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Risk factors for perinatal death in high-risk pregnant women at a tertiary hospital in Curitiba-PR, Brazil: a case-control study

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Abstract *A case-control study was carried out to estimate risk factors for perinatal mortality in a referral hospital for high-risk pregnancies in Curitiba-PR. Sociodemographic, maternal, pregnancy and concept characteristics data were obtained from the hospital records of 316 cases and 316 controls from 2013 to 2017. A hierarchical multiple logistic regression analysis was performed, remaining in the final model variables with p < 0.05. The results show an increased risk of perinatal death in mothers with blood type B (OR = 2.82; 95%CI: 1.07-7.43), who did not undergo prenatal care (OR = 30.78; 95%CI: 4.23-224.29), fetuses with congenital malformations (OR = 63.90; 95%CI: 27.32-149.48), born under 28 (OR = 24.21; 95%CI: 1, 10-531.81) and between 28-31 weeks of gestation (OR = 6.03; 95%CI: 1.34-27.17) and birth weight below 1,000g (OR = 51.94; 95%CI: 4.31-626.46), between 1,000-1,499g (OR = 11.17; 95%CI: 2.29-54.41) and between 1,500-2,499g (OR = 2.75; 25-6.06). Concepts of pregnancies with premature outcome, low birth weight and the presence of congenital malformations are the main risk factors for perinatal death. On the other hand, adequate prenatal care is an important protective factor.*

Key words *Perinatal death, High-risk pregnancy, Risk factors, Case-control studies*

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Introduction

Perinatal mortality is a key indicator of maternal and child health and reflects socioeconomic conditions and the quality of antenatal, intrapartum, and postnatal care[1]. Perinatal death is defined as a death occurring between the 22nd week of gestation and sixth completed day after birth and encompasses fetal deaths and early neonatal deaths[2]. The majority of perinatal deaths can be prevented by improving access to health services and the quality of preconception, antenatal, intrapartum, and postnatal care[3]. The analysis of fetal and early neonatal mortality together is important because the causes of death are similar and can be reduced using the same interventions[4,5].

In areas where pregnant women have access to quality health care, the leading causes of perinatal death are congenital birth defects, preterm birth, and intrauterine growth restriction, while in underserved regions, the main causes are asphyxia and infections[6]. In 2020, approximately 2.4 million children died in the first month of life worldwide, which is equivalent to around 6,700 deaths every day[7]. In addition, around 5,400 babies are stillborn every day. In 2019, there were approximately 2 million fetal deaths, with almost half occurring in the intrapartum period[8].

During the first two decades of this century, the reduction in the stillbirth rate was lower than in other age groups. The annual rate of reduction in the fetal mortality rate was just 2.3%, compared to a 2.9% reduction in neonatal mortality and 4.3% among children aged 1-59 months. In 2019, the global stillbirth rate was 13.9 per 1,000 births, representing a reduction of 35% in relation to 2000. However, there are striking differences in stillbirth rates between countries, with numbers ranging from 1.4 to 32.2 per 1,000 births and 84% of deaths occurring in low- and lower-middle income nations[8].

Statistics in Brazil show that the fetal mortality rate has fallen by 25%, from 10 per 1,000 births in 1996 to 7.5 in 2019[8], meaning that the country has already met the Every Newborn Action Plan target of ≤ 12 fetal deaths per 1,000 births by 2030[9]. However, these rates may be underestimated due to underreporting of deaths[10]. National data also reveal a reduction in the rate of neonatal deaths, from 25 per 1,000 live births in 1990 to 19 in 2000 and 9 in 2020, representing an annual rate of reduction of 3.6%[7]. However, the rate of decline in early neonatal deaths (0-6 days) was slower than that of late neonatal deaths (7-28 days). This is due to a reduction in infectious diseases coupled with a relative increase in the proportion of deaths due to complications of prematurity[11].

Despite efforts to identify factors related to adverse obstetric prognosis, it is still not possible to accurately predict pregnancy outcomes. Nevertheless, when risk factors are detected, it is important to be alert to potential complications. Most national studies on this topic use secondary data from vital statistics systems, which are known to be prone to underreporting problems[12] and do not enable the identification of various risk factors. Using data from patient records enables the collection of more detailed information on both the mother and conceptus. The aim of this study was to identify risk factors for perinatal death based on the analysis of maternal sociodemographic, pregnancy, and conceptus characteristics in a university referral hospital in Curitiba.

Methods

We conducted a case-control study in the Paraná Federal University Hospital (*Complexo Hospital de Clínicas da Universidade Federal do Paraná* – CHC-UFPR) in Curitiba. We included births and fetal and early neonatal deaths occurring between 1 January 2013 and 31 December 2017.

The sample size was calculated using the Fleiss method with continuity correction[13], adopting a 95% two-sided confidence interval (1-α), power (1-β) of 80%, control exposure proportion of 22%, 1:1 case-control ratio, and minimum detectable odds ratio of 1.70, resulting in a minimum sample of 305 cases and 305 controls. The sample was increased to 335 cases and 335 controls to account for potential losses and exclusions (5%) and to include the total number of perinatal deaths in the hospital over the five-year study period (2013-2017).

The case group consisted of perinatal deaths, comprising fetal and early neonatal deaths according to the definitions proposed by the International Classification of Diseases – 10th Revision (ICD-10)[2] and Ministry of Health[14]: gestational age of 22 completed weeks or birth weight ≥ 500 grams; intrauterine deaths and deaths occurring during the first seven days of life.

The control group was made up of newborns with a gestational age of at least 22 completed weeks or birth weight ≥ 500 grams based on the definition of newborn proposed by the ICD-10[2] who did not die during the early neonatal period. The

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controls were randomly selected from newborns delivered in the hospital during the study period (n = 8,396). The number of controls selected in each year of the study period was proportional to the number of perinatal deaths in the same year. Before selecting the controls, newborns who died during the first seven days of life were excluded and included in the case group. The controls were therefore selected from 8,257 newborns.

