# The role of parity in the mode of delivery in advanced maternal age women

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### Abstract

*Objectives: to describe the profile of Brazilian Advanced Maternal Age (AMA) women* ( $\geq$  35 years) according to parity, as well as to analyze the role of parity in the relationship between AMA and mode of delivery.

Methods: this is a cross-sectional study, based on the "Nascer no Brasil" (Born in Brazil) survey. The data were collected in 2011/2012. The chi-square test was performed to verify the association between parity and maternal, prenatal and delivery characteristics, maternal habits, pre-pregnancy diseases, maternal complications and obstetric history.

Results: of the 2,510 puerperal AMA women, 20.2% were nulliparous, 54.4% had one or two previous births and 25.4% had three or more previous births. The nulliparous women had higher schooling, higher economic class and adequate BMI, were white; and had better maternal habits when compared to multiparous. However, they were also more submitted to cesarean section, although without reported complications.

Conclusions: one cannot speak of AMA pregnant women as a homogeneous group in Brazil. There are inequalities that can be revealed via parity, since nulliparous women have maternal characteristics, habits and access to prenatal care and childbirth that are more advantageous than multiparous women.

Key words Maternal and child health, Maternal age, Complications at pregnancy, Delivery



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## Introduction

Advanced maternal age (AMA) is generally defined as the pregnancy of women 35 years or older. There has been a worldwide trend towards postponing pregnancy<sup>1,2</sup> especially in high-income countries.<sup>3</sup> In the United Kingdom, the average maternal age at birth increased considerably from 26.4 years old in the 1970s to 30.6, in 2018.4 In Spain, 38.7% of births came from mothers aged 35 or over in 2016.5 Middle and low income countries have also increased the frequency of AMA women. In Brazil, the percentage of births among AMA women doubled between 1994 and 2018, from 7.6% to 15.5%.6

The tendency to postpone motherhood has occurred due to the increase in life expectancy, the woman's search for more educational and professional opportunities, as well as the wide offer of safe contraceptive methods and greater access to assisted reproduction, 1,2,7 even if being aware of the higher chances of complications in a late pregnancy.<sup>8</sup>

Studies have shown that AMA women are more likely to have pre-gestational diseases (chronic hypertension and diabetes),<sup>9</sup> maternal complications (gestational hypertension, gestational diabetes, preeclampsia, placenta previa and placental abruption),<sup>10-12</sup> perinatal complications (low birth weight, prematurity and stillbirth)<sup>11</sup> and delivery via cesarean section.<sup>13</sup>

However, most studies have not considered the parity of AMA women as a confounding factor, since they present different maternal characteristics and outcomes.<sup>2,10</sup> In addition, in middle/low income countries, AMA women differ significantly in terms of sociodemographic characteristics and availability of obstetric services,<sup>14</sup> which is reflected in parity. In this context, this study aims to describe the profile of Brazilian AMA women ( $\geq$ 35 years) according to parity, as well as to analyze the role of parity in the relationship between AMA and mode of delivery.

### Methods

The data for the present study were obtained from the national hospital-based survey "Born in Brazil" (*Nascer no Brasil*), carried out between February 2011 and October 2012. The sample was selected in three stages. First, hospitals with 500 or more births/year were selected, which were stratified according to the macro-regions of the country (North, South, Northeast, Southeast and Midwest), location (capital or countryside) and type of sector (public, private or mixed). In the second stage, the number of days required to interview 90 puerperal women in each of the 266 hospitals selected in the first stage (minimum of 7 days) was defined, using the reverse sampling method. In the third stage, the puerperal women were sampled with an equal probability among those eligible, according to the order of occurrence of delivery. The interviews were conducted daily, including weekends and holidays by health professionals previously trained by the central research coordination team.

