Temporal analysis of maternal, care and newborns characteristics in the city of Guarapuava-PR from 2010 to 2019

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Abstract

Objectives: to analyze the temporal trend in maternal, care and newborns characteristics, in the city of Guarapuava, Paraná, Brazil in the period of 2010 to 2019.

Methods: ecological temporal tendency study is based on Sistema de Informações sobre Nascidos Vivos (Live Birth Information System). To verify changes on the topics, the Prais-Winsten generalized linear regression was applied.

Results: data from 28,919 live births were analyzed in 2019, 15.9% of the pregnancies were adolescents, 49.8% were cesarean deliveries and 9.2% were premature childbirths. A reduction in teenage pregnancy was observed, with annual percentage variation (APV) for mothers aged ten to 14 being -0.14% (p=0.005) and 15 to 19 years old -0.82% (p=0.004); there was an increase in mothers' schooling, with an APV of 60.09% (p=0.026) for eight to 11 years of schooling and 11.27% (p<0.001) for 12 or more; there was an increase of 15.33% (p<0.001) for seven or more prenatal consultations and a decrease in the Apgar classifications considering the risk, with scores from zero to two in the 1st minute with an APV=-0.12 (p=0.010) and scores from three to five in the 5th minute with APV=-0.07 (p=0.011).

Conclusions: The city of Guarapuava presents important decreased tendencies in early pregnancy and an increase in mothers' schooling, besides the changes regarding the conditions in which their children are born and how they are welcomed.

Key words *Time series studies, Health information systems, Birth certificates, Pregnancy in adolescence, Prenatal care*

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Introduction

The *Sistema de Informações sobre Nascidos Vivos* (Sinasc) (Information System on Live Births) was implemented nationally by the Ministry of Health in 1990 aiming to generate indicators on prenatal, childbirth care and the epidemiological profile on live births.[1,2] The *Declaração de Nascido Vivo* (DNV) (Live Birth Statement) is used as the standard document throughout the country.[3] Since its implementation, the system has evolved in terms of coverage and quality,[1,2] with estimated coverage of 98% in 2015.[1]

Time series studies from the 2000s onwards using Sinasc data have been carried out in local, regional and national level, showing changes in maternal, care and newborns characteristics.[4-12]

In two studies, one being local (Niterói-RJ) between 2000 and 2009[4] and the other national from 2008 to 2017,[9] there was a descrease on teenage pregnancy, but with the macro-regional diferences, the North and Northeast have the highest prevalence rates when comparing to the other macro-regions.[9] Childbirths also increased in Niterói-RJ[4] with mothers aged 35 or over and their schooling profile showed a significant improvement in the analyzed period. Another study was carried out with data from cities in the extreme South of Bahia State between 2002 and 2017 also highlights an improvement on pregnant women's schooling level of.[10]

With regard to the characteristics of care provided to pregnant women, several studies pointed out an increase of seven or more prenatal consultations,[7,10,11] although this increase is unequal when looking at schooling, race/color, age and marital status.[7,11] From the point of view in childbirth care, several studies highlight the increase in surgical birth rates.[4,5,10,12] A national survey from 2000 to 2010 showed an association between cesarean sections and an increase in maternal age and schooling,[5] and another national survey with data from 1994 to 2019 points out to a projection of 57.4% of cesarean sections in the country by 2030 and proportions of over 70% in the Southeast and South regions.[12]

Two local studies were carried out in Niterói-RJ[4] State and Botucatu-SP[6] State between 2000 and 2010 and a regional study in cities in the extreme South of Bahia State[10] between 2002 and 2007 and 2012 and 2017 that assessed newborns' characteristics shortly after childbirth, revealed an increase in prematurity[4,6,10] and a decrease in low birth weight.[4] While a national study was carried out between 2012 and 2019 reported a decreased trend in prematurity, from 10.87% to 9.95%, especially among the most vulnerable women (illiterate and indigenous);[8] also in this study, women aged 45 or over and with four to six prenatal consultations had the highest proportions of prematurity.[8]

The possibility of analyzing information from the system in a city level facilitates the planning on health actions and the implementation of programs in the area of care for women and children, and also supports the monitoring in committees of infant and maternal mortality. Considering the importance of decentralizing health actions, some studies have advocated the Sinasc data analysis at a local level,[4,6,10,13] but some cities have not yet carried out such studies.