The cases and control data were collected from the mothers' and newborns' physical patient records and entered into EpiData 4.6 (The EpiData Association, Denmark). Data analysis was performed using Stata 13.0 (Stata Corp., College Station, United States).

We used a hierarchical model, which is suited to the analysis of datasets with a large number of conceptually related variables[15]. Hierarchical models are used to analyze distal, intermediate, and proximate determinants based on conceptual framework that describes the relationship between risk factors whose effect is direct or mediated through other factors[16]. The variables analyzed by the present study were divided into four blocks:

Sociodemographic characteristics (distal block): maternal age and education level, mother's marital status, and municipality of residence.

Maternal characteristics (intermediate block I): mother knew she was pregnant, smoking, drinking, and drug addiction, blood type, underlying conditions, number of pregnancies, history of miscarriage, fetal death or neonatal death in previous pregnancy.

Current pregnancy characteristics (intermediate block II): type of pregnancy (singleton; multiple), adequacy of antenatal care, admission during pregnancy, complications during pregnancy: preeclampsia or eclampsia, diabetes, thyroid disorders, chorioamnionitis, amniotic fluid volume changes, placental abruption, centralization of fetal blood flow, and use of pregnancy medications.

Conceptus characteristics (proximal block): sex, gestational age, birth weight, intrauterine fetal growth, and congenital malformation.

Gestational age was calculated using an algorithm: (a) early ultrasound (up to 20 + 6 weeks); (b) late ultrasound; (c) date of last menstrual period (LMP); (d) physical examination by a pediatrician (Capurro). Birth weight for gestational age was determined using the INTERGROWTH-21st intrauterine fetal growth curve[17], adopting the following classifications: small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA). Conceptuses with a gestational age of under 24 weeks or 43 weeks and over were not assessed and were included in the "ignored" category together with those where information on intrauterine growth was not available. Antenatal care was considered adequate when the expectant mother had attended 3 appointments up to 27 weeks of gestation, 4 appointments between 28 and 33 weeks of gestation, 5 appointments between 34 and 36 weeks of gestation, and 6 appointments up to 37 weeks or over. This classification was based on Ministry of Health recommendations stating that women should have at least six antenatal appointments during pregnancy, preferably one in the first trimester, two in the second, and three in the third[18]. This classification is important to correct for potentially lower adequacy in cases of preterm birth[19].

First, univariate analysis was performed to estimate odds ratios and 95% confidence intervals. The cut-off point for the inclusion of variables in the logistic regression model was $p < 0.20$. The multivariate analysis was performed using a hierarchical logistic regression model. The first stage was performed using the pre-selected variables from the sociodemographic characteristics and maternal characteristics blocks ($p < 0.20$). Those that obtained a p-value of < 0.05 were included in the second stage together with the variables from the current pregnancy characteristics block. The variables that obtained a p-value of < 0.05 were then included in the third stage together with the variables from the conceptus characteristics block. The variables that obtained a p-value of < 0.05 in at least one of the categories were included in the final model. The accuracy of the final model was estimated using a receiver operating characteristic (ROC) curve[20].

The study protocol was approved by the University of São Paulo's School of Public Health's research ethics committee (reference nº 3.179.881).

Results

There were 335 perinatal deaths (196 fetal deaths and 139 early neonatal deaths) in the CHC-UFPR during the study period. After taking losses into account (missing mother or newborn medical records, inactive records, or cases that did not meet the inclusion criteria), the final sample was 316 perinatal deaths (183 fetal deaths and 133 early neonatal deaths) and 316 controls (Figure 1).

With regard to sociodemographic characteristics, not residing in Curitiba was a possible risk factor for perinatal death (OR = 1.34; 95%CI:

0.96-1.86) and was included in the multivariate analysis (Table 1). With regard to maternal characteristics, the fact that the mother did not know she was pregnant (OR = 8.18; 95%CI: 1.01-66.52) and having blood types AB or B were associated with an increased risk of perinatal death (OR = 3.74; 95%CI: 1.18-11.91 and OR = 1.42; 95%CI: 0.85-2.37, respectively). Having an underlying condition was a protective factor for perinatal death (OR = 0.44; 95%CI: 0.30-0.63). The variables smoking, drinking, and drug addiction were not included in the next stage of the model. Being nulliparous and having had more than three pregnancies increased the risk of an adverse outcome in the current pregnancy. History of miscarriage, fetal death, and neonatal death also increased the risk of perinatal death (Table 1).

Regarding pregnancy characteristics, adequacy of antenatal care, use of pregnancy medications, and complications commonly found in high-risk pregnancies (preeclampsia or eclampsia, diabetes, thyroid disorders, chorioamnionitis, amniotic fluid volume changes, placental abruption, and centralization of fetal blood flow) were included in the next stage of the model. The variables type of pregnancy and admission during pregnancy were not included (Table 1).

All the variables from the conceptus characteristics block except sex (gestational age, birth weight, intrauterine fetal growth, and congenital malformation) were included in the next stage of the model (Table 1).

The first blocks included in the hierarchical logistic regression model were the sociodemographic characteristics and maternal characteristics. After adjustment, the variable municipality of residence continued to be associated with an increased risk of perinatal death. The only variable not selected from the maternal characteristics block was the expectant mother knew she was pregnant. Next, the variables from the current pregnancy characteristics block were added, with adequacy of antenatal care, amniotic fluid volume changes, and use of pregnancy medications being carried forward to the final stage, when the variables from the conceptus characteristics block were added. The variables maternal blood type, adequacy of antenatal care, gestational age, birth weight, and congenital malformation were included in the final model (Table 2). The area under the ROC curve[21] was 0.9652, suggesting that the proposed model is good predictor of perinatal death (Figure 2).