In the end, 23,894 face-to-face interviews were carried out with the puerperal women, whose births took place at that maternity hospital, data collection from the maternal and newborn medical records, the pregnant woman's prenatal card and ultrasound exam reports, in addition to two waves of telephone interviews with the woman after delivery (six and twelve months) and interviews with the hospital managers. Women with live birth babies, regardless of gestational age and weight, or stillborn with birth weight  $\geq$ 500g and / or gestational age  $\geq$  22 weeks, were eligible. The study excluded women who had severe mental disorders, were foreigners or indigenous people who did not understand Portuguese or were deaf.

For this analysis, only puerperal women aged  $\geq$ 35 years (AMA) were inserted, and the information contained in the hospital interview with the puerperal woman, data from the prenatal card and from the maternal medical record were used. The latter was collected after the woman's discharge or on the 42<sup>nd</sup> day of hospitalization.

Maternal characteristics were considered: maternal schooling ( $\leq 7, 8$  to 10,  $\geq 11$  years), economic classification according to the Associação Brasileira de Institutos de Pesquisa de Mercado (Brazilian Association of Market Research Institutes) (economic classes A/B - high, C medium, D/E - low ), race / skin color (white, black, mixed, yellow and indigenous), pre-gestational Body Mass Index (BMI) - Kg/m<sup>2</sup> (<18.5 - underweight; 18.5-24 - normal; 25.0-29.9 - overweight; 30.0 or more - obesity), region of residence (North, Northeast, Southeast, South and Midwest), marital status (without a partner and with a partner) and paying job (yes and no). And as maternal habits: use of tobacco during pregnancy (yes and no), consumption  $\geq$  3 cigarettes/day or  $\geq$  15 cigarettes other than every day (yes and no) and suspicion of inappropriate use of alcohol during pregnancy (yes, when the woman obtained two points or more out of a total of seven using the TWEAK instrument).15

The variables related to prenatal care and childbirth were: prenatal care (only public sector and some private sector), professional in charge of prenatal care (physician, nurse, others; or patient did not have prenatal care), type of childbirth financing (public and private), pilgrimage for childbirth failed to be served at the first maternity hospital sought for childbirth (yes / no), type of delivery (vaginal / forceps, cesarean section with labor and cesarean section without labor) and minimum overall adequacy of prenatal care (adequate, inadequate).

The minimum adequacy of prenatal care recommended by the Ministry of Health was adopted, and adapted by Domingues *et al.*<sup>16</sup> Prenatal care was considered minimally adequate when the onset of care occurred until the 12<sup>th</sup> week of pregnancy; when the number of appointments was appropriate for gestational age at delivery; when at least one of the following routine tests was carried out: syphilis serology, fasting glucose blood test, urine test, HIV serology and ultrasonography; and when the pregnant women report on the instructions regarding the reference maternity hospital for delivery.

As pre-pregnancy diseases were included: diabetes and heart disease. The maternal complications addressed were: hypertensive disease (chronic hypertension, pre-eclampsia, eclampsia or HELLP syndrome), diabetes and urinary tract infection, all classified as present or absent. The presence or absence of multiple pregnancies was also taken into account. And the obstetric antecedents addressed were: number of previous cesarean sections (none, one and two or more), previous abortion/miscarriage, history of prematurity and history of low weight, the latter classified as present or absent.

For the definition of pregnancy complications that could be associated with the indication for cesarean delivery, any record, on the prenatal card or hospital record, of any of the following situations was considered: pre-existing medical diseases, hypertensive disorders, diabetes (gestational or otherwise), HIV infection, non-cephalic presentation of the newborn, intrauterine growth restriction, oligohydramnios, polyhydramnios, isoimmunization, placenta previa, placental abruption, foetal distress, preterm labor, post-maturity, macrosomia, severe congenital malformation, iteractivity (two or more previous cesareans), failed induction of labor and complications in labor progress (cephalopelvic disproportion, dyskinesia, dystocia, uterine rupture, prolonged expulsive period and uterine atony).17

All the analyses were performed according to parity: nulliparous (women without previous delivery), one or two previous deliveries and three or more previous deliveries. Initially, to verify the difference in proportions between parity and maternal characteristics, prenatal care, childbirth, maternal habits, pre-pregnancy diseases, maternal complications and obstetric antecedents, the chisquare test (Rao-Scott) was used, considering a 95% confidence interval. Subsequently, a flowchart was performed, aiming to identify the association between any complications during pregnancy, which could be an indication for cesarean section, and the final delivery route for the birth of the fetus.

