included studies. All studies reviewed were observational and used a survey methodology. There were seven cross-sectional studies[3,24–29] and two case-control studies.[30,31]

Setting

The studies were conducted in multiple countries. One study was conducted in Kenya.[25] Two studies were conducted in Egypt.[25,28] One study was conducted in the United States.[30] One study was conducted in Senegal[3] and four studies were conducted in Iran.[26–30]

Mental Health Assessment

Mental health was assessed through a variety of tools. Four studies used GHQ-28 questionnaire.[26,27,29,31] One study

Chart 1 Summary of 9 studies evaluating the effects of female circumcision on mental health

Author(year)	country	Study design	Sample size	Age (Mean)	Mean age at FGM/C	assessment tool(s)	Mental health outcomes investigated	Prevalence (%)	Main Findings	STROBE
Behrendt e Moritz (2005)[3]	Senegal	Cross-sectional	N = 47 23 circumcised women 24 uncircumcised women	22.9 ± 4.2	8.2 ± 2.7	- The Traumatic Life Event Questionnaire -semi structured interview	- PTSD - Anxiety - Affective disorders	- PTSD (30.4) - Anxiety disorders (26.2) - Affective disorders (21.7)	The circumcised women showed a significantly higher prevalence of PTSD (30.4%) and other psychiatric syndromes (47.9%) than the uncircumcised women.	16
Im et al. (2020)[24]	Kenya	cross-sectional	N = 143 circumcised women	20.52 ± 3.5 (circumcised-women) 20.20 ± 3.1 (Un-circumcised women)	NR	1- PCL-C 2- HSCL-25	- PTSD - Depression - anxiety - suicidal thoughts	PTSD (38.4) - Depression (37.76) - Anxiety (38.46)	- The FGM group had much higher PTSD scores ($p < .01$ (, more anxiety ($p < .01$) and depression ($p < .001$), lower subjective physical health ($p < .001$), more trouble socializing ($p < .05$), more suicidal thoughts ($p < .05$), and greater likelihood of using substances to cope with traumas ($p < .01$). - Most demographic factors were not significantly associated with the FGM practice, such as age, education, country of birth, and experience of living in a camp.	20
Obaid et al. (2019)[25]	Egypt	Cross-sectional	N = 200 100 circumcised women 100 uncircumcised women	22.5	NR	- HAM-A - Beck's Depression Inventory - DTS	- Anxiety - Depression - PTSD	PTSD (19%)	- No statistically significant difference between the FGM/c and control group in terms of anxiety ($p = 0.37$) and depression ($p = 0.71$).	18
Biglu et al. (2017)[26]	Iran	cross-sectional	N = 208 104 circumcised-women 104 unncircumcised	27.9 ± 5.61 (circumcised-women) 27.1 ± 4.26 (Un-circumcised women)	NR	- GHQ-28	- Insomnia - Anxiety - Severe depression - Social dysfunctions	NR	- The non-circumcised women were in better status than circumcised women regarding to the mental wellbeing ($p = 0.01$) - There was a significant association between FGM/C and education. the more education level of parents, the less their intensity to take their children towards FGM ($p = 0.03$). - Main reasons for FGM: Religious-reason (42.3%), tradition (26%), Cleanness (17.3%), Sexual desire control (9.6%) and Virginity (4.8%).	17
Daneshkhah et al. (2016)[27]	Iran	cross-sectional	N = 200 140 circumcised women 60 uncircumcised women	Range: 15 - 49	NR	- GHQ-28	- Somatic symptoms - Anxiety and insomnia - Social dysfunction - Severe depression	NR	- The calculated scores for general health status did not reveal significant differences between the two groups of participants ($P = 0.93$). - There was no significant difference in mental well-being score between the two groups ($P = 0.41$) - There was a statistically significant difference between the two groups in terms of parents' education level ($p < 0.00$). - The majority reason for FGM: religious beliefs and traditional rituals (57.1%).	20
Ibrahim et al. (2012)[28]	Egypt	cross-sectional	N = 220 164 circumcised women 56 uncircumcised women	29.6 ± 8.5 (circumcised-women) 28.7 ± 6.9 (Un-circumcised women)	NR	- symptoms check list 90	- Depression - Somatization - Anxiety - Phobia	NR	- Circumcised women were found to have a lower level of education. - Type II circumcised women were found to have higher scores in the domains of somatization ($p = 0.03$), depression ($p = 0.02$), anxiety ($p = 0.01$) and phobia ($p = 0.01$).	18
Koolaee et al. (2012)[29]	Iran	cross-sectional	N = 200 100 circumcised women 100 uncircumcised women	Range: 15 - 35	NR	- GHQ-28	- Sleep disorder - Depression	NR	- There were a significant difference between the two groups of participants in items of sleep disorder ($p = 0.00$) and general mental health between genital mutilated females and non-genital mutilated females.	19

Chart 1 (*Continued*)

Author(year)	country	Study design	Sample size	Age (Mean)	Mean age at FGM/C	assessment tool(s)	Mental health outcomes investigated	Prevalence (%)	Main Findings	STROBE
Lever et al. (2019)[30]	United States	Case-control	N = 13 circumcised women	34.0 ± 9.0	9.0 ± 6.1	- HSCL-25 - HTQR-IV	- Anxiety - Depression - PTSD	- Anxiety)92 (- Depression)100 (- PTSD (100)	- Survey of participants with the HSCL-25 instrument showed anxiety in 92% of participants and depression in 100% of participants. Examination of 7 participants with HTQR-IV instrument showed that all of them (100%) had PTSD criteria. - The most common symptoms in circumcised women: headaches, feeling lonely, crying and worrying too much about things, ...	18
Piroozi et al. (2020)[31]	Iran	Case-control	N = 247 122 circumcised women 125 uncircumcised women	35.7 ± 8.6 circumcised women 31.3 ± 7.2 uncircumcised women	NR	- GHQ-28	- Depression - Anxiety - Somatisation	- Depression (48.4) - Anxiety (62.3) - somatisation (54.1)	- More women with FGM presented with symptoms of a mental health disorder ($P = 0.03$). - The prevalence of symptoms of severe depression was significantly higher in the FGM group ($P = 0.02$). - A history of FGM and being in employment had a significant effect on presentation with symptoms of a mental health disorder ($p < .05$).	20