In the final model, maternal blood types A, B and AB were a risk factor for perinatal death (OR = 1.07; 95%CI: 0.55-2.06, OR = 2.82; 95%CI: 1.07-7.43, OR = 3.49; 95%CI: 0.52-23.46, respectively); however, only the association between having B blood type and increased risk of death was statistically significant. Not attending and missing information on antenatal care were risk factors for perinatal death (OR = 30.78; 95%CI: 4.23-224.29 and OR = 24.97; 95%CI: 11.15-55.91, respectively) (Table 3).

The lower the gestational age at birth the higher the risk of death. There was a 24-fold increase in the risk of death among extremely preterm infants (OR = 24.21; 95%CI: 1.10-531.81) and a six-fold increase among very preterm infants (OR = 6.03; 95%CI: 1.34-27.17). Being moderately preterm was not a risk factor (OR = 1.75; 95%CI: 0.78-3.93). The results also show that the lower the birth weight, the greater the risk of perinatal death. There was a 52-fold increase in the risk of perinatal death among infants weighing less than 1,000g (OR = 51.94; 95%CI: 4.31-626.46). Congenital malformation was an important risk factor for perinatal death (OR = 63.90 and p-value <0.001) (Table 3).

Discussion

The findings show increased risk of perinatal death among mothers with B blood type and who did not attend antenatal care, and among infants born before 32 weeks of gestation, weighing less than 2,500g at birth, and with congenital birth defects.

The association between maternal blood type and adverse pregnancy outcomes has been reported in the literature; however, evidence is scarce and findings are often controversial. A systematic review of articles published between 1965 and 2015 identified higher risk of pre-eclampsia in mothers with a non-O blood type[22], while a study in Turkey with 2,177 women reported an association between ABO blood types and low birth weight[23]. A multisite population-based case-control study in the United States involving 59 hospitals found an association between AB blood type and fetal death[24]. Our findings show an increased risk of perinatal death among mothers with B blood type. AB blood type was also associated with this outcome, but the association was not statistically significant in the final model. However, it is worth noting that AB is one of the rarest blood types and our sample power may not have been sufficient to confirm that this blood group is a risk factor for perinatal death. Further

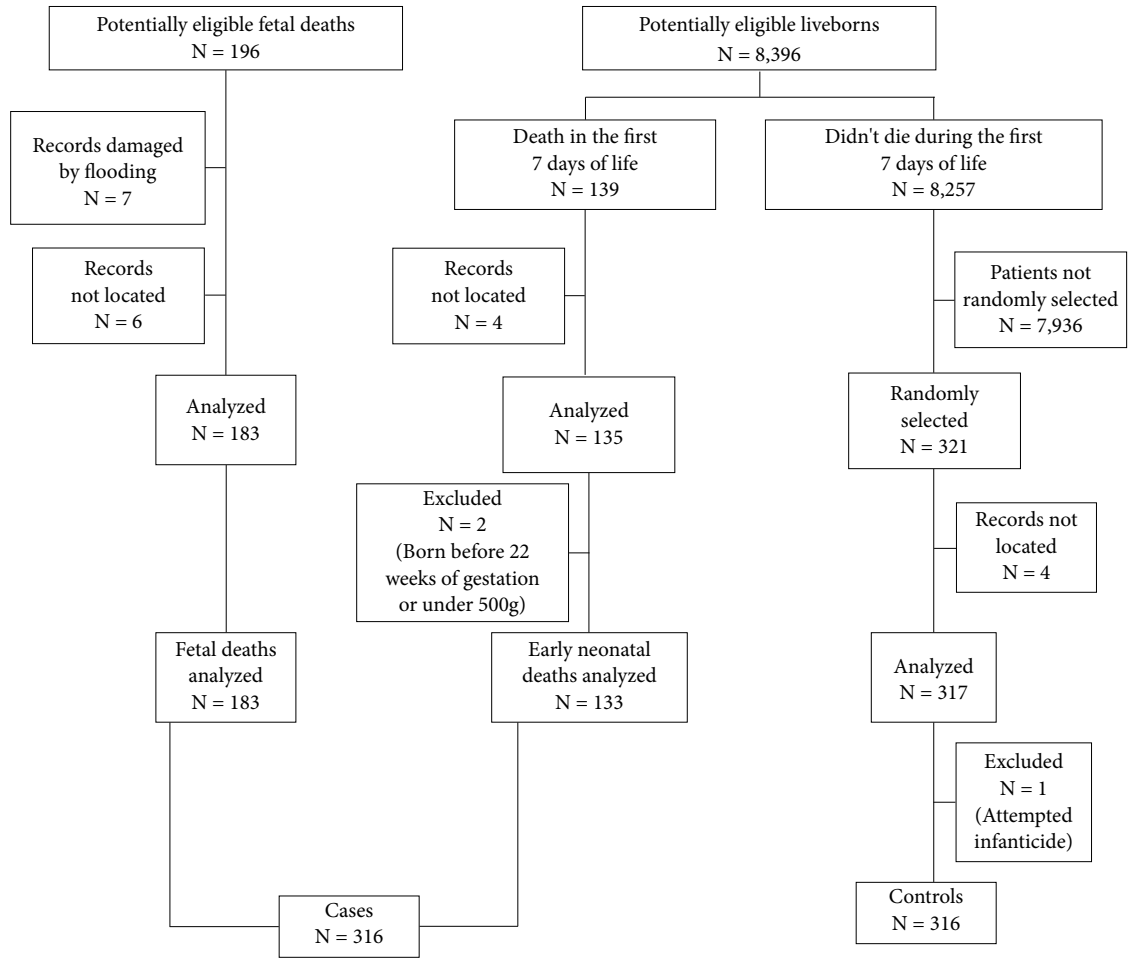

Figure 1. Flowchart of the case and control selection process. CHC-UFPR, 2013-2017.

Source: Authors.

research is therefore needed to elucidate the influence of maternal blood type on perinatal death.