The complex design of the sampling was taken into account throughout the statistical analysis. In addition, each stratum of selection received a calibration procedure due to basic sample weights to ensure that the distribution of the puerperal mothers was similar to that observed in the births of the population sampled in 2011, deriving weighted percentages.

The research was approved by the Research Ethics Committee of the *Escola Nacional de Saúde Pública da Fundação Oswaldo Cruz*, under number. 92/2010 and 2,041,963/2017 (CAAE: 63785517. 2. 0000. 5240). Each puerperal woman's digital consent was obtained after reading the informed consent form prior to the interview.

### Results

A total of 2,510 puerperal women  $\geq$ 35 years old participated in this analysis, 507 (20.2%) were nulliparous, 1,365 (54.4%) with one or two previous births and 638 (25.4%) with three or more previous births. It is possible to observe that nulliparous women have characteristics and maternal habits quite different from women with a history of three or more previous births, while the group of one or two births has characteristics intermediate to extreme groups. Nulliparous women have higher schooling background, belong more to the economic class with greater purchasing power, are mostly white, have a higher percentage of adequate BMI, proportionally are more in the Southeast compared to the others, and almost 80% of them have paying job. In addition, they had the lowest percentages for suspecting the inappropriate use of alcohol and smoking during pregnancy (Table 1).

As for the characteristics of prenatal care and childbirth, as a reflection of a better socioeconomic conditions, nulliparous women visit more private prenatal services with at least one consultation in the private sector; were mostly cared for by physicians, had more adequate prenatal care (although this characteristic was generally poor); they wandered less after childbirth care; had more private assistance for childbirth; and underwent more cesarean section Table 1

Variables	Total (N=2,510)		Nulliparous (N=507)		1 or 2 previous births (N=1,365)		≥ 3 previous births (N=638)		<b>p</b> #
	n	%	n	%	n	%	n	%	
Mother's characteristics									
Mother's schooling (years)									<0.001
≤ 7	750	30.1	32	6.3	294	21.7	424	67.2	
8 - 10	343	13.8	41	8.1	211	15.6	91	14.4	
≥11	1,399	56.1	432	85.5	851	62.8	116	18.4	
Socioeconomic classification									<0.001
Class D+E (low)	436	17.6	24	4.8	157	11.6	255	41.1	
Class C (middle)	1,050	42.5	197	39.2	573	42.5	280	45.1	
Class A+B (high)	986	39.9	281	56.0	619	45.9	86	13.8	
Race / skin color									<0.001
White	1,021	40.7	262	51.8	588	43.1	171	26.8	
Black	213	8.5	21	4.2	120	8.8	72	11.3	
Mixed	1,250	49.8	218	43.1	645	47.3	387	60.8	
Yellow	18	0.7	5	1.0	10	0.7	3	0.5	
Indigenous	6	0.2	0	-	2	0.1	4	0.6	
Pre-pregnancy BMI (Kg/m²)									
< 18.5	79	3.1	11	2.2	48	3.5	20	3.1	0.002
18.5 – 24.9	1,258	50.1	307	60.6	673	49.3	278	43.6	
25.0 – 29.9	812	32.4	131	25.8	460	33.7	221	34.7	
≥ 30.0	360	14.3	58	11.4	184	13.5	118	18.5	
Residence region									<0.001
North	140	5.6	11	2.2	57	4.2	72	11.3	
Northeast	724	28.8	148	29.2	395	28.9	181	28.4	
Sutheast	1,127	44.9	250	49.4	626	45.8	251	39.3	
South	375	14.9	72	14.2	205	15.0	98	15.4	
Midwest	144	5.7	25	4.9	83	6.1	36	5.6	
Marital status									0.007
Without partner	323	12.9	79	15.6	142	10.4	102	16.0	
With partner	2,185	87.1	428	84.4	1,223	89.6	534	84.0	
Paying job	_, : •••				.,	•			<0.001
Yes	1,514	60.3	396	78.1	856	62.7	262	41.1	
No	995	39.7	111	21.9	509	37.3	375	58.9	
Mother's habits									
Smoking during pregnancy									<0.001
Yes	246	9.8	14	2.8	107	7.9	125	19.7	
No	2,260	90.2	493	97.2	1,256	92.1	511	80.3	
≥3 cigarettes/day or ≥15 cigarettes									
other than every day									<0.001
Yes	183	7.3	10	2.0	69	5.1	104	16.4	
Νο	2,325	92.7	498	98.0	1,295	94.9	532	83.6	