GHQ-28: The General Health Questionnaire; PCL-C: The PTSD Check List – Civilian Version; HSCL-25: Hopkins Symptoms Checklist-25; HTQR-IV : Harvard Trauma Questionnaire Revised-Part IV; HAM-A :Hamilton Anxiety Rating Scale; DTS : Davidson Trauma Scale.

used PCL-C questionnaire.[24] Two studies used HSCL-25 questionnaire.[24,30] One study used Hamilton Anxiety Rating Scale HAM-A, Beck's Depression Inventory and Davidson Trauma Scale-DSM-IV.[25] One study used HTQR-IV questionnaire.[30] One study used The Traumatic Life Event Questionnaire[3] and another used symptoms check list 90 for Mental health assessment.[28]

Study Findings

Most of the studies showed a statistically significant relationship between depression,[24,28,30,31] anxiety,[3,24,28,30] PTSD,[3,24,30] somatization, phobia,[28] suicidal thoughts,[24] sleep disorder,[29,30] and female circumcision. Two studies did not find any statistically significant relationship between circumcised and uncircumcised women in terms of mental health disorders.[25,27] Some studies[26,27] found a significant relationship between parents' education level and circumcised girls, so that parents of the circumcised women had a low level of education while parents of the uncircumcised women had a high level of education. Two studies considered religious beliefs, tradition.[26,27] cleanness, sexual desire control and virginity[26] as the reasons for circumcision.

Discussion

This narrative review was conducted to examine mental health consequences of circumcision among women of reproductive age, provide preventive strategies and legal aspects of female circumcision. This narrative review study examined a limited number of studies on the psychological effects of FGM /C, which is a risky social and cultural practice that threatens mental health of circumcised women.[32] Review of included studies have shown that depression, anxiety and PTSD are the most common mental health disorders in circumcised women of reproductive age. Our findings are consistent with results of prior reviews. For example, the systematic review by Abdalla and Galea (based on 16 studies) in 2019[33] and the smaller review by Berg et al. (included 4 studies),[12] that have reported association between FGM/C and adverse mental health.

The psychological consequences of female circumcision can be explained by the following mechanisms: a person's concern about the state of their genitals, future married life, and fear of infertility, or when circumcision was delayed until adolescence or early adulthood due to parental weakness or as a sort of punishment.[34] On the other hand, the education provided in schools and public forums about the negative effects of circumcision puts a lot of psychological pressure on circumcised individuals.[35] Some researchers also believe that cultural acceptance of circumcision can reduce its psychological burden. For instance, in a society where the female reproductive system is considered dirty or a source of enthralling temptation, circumcision can provide psychological relief for a girl, and despite the pain, she feels satisfied with being clean and marriageable like other women in the society.[36] On the other hand, some argue that even

cultural embedment cannot protect against the psychological effects of female circumcision, such as PTSD and other psychiatric disorders.[3]

Since circumcision compromises normal healthy female genital tissue and sexuality in women, it violates women and girls' rights to have the highest attainable standard of health.[6] WHO in collaboration with UNICEF and the United Nations Population Fund issued the first joint statement on FGM / C in 1997.[37] In addition, WHO in collaboration with key agencies of the United Nations and international organizations, published a document entitled "Global strategy to stop health care providers from performing female genital mutilation" in 2010.[17]

The United Nations has also made the eradication of FGM / C one of its goals for sustainable development in 2003.[38] As a result of joint international efforts and legal frameworks in many countries, the number of women and men advocating for circumcision eradication is increasing, while its overall prevalence is declining. However, progress toward eradicating and reducing female circumcision is very slow.[39]

Prohibition laws have been enacted in some parts of the world to reduce circumcision among girls and women and all professional associations worldwide oppose this practice.[40] In 2015, the law was expanded to require all physicians, teachers, social and healthcare providers in England and Wales to report all cases of female genital mutilation to the police directly.[41] Another preventative aspect is effective educational interventions. Denison et al. (2009)[42] showed that community empowerment through education and multifaceted social activities was more effective than training health personnel in reducing the prevalence of female genital mutilation. Education is a key indicator of protecting women from circumcision. Therefore, human rights agencies and policymakers must increase women's knowledge and awareness of the consequences of circumcision by providing educational opportunities for girls.[26] Also since children's socialization begins in the family, and they learn life skills, parents' level of education can play an effective role in transferring knowledge and attitudes to children through social learning.[32]

Some researchers also believe that one of the most important ways to eradicate female circumcision is to develop the financial and executive capacity necessary to carry out basic programs and influence people in order to replace real values with harmful ones.[43] Mohamed et al.[44] also demonstrated the effectiveness of peer-to-peer workshops held in the UK to train local Somali women about female circumcision, its relationship with health and well-being, female circumcision laws and storytelling of circumcised women. In addition, religious leaders' involvement in understanding the need for change is one of effective measures in generating a transformation within culture.[36]

Female circumcision can affect women's lives through a variety of physical, psychological, social, and even sexual mechanisms. In addition to the pain caused by anatomical distortion, psychological dimensions of circumcision, such as increased anxiety, depression, affecting female identity and relationship mechanisms, such as feelings of shame and marital dissatisfaction can all have a significant impact on women's sexual function.[45] As a result, public efforts should be made to raise awareness, educate girls, women, and men, and design preventive interventions in order to eliminate female genital mutilation as a form of violence against women and girls.

