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Recurrence of preterm births: A population-based linkage with 3.5 million live births from the CIDACS Birth Cohort

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Abstract

Objective: To investigate the recurrence of preterm birth (PTB) among the poorest half of the Brazilian population.

Methods: A population-based retrospective study was conducted in Brazil with the live births of multiparous women extracted from the CIDACS Birth Cohort between 2001 and 2015. We used multivariate logistic regression to estimate the odds of recurrent PTB in second and third births.

Results: A total of 3 528 050 live births from 1 764 025 multiparous women were analyzed. The adjusted odds for the occurrence of a PTB given a previous PTB was 2.58 (95% confidence interval [CI] 2.53–2.62). Lower gestational age increased the odds of a subsequent PTB (<28 weeks: adjusted OR [aOR] 3.61, 95% CI 3.41–3.83; 28–31 weeks: aOR 3.34, 95% CI 3.19–3.49; and 32–36 weeks: aOR 2.42, 95% CI 2.38–2.47). Women who had two previous PTBs were at high risk of having a third (aOR 4.98, 95% CI 4.70–5.27). Recurrence of PTB was more likely when the inter-birth interval was less than 12 months.

Conclusion: In Brazil, a middle-income country, women with a previous PTB had an increased risk of a subsequent one. This association was affected by gestational age, the number of PTBs, severity of previous PTBs, and a short interval between births.

KEYWORDS
birth cohort, poor populations, preterm birth, recurrent preterm birth

1 | INTRODUCTION

Preterm births (PTBs) account for more than 10% of all births worldwide, and subsequent complications are the leading cause of death in children under the age of 5 years.[1] A preterm birth may have life-long effects, including neurological and cognitive deficits, visual and hearing impairment, and an increased risk of chronic diseases in adulthood.[2,3] Global estimates showed an increase in preterm birth

rates, from 9.8% in 2000 to 10.6% in 2014, which is equivalent to an estimated 14.64 million preterm births out of 139.95 million live births.[4] In Brazil, 11.2% of births are premature, which places the country among the 10 countries in the world with the highest PTB rates.[4]

A previous PTB has been reportedly associated with a subsequent one. Genetic, environmental, and behavioral risk factors shared between two pregnancies may contribute to the recurrence of PTB through placental dysfunction, recurrent intrauterine infections, and other obstetric complications, such as diabetes and hypertension.[5,6] A recent meta-analysis reported the absolute risk of PTB among women with a previous preterm birth to be 30%,[7] in which the earlier the gestational age of the previous birth, the higher the risk of a subsequent PTB.[8-10] However, only studies from high-income countries were included in the meta-analysis, most were hospital-based, and had a limited sample size. Data from low- and middle-income countries are in short supply. An example is a hospital-based study conducted in India with a sample of 291 women in which the PTB recurrence rate was estimated at 32%.[11]

In Brazil, a previous PTB has been identified as an important risk factor for subsequent PTBs.[12] However, there are no studies estimating the magnitude of this association. The aim of the present study was to investigate the recurrence of PTB among the poorest Brazilian population using data on more than 3.5 million live births from the Centre for Data and Knowledge Integration for Health (CIDACS) Birth Cohort. A better understanding of the magnitude and effects of a previous PTB on a future pregnancy, especially among a disadvantaged population, is essential to assist policies and individual level care.

2 | MATERIALS AND METHODS

A population-based retrospective cohort study was conducted using the CIDACS Birth Cohort. This cohort was created by linking data from the national live birth system of Brazil (Sistema de Informação sobre Nascimentos [SINASC]) and the 100 million Brazilian Cohort baseline for the period between January 1, 2001, and December 31, 2015.

The CIDACS Birth Cohort is composed of 24 695 617 live births. In general, the children included in the cohort were born from younger, unmarried, less educated mothers, and are more likely to be born via vaginal delivery, compared to children in the general Brazilian population.[13] In the present study, successive pregnancies were identified using the unique maternal identifier and the newborn's date of birth. The present study was approved by the Federal University of Bahia Collective Health Institute (ISC-UFBA) research ethics committee (CAAE registration numbers: 41695415·0·0000·5030 and 18022319·4·0000·5030) and the London School of Hygiene and Tropical Medicine (reference number 22817).

