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Editorial

Increase in cesarean sections in Brazil – a call to reflection

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Cesarean rates have increased progressively over the decades in all countries, and a high figure of 56% was reached in Brazil, second only to the Dominican Republic (59%) and well above the average of developing countries.¹ This scenario in our country motivated government and private sector initiatives, among which the *Projeto Parto Adequado* (“Adequate Childbirth Project”), with a view to reducing cesarean sections.² The set of these actions allowed for a stabilization and even a slight decrease in cesarean section rates according to data from the Information System on Live Births (Portuguese acronym: SINASC) of the Brazilian Ministry of Health. However, preliminary data from SINASC for 2022 pointed to a further increase in cesarean sections in Brazil (cesarean section rates: 2016: 55.4%; 2017: 55.7%; 2018: 55.9%; 2019: 56.3%; 2020: 57.2%; 2021: 57%)³ and motivated this reflection made by Brazilian obstetric schools.

Undoubtedly, the COVID-19 pandemic has profoundly affected healthcare in Brazil, accelerating trends and

highlighting weaknesses. In the obstetric scenario, the country already showed signs of an increase in cesarean rates from 2017 onwards, and the pandemic accentuated this process. Although the healthcare network was reorganized to maintain antenatal care during the pandemic, this was limited in practice, especially for patients at obstetric risk. As a result, pregnant women arrived at maternity hospitals with obstetric complications in more severe stages and the indication for cesarean sections to alleviate an unfavorable maternal-perinatal outcome. In addition, especially at the beginning of the pandemic, although there was no explicit guidance, many cesarean sections were performed under the mistaken belief that this would bring better maternal outcomes. With experience in the management of COVID-19, it was observed that whenever plausible, the resolution should be postponed until clinical stabilization of the pregnant woman. However, in cases with a precise indication of resolution of the pregnancy because of severe conditions,

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the possible mode of delivery was mostly the cesarean section.⁴

The fact that delivery care was challenging during the COVID-19 pandemic may also have contributed to the increase in cesarean sections. Factors such as restrictions on the presence of companion during hospitalization for childbirth in many services; lack of guidance to pregnant women for labor as participation in antenatal classes was lower because of social distancing⁵; fear of hospitalization, perceived as a source of transmission of the disease; and increased anxiety, sadness and fear with intense psychological distress caused by the pandemic and enhanced by the disruption of the support network for pregnant women⁶ may have contributed to the increase in cesarean rates in this period.

However, the COVID-19 pandemic also highlighted the fragility of the maternal and child care network in Brazil. The lack of synchronized and adequate management in the different maternity hospitals around the country and a fragile system of hierarchy for referring cases of high obstetric risk demonstrate the complexity of this problem. The continental size of our country, the heterogeneity of health services, the absence of a complete medical team each day of the week in small towns, as well as the existence of settings without implemented assistance care sometimes determine the performance of electively scheduled cesarean sections on days when the complete team is available for fear of obstetric emergency situations during labor.

Of course, it would be naive to credit the high cesarean rates in Brazil only to the COVID-19 pandemic. There are other well-known determinants that help compose this scenario, such as the lack of a culture of multidisciplinary teamwork in childbirth care; the scarce supply of pharmacological analgesia; imprecise indications for early delivery due to suspected impairment of fetal vitality and the underfunding of obstetric care, both at the institutional level and at the level of professionals who accompany deliveries. The high number of cesarean sections also ends up feeding back into this cycle, when women with previous cesarean sections are very often subjected to repeat cesarean sections because of the obstetric fear of rare cases of uterine rupture aggravated by the unavailability of prostaglandin E₂ in the national market. Avoiding the first cesarean is strategic to break this cycle. To this end, the systematic second opinion for the indication of cesarean section and the analysis of the Robson classification for the study of cesarean sections are strategies that can avoid cesarean sections not considered as the best clinical indication.

The cesarean culture also influences the legal world and is reflected in the obstetric team's fear of being sued for lawsuits in cases of malpractice, which certainly contributes to a more "early" or unnecessary indication of cesarean section. A survey by the American College of Obstetricians and Gynecologists (ACOG) in 2015 showed that 73.6% of North American gynecologists and obstetricians suffered at least one malpractice lawsuit (62% in obstetrics and 39% in gynecology).⁷ In the judicial sphere, it should be noted that the legislation regulating the performance of cesarean sections

at the pregnant woman's request and the right to labor analgesia, under the aegis of autonomy, even without medical indication, may also have influenced the increase in cesarean sections. However, given the difficulty in offering analgesia, especially pharmacological, in Brazilian maternity hospitals, many women end up requesting a cesarean section during labor, which contributes to the increase in the number of cesarean sections without medical indication. It is further presumed that Federal Law Number 14.443/2022,⁸ which updates the legislation on Family Planning in Brazil, effective as of March 2023, and which allows tubal ligation at the time of delivery, further increases cesarean rates. Finally, and although the Brazilian Federal Council of Medicine recognizes women's right to request a cesarean section⁹ from 39 completed weeks of pregnancy, guaranteeing the autonomy of the physician and the patient and the safety of the mother-fetus dyad, it is essential to guarantee that all pregnant women can be assured of a safe delivery. Otherwise, the woman's autonomy may be weakened by the lack of equity and the request for a cesarean section will simply reflect the lack of option for a respectful and pain-free delivery.

Although the cesarean section is a life-saving surgery, representing a great advance in obstetric practice and in the integral protection of the mother-fetus dyad, its reckless performance is associated with relevant immediate and future risks. Among the immediate maternal risks of a cesarean section, are the increase in intrapartum bleeding and postpartum hemorrhage, the increased risk of maternal infection/sepsis, thromboembolic conditions and injuries to pelvic organs, especially in emergency surgery. With regard to immediate fetal risks, iatrogenic prematurity (due to early term birth) and increased rates of transient tachypnea in newborns stand out. In addition, birth trauma can occur during a cesarean section.¹⁰ This surgery can still cause future complications such as reduced fertility, abnormal uterine bleeding and chronic pelvic pain,¹⁰ in addition to greater risks of pregnancy in a cesarean section scar, uterine rupture and placenta accreta. These obstetric complications are responsible for severe and potentially lethal maternal hemorrhagic conditions, and are associated with significant maternal morbidity and mortality.¹⁰⁻¹² The possible future risks of fetuses born by cesarean section include alterations in the intestinal microbiome, as well as higher rates of immunological dysfunctions, metabolic disorders (such as obesity and asthma) and cognitive disorders (such as hyperactivity).¹⁰ Considering such high cesarean rates and the immediate and future risks determined by this surgery in women and fetuses, there is need for a reflection that results in strategies to reduce unnecessary cesarean sections in our country.

The initial strategy must include antenatal actions. Health literacy will allow women to have an active role and make more appropriate informed decisions about childbirth.¹³ The formation of groups of pregnant women to discuss the types of childbirth, physiology and stages of normal childbirth; encouraging the presence of a companion during antenatal care, so that they receive information and help the pregnant woman, transmitting her security; encouraging pregnant

women and companions to visit the reference maternity hospital in order to provide greater security at the time of delivery; agreeing on a birth plan during antenatal care; and guidance on non-pharmacological pain control methods are measures that should be encouraged to reduce cesarean section rates.

Listening to women's expectations for their childbirth is essential for encouragement in this route of birth. In 2018, the World Health Organization (WHO) published¹⁴ a summary of these aspirations: care provided by a sensitive, attentive, kind and respectful team; presence of a companion (having a person she chooses by her side will bring emotional security and comfort); accurate birth interventions; autonomy (being informed and participating in decisions); labor analgesia (non-pharmacological and also pharmacological whenever requested); delivery outcome with healthy mother and newborn.

Feeling pain during labor is one of women's biggest fears. Brazil faces an enormous shortage of pharmacological analgesia for childbirth. This has been identified as one of the factors that most influence the choice for a cesarean section. Few hospitals provide anesthesiologists 24 hours a day to offer labor analgesia if requested by the pregnant woman. If we want to guarantee women a pain-free delivery and thus reduce cesarean rates, access to and availability of analgesia for all women who request it is one of the main challenges to be faced. Discussing new models of anesthetic care during labor, as in countries with a wide supply of labor analgesia, such as the United States and France, may be opportune.

The need to organize the maternal and child healthcare network is urgent. Health equipment should be restructured in a rational way, reducing the number of maternity hospitals in cities with a low population rate, whose residents can be attended in regional hospitals. This restructuring will provide greater security for the mother-fetus dyad, ensuring professional structure and permanent material resources, linked to the primary objective of improving childbirth care, reserving cesarean section for the best indicated cases. In addition, these reference centers for childbirth would have an appropriate space for parturition, with LDRP models (space for labor, delivery, recovery and postpartum room), where the parturient woman and her companion would remain in an embracing environment with privacy and dignity, linked to an obstetric center that guarantees safety and prompt intervention whenever necessary. Certainly, the presence of a multidisciplinary delivery team is beneficial and associated with a reduction in cesarean rates.

Although the WHO is focused on ensuring that cesarean sections are performed whenever necessary rather than seeking to achieve a specific cesarean rate,¹⁵ it is undeniable that Brazil performs more cesarean sections than women want or need. In this editorial, we analyzed some factors that may be associated with high cesarean rates in Brazil. The joint work of health authorities, medical societies, universities, managers and the multidisciplinary team in teaching, embracement and adequate, safe and respectful care is essential for cesarean rates to truly decrease and not rise again.

Conflicts to Interest

None to declare.

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The Impact of the COVID-19 Pandemic on the Care of Women Experiencing Abortion in a University Hospital in Brazil

O Impacto da pandemia de COVID-19 no atendimento de mulheres que vivenciam o aborto em um hospital universitário no Brasil

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Abstract

Objective To evaluate the impact of the coronavirus disease 2019 (COVID-19) pandemic on the care of patients with miscarriage and legal termination of pregnancy in a university hospital in Brazil.

Methods A cross-sectional study of women admitted for abortion due to any cause at Hospital da Mulher Prof. Dr. J. A. Pinotti of Universidade Estadual de Campinas (UNICAMP), Brazil, between July 2017 and September 2021. Dependent variables were abortion-related complications and legal interruption of pregnancy. Independent variables were prepandemic period (until February 2020) and pandemic period (from March 2020). The Cochran-Armitage test, Chi-squared test, Mann-Whitney test, and multiple logistic regression were used for statistical analysis.

Results Five-hundred sixty-one women were included, 376 during the prepandemic period and 185 in the pandemic period. Most patients during pandemic were single, without comorbidities, had unplanned pregnancy, and chose to initiate contraceptive method after hospital discharge. There was no significant tendency toward changes in the number of legal interruptions or complications. Complications were associated to failure of the contraceptive method (odds ratio [OR] 2.44; 95% confidence interval [CI] 1.23–4.84), gestational age (OR 1.126; 95% CI 1.039–1.219), and preparation of the uterine cervix with misoprostol (OR 1.99; 95% CI 1.01–3.96).

Conclusion There were no significant differences in duration of symptoms, transportation to the hospital, or tendency of reducing the number of legal abortions and increasing complications. The patients' profile probably reflects the impact of the pandemic on family planning.

Keywords

- ▶ CLAP MUSA network
- ▶ perinatal information system
- ▶ population surveillance
- ▶ abortion
- ▶ EviSIP
- ▶ COVID-19

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Resumo

Objetivo Avaliar o impacto da pandemia de *coronavirus disease 2019* (Covid-19) no atendimento de pacientes com aborto espontâneo e interrupção legal da gravidez em um hospital universitário no Brasil.

Métodos Estudo transversal com mulheres admitidas por aborto por qualquer causa no Hospital da Mulher Prof. Dr. J. A. Pinotti da Universidade de Campinas (UNICAMP), Brasil, entre julho de 2017 e setembro de 2021. As variáveis dependentes foram complicações relacionadas ao aborto e interrupção legal da gravidez. As variáveis independentes foram período pré-pandemia (até fevereiro de 2020) e período pandêmico (a partir de março de 2020). O teste de Cochran-Armitage, teste do qui-quadrado, teste de Mann-Whitney e regressão logística múltipla foram utilizados para análise estatística.

Resultados Foram incluídas 561 mulheres, 376 no período pré-pandemia e 185 no período pandêmico. A maioria das pacientes durante a pandemia era solteira, sem comorbidades, teve gravidez não planejada e optou por iniciar método anticoncepcional após a alta hospitalar. Não houve tendência significativa para mudanças no número de interrupções legais ou complicações. As complicações foram associadas a: falha do método contraceptivo (razão de chances [RC] 2,44; intervalo de confiança [IC] 95% 1,23–4,84), idade gestacional (RC 1,126; IC 95% 1,039–1,219) e preparo do colo uterino com misoprostol (RC 1,99; IC 95% 1,01–3,96).

Conclusão Não houve diferenças significativas na duração dos sintomas, transporte ao hospital ou tendência de redução do número de abortos legais e aumento de complicações. O perfil das pacientes provavelmente reflete o impacto da pandemia no planejamento familiar.

Palavras-chave

- ▶ rede CLAP MUSA
- ▶ sistema de informação perinatal
- ▶ vigilância populacional
- ▶ aborto
- ▶ EviSIP
- ▶ COVID-19

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has affected health services around the world, requiring prioritization of the professional team and hospitals to meet the growing demand for cases complicated by the infection. Thus, the health system was structured in such a way to care for infected patients, limiting their surgical care to emergency procedures, leaving their surgical centers available to be transformed into intensive units and saving personal protective equipment.¹ Likewise, the general population was affected, losing track of its chronic diseases and measures to promote health and prevent illness and injury. Mandatory home isolation was instituted in several countries, and people were advised to seek medical attention only in urgent and emergency cases. Given these facts, these changes affected when patients seek and how they receive their medical care.²

In relation to women in abortion situations, they had greater difficulty in accessing health services, since the basic health networks restricted their care; public transport reduced its fleet; the fear and the need for home isolation left the population without adequate screening or isolated until the appearance of alarm signals, delaying their care, diagnosis, and proper management, just as hospitals reduced the number of available beds, reserving hospitalization only for more critical cases, among other various socioeconomic and political factors that have impacted our current global health condition.³

With this in mind, in March 2020, the American College of Surgeons (ACS) recommended delay of all nonessential invasive procedures, reinforcing, however, the importance of not delaying gynecologic emergency procedures, including ectopic pregnancy and miscarriage.⁴ Likewise, the American College of Obstetricians and Gynecologists (ACOG) stated that care for women in abortion situations should be guaranteed by community- and hospital-based clinicians, as sometimes a delay of weeks or days may increase the risks or potentially make it completely inaccessible.⁵

The COVID-19 pandemic triggered several changes in the flow of care for women experiencing an abortion. In the context outside the institution, we supposed that the reduction in the number of consultations available in basic health units and the reduction in the availability of public transport would delay the care, diagnosis, and assistance of these women, resulting in longer time experiencing symptoms and getting to the hospital. In the internal context of the institution, we can mention a reduction in the number of spaces available for hospitalization due to the need for distance between beds, and the reduction in the availability of intensive care unit (ICU) beds could limit the access of these patients to tertiary assistance.

This scenario raises the following research question: What influence did the changes in routine resulting from the COVID-19 pandemic have on the quality of care for women experiencing abortion in a university hospital? The aim of this study was to evaluate the impact of the COVID-19

pandemic on the care of patients with miscarriage and legal termination of pregnancy in a university hospital in Brazil.

Methods

The multicentric network MUSA—Women in Abortion Situations—is a network created by the Latin American Center for Perinatology (CLAP, in the Portuguese acronym) to improve care for women undergoing any kind of pregnancy loss during the first half of pregnancy (spontaneous or induced ones) in Latin America and the Caribbean.⁶ It includes several hospitals, called sentinel centers, which periodically send their data regarding the pregnancy cycle for registration in the Perinatal Computerized System (SIP, in the Portuguese acronym), a software developed by CLAP that helps health facilities register data related to pregnancy and epidemiologic monitoring. Our institution, University of Campinas Women's Hospital (UNICAMP) is a tertiary referral hospital for cases of complications related to pregnancy in municipalities in the region and experiences an average of 250 births and 20 cases of first trimester pregnancy loss per month. Our hospital has been a sentinel institution of the MUSA network since July 2017, prospectively collecting data which have already been used in other cross-sectional studies. However, this is the first work performed during the COVID-19 pandemic. The hospital follows the laws of Brazil regarding the legal termination of pregnancy, in which abortion is allowed only in cases of risk of maternal death, sexual violence, and fetal anencephaly.^{7–19}

The sentinel centers of the MUSA network regularly provide information on maternal morbidity in early pregnancy loss, termination methods for uterine evacuations, incidence of complications related to pregnancy termination, incidence of preoperative antibiotic use and prescription of contraception before hospital discharge. Through SIP, it is possible to carry out epidemiological monitoring and comparisons between different sentinel centers over time. Representatives from each sentinel center also hold regular online meetings to discuss the data collected, conduct scientific discussions on the topic of women's health in abortion situations, and encourage good clinical practices for safe abortion.

This cross-sectional study with epidemiological surveillance data was conducted between July 2017 and September 2021. All cases from the SIP-abortion database from July 1st, 2017, to September 30th, 2021, were included. The inclusion criteria were women admitted for spontaneous pregnancy loss (inevitable miscarriage, complete, incomplete, or missed abortions) and legal interruption of pregnancy due to any cause or any age group who visited our hospital. The exclusion criteria were women with bleeding during pregnancy who did not have a confirmed abortion and women with ectopic or molar pregnancies. The research ethics committee of our institute approved this study (approval number CAAE: 56933116.0.1001.5404).

The dependent variables evaluated were: abortion-related complications (infection, excessive bleeding, and intraoperative complications, such as postspinal anesthesia head-

ache, disseminated intravascular coagulation, reapproach, and allergic reaction) and legal interruption of pregnancy.

The independent variables were Pre-pandemic period (PrP): from July 1st, 2017, until February 29th, 2020; and pandemic period (PP): from March 1st, 2020, to September 30th, 2021.

The control variables were patients' clinical and socio-demographic characteristics, such as age, education, marital status, living status, health records, number of pregnancies, number of births, number of abortions, body mass index (BMI), active smoking, illegal drug use, alcohol use, planned pregnancy, pregnancy resulting from contraceptive failure, date of admission at the hospital, if it is a medically induced abortion for legal reasons, gestational age, presence of any complications, and admission data, besides duration of transportation and symptoms.

Initially, a descriptive analysis of the data was performed. For continuous variables, the mean, standard deviation, median, minimum, maximum, and quartiles were calculated. For categorical variables, the relative frequencies were calculated. To assess whether there was a change in the trend in the occurrence of the outcome variables, the Cochran-Armitage trend test was performed. To evaluate the association between abortion-related complications and the independent variables, the Chi-squared or Fisher exact tests were performed for categorical variables, and the Mann-Whitney or Kruskal-Wallis tests for continuous variables. To evaluate the factors independently associated with abortion-related complications, a multiple logistic regression was performed, with "stepwise" selection criteria for variables. The significance level assumed was 5%. The software used for the analyses was the SAS System for Windows, version 9.2. (SAS Institute Inc., Cary, NC, USA).

Results

During the study period, 561 women in a situation of abortion were included; 376 during the PrP and 185 during the PP. From the PrP, 50 women had abortion induced for legal reasons and 326 had other types of abortion. During the PP, 20 patients had legal abortions, and 165 had other types. During the PrP, it was observed that the mean maternal age was 30.13 ± 7.55 years, while in the PP, it was 30.21 ± 7.55 years. The mean gestational age was 11.03 ± 3.56 weeks in the PrP and 11.39 ± 3.53 weeks in the PP. The mean number of previous births was 1.18 ± 1.22 births in the PrP and 1.41 ± 1.19 in the PP ($p = 0.014$). The mean body mass index (BMI) was 27.25 ± 5.90 in the PrP and 26.16 ± 6.09 in the PP ($p = 0.014$). The duration of symptoms was 3.59 ± 7.80 days, and the duration of transportation was 53.16 ± 125.57 minutes in the PrP, while in the PP, it was 4.30 ± 7.99 days and 33.94 ± 18.81 minutes, respectively (► **Table 1**).

In the PrP, 60.93% of the patients were married or living in a stable relationship, while 51.65% in the PP were single ($p = 0.005$). In the PrP, 91.96% of patients did not have comorbidities, compared with 96.74% in the PP ($p = 0.031$). In the PrP, 12.1% of patients declared drinking alcohol, while only 5.41% did in the PP ($p = 0.013$). A total of 32.71% of pregnancies were planned during the PrP, whereas 24.32%

Table 1 Clinical and sociodemographic characteristics of women in abortion situations - quantitative variables ($n = 561$)

Period	Variable	Mean	SD	Median	Min	Max	P-value*
Pre-pandemic	Age ^a	30.13	7.55	30.0	12.0	48.0	0.806
	Births ^b	1.18	1.22	1.0	0	7.00	0.014
	BMI ^c	27.25	5.90	26.45	15.60	45.34	0.014
	Gestational age ^d	11.03	3.56	10.43	2.14	24.71	0.232
	Duration of symptoms ^e	3.59	7.80	1.00	0	90.00	0.872
	Duration of transportation ^f	53.16	125.57	30.00	0	1800.0	0.136
Pandemic	Age	30.21	7.55	30.0	11.0	46.0	
	Births ^g	1.41	1.19	1.00	0	5.00	
	BMI ^h	26.16	6.09	24.65	14.57	51.86	
	Gestational age ⁱ	11.39	3.53	10.71	5.00	23.43	
	Duration of symptoms ^j	4.30	7.99	1.00	0	40.00	
	Duration of transportation ^k	33.94	18.81	30.00	5.00	40.00	

Abbreviations: BMI, body mass index; Min, minimum; Max, maximum; SD, standard deviation.

Missing data: a = 1; b = 19; c = 27; d = 5; e = 13; f = 6; g = 23; h = 4; i = 7; j = 18; k = 19.

*P-value referring to the Mann-Whitney test for comparing values between pre pandemic and pandemic group.

were had been planned in the PP ($p = 0.042$). In the PrP, most patients (42.36%) were accompanied by their partners, while in the PP, most patients (45.36%) came alone ($p = 0.012$). In the PrP, most patients (62.73%) chose not to initiate contraceptive methods at hospital discharge, while in the PP, 53.01% chose to initiate ($p < 0.001$). In the PrP, most uterine-emptying procedures involved medication plus uterine curettage (41.49%), while in the PP, 40.44% underwent manual intrauterine aspiration ($p < 0.001$) (► **Table 2**).