One of the study's limitations was the lack of evidence on the psychological effects of circumcision on circumcised women of reproductive age. Furthermore, in the studies, mental health variables were not measured with a single instrument, which may be one of the limitations of the current study.

Conclusion

All forms of female circumcision may be harmful to one's health. Women who have undergone widespread forms of circumcision are more likely to develop mental disorders. As the psychosocial effects of circumcision can affect the sexual experience of circumcised women, addressing this issue, emphasizing its legal aspects, and providing preventative solutions can improve physical, mental, social, and even sexual health in circumcised women.

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

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Family-centered Cesarean Section for Placenta Accreta Spectrum: Questions and an Addition

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Dear Editor,

Nieto-Calvache et al.[1] showed that family-centered cesarean section (FCS) was possible in 53.8% of patients undergoing cesarean section (CS) for placenta accreta spectrum (PAS). Main concepts of FCS are: earlier skin-to-skin contact and cesarean delivery in a relaxed atmosphere.[2] The rationale of this study accords with this: even in PAS-CS/surgery, 1) FCS will enable earlier skin-to-skin contact, and 2) a "companion" in the surgery theater will lower the patient's stress during CS, possibly reducing the occurrence of posttraumatic stress disorder. I fully agree with the first point. Data showed that FCS enabled earlier skin-to-skin contact at CS in general.[2] Recommending earlier skin-to-skin contact even at PAS-CS is reasonable. Regarding the second point, I wish to ask two questions and make one addition.

The first question regards the meaning of "companion." Nieto-Calvache et al.[1] state the importance of the presence of a "companion" in the surgical theater. Companion has various meanings: partner (husband), pregnant woman's mother (or a relative), doula, or other person. Does a companion mean a doula? A doula is a professional who takes care of a pregnant woman during pregnancy, labor, and postpartum. Their presence is considered to lower the delivering woman's stress, facilitating comfortable labor, and reducing delivery-related psychological trauma.[3] A doula, different from a partner or a relative, is a medical or obstetric professional, and thus having a doula in the surgical theater may cause less concerns of staff and anesthesiologists.

The second question regards the follow-up system of the corresponding mother and baby. Follow-up may be important in preventing, or the early detection of, posttraumatic stress disorder. I wish to know how women after PAS-CS are followed in Nieto-Calvache et al.'s institute.[1] In many Japanese institutes, obstetric nurses or midwives psychologically support mothers during CS: I believe that this is also performed in many other countries. In our institute, we allocate a nurse or midwife to a high-risk pregnant woman (such as a woman with PAS) on an individual basis. This nurse or midwife takes care of the corresponding woman during pregnancy, labor, and postpartum. In postpartum, through a telephone interview, the attending nurse or midwife checks the mother and baby's condition. If there are signs of psychological problems, they contact a health care center in the corresponding area, and support the woman and baby. In Japan, this system works in a similar manner to the doula-system.

Another consideration is a specific aspect of PAS-CS/surgery. Women with PAS are informed that PAS-CS/surgery may sometimes cause mortality. In an advanced cancer surgery, when a patient is informed of surgery-related mortality, one may refuse surgery, depending on the mortality rate. However, in PAS, this is not an option and may cause a marked stress.[4,5]

Nieto-Calvache et al.[1] did not show that FCS at PAS-CS reduces the occurrence of posttraumatic stress disorder. They should not be blamed for this because the purpose of their study was to show that FCS can be performed even at PAS-CS. I believe that, theoretically, this system will reduce maternal psychological sequelae, and thus can be employed depending on the institutes' situation. When introducing this system, I believe that clarifying who the "companion" is may be important as the first step. Understanding the concept of the doula and/or attending obstetric nurse system may help doctors formulate a total-care and follow-up system for the PAS-mother and baby, the second step. Paying attention to stress unique to PAS-patients may be the third step for its establishment.

Lastly, regional anesthesia and stable vital signs (reduced blood loss) are prerequisites of FCS at PAS-CS. An excellent team like Nieto-Calvache et al.[1] made this possible. Less experienced teams should proceed with caution in a step-by-step manner.

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Reply from the authors

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We appreciate Professor __'s comments regarding our paper[1] on family-centered birth for patients with placenta accreta spectrum (PAS):

- Who should be the companion during a family-centered PAS surgery?
- How to offer continuous support to the patient and her family after the surgery?
- How should risky information be delivered to the patient?
- What type of anesthesia is indicated in each case and how interdisciplinary management affects or is affected by the presence of a companion in the operating room?

Professor _____ points out several questions that go far beyond the usual questions when facing PAS and we agree with him that experience is required to answer these questions, but above all, having overcome the basic problems that most reference hospitals are concerned with in regard to PAS (reduce bleeding and serious complications, prevent mortality and provide hospitals with the basic resources for optimal care).

Having overcome those "priority" problems, it is easier to think about offering the highest quality during the management of PAS, including key dimensions but generally overshadowed by the risk of dying, such as the psychological impact on the patient and her family,[2] the decrease in care costs, fertility preservation, the opinion of the patients about losing her uterus[3] and humanization of birth.

Training in the management of PAS is difficult; multiple factors are required, including personal and group will, a hospital with a high flow of patients that supports the improvement, and the inclusion of quality policies such as self-assessment, research, and inter-institutional collaboration. Additionally, the support of other hospitals in the region is required, that choosing to transfer patients to the reference center instead of admitting with them and trying to solve the problem themselves.