Data were obtained from SINASC. SINASC includes information on the mother (e.g., maternal age, level of education, marital status, and ethnicity), pregnancy information (e.g., antenatal appointments, length of gestation, and multiple fetuses), and information on the newborn (e.g., birth weight and sex).[14] The 100 million Brazilian Cohort is primarily built from the Cadastro Único (CadUnico), a shared register for more than 20 social programs, which covers the poorest half of the Brazilian population (families with a monthly income equal to or below three minimum wages [~750 USD]).[15]

SINASC live birth records were linked with the 100 million Brazilian Cohort using the following variables: mother's name, maternal age at birth, maternal date of birth, and the mother's municipality of residence at the time of delivery. Missing, implausible names, and duplicates were excluded. The linkage was performed using CIDACS RL-Record Linkage, a novel record-linkage tool developed to link large-scale administrative datasets at CIDACS.[16,17] Linkage procedures were conducted at CIDACS in a strict data protection environment, and according to ethical and legal regulations.[18]

The study population included live births of multiparous women aged 14–49 years, who started to be followed up in the CIDACS Birth Cohort as nulliparous. The following were excluded: multiple births, live births with congenital anomalies, those weighing less than 500 g or with a gestational age under 22 weeks, and with missing information on gestational age. Also excluded were those with a birth date before the date of the mother's entry into the cohort, and those with no information about siblings (Figure 1 and Figure S1).

The main outcome of the present study was PTBs in the second and third pregnancies, defined as a live birth at less than 37 weeks of gestation. Gestational age was defined as completed weeks. Since PTB tends to recur in a subsequent delivery, offspring were compared according to the gestational age at birth of the first pregnancy. Recurrence of PTB for the third birth was defined as a PTB after a PTB for the first and/or second pregnancy.

The following covariates were considered in the analyses: mother's residential area (urban/rural), household overcrowding (up to two inhabitants per room or more than two inhabitants per room), mother's self-declared race/skin color (white, mixed race, black, or indigenous), mother's level of education (up to 3 years, 4–7 years, or 8 years or more of formal education), mother's marital status (married: married or in a stable relationship, or unmarried: single, divorced, or widowed), number of prenatal visits (none, 1–3 visits, 4–6 visits, or 7 or more visits), inter-birth interval (less than 12 months, 12–24 months, or 24 months or more), type of delivery (vaginal or cesarean), and maternal age (14–19 years, 20–34 years, or 35–49 years). Household overcrowding, an important marker of poverty and social deprivation,[19] was calculated by dividing the number of individuals living in the house and the number of rooms. If it was impossible to estimate the inter-pregnancy interval, the inter-birth interval was estimated (in months) by the difference between the second or third child's birthdate and that of the previous child.

Logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval [CI] to estimate the association between PTB in the first pregnancy and the consequent risk in the second. The reference was the first pregnancy at term. To avoid introducing bias from factors that may have changed due to a poor outcome in the first birth, the following were adjusted for: mother's residential
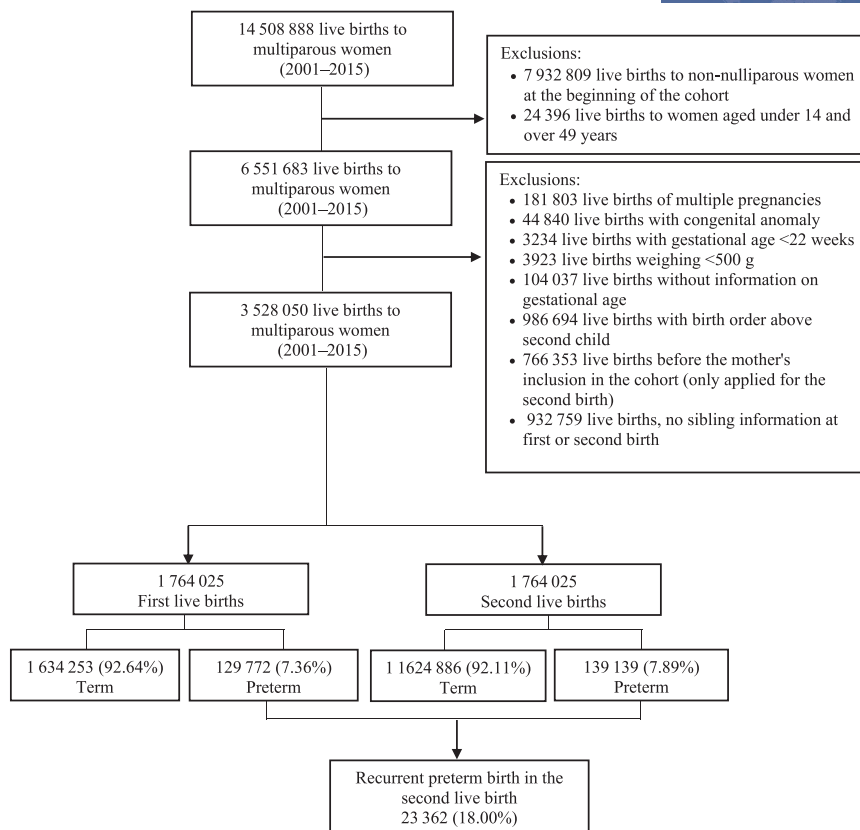
FIGURE 1 Study population flow diagram

area, family density, self-declared race/skin color, mother's level of education, marital status, number of prenatal visits, maternal age, type of delivery, and newborn's year of birth at the time of the first birth. Individuals with missing observations in any of the variables were excluded from the multiple models.

The OR of a preterm birth in the third pregnancy was also estimated using logistic regression, adjusted by the covariables mentioned above. The reference group was first and second pregnancy at term. The results of PTB were presented based on the order of birth to term and previous PTBs: Term/Term (reference category), Preterm/Term, Term/Preterm, and Preterm/Preterm.

Under the hypothesis that a short interval between pregnancies increases the chances of recurrent PTBs, an analysis was performed stratified by the inter-birth interval (less than 12 months, 12–24 months, and 24 months or more).

Additional analyses were performed with live births after 2011 due to changes in the gestational age in the live birth records on SINASC from this date[20] (Supplementary Material).

All data were processed and analyzed using STATA version 15.1 (StataCorp., College Station, TX, USA).

3 | RESULTS

The CIDACS Birth Cohort population is composed of 14 508 888 live births from multiparous women. After applying the exclusion

criteria, 3 528 050 live births from 1 764 025 multiparous women were selected to participate in this study. Overall, 129 772 (7.36%) of the women had a PTB in the first pregnancy and 139 139 (7.89%) in the second, 23 362 (18.00%) of which were classified as a recurrent PTB (Figure 1). The population characteristics according to the PTB status in the first pregnancy are described in Table 1. Compared to term live births, preterm live births were more likely among younger mothers who live in crowded households and who had attended fewer prenatal care appointments (Table 1).

The adjusted PTB OR after a previous PTB was 2.58 (95% CI 2.53–2.62) compared to a first birth at term. It was also observed that most of the second PTBs occurred in the same gestational age group as the first birth (Figure 2). Lower gestational age at the first birth increased the odds of a subsequent PTB (32–36 weeks: adjusted OR [aOR] 2.42, 95% CI 2.38–2.47; 28–31 weeks: aOR 3.34, 95% CI 3.19–3.49; <28 weeks: aOR 3.61, 95% CI 3.41–3.83) (Figure 3).

Live births to women with PTBs in the two previous pregnancies (compared to those of women with two at term births) were 4.98 (95% CI 4.70–5.27) times more likely to result in a third PTB. The OR of a third pregnancy with a premature delivery was 2.42 (95% CI 2.34–2.50) among live births of women with a first birth at term, followed by a PTB, and higher than among women with a PTB first followed by a second birth at term (OR 1.73, 95% CI 1.67–1.80) (Figure 4).