Our findings show that there was a 30-fold increase in the risk of perinatal death among women who did not attend antenatal care. Inadequate antenatal care also increased the chance of perinatal death, but the association was not statistically significant. Missing information on antenatal care in patient records was a significant risk factor for perinatal death, with missing information being more frequent in cases than controls (62% versus 15%) and in cases of fetal deaths than in neonatal deaths (95% versus 17%) (data not presented). This may be partially explained by the reluctance of professionals to record adverse outcomes[25]. A study with 1,815 women in Brazil using data from the Birth in Brazil survey (*pesquisa Nascer no Brasil*) revealed health inequities and low quality of care, despite high antenatal care coverage[26]. It is possible that some mothers in our sample did not attend antenatal care because they encountered difficulties accessing services. On the other hand, not attending antenatal care may also be an indication of difficulties accepting pregnancy. It is worth noting that 8 women in our sample did not know they were pregnant.

Conceptus characteristics were important factors in the present study, with three of the five variables from this block being included in the final model: gestational age under 32 weeks, low birth weight (< 2,500g), and congenital malformation, which are variables related to fetal viability.

Table 1. Distribution (N and %) of cases and controls, odds ratios (OR), 95% confidence intervals (95%CI), and p-values of the maternal sociodemographic, current pregnancy, and conceptus characteristics. CHC-UFPR, 2013-2017.

Variables	Cases		Controls		OR	95%CI	P
	n	%	n	%			
Sociodemographic characteristics							
Maternal age							
< 20	36	11.39	44	13.92	0.81	0.50 - 1.32	0.403
20 to 34	201	63.61	200	63.29	1.00	Reference	
≥ 35	79	25.00	72	22.78	1.09	0.75 - 1.59	0.646
Maternal education level							
0 to 8 years	97	30.70	110	34.81	0.79	0.46 - 1.35	0.389
9 to11 years	176	55.70	166	52.53	0.95	0.57 - 1.57	0.847
12 or more years	39	12.34	35	11.08	1.00	Reference	
Ignored	4	1.27	5	1.58	0.72	0.18 - 2.92	0.642
Maternal marital status							
With partner	227	71.84	228	72.15	1.00	Reference	
Without partner	87	27.53	87	27.53	1.00	0.71 - 1.42	0.980
Ignored	2	0.63	1	0.32	2.01	0.18 - 22.39	0.563
Municipality of residence							
Curitiba	194	61.39	215	68.04	1.00	Reference	
Other	122	38.61	101	31.96	1.34	0.96 - 1.86	0.081
Maternal characteristics							
Knew she was pregnant							
Yes	308	97.47	315	99.68	1.00	Reference	
No	8	2.53	1	0.32	8.18	1.01 - 66.52	0.019
Smoker							
Yes	53	16.77	58	18.35	0.92	0.61 - 1.40	0.710
No	249	78.80	252	79.75	1.00	Reference	
Ignored	14	4.43	6	1.90	2.36	0.89 - 6.27	0.075
Drinker							
Yes	17	5.38	17	5.38	1.04	0.52 - 2.08	0.906
No	281	88.92	293	92.72	1.00	Reference	
Ignored	18	5.70	6	1.90	3.13	1.22 - 8.04	0.013
Drug addiction							
Yes	11	3.48	13	4.11	0.88	0.39 - 2.00	0.764
No	285	90.19	297	93.99	1.00	Reference	
Ignored	20	6.33	6	1.90	3.47	1.37 - 8.83	0.005
Maternal blood type							
A	109	34.49	126	39.87	1.00	0.70 - 1.41	0.983
B	42	13.29	34	10.76	1.42	0.85 - 2.37	0.174
O	132	41.77	152	48.10	1.00	Reference	
AB	13	4.11	4	1.27	3.74	1.18 - 11.91	0.016
Ignored	20	6.33	0	0.00	.	.	.
Underlying condition							
Yes	197	62.34	250	79.11	0.44	0.30 - 0.63	< 0.001
No	119	37.66	66	20.89	1.00	Reference	
Number of pregnancies							
Nulliparous	115	36.39	101	31.96	1.24	0.88 - 1.75	0.211
1 to 3	163	51.58	178	56.33	1.00	Reference	
4 or more	38	12.03	37	11.71	1.12	0.68 - 1.85	0.653

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Table 1. Distribution (N and %) of cases and controls, odds ratios (OR), 95% confidence intervals (95%CI), and p-values of the maternal sociodemographic, current pregnancy, and conceptus characteristics. CHC-UFPR, 2013-2017.