Addressing the concept of "center of excellence" for PAS is almost impossible for hospitals in settings with limited resources. Requirements such as more than 5 years of experience, 100 patients (2–3 per month) treated and availability of many human and technological resources,[4,5] seem unattainable for most hospitals,[6] at least in Latin America.[7] In this context, joining efforts between hospitals in the same region is perhaps the only feasible strategy to improve the results of PAS management.

Most interdisciplinary groups choose to go through their "training curve" alone, without sharing their successes and failures with other groups, and even more serious, without being advised (and less supervised) by other groups with more experience. This is shown by the multiplicity of management options published,[8,9] each one defended by the group that applies it, and the small number of multicenter prospective studies evaluating the same management strategy in different hospitals (which would require that at least one hospital gives in, and applies the surgical technique used in another hospital) or by comparing two different management strategies head-to-head (which implies that several hospitals apply at least two different surgical techniques, which requires training in the technique preferred by another group).

Our group has experienced the difficulties of the traditional individualistic approach. In our city (with 2.2 million inhabitants), there were 10 hospitals that considered themselves reference centers for PAS, operating around 3 cases per year, without sharing any type of information with the other hospitals. Additionally, there was no clear pathway of care for PAS in our country, nor education or research initiatives at the regional level. Considering the economic and cultural limitations of our region, we have invested time in evaluating the usefulness of sharing knowledge,[10] with an emphasis on mistakes made, improvement opportunities[11] and collaborative research. To our surprise, very inexpensive strategies such as informal telemedicine,[12] virtual education and communication facilitated by free or low-cost platforms[13] have

had a positive impact on the diagnostic and therapeutic performance of various PAS teams.

Of course, our appreciations must be confirmed with additional studies, but we cannot stop emphasizing the importance of collaborative work to travel faster on the path to excellence and address elements such as patient preferences (choosing who accompanies her in elective surgery, deciding whether to preserve her uterus or her fertility in selected cases, etc.) and the family psychological impact of this serious diagnosis; without neglecting strategies to make the management of PAS increasingly safer.

Conflicts to Interest

The authors have no conflicts of interest to declare.

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FEBRASGO POSITION STATEMENT

Cervical cancer in pregnancy

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The National Commission Specialized in Gynecology Oncology of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) endorses this document. The production of content is based on scientific evidence on the proposed theme and the results presented contribute to clinical practice.

Key points

- The incidence of cancer during pregnancy has increased given women's tendency to delay pregnancy. Cervical cancer is the third most commonly diagnosed neoplasm during pregnancy.
- Screening and diagnosis should be performed as in non-pregnant patients; cervical cytology is an obligatory antenatal exam, and colposcopy with biopsy may be performed at any time of pregnancy.
- Pregnancies complicated by the diagnosis of cancer should always be carried out in a reference center by a multidisciplinary team.
- The termination of pregnancy for standard treatment in specific situations is supported by law.
- Neoadjuvant chemotherapy is a safe alternative treatment during pregnancy to allow reaching fetal maturity. Response rates are high and neoplastic progression during pregnancy is reported in only 2.9% of cases. The risk of fetal malformations from chemotherapy is similar to that of the general population. However, chemotherapy is associated with intrauterine growth restriction, low birth weight, and neonatal myelotoxicity.
- In the absence of disease progression, the pregnancy should be carried to term.

Recommendations

- Screening for cervical cancer in pregnant women should be the same as in other women.
- Treatment of precursor lesions (CINII or III) should be performed after delivery as the risk of progression during pregnancy is minimal.
- Staging of invasive lesions should preferably be performed using magnetic resonance imaging of the abdomen without contrast, and chest X-ray with abdominal protection.
- The therapeutic decision will take into account stage, gestational age and the patient's desire to maintain the pregnancy.
- There is legal support for terminating pregnancies in patients with cervical cancer and gestational age < 22 weeks to allow for standard care (surgery or radiotherapy with or without concomitant chemotherapy).
- The alternatives for patients who wish to preserve the pregnancy are: expectant management, conization/trachelectomy with or without pelvic lymphadenectomy or neoadjuvant chemotherapy with carboplatin and paclitaxel.
- In patients with invasive disease at the moment of delivery corporal (classical) cesarean incision is indicated. Vaginal birth is contraindicated in this scenario.
- After delivery, the patient should receive standard care according to the stage of the disease.

Background

Cervical cancer is the most common gynecological cancer in pregnancy, with an estimate of 0.1-12 per 10,000 pregnancies. For cervical intraepithelial neoplasia, incidence rates range from 1.3 to 2.7 per 1,000.[1-3] Studies have not shown differences in the oncological prognosis of women with cervical cancer diagnosed during pregnancy compared to that in non-pregnant women.[1-3] The growing number of pregnant patients treated for a neoplasm and the follow-up of children resulting from these pregnancies generate safety in the use of various chemotherapy drugs during pregnancy. This has reflected in a greater number of pregnancies carried to term and better neonatal and neuropsychomotor development outcomes for these children.[1,3]

What is the conduct related to the pregnant patient with altered Pap smear?

Screening for pre-neoplastic lesions and cervical cancer in pregnant women should be performed using colpocytology following the recommendations for periodicity and age range for non-pregnant women. Visiting a health service for antenatal care should always be considered as an opportunity for screening.[1,4] Patients with altered cervical cytology should be referred for colposcopy. There is no contraindication for performing a biopsy at any stage of pregnancy.[4] In patients with a histological diagnosis of CINII or CINIII, treatment should be postponed until after delivery, given the minimal risk of neoplastic progression during pregnancy. Follow up with colposcopy every 12 weeks should be carried out. The biopsy should be repeated only if invasion is suspected. Diagnostic conization is indicated in pregnancy only if staging or confirmation of residual invasive disease change the timing and type of delivery. Otherwise, this procedure should be postponed to the postpartum period.

What is the management of pregnant patients with a suspected lesion of invasive cervical neoplasia?