In view of the above, the aim of this study was to describe the temporal trend on maternal, care and newborns characteristics in the city of Guarapuava-PR from 2010 to 2019, based on data obtained from Sinasc, in an attempt to ascertain whether there have been any changes in these characteristics over the evaluated time.

Methods

This is an ecological temporal trend study on maternal, care and newborns characteristics in the city of Guarapuava-PR in a ten-year period (2010 to 2019) using data available on Sinasc in 2021.

Sinasc allows the following selections: city; place of birth; mother's age, schooling and marital status; length of pregnancy; type of pregnancy; adequacy of the number of prenatal consultations; type of delivery; prenatal consultations; sex; newborn's color/race; Apgar 1st and 5th minute; birth weight; congenital anomaly and type of congenital anomaly.

The study participants were all live births and their mothers considering births by residence from 2010 to 2019, were available on Sinasc.

The maternal variables considered for the study were: age; schooling; marital status and type of pregnancy; the care variables were: place of birth; type of delivery; number of prenatal consultations; the newborns variables were: length of pregnancy; gender; color/race; 1st minute Apgar; 5th minute Apgar; birth weight and congenital anomaly.

The dependent variables were maternal, care and newborns. As an independent variable, we used the years of the time series (2010 to 2019). The categorization of most of the variables followed the distribution adopted in Sinasc and in studies based on this system and its variables.[4-6,14,15]

The data was extracted from the *Departamento de Informática do Sistema Único de Saúde* (DATASUS)[15]

(Informatics Department of the Public Health System) and entered into the Microsoft Excel® program for later analysis.

Incompleteness data was calculated based on the number of missing data for each of the maternal, care and newborns variables in the years covered by the study, using the scale suggested by Romero and Cunha[16] as a reference point: excellent, when the variable is incomplete by less than 5%; good (5 to 10%); fair (10 to 20%); poor (20 to 50%); and very poor (50% or more).

The time trend analysis of the characteristics mentioned was carried out using the generalized Prais-Winsten[17] linear regression in the IBM SPSS (Statistical Package for the Social Sciences) version 25.0. This regression method was chosen because of the autocorrelation serial often found in population data measurements.[17]

According to Antunes and Cardoso[17] the prevalence values of the maternal, care and newborn characteristics analyzed in the city should be log-transformed in order to reduce the heterogeneity of variance in the regression analysis residuals.

The rates of annual increase in the prevalence of maternal, care and newborns characteristics, as well as the respective confidence intervals, were obtained by applying the following formulas:[17,18]

$$\text{Annual increase rate}=(-1+10^{\beta})*100\%$$

$$CI95\%=-1+10^{(\beta\pm t(0.05;n-1)xEP)}$$

The regression coefficient (β) and the standard error (SE) of the beta estimate were provided by the Prais-Winsten regression, and the t-value was obtained from the two-tailed Student's t-distribution table, with a 5% significance level, considering the number of years in the series -1[10,18,19]

The time trend was interpreted by looking at the confidence interval; when the value zero was contained in the interval, the trend was considered stationary; otherwise, the trend would be increasing while the rate of increase was positive, or decreasing when it was negative, when $p<0.05$.

Due to the nature of the study and the use of a database in the public domain and without the possibility of identifying the individual, the study did not need to be assessed by a *Comitê de Ética em Pesquisa com Seres Humanos* (COMEP) (Human Research Ethics Committee), in accordance with *Conselho Nacional de Saúde* (CNS) (National Health Council) Resolution 510 of April 7, 2016.[20]

Results

Data was analyzed referring toa total of 28,919 newborns between 2010 and 2019, taking into account births per household in the city of Guarapuava-PR. Regarding data incompleteness, there was a 100% reduction in incompleteness for the variables "Apgar 1st minute" and "Apgar 5th minute", both of which went from 0.2% of ignored data in 2010 to 0% in 2019 (Table 1). The variables "mother's age", "place of birth", "type of delivery", "child's sex" and "birth weight" did not show missing records in any of the years evaluated.

Among the main maternal characteristics, the prevalence of teenage pregnancy was 22.1% in 2010 and 15.9% in 2019, as described in Table 2. Regarding the variation and trend of these characteristics, there was a decrease in the proportion of teenage mothers (10-14 and 15-19 years) and an increasing trend in the 30-34 and 35-39 age groups. The "mother's schooling" variable (in years of schooling) showed a decreased trend for lower levels of schooling (none, one to three and four to seven years) and an increased trend for higher levels of schooling (8-11 and 12 or more). As for the "mother's marital status" variable, the proportion of widowed mothers showed a decreased trend (Table 2).