Since the beginning of the evaluation period, 70 women (12.47%) had undergone legal interruption. We did not observe a significant tendency toward an increase or decrease in the number of legal interruptions. (Cochran-Armitage test: $Z = -0.28$; $p = 0.783$) (► **Fig. 1**).

Since the beginning of the evaluation period, 31 women (5.53%) had abortion-related complications. Among the complications, we found that the most frequent were: infection, with 13 cases (2.32%), and 8 cases of sepsis (1.43%); excessive bleeding, with 9 cases (1.60%), and 2 cases of hypovolemic shock (0.36%); and other complications, with 6 cases (1.07%), which include post-spinal anesthesia headache, disseminated intravascular coagulation, reapproach, and allergic reaction. We did not observe a significant tendency toward an increase or decrease in the number of complications. (Cochran-Armitage test: $Z = 0.05$; $p = 0.960$) (► **Fig. 2**).

After analyzing the factors associated with a higher prevalence of complications, considering the PP and PrP as independent variables, we observed that the pandemic period was not associated with a higher occurrence of complications. We observed that the factors associated with the occurrence of complications were: failure of contraceptive method ($p = 0.002$); no cervical preparation with misoprostol ($p = 0.006$); type of procedure performed for uterine evacuation, with curettage being the method with the highest number of complications ($p = 0.009$); maternal age, with a higher number of complications

among younger patients ($p = 0.031$); gestational age, with more complications in more advanced pregnancies ($p = 0.010$); and duration of symptoms, with more complications associated with longer duration ($p = 0.045$) (► **Tables 3 and 4**).

In the multiple logistic regression model, it was found that the variables significantly related to complications were: failure of the contraceptive method, with a risk 2.4 times greater (odds ratio [OR] 2.44; 95% confidence interval [CI] 1.23–4.84); gestational age, with an increase of 12.6% for every 1 week of gestational age (OR 1.126; 95% CI 1.039–1.219); and lack of uterine cervix preparation with misoprostol, raising 2.0 times the risk of complications (OR 1.99; 95% CI 1.01–3.96) (► **Table 5**).

Discussion

The COVID-19 pandemic has affected health services around the world and has changed how the general population experienced their diseases and sought health assistance. In relation to women in abortion situations, we supposed that changes outside the institution could hinder assistance of these women, and changes inside the institution could limit their access to the hospital. These facts brought us to the importance of evaluating the impact of the COVID-19 pandemic on the care of patients with miscarriages and legal termination of pregnancy in a university hospital in Brazil.

Although we have experienced these external changes, we did not observe great differences in the duration of symptoms and time of transportation to our hospital. We imagine that, as most primary care services were closed or turned to care for patients suspected of having COVID-19, the patients probably sought our emergency room as a first form of care, as well as assuming that access to public transport was guaranteed in our city and region of coverage. However, this is not what we expected, as facing COVID-19 pandemic changes in transportation contributed to increase health

Table 2 Clinical and sociodemographic characteristics of women in abortion situations - categorical variables (n = 561)

	PrP n	PrP %	PP n	PP%	P-value*
Age^a					
< 20 years	24	6.40	12	6.49	0.988
20–29 years	160	42.67	79	42.70	
30–39 years	144	38.40	69	37.30	
40–49 years	47	12.53	25	13.51	
Marital status^b					
Married/cohabiting	223	60.93	88	48.35	0.005
Single/other	143	39.07	94	51.65	
Comorbidities^c					
No	343	91.96	178	96.74	0.031
Yes	30	8.04	6	3.26	
Alcohol intake					
No	327	87.90	175	94.59	0.013
Yes	45	12.10	10	5.41	
Planned pregnancy^e					
No	251	67.29	140	75.68	0.042
Yes	122	32.71	45	24.32	
Companion^f					
Partner	158	42.36	53	28.96	0.012
Family	64	17.16	31	16.94	
Other	23	6.17	16	8.74	
None	128	34.32	83	45.36	
Contraception^g					
No	234	62.73	86	46.99	< 0.001
Yes	139	37.27	97	53.01	
Uterine emptying procedures^h					
None	34	9.04	13	7.10	< 0.001
MVA	0	0.00	74	40.44	
VA	0	0.00	1	0.55	
CTG	146	38.83	69	37.7	
MED	40	10.64	16	8.74	
CTG/MED	156	41.49	10	5.46	

Abbreviations: CTG, curettage; MED, medicated; MVA, manual vacuum aspiration; PP, pandemic period; PrP, pre-pandemic period; VA, vacuum aspiration.

Missing data: a = 1; b = 13; c = 4; d = 4; e = 3; f = 5; g = 5, h = 3. *p-value referring to the Chi-squared test for comparing values between pre pandemic and pandemic group.

Missing data: a = 11; b = 2; c = 2.

disparities, hindering access to healthcare to low-income families.⁸

Regarding demographic aspects, we found that, during the pandemic, most patients were single, without comorbidities, experiencing abortions as a result of unplanned pregnancy and chose to start contraceptive methods at hospital discharge. These findings make us reflect on how the pandemic may have impaired family planning and access

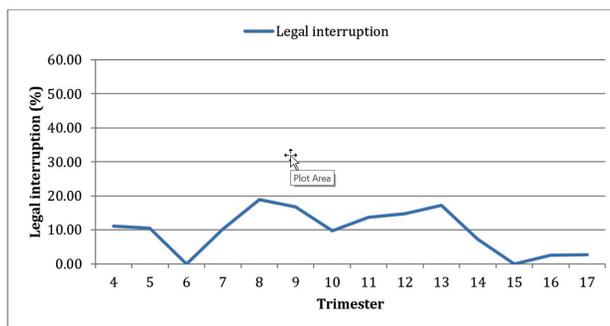


Fig. 1 Number of legal interruptions of pregnancy between July 2017 and September 2021 by trimestral period. Cochran-Armitage test: Z = -0.28; p = 0.783.

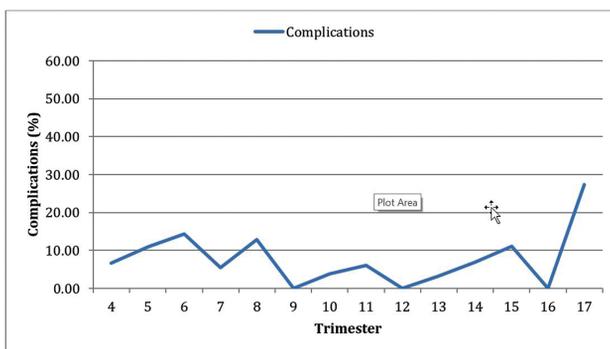


Fig. 2 Number of complications associated with abortion between July 2017 and September 2021 by trimestral period. Cochran-Armitage test: Z = 0.05; p = 0.960.

Table 3 Factors associated with complications - categorical variables (n = 561)

Variables	Complications		P-value
Contraceptive ^a	No (n/%)	Yes (n/%)	p = 0.002
No	399/77.93	21/55.26	
Yes	113/22.07	17/44.74	
Misoprostol use ^b			p = 0.006
No	203/39.04	24/61.54	
Yes	317/60.96	15/38.46	
Uterine evacuation ^c			p = 0.009
None	45/8.65	2/5.13	
MVA	68/13.08	6/15.38	
VA	0/0	1/2.56	
CTG	194/37.31	21/53.85	
MED	56/10.77	0	
CTG/MED	157/30.19	9/23.08	

Abbreviations: CTG, curettage; MED, medicated; MVA, manual vacuum aspiration; VA, vacuum aspiration.

Missing data: a = 11; b = 2; c = 2.

to contraceptive methods. We have learned from previous public health emergencies, such as the Ebola outbreak, that the impact of an epidemic on sexual and reproductive health is not a direct consequence of the infection, but an indirect

Table 4 Factors associated with complications - quantitative variables ($n = 561$)

Complication	Variable	Mean	SD	Median	Min	Max	P-value
No	Age ^a	30.34	7.59	30.0	11.0	48.0	0.031
	Gestational age ^b	11.01	3.44	10.43	8.43	24.71	0.010
	Duration of symptoms ^c	3.51	6.69	1.00	0	60.00	0.045
Yes	Age	27.69	6.52	26.0	16.0	41.0	
	Gestational age ^d	13.03	4.54	14.00	4.00	20.29	
	Duration of symptoms ^e	7.77	16.47	2.00	0	90.00	

Abbreviations: SD, standard deviation; Min, minimum; Max, maximum.
Missing data: a = 1; b = 9; c = 30; d = 3; e = 1.

Table 5 Factors associated with complications - Multiple logistic regression ($n = 503$)

Variables	Categories	OR	OR (95% CI)	P-value
Contraceptive	No (ref.)	1.00	—	—
	Yes	2.77	1.34–5.74	0.006
Gestational age	Continuous variable (weeks)	1.149	1.051–1.256	0.002
Misoprostol use	Yes (ref.)	1.00	—	—
	No	2.18	1.05–4.51	0.037

Abbreviations: CI, confidence interval; OR, odds ratio; ref, reference.
No complications: $n = 469$; complications: $n = 34$.

Cases with missing variables were not included in the multiple analysis. Stepwise criteria for variable selection.

result from strained health care systems, disruptions in care and redirected resources.⁹ Riley et al.⁹ estimated that a decline of 10% in the use of short- and long-acting reversible contraceptive methods in low- and middle-income countries due to reduced access would result in 49 million women without family planning support and 15 million unintended pregnancies over a year.

We observed an increasing in the number of women who were hospitalized without companions. It might be influenced by the internal restructuring of our service, since it restricted the number of companions and hospital visits during the pandemic period. However, our hospital guaranteed and prioritized the presence of companions for adolescents, victims of sexual violence, and women with important physical and emotional needs.

A new tendency was also observed in our hospital. Most uterine evacuation procedures performed during the pandemic were manual vacuum aspirations (MVAs), comparing to the previous tendency of using medicine for cervix preparation and curettage. Since the implementation of the MUSA network in our hospital, it was possible to generate data to assess our trends in clinical practice patterns, and the data were necessary for analyses of the safety of abortion practices and to purpose improvements in the quality of patient care and overall health outcome. In 2020, we began an intense process to insert MVA into our care practice, training the technical team, as well as modifying the institutional protocol and making MVA a priority method of uterine evacuation for abortions up to 12 weeks of gestational age, following the recommendation of the World Health Organization (WHO) and the Federation of Gynecology and Obstet-

rics (FIGO).¹⁰ The adherence to the implementation was probably facilitated by the period of the pandemic, since it is a quick and easy procedure, with a lower risk of complications; it requires less complex anesthetic procedures and has a rapid recovery, allowing early hospital discharge.^{10,11}

We feared that external changes in health services organization and in people behavior during the pandemic could restrict women access to our hospital, resulting in a decrease of number of legal terminations of pregnancy and an increase in abortion-related complications. However, we did not observe this tendency, corroborating the hypothesis previously mentioned that patients sought for emergency attendance after primary care and that the access to our hospital was maintained during the pandemic period. This result differs from those of national data, which showed that only 55% of the 76 hospitals in our country that provide legal abortions were operating in 2019.¹²

Our multivariate analysis showed that the variables significantly related to complications were failure of the contraceptive method, higher gestational age, and no preparation of the uterine cervix with misoprostol.

It is known that women using contraceptive methods can possibly not recognize symptoms of pregnancy, resulting in late diagnosis and delay in seeking medical attention, increasing the risk of infection and/or hemorrhage.¹³ Also, because of the unplanned pregnancy, women need to face some unexpected issues, such as finding transportation or companion and justifying absence at work. Fear, embarrassment, or stigma are also barriers to seek care.^{16,17} Besides, failure of contraceptive methods might reflect the contraceptive use pattern of our country, in which oral contraceptives and

condom are predominant compared with long-acting reversible contraceptives, such as intrauterine devices.¹³

Our study showed that each week of gestational age increased 12.6% the risk of complications, while another study showed an increase in the number of complications by up to 20% in each week.¹⁸ Pregnancies with higher gestational ages mean higher uterine volume, bigger amount of retained products of conception, and possible chorioamnionitis.¹³ The main complications include uterine perforation, cervical laceration, hemorrhage, uterine rupture, and infection.¹⁴

Preparing the cervix prior to the procedure reduces this risk to less than 1% of cases.¹⁵ Compared with manual dilation alone, it improves cervical dilation, shortens procedure times and decreases the risk of complications intraoperatively, such as cervical laceration and uterine perforation.¹⁴

This study had some limitations. First, it was a cross-sectional study; thus, a cause-effect relationship could not be established. Furthermore, it was not possible to differentiate provoked abortion from spontaneous abortion, except in cases of legal induction. However, our study was important to evaluate the impact of the COVID-19 pandemic, which caused changes all over the world and could impact negatively in women's experiencing abortion.

We were pleased to find that our patients apparently did not have difficulties accessing our health service, mostly because we maintained and prioritized care for women in abortion situations despite all the reorganization and limitation we have suffered internally in the context of the pandemic.

Conclusion

Our service did not reduce its volume of abortion attendance during the COVID-19 pandemic. Significant differences in the duration of symptoms and transportation to the hospital were not observed, neither was there a tendency to reduce the number of legal abortions, or an increase in complications. Despite reorganization of hospital function due to this public health emergency, we were one of 55% of services still providing legal abortions in our country. Our patients' profiles reflect the impact of the pandemic on sexual and reproductive health. This outbreak situation showed us that, in our institution, the infection might not have directly affected how women have experienced abortion, but how the reorganization of health system impacted on family planning.

Contributions

P. B. F. D., A. A. J., C. C. N., N. V. J. and L. F. B. contributed to project development, data collection, study conception and design. P. B. F. D. wrote the manuscript. N. N. V. J. and L. F. B. reviewed and edited the final version. All authors reviewed and approved the final manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Evaluation and Comparison of Respiratory Muscular Strength, Functionality, and Pelvic Floor in the Immediate Postpartum of Normal and Cesarean Birth

Avaliação e comparação da força muscular respiratória, funcionalidade, e de assoalho pélvico no puerpério imediato de parto normal e cesárea

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Abstract

Objective: To evaluate and compare peripheral, pelvic floor, respiratory muscle strength, and functionality in the immediate puerperium of normal delivery and cesarean section.

Methods: This is a cross-sectional study that verified respiratory, pelvic floor, peripheral, and functional muscle strength through manovacuometry, pelvic floor functional assessment (PFF), dynamometry, and the Time Up and Go (TUG) test, respectively. The groups were divided according to the type of delivery, into a cesarean section group and a normal parturition group.

Results: The sample was composed of 72 postpartum puerperae, 36 of normal parturition, and 36 of cesarean section, evaluated before hospital discharge, mean age ranged from 25.56 ± 6.28 and 28.57 ± 6.47 years in puerperae of normal parturition and cesarean section respectively. Cesarean showed higher pelvic floor strength (PFF) compared to normal parturition ($p < 0.002$), but puerperae from normal delivery showed better functionality ($p < 0.001$). As for peripheral muscle strength and respiratory muscle strength, there was no significance when comparing the types of parturition.

Conclusion: There is a reduction in pelvic muscle strength in puerperae of normal delivery and a decrease in functionality in puerperae of cesarean section.

Keywords

- ▶ Postpartum period
- ▶ Cesarean section
- ▶ Pelvic floor
- ▶ Physical performance

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Resumo

Objetivo: Avaliar e comparar o pavimento pélvico periférico, a força muscular respiratória e a funcionalidade no puerpério imediato do parto normal e da cesariana.

Métodos: Este é um estudo transversal que verificou a força muscular respiratória, pavimento pélvico, periférico e funcional através da manovacuometria, avaliação funcional do pavimento pélvico (PFF), dinamometria, e o teste Time Up e Go (TUG), respectivamente. Os grupos foram divididos de acordo com o tipo de parto, num grupo de cesariana e num grupo de parto normal.

Resultados: A amostra foi composta por 72 puérperas pós-parto, 36 de parto normal e 36 de cesariana, avaliados antes da alta hospitalar, a idade média variou entre $25,56 \pm 6,28$ e $28,57 \pm 6,47$ anos em puérperas de parto normal e cesariana, respectivamente. A cesariana mostrou maior resistência do pavimento pélvico (TFP) em comparação com o parto normal ($p < 0,002$), mas as puérperas de parto normal mostraram melhor funcionalidade ($p < 0,001$). Quanto à força muscular periférica e à força muscular respiratória, não houve significado ao comparar os tipos de parto.

Conclusão: Há uma redução da força muscular pélvica em puérperas de parto normal e uma diminuição da funcionalidade em puérperas de cesarianas.

Palavras-chave

- ▶ Período pós-parto
- ▶ Cesárea
- ▶ Assoalho pélvico
- ▶ Desempenho físico

Introduction

The puerperium or postpartum is defined by a variable temporal period in which the changes that occur due to pregnancy and childbirth in the woman's body return to their pre-pregnancy state.¹ During pregnancy and the puerperium several physiological adaptations and changes occur in the cardiovascular, endocrine, tegumentary, urinary, gastrointestinal, respiratory, and musculoskeletal systems in the maternal organism, which consequently triggers anatomical and functional changes.^{2,3}

Normally the return to pre-pregnancy conditions, such as regression and recovery of the uterine musculature and vaginal mucosa, occurs in an average of six to eight weeks.¹ Thus, pregnancy and the route of delivery are risk factors for alterations in the pelvic floor (PF) muscle strength and may also lead to some changes in anatomical position and pelvic muscles, as well as changes in the viscera and perineum.^{2,4} Besides the mechanical and biochemical alterations, there are also important adaptations and modifications in lung volumes and capacities, due to the growth of the uterus, causing modifications in the resting position of the diaphragm and in the configuration of the chest wall, thus interfering in the strength of the inspiratory and expiratory respiratory muscles.⁵⁻⁸

The type of parturition is linked to the woman's recovery time and, therefore, may contribute to functional limitations. The change of the female body and the return of body systems to pre-pregnancy may impair her activities of daily living (ADLs).⁹ Both parturitions can interfere in the functionality of the puerpera, in vaginal childbirth, part of the woman may suffer some type of perineal trauma due to spontaneous lacerations and/or episiotomies, these lacerations may be associated with morbidities that can interfere with the performance of usual activities.^{10,11} As for the cesarean section, the abdominal incision causes trauma to the woman's body, generating pain in the scar, less bowel

movement, accumulation of gases, and restricted physical mobility, which can cause losses in postpartum recovery.¹²

Thus, in view of the above-mentioned alterations, the objective of this study was to evaluate and compare respiratory muscle strength, pelvic floor muscle strength, peripheral muscle strength, and functionality in women who underwent normal parturition and cesarean section.

Methods

This is a cross-sectional study, developed at Hospital Fêmina, belonging to Grupo Hospitalar Conceição, in Porto Alegre/RS, carried out from October 2016 to May 2017. The project was approved by the Ethics and Research Committee of the Centro Universitário Metodista - IPA with opinion number 1.709.047.

Inclusion criteria were women over 18 years of age, primiparous or multiparous, not implying the number of previous pregnancies, up to the 4th day of immediate puerperium from cesarean or normal delivery, without previous respiratory diseases, with a minimum gestational age of 37 weeks and hemodynamically stable. The exclusion criteria were inability to perform any of the tests, previous history of abortions or surgeries, twin pregnancy, and diagnosis of uncontrolled hypertension or diabetes mellitus. All patients included in the study signed an informed consent form.

For the data collection procedure, the medical records were evaluated as a preselection, and demographic data were collected. The assessments were performed at a single time, following the order of respiratory muscle strength assessment, pelvic floor strength assessment, peripheral strength assessment, and lastly, functionality assessment. Vital signs, as well as weight and height, were collected from the patient's hospital chart. The postpartum women were intentionally allocated according to the type of parturition.

Respiratory muscle strength was assessed by manovacuometry, with an analog manovacuometer (MVD 120, Globalmed, Porto Alegre, RS). To evaluate Maximum Inspiratory Pressure (MIP), the pregnant woman was asked to exhale up to residual volume and then, immediately, to place the mouthpiece, inhaling up to total lung capacity, maintaining two seconds of sustained force, and finally removing the mouthpiece. And, to evaluate the Maximum Expiratory Pressure (MEP), the participant performed the reverse procedure, requesting at the end, an expiration up to the residual volume. During the measurements, the pregnant women were properly positioned in a sitting position, there was a rest interval between one evaluation and the other, a nose clip was also used in both maneuvers to better determine the pulmonary pressures, and each measurement was requested three repetitions, and the best result was used. With the results obtained, the predictive equations of maximum respiratory pressures proposed by another study were performed.¹³

Pelvic floor muscle strength was measured through the pelvic floor assessment (FPA), which was performed with the patient in a gynecological position in bed and through palpation, instructions were given to contract the perineal muscles and then repeat this same contraction with the examiner's index and middle fingers introduced into the vagina, considering, according to the Oxford Scale, a variation of 0 to 5 degrees of muscle strength in this palpation.^{14,15} These are characterized as 0 - no contraction, 1 - only slight and not sustained contraction, 2 - low intensity contraction with some support, 3 - moderate contraction and there is increased intravaginal pressure (compression of the fingers and some elevation of the vaginal wall), 4 - good contraction (moderate - possible to squeeze the examiner's fingers) and the elevation of the vaginal wall goes towards the symphysis pubis, and 5 - strong, sustained and maintained contraction towards the symphysis pubis.¹⁵

Peripheral muscle strength was measured by dynamometry using palmar grip strength assessed by an upper limb dynamometer (eClear, EH101). Thus, the patients were positioned with the headboard at 90 degrees to the bed, using the dominant upper limb adducted parallel to the trunk, with elbow flexion at 90 degrees and forearm and wrist in neutral position. The pregnant woman was instructed to press the

handgrip with her maximum force and no external body movement. The measurement was performed three times, thus using the highest value.¹⁶

And, finally, the functionality evaluation was performed using the Time Up and Go (TUG) test, which consists in measuring, in seconds, the time needed by the patient to get up from a standard armchair, with a height of approximately 46 cm, and walk a distance of 3 m, go around the cone, and return to the chair sitting down again, thus evaluating the functional mobility.¹⁷

All data were stored and analyzed in the software Statistical Package for the Social Sciences for Windows (SPSS) 20.0, and treated with descriptive analysis through mean and standard deviation and categorical data with absolute and percentage values. Intra-group data were evaluated using Student's t-test for repeated measures, and, inter-group comparison using Student's t-test for independent samples. Spearman's Correlation test was used for the correlation of the variables. The significance level adopted was 5%.