Suspicious cervical lesions in pregnant patients should be investigated through incisional biopsy. After confirmation of malignancy, imaging staging should preferably be performed using chest X-ray with abdominal protection and magnetic resonance imaging of the entire abdomen without contrast, considering that gadolinium is associated with rheumatological diseases in children and neonatal death. When magnetic resonance imaging is not available, an ultrasound of the entire abdomen can be performed with emphasis on the kidneys and urinary tract.[1,3,5]

Which centers are able to manage patients with cervical cancer diagnosed during pregnancy?

These patients should be treated in a reference center with a multidisciplinary team (oncological gynecologists, clinical oncologists, obstetricians specializing in high-risk pregnancies, neonatologists, radio-oncologists and psychologists). Treatment depends on staging, gestational age and the desire to preserve the pregnancy, always on an individual basis and after multidisciplinary discussion, taking into account the risks of postponing or modifying the treatment for that patient.

Is it possible to legally terminate pregnancy in pregnant patients with cervical cancer?

It is impossible to carry out standard therapy for cervical cancer (radical surgery and/or pelvic radiotherapy) and maintain the pregnancy. Therefore, the termination of pregnancy up to 22 weeks in patients with cervical cancer is provided for in article 128 of the Brazilian Penal Code (necessary or therapeutic abortion when there is a risk to the mother's life)[6] and by Ordinance GM/MS number 1.508 from the Ministry of Health.[7] After this gestational age, the fetus is considered viable in most centers and the management must be individualized. Termination of pregnancy followed by standard oncologic treatment is recommended in patients with locally advanced disease or with positive lymph node. In this context, patients who choose to continue with the pregnancy should be informed they will not undergo standard oncological treatment, which could result in compromised maternal prognosis and increased obstetric risks.[1,3]

How should pregnancy be terminated?

For termination of pregnancy in patients with cervical cancer, the following are required:

- The evaluation of at least two professionals; one of them must be a specialist in the disease causing the interruption:
- Medical record with medical justifications detailing the maternal risk;
- The consent and/or informed consent signed by the pregnant woman or her family, unless this is impossible in situations of imminent risk to her life;
- Support and monitoring by a multidisciplinary team, especially psychologists.

Judicial authorization, police reports or communication to the Regional Council of Medicine are not required. The method of termination of pregnancy depends on gestational age and staging. In patients with early-stage disease, a radical hysterectomy can be performed with the fetus in situ. In locally advanced disease during the first trimester, abortion with evacuation of the conceptus is indicated. When surgical abortion is not feasible given the presence of a tumor obliterating the cervical OS, radiotherapy can be started with the intrauterine conceptus. This results in a miscarriage within three weeks.[1,3] Over 16 weeks, preference is given to feticide before starting treatment or evacuation.

How should be the management of pregnant patients with stage IA1 or IA2 cervical cancer?

Conservative surgical treatment, such as conization, is recommended preferably between 14 and 22 weeks. After this gestational age, due to the risk of bleeding and pregnancy loss, quarterly surveillance should be carried out with colposcopy until delivery, and definitive treatment six weeks after delivery. Conization with high-frequency surgery is associated with less bleeding and complications.[1,8] The indication for cerclage is controversial.

What is the role of lymphadenectomy in pregnant patients with cervical cancer?

Lymph node metastasis is one of the main prognostic factors in cervical cancer. For this reason, some authors advocate performing staging lymphadenectomy to truly determine the staging and prognosis and therefore, bet-

ter select the candidates to continue the pregnancy. It is feasible up to 20 weeks, since after this gestational age, the uterine volume compromises the surgical field and the number of resected lymph nodes drops considerably, hence it is not considered appropriate for staging purposes.[1,3] The route of choice is laparoscopic in experienced hands, as it is associated with faster recovery and better postoperative pain control. Sentinel lymph node screening is not recommended in pregnant women given the risk of patent blue anaphylaxis and the lack of safety data with the use of technetium and indocyanine green during pregnancy. In case of positive lymph nodes, the tendency is to interrupt the pregnancy to allow standard treatment. Patients who refuse the interruption should be advised to undergo treatment with neoadjuvant chemotherapy performed until three weeks before delivery.

How should be the management of pregnant patients up to 20 weeks and cervical cancer stages IB1 and IB2?

Several studies in patients with cervical cancer have shown a negligible risk of parametrial involvement when the pelvic lymph nodes are negative.[9] Therefore, by taking into account the significant morbidity of radical trachelectomy during pregnancy, such as pregnancy loss and bleeding, there is support in the literature to manage these patients with pelvic lymphadenectomy and wide conization or simple trachelectomy to obtain free margins, followed by cerclage. A multidisciplinary team, including radiologists, should perform the surgical planning with the aim of assessing the chance of resection of tumor free margin, maintaining a safe distance from the internal cervical os. In cases when a free-margin conization is not feasible, surgery is not recommended.

How should be the management of pregnant patients over 20 weeks and diagnosis of cervical cancer stages IB1 and IB2?

The case series study of patients with a diagnosis of cervical cancer restricted to the cervix at the end of the second trimester and in the third trimester, who underwent expectant management with surveillance of progression showed excellent oncological outcomes, hence this treatment is an option.[8] In patients diagnosed at the beginning of pregnancy, or when expectant management is not considered prudent due to other prognostic factors (deep stromal invasion, angiolymphatic invasion or unfavorable histological types), neoadjuvant chemotherapy with carboplatin and paclitaxel is indicated every three weeks, starting after 14 weeks of pregnancy. If there is no progression, treatment should be carried out until 34/35 weeks to allow for full-term delivery. Given the risk of maternal and neonatal complications, such as infection and hemorrhage, chemotherapy should be discontinued three weeks before the planned date of delivery.[1,3]

How should be the management of pregnant patients with locally advanced tumor who wish to preserve the pregnancy?

