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Factors Associated with Prematurity: A Case-Control Study

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ABSTRACT

Background: The rate of premature births has been increasing in recent years and preterm birth figures as one of the main causes of infant mortality. **Objective:** To identify the factors associated with prematurity. **Methods:** This is a case-control study conducted in a municipality in the northeast of Brazil between August and December 2015, using data from the Brazilian live birth information system (SINASC) and the Four-Leaf Clover Strategy Database. Information was collected on the conditions of pregnancy, prenatal care, and delivery. Live newborns with gestational age (GA) less than 37 weeks were considered as cases, and live births with GA ≥37 weeks as controls. **Result:** The study consisted of 339 live births, with 147 premature newborns - the cases, and 192 term children - the controls. For the cases, in the univariate analysis, mothers who delivered one or more children weighing <2,500g, use of cigarettes, fewer prenatal consultations, fewer ultrasound scans, complications during pregnancy, less dental care during pregnancy, and hospitalization during pregnancy presented statistical significance when compared to controls. The hierarchical multiple logistic regression analysis showed that mothers who had <7 consultations during prenatal care ($p<0.01$) and those who had hospitalization during pregnancy ($p<0.01$) were more likely to have preterm delivery. **Conclusion:** In this study, the variables associated with prematurity were hospitalization during pregnancy and the number of prenatal consultations being less than seven. In summary, it is necessary to understand all the factors involved with prematurity and to be attentive during prenatal care to minimize their effects.

INTRODUCTION:

In the past two decades, Brazil has experienced a significant decrease in infant mortality, from 47.1 deaths per 1,000 live births in 1990 to 12.8 in 2017.[1]Although neonatal mortality (0 to 27 days) has been reduced by more than half, from 23.1 deaths per thousand live births in 1990 to 9.5 in 2017,[2]it remains at high levels, when comparing this rate in more developed countries.

Among the leading causes of infant deaths are perinatal factors: prematurity, perinatal infections, asphyxia/hypoxia, and maternal factors. Congenital malformations that lead to death considered non-preventable are responsible for only 20% of deaths.[3]In the first year of life, prematurity is one of the main perinatal causes that lead to death, and it is one of the greatest challenges for reducing infant mortality.[4]

Recently, the prevalence of preterm births in Brazil, as well as in the world, has been increasing.[5] The Brazilian Health Report – 2019[1] presented an increase in the prematurity rate, from 7.01 in 2010 to 11.8 in 2017, with an increase in the proportion of deaths related to this cause. From this, it is possible to identify how prematurity configures a high risk of death in the first year of life.

Knowing the risk factors that are associated with prematurity, as well as the protective factors to prevent preterm births, is of great importance for the performance of managers and health professionals when aiming to improve the conditions of delivery and survival of children. Based on this understanding, this study aimed to identify the factors associated with prematurity.

MATERIALS AND METHODS:

This is a case-control study using data from the Brazilian live birth information system (SINASC) and the Four-Leaf Clover Strategy Database, a municipal database. The Four-Leaf Clover Strategy is responsible for a systematic daily collection of data on prenatal care, delivery, and condition of the newborn in the municipality through interviews and questionnaires with mothers in all the maternity clinics and hospitals in the municipality of Sobral, Ceará. This information enables the monitoring of the quality of prenatal care, delivery, and the birth conditions of the neonates.

Data was collected on the conditions of pregnancy, prenatal care, and delivery. The study was carried out in the municipality of Sobral, located in the northeast of Brazil, with an estimated

population of 210,711 inhabitants.[6] The data obtained refer to live births between August and December 2015. Ultrasound scans performed before 20 gestational weeks were used to calculate gestational age (GA). Live newborns with GA less than 37 weeks (as defined by the World Health Organization)[7] were considered as cases, and live births with GA ≥37 weeks as controls. The selection of cases and randomized controls was performed during the same period. All birth data was extracted from the SINASC and the Four-Leaf Clover Strategy databases. Newborns with malformations incompatible with life and premature fetuses weighing less than 500g were excluded from the study.

The outcome variable was preterm birth, and the study variables were subdivided into 5 blocks: I - Sociodemographic characteristics of the pregnant woman; II - Maternal reproductive history; III –Conditions of pregnancy; IV- Prenatal care and complications during pregnancy; and V – Conditions of delivery.