Results

The sample was composed of 72 pregnant women, 36 in the normal parturition group and 36 in the cesarean group. The characterization of the sample is described in ► **Table 1**. The mean age of the women in the normal group was 25.56 ± 6.28 versus 28.57 ± 6.47 for the cesarean section. When comparing the ratio of pre-delivery weight and parturition performed, women with higher weight 86.35 ± 14.86 kg performed cesarean section versus 73.38 ± 11.84 kg in normal parturition ($p < 0.001$). It was also noted that babies born with a lower birth weight of 3.08 ± 0.49 kg were conceived by normal parturition and those with a higher birth weight of 3.43 ± 0.50 kg by cesarean section ($p < 0.001$).

When muscle strength and functionality were compared (► **Table 2**), postpartum women who had vaginal parturition showed a decrease in pelvic floor strength of 1.36 ± 1.11 compared to a cesarean of 2.17 ± 1.17 ($p < 0.002$). On the other hand, women who had a vaginal delivery were more functional when compared to the TUG of 13.21 ± 4.85 s compared to those who had a cesarean delivery of 21.17 ± 10.85 s ($p < 0.001$). As for the respiratory muscle

Table 1 Characterization of the sample

Variables	Puerperae Normal Parturition (n = 36)	Puerperae Cesarean Births (n = 36)	p-value
Age (years)	$25,56 \pm 6,28$	$28,57 \pm 6,47$	0,051
Height (m)	$1,6 \pm 0,05$	$1,62 \pm 0,07$	0,167
Prepartum weight (Kg)	$73,38 \pm 11,84$	$86,35 \pm 14,86$	0,001
Pregestational weight (Kg)	$62,59 \pm 12,08$	$72,69 \pm 14,21$	0,017
Newborn length (cm)	$48,21 \pm 2,29$	$48,80 \pm 1,91$	0,217
Newborn weight (Kg)	$3,08 \pm 0,49$	$3,43 \pm 0,50$	0,001
Gestational age (weeks)	$39,00 \pm 1,18$	$39,00 \pm 1,19$	1.00

Values described as mean \pm standard deviation; m= meters; Kg= kilograms; RN= newborn; cm= centimeters.

Table 2 Comparison of muscle strength and functionality

Variable	Puerperae Normal Parturition (n = 36)	Puerperae Cesarean Births (n = 36)	p-value
PFF	1,36 ± 1,11	2,17 ± 1,17	0,002
MEP (cmH2O)	33,42 ± 18,40	25,46 ± 10,76	0,027
MIP (cmH2O)	33,44 ± 16,29	33,17 ± 13,29	0,913
Handgrip (Kgf)	22,78 ± 5,71	24,31 ± 5,27	0,217
TUG (s)	13,21 ± 4,85	21,17 ± 10,85	0,001

Values described as mean ± standard deviation; with a significance level of $p > 0.05$; m= meters; PFF = pelvic floor functionality assessment; MEP= maximal expiratory pressure; MIP = maximal inspiratory pressure; cmH2O= centimeters of water; Kgf = kilograms of force; TUG= Time Up Go; s= seconds.

strength and peripheral strength tests, there was no significant difference in relation to the type of parturition.

Discussion

The present study found that women who had a normal parturition are more functional compared to those with a cesarean parturition, but FPA is more decreased after normal delivery than in cesarean parturition. And yet, we demonstrated that the muscle strength and functionality tests performed on women in the immediate postpartum period were safe and feasible since there was no need for any interruption, nor the presence of adverse events associated with the execution of the evaluations.

In our study sample, most of the women who had higher prepартum BMI had a cesarean section, not a normal parturition. Trajner-Bregar et al. conducted a study whose objective was to verify whether the maternal pre-pregnancy weight and weight gain during pregnancy were associated with increased cesarean rates, and their results are similar to ours, concluding that the combination of pre-pregnancy BMI and weight at the time before giving birth is an important determinant of cesarean rates among women.¹⁸ Another study that corroborates our findings is by Li et al.¹⁹ who evaluated the associations between pregestational BMI and weight gain in pregnant women in China alone, and their data revealed that high maternal pregestational BMI and excessive weight gain during pregnancy were associated with cesarean parturition.

Another significant finding of our study was in relation to the weight of the newborn, showing that women in our sample who gave birth to lower birth weight babies, in most cases, had a normal parturition and respectively, of higher weight by cesarean. In a literature review conducted by the Brazilian Medical Association, with the objective of updating the indication for cesarean section and verifying neonatal and perinatal morbidity and mortality in relation to small-for-gestational-age pregnancies, it showed that there is insufficient evidence to recommend planned cesarean section in small-for-gestational-age pregnancies.²⁰

Regarding the comparison of PFF and type of parturition, we demonstrated in this study that women who underwent cesarean had a higher PFF compared to those who chose natural. Barbosa et al.,⁴ in their study, analyzed the influence of the route of parturition on pelvic floor strength; the test

used in their study was the same used in ours, and their data agree with our results when they conclude that in their sample vaginal partum decreased PFF in primiparous women when compared to cases that underwent cesarean section and to nulliparous women.⁴

In a recent systematic review, the impact of the type of parturition on pelvic floor muscles was evaluated by 3D ultrasound, corroborating our data, vaginal parturition showed a decrease in muscle strength in this region, besides being associated with changes in the levator ani muscle, bladder neck mobility, and increased hiatal area, thus presenting a risk factor for prolapse and urinary incontinence.²¹ Riesco et al.²² found that there is a positive correlation between the evaluation of pelvic floor strength when checked with perineometry and/or with digital vaginal palpation, emphasizing the efficacy of the method chosen by us to evaluate PFF; in the same study, they also point out that in pregnancy, changes in PFF generally occurs due to the overload during the gestational period.²²

Barbosa et al.⁴ pointed out that regardless of the choice of parturition route, the increase in maternal body weight and the weight of the pregnant uterus will increase the pressure on the pelvic floor muscles during pregnancy, overloading them. A study that evaluated pelvic floor function in 90 pregnant women using perineometry and PFF, with a mean age of 27.6 years, showed that half of the evaluated pregnant women over 30 years of age had grade 5 in PFF and that overweight pregnant women were five times more likely to achieve only grade 3 when compared to pregnant women with BMI within normal values.¹⁵

The mode of birth is linked to a woman's recovery time and therefore may contribute to functional limitations.²³ Vaginal parturition can result in trauma and perineal discomfort and the incision area of a cesarean section is a predisposing factor to morbidity in the puerperium.²⁴ Some studies suggest that the TUG is a functional test that is simple and can be applied with few resources and is able to assess and quantify functional performance, with basic mobility skills included.²⁵⁻²⁷ In a study that evaluated 106 primiparous puerperae, 53 parturition vaginally and 53 by cesarean section, it was shown that puerperae who had a vaginal delivery needed less time to perform the TUG, demonstrating a better functional performance in a vaginal parturition, corroborating our findings where women who had a cesarean section were less functional than women who

had a vaginal parturition.²⁵ However, it is noteworthy that puerperal women present a worse result in the TUG test regardless of the type of delivery, when compared to non-parturient women, revealing that functionality in these puerperae is affected, and this result may interfere with their ADLs after leaving the hospital, associating them with mortality, quality of life (QoL) and also with risk of falls.²⁷

There is still a great need for research in this area, but our findings may help in determining functional disability, identifying potential patients who would need physical therapy treatments, and helping to determine the appropriate treatment for each type of patient. This study has the positive point of being one of the only ones to evaluate respiratory, peripheral, and pelvic floor muscle strength, as well as functionality in puerperal women. Knowledge of the changes in these variables in this population is extremely important in order to reduce complications during hospitalization and ensure functional discharge of patients. A possible negative point was the lack of studies present in the literature for direct comparison with the study population, thus requiring comparison with another population.

Conclusion

Based on the findings, it was found that there is a reduction in pelvic floor strength in the immediate postpartum period of vaginal parturition in relation to cesarean, on the other hand, women who underwent normal parturition are more functional in relation to those who underwent natural. Respiratory and peripheral muscle strength did not change regardless of the type of parturition.

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

None to declare.

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Maternal Blood Fatty Acid Levels in Fetal Growth Restriction

Níveis sanguíneos maternos de ácidos graxos na restrição do crescimento fetal

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Abstract

Objective: To assess the maternal blood levels of fatty acids (FAs) in pregnancies with fetal growth restriction (FGR).

Methods: This prospective cross-sectional study included pregnant women with gestational age between 26 and 37 + 6 weeks with FGR and appropriate for gestational age (AGA) fetuses. The levels of saturated, trans, monounsaturated, and polyunsaturated FAs were measured using centrifugation and liquid chromatography. The Student's t-test, Mann–Whitney test, and general linear model, with gestational age and maternal weight as covariants, were used to compare FA levels and the FGR and AGA groups. The Chi-square was used to evaluate the association between groups and studied variables.

Results: Maternal blood sample was collected from 64 pregnant women, being 24 FGR and 40 AGA. A weak positive correlation was found between the palmitoleic acid level and maternal weight ($r=0.285$, $p=0.036$). A weak negative correlation was found between the gamma-linoleic acid level and gestational age ($r=-0.277$, $p=0.026$). The median of the elaidic acid level (2.3 vs. 4.7 ng/ml, $p=0.045$) and gamma-linoleic acid (6.3 vs. 6.6 ng/ml, $p=0.024$) was significantly lower in the FGR than the AGA group. The palmitoleic acid level was significantly higher in the FGR than AGA group (50.5 vs. 47.6 ng/ml, $p=0.033$).

Conclusion: Pregnant women with FGR had lower elaidic acid and gamma-linoleic acid levels and higher palmitoleic acid levels than AGA fetuses.

Keywords

- ▶ Fetal growth restriction
- ▶ Maternal blood
- ▶ Appropriate for gestational age
- ▶ Fatty acids

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Resumo

Objetivo: Avaliar os níveis sanguíneos maternos de ácidos graxos (AGs) em gestações com restrição de crescimento fetal (RCF).

Métodos: Este estudo prospectivo transversal incluiu gestantes com idade gestacional entre 26 e 37 semanas e 6 dias com RCF e fetos adequados para a idade gestacional (AIG). Os níveis de ácidos graxos saturados, trans, monoinsaturados e poliinsaturados foram medidos usando centrifugação e cromatografia líquida. O teste t-Student, o teste de Mann-Whitney e o modelo linear geral, com idade gestacional e peso materno como covariantes, foram utilizados para comparar os níveis de AGs e os grupos RCF e AIG. O teste Qui-quadrado foi utilizado para avaliar a associação entre os grupos e as variáveis estudadas.

Resultados: Amostra de sangue materno foi coletada de 64 gestantes, sendo 24 RCF e 40 AIG. Uma correlação positiva fraca foi encontrada entre o nível de ácido palmítico e o peso materno ($r = 0,285$, $p = 0,036$). Uma correlação negativa fraca foi encontrada entre o nível de ácido gama-linoleico e a idade gestacional ($r = -0,277$, $p = 0,026$). A mediana do nível de ácido eláidico (2,3 vs. 4,7 ng/ml, $p = 0,045$) e ácido gama-linoleico (6,3 vs. 6,6 ng/ml, $p = 0,024$) foram significativamente menores no grupo RCF do que no grupo AIG. O nível de ácido palmítico foi significativamente maior no grupo RCF do que no grupo AIG (50,5 vs. 47,6 ng/ml, $p = 0,033$).

Conclusão: Gestantes com RCF apresentaram níveis mais baixos de ácido eláidico e ácido gama-linoleico e níveis mais elevados de ácido palmítico do que os fetos AIG.

Palavras-chave

- ▶ Restrição de crescimento fetal
- ▶ Sangue materno
- ▶ Adequado para idade gestacional
- ▶ Ácidos graxos

Introduction

Fetal growth restriction (FGR) is an intercurrent that affects 5%–10% of pregnancies, the second leading cause of perinatal mortality, and is responsible for approximately 30% of stillbirths, in addition to determining a higher frequency of premature births and intrapartum asphyxia.¹

Nowadays, there is no effective treatment to decrease or stop placental insufficiency progression, thus fetal vitality assessment and the decision regarding the delivery are the main strategies in the management of these fetuses.² Within this context, finding an effective, non-invasive, and low-cost treatment would be important to decrease the FGR rates. Maternal dietary supplementation with omega-3 polyunsaturated fatty acids (PUFAs) during pregnancy has been shown to increase gestational duration, increase fetal growth, and decrease the risk of pregnancy complications, although its precise mechanisms remain uncertain.³

Fatty acids (FAs) are long-chain organic acids and basic compounds of lipids, which are classified into saturated and unsaturated. Saturated FAs (SFAs) are those with single carbon bonds, mainly found in fat animal products in solid-state. Unsaturated FAs have carbons that make one or more double bonds exist mainly in vegetables in liquid form. Unsaturated FAs can be further classified into monounsaturated—with only one carbon double bond and polyunsaturated—with two or more double bonds.^{4,5}

Some benefits of maternal supplementation of omega-3 PUFAs have been described in the literature, such as reduction of depression during pregnancy and after delivery⁶ and decreased preterm birth in pregnant women with low total omega-3 PUFA status early in pregnancy.^{6,7} However, whether

omega-3 PUFAs interfere with fetal growth remains unclear, particularly in those cases with FGR. Therefore, establishing the relationship between a diet rich in omega-3 PUFAs and fetal growth is necessary to elucidate the anti-inflammatory power of this FA in this disease.

This study aimed to compare the maternal blood levels of FAs in pregnancies with FGR and appropriate for gestational age (AGA) fetuses.

Methods

This cross-sectional study was conducted between February 2017 and May 2021 and approved by the Research Ethics Committee of the Federal University of São Paulo (UNIFESP) (n: 2.004.104). All participants signed the consent form. During this period, FAs were analyzed in pregnant women who were divided into two groups: 1) early- and late-onset FGR and 2) AGA. Fetal growth restriction (FGR) was defined according to the Delphi criteria.⁸ Early-onset FGR - gestational age (GA) was <32 weeks and estimated fetal weight (EFW) or abdominal circumference (AC) < 3rd percentile for the GA⁹ or absent end-diastolic flow in the umbilical artery (UA) Doppler, EFW or AC < 10th percentile for the GA⁹ associated with a mean pulsatility index (PI) of uterine artery Doppler or PI UA Doppler > 95th percentile for the GA.^{10,11} Late-onset FGR - GA > 32 weeks and EFW or AC < 3rd percentile for the GA,⁹ EFW or AC < 10th percentile for the GA⁹ associated with a mean PI UA Doppler > 95th percentile for the GA,¹¹ cerebral placental ratios < 5th percentile for the GA,¹² or AC and/or EFW crossing centiles of > 2 quartiles on growth centiles. Appropriate for gestational age (AGA) was if the values come from

10th and 90th percentiles according to the table proposed by Hadlock et al.⁹

Following the FGR diagnosis, pregnant women were assessed at the Fetal Growth Restriction Sector of the Department of Obstetrics, UNIFESP. The inclusion criterion was singleton pregnancy with GA between 26 and 37 + 6 weeks confirmed by ultrasonography performed up to the 13th week. The exclusion criteria were pregnant women in labor and fetuses with structural malformations and/or chromosomal disorders.

The following FAs were assessed: 1) SFAs: myristic, palmitic, and stearic acids; 2) trans FA (TFA): elaidic acid; 3) monounsaturated FAs: palmitoleic and oleic acids; 4) omega-6 PUFAs: linoleic, dihomogamma-linoleic, arachidonic, and gamma-linoleic acids; and 5) omega-3 PUFAs: alpha-linolenic, eicosapentaenoic, and docosahexaenoic acids.

Maternal blood samples were collected, centrifuged, and sent for laboratory analysis within 24 h. Fatty acid levels were assessed according to the methodology proposed by Kolarovic and Fournier.¹³ This method consisted of initially extracting the total lipid from the plasma. Briefly, 500 µl of plasma was mixed with 500 µl of water by Vortex for 30 sec with 100 µl "internal standard" containing 0.857 mg of heptadecanoic acid/ml as a phospholipid dissolved in chloroform. A mixture of hexane and 2-propanol at 4 ml containing 25 mg of di-tert-butyl methyl phenol was added.

Phospholipids were isolated by liquid chromatography using an aminopropyl column (Sep Pak Cartridges; Waters, Milford, MA) as described by Agren et al.¹⁴ The phospholipid fractions obtained on the columns were vacuum dried, and each well was added with 100 µl of chloroform. Fatty acid methyl ester was formed according to the method by Lepage et al.¹⁵ A gas chromatograph (model HP-5890 Series II; Hewlett-Packard, Palo Alto, CA) equipped with a flame ionization detector was used to quantify FA methyl esters.

Chromatography was performed using a 60-m wide capillary column, 0.32-mm internal diameter, and 20-µm film thickness (Sp 2330FS; Supelco Inc, Bellefonte, Palo Alto, CA). A 29:1 split ratio injector and detector were maintained at 250°C and 275°C, respectively, and nitrogen was used as a carrier gas. The docosahexaenoic and eicosapentaenoic acid proportions were calculated as a weight percentage (% by weight) of the total detected FAs with 14–24 carbon atoms.

Maternal eating habits and smoking variables were collected using a standardized questionnaire which was applied before the collection of blood samples.

To evaluate the effect of FGR and AGA fetuses on the levels of maternal FAs, a power analysis was performed to calculate the sample size on the basis of the Cohen effect of 0.7 to achieve a power of 80% and an alpha of 5% to detect the differences in the evaluated parameters.¹⁶ Using the software G 3.1, the results suggested a total sample size of 62 pregnant women.

Data were collected in an Excel 2007 spreadsheet (Microsoft Corp., Redmond, WA, USA) and analyzed using statistical software Statistical Package for the Social Sciences version 15.0 (SPSS Inc., Chicago, IL, USA) and Prisma GraphPad version 7.0 (GraphPad Software; San Diego, CA, USA). The

D'Agostino and Pearson normality test was used to analyze if the values come from the Gaussian distribution. The non-parametric distribution variables were presented as medians and interquartile ranges. The normal distribution variables were presented as mean and standard deviation. Categorical variables were described as absolute and percentage frequencies and represented in Tables. The Student's t-test, Mann-Whitney test, and general linear model, with GA and maternal weight as covariant, were used to compare the FA levels between the groups. The correlation between the FA levels, GA, and maternal weight was performed using the Pearson and Spearman tests. The Chi-square test was used to study the difference between categorical variables and their proportions. General linear regression was performed to assess the ability of gestational age to predict FA levels in the maternal blood sample. A *p*-value of <0.05 was considered statistically significant.

Results

Maternal blood samples were collected from 67 pregnant women; however, 3 were excluded from the analysis due to blood coagulation (*n* = 2) and gestational age beyond the period (*n* = 1). The maternal characteristics, such as maternal age, parity, height, weight, body mass index (BMI), gestational age, and EFW on the day of maternal blood sample collection, are shown in **Table 1**. The mean EFW was significantly lower in the FGR than AGA fetuses (1,439.0 vs. 1,717.0 g, *p* = 0.041).

Considering all cases, a weak positive correlation was found between the palmitoleic acid level and maternal weight (*r* = 0.285, *p* = 0.036). No significant correlation was found between the palmitoleic acid level and gestational age (*r* = -0.181, *p* = 0.150) (**Fig. 1**). Although significant, only 8.6% of the palmitoleic acid level was linearly related to maternal weight. The increased maternal weight of 1.0 kg

Table 1 Comparison of maternal characteristics between appropriate for gestational age (AGA) and fetal growth restriction (FGR) fetuses

Maternal Characteristics	FGR (N = 24)	AGA (N = 40)	<i>p</i> -value
Age (years)	23.0 (19.0–29.0)	22.5 (17.0–32.2)	0.561 †
Parity			0.220 §
Primiparous	52.6% (10/19)	72.4% (21/29)	
Multiparous	47.4% (9/19)	27.6% (8/29)	
Height (m)	1.59 (0.06)	1.62 (0.08)	0.132 <i>f</i>
Weight (kg)	65.2 (13.4)	69.4 (14.8)	0.292 <i>f</i>
BMI (kg/m ²)	26.0 (4.8)	26.6 (4.4)	0.654 <i>f</i>
Gestational age (weeks)	32.2 (3.2)	31.3 (3.0)	0.259 <i>f</i>
Estimated fetal weight (grams)	1439.0 (461.3)	1717.0 (537.9)	0.041 <i>f</i>

BMI: body mass index. Mann-Whitney †: median (interquartile range); Student's t-test *f*: mean (standard deviation); Chi-square §: Percentage (*n*/*N*). *p* < 0.05, statistically significant.

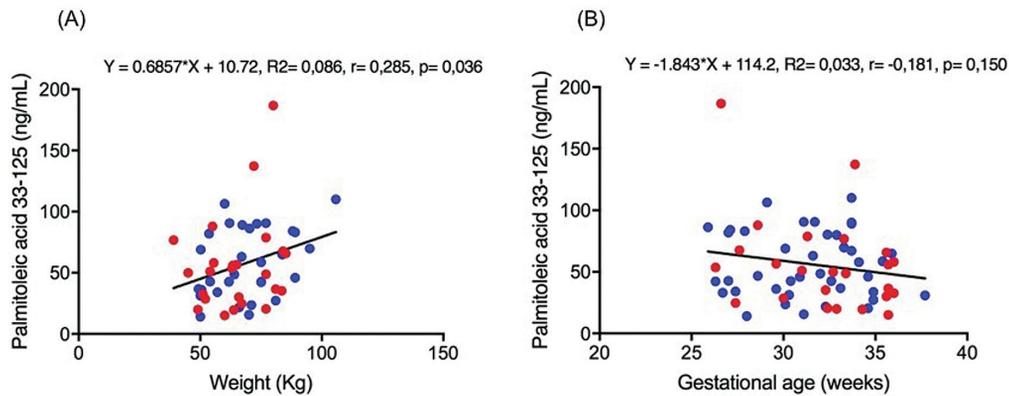


Fig. 1 Correlation between the maternal palmitoleic acid levels with appropriate for gestational age (blue dots), fetal growth restriction (red dots), maternal weight (A), and gestational age (B). Spearman test, $p < 0.05$.

Table 2 Maternal fatty acids levels with fetal growth restriction (FGR) and appropriate for gestational age (AGA) fetuses

Fatty acids	FGR (n = 24)	AGA (n = 40)	p-value
Myristic acid 15–60 (ng/mL)	22.6 (18.5–42.9)	28,8 (20–41.8)	0.375 †
Palmitic acid 320–1075 (ng/mL)	704.6 (277.3)	738.0 (253.5)	0.624 ‡
Stearic acid 127–305 (ng/mL)	165.5 (54.3)	174.4 (51.1)	0.514 ‡
Elaidic acid <10 (ng/mL)	2.3 (1.8–5.4)	4.7 (2.85–6.8)	0.045 †
Palmitoleic acid 33–125 (ng/mL)	50.5 (29.0–67.1)	47.6 (33.9–81.5)	0.033 §
Oleic acid 260–1250 (ng/mL)	469.2 (320.2–624.5)	522.1 (403.8–631.1)	0.315 †

Mann-Whitney †: median (interquartile range); Student's t-test ‡: mean (standard deviation); General Linear Model with maternal weight as covariant §: median (interquartile range). $p < 0.05$, statistically significant.

was responsible for increasing the palmitoleic acid level by 0.68 ng/ml. No significant correlation was found between the other studied saturated, trans, and monounsaturated FA levels and maternal weight (► **Supplementary Material Figure S1**). No significant correlation was found between the studied saturated, trans, and monounsaturated FA levels and gestational age (► **Supplementary Material Figure S2**).