The analyses stratified by the inter-birth interval showed that the shorter the interval, the greater the risk of a recurrent PTB. The risk of recurrence was higher in the inter-birth interval of less than

TABLE 1 Mother's sociodemographic characteristics, prenatal care, and type of delivery on the first birth, 2001–2015 (n=1 764 025)[a]

First birth variables	Missing data	Total population (n = 1 764 025)	Term birth (n = 1 634 253)	Preterm birth (n = 129 772)
Urban/rural area of residence				
Urban	72 395 (4.10)	1 303 734 (77.07)	1 205 132 (76.88)	98 602 (79.46)
Rural		387 896 (22.93)	362 403 (23.12)	25 493 (20.54)
Household overcrowding				
≤2 inhabitants per room	131 777 (7.47)	1 015 851 (62.24)	946 688 (62.60)	69 163 (57.67)
>2 inhabitants per room		616 397 (37.76)	565 627 (37.40)	50 770 (42.33)
Maternal race/ethnicity				
White	144 507 (8.19)	541 650 (33.45)	501 731 (33.44)	39 919 (33.55)
Brown/Mixed race "parda"		934 694 (57.71)	866 655 (57.76)	68 039 (57.17)
Black		132 622 (8.19)	122 564 (8.17)	10 058 (8.45)
Indigenous		10 552 (0.65)	9564 (0.64)	988 (0.83)
Maternal level of education				
≥8 years of formal study	26 192 (1.48)	951 910 (54.78)	881 011 (54.72)	70 899 (55.48)
4–7 years of formal study		654 220 (37.65)	605 495 (37.61)	48 725 (38.13)
≤3 years of formal study		131 703 (7.58)	123 538 (7.67)	8165 (6.39)
Marital status				
Married, civil union	21 486 (1.22)	542 199 (31.12)	503 711 (31.20)	38 488 (30.00)
Single, divorced, widowed, widow		1 200 340 (68.88)	1 110 540 (68.80)	89 800 (70.00)
Number of prenatal visits				
None	16 542 (0.94)	22 373 (1.28)	18 614 (1.15)	3759 (2.93)
1–3		143 507 (8.21)	119 919 (7.41)	23 588 (18.41)
4–6		670 595 (38.38)	610 347 (37.69)	60 250 (47.03)
≥7		911 006 (52.13)	870 501 (53.76)	40 505 (31.62)
Maternal age at birth (years)				
14–19	0 (0.0)	1 057 494 (59.95)	972 640 (59.52)	84 854 (65.39)
20–34		697 675 (39.55)	653 556 (39.99)	44 119 (34.00)
35–49		8856 (0.50)	8057 (0.49)	799 (0.61)
Type of delivery				
Vaginal	1622 (0.09)	1 104 033 (62.64)	1 020 453 (62.50)	83 580 (64.46)
Cesarean		658 370 (37.36)	612 288 (37.50)	46 082 (35.54)

[a]Values are given as number (percentage).

12 months (aOR 2.86, 95% CI 2.60–3.15), followed by 12–24 months (aOR 2.54, 95% CI 2.45–2.63) and 24 months or more (aOR 2.53, 95% CI 2.48–2.58) (Table 2). It was also observed that the live births of women with two previous PTBs and an inter-birth interval of less than 12 months were more likely to have a third PTB (aOR 6.53, 95% CI 4.91–8.69), followed by 12–24 months (aOR 5.52, 95% CI 4.96–6.14) and 24 months or more (aOR 4.69, 95% CI 4.31–4.98) (Table 3).

An analysis restricted to births after 2011 had similar aORs (Tables S1 and S2).

4 | DISCUSSION

In the present study, live births to women with a previous PTB were over twice as likely to have a subsequent PTB, compared to those

with a birth at term on their first pregnancy. In addition, the lower the gestational age at the first birth, the higher the odds of a subsequent PTB. The third birth of women with two previous PTBs was five times more likely to be a PTB when compared to those with two previous at term births. For women with a history of one previous PTB and one previous term birth, the closer the last PTB, the higher the risk of a PTB in the third pregnancy.