With regard to the indicators related to care characteristics, Table 3 shows that more than ninety percent of births took place in hospitals. The number of births in hospitals showed a decreased trend, while the number of births in other health establishments showed an increased trend. The percentage of cesarean sections was close to that of vaginal births (50%) and the trend of vaginal and cesarean births showed a stationary trend. As for the number of prenatal consultations carried out by the mother, there was an increased trend towards seven or more consultations (Table 3).

From the data obtained on the newborns' characteristics (Table 4), prematurity, considering live births under 37 weeks, was 6% in 2010 and rose to 9.2% in 2019. For the "color/race" variable, there was a decreased trend for the identification of "white" and an increased trend for "mixed color". With regard to the Apgar score in the 1st minute of the newborns' life, there was a decreased trend for those who received a score between zero and two. As for the Apgar score in the 5th minute, there was a decreased trend in newborns classified with scores between three and five. The prevalence of low birth weight (<2,500 grams) was 8.4% in 2010 and 2019. There was a decreased trend for the birth weight ranging from 2,500 to 2,999 grams (Table 4).

Table 1

Variables with incompleteness in the Sistema de Informações sobre Nascidos Vivos (Sinasc) (Live Birth Information System) in the city of Guarapuava-PR from 2010 to 2019.

Variable	Year(s)	Incompleteness (%)	Missing data (n)
Mother's schooling	2013	0.1	3
Marital status	2011	0.6	17
	2017	0.1	2
	2019	0.4	11
Type of pregnancy	2015	0.1	4
Number of prenatal consultations	2011	0.2	7
Length of pregnancy	2012	0.3	7
	2013	0.1	3
	2016	0.1	3
	2017	0.1	2
Child's Color/Race	2012	0.1	4
	2015	0.1	3
	2017	0.1	3
	2018	0.1	3
	2019	0.2	7
Apgar score at 1st minute	2010	0.2	5
	2011	0.2	5
	2012	0.1	3
	2015	0.1	2
	2016	0.1	4
	2017	0.1	2
Apgar score at 5th minute	2010	0.2	5
	2011	0.2	5
	2012	0.1	4
	2015	0.1	2
	2016	0.1	4
	2017	0.1	2
Congenital anomaly	2011	0.1	2
	2012	0.4	10
	2013	0.1	4
	2014	0.1	2
	2015	0.1	2
	2016	0.3	8
	2018	0.2	5
	2019	0.1	2

Table 2

Variation and trends in maternal characteristics according to data from the Sistema de Informações sobre Nascidos Vivos (Sinasc) (Live Birth Information System) in the city of Guarapuava-PR from 2010 to 2019.

Maternal characteristics	% 2010	% 2019	APV	CI95%	*p**	Trend
Age (years)						
10 - 14	1.3	0.8	-0.14	-0.21; -0.06	0.005	Decreasing
15 - 19	20.8	15.1	-0.82	-0.93; -0.55	0.004	Decreasing
20 - 24	24.6	23.8	-0.07	-0.58; 1.07	0.841	Stationary
25 - 29	23.1	26.0	0.87	-0.06; 2.75	0.080	Stationary
30 - 34	17.8	18.8	0.73	0.15; 1.62	0.020	Increasing
35 - 39	9.2	12.0	1.17	0.51; 2.11	0.002	Increasing
40 - 44	3.0	3.2	0.10	-0.06; 0.29	0.190	Stationary
45 or more	0.1	0.3	0.03	-0.02; 0.07	0.233	Stationary
Schooling (Years of studying)						
None	1.0	0.2	-0.18	-0.25; -0.10	0.001	Decreasing
1 - 3	8.0	1.0	-0.82	-0.94; -0.40	0.014	Decreasing
4 - 7	34.0	15.7	-0.99	-1.00; -0.95	<0.001	Decreasing
8 - 11	40.0	57.6	60.09	1.25; 1659.00	0.026	Increasing
12 or more	17.0	25.4	11.27	4.42; 26.81	<0.001	Increasing
Marital status						
Single	66.6	67.3	0.59	-0.53; 4.41	0.418	Stationary
Married	31.9	27.3	-0.55	-0.83; 0.22	0.114	Stationary
Widow	0.5	0.2	-0.12	-0.21; -0.03	0.019	Decreasing
Separated	0.9	0.8	-0.09	-0.24; 0.10	0.303	Stationary
Consensual union	0.1	4.0	0.66	-0.54; 5.04	0.404	Stationary
Type of pregnancy						
single	98.3	98.6	0.12	-0.09; 0.38	0.246	Stationary
Double or more	1.7	1.4	-0.12	-0.28; 0.07	0.189	Stationary