The variables were analyzed for association with those that could be identified as risk or protective factors for preterm birth. Fisher's exact test was performed to identify an association between the independent variables and the outcome. A significant association was considered when the p-value was less than 0.05. To perform the multivariate analysis, the logistic regression technique was used with significant variables ($p<0.05$) and variables that did not present statistical significance, but with $p<0.20$, being selected to compose the model. Univariate and multivariate data analysis was performed using SPSS version 20.0.

The experimental proposal was submitted to the Scientific Committee of the Secretariat of Health of Sobral, protocol number 0011/2016 and approved by the Research Ethics Committee of the State University Vale do Acaraú, protocol number 1,590,501.

RESULT AND DISCUSSION:

RESULTS

The study consisted of 339 live births, with 147 premature newborns - the cases, and 192 term births - the controls. To preterm infants, 67 (45.6%) weighed less than 2,500g and 80 (54.4%) weighed ≥2,500g. Among the controls, 9 (4.7%) had weight <2500g. In the cases, 11 (7.5%) were classified as extremely preterm infants (≤28 weeks), 19 (12.9%) were moderately

premature infants (28 to 31 weeks) and 117 (79.6%) were mildly preterm infants (32 to 36 weeks), according to the Lumley classification.[8]

Block I - Sociodemographic characteristics of the pregnant women: maternal age, place of residence, marital status, ethnic group/skin color, maternal education, and monthly income were assessed. No variable showed a significant difference between the case and control groups ($p<0.05$), and no variable was classified for the multivariate model ($p<0.20$).

Block II - Maternal reproductive history: in the univariate analysis, 'the number of children <2,500g'variable presented a significant difference between the case and control groups ($p<0.05$), with mothers who had one or more children weighing less than 2,500g being more prevalent in the case group. In addition to this, the 'vaginal delivery' and 'inter delivery interval variable was classified for multivariate analysis (Table 1).

Table No. 1: Variables related to maternal reproductive history and its relationship with prematurity in Sobral-CE, 2015

Variable	Case (premature NB)		Control		p
	n	%	n	%	
Previous pregnancy					
None	65	44.2	90	46.9	0.63
One or more	82	55.8	102	53.1	
Abortions					
None	50	61.0	67	65.7	0.50
One	27	32.9	26	25.5	
Two	2	2.4	6	5.9	
Three or more	3	3.7	3	2.9	
Number of live births					
None	4	4.9	7	6.9	0.83
One	44	53.7	56	54.9	
Two	23	28.0	24	23.5	
Three	7	8.5	7	6.9	
Four or more	4	4.9	8	7.8	
Number of stillbirths					
None	78	95.1	96	94.1	0.91
One	3	3.7	5	4.9	
Two	1	1.2	1	1.0	
Vaginal deliveries					
None	29	35.4	50	49.0	0.08
One to three	49	59.8	44	43.1	
Four or more	4	4.9	8	7.8	
Cesarean deliveries					
None	54	65.9	58	57.4	0.25
One	20	24.4	36	35.6	
Two	8	9.8	6	5.9	
Three or more	0	0.0	1	1.0	
Number of children <2500g					
None	72	87.8	98	96.1	0.03*
One or more	10	12.2	4	3.9	
Number of child deaths <1 year of age					
None	80	97.6	98	96.1	0.57
One or more	2	2.4	4	3.9	
Deliveries < 37 weeks					
None	74	92.5	95	95.0	0.40
One	6	7.5	4	4.0	
Two or more	0	0.0	1	1.0	
Interdelivery interval					
Up to 36 months	46	57.5	40	43.0	0.06
37 months or more	34	42.5	53	57.0	
Contraceptive method					
Yes	59	41.0	76	40.2	0.89
No	85	59.0	113	59.8	

Fisher's exact test. * Significant. NB = newborn.

Block III –Conditions of pregnancy: assessment of pregnancy and conditions of delivery. The 'use of cigarette variable showed a significant difference between the case and control groups ($p<0.05$), women who smoked during their pregnancy were more prevalent in the case group. The 'use of cigarettes' and 'use of illicit drugs' variables were classified for testing in the multivariate analysis (Table 2).