The present study has the largest sample size to estimate the risk of PTB in a second or third subsequent pregnancy using a population-based approach and conducted in a middle-income country. Although the association between PTB in a previous and subsequent pregnancy had been observed, the mechanisms underlying this association are not well understood. It has been suggested that specific maternal factors can predispose women to PTBs, since they have been associated with repeated placental complications,
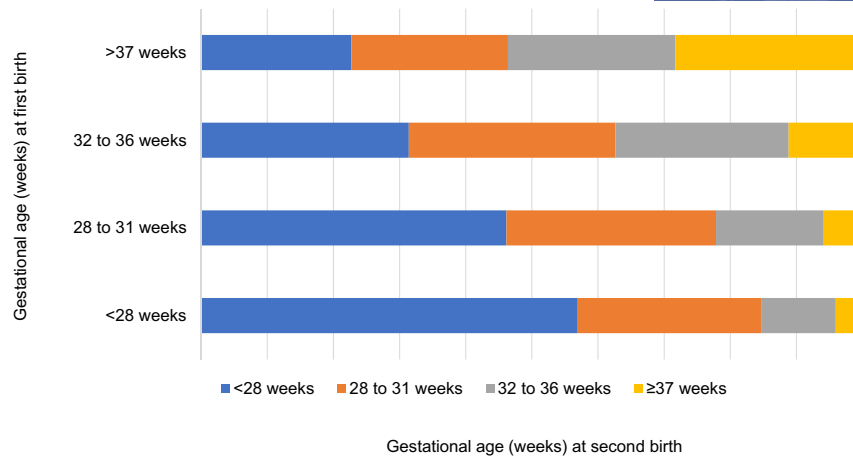
FIGURE 2 Gestational age at second birth by gestational age on the first birth