► **Table 2** shows the comparison of the saturated, trans, and monounsaturated FA levels in FGR and AGA fetuses. The median elaidic acid level was significantly lower in FGR than

in AGA fetuses (2.3 vs. 4.7 ng/ml, $p = 0.045$). The median palmitoleic acid level was significantly higher in FGR than in AGA fetuses using the maternal weight as a covariant (50.5 vs. 47.6 ng/ml, $p = 0.033$).

Considering all cases, a weak negative correlation was found between the gamma-linoleic acid level and gestational age ($r = -0.277$, $p = 0.026$). No significant correlation was found between the gamma-linoleic acid level and maternal weight ($r = 0.147$, $p = 0.286$) (► **Fig. 2**). Although significant, only 7.6% of the gamma-linoleic acid level was linearly

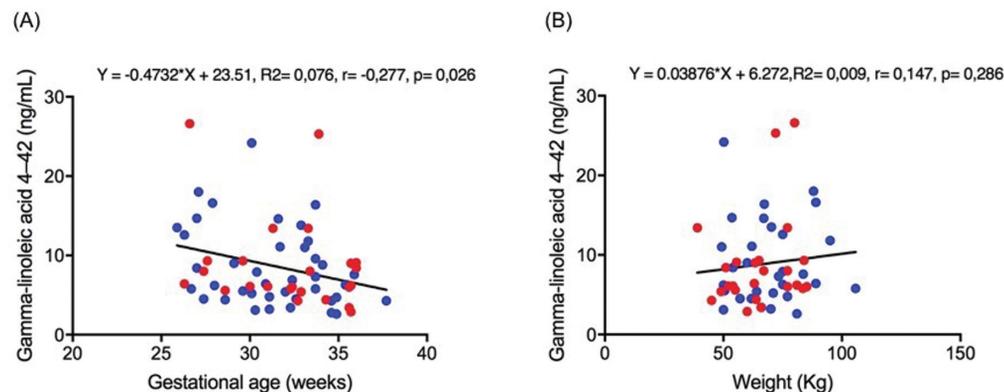


Fig. 2 Correlation between the maternal gamma-linoleic acid levels with appropriate for gestational age (blue dots), fetal growth restriction (red dots), gestational age (A), and maternal weight (B). Spearman test, $p < 0.05$.

Table 3 Maternal omega-6 polyunsaturated fatty acid levels with appropriate for gestational age (AGA) and fetal growth restriction (FGR) fetuses

Omega-6 polyunsaturated fatty acid	FGR (n = 24)	AGA (n = 40)	p-value
Linoleic acid 576–1300 (ng/mL)	895.5 (737.9–1110)	928.5 (773.7–1237)	0.284 †
Dihomo gamma-linoleic acid 38–105 (ng/mL)	57.9 (40.1–81.6)	61.8 (47.7–78.4)	0.579 †
Arachidonic acid 108–422 (ng/mL)	239.6 (196.8–291.4)	240.0 (181.3–309.7)	0.769 †
Gamma-linoleic acid 4–42 (ng/mL)	6.3 (5.6–9.2)	6.6 (4.5–11.6)	0.024 §

Mann-Whitney †: median (interquartile range). General linear model with gestational age as covariant §: median (interquartile range). $p < 0.05$, statistically significant.

Table 4 Maternal omega-3 polyunsaturated fatty acid levels with appropriate for gestational age (AGA) and fetal growth restriction (FGR) fetuses

Omega-3 polyunsaturated fatty acid	FGR (n = 24)	AGA (n = 40)	p-value †
Alpha-linoleic acid 3–21 (ng/mL)	21.0 (14.5–31.7)	22.1 (18.0–29.1)	0.569
Eicosapentaenoic acid 5–73 (ng/mL)	5.5 (4.1–8.7)	8.3 (4.7–12.0)	0.111
Docosahexaenoic acid 34–160 (ng/mL)	87.0 (53.2–115.6)	85.4 (67.2–109.3)	0.841

Mann-Whitney †: median (interquartile range); $p < 0.05$, statistically significant.

related to the gestational age. The increased gestational age of 1 week was responsible for decreasing the gamma-linoleic acid level by 0.47 ng/mL. No significant correlation was found between other omega-6 polyunsaturated FA levels and gestational age (► **Supplementary Material Figure S3**). No correlation was found between the omega-6 PUFA levels and maternal weight (► **Supplementary Material Figure S4**).

► **Table 3** shows the comparison of the omega-6 PUFA levels in FGR and AGA fetuses. The median gamma-linoleic acid level was significantly lower in FGR than in AGA fetuses using the maternal weight as a covariant (6.3 vs. 6.6 ng/mL, $p = 0.024$) (► **Table 3**).

Considering all cases, no significant correlation was found between the maternal omega-3 PUFA levels and maternal weight (► **Supplementary Material Figure S5**), as well as the gestational age (► **Supplementary Material Figure S6**). ► **Table 4** shows the comparison of maternal omega-3 PUFA levels in FGR and AGA fetuses. No significant differences were found between the two groups regarding the omega-3 PUFA levels. ► **Table 5** shows the comparison of maternal eating habits and smoking between FGA and AGA fetuses, which revealed no statistical differences.

Discussion

Omega-3 PUFAs are beneficial in the regulation of maternal and fetal metabolic function, inflammation, immunity, macrosomia, oxidative stress, pre-eclampsia, FGR, preterm birth, offspring metabolic function, and neurodevelopment.¹⁷ PUFAs have antioxidant activity, thus dietary supplementation of these substances during pregnancy has the potential to prevent or control placental disorders and promote fetal growth.¹⁸ In our study, maternal FAs levels showed different behaviors in pregnant women with FGR and AGA fetuses.

Table 5 Maternal eating habits and smoking of appropriate for gestational age (AGA) and fetal growth restriction (FGR) fetuses

	AGA (n = 40)		FGR (n = 24)		p-value*
Fish					0.751
No	33	82.5%	19	79.2%	
Yes	7	17.5%	5	20.8%	
Milk					0.543
No	8	20.0%	7	29.2%	
Yes	32	80.0%	17	70.8%	
Fry					0.589
No	12	30.0%	9	37.5%	
Yes	28	70.0%	15	62.5%	
Smoking					0.297
No	32	80.0%	22	91.7%	
Yes	8	20.0%	2	8.3%	
Olive oil					0.207
No	15	37.5%	13	54.2%	
Yes	25	62.5%	11	45.8%	

Chi-square *. $p < 0.05$, statistically significant.

Bobiński et al.¹⁹ evaluated the maternal diet with AGA, preterm delivery, and small for gestational age (SGA) fetuses. Diet components were assessed by dietary questionnaire, and the authors concluded that the predictive factor was higher content of short- and medium-chain FAs in the maternal diet for AGA fetuses. In another study, Bobiński et al.²⁰ assessed the FA levels of the fetus (cordocentesis) and mothers who delivered full-term, SGA, and preterm newborns and concluded that the placental-fetal transport of FAs

in full-term was different from SGA and preterm newborns. A previous study from our group compared the maternal blood levels of 40 SGA and 24 AGA fetuses and revealed no significant difference in SFAs, TFAs, monounsaturated, and PUFAs.²¹ The present study is a secondary analysis of a larger study in which we compared SGA and FGR with the intention of evaluating whether placental insufficiency could interfere with maternal levels of FAs, given that SGA are investigated whether essential FA. As the sample sizes of both studies are similar, this could constitute a limitation of the study.

Our study revealed that maternal blood levels of TFAs (elaidic acid) and omega-6 PUFAs (gamma-linoleic acid) were lower in FGA than in AGA fetuses. Das²² in a review article investigated whether essential FA metabolism and their long-chain metabolite concentrations (long-chain polyunsaturated FAs [LCPUFAs]) are altered in FGR. He revealed that low-birth-weight infants have decreased LCPUFA concentrations, especially arachidonic acid.

FAs modulate angiogenesis as observed by increased tube formation and angiogenic growth factor secretion in first-trimester human placental trophoblasts. During the third trimester of pregnancy, placental preferential transport of maternal plasma LCPUFAs is of critical importance for fetal growth and development.²³ Cetin et al.²⁴ assessed the fetal and maternal FA profiles in utero in 11 AGA and 10 FGR fetuses by cordocentesis between 19 and 39 weeks. Total plasma FA levels were significantly higher in the mother than in both AGA and FGR fetuses. The authors conclude that FGR could be related to inadequate transplacental supply as well as inadequate fetal enzymes for elaborating these metabolically relevant conditionally essential FAs.

Alvino et al.²⁵ compared the maternal FA levels between two groups (AGA, n = 42) and (FGR, n = 25). FGR was defined as AC measurement < 10th percentile for GA. These authors observed that maternal total FA levels were similar between AGA and FGR, except the arachidonic acid/linoleic acid ratio which was. These authors observed that maternal total FA significantly lower in FGR than in AGA fetuses.

Our study revealed no differences regarding eating habits and smoking between pregnant women with FGR and AGA fetuses. Middleton et al.²⁶ performed a systematic review including 70 randomized controlled trials and compared omega-3 LCPUFA interventions (supplements and food) with placebo or no omega-3 PUFAs. They revealed a reduced risk for low-birth-weight newborns; however, little or no difference in SGA and FGR. Saccone et al.,²⁷ in a systematic review, assessed the maternal supplementation of LCPUFAs regarding perinatal outcomes, included 34 randomized controlled trials, and revealed that LCPUFA supplementation was not associated with obstetrical disorder prevention, such as preterm birth, pre-eclampsia, gestational diabetes mellitus, SGA, and FGR. Chen et al.²⁸ included 21 randomized controlled trials and revealed that fish oil supplementation was associated with higher birth weight, birth length, and head circumference, and a 23% lower risk of low-birth-weight. No benefit was found from fish oil supplementation about the risk of FGR or stillbirth.

For the correct analysis of all FAs assessed in the present study and their real interference in fetal growth and development, a rigorous analysis of the diet of pregnant women should have been established. Not only if the type of food ingested daily contained fat of animal or vegetable origin, as well as the intake of fish, vegetables, cocoa, olive oil, milk oils, nuts, coconut, among others, so common in our diet. The amount of these foods as well as their origin are essential to establish the correct influence of the diet in the determinism of FGR. A limitation in our study was not to accurately establish the diet of the participating pregnant women. As strength, it is the first study that compared the maternal FAs between AGA and FGR using a specific methodology.

Conclusion

In summary, pregnant women with FGR had lower blood elaidic acid and gamma-linoleic acid levels and higher palmitoleic acid levels than AGA fetuses. Maternal eating habits and smoking did not show significant differences between FGR and AGA fetuses.

Contributions

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

Conflicts to Interest

None to declare.

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Age and Type of Delivery as Risk Indicators for Maternal Mortality

Idade e tipo de parto como indicadores de risco para mortalidade materna

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Abstract

Objective: This study assessed maternal mortality (MM) and related factors in a large-sized municipality in the Southeastern region of Brazil (Campinas, São Paulo) during the period 2000-2015.

Methods: This study consisted of two phases: 1. An analytical nested case-control phase that assessed the impact of individual and contextual variables on MM; and 2. an ecological phase designed to contextualize maternal deaths by means of spatial analysis. The case group consisted of all maternal deaths ($n=87$) and the control group consisted of 348 women who gave birth during the same period. Data analysis included descriptive statistics, association, and multiple logistic regression (MLR) tests at $p < 0.05$ as well as spatial analysis.

Results: Maternal Mortality Ratio was 37 deaths per 100.000 live births. Deaths were dispersed throughout the urban territory and no formation of cluster was observed. MLR showed that pregnant women aged ≥ 35 years old ($OR=2.63$) or those with cesarean delivery ($OR=2.51$) were more prone to maternal death.

Conclusion: Maternal deaths were distributed dispersedly among the different socioeconomic levels and more prone to occur among older women or those undergoing cesarean deliveries.

Keywords

- ▶ Maternal mortality
- ▶ Observational study
- ▶ Socioeconomic factors

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Resumo

Objetivo: Esse estudo avaliou a mortalidade materna (MM) e fatores relacionados em um município de grande porte da região sudeste do Brasil (Campinas, São Paulo) no período de 2000-2015.

Métodos: Esse estudo consistiu de duas fases: 1. Uma fase analítica de caso-controle que avaliou o impacto de variáveis individuais e contextuais na MM; 2. Uma fase ecológica delineada para contextualizar as mortes maternas por meio de análise espacial. O grupo caso consistiu de 87 mortes maternas e o grupo controle de 348 mulheres que tiveram bebês durante o mesmo período. Os dados foram analisados por estatística descritiva, testes de associação e regressão logística múltipla (RLM) ($p < 0,05$) assim como análise espacial.

Resultados: A taxa de mortalidade materna foi de 37 mortes para cada 100.000 nascidos vivos. As mortes foram dispersas por todo o território urbano e não se observou formação de clusters. Na RLM observou-se que mulheres grávidas com idade ≥ 35 anos ($OR = 2,63$) ou aquelas que passaram por cesárea ($OR = 2,51$) foram mais propensas à morte materna.

Conclusão: As mortes maternas foram distribuídas dispersamente entre os diferentes níveis socioeconômicos e mais propensas a ocorrer entre mulheres ≥ 35 anos de idade ou que passaram por cesárea.

Descritores

- ▶ Mortalidade materna
- ▶ Estudo observacional
- ▶ Fatores socioeconômicos

Introduction

Maternal mortality (MM) represents social and economic status in a country. Reducing MM is one of the goals of the Sustainable Development Goals (SDG)¹ and eliminating avoidable MM must be achieved by 2030.¹⁻³

Despite the reduction of 38% in global Maternal Mortality Ratio (MMR) from 2000 (342 deaths per 100,000 livebirths) to 2017 (211 deaths per 100,000 livebirths)¹ several challenges have to be overcome, especially in low- and middle-income countries. In Brazil, the MMR in 2017 was 60/100,000.⁴ The Brazilian Ministry of Health has proposed actions such as the National Policy for Comprehensive Healthcare for Women,⁵ the National Agreement for the Reduction of Neonatal and Maternal Mortality⁶ and the Stork Network⁷ that aim to reduce maternal mortality by means of qualified and humanized care.

Many factors can affect MM such as healthcare access, healthcare quality during antenatal care, childbirth and puerperium care, quality of obstetric emergencies assistance,⁸ age,^{9,10} years of education,⁹ antenatal appointments,¹ marital situation,⁹ and socioeconomic factors.^{11,12} It is also known that maternal mortality rate is associated with healthcare system factors and the disease burden in a country.¹¹

Public policies for reducing maternal morbimortality require that the government takes specific and systematic actions on reformulating these policies.¹³

MM surveillance and the analysis of factors associated with adverse outcomes are key to subsidize political decision-making and to contribute to an efficient resource allocation for MM reduction.

This study aimed to assess maternal mortality and related factors in Campinas, São Paulo, a large-sized municipality of the Brazilian Southeast region between 2000-2015.

Methods

This observational study was performed in a large-sized municipality, Campinas, located in the countryside of São Paulo State, Brazil. At the time of data collection (2000-2015), Campinas presented Municipal Human Development Index of 0.805¹⁴ and a population of 1,135,623 inhabitants with 33% of women in reproductive age.¹⁵ A total of 63 (sixty-three) health centers, acting on the Family Health Strategy model, worked with well-delimited territories, client subscriptions, and multi-professional teams providing primary health care and some medium complexity procedures. Specialized care was provided by more than 20 public reference units and by the urgency and emergency system.¹⁶ There are seven maternity units in the city and all of them assist women living in Campinas. One maternity assists Unified Health System (SUS) patients, two assist SUS and health insurance patients and four assist only private patients.

Two phases composed the study design: an analytical nested case-control phase that assessed the impact of individual and contextual variables on maternal mortality during the period 2000-2015, and an ecological phase designed to contextualize maternal deaths by means of descriptive and spatial analysis.

For the nested case-control phase, the case group was comprised of all maternal deaths ($n = 87$) registered in the Mortality Information System and investigated by the Municipal Committee of Maternal Mortality Surveillance during the period 2000-2015.¹⁵ The control group was comprised of 348 women who gave birth during the same period and were randomly selected from the Information System on Live Births. The number of controls was determined using a 4:1 ratio, as there is no statistical gain to justify higher ratios.¹⁷ The final sample size ($n = 435$) provided a test power of 0.80

($\beta = 20$), a significance level of 5% ($\alpha = 0.05$) for a minimum detectable Odds Ratio of 2.0.

Collected data included clinical variables: antenatal care (at least one appointment), number of antenatal appointments, number of previous pregnancies, number of fetuses and type of birth; as well as sociodemographic variables: age (years), education (completed study years), marital status/situation and the contextual variable: socioeconomic level. The Municipal Health Department built three socioeconomic levels (Low, Middle, and High) for each area covered by the healthcare clinics using data from the Demographic Census of 2000 and considering the following variables: percentage of people responsible for the household having an income of 10 minimum wages or more, percentage of people earning less than 2 minimum wages, percentage of people responsible for households that has more than 10 years of education, and percentage of people that has less than 1 year of education. According to this criteria, all the areas covered by the healthcare clinics were divided in order to guarantee a third of the population in each of those three socioeconomic levels.¹⁸ After descriptive analysis of the data, regression logistic models were estimated to analyze the individual associations of each independent variable with the outcome variable. The variables age, education, marital status, antenatal care, number of antenatal appointments, pregnancy, and type of delivery were dichotomized based on a previous study¹⁷ The variables that presented a p value of $p \leq 0.20$ in the individual association analysis (crude) were tested in a multiple logistic regression model, with variables at $p \leq 0.05$ remaining in the final model when analyzed together. All analyses were performed in the SAS Program (SAS Institute Inc., Cary, NC, USA, Release 9.2, 2010).

Thematic maps were designed to geofence maternal deaths according to socioeconomic levels. Two information plans were used: "points" which consisted of data about household address of the maternal death cases that were after converted into geographical coordinates by BatchGeo program¹⁹; and "polygons" which consisted of the municipality's urban area divided into health units' coverage areas, whose data were provided by the Municipal Health Department. Both information layers were merged in QGIS Desktop® computer program (version 2.8.1).

Maternal Mortality Ratio (total of maternal deaths/total of live births*100,000) was calculated for the municipality and for each socioeconomic level.

This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and approved by the Research Ethics Committee of the Piracicaba Dental School, State University of Campinas (Protocol 130/2014).

Results

Maternal deaths ($n = 87$) occurred among women 16 to 44 years old. Most of them studied 4 years or more (96%), 24.5% graduated from high school and 13% held a college degree (► **Table 1**). The majority was married (52%), had more than 4 antenatal appointments (83%), had already

Table 1 Sociodemographic characterization of the cases of maternal deaths and controls

Sociodemographic characteristics	n(%)	
	Cases (87)	Controls (348)
Age (years)		
< 35	63 (72.4)	304 (87.4)
≥ 35	24 (27.6)	44 (12.6)
Education (years)		
< 4	2 (3.8)	9 (2.6)
≥ 4	51 (96.2)	338 (97.4)
Marital status		
Single / Divorced / Widow	41 (48.2)	143 (41.1)
Married	44 (51.8)	205 (58.9)
Socioeconomic		
Low	46 (53.5)	157 (45.1)
Medium	23 (26.7)	102 (29.3)
High	17 (19.8)	89 (25.6)

Missing information: Education ($n = 35$), Marital status ($n = 2$), Socioeconomic ($n = 1$).

been pregnant (61%) and had a single pregnancy (95%). A total of 81% underwent cesarean delivery.

Among maternal deaths assessed by the Municipal Committee of Maternal Mortality Surveillance, based on a missed opportunity, 65.5% were considered avoidable, of which 77.0% were pregnant woman with at least one antenatal care appointment. ► **Table 2** shows the causes of maternal deaths. A total of 54.2% were due to direct causes (hypertensive disorders, hemorrhages and infections, mainly); 45.8% were due to indirect causes (circulatory system diseases, digestive system diseases, pre-existing hypertension and respiratory system diseases).

► **Table 3** shows the results of association and multiple logistic regression tests. There was a significant association between maternal death and women's age ($p = 0.0008$), antenatal care ($p < 0.0001$), number of pregnancies ($p < 0.0001$), and the type of delivery ($p = 0.0042$). All women with no antenatal care ($n = 10$) and with multiple pregnancies ($n = 31$) were from case group, so that was not possible to calculate their odds ratio. The results of multiple logistic regression analysis showed that older pregnant women (OR = 2.63) or those with cesarean delivery (OR = 2.51) were more prone to maternal death.

The spatial distribution showed that 53.5% of deaths occurred in the low socioeconomic level (1), 26.7% in the intermediate level (2) and 19.8% in the high level (3). Deaths were dispersed throughout the urban territory and no formation of cluster was observed (► **Figure 1**). Only a minor concentration of maternal deaths occurred in low-socioeconomic level stratum, or the most vulnerable areas of the city. However, this discrete concentration was not enough to characterize a cluster.

Maternal Mortality Ratio (MMR) for the period 2000-2015 was 37.1 death per 100,000 live births (37.1/100,000LB).