Variables	Cases		Controls		OR	95%CI	P
	n	%	n	%			
Previous miscarriage							
Yes	80	25.32	74	23.42	1.26	0.84 - 1.88	0.257
No	121	38.29	141	44.62	1.00	Reference	
Not applicable*	115	36.39	101	31.96	1.33	0.92 - 1.91	0.125
Previous fetal death							
Yes	24	7.59	12	3.80	2.29	1.11 - 4.75	0.021
No	177	56.01	203	64.24	1.00	Reference	
Not applicable*	115	36.39	101	31.96	1.31	0.93 - 1.83	0.118
Previous neonatal death							
Yes	10	3.16	4	1.27	2.76	0.85 - 9.00	0.079
No	191	60.44	211	66.77	1.00	Reference	
Not applicable*	115	36.39	101	31.96	1.26	0.90 - 1.75	0.175
Current pregnancy characteristics							
Type of pregnancy							
Singleton	288	91.14	296	93.67	1.00	Reference	
Multiple	28	8.86	20	6.33	1.44	0.79 - 2.62	0.230
Adequacy of antenatal care							
Adequate	97	30.70	248	78.48	1.00	Reference	
Inadequate	11	3.48	17	5.38	1.65	0.75 - 3.67	0.211
Did not attend antenatal care	13	4.11	3	0.95	11.08	2.97 - 41.33	< 0.001
Ignored	195	61.71	48	15.19	10.39	6.56 - 16.44	< 0.001
Admission during pregnancy							
Yes	52	16.46	51	16.14	1.02	0.67 - 1.56	0.914
No	264	83.54	265	83.86	1.00	Reference	
Preeclampsia or eclampsia							
Yes	24	7.59	12	3.80	2.08	1.02 - 4.25	0.040
No	292	92.41	304	96.20	1.00	Reference	
Diabetes during pregnancy							
Yes	33	10.44	57	18.04	0.53	0.33 - 0.84	0.006
No	283	89.56	259	81.96	1.00	Reference	
Thyroid disorders							
Yes	54	17.09	67	21.20	0.77	0.51 - 1.14	0.189
No	262	82.91	249	78.80	1.00	Reference	
Chorioamnionitis							
Yes	17	5.38	5	1.58	3.54	1.28 - 9.77	0.009
No	299	94.62	311	98.42	1.00	Reference	
Amniotic fluid volume changes							
Yes	38	12.03	15	4.75	2.74	1.47 - 5.13	0.001
No	278	87.97	301	95.25	1.00	Reference	
Placental abruption							
Yes	20	6.33	6	1.90	3.49	1.37 - 8.87	0.005
No	296	93.67	310	98.10	1.00	Reference	
Centralization of fetal blood flow							
Yes	15	4.75	4	1.27	3.89	1.27 - 11.92	0.011
No	301	95.25	312	98.73	1.00	Reference	
Use of pregnancy medications							
Yes	199	62.97	181	57.28	1.27	0.92 - 1.75	0.144
No	117	37.03	135	42.72	1.00	Reference	

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Table 1. Distribution (N and %) of cases and controls, odds ratios (OR), 95% confidence intervals (95%CI), and p-values of the maternal sociodemographic, current pregnancy, and conceptus characteristics. CHC-UFPR, 2013-2017.

Variables	Cases		Controls		OR	95%CI	P
	n	%	n	%			
Conceptus characteristics							
Sex							
Female	142	44.94	157	49.68	1.00	Reference	
Male	167	52.85	159	50.32	1.16	0.85 - 1.59	0.351
Ignored	7	2.22	0	0.00	.	.	.
Gestational age							
Under 28	94	29.75	1	0.32	322.82	23.72 - 4393	< 0.001
28 to 31	70	22.15	7	2.22	34.34	12.82 - 92.03	< 0.001
32 to 36	70	22.15	46	14.56	5.23	3.22 - 8.47	< 0.001
37 and over	76	24.05	261	82.59	1.00	Reference	
Ignored	6	1.90	1	0.32	20.61	2.32 - 182.98	< 0.001
Birth weight							
≥ 999	116	36.71	2	0.63	198.17	28.50 - 1378	< 0.001
1,000 to 1,499	44	13.92	7	2.22	21.48	8.27 - 55.77	< 0.001
1,500 to 2,499	78	24.68	44	13.92	6.06	3.70 - 9.92	< 0.001
2,500 to 3,999	72	22.78	246	77.85	1.00	Reference	
≥ 4,000	4	1.27	17	5.38	0.80	0.26 - 2.47	0.703
Ignored	2	0.63	0	0.00	.	.	.
Intrauterine fetal growth							
SGA	105	33.23	40	12.66	4.51	2.89 - 7.03	< 0.001
AGA	138	43.67	237	75.00	1.00	Reference	
LGA	31	9.81	38	12.03	1.40	0.83 - 2.36	0.202
Ignored	42	13.29	1	0.32	72.13	8.38 - 620.70	< 0.001
Congenital birth defect							
Yes	155	49.05	23	7.28	12.26	7.14 - 21.06	< 0.001
No	161	50.95	293	92.72	1.00	Reference	

SGA: small for gestational age; AGA: appropriate for gestational age; LGA: large for gestational age. * Nulliparous.

Source: Authors.

The findings show that the risk of perinatal death increased with decreasing birth weight and gestational age. Conceptuses weighing less than 1,000g were 52 times more likely to die than those weighing ≥ 2,500g and there was a 24-fold increase in the risk of death among infants born before 28 weeks. The elevated risk of death among conceptuses with a low birth weight and preterm infants reflects the characteristics of the study population: 75% of the cases were preterm and had low birth weight, with 36.7% weighing under 1,000g. When these variables were included in the model, the associations between complications during pregnancy such as chorioamnionitis, amniotic fluid volume changes, and use of pregnancy medications and perinatal death lost their significance. This may be because these factors are part of the causal network that leads to prematurity and low birth weight. Similar findings were observed for infants born to mothers with a history of fetal death, which is another factor in the causal pathway to prematurity.

Congenital malformation resulted in a 64-fold increase in the chance of perinatal death in the final model. It is worth highlighting that almost half of the individuals in the case group had some type of congenital anomaly. Although approximately 50% of congenital anomalies cannot be linked to a specific cause, there are known risk factors for congenital malformation, including genetical, socioeconomic, and environmental factors, and infection[27]. Vital statistics in the

Table 2. Distribution (N and %) of cases and controls, crude and adjusted odds ratios (OR), 95% confidence intervals (95%CI), and p-values of maternal sociodemographic, current pregnancy, and conceptus characteristics. CHC-UFPR, 2013-2017.