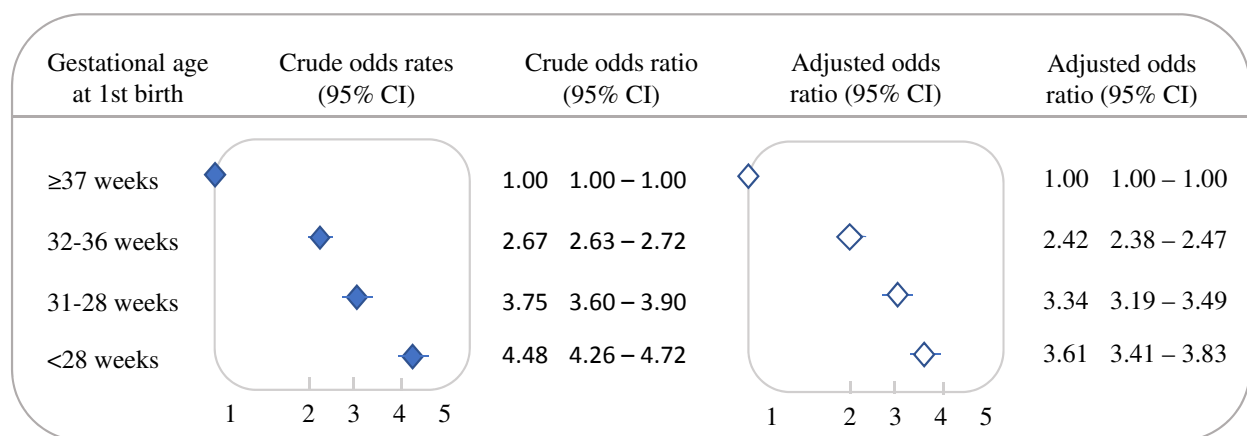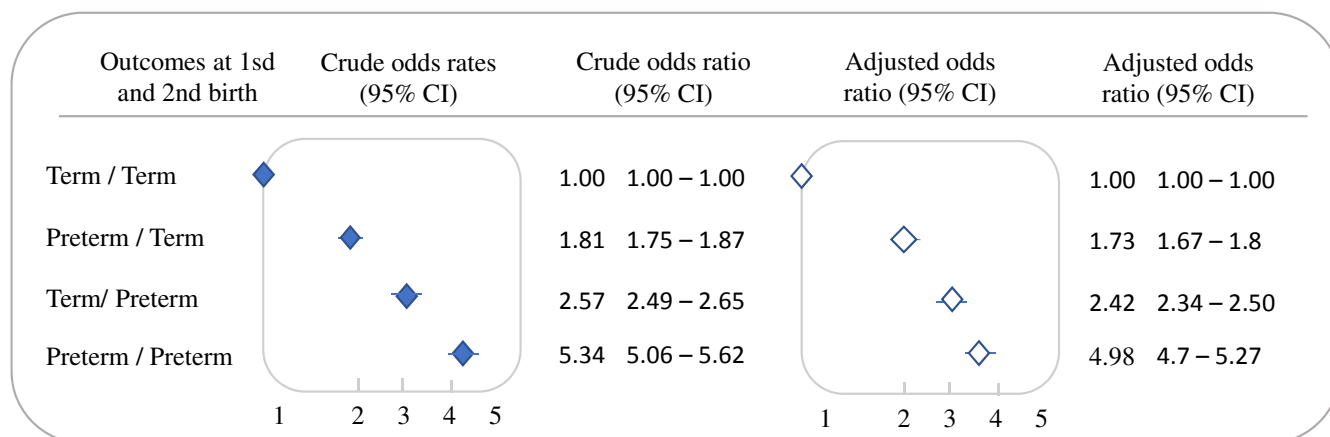| Gestational age at 1st birth	Crude odds rates (95% CI)	Crude odds ratio (95% CI)		Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	
≥37 weeks		1.00	1.00 − 1.00		1.00	1.00 − 1.00
32-36 weeks		2.67	2.63 − 2.72		2.42	2.38 − 2.47
31-28 weeks		3.75	3.60 − 3.90		3.34	3.19 − 3.49
<28 weeks		4.48	4.26 − 4.72		3.61	3.41 − 3.83

FIGURE 3 Recurrent preterm birth (<37 weeks of gestation) in the second pregnancy by gestational age of the first birth, 2001–2015 ($n = 1\,764\,025$). Unadjusted (filled diamonds) and adjusted (open diamonds) odds ratio by mother's residential area, household overcrowding, mother's self-declared race/skin color, mother's level of education, mother's marital status, number of prenatal visits, maternal age, type of delivery, and newborn's year of birth at the time of the first birth. Abbreviation: CI, confidence interval

and are more susceptible to recurrent intrauterine infections and underlying disorders between pregnancies (e.g., diabetes and hypertension).[5] Similarly, risk factors shared between pregnancies (e.g., smoking during pregnancy) may also contribute to the recurrence of a PTB.[6,21]

The risk of a subsequent PTB increased as the inter-birth interval decreased. The biological mechanisms that may explain this finding are related to the time it takes for the uterus to return to its normal state, including resolution of the inflammatory condition associated with the previous pregnancy.[5] A further explanation is the depletion of maternal vitamins and folate, since maternal stores of essential vitamins, minerals, and amino acids are consumed during pregnancy, and a short interval decreases the opportunity to replace these nutrients between pregnancies.[5,22]

The results described in this study are consistent with the literature,[8,9,21,23] except that the estimates of risk in these studies were much higher for the subsequent second or third birth. The reasons for these differences are unclear, but may be due to the

differences in data sources, or the populations studied. One potential explanation for these differences may be that some studies included stillbirths in their analyses.[8,9] The number of stillbirths that occur before 37 weeks of gestation is much higher than the number of preterm live births, which may increase the magnitude of the association. A further difference is the population in the present study; only the poorest population from a middle-income country was included. Therefore, there is a more comprehensive array of structural and social causes associated with the occurrence of a PTB, which may have influenced the observation of the underlying biological probabilities estimated in the study. In all analyses, adjusting for demographic and obstetric factors reduced the estimated risk for recurrent preterm delivery, suggesting that unmeasured variables other than those observed, including the presence of chronic maternal diseases and infections, access to health care, and other social determinants (which are not available in the present dataset), may play an important role in the occurrence of PTBs. The third point is the sample size, which was