Table 2 Causes distribution of maternal death

Death cause (ICD 10)	No.	%
Direct Obstetric causes	45	52.0
Hypertensive Disorders (O12-O16)	13	15.0
Hemorrhage (O72-O72.2)	07	8.0
Infections (O85-O86.8)	06	7.0
Embolism (O88.1)	03	3.5
Pregnancy leading to abortion (O01-O08)	03	3.5
Premature Placental Separation (O45-O45.9)	02	2.5
Genitourinary system infection (O23.1-O23.4)	02	2.5
Circulatory system disease (O99.4)	02	2.5
Puerperal cardiomyopathy (O90.3)	02	2.5
Respiratory system disease (O99.5)	01	1.0
Excessive vomit during pregnancy (O21.1)	01	1.0
Other kinds of uterine atony (O62.2)	01	1.0
Deep thrombophlebitis during puerperium (O87.1)	01	1.0
Infection in the amniotic sac and membranes (O41.1)	01	1.0
Indirect Obstetric causes	38	43.5
Circulatory system diseases (O99.4)	09	10.5
Digestive system diseases (O99.6)	04	5.0
Respiratory system diseases (O99.5)	03	3.5
Chronic systemic arterial hypertension (O10-O11)	03	3.5
Viral hepatitis complicating pregnancy (O98.4)	02	2.5
Genitourinary system infection (O23)	02	2.5
Other specified diseases and affections (O99.8)	02	2.5
Obstetric origin embolism (O88.2-O88.8)	02	2.5
Post-labor coagulation deficiency (O72.3)	01	1.0
Puerperal Infection (O85)	01	1.0
Pregnancy leading to abortion (O07.8)	01	1.0
Pregnancy complications sequelae (O94)	01	1.0
Non-specified puerperal complication (O90.9)	01	1.0
Other viral diseases (O98.5)	01	1.0
Nervous system diseases (O99.3)	01	1.0
Other kinds of uterine atony (O62.2)	01	1.0
Assistance performed due to uterine tumor body (O34.1)	01	1.0
Other puerperal complications (O90.8)	01	1.0
Other non-specified urinary system infections (O23.9)	01	1.0
Inconclusive (Cases 1, 2, and 3)*	03	3.5
Late Maternal Death	01	1.0
Total	87	100.0

*Inconclusive cases: Case 1) 28 years old, single, brown, with antenatal care, cesarean section, death in the postpartum period, live newborn, gestation duration from 37 to 41 weeks, low socioeconomic status. Case 2) 19 years old, single, white, with antenatal care, cesarean section, postpartum death, live newborn, gestation duration 36 weeks, low socioeconomic status. Case 3) 30 years old, single, white, tubal pregnancy, did not give birth, middle socioeconomic status.

Discussion

This study assessed maternal deaths and related factors in a Brazilian large-sized municipality during 2000–2015. Maternal mortality is a serious public health issue and became a social development indicator and it is considered an individual, family and social tragedy.²⁰

Our findings showed that women aged 35 years or more were more prone to death than younger women, result similar to others.^{9,17} Age has been considered an important factor to assess the pregnancy's risk, since women older than 35 years can be more prone to preeclampsia.²¹ Maternal age was significantly associated to preeclampsia in a study conducted in Sweden and China.²¹ These findings imply that attention should be given to older pregnant women in order to diagnose early the risks of pregnancy-induced hypertension with proper monitoring of clinical status. For preeclampsia prevention, only calcium supplementation (calcium carbonate, 1,000–2,000 mg/day) and low-doses aspirin daily (50–170 mg) are considered effective in clinical practice.²²

Cesarean delivery prevalence in the present study was 65.4%, a superior rate than that found (43.3%) among Brazilian pregnant women assisted at the Unified Health System (SUS).²³ Pregnant women with cesarean delivery presented more chance of dying than those with vaginal birth. Studies show that cesarean delivery can contribute to increase the risk of maternal death^{17,24} and maternal morbidity.²⁵ Cesarean delivery should be indicated properly and corresponds to a strategy of future pregnancy-related deaths prevention when only performed when medically indicated.⁹ This study did not investigate the presence of obstetric morbidity and the proper cesarean indication.

Antenatal care was highly associated with maternal death in our study. In a similar study an inverse and significant correlation between maternal mortality ratio and antenatal care coverage was found.¹¹ The proper antenatal care classifies the pregnant woman's risk and specialized professionals can monitor it.²⁶ Although the municipality has a pregnancy risk classification protocol,²⁷ among the avoidable maternal deaths, 77% of pregnant women attended antenatal care, a fact that suggests a need for investigating the quality of the antenatal care and hospital assistances.

Number of previous pregnancies presented a highly significant association with maternal mortality. First pregnancy showed more chances of maternal death in comparison with the multiparous ones. Similar results were found in China and Sweden where being nulliparae was highly associated with preeclampsia.²¹ By analyzing our data bank, among women in their first pregnancy, 45% showed comorbidities (50% hypertensive disorders), 84% attended antenatal appointments, 55% had more than 4 appointments, 6% had twin pregnancies, 10% aged 35 years or older and 61% underwent cesarean deliveries. The fact that almost half of women showed comorbidities could partially explain our findings, since such pregnant women should have a proper risk classification and monitoring. Recent study in the United States shows that pregnant women are presenting poorer health overtime.²⁸

The MMR was 37.1/100,000LB, a value within Brazilian findings that ranged from 29.4/100,000LB to 83.3/100,000LB.²⁷ Recent data showed a Brazilian MMR of 57.6/100,000 live births²⁹ and 60/100,000LB,¹ whereas a global MMR of 211/100,000LB.¹ Projection of MMR for 2030 based on the Sustainable Development (SDG) goal is

Table 3 Factors associated to increased risk of maternal death, by association and multiple logistic regression analysis for maternal death

Variable	N (% ^S)	Maternal Deaths – Cases (n = 87)	Non-deaths – Controls (n = 348)	&crude OR (#IC95%)	p-value	&OR adjusted (#IC95%)	p-value
	N (% ^S)						
Age (years)							
< 35	367 (84.4)	63 (72.4)	304 (87.4)	Ref		Ref	
≥ 35	68 (15.6)	24 (27.6)	44 (12.6)	2.63 (1.49-4.64)	0.0008	2.63 (1.41-4.91)	0.0025
Education (years)							
< 4	11 (2.8)	2 (3.8)	9 (2.6)	1.47 (0.31-7.01)	0.6258	–	–
≥ 4	389 (97.2)	51 (96.2)	338 (97.4)	Ref			
Marital status							
Single / Divorced / Widow	184 (42.5)	41 (48.2)	143 (41.1)	1.34 (0.83-2.15)	0.2332	–	–
Married	249 (57.5)	44 (51.8)	205 (58.9)	Ref			
Antenatal care							
Yes	416 (97.6)	70 (87.5)	346 (100.0)		<0.0001	–	–
No	10 (2.4)	10 (12.5)	0 (0.0)	–			
Number of Appointments							
0-3 appointments	81 (20.1)	10 (17.2)	71 (20.6)	0.80 (0.39-1.67)	0.5579	–	–
> 4 appointments	322 (79.9)	48 (82.8)	274 (79.4)	Ref			
Gemelarity							
No	396 (97.3)	56 (94.9)	340 (97.7)	Ref		–	–
Yes	11 (2.7)	3 (5.1)	8 (2.3)	2.28 (0.59-8.84)	0.2346		
Pregnancy							
Nulliparous~	31 (7.3)	31 (38.8)	0 (0.0)	–	<0.0001	–	–
Multiparous	393 (92.7)	49 (61.3)	344 (100.0)				
Type of delivery							
Vaginal	144 (34.6)	13 (19.1)	131 (37.6)	Ref		Ref	
Cesarean	272 (65.4)	55 (80.9)	217 (62.4)	2.55 (1.34-4.85)	0.0042	2.51 (1.32-4.80)	0.0053
Socioeconomic							
Low	203 (46.8)	46 (53.5)	157 (45.1)	1.53 (0.83-2.83)	0.1722	–	–
Medium	125 (28.8)	23 (26.7)	102 (29.3)	1.18 (0.59-2.35)	0.6368		
High	106 (24.4)	17 (19.8)	89 (25.6)	Ref			

^SPercentage in the column; &Odds ratio; #Confidence Interval; ~Among women in their first pregnancy, 45% showed comorbidities (50% hypertensive disorders), 84% attended antenatal appointments, 55% had more than 4 appointments, 6% had twin pregnancies, 10% aged 35 years or older and 61% underwent cesarean deliveries. Statistical tests: simple and multiple logistic regression models.

less than 70/100,000LB for the world and that none country should have a MMR over 140/100,000LB. Therefore, efforts at all government levels should be directed towards this goal.

According to spatial analysis, although no formation of cluster was observed, a discrete concentration of deaths in the low socioeconomic level was verified. Therefore, a need for continuous investments in public policies aimed to ensure access equity and quality in health care is suggested.

In the present study, 54% of maternal deaths were due to direct causes such as hypertension, hemorrhage and infections, corroborating with other Brazilian study²⁹ and similar

to data from maternal death worldwide.³⁰ Direct obstetric causes result from obstetric complications during pregnancy, labor or puerperium, whereas indirect causes result from pre-existing medical conditions that were aggravated by pregnancy.¹ The findings of this study and of two previous investigations in the same municipality indicate a decrease in the prevalence of direct causes.^{31,32} However, 61% of the deaths by direct causes were avoidable, indicating the need for improving access and quality in the antenatal, labor and providing puerperium assistance, and for providing efficient actions for the reduction of maternal mortality. Causes of

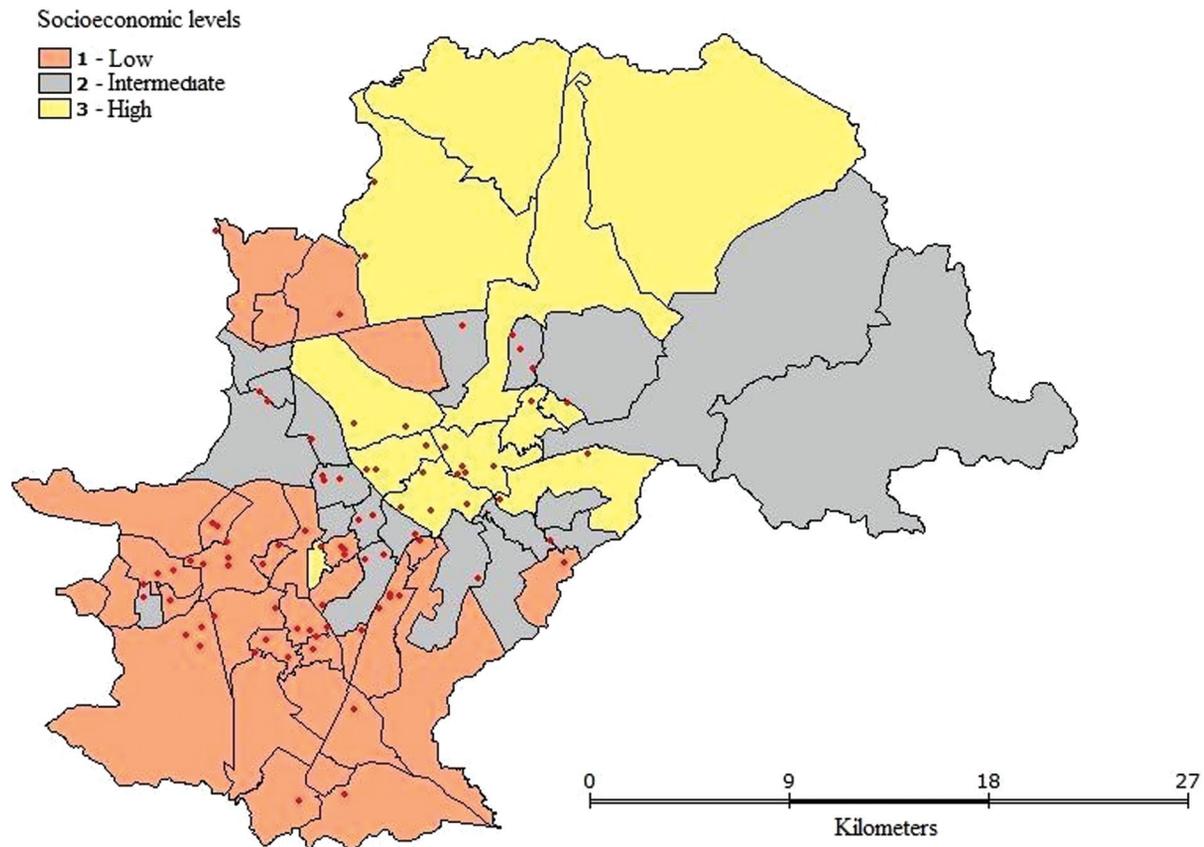


Fig. 1 Spatial distribution of maternal deaths.

maternal mortality are related to the development level of a region. Less developed ones usually have more deaths due to direct causes such as hypertension diseases, hemorrhage and infections. Such causes tend to decrease progressively as the region develops so that indirect causes usually related to more complex diseases prevail.³³

An important action that could be efficient in the prevention of maternal mortality is the incorporation of maternal near miss analysis by assessing cases of pregnant women with serious complication during antenatal, labor or puerperium and that survived. The study of such cases can subsidize healthcare systems to deal with maternal near miss in a multidimensional manner.³⁴

Maternal Mortality rate can also be affected during times of crisis. In a recent ecologic study performed in Brazil, the authors evaluated the impact of COVID-19 pandemic on maternal mortality by comparison of data from 2020 with data from 2010-2019 and found an increase of 40% on maternal mortalities on pregnancies considered low-risk.³⁵ Authors of a multinational cohort study, found similar results, showing increase in severe morbidity and mortality.³⁶ During health emergencies specific programs should be proposed and implemented to protect the health of the pregnant women and their offspring.

As a limitation of this study, we should mention the time frame of more than 5 years, the use of secondary

data and the absence of external validity of the results. The strengths include the quality of data since all maternal deaths were investigated by the Municipal Committee of Surveillance in Maternal and Child Mortality.

Conclusion

In conclusion, maternal deaths were mostly avoidable, distributed dispersedly among the different socioeconomic levels and more prone to occur among older women or those undergoing cesarean deliveries. The development of programs to increase awareness of the risks of cesarean section and risks associated to advanced maternal age together with improvement on quality of care may have an impact on the maternal mortality.

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

None to declare.

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Fertility Does not Quarantine: Coronavirus Disease 2019 Pandemic Impacts on in Vitro Fertilization Clinical Pregnancy Rates

Fertilidade não fica em quarentena: impacto da pandemia COVID-19 nas taxas de gravidez clínica em fertilização in vitro

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Abstract

Objective To understand the impact of the coronavirus disease 2019 pandemic on in vitro fertilization (IVF) clinical pregnancy rates and analyze factors that may have influenced their outcome.

Methods This was a retrospective observational study conducted at a tertiary-care Brazilian fertility center. All fresh IVF and embryo warming cycles performed from March 11 to December 31, 2018–2021 were analyzed, and their data were used to calculate fertilization, embryo cleavage, cycle cancellation, embryo transfer (ET), and clinical pregnancy rates. Statistical tests were used to evaluate the alterations found. Logistic regression models were used to explore the association of the categorical variables with the observed clinical pregnancy rates. Data from 2018 and 2019 (prepandemic) and 2020 and 2021 (pandemic) were grouped.

Results A total of 756 cycles were analyzed ($n = 360$ prepandemic and $n = 396$ pandemic). The age group of the patients, fertilization rates, and cleavage rates did not have significant differences ($p > 0.05$). There was a reduction in the percentage of fresh IVF and an increase in embryo warming cycles ($p = 0.005$) during the pandemic. There was also an increase in fresh cycle cancellations ($p < 0.001$) and a reduction in ET

Keywords

- ▶ assisted reproductive techniques
- ▶ fertilization in vitro
- ▶ pregnancy
- ▶ COVID-19
- ▶ SARS-CoV-2

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rates ($p < 0.001$). The pandemic had a negative impact on clinical pregnancy rates ($p < 0.001$) especially due to the increase in fresh cycle cancellations ($p < 0.001$).

Conclusion Embryo warming cycles with subsequent frozen-thawed ET were presented as a viable alternative to continue assisted reproductive treatments against pandemic restrictions on fresh cycles, ensuring clinical pregnancy, albeit at a lower rate than that of the prepandemic period.

Resumo

Objetivo Compreender os impactos da pandemia de COVID-19 nas taxas de gravidez clínica em fertilização in vitro (FIV) e analisar fatores que possam ter influenciado seu resultado.

Métodos Foi realizado um estudo observacional retrospectivo em um centro brasileiro de reprodução assistida. Todos os ciclos de FIV com embriões frescos e descongelados realizados entre 11 de março e 31 de dezembro, 2018-2021 foram analisados, e seus dados utilizados para cálculo das taxas de fertilização, clivagem embrionária, cancelamento de ciclos, transferência de embriões (TE) e gravidez clínica. Testes estatísticos avaliaram significância das alterações encontradas e modelos de regressão logística exploraram associação das variáveis categóricas estudadas com as taxas de gravidez clínica observadas. Os dados de 2018 e 2019 (pré-pandemia) e 2020 e 2021 (pandemia) foram agrupados.

Resultados Foram analisados um total de 756 ciclos ($n = 360$ na pré-pandemia e $n = 396$ na pandemia). A faixa etária das pacientes e as taxas de fertilização e de clivagem não tiveram alterações significativas ($p > 0,05$). Na pandemia, houve redução da porcentagem de ciclos de FIV com embriões frescos e aumento dos com descongelamento ($p = 0,005$). Também foi notado aumento das taxas de cancelamentos de ciclos com embriões frescos ($p < 0,001$) e redução do número de TEs ($p < 0,001$). A pandemia exerceu impacto negativo na taxa de gravidez clínica ($p < 0,001$), especialmente devido ao aumento de cancelamentos dos ciclos a fresco ($p < 0,001$).

Conclusão Frente às limitações pandêmicas impostas aos ciclos com embriões frescos, os ciclos de descongelamento de embriões se apresentaram como alternativa viável à continuidade dos ciclos de FIV, garantindo gravidez clínica ainda que em taxas inferiores às do período pré-pandêmico.

Palavras-chave

- ▶ tecnologias de reprodução assistida
- ▶ fertilização in vitro
- ▶ gestação COVID-19
- ▶ SARS-CoV-2

Introduction

Since the first report of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the city of Wuhan (China) in December 2019, the disease has spread rapidly and was characterized as a pandemic by the World Health Organization on March 11, 2020.^{1,2} There was a need for emergency measures to contain transmission, mitigate the risk of community contamination and avoid the collapse of health systems.^{3,4}

Health authorities have advised the suspension of elective procedures, including the performance of new in vitro fertilization (IVF) treatment cycles.^{5,6} The American Society of Reproductive Medicine and the European Society for Human Reproduction and Embryology published guidelines recommending a cryopreservation approach for patients who needed more urgent treatment.^{7,8}

In vitro fertilization is an assisted reproduction technology that consists of ovarian stimulation and egg capture, forming

embryos that will be cultured, selected, and transferred into the uterus of infertile patients. In vitro fertilization can be performed by fresh cycles with immediate embryo transfer (ET) or through embryo warming cycles initially using the freeze-all embryo approach followed by the frozen-thawed ET (FET) at an opportune time.⁹ For better effectiveness, the treatment must be performed at the right time, depending on the individual clinical condition of each patient; delay in its initiation significantly reduces the probability of pregnancy, as well as causes psychological suffering.^{3,5,10}

Estimates indicate that > 1.5 million IVF cycles are performed each year worldwide, resulting in ~ 400,000 live births.¹¹ Of all babies born each year in the UK and in the US, ~ 3 and 2%, respectively, are conceived through assisted reproduction technologies.¹²⁻¹⁴ Studies also indicate that the number of children who could be born by artificial methods, if there were no restrictions, could be as significant as the total number of deaths attributed to coronavirus disease 2019 (COVID-19).¹⁴

The present study aimed to understand the impact of the COVID-19 pandemic on IVF clinical pregnancy rates and analyze factors that may have influenced their outcome.

Methods

This was a retrospective observational analysis of medical records from a single tertiary-care fertility center located in Curitiba, state of Paraná, Brazil. Data from all patients who underwent IVF procedures (fresh and embryo warming cycles) from March 11 to December 31, 2018–2021, were included. No exclusion criteria were applied.

The following information was collected: mean age, number of cycles, IVF cycle pattern (fresh or embryo warming) performed, amount of fresh ETs and FETs, and clinical pregnancies observed. The number of cancellations was also analyzed when the cycles were interrupted before ET. Information regarding the number of recovered oocytes per cycle, the number of fertilized oocytes (with formation of two pronuclei), and the number of cleaved embryos were also collected. Data from medical records were extracted using GoldenSkill software.

Based on the data collected, clinical pregnancy, ET, and cycle cancellation rates were calculated. Clinical pregnancy rate was defined as the number of pregnancies diagnosed by ultrasonographic visualization of one or more gestational sacs, yolk sacs, and embryos over the number of cycles initiated. The ET rate consisted of the number of fertilized ET divided by the number of initiated cycles. The cycle cancellation rate corresponded to the number of interrupted cycles before ET over the number of cycles.¹⁵

Fertilization and embryo cleavage rates were calculated from laboratory data. The fertilization rate consisted of the number of fertilized oocytes (with the formation of two pronuclei) relative to the number of oocytes retrieved. The cleavage rate was described as the number of embryos cleaved in relation to the number of oocytes with two pronuclei formed. According to the Brazilian national embryo production system protocol, these indicators have been used as efficiency parameters in assisted reproduction, reflecting the quality of oocyte/embryonic manipulation, laboratory inputs, and IVF laboratory environment.¹⁶

The study followed the ethical principles of the Declaration of Helsinki and was approved by the research ethics committee of the local institution (CAAE:45576221.6.0000.0020). Since the study was retrospective and there was no direct contact with patients, informed consent was waived, in accordance with resolution 466/2012 of the Brazilian National Research Ethics Commission.

The population of the present study corresponded to the estimated 175,606 IVF cycles performed in Brazil between 2018 and 2021. This estimate was calculated from the 12th and 13th Brazilian national embryo production system protocols, which revealed the performance of 43,098 and 44,705 IVF cycles in Brazil in 2018 and 2019, respectively.¹⁶ As the protocol was not updated during the pandemic period, the study assumed that the number of cycles performed during the pandemic remained similar to the prepandemic period. The calculated sample size was 384 cycles.

The data obtained were organized in a Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheet and described as means and standard deviations (SDs) for quantitative variables and as frequencies and percentages for qualitative/categorical variables.

The authors grouped the data from 2018 and 2019 as the prepandemic group, and 2020 and 2021 as the pandemic group.

Initially, the Kolmogorov-Smirnov test was performed to verify the normal (Gaussian) distribution of the sample. Based on the results obtained, the Student t-test for independent samples was applied for parametric continuous variables ($p > 0.05$) or the Mann-Whitney test for nonparametric continuous variables ($p < 0.05$). The Pearson chi-squared test and the Fisher exact test were used for categorical variables.

Logistic regression models were adjusted for univariate and multivariate analyses of associations between independent categorical variables analyzed with a $p < 0.2$ and clinical pregnancy rates (dependent variable). A Wald test was used to assess the significance of each variable. The odds ratio (OR) was used as the estimated association measure.

The statistical analysis assumed a confidence level of 95% and a standard error of 5%. Differences were considered statistically significant at $p < 0.05$. IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA) was used for statistical calculations and inferential analyses.