Neoadjuvant chemotherapy with carboplatin and paclitaxel is indicated every three weeks, starting after 14 weeks of pregnancy. If there is no progression, treatment should be performed until 34/35 weeks and delivery at term.[10] Radiochemotherapy can be started two weeks after delivery.[1,3]

How should be the management of pregnant patients with stage IVB cervical cancer?

Palliative chemotherapy may be offered. Immunotherapies with recombinant humanized monoclonal antibodies such as bevacizumab and pembrolizumab are contraindicated during pregnancy.[1-3] Early referral to palliative care for control of pain and other symptoms is fundamental in the context of advanced and metastatic disease, contributing not only to improve the quality of life, but also to increase the survival of these patients.

How should birth planning be in pregnant patients with cervical cancer?

In cases in which there is no progression of the disease or obstetric indication of anticipation of delivery, the ideal moment of delivery should be at the term of pregnancy. The mode of delivery is cesarean section when there is invasive cervical disease, with a corporal cesarean section to avoid the risk of extending the hysterotomy to the cervix and the consequent tumor laceration, with contamination of the abdominal cavity.[1,3] Vaginal delivery is contraindicated in patients with invasive cervical cancer, as it poses maternal and fetal risk. In addition to the risk of tumor bleeding and obstruction of the birth canal, the literature describes 20 cases of implantation in a laceration of the birth canal or episiotomy with a fatal outcome in most cases.[1,3] Arakawa et al.[11] reported two cases of children who developed squamous cell carcinoma of the lung after vaginal delivery in a patient with the same neoplasm in the uterine cervix. In patients treated with free-margin conization and without evidence of cervical disease, the mode of delivery is obstetric.[1,3]

How should definitive treatment be performed after childbirth?

The definitive treatment will depend on the patient's reproductive desire.

Patients with reproductive desire:

- Fertility-preserving treatment options can be offered to patients with stage up to IB1 and the surgical options are conization or radical trachelectomy with or without lymphadenectomy. The ideal time for surgery is four to six weeks after delivery.

Patients without reproductive desire:

- Patients with surgical treatment indication: Extrafascial or radical hysterectomy and pelvic lymphadenectomy can be performed right after the cesarean or six weeks later. The decision regarding the best moment for definitive surgical treatment must be individualized, taking into account the tumor biology, the patient's surgical risk and the surgeon's experience. Hysterectomy right after cesarean is associated with increased blood loss and perioperative complications, such as surgical wound infection and urinary tract infection. [12] In addition, sentinel lymph node biopsy is not feasible in this scenario. Waiting six weeks after delivery could allow this less morbid lymph node evaluation.
- Patients with indication of chemoradiotherapy can start treatment two weeks after delivery

Final considerations

The concomitant diagnosis of cancer and pregnancy is a rare and dramatic situation. The medical literature is limited to case series and a consensus of the European Society of Gynecological Oncology/European Society for Medical Oncology (ESGO/ESMO); guidelines must always be interpreted with caution. Multidisciplinary and individualized evaluation is the best way to ensure the best outcome for the mother and, when there is a desire to preserve the pregnancy, for the fetus.

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About the journal

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The *Revista Brasileira de Ginecologia e Obstetrícia* (RBGO - Revista Brasileira de Ginecologia e Obstetrícia – ISSN 1806-9339) is a monthly scientific publication of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo). It is aimed at obstetricians, gynecologists and professionals in related areas with the purpose to publish research results on relevant topics in the field of Gynecology, Obstetrics and related areas. The journal is open to national and international contributions and accepts submissions in English only.

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- SciELO – *Scientific Electronic Library on-line*;
- Lilacs –Latin American and Caribbean Health Sciences Literature

Intellectual property

Sponsors

RBGO does not receive any type of support from funding sources. It is fully maintained by the Brazilian Federation of Gynecology and Obstetrics Associations and receives sponsorships.

Responsibilities of the Editorial Board

Responsibilities of the Editor-in-Chief

- Ensure that the journal is published within the established deadlines.
- Ensure the quality of selected texts and their appropriateness to the interests of readers.
- Establish the policy for manuscript submission, peer review, reviews and resubmission.
- Ensure that articles are reviewed and accepted only on the basis of scientific merit and not on the basis of any influence, whether commercial or personal.
- Maintain transparency throughout the manuscript review and editing process.
- Investigate all complaints and/or doubts related to submissions to the journal, whether accepted or not, and give authors the opportunity to respond whenever necessary.
- Provide support for the selection process of members of the journal's editorial board to define the types of publication and selection criteria for manuscripts accepted by the journal.
- Develop policies and procedures to attract scientific quality manuscripts.
- Examine the digital proofs of the journal, ensuring their quality.
- Adopt procedures protecting ethical issues, conflicts of interest and compliance with the policies adopted by the Brazilian Federation of Gynecology and Obstetrics Associations to which it is affiliated.
- Treat all individuals with respect, impartiality and without discrimination based on gender identity, race, sexual orientation, religion or political beliefs and geographic region.

- Maintain impartiality and clarity in the publication of sponsored supplements and/or with any other type of sponsorship/funding.
- Ensure open access and describe in all articles the Creative Commons license modality adopted by the journal.
- Ensure the organization of all documents related to the journal submission process.

Associate Editor responsibilities

- Read and evaluate the scientific quality of manuscripts received from the Editor-in-Chief.
- Appropriately choose the reviewers of manuscripts under their responsibility.
- Expedite the progress of evaluations made by reviewers and keep the review process within the schedule established by the Editor-in-Chief.
- Analyze the opinions issued by reviewers and assist them in preparing recommendations to authors.