Table No. 2: Variables related to conditions of pregnancy and their relationship with prematurity Sobral-CE, 2015

Variable	Case (premature NB)		Control		p
	n	%	n	%	
Current pregnancy was planned					
Yes	77	52.7	108	56.8	0.45
No	69	47.3	82	43.2	
Work outside the home					
Yes	48	33.1	52	27.8	0.30
No	97	66.9	135	72.2	
Domestic activities with children					
Yes	75	51.7	96	51.1	0.91
No	70	48.3	92	48.9	
Physical effort during pregnancy					
Yes	64	90.1	81	94.2	0.34
No	7	9.9	5	5.8	
Use of cigarettes					
Yes	8	5.4	2	1.0	0.02*
No	139	94.6	189	99.0	
Use of alcoholic beverages					
Yes	7	4.8	4	2.1	0.22
No	140	95.2	187	97.9	
Use of drugs					
Yes	4	2.8	1	0.5	0.17
No	139	97.2	188	99.5	
Physical aggression					
Yes	3	2.1	3	1.6	0.99
No	142	97.9	185	98.4	

Fisher's exact test. * Significant. NB = newborn.

Block IV - Prenatal care and complications during pregnancy. The variables that showed a significant difference were 'number of prenatal consultations', women in the case group had fewer prenatal consultations than those in the control group ($p<0.01$); 'undergoing ultrasonography' (USG), pregnant women in the control group underwent more USGs than those

in the case group (p=0.01); 'complications during pregnancy were more frequent in the case group (p<0.01); for the 'dental care' variable, women in the control group had more dental care during pregnancy than those in the case group (p=0.02); and 'hospitalization during pregnancy, there were more hospitalizations in the case group than in the control group (p<0.01) (Table 3).

Table No. 3: Variables related to prenatal care and its relationship with prematurity Sobral-CE, 2015

Variable	Case (premature NB)		Control		P
	n	%	n	%	
Number of prenatal consultations					
1-3 consultations	6	4.1	3	1.6	<0.01
4-6 consultations	32	22.1	14	7.5	
7 or more consultations	107	73.8	169	90.9	
Where the prenatal care was provided					
Family health center	126	87.5	178	93.7	0.05
Private clinic	18	12.5	12	6.3	
Gestational age at the 1st consultation					
1st trimester (up to 13 weeks)	119	86.2	163	87.6	0.92
2nd trimester (14 to 28 weeks)	18	13.0	22	11.8	
3rd trimester (after 28 weeks)	1	0.7	1	0.5	
Underwent prenatal testing					
Yes	122	98.4	179	100.0	0.17
No	2	1.6	0	0.0	
Testing status					
Complete	4	3.3	11	6.4	0.23
Incomplete	119	96.7	161	93.6	
Underwent USG					
Yes	110	90.2	168	97.7	0.01*
No	12	9.8	4	2.3	
Complications during pregnancy					
Yes	106	72.6	100	52.4	<0.01*
No	40	27.4	91	47.6	
Dental care during pregnancy					
Yes	92	63.4	141	75.0	0.02*
No	53	36.6	47	25.0	
Hospitalization during pregnancy					
Yes	40	27.2	19	9.9	<0.01*
No	107	72.8	172	90.1	

Fisher's exact test. * Significant. NB = newborn.

Block V: Conditions of delivery - Cesarean deliveries were prevalent in both preterm infants (62.6%) and controls (63.5%), with no significant association between cesarean section and prematurity (Table 4).

Table No. 4: Variables associated with prematurity after logistic regression. Sobral-CE, 2015

Variable	Case		Control		p	OR	CI	p	Adjusted OR	CI
	n	%	n	%						
Number of prenatal consultations										
Up to 6 consultations	41	24.3	15	9.1	<0.01*	3.2	1.7, 6.1	0.03*	2.2	1.1, 4.5
7 or more consultations	128	75.7	150	90.9		Ref			Ref	
Hospitalization during pregnancy										
Yes	43	25.4	16	9.5	<0.01*	3.3	1.8, 6.1	<0.02	2.4	1.2, 4.9
No	126	74.6	153	90.5		Ref			Ref	

After a hierarchical logistic regression analysis carried out with all significant associations and those with p<0.20, a significant association with prematurity remained for the 'number of prenatal consultations' and 'hospitalization during pregnancy' variables.

The hierarchical multiple logistic regression analysis shows that mothers who had less than 7 consultations in prenatal care (p<0.01) and those who had hospitalization during pregnancy (p<0.01) were more likely to have preterm delivery.

DISCUSSION

In the discussion of the findings, we opted for a dialogue with the literature that served as the basis for this study, with the main variables in the present study being commented on and compared with the referenced studies. We tried to show agreement and disagreement as to whether these are significant risk factors associated with prematurity.