Results

A total of 756 IVF cycles were analyzed, including 360 during the prepandemic period and 396 during the pandemic. Of these, 590 (78.04%) were fresh cycles (297 [82.5%] in the prepandemic group, and 293 [73.99%] in the pandemic group) and 166 (21.96%) were embryo warming cycles (63 [17.5%] in the prepandemic group, and 103 [26.01%] in the pandemic group) ($p = 0.005$) (► **Figure 1**).

Female age was 40 ± 0.8 years old prepandemic and 39 ± 0.7 years old during the pandemic ($p = 0.423$). The percentage of women ≥ 35 years old was 87.83%, with 319 (88.61%) in the prepandemic period and 345 (87.12%) in the pandemic period ($p = 0.466$). In the laboratory

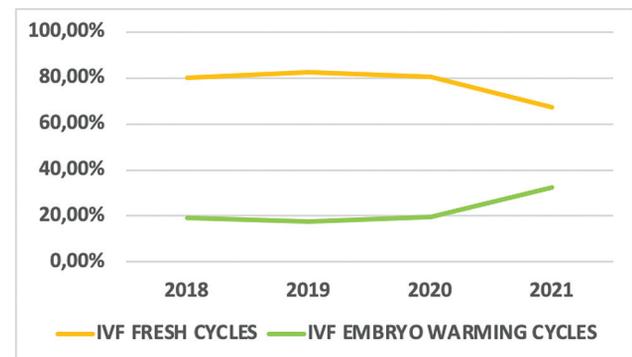


Fig. 1 Behavior changes in IVF (fresh and embryo warming cycles) during the COVID-19 pandemic. IVF: in vitro fertilization; COVID-19: coronavirus disease 2019

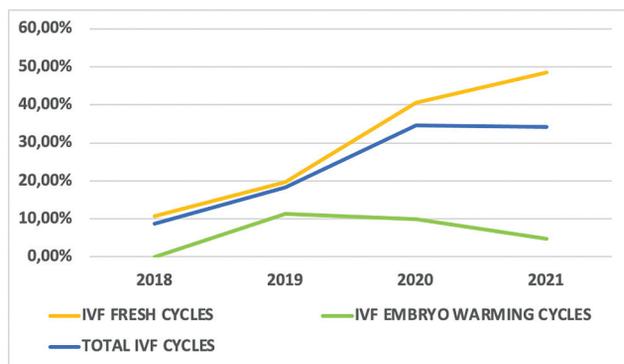


Fig. 2 Behavior changes in IVF cancellation rates (fresh and embryo warming cycles) during the COVID-19 pandemic. IVF: in vitro fertilization; COVID-19: coronavirus disease 2019

characteristics of the IVF fresh cycles, there was a recovery of 2,026 oocytes in the prepandemic period and 1,836 oocytes in the pandemic period ($p = 0.761$); the fertilization rate was 75.7% in the prepandemic period and 76.2% in the pandemic period ($p = 0.744$); the cleavage rate was 86.25% in the prepandemic period and 92.15% in the pandemic period ($p = 0.122$). The embryo warming cycles laboratory variables were not available for analysis. During the analysis period, 184 (24.34%) IVF cycles were canceled (48 [13.33%] in the prepandemic group, and 136 [34.34%] in the pandemic group) ($p < 0.001$). The cancellation rate of fresh cycles was 44 (14.81%) in the prepandemic period, which increased to 129 (44.03%) in the pandemic period ($p < 0.001$). As for the embryo warming cycles, 4 (6.35%) cycles were canceled in the prepandemic period and 7 (6.8%) in the pandemic period ($p = 0.593$) (► **Figure 2**).

A total of 572 (75.66%) IVF cycles involved ET, 312 (86.66%) in the prepandemic group versus 260 (65.66%) in the pandemic group ($p < 0.001$); regarding the fresh ET approach, there were 253 (85.18%) versus 164 (55.97%) ($p < 0.001$); as

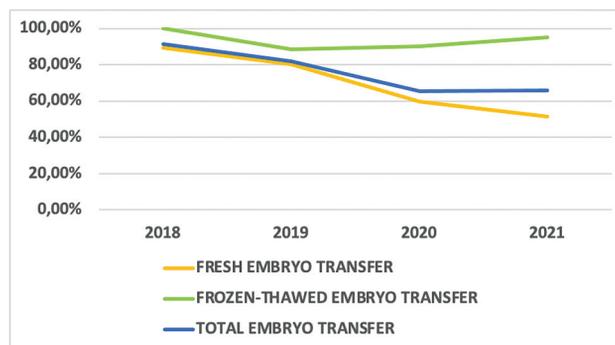


Fig. 3 Behavior changes in IVF fresh and frozen-thawed embryo transfer rates during the COVID-19 pandemic. IVF: in vitro fertilization; COVID-19: coronavirus disease 2019

for the FET approach, there were 59 (93.65%) versus 96 (93.2%) ($p = 0.482$) (► **Figure 3**).

Regarding the clinical pregnancy rates per cycle, 127 (35.28%) were in the prepandemic period versus 91 (22.98%) in the pandemic period ($p < 0.001$); pregnancies in fresh cycles with ET were 107 (36.03%) versus 67 (22.87%) ($p < 0.001$); pregnancies in embryo warming cycles with FET were 20 (31.75%) versus 24 (23.3%) ($p = 0.278$) (► **Figure 4**).

Among the analyzed categorical variables, logistic regression identified that the cancellation of IVF fresh cycles was the only factor related to a significant reduction in clinical pregnancy rates during the pandemic (OR 0.052; $p < 0.001$). The other variables did not show any statistical significance.

Discussion

At the beginning of the COVID-19 pandemic, studies focused on the SARS-CoV-2 respiratory effects and multisystemic inflammatory syndrome.¹⁷ It was only during the second wave of the disease in Canada that Madjunkov et al.¹⁸

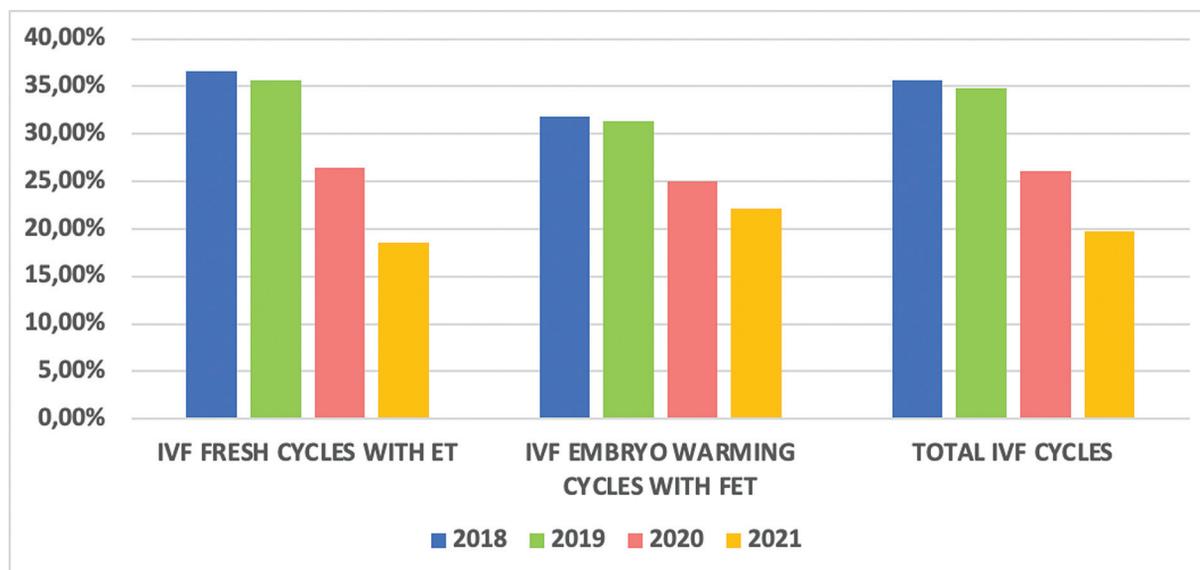


Fig. 4 Behavior changes in IVF clinical pregnancy rates (fresh cycles with ET and embryo warming cycles with FET) during the COVID-19 pandemic. IVF: in vitro fertilization; ET: embryo transfer; FET: frozen-thawed embryo transfer; COVID-19: coronavirus disease 2019

synthesized the effects of COVID-19 on biological and assisted reproduction. This review pointed to the possibility of viral tropism to angiotensin-converting enzyme 2 receptors expressed in male and female reproductive organs. It also highlights the importance of future studies that measure in precise numbers the repercussions of the pandemic on assisted reproduction technologies, considering that the observed impacts have a potential negative effect on maternal-fetal-neonatal health.¹⁸

In this context, the present study sought to fill the gap in the literature by quantifying the pandemic impacts on clinical pregnancy rates in women who underwent IVF fresh or embryo warming cycles. In Brazil, assisted reproductive technologies are not covered by the Brazilian unified public healthcare system (SUS, in the Portuguese acronym) or private health insurance plans.¹⁹ Access by interested parties depends mainly on the availability of private financial resources, implying not only the cost of fertilization cycles but also the payment of complementary exams and the purchase of medications.²⁰

The data revealed considerable differences in IVF procedures during the pandemic. A significant increase in the total number of IVFs was associated with a significant change in the pattern of cycles. In line with health authorities imposing restrictions on suspending and postponing the start of new IVF fresh cycle treatments, there was a higher prevalence of embryo warming cycles and a reduction in fresh cycles.^{5,6}

In the context of restrictive measures, human reproduction societies recommend a cryopreservation approach, preferably in patients with malignancies, autoimmune, and hematological disorders, as well as in those who need gonadotoxic treatments.^{7,8} However, women with an increased possibility of infertility (advanced age, low ovarian reserve, and/or a previous history of ovarian stimulation) were not included as priorities, which justifies the maintenance of the age pattern observed in patients who underwent IVF before and during the pandemic.^{10,21} In a study by the Ethics Committee of the American Society for Reproductive Medicine, it was found that the delay in starting treatment in these patients has devastating outcomes similar to those selected by the authorities.²² The epidemiological analysis of the literature indicates that the neglected group corresponds to ~ 30 to 50% of patients seeking IVF.^{14,23}

The IVF fresh cycle laboratory variables (number of oocytes recovered, fertilization rate, and cleavage rate) did not show significant changes between the analyzed periods. Although the embryo warming cycle laboratory variables could not be analyzed, it is hypothesized that they have also remained unchanged due to the lack of updated reference protocols.

The present study also verified that the IVF clinical pregnancy rates at the analyzed center suffered a negative impact during the pandemic. Despite the significant reduction in uterine ET rates during this period, inferential analysis attributed the cancellation of fresh cycles to this result. The literature attributes the reason for cancellations to the health restrictions imposed as well as the economic recession inherent to the pandemic.^{24,25}

Cancellation of IVF cycles has also been identified in the literature as an important trigger of emotional stress in many patients seeking treatment for infertility.^{26,27} Marom Haham⁵ revealed that despite the risks of viral contamination and vertical transmission, most patients who had their IVF cycles suspended or postponed faced episodes of anxiety and frustration as they would still like to continue the treatment. The sharp decline in fertility and the reduction in IVF success in women > 35 years old may explain why patients in this age group feel more anxious to resume treatment during the pandemic.

In view of the outcomes of COVID-19 infection during pregnancy, no major concerns have been reported. Setti et al.¹⁵ evaluated the outcomes of the first trimester of pregnancy in asymptomatic patients who were being treated with assisted reproductive technologies. The study did not demonstrate an increased risk of miscarriage, nor did it show other changes that were exacerbated during the pandemic.¹⁵ Kotlyar et al.²⁸ described that the risk of vertical transmission in the 3rd trimester of pregnancy occurs in a minority of cases without bringing greater complications to the fetus. The fear of viral contamination during pregnancy, with the possibility of harming the fetus, is not supported as a justification for the suspension of IVF cycles.¹⁸

The reduction in pregnancy rates behaved in a peculiar way depending on the IVF cycle pattern and transfer method used. Although a systematic review and meta-analysis by Zaat et al.⁹ showed an extremely small difference in pregnancy rates between the fresh ET and FET approaches, our study revealed that during the pandemic period, there was a significant reduction in pregnancy rates with the fresh ET approach, while those by FET remained unchanged. This represents the value of embryo warming cycles with FET as a viable alternative to fertility preservation in a scenario where fresh ET is limited. It is hypothesized that the reduction in pregnancy rates could have been much greater if the FETs had suffered more pronounced limitations. According to Madjunkov et al.,¹⁸ the embryo warming cycles with FET proved to be safe in avoiding viral contamination of the sample in cryopreservation laboratories due to the rigid air control systems and negative pressure chambers.

The limitations of the present study include its retrospective design, data collection from a single center, and the analysis conducted up to the moment of clinical pregnancy diagnosis. Due to unavailability of data, it was not possible to completely analyze the demographic characteristics of the patients, nor observe the evolution of pregnancy and neonatal outcomes. Thus, we encourage the performance of new multicenter studies that compare the impacts of the COVID-19 pandemic in different regions, as well as studies that evaluate the entire gestation period of patients, allowing for an understanding of the impacts of the pandemic on the quality of gestation and birth rate from IVF procedures.

Conclusion

Based on the data analysis of a tertiary-care Brazilian fertility center, the present study identified that the pandemic had a

negative impact on IVF clinical pregnancy rates, especially due to the significant increase in fresh cycle cancellation rates. The present study also highlights the value of embryo warming cycles with FET as a viable alternative to continue assisted reproductive treatments against pandemic restrictions. Although fresh cycles have been limited and many of them interrupted by health system overload that were focused on the exclusive care of COVID-19 patients, the FET approach ensured clinical pregnancy, albeit at a lower rate than the prepandemic period.

Contributions

Vieira F. A., Pasquini Neto R., and Pachniki J. P.A. contributed to the conception and design of the study. Vieira F. A. and Pasquini Neto R. performed data collection, statistical analysis, and prepared the manuscript. Morila M. C. G., Curimbaba J. B. and Pasquini D. S. assisted in the writing of the manuscript and edited the manuscript according to the journal's instructions for authors. Felchner P. C. Z., Wandresen G., and Pachniki J. P.A. helped in the interpretation of data and revised the manuscript. All authors have read and approved the final content of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Technologies Applied to the Mental Health Care of Pregnant Women: A Systematic Literature Review

Tecnologias aplicadas aos cuidados em saúde mental de grávidas: revisão sistemática da literatura

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Abstract

Objective: This article aims to review the literature regarding the use of technologies to promote mental health for pregnant women. We seek to: understand the strategies that pregnant women use for mental health care. Also, we investigate the existence of scientific evidence that validates such practices.

Methods: This study follows the PRISMA guidelines for systematic reviews. We analyze 27 studies published between 2012 and 2019. We include publications in Portuguese, English, and Spanish.

Results: The results revealed several different possibilities to use technology, including the use of text messages and mobile applications on smartphones. Mobile applications are the most commonly used approaches (22.5%). Regarding the strategies used, cognitive-behavioral approaches, including mood checks, relaxation exercises, and psychoeducation comprised 44.12% of the content.

Conclusion: There is a need for further investigation and research and development efforts in this field to better understand the possibilities of intervention in mental health in the digital age.

Keywords

- Pregnancy
- Telemedicine
- Mental health
- Prenatal care
- Pregnancy complications

Resumo

Palavras-chave

- Gravidez
- Telemedicina
- Saúde mental
- Cuidado pré-natal
- Complicações da gravidez

Objetivo: Este artigo objetiva revisar a literatura quanto ao uso das tecnologias como promotoras de saúde mental de gestantes. Desta forma, compreender quais são as estratégias utilizadas no cuidado da saúde mental dessas mulheres, assim como verificar se há evidências científicas que justifiquem a implementação dessas práticas.

Métodos: Este estudo segue o protocolo PRISMA para revisões sistemáticas de 27 estudos publicados em 2012-2019, incluindo publicações em português, inglês e espanhol.

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Resultados: Os resultados revelaram diferentes possibilidades de utilização da tecnologia, sendo o uso de mensagens de texto e de aplicativos em smartphones mais os utilizados (22,5%). No que se refere às ferramentas utilizadas, estratégias cognitivo-comportamentais, tais como verificação do humor, exercícios de relaxamento e psicoeducação compreenderam 44,12% do conteúdo.

Conclusão: Verifica-se a necessidade de mais investimentos nessa área para que se possa compreender as possibilidades de intervenção em saúde mental na era digital.

Introduction

Pregnancy is an important period in a woman's life being characterized by substantial changes. Specifically, pregnancy leads to several changes in the women's body, affecting organs, systems, and cycles, which impact physical, hormonal, and psychosocial aspects of a woman's life. Such changes also have a direct impact on the mental health of pregnant women.¹⁻⁴ Therefore, pregnancy demands specialized care for women's health. Such care is particularly important when risk factors exist.

Health outcomes for mental health during pregnancy and postpartum are linked to numerous risk factors. Risk factors include the history of mental illness, unwanted pregnancy, use of alcohol or illicit substances, low education level, financial burden, and unemployment. In addition to that hormonal changes may also result in symptoms related to anxiety and depression, which can lead to psychological suffering.⁵⁻⁷ Among protective factors that reduce risk, we can highlight prenatal care, education, and social support.^{3,8}

Among protective factors, we also remark the importance of activities that promote mental health during pregnancy. Such activities encompass multidisciplinary expertise,^{9,10} aiming to reduce risk factors while augmenting protective ones.¹¹ More specifically, mental health interventions train women by offering support, educative information, and preparation during their pregnancy, aiding pregnant women not only to recognize and express their emotions,¹² but also to learn strategies to cope with emotions.

There are several ways to provide care and support for pregnant women, including the use of technologies, mobile devices, smartphones, as well as monitoring equipment, personal assistants, and other wireless devices.¹³⁻¹⁶ The usage of technology to promote health, defined by the World Health Organization (WHO) as mobile health (mHealth), is innovative and seeks to promote prenatal care.¹⁷ The definition of mobile health (mHealth) is a "public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices" (p. 6).¹⁸ Technology usage for healthcare in general contributes to improve information dissemination. It also facilitates healthcare delivery, and coordination among specialized services. Lastly, it also involves pregnant women more closely and actively in their own healthcare practices.^{18,19}

According to recent literature reviews on mHealth during pregnancy, technological interventions that support health-care strategies result in positive outcomes, for example by accelerating the access to health services,¹⁷ reducing patients' concerns, reducing symptoms of anxiety and depression,²⁰ and managing pregnancy risks when those exist (e.g., in case of gestational diabetes).¹⁵

The type of technology used varies, ranging from web-based informative programs to remote monitoring, telehealth, mobile care, and online psychotherapy.²¹⁻²⁵ Taking into account that child-bearing age women are frequent users of technology, and the growing need to investigate evidence-based approaches around this topic,²² this paper aims to review the literature regarding the use of mHealth technologies to promote mental health for women during pregnancy and postpartum. Our goal is to better understand what the strategies are employed in mental health care for these women, as well as to identify the scientific evidence that validate such practices.

Methods

We conducted a systematic literature review seeking to analyze research studies previously published, and to systematically understand the topic of interest.²⁶ We aim to synthesize previous studies, and to obtain a unified view of research findings by following a scientific and systematic process. Therefore, we structured our systematic review based on a scientific investigation that includes several decision points regarding the inclusion and exclusion of research studies according to a pre-defined set of criteria. Our approach also seeks to assess the validity of the findings obtained with the literature review.²⁷ Specifically, the search was carried out following conventional scientific standards as outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA).²⁸

The analysis of the literature included six steps: (1) identification of the topic of interest and research questions; (2) definition of the inclusion and exclusion criteria; (3) gathering and selection of related work; (4) categorization of selected work; (5) analysis and interpretation of the results; and (6) presentation of a synthesis of the topic investigated. The inclusion criteria defined by the authors are papers published in Portuguese, English, or Spanish whose document is available online; studies published and

indexed in the following bases Lilacs, Medline/PubMed, PsycINFO, Scielo, Scopus and Web of Science; work related to the topic of interest (use of mHealth technology to promote mental health for pregnant women). The papers were selected for analysis regardless of their publication dates. For analysis, we excluded papers that present results related to babies, children, or postpartum.

The descriptors selected were also pre-defined based on terms presented in the Descriptors in Health Science (*Descritores em Ciências da Saúde* - DeCS) and Medical Subject Headings (MeSH). The search took place in January 2020, using crossed-reference descriptors and Boolean operations including terms in Portuguese, English, and Spanish. The descriptors used were: 1) Gestantes "Pregnant Women" "Mujeres Embarazadas", 2) Complicações da gravidez "Pregnancy Complications" "Complicaciones del Embarazo", 3) Transtornos mentais "Mental Disorders" "Trastornos Mentales", 4) Ansiedade "Anxiety" "Ansiedad", 5) Depressão "Depression" "Depresión", 6) Estresse psicológico "Stress, Psychological" "Estrés Psicológico", 7) Cuidado pré-natal "Prenatal care" "Atención Prenatal", 8) Sistemas de apoio psicossocial "Psychosocial Support Systems" "Sistemas de Apoyo Psicosocial", 9) Apoio social "Social Support" "Apoyo Social", 10) Fatores de risco "Risk Factors" "Factores de Riesgo", 11) Telefone celular "Cell Phone" "Teléfono Celular" e 12) Telemedicina "Telemedicine" "Telemedicina". The descriptors mentioned above were distributed in 15 search strings, defined as follows (►Chart 1).

The advanced search resulted in 1,010 papers. Two researchers used the tool EndNote Web to organize the data and followed the protocol PRISMA to proceed with the review.²⁸ Also, the authors used a validated technique²⁸ (PRISMA) to extract data directly from the primary source and as such select relevant information from the publications gathered for further analysis. The data analysis relied on descriptive statistics, and content analysis. Content analysis encompasses a series of analysis techniques for communication. It employs systematic procedures and objectives, aiming to describe the information obtained.²⁹ After reading all articles, the authors grouped the information in categories by completing a categorical content analysis. The review was not registered.

Results

Initially, we obtained 1,010 references from the databases used. After refining the search to identify duplicated work, we excluded 192 studies. Then, we discarded 681 articles, because the title of the work was not relevant to the review according to our inclusion criteria. After carefully reading the abstracts, we excluded 68 articles, and 69 publications remained for analysis. Lastly, after searching for the full documents, we excluded 42 studies because after reading the full papers of the studies we noticed that those did not meet our inclusion criteria. Thus, we obtained 27 papers for in-depth analysis, as illustrated in the ►Figure 1.