Variables	Cases		Controls		Crude OR	95%CI	P	Adjusted OR	95%CI	P
	n	%	n	%						
Logistic regression 1										
Municipality of residence										
Curitiba	194	61.39	215	68.04	1.00	Reference		1.00	Reference	
Other	122	38.61	101	31.96	1.34	0.96 - 1.86	0.081	1.42	1.01 - 2.01	0.046
Knew she was pregnant										
Yes	308	97.47	315	99.68	1.00	Reference		1.00	Reference	
No	8	2.53	1	0.32	8.18	1.01 - 66.52	0.019	7.29	0.85 - 62.35	0.070
Maternal blood type										
A	109	34.49	126	39.87	1.00	0.70 - 1.41	0.983	1.12	0.78 - 1.61	0.536
B	42	13.29	34	10.76	1.42	0.85 - 2.37	0.174	1.75	1.03 - 2.96	0.038
O	132	41.77	152	48.10	1.00	Reference		1.00	Reference	
AB	13	4.11	4	1.27	3.74	1.18 - 11.91	0.016	4.14	1.28 - 13.37	0.018
Ignored	20	6.33	0	0.00	.	.	.	.	.	.
Underlying condition										
Yes	197	62.34	250	79.11	0.44	0.30 - 0.63	<0.001	0.42	0.29 - 0.62	< 0.001
No	119	37.66	66	20.89	1.00	Reference		1.00	Reference	
Previous fetal death										
Yes	24	7.59	12	3.80	2.29	1.11 - 4.75	0.021	2.81	1.34 - 5.90	0.006
No	177	56.01	203	64.24	1.00	Reference		1.00	Reference	
Not applicable*	115	36.39	101	31.96	1.31	0.93 - 1.83	0.118	1.28	0.90 - 1.83	0.173
Previous neonatal death										
Yes	10	3.16	4	1.27	2.76	0.85 - 9.00	0.079	3.51	1.04 - 11.88	0.043
No	191	60.44	211	66.77	1.00	Reference		1.00	Reference	
Not applicable*	115	36.39	101	31.96	1.26	0.90 - 1.75	0.175	.	.	.
Logistic regression 2										
Municipality of residence										
Curitiba	194	61.39	215	68.04	1.00	Reference		1.00	Reference	
Other	122	38.61	101	31.96	1.34	0.96 - 1.86	0.081	1.07	0.71 - 1.63	0.738
Maternal blood type										
A	109	34.49	126	39.87	1.00	0.70 - 1.41	0.983	1.16	0.75 - 1.80	0.497
B	42	13.29	34	10.76	1.42	0.85 - 2.37	0.174	1.68	0.89 - 3.18	0.108
O	132	41.77	152	48.10	1.00	Reference		1.00	Reference	
AB	13	4.11	4	1.27	3.74	1.18 - 11.91	0.016	6.47	1.73 - 24.26	0.006
Ignored	20	6.33	0	0.00	.	.	.	.	.	.
Underlying condition										
Yes	197	62.34	250	79.11	0.44	0.30 - 0.63	< 0.001	0.47	0.29 - 0.74	0.001
No	119	37.66	66	20.89	1.00	Reference		1.00	Reference	
Previous fetal death										
Yes	24	7.59	12	3.80	2.29	1.11 - 4.75	0.021	2.68	1.12 - 6.42	0.027
No	177	56.01	203	64.24	1.00	Reference		1.00	Reference	
Not applicable*	115	36.39	101	31.96	1.31	0.93 - 1.83	0.118	1.22	0.80 - 1.87	0.356
Previous neonatal death										
Yes	10	3.16	4	1.27	2.76	0.85 - 9.00	0.079	2.92	0.71 - 11.93	0.136
No	191	60.44	211	66.77	1.00	Reference		1.00	Reference	
Not applicable*	115	36.39	101	31.96	1.26	0.90 - 1.75	0.175	.	.	.

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Table 2. Distribution (N and %) of cases and controls, crude and adjusted odds ratios (OR), 95% confidence intervals (95%CI), and p-values of maternal sociodemographic, current pregnancy, and conceptus characteristics. CHC-UFPR, 2013-2017.

Variables	Cases		Controls		Crude OR	95%CI	P	Adjusted OR	95%CI	P
	n	%	n	%						
Adequacy of antenatal care										
Adequate	97	30.70	248	78.48	1.00	Reference		1.00	Reference	
Inadequate	11	3.48	17	5.38	1.65	0.75 - 3.67	0.211	1.55	0.63 - 3.84	0.341
Did not attend antenatal care	13	4.11	3	0.95	11.08	2.97 - 41.33	< 0.001	10.13	2.47 - 41.60	0.001
Ignored	195	61.71	48	15.19	10.39	6.56 - 16.44	< 0.001	11.59	7.49 - 17.96	< 0.001
Preeclampsia or eclampsia										
Yes	24	7.59	12	3.80	2.08	1.02 - 4.25	0.040	1.51	0.61 - 3.75	0.375
No	292	92.41	304	96.20	1.00	Reference		1.00	Reference	
Diabetes during pregnancy										
Yes	33	10.44	57	18.04	0.53	0.33 - 0.84	0.006	0.55	0.30 - 1.01	0.054
No	283	89.56	259	81.96	1.00	Reference		1.00	Reference	
Thyroid disorders										
Yes	54	17.09	67	21.20	0.77	0.51 - 1.14	0.189	1.10	0.65 - 1.87	0.720
No	262	82.91	249	78.80	1.00	Reference		1.00	Reference	
Chorioamnionitis										
Yes	17	5.38	5	1.58	3.54	1.28 - 9.77	0.009	3.13	0.97 - 10.13	0.057
No	299	94.62	311	98.42	1.00	Reference		1.00	Reference	
Amniotic fluid volume changes										
Yes	38	12.03	15	4.75	2.74	1.47 - 5.13	0.001	3.88	1.87 - 8.05	< 0.001
No	278	87.97	301	95.25	1.00	Reference		1.00	Reference	
Placental abruption										
Yes	20	6.33	6	1.90	3.49	1.37 - 8.87	0.005	2.32	0.72 - 7.48	0.160
No	296	93.67	310	98.10	1.00	Reference		1.00	Reference	
Centralization of fetal blood flow										
Yes	15	4.75	4	1.27	3.89	1.27 - 11.92	0.011	2.77	0.76 - 10.06	0.122
No	301	95.25	312	98.73	1.00	Reference		1.00	Reference	
Use of pregnancy medications										
Yes	199	62.97	181	57.28	1.27	0.92 - 1.75	0.144	1.53	1.01 - 2.34	0.047
No	117	37.03	135	42.72	1.00	Reference		1.00	Reference	

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United States over the past decade show that congenital birth defects accounted for 20% of child deaths in the country[28]. In Brazil, malformations are responsible for 22.8% of deaths during the first 4 weeks of life[29], which is close to rates in developed countries. It is estimated that about 94% of severe birth defects occur in low- and middle-income countries. Poor socioeconomic conditions are indirectly related to congenital anomalies due to increased risk of exposure to agents or factors such as infection and alcohol and poor access to sufficient nutritious foods and health care[27]. Infectious diseases associated with malformations include syphilis, which remains a major public health problem worldwide[30].