Outcomes at 1sd and 2nd birth	Crude odds rates (95% CI)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Term / Term	◆	1.00 1.00 – 1.00	◇	1.00 1.00 – 1.00
Preterm / Term	◆	1.81 1.75 – 1.87	◇	1.73 1.67 – 1.8
Term/ Preterm	◆	2.57 2.49 – 2.65	◇	2.42 2.34 – 2.50
Preterm / Preterm	◆	5.34 5.06 – 5.62	◇	4.98 4.7 – 5.27

FIGURE 4 Recurrent preterm birth (<37 weeks) in the third pregnancy by term vs preterm birth in the first and second births, 2001–2015 (n = 544 665). Unadjusted (filled diamonds) and adjusted (open diamonds) odds ratio by mother's residential area, household overcrowding, mother's self-declared race/skin color, mother's level of education, mother's marital status, number of prenatal visits, maternal age, type of delivery, and newborn's year of birth at the time of the first birth. Abbreviation: CI, confidence interval

TABLE 2 Premature birth (<37 weeks of gestation) on the second live birth by preterm birth in the first live birth and inter-birth interval, 2001–2015 (n = 1 764 012)[a]

		Preterm on second birth	
Inter-birth interval (months)	Preterm on first birth (weeks)	Unadjusted	Adjusted[b]
<12	≥37	Reference	Reference
	<37	3.48 (3.21–3.77)	2.86 (2.60–3.15)
12–24	≥37	Reference	Reference
	<37	2.97 (2.88–3.06)	2.54 (2.45–2.63)
≥24 months	≥37	Reference	Reference
	<37	2.70 (2.65–2.75)	2.53 (2.48–2.58)

[a]Values are given as odds ratio (95% confidence interval).

[b]Analysis adjusted by mother's residential area, household overcrowding, mother's self-declared race/skin color, mother's level of education, mother's marital status, number of prenatal visits, maternal age, type of delivery, and newborn's year of birth at the time of the first birth.

small and hospital-based in some studies, and this may have led to an overestimation of the measures, due to the inclusion of a higher proportion of high-risk pregnancies.[21,23] Finally, this difference may have occurred due to the misclassification of PTBs in the Brazilian dataset. SINASC gathers secondary data on gestational age at birth. However, until 2010 the gestational age at birth was collected over wide intervals of weeks of gestation,[20] and the prematurity rate was considered underestimated when compared to results from local studies with primary data collection.[24] From 2011, although SINASC started to collect the gestational age as a continuous variable, the mother's last menstruation was prioritized as a method of calculating the gestational age in weeks.[20] This can be a flawed method, due to circumstances such as individual variations in the length of the menstrual cycle and recall biases in particular.[24]

It is known that effective preventive measures and interventions during pregnancy can reduce the biological, social, and behavioral risk factors associated with PTBs.[25] Services provided during prenatal care

for all pregnant women and women at high risk of PTB should include the identification and treatment of pre-existing conditions (e.g., diabetes, asthma, and other chronic conditions), sexually transmitted diseases, and other infections and pregnancy complications (e.g., hypertensive disorders of pregnancy and antepartum hemorrhage), nutritional support, including multiple nutrient supplementation, and counseling to reduce risky behaviors, among others.[25,26] There is increasing, almost universal coverage of prenatal care in Brazil. However, regional and social inequalities persist in the access to adequate prenatal care, contributing to the high rates of premature birth observed in the country.[27]

The present study has both strengths and weaknesses. It is the first study to assess the recurrence of PTB in a poor population of a middle-income country. The large sample size enabled the analysis of the recurrence of PTB in subsequent second and third births, and to perform an analysis stratified by the interval between births. However, the present study has a number of limitations. The first is regarding the use of secondary data. The proportion of PTBs