APV=Annual Percentage Variation; CI=Confidence Interval; *Linear regression - *Prais-Winsten* method.

Table 3

Variation and trends in care characteristics according to data from the Sistema de Informações sobre Nascidos Vivos (Sinasc) (Live Birth Information System) in the city of Guarapuava-PR from 2010 to 2019.

Care characteristics	% 2010	% 2019	APV	CI95%	*p**	Trend
Place of birth						
Hospital	99.3	91.1	-0.89	-0.98; -0.34	0.027	Decreasing
Other health facility	0.1	8.5	8.33	0.68; 50.78	0.021	Increasing
At home	0.5	0.3	-0.02	-0.09; 0.06	0.619	Stationary
Other	0.0	0.1	0.00	-0.02; 0.03	0.713	Stationary
Type of delivery						
Vaginal	51.5	50.2	-0.29	-0.83; 2.01	0.605	Stationary
Cesarean section	48.5	49.8	0.41	-0.67; 5.01	0.605	Stationary
Number of prenatal consultations						
None	1.0	0.0	-0.21	-0.29; -0.13	0.001	Decreasing
1 - 3	3.7	3.9	0.026	-0.30; 0.51	0.883	Stationary
4 - 6	25.9	15.9	-0.92	-0.96; -0.86	<0.001	Decreasing
7 or more	69.4	80.2	15.33	7.97; 28.73	<0.001	Increasing

APV=Annual Percentage Variation; CI=Confidence Interval; *Linear regression - *Prais-Winsten* method.

Table 4

Variation and trends in newborns' characteristics according to data from the Sistema de Informações sobre Nascidos Vivos (Sinasc) (Live Birth Information System) in the city of Guarapuava-PR from 2010 to 2019.

Newborns' characteristics	% 2010	% 2019	APV	CI95%	*p**	Trend
Length of pregnancy (weeks)						
<27	0.4	0.4	-0.02	-0.09; 0.06	0.583	Stationary
28 - 31	0.6	1.3	0.05	-0.09; 0.21	0.451	Stationary
32 - 36	5.0	7.5	0.24	-0.77; 5.64	0.780	Stationary
37 - 41	93.4	90.3	0.09	-0.95; 22.39	0.949	Stationary
42 or more	0.5	0.5	-0.28	-0.80; 1.57	0.583	Stationary
Sex						
Male	50.0	51.6	0.26	-0.44; 1.88	0.538	Stationary
Female	50.0	48.4	-0.20	-0.65; 0.80	0.548	Stationary
Color/race						
White	97.6	75.3	-0.99	-1; -0.51	0.034	Decreasing
Black	0.4	1.8	0.28	-0.07; 0.74	0.121	Stationary
Yellow	0.1	0.1	-0.02	-0.12;0.09	0.686	Stationary
Mixed color	1.9	22.4	136.40	1.09; 9048.99	0.032	Increasing
Indigenous	0.0	0.2	0.02	-0.02; 0.05	0.346	Stationary
Apgar score 1st minute						
0 - 2	0.9	0.5	-0.12	-0.19; -0.04	0.010	Decreasing
3 - 5	2.5	1.3	-0.16	-0.32; 0.04	0.104	Stationary
6 - 7	6.0	4.4	-0.26	-0.59; 0.34	0.288	Stationary
8 - 10	90.4	93.8	0.87	-0.02; 2.6	0.066	Stationary
Apgar score 5th minute						
0 - 2	0.3	0	-0.10	-0.27; 0.12	0.317	Stationary
3 - 5	0.6	0.3	-0.07	-0.11; -0.02	0.011	Decreasing
6 - 7	1.2	1.0	-0.26	-0.59; 0.35	0.666	Stationary
8 - 10	97.7	98.6	0.24	-0.08; 0.66	0.152	Stationary
Birth weight (grams)						
<1,000	0.5	0.5	0	-0.06; 0.07	0.936	Stationary
1,000 – 1,499	0.5	1.0	0.04	-0.05; 0.13	0.394	Stationary
1,500 – 2,499	7.4	6.9	-0.03	-0.25; 0.25	0.804	Stationary
2,500 – 2,999	23.5	22.3	-0.40	-0.52; -0.27	0.001	Decreasing
3,000 – 3,999	64.4	65.2	0.50	0; 1.24	0.057	Stationary
4,000 or more	3.6	4.1	0.13	-0.03; 0.3	0.102	Stationary
Congenital anomaly						
Yes	0.8	0.4	-0.05	-0.16; 0.07	0.336	Stationary
No	99.2	99.5	0.06	-0.07; 0.20	0.381	Stationary