The findings regarding the GA of premature infants show the same results found in a study in Londrina-PR by Silva *et al* (2009),[9] in Campina Grande-PB by Assunção *et al*(2011),[10] and in Botucatu-SP by Balbi *et al*(2016).[11]It is important to highlight that in this study, 79.6% of preterm infants had GA between 32 and 36 weeks, being therefore classified at moderate preterm infants. Some studies discuss the possible association between elective cesarean sections and

preterm births almost at term;[12] authors such as Raju (2006),[13] Lajos *et al* (2015),[14] and Torres-Muñoz *et al*(2015)[15] found that cesarean section is a risk factor for prematurity. Although our study did not report any significant differences between the case and control group regarding cesarean delivery, it is important to highlight that 68.4% of moderately preterm infants (32-36 weeks) were born by cesarean delivery. It is also worth noting that the cesarean section rate in the municipality is currently at 62% of deliveries, a considerably high rate, which perhaps explains why there is no significant difference between cases and controls.

In Brazil, few studies have been conducted specifically on the birthweight of premature newborns, one such study in the city of São Paulo was conducted to identify the prevalence of low birth weight between 2007 and 2013, in this population 57.35% of preterm newborns were considered low birth weight.[16]Another study, in the north of Brazil, was performed to estimate the proportion of low birth weight and identify the associated factors. For the newborns with GA 22-31 weeks, 12.5% of these infants weighed more than 2,500g at delivery, and for those with GA 32-36 weeks this percentage increased to 22.81%.[17]In an ecological time-series study of births between 2000 and 2013 in the south of Brazil, the authors reported that in the first three-year period (2000-2002) the OR for preterm neonates having low birth weight was 36.72, and in the second three-year period (2011-2013) this OR increased to 38.76.[18]In the present study, 54.4% of the newborns in the preterm group weighed more than 2,500g. This high percentage may be associated with the fact that there was a large concentration of deliveries with GA between 32 and 36 weeks.

In the studies by Assunção *et al* (2011),[10], and Silva *et al* (2009),[9] socioeconomic conditions were identified as a risk factor for prematurity. Although the profile of the pregnant women who had a premature birth was less favorable when compared to the control group, in the present study no significant association was identified. Nevertheless, it is remarkable that approximately half of the pregnant women in the cases and controls live on less than a minimum wage. These data reflect the socioeconomic reality of the municipality, where 80% of heads of households receive less than a minimum wage. In the municipalities where there is a trend to greater income stratification, it should be possible to observe the relationship between income and premature births more clearly.

The 'previous pregnancy' variable presented relevance in the univariate analysis, but this effect disappeared in the multivariate analysis. In the study by Almeida *et al*(2012),[19] primiparity was identified as a risk factor for preterm childbirth. In our study, vaginal delivery in previous pregnancies proved to be a protective factor in the univariate analysis; however, no significant differences were observed in the multivariate analysis. Similar results were not found in other studies.

The relationship between the number of previous low-birth-weight infants (<2,500g) and prematurity was not significant. Although there were preterm infants among the low-birth-weight neonates and this finding was higher among the cases (n=7) than in the controls (n=4), the values were too small to allow for better analysis. Also, the results on previous preterm delivery did not represent a significant risk factor, which differs from what was found in the literature. The Multicentric Study of Prematurity Investigation in Brazil (*EstudoMulticêntrico de Investigação da Prematuridade no Brasil – EMIP*), identified that aprevious premature delivery increases the chancesof a preterm birth.[14]

The data found in this study are in agreement with those from Silva *et al* (2009)[9] regarding the inter-delivery interval. In our study, there was also no significant relationship between inter-delivery interval and prematurity. The multicenter study carried out by Lajos *et al* (2015)[14] associated premature birth with previous abortion, in our study this variable did not present significance.

Machado (2012),[20] in a study conducted in the city of Porto (Portugal), found that active exposure to smoking during pregnancy increased the risk of premature birth approximately 2-fold. A study to estimate the prevalence of premature births in Brazil, funded by UNICEF,[21] also pointed to maternal smoking as one of the main causes of prematurity and low birth weight in neonates. Other studies also point to maternal smoking as one of the factors associated with prematurity;[14,22-25] however, in this study, this variable (maternal smoking) only had an important association (p=0.05) in the first part of the analysis, being superseded by other variables in the multivariate analysis. Other complications may have represented a greater burden, outweighing the effect of smoking during pregnancy.