Responsibilities of Reviewers

- Reviewers have the responsibility to review the manuscript objectively and fairly.
- Critically analyze manuscripts by offering suggestions to improve quality and contribute to the decision-making process.
- Maintain the confidentiality of any information provided by the editor.
- Maintain strict confidentiality during the review process. The reviewer must not share information from a manuscript prior to completion of the review and prior to acceptance and publication.
- Inform the editor about any similarity of articles under review to be published or ongoing studies that may be considered plagiarism.
- Disclose any potential conflicts of interest (financial, institutional, collaborative, or other relationships between reviewer and author). If there is a conflict of interest or if the reviewer does not have the necessary expertise, the manuscript must be immediately returned to the editor for the selection of another reviewer.

Responsibilities of the Author(s)

- Attest to the originality of the submitted study and confirm the article is not being considered elsewhere, nor accepted for publication in another journal.
- Ensure approval by the Research Ethics Committee of the institution where the study was developed.
- Participate sufficiently in the work to take public responsibility for its content. Authors' contributions can be made in different ways: conceptual, intellectual, experimental and analytical, and by participating in the writing and review of the manuscript. The final approval of the version to be submitted must be approved and signed by all authors responsible for all aspects of the work (typed or printed name is not acceptable).
- Ensure that studies including humans or animals comply with national and international requirements and guidelines (Declaration of Helsinki [2013], Declaration of Human and Animal Rights [Unesco, 1978]). This information must be stated in the manuscript, and the protocol number or exemption status of approved protocols must be stated in the manuscript at the time of submission for review.
- Inform the registration number referring to the research approval report at the National Council for the Control of Animal Experimentation (Concea). Studies involving animal experiments must comply with Law No. 11.794, of October 8, 2008, which establishes procedural rules for the scientific use of animals in Brazil. International manuscripts must submit local ethical documentation to proceed with the submission process. Any manuscript involving animal or human experiments submitted without proof of approval by institutional or local research committees will not be reviewed and will be returned to authors.
- Inform potential conflicts of interest in a written statement signed by all authors.
- Inform the journal editor when a major error is found in the study and provide all necessary information for publication correction, errata and retraction.
- Provide data records associated with the study when requested by the editor.
- Provide the definitive list of authors and their order at the time of original submission, containing the author registration with the respective Open Researcher and Contributor Identifier (ORCID) at https://orcid.org/signin. Any addition, removal or rearrangement of authors' names in the authorship list should be done only before the manuscript is accepted and only if approved by the journal editor. If that is the case, the corresponding author must obtain agreement of the other authors in writing, justifying the reason for alteration (addition, removal or rearrangement), and send the request by letter or e-mail. The editor will consider adding, deleting or rearranging authors after acceptance of the manuscript only in exceptional circumstances. If the manuscript has already been published in an online edition, any requests approved by the editor will result in rectification.
- Meet the deadlines for corrections and clarifying answers to questions made by reviewers.
- Use language that promotes social inclusion. The manuscript content must respect readers and not contain anything that could imply that an individual is superior to another because of age, sex, race, ethnicity, culture, sexual orientation, disability or health condition. Writing must be free from prejudice, stereotypes, slang, references to the dominant culture and/or cultural assumptions. The recognition of diversity is sensitive to differences, promotes equal opportunities and expresses respect for all people.

Scientific misconduct

Presenting results of animal or clinical research conducted without proper approval and written informed consent, as set out above, is considered unethical scientific behavior. Duplicate publication or when results are falsified, fabricated or plagiarized is also considered unethical. The RBGO allows the partial presentation of data from a manuscript in another means of dissemination, although in these cases, the author must acknowledge the previous presentation and identify the source. The citation of the original publication is essential in the disclosure. Splitting data, analysis and presentation of the same study into smaller units (practice called "salami slicing") should be avoided. Thus, the author must acknowledge in his or her cover letter any similar publications or manuscripts that have been submitted for publication based on the same material.

Investigation of scientific misconduct

Submission of an article implies that the work described has not been previously published, except in the form of an abstract, published lecture or academic thesis. Scientific misconduct may be suspected during the manuscript review process by reviewers. Thus, the RBGO may use additional resources to investigate the author's unethical conduct in order to certify the originality or plagiarism of the article (examples: Crossref Similarity Check, iThenticate and others). All suspected cases will be investigated initially by the Editor-in-Chief and by the Ethics and Professional Defense Committee of the Brazilian Federation of Gynecology and Obstetrics Associations. The author will be notified in writing of the allegations and asked to provide useful information to the investigation, including access to all original data, notes and copies of previous publications. The author's affiliation may also be contacted.

Retraction policy

The retraction policy of the RBGO is based on COPE's Retraction guidelines for advice and guidance for editors (DOI: https://doi.org/10.24318/cope.2019.1.4).

Editors will consider a publication retractable in case:

- It is plagiarism;
- It reports unethical research;
- It contains material or data without authorization for use;

- The copyright has been infringed or there is any other serious legal issue (e.g. defamation, privacy);
- There is clear evidence that results are unreliable, either as a result of a major error (e.g. miscalculation or experimental error) or as a result of fabrication or falsification of data and/or images, for example;
- Findings have been previously published elsewhere without proper attribution to prior sources or disclosure to the Editor, permission for republication or justification (i.e. cases of redundant publication);
- It has been published solely based on a compromised or manipulated peer review process;
- The author(s) have not disclosed a major conflict of interest which, in the Editor's opinion, may have unduly affected the interpretations of the work or the editors' and reviewers' recommendations.

Retraction notices must:

- Be linked to the retracted article in all versions printed or online;
- Clearly identify the retracted article (e.g. including the title and authors in the retraction header or citing the retracted article);
- Be clearly identified as a retraction (i.e. distinct from other types of correction or comment);
- Be published promptly to minimize harmful effects;
- Be freely available to all readers (i.e. open access or available only to subscribers);
- Inform who is removing the article;
- Indicate the reason(s) for the retraction;
- Be objective and factual and avoid aggressive language.