continue

#Chi-square Test.

Variables	Total (N=2,510)		Nulliparous (N=507)		1 or 2 previous births (N=1,365)		≥ 3 previous births (N=638)		p#
	n	%	n	%	n	%	n	%	
Suspected misuse of alcohol									
during pregnancy									
3 or + doses to feel high (2 points) Partner/parents complain when	114		19		44		51		
drinks (2 points)	116		9		47		60		
Usually drinks in the morning									
(1 point)	12		0		3		9		
Awoke without memory of the									
night before (1 point)	14		1		7		6		
Felt she should decrease/stop									
drinking (1 point)	133		11		56		66		
Measure of alcohol use suspicion:									<0.001
Did not drink alcohol or a point	2,308	93.5	483	95.8	1,277	95.2	548	88.1	
Two or more points	160	6.5	21	4.2	65	4.8	74	11.9	
Characteristics of prenatal and birth									
Place of Prenatal									<0.001
Only public sector	1,335	53.9	145	28.6	656	48.2	534	88.0	
Some at private sector	1,140	46.1	362	71.4	705	51.8	73	12.0	
Professional in charge of prenatal									<0.001
Physician	2,059	82.6	461	90.9	1.170	86.0	428	68.6	
Nurse	395	15.9	45	8.9	181	13.3	169	27.1	
Other	11	0.4	1	0.2	6	0.4	4	0.6	
Did not have prenatal	27	1.1	0	-	4	0.3	23	3.7	
Minimum global adequacy of prenatal									0.038
Inadequate	2,139	85.3	416	81.9	1,159	85.0	564	88.5	
Adequate	370	14.7	92	18.1	205	15.0	73	11.5	
Type of birth financing									<0.001
Public	1,632	65.0	212	41.8	817	59.9	603	94,7	
Private	877	35.0	295	58.2	548	40.1	34	5,3	
Pilgrimage for childbirth care									<0.001
Yes	354	14.1	40	7.9	198	14.5	116	18,2	
No	2,155	85.9	467	92.1	1.166	85.5	522	81,8	
Mode of delivery									<0.001
Vaginal / Forceps	850	34.6	63	12.7	401	30.2	386	61.0	
Cesarean section without labor	1,496	60.8	414	83.3	860	64.7	222	35.1	
Cesarean section with labor	113	4.6	20	4.0	68	5.1	25	3.9	

Table 1

concluded

#Chi-square Test.

without labor (Table 1).

There was no statistically significant difference between groups for pre-pregnancy diseases and maternal complications during pregnancy. For obstetric history, women with three or more previous births had more history of abortion, prematurity and

low birth weight, compared to those with one or two previous births; while for previous cesarean section, the percentages were lower (Table 2).

Approximately 65% (n=329) of nulliparous women had some pregnancy complications that could be associated with the indication for cesarean section. Of these, 91.2% had cesarean sections, with or without labor. However, among women without these complications, the rate of cesarean section was also high (n=178), about 80% (p=0.02) (Figure 1).

Among the puerperal women with one or two previous births, 58.6% (n=780) had some pregnancy complications that could be associated with the indication for cesarean section. Of these, 80.0% had cesarean sections, with or without labor. Among women without complications, cesarean delivery was 56.4% (n=550), with a significant difference (p<0.001) (Figure 2).