TABLE 3 Recurrent preterm birth (<37 weeks) on the third live birth by term vs preterm birth on the first and second live births and inter-birth interval, 2001–2015 (n = 544 665)[a]

Inter-birth interval (months)	First and second birth outcomes	Preterm on third birth	
		Unadjusted	Adjusted[b]
<12	Term/Term	Reference	Reference
	Preterm/Term	1.91 (1.55–2.35)	1.75 (1.38–2.21)
	Term/Preterm	3.36 (2.88–3.93)	3.15 (2.65–3.74)
	Preterm/Preterm	7.55 (5.88–9.70)	6.53 (4.91–8.69)
12–24	Term/Term	Reference	Reference
	Preterm/Term	1.83 (1.71–1.96)	1.71 (1.58–1.85)
	Term/Preterm	2.77 (2.62–2.93)	2.59 (2.43–2.76)
	Preterm/Preterm	6.03 (5.48–6.63)	5.52 (4.96–6.14)
≥24	Term/Term	Reference	Reference
	Preterm/Term	1.79 (1.72–1.86)	1.74 (1.66–1.82)
	Term/Preterm	2.37 (2.27–2.46)	2.28 (2.18–2.38)
	Preterm/Preterm	4.79 (4.49–5.12)	4.64 (4.31–4.98)

[a]Values are given as odds ratio (95% confidence interval).

[b]Analysis adjusted by mother's residential area, household overcrowding, mother's self-declared race/skin color, mother's level of education, mother's marital status, number of prenatal visits, maternal age, type of delivery, and newborn's year of birth at the time of the first birth.

recorded on SINASC-Brazil was found to be underestimated by 15%,[28] and misclassification, based on the criteria used to assess the gestational age at birth information (the date of the last menstrual period in most cases), may have occurred. However, they are probably non-differential errors and, therefore, the results of the present study may be underestimated, that is, the magnitude of the association found may be even higher than that found in the present analysis. In addition, it was not possible to classify the PTB subtypes (spontaneous, or with medical indication) due to a lack of information in our dataset. Second, residual confounding is possible, since data on maternal health conditions (e.g., co-morbidities such as diabetes and infections), as well as access, the quality of local health services, or special care for women with high-risk pregnancies, were not available in the present dataset. In addition, the database does not allow for the evaluation of whether cases with previous PTBs had any intervention in subsequent pregnancies. Third, the present study was conducted among the poorest population of a middle-income country with a history of major social and health inequalities, which may limit the generalizability of these findings.

In conclusion, the present study showed an increased risk of a subsequent PTB in women who had a PTB in their previous pregnancy. This association was affected by gestational age, the number and order of previous PTBs, and the interval between births. These findings may contribute to clinical practice, the care of women with a history of previous PTBs, and to support policies for the prevention of high-risk pregnancies and PTBs. The study highlights the importance of expanding access and the quality of prenatal care, introducing protocols for early identification, and the clinical management of women with a previous PTB, or who are at risk of a PTB, including a previous PTB birth, and applying timely therapeutic approaches. Further research is recommended to analyze the impact of effective interventions in reducing the rates of PTB. Furthermore, studies are required in different low- and middle-income settings to uncover more evidence in such contexts, and for subsequent investigations according to PTB subtypes.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

ASR and RCRS conceptualized and designed the study, drafted the initial manuscript, carried out the analyses, and revised the

manuscript. ESP, MFA, and RLF conceptualized and designed the study, contributed to data interpretation, and critically reviewed the intellectual content of the manuscript. ILR, FJAO, and NO contributed to data analysis, interpretation, and critical review of the manuscript. MLB, LCR, and MYI conceptualized and designed the study, acquired data, contributed to data interpretation, and critically reviewed the intellectual content of the manuscript. All authors approved the final submitted version of this manuscript, and accepted accountability for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data described in the manuscript, code book, and analytic code will be made available upon request.

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