Although 33.2% of the conceptuses in the case group were SGA, this condition was not a risk factor when adjusted with the other variables. This may be because fetal growth restriction is one of the factors in the causal pathway to prematurity[31]. Furthermore, the number of conceptuses with fetal growth restriction may be greater than shown as it was not possible to measure infants born before 24 weeks gestation (30 perinatal deaths) (data not presented).

The literature shows that one of the factors that increase pregnancy risk is extremes of maternal age. A systematic review and meta-analysis of 96 population-based studies showed that maternal age older than 35 years was associated

Table 2. Distribution (N and %) of cases and controls, crude and adjusted odds ratios (OR), 95% confidence intervals (95%CI), and p-values of maternal sociodemographic, current pregnancy, and conceptus characteristics. CHC-UFPR, 2013-2017.

Variables	Cases		Controls		Crude OR	95%CI	P	Adjusted OR	95%CI	P
	n	%	n	%						
Logistic regression 3										
Maternal blood type										
A	109	34.49	126	39.87	1.00	0.70 - 1.41	0.983	1.05	0.53 - 2.09	0.882
B	42	13.29	34	10.76	1.42	0.85 - 2.37	0.174	3.12	1.13 - 8.64	0.029
O	132	41.77	152	48.10	1.00	Reference		1.00	Reference	
AB	13	4.11	4	1.27	3.74	1.18 - 11.91	0.016	4.06	0.62 - 26.71	0.145
Ignored	20	6.33	0	0.00	.	.	.	.	.	.
Underlying condition										
Yes	197	62.34	250	79.11	0.44	0.30 - 0.63	< 0.001	1.56	0.72 - 3.38	0.255
No	119	37.66	66	20.89	1.00	Reference		1.00	Reference	
Previous fetal death										
Yes	24	7.59	12	3.80	2.29	1.11 - 4.75	0.021	3.12	0.64 - 15.22	0.159
No	177	56.01	203	64.24	1.00	Reference		1.00	Reference	
Not applicable*	115	36.39	101	31.96	1.31	0.93 - 1.83	0.118	0.64	0.33 - 1.27	0.204
Adequacy of antenatal care										
Adequate	97	30.70	248	78.48	1.00	Reference		1.00	Reference	
Inadequate	11	3.48	17	5.38	1.65	0.75 - 3.67	0.211	1.25	0.24 - 6.57	0.789
Did not attend antenatal care	13	4.11	3	0.95	11.08	2.97 - 41.33	< 0.001	26.78	3.48 - 206.09	0.002
Ignored	195	61.71	48	15.19	10.39	6.56 - 16.44	< 0.001	24.42	10.72 - 55.60	< 0.001
Amniotic fluid volume changes										
Yes	38	12.03	15	4.75	2.74	1.47 - 5.13	0.001	1.12	0.34 - 3.72	0.852
No	278	87.97	301	95.25	1.00	Reference		1.00	Reference	
Use of pregnancy medications										
Yes	199	62.97	181	57.28	1.27	0.92 - 1.75	0.144	0.52	0.25 - 1.05	0.069
No	117	37.03	135	42.72	1.00	Reference		1.00	Reference	
Gestational age										
Under 28	94	29.75	1	0.32	322.82	23.72 - 4393	< 0.001	24.66	0.82 - 744.27	0.065
28 to 31	70	22.15	7	2.22	34.34	12.82 - 92.03	< 0.001	6.63	1.07 - 41.28	0.043
32 to 36	70	22.15	46	14.56	5.23	3.22 - 8.47	< 0.001	2.24	0.88 - 5.69	0.089
37 and over	76	24.05	261	82.59	1.00	Reference		1.00	Reference	
Ignored	6	1.90	1	0.32	20.61	2.32 - 182.98	< 0.001	0.00	.	0.990
Birth weight										
≥ 999	116	36.71	2	0.63	198.17	28.50 - 1378	< 0.001	69.53	3.50 - 1381.85	0.005
1.000 to 1.499	44	13.92	7	2.22	21.48	8.27 - 55.77	< 0.001	16.72	2.45 - 114.09	0.004
1.500 to 2.499	78	24.68	44	13.92	6.06	3.70 - 9.92	< 0.001	2.94	1.04 - 8.29	0.042
2.500 to 3.999	72	22.78	246	77.85	1.00	Reference		1.00	Reference	
≥ 4.000	4	1.27	17	5.38	0.80	0.26 - 2.47	0.703	0.55	0.08 - 3.81	0.543
Ignored	2	0.63	0	0.00	.	.	.	.	.	.
Intrauterine fetal growth										
SGA	105	33.23	40	12.66	4.51	2.89 - 7.03	<0.001	1.66	0.65 - 4.25	0.286
AGA	138	43.67	237	75.00	1.00	Reference		1.00	Reference	
LGA	31	9.81	38	12.03	1.40	0.83 - 2.36	0.202	2.48	0.80 - 7.65	0.114
Ignored	42	13.29	1	0.32	72.13	8.38 - 620.70	< 0.001	4687793	.	0.989
Congenital birth defect										
Yes	155	49.05	23	7.28	12.26	7.14 - 21.06	< 0.001	85.37	33.01 - 220.77	< 0.001
No	161	50.95	293	92.72	1.00	Reference		1.00	Reference	

SGA: small for gestational age; AGA: appropriate for gestational age; LGA: large for gestational age. * Nulliparous.