Among the puerperal women with three or more previous births, 59.7% (n=378) had some pregnancy complications that could be associated with the indication for cesarean section. Of these, about 57.9% had a cesarean section. Among women with no indication for cesarean section (n=255), only 10.2%

received this type of intervention (p<0.001) (Figure 3).

# Discussion

Using representative data from a Brazilian survey, it was possible to show that AMA nulliparous in Brazil had better socioeconomic conditions, maternal habits and prenatal and childbirth care when compared to multiparous women. However, they underwent cesarean sections more often, although with no reported complications. There was no statistical difference according to the parity of AMA women to pre-gestational diseases and maternal complications during pregnancy.

AMA women form a heterogeneous group in middle-income countries. Those who postpone their

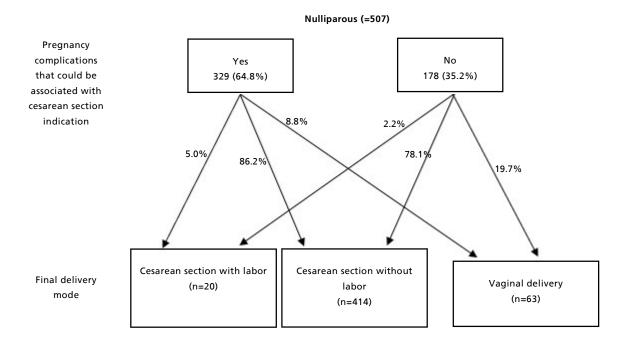
Table 2

Variables	Total (N=2,510)		Nulliparous (N=507)		1 or 2 previous births		≥ 3 previous births (N=638)		<i>p</i> #
	n	%	n	%	(N=1,365) n %		n	%	—
Pre-pregnancy diseases				,.		<i>,</i> •		<i>,</i> •	
Diabetes	67	2.8	8	1.6	41	3.0	20	3.1	0.243
Cardiac disease	29	1.2	7	1.4	13	1.0	9	1.4	0.782
Maternal complications									
Urine infection	300	12.0	53	10.4	155	11.4	92	14.4	0.146
Hypertensive disease*	521	20.8	108	21.3	261	19.1	152	23.8	0.280
Gestational diabetes	374	14.9	67	13.2	215	15.8	92	14.4	0.403
Multiple gestation	52	2.1	16	3.2	20	1.5	16	2.5	0.212
Previous obstetric history									
Previous abortion/miscarriage	755	30.1	114	22.4	402	29.5	239	37.5	<0.001
Low weigth history	274	13.7	-		130	9.5	144	22.6	<0.001
Prematury history	252	12.6	-		141	10.3	111	17.4	<0.001
Previous C-sections									
None	1,067	53.3	-		605	44.3	462	72.5	<0.001
One	678	33.9	-		593	43.4	85	13.3	
Two or more	257	12.8	-		167	12.2	90	14.1	

#Chi-square Test; \* Hypertensive disease = chronic hypertension, pre-eclampsia, eclampsia and HEELP syndrome.

#### Figure 1

Trajectory by type of delivery among nulliparous women, according to pregnancy complications that could be associated with the indication for cesarean section. Brazil, 2011-2012.



\*10 women were lost along the flowchart.

first birth to age 35 or more have more advantageous social and demographic characteristics, similar to pregnant women in high-income countries, while large multiparous women are characterized by less favorable indicators. Similar studies carried out in middle-income countries and in Brazil, also showed about 20% of the sample composed of nulliparous women<sup>1,2,18</sup> and had the highest percentages of paying jobs.<sup>2</sup>