APV=Annual Percentage Variation; CI=Confidence Interval; *Linear regression - Prais-Winsten method.

Discussion

The variables analyzed using Sinasc over the ten years of the study in the city of Guarapuava-PR showed excellent data completeness. Regarding to maternal characteristics, the decrease in teenage pregnancies and the increase in maternal schooling levels were highlighted. In terms of care, there was a decrease in births in hospital environment and an increase in births in other health facilities, as well as an increase in pregnant women having seven or more prenatal consultations. Newborns showed a decreased trend in white racial identification and an increase in mixed color racial identification, as well as a decrease in lower Apgar scores in the 1st and 5th minutes.

In terms of data completeness, the city of Guarapuava showed high rates of completion, and there was a general increase on the information of the categories that had some percentage of data ignored in the initial years of the survey. According to Romero and Cunha's criteria,[16] all the variables, except marital status in 2016, had an "excellent" rating, since none of them had more than 5% incompleteness over the studied years. This quality of data is of great importance for studies such as this one, providing a basis sociodemographic analysis.[2,10,21]

With the changes made to the DNV since 2011 and the work of the Cities Health Departments in training staff to fill it out the questionnaire correctly, there has been a significant improvement in the completeness of most of the Sinasc variables.[1,14]

Despite this improvement, a review of the literature on analyzing the quality of Sinasc data points out to the main factors that can lead to ignored or blank data that still persist, such as: deficiencies related to the professional responsible for filling out the DNV, methodological problems in the definitions of how to fill in the variables and data that is difficult to obtain due to the lack of knowledge or refusal of the informant.[21]

Regarding the maternal profile, there was a reduction in teenage pregnancies, which corroborates a national study that showed a reduction of 37.2%, with the percentage of teenage mothers decreasing from 23.4% in 2000 to 14.7% in 2019.[22] While two studies were carried out in the North region reported higher prevalences of teenage pregnancy, 25.48% in Acre State between 2015 and 2019 and the values ranging from 14.2% to 21.4% in the health regions of Rondônia State in 2019.[23,24] These findings reinforce regional differences, showing that the South and Southeast regions show an improvement in this indicator when compared to the North, Northeast and Midwest regions.[9,22] The findings of trends in maternal characteristics are comparable to those studies in other Brazilian regions which have also pointed out to a reduction in teenage pregnancies,[4,9,22] an increase in the number of older mothers[4] and an increase in these women's schooling level.[4,10]

Brazil, like other developing countries, underwent significant modernizations in terms of economic and social development during the 20th century, which were accompanied by important changes in demographic issues.[25] The increase in schooling, which was related to better use of health services, associated with the greater inclusion of women in the job market and access to and improvement of contraceptive methods, has led many women to overcome social determinants and seek family planning, reducing their fertility rates and having pregnancies at older ages than before.[25,26]

Thus, the data obtained for both maternal age and schooling in the city of Guarapuava is in line with this scenario of advances in education and family planning. However, it is important for local health care to be prepared for the possible consequences of the trend towards pregnancies at older ages, in view of the repercussions as in gestational, maternal and perinatal levels.[4,25,26]

Regarding the results on women's marital status analyzed, findings in the literature describe a possible association between the absence of marital support and the tendency to manifest depressive conditions and high levels of stress among pregnant women,[23,24] while the presence of marital support was associated with greater adherence at prenatal care. Thus, the decreased trend in the prevalence of widowed mothers found may indicate a beneficial factor for the local health situation.