Chart 1 Search strategy

Search strings

Gestantes AND Complicações da gravidez AND transtornos mentais AND Cuidado pré-natal AND Sistemas de apoio psicossocial AND Apoio social AND Fatores de risco AND Telefone celular

Pregnant women AND Pregnancy complications AND Mental disorders AND Prenatal care AND Psychosocial support systems AND social support AND Risk factors AND Telemedicine

Pregnant women AND Pregnancy complications AND Anxiety AND Prenatal care AND Psychosocial support systems AND social support AND Risk factors AND Cell phone

Pregnant women AND Pregnancy complications AND Anxiety AND Prenatal care AND Psychosocial support systems AND social support AND Risk factors AND Telemedicine

Pregnant women AND Pregnancy complications AND depression AND Prenatal care AND Psychosocial support systems AND social support AND Risk factors AND Cell phone

Pregnant women AND Pregnancy complications AND depression AND Prenatal care AND Psychosocial support systems AND social support AND Risk factors AND Telemedicine

Pregnant women AND Pregnancy complications AND Stress psychological AND Prenatal care AND Psychosocial support systems AND social support AND Risk factors AND Cell phone

Pregnant women AND Pregnancy complications AND Stress psychological AND Prenatal care AND Psychosocial support systems AND social support AND Risk factors AND Telemedicine

Pregnant women AND Mental disorders AND Prenatal care AND Psychosocial support systems AND Risk factors AND Cell phone

Pregnant women AND Mental disorders AND Cell phone

Pregnant women AND Mental disorders AND Telemedicine

Pregnant women AND Anxiety AND Cell phone

Pregnant women AND Anxiety AND Telemedicine

Pregnant women AND depression AND Cell phone

Pregnant women AND depression AND Telemedicine

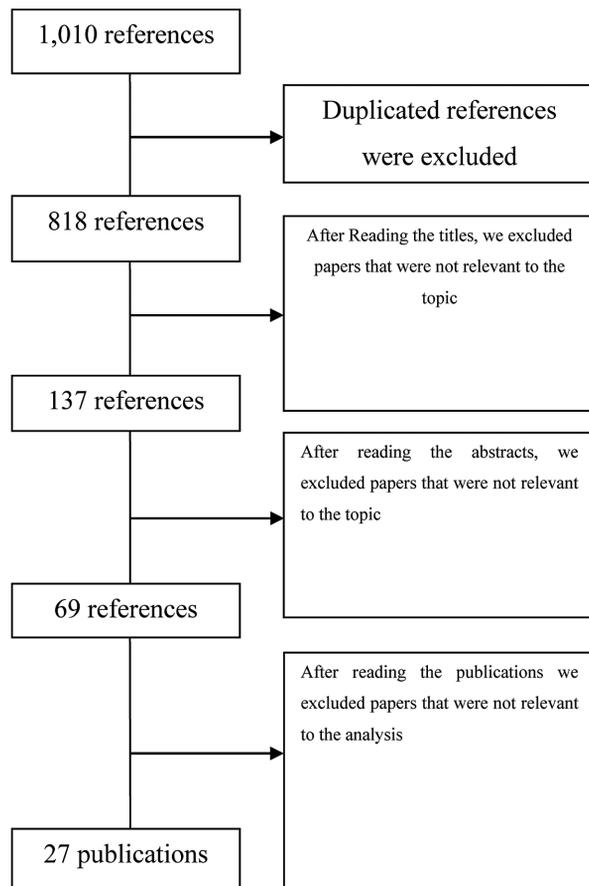


Fig. 1 Selection of related work through the application of pre-defined exclusion and inclusion criteria.

In our analysis, we identified the journals where the articles were published, to identify those that most frequently publish articles related to the topic. We noticed that the journals *Annual Review of Cybertherapy and Telemedicine*, *BMC Psychiatry*, *Journal of Medical Internet Research* and *PLOS ONE* published each two papers related to the topic. We also noticed that, based on the research field of the first author, 29.6% of the articles were led by investigators from Health Sciences, followed by Psychology (18.5%) and Psychiatry (18.5%), as listed in ► **Table 1**. Among the 27 papers analyzed, 7 (25.9%) reported literature reviews, thus we advance the

Table 1 Research fields from the first author

Research Field	Count	Percentage
Health Sciences	8	29.6
Psychology	5	18.5
Psychiatry	5	18.5
Medical Sciences	4	14.8
Nursing	2	7.4
Anthropology	1	3.7
Social Sciences	1	3.7
Health, arts, and design	1	3.7
Total	27	100.00

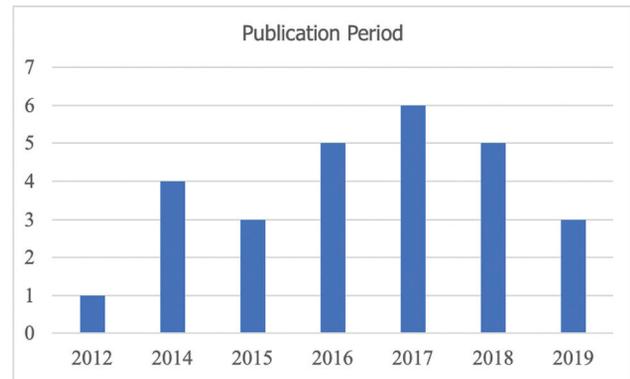


Fig. 2 Publication period.

state-of-the-art by updating the current analysis of the literature in the domain.

Our search did not return results from papers published in Portuguese, reporting studies carried out in Brazil. Moreover, the United States is the country with the largest number of studies in the domain – eight in total (29.6%), followed by Italy – with four (14.8%). Australia, Canada, United Kingdom and The Netherlands that conducted two studies each (7.4%). Also, there was only one study reported from Norway, Spain, Sweden, Germany, and Nigeria (3.7%). Lastly, the papers analyzed were published after 2012, as ► **Figure 2** shows.

Regarding the type of technology used, the use of Short Message Service (SMS) and applications for mobile phones were commonly found (9 publications each – 22.5%), followed by phone calls and telehealth in general (5 publications each – 12.5%). One result returned for strategies related to audio recordings, online therapy (self-paced), video usage, voice-over-PowerPoint, and website (2.5%). Two studies reported voice messages and computer-assisted therapy (5.0%). Two publications did not specify the type of technology used (5.0%). ► **Chart 2** summarizes the main aspects of each analyzed text, namely: main author, year of publication, study design, sample size and characteristics of the technology presented.

Regarding the information available in the technology, we conducted Content Analysis²⁹ aiming to identify the strategies used to deliver information, support, or intervention provided. We noticed a prevalent use of techniques and methods based on cognitive-behavioral approaches (44.12%). Regarding the tools available in the technology, we highlight journaling, mentioned five times (7.35%), relaxation exercises, meditation, guided imagery, and psychoeducation, which were mentioned three times (7.35%), along with non-specified techniques based on cognitive-behavioral therapy. Furthermore, strategies including sleep hygiene, *mindfulness*, breathing exercises, feedback, encouragement messages, behavioral activation, journaling, problem-solving, planning of positive activities, and self-care strategies were also listed as techniques and methods based on cognitive-behavioral approaches. The results obtained are presented in ► **Table 2**.

The period to use the tools ranged from 1 to 40 weeks, depending on the characteristics of the intervention. On

Chart 2 Characteristics of the technologies used for pregnant women care

Author Year	Study design	Study population	Sample size	Technology features
Carissoli et al. (2017) ³⁰	Longitudinal	Italian women, primiparous and in the third trimester of pregnancy	78	BenEssere Mamma is a mobile app consisting of a four-week pregnancy wellness self-help program. The app includes an experimental area with a set of daily relaxation exercises and guided imagery exercises and an emotional awareness area with a mood diary in which the user can record notes about her emotional state, thoughts and events that happen during the session.
Carissoli et al. (2016) ¹³	Longitudinal	women who participate in an aquatic gymnastics course for pregnant women, being over 18 years of age in low-risk pregnancies.	12	BenEssere Mamma is a mobile app consisting of a four-week pregnancy wellness self-help program. The app includes an experimental area with a set of daily relaxation exercises and guided imagery exercises and an emotional awareness area.
Davis et al. (2014) ¹⁴	Longitudinal	Study 1 and 2: Pregnant women attending appointments at the Obstetrics and Gynecology Clinic at the University of Kansas Medical Center	Study 1: 68; Study 2: 5	daily text messages (a total of five text messages per week, successively focused on one of three health topics) and three 20-minute voice-over-PowerPoints
Oyeyemi and Wynn (2015) ¹⁷	Revision	Healthy pregnant women in Bangkok, Thailand	68	Simple use of cell phones or radio communication to either make calls or send text messages/short message services (SMS)
Dalton et al. (2018) ³¹	Cross-sectional	Pregnant women between 10 and 14 weeks	124	Focus groups with pregnant women to define the information needed in the app, in terms of design, literature, content and usability. Control group and later the experimental group.
Chilelli et al. (2014) ¹⁵	Theoretical study Revision	Theoretical study of Telemedicine for the care of gestational risk caused by diabetes	n/a	Telemedicine has the potential to revolutionize current methods to manage pregnancy complicated by diabetes, bringing benefits to both patients and healthcare
Whittaker et al. (2012) ³²	Longitudinal	Pregnant women and mothers of infants.	100	Analysis with specialists and informal groups with pregnant women to determine the themes.
Felder et al. (2017) ³³	Longitudinal	Women at risk of postpartum depression	123	Eight-session Web-based program, with guided mindfulness and yoga practices, cognitive-behavioral strategies, and psychoeducation, consistent with MBCT
Osma et al. (2016) ³⁴	Cross-sectional	English and Spanish speaking women, currently pregnant or within 1 year of giving birth	509	Anonymous online survey to assess access to Information and Communication Technology tools, examine the frequency of searching for health information through online and mobile methods, and identify behaviors related to the access of pregnant and postpartum women to health-related applications.

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Author Year	Study design	Study population	Sample size	Technology features
Forsell et al. (2017) ²¹	Longitudinal	Pregnant women, with a gestational age between 12-28 weeks and with major depression	42	A modified version of an existing online CBT model was added/adapted to questions closer to the relationship between depression and pregnancy
Nair et al. (2018) ²²	Revision	Studies recruited postnatal, perinatal, prenatal, and postpartum women	42 to 852	Traditional phone calls, email and smartphone apps, websites, and chatrooms.
Hantsoo et al. (2017) ³⁵	Cross-sectional	Pregnant women, non-pregnant women and men	312	TTVideo - Patient conducts psychotherapy sessions with the therapist via a web camera, using video chat technology, rather than participating in in-person sessions at the therapist's office. TAComp - The patient completes the psychoeducational modules (usually CBT) through a computer interface. This is complemented with brief face-to-face sessions with a therapist. TOSelf-guided - The patient selects and administers an online program without any interaction with a therapist. The patient completes computer-based exercises at home at their own pace.
Evans et al. (2017) ¹⁶	Longitudinal	Women who started the study with scores indicative of depression	318	A nurse-delivered telephone support
Faherty et al. (2017) ²³	Longitudinal	Women attending antenatal care at an obstetric clinic affiliated with an urban teaching hospital, serving predominantly minority, racial and ethnic backgrounds, where patients are routinely screened for perinatal depression	36	An application administered by daily surveys (2 questions) and weekly (PHQ-9 and GAD-7). The app measured daily mobility (distance traveled on foot) and travel radius.
Kingston et al. (2017) ³⁶	Cross-sectional	Pregnant women	636	A web-based automated electronic screening intervention group and a paper-based control group
Bischoff et al. (2019) ³⁷	Longitudinal	Pregnant women at the end of the second trimester with or without a psychiatric diagnose.	240	Phone calls and messages from nurses to women who have had a group CBT intervention
Gureje et al. (2015) ³⁸	Longitudinal	Pregnant women with a gestational age between 16 and 28 weeks who tested positive on the Edinburgh Postnatal Depression Scale (EPDS score ≥ 12)	686	Clinical support and supervision, provided mainly by mobile phone, were provided by general practitioners and psychiatrists. Automated text voice messages, also delivered by cell phones, were used to facilitate patient adherence to clinical appointments and 'homework' tasks.

(Continued)

Author Year	Study design	Study population	Sample size	Technology features
Green et al. (2019) ²⁴	Longitudinal	Pregnant women	10	Healthy Moms, uses an existing artificial intelligence system called Tess (Zuri in Kenya) to conduct conversations with users. It works by engaging a patient in a conversation through a variety of trusted channels, including text messages (SMS).
Lee et al. (2016) ²⁵	Revision	Pregnant women	n/a	Health information via SMS, psychological intervention, and personalized exercises via audio recordings
Scherer et al. (2014) ³⁹	Longitudinal	Pregnant women between 18 and 32 weeks of gestation diagnosed with preterm delivery	1	An online self-help program for managing anxiety and stress for pregnant women with preterm labor
Gilbert et al. (2015) ⁴⁰	Longitudinal	Minority pregnant women	724	A smoking cessation program using a cell phone intervention through text messaging and medication use
van den Heuvel et al. (2018) ⁴¹	Revision	Studies reporting the use of eHealth during prenatal, perinatal, and postnatal care	1 to 1880	eHealth information and use, lifestyle, pregnancy risk, mental health, telemonitoring and teleconsultation.
Halili et al. (2018) ⁴²	Cross-sectional	Women who were pregnant or gave birth to a baby within six months of the first scheduled focus group	13	The app includes syncing with a newer © Fitbit device, the Charge 2 fitness tracker, which offers sleep, exercise, and diet tracking, as well as daily step counts, as well as mental health and mindfulness techniques that are complemented by content from the application.
Fantinelli et al. (2019) ⁴³	Revision	Telemedicine for Gestational Diabetes Mellitus: an assessment of the psychological dimensions	13	Telemedicine
Hantsoo et al. (2018) ⁴⁴	Longitudinal	Pregnant women with depressive symptoms (PHQ-9 ≥ 5) at <32 weeks of gestation	72	A mood tracking and alerting mobile app to improve mental health care delivery in a high-risk obstetric population.
Sondaal et al. (2016) ²⁰	Cross-sectional	1) Pregnant women 2) Pregnant women with HIV	1) 61 2) 40	Unidirectional text messaging
Snaith et al. (2014) ⁴⁵	Longitudinal	Low-risk nulliparous pregnant women	840	The women received a telephone support intervention

average the technology use lasted around 13 weeks. The interventions similar to the ones proposed by Carissoli et al. (2016)¹³ were shorter. Specifically, these authors investigated the user experience with a mobile app for the well-being of pregnant women, during one week, aiming to bring awareness to their affective states, besides also teaching them strategies to cope with anxiety and stress. We also found studies, like the one conducted by Gureje et al. (2015),³⁸ which were extended – initially beginning with

eight weekly sessions but including additional sessions during pregnancy on demand as well as an intervention six weeks after the birth of the child, depending on the levels of depressive symptoms notice in the mother during postpartum. In this case, specifically, the support and the clinical supervision were delivered mainly via mobile phone by doctors and psychiatrists. Besides this, they sent patients text and voice messages automatically, through mobile phones, in order to: (a) improve the compliance of

Table 2 Content Analysis for Technology Use

Categories	Strategy	Count	Percentage	Total
Cognitive behavioral therapy techniques and methods				44.12%
	Humor records	5	7.35%	
	Relaxation and stress reduction techniques	4	5.88%	
	Meditation	3	4.41%	
	Guided discovery	3	4.41%	
	Exercise not specified	3	4.41%	
	Psychoeducation	3	4.41%	
	Sleep hygiene	2	2.94%	
	Mindfulness	1	1.47%	
	Feedback/ encouragement messages	1	1.47%	
	Behavior activation	1	1.47%	
	Problem resolution	1	1.47%	
	Journaling and Thought Records	1	1.47%	
	Positive activity scheduling	1	1.47%	
	unspecified self-care	1	1.47%	
Social support				14.71%
	General social support	3	4.41%	
	Optional exercises for partners	2	2.94%	
	Support groups	1	1.47%	
	Facilitated health services	1	1.47%	
	Reminders to events, and appointments	1	1.47%	
	Contact the practitioners	1	1.47%	
	Experience reports	1	1.47%	
Mother-baby Link				2.94%
	Connecting to the bay in the womb	1	1.47%	
	Music listening	1	1.47%	
Non-psychological aspects				23.53%
	Healthy diet	4	5.88%	
	Active life	3	4.41%	
	General prenatal information	2	2.94%	
	Infectious disease	1	1.47%	
	Fetal development	1	1.47%	
	Physical changes	1	1.47%	
	Orientation for medical procedures	1	1.47%	
	Glucose level monitoring	1	1.47%	
	General postnatal information	1	1.47%	
	Breastfeeding	1	1.47%	
Substance abuse				4.41%
	Alcohol	1	1.47%	
	Tobacco	1	1.47%	
	Other substances	1	1.47%	
Not cited		5	7.35%	7.35%
Not applicable		2	2.94%	2.94%
Total		68	100%	100%

Table 3 Mental illnesses and pathologies

Pathologies	Frequency	Percentage
Depression	12	40.0
Anxiety	1	3.3
Diabetes	1	3.3
Stress	1	3.3
High risk pregnancy	1	3.3
HIV	1	3.3
Pre-term birth	1	3.3
Tobacco use	1	3.3
Not applicable	11	36.7
Total	30	100.0

patients with clinical appointments and (b) follow up on their recommendations. Additional studies applied telemedicine to monitor women throughout their pregnancies.^{16,45}

In our analysis, we investigated whether the objectives of the studies included the study of technology usage, specifically regarding certain pathologies, or co-morbidities occurring during pregnancy. As a result, we found that 59.3% (16 papers) described the usage of technology related to treat specific pathologies. Also, 40.7% (11 papers) did not mention such objective. The pathologies mentioned are listed in ► **Table 3**.

Discussion

By providing an overview of the literature, this study aimed to evaluate the applicability, the benefits, and limitation related to technology usage in prenatal care, specifically regarding mental health. This review shows that the interventions have a wide range of applications in what regards prenatal care. The categorical analysis indicates that general aspects beyond psychological factors are also covered, including clinical factors, obstetrics, and socioeconomic aspects. Thus, we noticed that the multi-disciplinary approaches are emphasized in the studies analyzed.

For example, Oliveira-Ciabati et al. (2017)⁴⁶ identified that a short text message service is potentially useful for improving coverage of antenatal health practices, including syphilis and HIV testing. However, only a fifth of eligible women showed interest in and applied to join this project. Thus, the authors recognize the importance of further encouraging participants to use such tools, realizing that there are still several obstacles that need to be overcome in order to be successful in expanding the proposed interventions.

Our results show that most studies were carried out in developed countries. Hence, it is crucial to further discuss the possibilities to implement healthcare strategies driven by

technology also in low- and middle-income countries, seeking to identify their specific characteristics, resources, contextual aspects and patients' needs. According to a report published by the Brazilian Institute of Geography and Statistics (IBGE) in 2018,⁴⁷ the Internet was used in 79.1% of Brazilian homes, but 99.2% of the homes had access to the Internet through a mobile phone. When compared to 2017, the Internet usage grew (74.9%). Still, it is important to highlight the inequalities in what regards access to Information and Communication Technologies (ICTs) seeking to provide a more democratic use for such services.

In what regards the information available through technology considering the usage of cognitive-behavioral strategies, the literature provides evidence that support the efficacy of cognitive-behavioral therapies, especially from the third-wave cognitive behavioral therapy, to improve the patients' health outcomes as well as symptoms of depression, anxiety, and overall quality of life after treatment. Furthermore, the results indicate a significant efficacy obtained when such treatments are compared to control treatments for active management of depression and anxiety.⁴⁸

Because we selected publications based on a set of pre-defined descriptors, this review is not comprehensive. Despite the limitations of this study, the results obtained contribute to augment the discussion around the usage of technology for healthcare, and specifically for Psychology. In this context, it is relevant to consider technology use for mental health along with quality of care, data security, opportunities involved, efficacy, efficiency, and patient focus. To facilitate the implementation and usage of technology strategies, policy makers must consider the international legislation to implement and validate this new format in the delivery of health services.⁴¹

Conclusion

Technology usage has been vastly explored for health interventions. Regarding their usage for mental health during pregnancy, this analysis of the literature suggests a growth in its development, as well as the need to further develop and study it in Brazil and Latin America, since we could not find any articles published in such countries. Still, these practices have a vast array of applications, for multiple purposes, even when focusing on prenatal care. Overall, we noticed a large adoption of apps and smartphones, as well as SMS. Also, technology has shown to be relevant in promoting and facilitating psychological interventions, in special using techniques and methods that adopt cognitive behavioral approaches. The duration of the interventions varied substantially, indicating diverse possibilities of use for tools and interventions in what regards screening, treating, or monitoring mental health. We highlight thus, that the use of technology for mental health among pregnant women is still being investigated as a potential mechanism for health-care delivery. In this context, despite the limitations involved in this scientific study, we notice the need to further investigate, research and develop this domain, to explore interven-

tions that could improve the quality of prenatal care, contributing to protect women's and children's health.

Conflicts to Interest

None to declare.

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Mimicking Mother Nature in the Field of Human Reproduction?

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Dear Editor,

Although humans have made significant progress in understanding reproductive events, nature still has more information to reveal. Towards the end of the 19th century, humans started studying reproductive processes such as gametogenesis, fertilization, and embryo development.¹ Since sperm and egg roles in fertilization were introduced in 1870 for the first time, reproductive biologists tried to emulate the natural reproductive processes despite the significant lack of knowledge regarding *in vivo* reproductive mechanisms. In the quest to mimic or overcome natural reproduction processes, numerous attempts have been made to produce embryos from non-germ cells.^{2,3} These trials ultimately culminated in the birth of Dolly the sheep⁴ as a result of somatic cell nuclear transfer, starting a new era of cloning or asexual reproduction. Though not fully understood at the time (1959), the work of Chang⁵ regarding the fertilization of rabbit ova *in vitro*, paved the way for the application of artificial reproductive techniques (ART) in humans. Ever since then, it has always been considered that the best evidence for these technologies to be accepted is that the progeny derived from ART are capable of reproducing naturally, especially those conceived by *in vitro* fertilization (IVF). Researchers have tried to ensure *in vitro* maturation of the spermatogonial stem cells transplanted in testes, separated into small pieces, and cultured on agarose, which migrated towards the basal membrane and settled on it, as in the *in vivo* process.⁶ On the other hand, have reported

that after ovary tissue cryopreservation and orthotopic transplantation result in a 76% spontaneous pregnancy live baby rate in 119 human females 13 out of 119 of these patients need also *in vitro* maturation of the oocytes,⁷ which allows to postulate that the cryopreservation of ovarian tissue could be a promising method to preserve fertility in humans. However, transformation of the experience and data obtained from animals to humans has been failing.