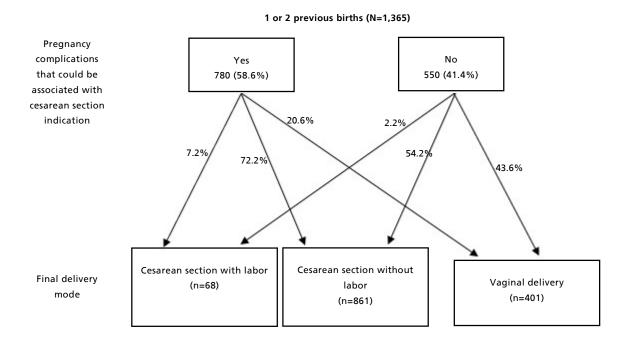
In addition, nulliparous women in middleincome countries are like AMA women in highincome countries compared to younger women, as they have higher schooling,<sup>19,20</sup> higher economic class,<sup>21</sup> race/skin color white<sup>21</sup> and adequate prepregnancy BMI.<sup>19,22</sup> On the other hand, large multiparous AMA women represent the lack of opportunity and family planning, typical of low-income countries,<sup>22</sup> as they start the experience of motherhood early and continue to generate children at an advanced age.

The broader access to schooling and paying jobs of nulliparous probably contribute to better lifestyle habits, justifying the lower percentage of tobacco and alcohol use during pregnancy. Also, the higher frequency of adequate BMI, which suggests more adherence to balanced food consumption, contributes to the achievement of more favorable obstetric results.<sup>23</sup> A Swedish study showed that about 15% of hypertensive disorders, pre-existing diabetes and gestational diabetes could be potentially avoided, due to the fact that pregnant women are not obese.<sup>24</sup>

In high-income countries, where nulliparous and multiparous women have similar socioeconomic conditions and prenatal care and childbirth, usually maternal complications, such as: hypertensive disease and gestational diabetes are more present among nulliparous.<sup>22,25</sup> However, in this study, which aimed only at describing the profile of AMA women, without controlling for confounding factors for maternal complications, parity did not influence pre-pregnancy diseases and maternal complications during pregnancy, possibly because of better socioeconomic conditions and maternal habits of nulliparous women minimized the effect of parity. Regardless of possible reasons, it is important to carefully monitor patients with such changes, as the percentage of hypertensive disease and diabetes has shown to be high and tends to increase as maternal age increases.7 Furthermore, such changes are

#### Figure 2

Trajectory by mode of delivery among women with 1 or 2 previous birth deliveries, according to pregnancy complications that could be associated with the indication for cesarean section. Brazil, 2011-2012.



\*35 women were lost along the flowchart.

responsible for negative perinatal outcomes such as admission to the intensive care unit, neonatal hypoglycemia, prematurity and newborn's difficulty of breathing.<sup>24</sup>

Combined with good socioeconomic conditions and maternal habits, nulliparous also had more access to prenatal care and childbirth in the private sector. The same was observed in urban India, a middle-low income country, where women prefer this service because they believe that the healthcare is more qualified, and especially because they think private emergency obstetric care is more easily available.<sup>26</sup>

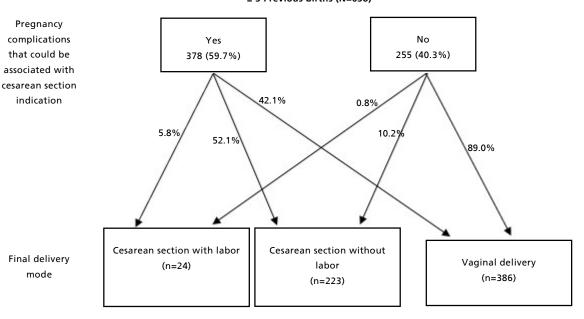
On the other hand, multiparous AMA women, associated with a history of three or more previous births, had more inadequate prenatal care and made more pilgrimage to childbirth. These results point to healthcare system failures in coordination and comprehensiveness at the time of delivery, which according to Leal *et al.*,<sup>27</sup> is associated with negative outcomes for the newborn (prematurity, low birth weight, Apgar in the 5<sup>th</sup> minute and neonatal near miss), especially in the group of pregnant women with complications, which are often not referred to hospitals with an intensive care unit, revealing the disarticulation of the system to provide highly complex care to those who really need it.