There was also an evidence of decreased trend for childbirths in hospitals and an increased trend in other health facilities. No studies were found that investigated changes in the pattern of seeking out other health facilities for childbirth. The literature consulted describes that in Brazil, 2-3% of childbirths take place in other health facilities that are not counted as hospital childbirths, and depending on the State and region of the country this figure can reach 9%.[27] This result requires further investigation for this change, possibly considering other variables such as maternal/family income.

Cesarean deliveries were close to the 50% level, which is high for the city, but this is the reality in cities and States that have reported figures that can reach 60% and more than 80% depending on the evaluated health region.[4,24,28] The stationary trend in cesarean deliveries should be analyzed by health managers as a result in being improved, seeking a decrease in births by this form of delivery. A study carried out in Patos de Minas-MG State between 2011 and 2015 found a significant association between surgical deliveries and maternal age over 35 and a higher number of prenatal consultations.[13]

Despite the stationary trend related to cesarean deliveries, there was an increase in the number of prenatal consultations attended by seven or more pregnant women in this study. This result represents a significant advance for the city of Guarapuava, which in 2006 stood out among the cities in the regional health district in Paraná State as having the highest rate of pregnant women with an insufficient number of prenatal consultations (51.3%).[29] This increase in adherence and access to prenatal care is also described in other national studies[1,7,11] and local data,[10,23] which signals an important advance when it comes to pregnant women and newborns' health in Brazilian cities.

The prevalence of prematurity was similar to other studies4,[24,28] and the trend in rates was stationary. Local studies was carried out in Niterói-RJ State between 2000 and 2009,[4] in Botucatu-SP State between 2001 and 2010,[6] and in States in the extreme South of Bahia between 2002 and 2007 and 2012 and 2017[10] showed an increase in the trend of prematurity, while a national study was carried out between 2012 and 2019[8] signaled a decreased trend in these rates. The cities should join forces to reduce prematurity rates by monitoring premature births, identifying their determinants and following the evolution of their occurrence in specific contexts, in order to draw up policies and early interventions for the health of pregnant women and children.[6]

There has been an increasing trend towards identifying newborns as mixed color which, from the point of view of health management, is essential to analyze vulnerabilities and intervention needs.[30] Although race/color is an objective variable, it can have a subjective classification due to the circumstances and context of the investigation.[30] In the city of Guarapuava, it was possible to verify that those responsible for the newborn seem to be more capable and confident in identifying the color of their child.

A decreased trend was recognized in some risk in the Apgar scores, an important factor for the scenario of the city, given that in the study by Melo and Mathias,[29] the city of Guarapuava stood out for its high rate of Apgar scores of less than eight in the 5th minute, a score which can indicate fetal anoxia and is related to a greater demand of resources and a greater risk of morbidity and mortality for the newborn.[3,29]

The proportion of low birth weight was similar to local and State studies,[4,24,28] and a decreased trend was identified in the birth weight ranging in 2,500 to 2,999 grams, considered as sufficient for World Health Organization standards. However, there were no changes in trends for other weight categories, which is of no concern to the city at the moment, although constant monitoring of this variable is necessary.

The limitations of this study include the use of secondary data obtained directly from Sinasc, which depends on entering the data contained in the DNV, which was not analyzed in the current study; and the fact that other variables collected in the DNV, which are not publicly available in Sinasc, such as the mother's color/race, parity and maternal occupation, were not evaluated.

The study showed changes in the maternal-infant, and care at birth characteristics in the city of Guarapuava-PR between 2010 and 2019. A new reproductive profile was observed, with a trend towards an increase in women's age and schooling, the search for health facilities other than hospitals for childbirths, as well as an increase in the number of prenatal consultations. In addition, there was a greater racial identification of the newborn, as well as some trends in relation to their survival which are extremely important for assessing the quality of the health service offered, both in prenatal care and during the perinatal period, such as the Apgar score.

Further studies are needed as for specific factors that lead to the trends in each variable and other variables included in the DNV that were not analyzed, but which may interfere with maternal and neonatal health outcomes.

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Authors' contribution

Jardim IMM: data collection, analysis and interpretation; writing and final revision of the manuscript. Melhem ARF: analysis, interpretation of data and final revision of the manuscript.

Saldan PC: study design, data analysis and interpretation, drafting and final revision of the manuscript. All the authors have approved the final version of the article and declare no conflicts of interest.

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