Retractions are generally inappropriate if:

- Authorship is disputed, even though there is no reason to doubt the validity of findings;
- The main conclusions of the work are still reliable and the correction can sufficiently address the errors or concerns;
- An editor has inconclusive evidence to support the retraction or is awaiting additional information, such as from an institutional investigation;
- Authors' conflicts of interest were reported to the journal after publication, but in the editor's opinion, they likely did not exert influence in interpretations, recommendations or conclusions of the article;

The RBGO will follow the flowchart suggested by COPE (DOI:**https://doi.org/10.24318/cope.2019.2.7**) to track an undisclosed conflict of interest in a published article.

Receipt of articles deposited in preprint repositories

Manuscripts submitted and coming from preprint repositories will necessarily be peer-reviewed and receive the definitive DOI issued by the RBGO if approved. Manuscripts submitted for analysis by the RBGO editorial board cannot contain references to articles that have not been published in scientific journals and that have fully complied with the peer review process.

Instructions to authors for manuscript submission

The material sent for analysis must not have been submitted simultaneously for publication in other journals or previously published. The selection of manuscripts for publication involves evaluation of originality, relevance of the topic, quality of the methodology used, its updating and whether it is appropriate and interesting to readers, in addition to adequacy to the editorial standards adopted by the journal.

Evaluation of manuscripts

Manuscripts in English submitted to the journal are received by the editorial office that checks the mandatory documentation and analyzes if the editorial rules contained in instructions to authors have been complied with. If the process is in accordance, the manuscript is sent to the editor-in-chief, who will make an initial merit assessment of the submitted manuscript. If the editor-in-chief concludes the work is in favorable scientific and technical conditions, the manuscript will be forwarded to associate editors, who, in turn, will appoint reviewers (double mind process) to evaluate the work. The reviewers' opinions and the editor's instructions will be sent to authors so they are aware of the editor's decision, criticism and eventual changes to be introduced. Authors must resubmit the text with the suggested changes within the requested deadline. When resubmitting the manuscript, the requested corrections must be highlighted in the text (marked in yellow). In cases of disagreement with the suggestions, the authors must include the justifications and observations in comment balloons. Authors must be assertive and punctual with the inquiry, supporting the hypothesis with references. **IMPORTANT!** Authors must comply with the deadlines. Failure to do so will result in a delay in their publication or even in the shelving of the process. Authors can request the suspension of the process and withdrawal of the work at any point in the process of analyzing and editing the text, except when the manuscript is accepted for publication. The concepts and statements contained in the articles are the responsibility of the authors.

Preparing a manuscript for submission

Mandatory documents for submission

When submitting a manuscript to the RBGO, documents listed below must be attached to the ScholarOne submission platform. Note that failure to submit or incomplete documentation will result in cancellation of the submission process. Mandatory documentation for online submission:

- Authorization for copyright transfer signed by all authors (scanned and attached) – **Template**;
- In accordance with chapter XII.2 of CNS Resolution No. 466/2012, in Brazil, research involving human beings needs to inform the registration number referring to the Certificate of Presentation for Ethical Assessment (CAAE) or the number of the research approval report (CEP/Conep) in the Research Ethics Committee. In the case of manuscripts involving animal experimentation, it must be indicated if it complies with Law No. 11.794 of 8 October, 2008, which establishes procedures for the scientific use of animals in Brazil, informing the registration number referring to approval of the research at the National Council for the Control of Animal Experimentation (Concea). International manuscripts must submit local ethical documentation to proceed with the submission process;
- The cover letter must be written with the purpose of justifying the publication. Authors must be identified with the respective Open Researcher and Contributor Identifier (ORCID), the authors' affiliation institution and the intention of publication. The qualification/title of the corresponding author must be included.

Title page:

- Title of the manuscript in English with a maximum of 18 words;
- Full name of authors without abbreviations (include a maximum of 8 authors per article, except in the case of multicenter studies, consensus, guidelines and position statements of societies or research groups);
- Corresponding author (full name, qualification/title and contact e-mail);
- Institutional affiliation of each author. Example: Department of Gynecology and Obstetrics, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil (Departamento de Ginecologia e Obstetrícia da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto, SP, Brazil);
- Conflicts of interest: authors must inform any potential conflict of interest, whether of resources, political, economic for developing the study or of intellectual property;
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from the agencies Conselho Nacional de Pesquisa (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Capes), or any other state research support agency (eg. Fapesp), should be mentioned with the number of the research process or grants awarded;

- Contributions: according to the criteria for scientific authorship of the International Committee of Medical Journal Editors (ICMJE), authorship credit should be based on three conditions that must be fully met: (1) substantial contributions to conception and design, data collection or analysis and interpretation of data; (2) article writing or relevant critical review of intellectual content; and (3) final approval of the version to be published.

Manuscript

The Revista Brasileira de Ginecologia e Obstetrícia(RBGO) publishes the following categories of manuscripts:

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

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

Manuscript structure

Title

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

Abstract

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

1. Abstract: for original articles

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

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

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

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

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

2. Abstract: for systematic review articles

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

Objective: State the main objective of the article.

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

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

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

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

Conclusions: State the main conclusions and their clinical utility.

3. Abstract: for integrative/scoping reviews

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

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

Keywords

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

Manuscript body

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

Introduction

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

Methods

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

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

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

Randomized clinical trial:

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

Systematic reviews and meta-analyses:

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

Observational studies in epidemiology:

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

Qualitative studies:

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

Results

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

Discussion

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

Conclusion

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

References

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

Submission of manuscripts

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

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