In high, middle, and low-income countries, for AMA women, the risk of cesarean delivery decreases as parity increases, showing that previous births have a beneficial effect on the cesarean rate. However, many studies do not take into account the effect of the type of cesarean section (antepartum, intrapartum or labor induction)<sup>3,10,13</sup> which can be influenced by the biological development of pregnancy, as the advanced maternal age itself implies the decline of physiological functions of the genital tract, uterine musculature and hormonal system, or by cultural and social factors, which lower the threshold for the need for cesarean sections for AMA women.<sup>18,19</sup>

In this study, about 80% of nulliparous and 10% of multiparous AMA women, without any complications that justified the indication for cesarean section, received this surgical procedure. Also, almost all of them received it, without labor, indicating a planned cesarean section. A study carried out in the Nordic countries (Denmark, Finland,

#### Figure 3

Trajectory by mode of delivery among women with 3 or more previous birth deliveries, according to pregnancy complications that could be associated with the indication for cesarean section. Brazil, 2011-2012.



≥ 3 Previous births (N=638)

\*5 women were lost along the flowchart.

Iceland, Norway and Sweden) between 2000 and 2011, found that only 2.9% of women received cesarean section without labor and about 30% of nulliparous AMA women with single pregnancy, cephalic presentation and term baby, who required induction had cesarean section as a result, while only 10% of multiparous AMA women had the same outcome.<sup>28</sup>

The higher frequency of cesarean sections among nulliparous AMA women can be justified by the mistaken theory that age itself would be a risk factor for having vaginal delivery; by the maternal preference for cesarean section; by AMA women's risk perception to lower the threshold of the obstetrician for intervention; by the fact that pregnancy is considered "precious" when the woman is at the threshold of reproductive life; and also by the professional's concern with "medical-legal problems", especially among those women who still do not have any children.<sup>19</sup>

In Brazil, the surplus difference can be justified by sociodemographic factors and characteristics of the healthcare service,<sup>29,30</sup> since in Nordic countries the social inequality is lower and the universal healthcare system covers almost 100% of the population. A study carried out in the North, South, Southeast and Midwest regions of Brazil, in public and private hospitals, corroborates this finding, as it found a higher percentage of pregnant women without comorbidities who underwent cesarean section in the group cared for at the private sector compared to the public sector.<sup>29</sup>

National and international initiatives have been carried out trying to make the birth process more physiological. Institutional strategies and organization for healthcare networks were designed so as to encourage normal delivery and reduce cesarean sections without indication. Also, criteria for elective cesarean sections were set for women with habitual risk who want this type of childbirth (from the 39th gestational week). However, advances are still little.<sup>29</sup>

Despite the comprehensive data set, the study has limitations. The design does not allow causal interpretation of the studied associations, in addition to the little control of confounding factors for maternal complications, since the objective of the study was only to describe the profile. It does not present data on assisted reproduction, which can correlate with maternal age. The indication for cesarean section is subjective and the existing classifications may not accurately reveal its indication. On the other hand, the strengths in this study are to have a representative sample of Brazil, to involve women from the public and private sector, and to analyze the cesarean section according to obstetric risk and labor.

These results expose the heterogeneity of pregnant AMA women in Brazil. Women's parity can reveal social and access inequalities, since nulliparous women had more advantageous maternal characteristics, habits and prenatal and childbirth care than women with three or more previous births. On the other hand, nulliparous women usually undergo more unnecessary cesarean sections. The Brazilian healthcare system needs to get organized in order to serve this group that is becoming increasingly expressive, offering nulliparous women the possibility of inducing labor and providing guidance on the greatest risk of unnecessary interventions, as well as meeting the demand for different family planning methods, as well as ensuring the necessary resources for large multiparous women, so that inequities are minimized during prenatal care and childbirth.

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# Authors' contribution

Study design and planning: Martinelli KG, Gama SGN, Santos Neto ET. Analysis and interpretation of data, preparation and writing of the manuscript: Martinelli KG, Gama SGN. Critical review of the manuscript: Gama SGN, Santos Neto ET. All authors approved the final version of the article.

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