Researchers hope that during these *in vitro* processes, all the cellular events occur in exactly the same fashion as to mimic the *in vivo* scenario, ultimately resulting in new births. Hence, the importance of demonstrating that Dolly could produce offspring through natural mating. Consequently, the potential for humans to produce offspring from gametes generated *in vitro* is exciting, but in some way rather pretentious as it assumes that the events that happen *in vitro* are the same as those that occur *in vivo*. It is undeniable that all these reproductive developments have amazed society. Although there is plenty of literature supporting the possibility, there are still many key questions to be resolved, such as “What minimum number of cells to obtain a blastocyst to obtain a pregnancy, what is the relationship between the number of cells required to obtain a favorable result?”, “In case of cloning how many nuclei are needed to be injected to produce an embryo?” or the efficiency and scalability of such methods to produce enough gametes for assisted conception treatments and will they be safe to use? Undeniably it appears as if Mother Nature is reminding humans that we

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are still far from replicating the efficiency of natural reproduction. Louise Brown, the first human born through IVF (test-tube baby), is currently 43 years old and has two living children of her own from natural birth. However, more research is required to obtain better success rates and ensure these *in vitro* processes are safe in all aspects.⁸

In cattle, procedures involving *in vitro* oocyte maturation and embryo production find it difficult to achieve 40 births from 100 embryos. Furthermore, to create 100 embryos, it is necessary to start with about 400 oocytes⁹; thus, a 10-fold reduction is experienced: 400 oocytes leading to 40 births. Considering the inefficiency of *in vitro* produced embryos and the response of gametes it is about one-hundredth of that obtained by naturally produced gametes and conditions.¹⁰ An explanation could be associated with the fact that bovine blastocysts obtained *in vitro* have fewer cells than their *in vivo* counterparts.⁹ On the other hand, another example, is the need to use thousands of parental cells to obtain few colonies with spermatogenesis inside the testis, although systems should allow the generation of a larger number every day.³ It would seem very obvious to believe that researchers have been appropriating step by step every event that nature allows them to know. Two works were recently published on the generation of embryo-like structures "the first synthetic embryo" going over the interaction between intergametes: spermatozoa and oocytes.^{11,12} The living structures are expected to further a deep understanding of embryogenesis. Finally, once the problem is fully understood, as described earlier (i.e. all events contributing as a unit in its entirety), it can be concluded that nature shows plasticity on a daily basis. In the end, nature will reveal its answers progressively as knowledge translates into understanding. Ultimately it is almost as if we were to engage in dialogue with Mother Nature and asked her to reveal her secrets based on our knowledge and understanding of live births, matured eggs, spermatozoa, and oocytes potentially derived from different cell types. However, nature always has the upper hand and it is as if she would respond with: "Only when you are capable of matching some of my processes, I will let you in on the next secret step. However, it is clear that there is still a long way to go because your way of thinking possibly is not correct. Once you understand all the possibilities, you will increase the efficiency of each process you are interested in". The advances in knowledge and control of

reproductive events during the preceding 100 years are undeniable, but to try and mimic nature and expect similar results and outcomes we have to make a fundamental paradigm shift in how we approach the problem at hand. When it comes to interventions and reproduction processes in humans and other species, acceptable milestones have been achieved but that does not imply that all are acceptable and good.

Conflicts to Interest

None to declare.

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FEBRASGO POSITION STATEMENT

Fertility preservation in gynecologic cancer patients

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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.

Keypoints

- Fertility preservation in cancer patients is possible through conservative surgery or assisted reproduction techniques.
- Patients of childbearing age with a diagnosis of malignancy benefit from reproductive counseling.
- Oncological and reproductive information results in lower rates of regret, even when the patient chooses to abandon conservative treatment.
- Criteria for indicating conservative treatment in cervical, endometrial and ovarian cancer are presented in this position statement.
- Conservative treatment modalities in cervical, endometrial and ovarian cancer are discussed together with the respective oncological and reproductive outcomes.

Recommendations

- Inform the patient about the types of conservative treatment, oncological outcomes and reproductive chances.
- Patients with histological diagnosis of cervical and endometrial cancer should be properly staged by clinical examination and imaging tests. Magnetic resonance imaging (MRI) is the imaging method that best defines tumor size and preoperative extent of the neoplasm.
- In patients with early cervical cancer with squamous, adenocarcinoma, and adenosquamous histologies, possible conservative surgeries are: conization with margins free of tumor and free of high-grade squamous intraepithelial lesion (HSIL) at stage IA1 without lymphovascular space involvement (LVSI). Radical trachelectomy with pelvic lymphadenectomy at stages IA1 with LVSI, IA2 and IB1 (up to 2 cm) with or without LVSI. There is no indication of radical treatment after pregnancy.
- Other fertility-sparing surgeries on the cervix include oophoropexy and uterine transposition.
- Patients with stage IA well-differentiated endometrioid histologic type endometrial cancer may be treated with a levonorgestrel-releasing intrauterine system (LNG-IUS) and/or high-dose progestins, either orally or intramuscularly. Hysteroscopic tumor resection preceding hormone therapy has better results. After conservative treatment of endometrial cancer, it is recommended that pregnancy occurs as soon as there is neoplasm remission.
- Suspected ovarian cyst in a patient with reproductive desire should be evaluated by ultrasound performed by an experienced professional associated with tumor markers.
- Fertility-sparing surgery in ovarian cancer consists of preserving the uterus with or without preservation of the contralateral annex. Young patients with low-grade stage IA epithelial histology (G1 and G2), stage IA/IC non-epithelial histology and low malignant potential (borderline) are candidates. Complementation of surgery is recommended after the end of pregnancy for patients with invasive epithelial disease, and is not necessary for non-epithelial and borderline tumors.
- Assisted reproduction techniques, such as cryopreservation of oocyte, embryo or ovarian tissue may be necessary and thus offered to patients.

Background

Gynecological cancer directly affects fertility, as treatment consists of surgical removal of the reproductive system and/or exposure to gonadotoxic agents. However, patients in early stages who meet established criteria can be treated with fertility-sparing surgeries and reach equivalent oncological results to those of traditional treatments. Fertility preservation techniques such as cryopreservation of oocytes, embryos and ovarian tissue may also be offered in some situations. The American Society of Clinical Oncology (ASCO) has published recommendations on fertility preservation with the aim of raising awareness on the topic, and, together with the American Society for Reproductive Medicine (ASRM), they recommend that patients of childbearing age with cancer undergo reproductive counseling. These patients have lower rates of regret, even when they choose to abandon conservative treatment.⁽¹⁾ Interest in fertility preservation has increased in recent decades, both because women delay pregnancy and because of the higher incidence of cancer in young people. The incidence rate of all cancers increased by 29% between 1973 and 2015 in adolescents and young adults of both sexes.⁽²⁾ Cervical cancer in women aged 20-29 years increased annually by an average of 10.3% between 2000 and 2009.⁽³⁾ Failure to advise cancer patients about the possibilities of preserving fertility may raise questions in the future; in some countries, this is already considered medical malpractice.

Cervical cancer

Because it affects young women, has high incidence and mortality rates, cervical cancer has great importance among gynecological tumors. In the United States of America, about half of all fertile women diagnosed with early-stage cervical cancer meet the criteria for conservative surgery. Once the histological diagnosis is made, staging is the initial condition for treatment.

When are conservative surgeries indicated?

Conization: In stage IA1 without LVSI, conization or trachelectomy with surgical margins free of tumor and free of HSIL serves as diagnosis and treatment in women who wish to preserve the uterus. It should be a single non-fragmented specimen.⁽⁴⁻⁶⁾

Radical trachelectomy with pelvic lymphadenectomy: The preferred treatment in stages IA1 with LVSI, IA2 and IB1 with or without LVSI.⁽⁴⁻⁷⁾ The surgery is performed vaginally, associated with laparoscopic pelvic lymph node dissection, laparotomy abdominal approach or minimally invasive surgery (MIS), videolaparoscopic or robotically. In the International Radical Trachelectomy Assessment (IRTA) study, open surgery was compared with minimally invasive surgery, and no difference in survival and recurrence was found, although further studies are needed to confirm the safety of MIS.⁽⁸⁾

The criteria to be followed are reproductive age, desire to preserve fertility, tumors of up to 2 cm (the greatest diameter), squamous, adenocarcinoma and adenosquamous histological types, absence of parametrial invasion, lymph node metastasis and infertility. Other histological types, such as neuroendocrine and non-human papillomavirus (HPV)-associated adenocarcinoma are contraindicated for conservative treatment.⁽⁴⁻⁷⁾ Magnetic resonance imaging (MRI) is the best imaging method to assess the preoperative extent of the neoplasm, such as tumor size, depth of stromal invasion, distance between the upper part of the tumor and the internal orifice, lymph node metastasis, and parametrial invasion.⁽⁴⁻⁶⁾ Positron emission tomography (PET) is superior to MRI and computed tomography (CT) in the evaluation of lymph node metastasis.

Sentinel lymph node

The the sentinel lymph node mapping and immunohistochemical analysis is recommended for the identification of low-volume metastases (isolated tumor cells and micrometastases). The anatomopathological analysis of intraoperative frozen section has the advantage of contraindicating surgery, in addition to allowing ovarian transposition in the same surgical time. The disadvantage is the risk of not identifying low-volume metastases.⁽⁹⁾ The International Federation of Gynecology and Obstetrics (FIGO) suggests freezing sentinel lymph nodes and, if negative, completing the surgery or, alternatively, trachelectomy in a second time after the anatomopathological paraffin examination of the lymphadenectomy.⁽⁴⁾

What is the role of parametrectomy?

The need for parametrectomy in low-risk stages IA2 and IB1 is the subject of study. In a meta-analysis comparing simple trachelectomy or conization with radical trachelectomy, similar oncological results were found, with less fetal loss in the conization groups.⁽¹⁰⁾ The prospective ConCerv study comprised the analysis of simple hysterectomy or conization + pelvic lymphadenectomy in stage IB1 patients in specimens of conization with free margins, without LVSI and without suspected lymph node metastasis, squamous and adenocarcinoma histological types, and the recurrence rate was similar to that of radical treatment.⁽¹¹⁾ After the completion of two other ongoing studies – SHAPE and GOG 278 – that aim to compare the oncological results of simple hysterectomy and radical hysterectomy in early stages, the evidence will be more robust regarding the need for parametrectomy.

Tumors larger than 2 cm

In patients with tumors larger than 2 cm, neoadjuvant chemotherapy is a possibility. The cisplatin paclitaxel

regimen is the most commonly used, even though carboplatin and paclitaxel have less toxicity. A recent meta-analysis showed 39% of pathological complete response and 45.6% of partial response.⁽¹²⁾ The multicenter CONTESSA study, scheduled to end in 2025, estimates a good response in more than 70% of patients. It remains unclear if lymph node dissection should be performed before chemotherapy, if the surgery to be performed after chemotherapy is radical trachelectomy or conization, and what is the best chemotherapy regimen.

Oncology results

Conservative surgery performed according to indication criteria does not differ from radical hysterectomy in terms of oncological safety.⁽⁴⁻⁶⁾ The recurrence and 5-year mortality rates of radical trachelectomy are 3-6% and 1.6-5%, respectively.^(13,14) Two systematic reviews analyzed different approaches to radical trachelectomy. Recurrence and death from cancer were, respectively, 4% and 1.7-2% vaginally, 4.7% and 1.4% in laparotomy, and 7.5% and 1.3% in the laparoscopic route. Recurrence rates were associated with tumor size greater than 2 cm and LVSI.^(13,14)

Reproductive results

Infertility after radical trachelectomy occurs in 14-41%, and some patients may require assisted reproduction techniques.⁽¹⁵⁾ Although first trimester abortion is comparable to that of the general population, second trimester miscarriage is more frequent. Prematurity occurs in 28-38% of pregnant women and, before 32 weeks in 12%.^(14,16) Fetal loss in the second trimester and prematurity before 32 weeks result from premature rupture of membranes secondary to cervical insufficiency. Cerclage can be performed vaginally, but the abdominal route has better results. It is preferably performed at the same surgical time. Pregnancy rates range from 55-65.8% and the rate of live newborns is 70%.^(14,17) In the series by Speiser et al., of the 212 patients treated, 76 (35.8%) were planning to become pregnant up to five years after surgery. Fifty out of these 76 became pregnant, resulting in a pregnancy rate of 65.8%. However, the pregnancy rate for all 212 patients was 24% (50/212).⁽¹⁷⁾ Pregnancy is considered high risk and antenatal care is performed at a referral center. As for specific procedures to be adopted for these patients, evidence is scarce and based only on observational studies. Vaginal progesterone and cerclage, investigation of asymptomatic bacteriuria, and cervical length follow-up by ultrasound are suggested. Elective cesarean section is preferred.⁽⁹⁾

How is the follow-up performed?

Reviews every 3-4 months in the first two years, every six months from the third to the fifth year, and annual-

ly thereafter.⁽⁴⁻⁶⁾ In addition to anamnesis and physical examination, cervicovaginal cytology is recommended annually. A follow-up period of 6-12 months is advised for pregnancy.⁽¹⁾ There is no indication of radical treatment after pregnancy.

What are the alternatives for conservative surgery?

Ovarian transposition or oophoropexy conserves ovarian function by suspending the gonads out of the radiation field. The ovaries are fixed above the iliac crests and clips are placed to guide the radiotherapist. The dose of pelvic radiotherapy for cervical cancer is 40 to 50 Gy, and ovarian failure occurs at lower doses, between 2 and 12 Gy. The best results are in patients younger than 40 years and after brachytherapy, compared with external beam radiotherapy. When cryopreservation is intended, oocyte aspiration is preferably performed during surgery. Note that ovarian transposition is justified mainly for the maintenance of fertility and oocyte capture, and less justified for the maintenance of hormonal function. Another feasible surgery is uterine transposition, initially proposed for cancer of the rectum and other pelvic tumors that require irradiation. In 2020, it was described in a patient with cervical cancer undergoing fertility-sparing surgery who required external radiotherapy due to micrometastasis in pelvic lymph nodes.⁽¹⁸⁾

Endometrial cancer

It mainly affects postmenopausal women, even though 4% occur before the age of 40 years and 6.4% between 20 and 44 years of age.⁽¹⁹⁾ In these age groups, tumors are generally well differentiated. Around 10% are associated with Lynch Syndrome (LS).

How is conservative treatment performed and when is it possible?

The preservation of the uterine body, fallopian tubes and ovaries in patients with endometrial carcinoma is limited to the well-differentiated endometrioid histological type (G1), stage IA without myometrial infiltration. In addition to clinical and family history, with attention to the possibility of LS, the patient is advised about weight loss and informed about the risks and the need to complement treatment after pregnancy. Referral to a bariatric surgeon may be necessary and if there are other comorbidities, to a specialist in preconception counseling.⁽¹⁾ Magnetic resonance is the imaging method that best defines myometrial invasion, cervical invasion, and lymph node metastasis.^(20,21) The preferred conservative treatment is hormonal with oral systemic progestogen, such as medroxyprogesterone acetate (MPA) or megestrol acetate (MA), or with an intrauterine levonorgestrel device (LNG-IUD). Medroxyprogesterone acetate doses range from 2.5 to 1,500 mg/day, more frequently between 400-600 mg/day.^(20,21) The reported doses of MA

are from 10 to 400 mg/day, most commonly 160-320 mg/day.⁽²⁰⁻²²⁾ Evidence is limited on which one is more effective, what is the duration of treatment, and what is the safest dose. Some studies suggest better responses with lower doses, such as 10 mg/day of MPA and 160 mg/day of MA.^(22,23) Treatment duration varies from eight weeks to nine months. Side effects may occur, such as weight gain, thrombosis, mood swings, headache and breast tension. LNG-IUD can be used alone or in combination with systemic progestogen, with the combination considered preferred.^(1,24) Hysteroscopic resection of the tumor and adjacent endometrium preceding LNG-IUD or progestogen has better rates of complete response, higher rates of pregnancy and fewer hysterectomies.⁽²⁵⁾ Other medications are proposed, such as GnRH analogues, aromatase inhibitors and metformin. The risk of recurrence or persistent disease is greater with conservative treatment compared to hysterectomy, and surgical staging is indicated after pregnancy. Even at a presumed early stage, the risk of synchronous ovarian cancer is 4-25% in women younger than 45 years.⁽²⁶⁾ Another warning factor is the possibility that LS may be involved in the etiology of the tumor in a young patient whose molecular diagnosis is difficult with conservative treatment. An alternative to conservative surgery is preservation of only the macroscopically normal ovaries. In a study of women with G1 endometrial carcinoma under 50 years of age who underwent surgery, survival was significantly higher in the group that had their ovaries preserved given the lower cumulative risk of cardiovascular disease.⁽²⁷⁾

Oncology results

Complete response rates range from 48% to 96%, considering all types of treatment.^(24,28) Recurrence among patients who achieve complete response ranges from 25% to 47%.^(1,22,24) In terms of efficacy, oral progestogens have more side effects and greater recurrence than LNG-IUD, although data are still inconsistent.⁽²¹⁾ Treatment with LNG-IUD with or without oral progestin results in a complete response in 63-96% of patients.^(24,29,30) In a recent meta-analysis, complete response occurred in 79.7%, with 35.3% of recurrence.⁽³¹⁾ In a randomized study of patients with G1 adenocarcinoma and atypical hyperplasia treated with LNG-IUD alone compared to the combination of weight loss, and metformin use, complete response rates after six months were 61%, 67%, and 57%, respectively. Considering adenocarcinoma and atypical hyperplasia in the three groups, remission occurred in 43% and 82%, respectively.⁽³²⁾

Obstetric results

Pregnancy rates vary from 32-53% and rates of live births from 28-69.4%.^(22,31) The highest chances occur in women up to 35 years of age, with treatment

combining hysteroscopic resection + progestogens and with up to three years of follow-up.⁽³¹⁾ In the series treated with hysteroscopic resection and LNG-IUD, the rate of live births was 83% among the 63% of patients who achieved a complete response.⁽²⁸⁾ Pregnancy is recommended as soon as neoplasm remission is achieved (two negative biopsies), since there is a risk of recurrence.

How should patient follow-up be?

The patient is alerted about bleeding and given lifestyle advice. The first histological control is performed three months after the start of treatment. In the case of complete response, histological control is quarterly. Pregnancy is suggested after two negative endometrial samples.⁽¹⁾ If there is no response, increase the progestin dose and follow the quarterly control. If there is no response or progression after nine months, definitive surgical treatment is indicated.⁽²¹⁾

Ovarian cancer

Ovarian cancer is less common than cervical and uterine cancer, but it is the most lethal. Most occur after menopause and 11.8% occur before the age of 45 years, generally at an early stage and with a better prognosis.^(19,33)

How to manage the patient with a desire to become pregnant?

The evaluation of the patient with a pelvic mass includes, in addition to anamnesis and physical examination, an ultrasound performed by an experienced professional. A family history of ovarian cancer is the most important risk factor to consider. Although tumor markers help, they are unspecific; CA-125, alpha-feto-protein (α -FP), human chorionic gonadotropin (hCG) and lactate dehydrogenase (LDH) are the most used. The most frequent histological types in childhood and adolescence are germ cell types and, in reproductive adulthood, epithelial types. The patient should be informed that intraoperative frozen section has limitations, with sensitivity and specificity around 90% and 99.5%, respectively. When the frozen section diagnosis is a borderline tumor, in 21% of the cases the result in the paraffin will be an invasive tumor.⁽³⁴⁾ Therefore, the fertility-sparing surgical planning may change after the final histopathological result. For this reason, many authors suggest the management of suspicious ovarian lesions in two steps in patients who wished to maintain fertility, awaiting the definitive histopathology for decision making. Fertility-sparing surgery provides for preservation of the uterus with or without preservation of the contralateral annex. It is acceptable in young patients with low-grade stage IA epithelial histology (G1 and G2), non-epithelial germ cell and sex

cord stromal histology stage IA/IC and low malignant potential (borderline).^(35,36) Approximately one-third of borderline tumors occur in women under 40 years of age. In stage I, survival rates reach 99%, and unilateral salpingo-oophorectomy associated with collection of peritoneal lavage, omentectomy and biopsy of any peritoneal alteration is the conservative treatment option.^(35,36) Considering that the definitive histologic diagnosis may change the therapeutic plan, oocyte or embryo cryopreservation is advised in patients with an ovarian tumor suspected of malignancy.

Conservative surgery results

A systematic review of 120 studies resulted in 54% of pregnancy in patients treated conservatively for borderline tumors.⁽³⁷⁾ According to a recent study, there was no worse obstetric outcome in pregnancies after fertility-sparing surgery for ovarian cancer compared to low-risk pregnancies.⁽³⁸⁾ Complementation of surgery is recommended after termination of pregnancy for patients with invasive epithelial disease, and is not necessary for non-epithelial or borderline tumors.

How should follow-up of the patient with conservative surgery be?

Follow-up is quarterly in the first two years and every six months between the third and fifth years. Imaging examination is recommended annually.

The importance of fertility assessment and assisted reproduction techniques

Patients with cancer and the desire to preserve fertility, when evaluated by a reproduction specialist, have better conditions for a safe choice, as they receive information about age and fertility, ovarian reserve and their reproductive potential. The multidisciplinary discussion with clinical oncologist, radiotherapist, pathologist and psychologist is important for therapeutic planning and follow-up. In early stages, conservative surgeries are the first fertility-sparing options. However, it may be interesting or even necessary to add fertility preservation techniques that include oocyte, embryo or ovarian tissue cryopreservation. The first two are more widespread and in two weeks, ovarian hyperstimulation is performed. The main difference between these techniques is that the embryo belongs to the couple, while the oocyte belongs to the patient. More than half of patients with a partner prefer oocyte cryopreservation without fertilization or adhere to both techniques (oocyte and embryo cryopreservation).⁽³⁹⁾

Final considerations

Fertility-sparing treatment in women with gynecological cancer is premised on the patient's desire and po-

tential to become pregnant, although without worsening the oncological outcome. Careful selection is one of the most critical phases of this process. The care of the patient candidate for conservative treatment must be multidisciplinary in a reference center, and reproductive counseling with a specialist in assisted reproduction is recommended. Sentinel lymph node and ultrastaging is stimulated in cervical-sparing surgery. The evaluation of the ovarian reserve and of reproductive possibilities is performed by a specialist in reproduction. Assisted reproduction techniques do not compromise the outcome and can add reproductive results to conservative surgical treatment.

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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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cles 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/srqf/>

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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