Authors such as Tuon (2014)[24] and Silveira *et al* (2008)[23] found, in their respective studies, an association between prematurity and physical effort during pregnancy. The present study did not witness this association, despite the percentage of preterm deliveries being higher in the case group for the mothers who worked outside the home and performed domestic activities with children during pregnancy. The use of alcohol and illicit drugs during pregnancy was also not significant in this study. It is believed that mothers are still afraid to mention such conditions in their interviews. Pizzani *et al* (2012)[25] pointed out the use of alcohol and drugs as social factors that contribute to the occurrence of prematurity.

The adjusted OR for the variable 'number of prenatal consultations' was 2.9, showing that women who had up to 6 consultations were 2.9 times more likely to progress to preterm delivery than women who had 7 or more consultations. Furthermore, it was witnessed that the mothers in the group of cases had less time for consultations. Considering that more than 80% of pregnant women in the case group started prenatal consultations up to 13 weeks of pregnancy, and that, according to the prenatal protocol of the Brazilian Ministry of Health,[26]which recommends fortnightly consultations after 28 weeks, it is possible to conclude that there was enough time to have 7 or more prenatal consultations. The number of consultations presented by the pregnant women in the case group was insufficient, justifying the fact that this condition remained a risk factor for prematurity at the end of the multivariate analysis. These findings are in agreement with the studies carried out by Almeida *et al* (2012),[19] Silveira *et al* (2008),[23]Tuon (2014),[24]Lajos*et al*(2015),[14]and Assunção *et al* (2011),[10] who reported the insufficient number of consultations or inadequate prenatal as a risk factor for preterm birth. Silva *et al* (2009)[9] observed that mothers who did not have prenatal care were five times more likely to have children born before 37 weeks of gestation.

In the univariate analysis, USG showed significance (p=0.01), presenting itself as a protective factor for the outcome, but this variable did not remain significant in the final model. The Brazilian Ministry of Health proposes, at least, one USG during prenatal care, in the first trimester.[26] The performance of this scan in early pregnancy is related to a better determination of GA, early detection of multiple pregnancies, and clinically unsuspected fetal malformations. The study by Tuon (2014)[24] associated the non-performance of USG with premature birth.

Regarding maternal complications during pregnancy, it was observed that the variables showed an important adjustment in the multivariate analysis, suggesting that more than one of these conditions could be present and that some of them may have led to the mother's hospitalization during pregnancy. As in the present study, other studies have observed that mothers who were hospitalized during pregnancy have a higher risk of preterm birth. Silva *et al* (2009),[9] Almeida *et al* (2012),[19], and Oliveira *et al* (2015)[18] related the presence of clinical complications during pregnancy as a risk factor for preterm delivery.

Women hospitalized during pregnancy were 3 times more likely to have a premature birth in our study than those who were not hospitalized, Assunção *et al* (2011)[10] found in their study, a 5.6 times greater risk of premature birth in mothers who were hospitalized during pregnancy. Silva and Fensterseifer (2015)[27] estimated this increase to be 5.5 times greater. Maternal complications during pregnancy and, especially, hospitalization are indicators that there were problems with the pregnancy. The risk of premature labor (p=0.01) presented a strong association with preterm birth, but this association disappeared in the final model. This complication was expected to be more frequent in the case group since it precedes premature labor itself; in the control group, only one record of this complication was observed.

Urinary tract infections (UTI) and genital infections were not associated with preterm delivery in this study, despite being one of the most frequent complications in pregnant women.[28,29] A possible explanation may be the fact that the difference in the occurrence of these infections between cases and control was very small. Although this study did not show an association between UTI and premature birth, several other authors identified this correlation.[9,12,19]

The studies by Balbi *et al* (2016)[11] and Lajos *et al* (2014)[14] associate the increase in premature births with the increase in cesarean sections in Brazil. The present study did not identify this association.

CONCLUSION:

The variables that remained associated with prematurity were 'hospitalization during pregnancy and the 'number of prenatal consultations' being up to six. The mediation of numerous factors, which interfere with prematurity, prevents the establishment of direct causal relationships, even for those variables that showed significant differences between the two groups. The results

indicate that some variables had greater weight in the association with prematurity. It is necessary to understand and list all the factors involved with preterm delivery and to be attentive during prenatal care to minimize their effects to avoid prematurity. The results of this study show that the variables that had greater influence in the association with prematurity may be sensitive to quality prenatal care performed in the primary care network. The reduction of infant mortality, the main component of which is neonatal mortality, is fundamentally due to an improvement in prenatal care.

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