Source: Authors.

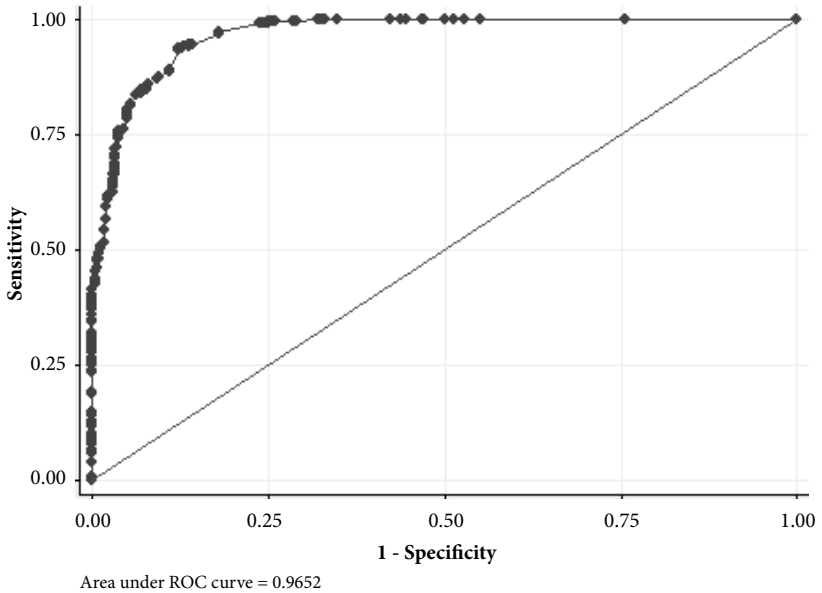

Figure 2. ROC curve to estimate the accuracy of the multiple logistic regression model for predicting perinatal death with five independent variables. CHC-UFPR, 2013-2017.

Source: Authors.

with an increase of 65% in the odds of stillbirth when compared with younger women[32]. A study of 661,062 pregnant teenagers in the United States showed that teen pregnancies were associated with increased odds of preterm birth, fetal growth restriction, and congenital birth defects[33]. In the present study, we observed a slight increase in the risk of perinatal death in women aged ≥ 35 years; however, the association was not statistically significant. Maternal education level has also been shown to be an important factor influencing maternal and child health. Data from the Birth in Brazil survey reveal an association between neonatal mortality and low maternal education level[29]. Our findings in contrast showed that the risk of perinatal death increased with increasing education level. Although this association was not statistically significant, this finding may be due to the specific characteristics of the study population. Many of the women with a higher level of education were attending private antenatal care services and were referred to the CHC-UFPR because they had conditions that are known to increase the risk of complications and need specialized care, such as congenital birth defects for example.

Smoking, drinking, and drug addiction were not shown to affect the odds of perinatal death. However, it is striking that almost 20% of the women were smokers. This is far higher than the rate in the general female population, which, according to the National Health Survey, was 9.8% in 2019[34] and 11% in 2013[35]. In addition, 3.5% of women in the case group and 4.1% in the control group reported using drugs. In this respect, a meta-analysis of eight studies involving 626 women showed that drug use can lead to higher preterm birth rates and low birth weight[36].

Study limitations include missing information in the patient records, including sociodemographic data. As other studies have shown, lack of information in hospital records, especially pregnancy data[37], is common[37,38]. In the present study, missing information prevented the analysis of variables such as income, maternal nutritional status, and paternal age. All variables with information in more than 50% of the patient records were included, adopting the category "ignored" for cases where information was missing. However, missing information can either be due to the absence of the condition or the fact that the information was not recorded. Patient record

Table 3. Results of the multiple logistic regression analysis, distribution (N and %) of cases and controls, adjusted odds ratios (OR), 95% confidence intervals (95%CI), and p-values of the variables. CHC-UFPR, 2013-2017.

Variables	Cases		Controls		Adjusted OR	95%CI	P
	n	%	n	%			
Maternal blood type							
A	109	34.49	126	39.87	1.07	0.55 - 2.06	0.848
B	42	13.29	34	10.76	2.82	1.07 - 7.43	0.035
O	132	41.77	152	48.10	1.00	Reference	
AB	13	4.11	4	1.27	3.49	0.52 - 23.46	0.198
Ignored	20	6.33	0	0.00	.	.	.
Adequacy of antenatal care							
Adequate	97	30.70	248	78.48	1.00	Reference	
Inadequate	11	3.48	17	5.38	1.46	0.28 - 7.61	0.656
Did not attend antenatal care	13	4.11	3	0.95	30.78	4.23 - 224.29	0.001
Ignored	195	61.71	48	15.19	24.97	11.15 - 55.91	< 0.001
Gestational age							
Under 28	94	29.75	1	0.32	24.21	1.10 - 531.81	0.043
28 to 31	70	22.15	7	2.22	6.03	1.34 - 27.17	0.019
32 to 36	70	22.15	46	14.56	1.75	0.78 - 3.93	0.176
37 and over	76	24.05	261	82.59	1.00	Reference	
Ignored	6	1.90	1	0.32	4.67	0.32 - 68.9	0.262
Birth weight							
≥ 999	116	36.71	2	0.63	51.94	4.31 - 626.46	0.002
1,000 to 1,499	44	13.92	7	2.22	11.17	2.29 - 54.41	0.003
1,500 to 2,499	78	24.68	44	13.92	2.75	1.25 - 6.06	0.012
2,500 to 3,999	72	22.78	246	77.85	1.00	Reference	
≥ 4,000	4	1.27	17	5.38	1.11	0.22 - 5.60	0.900
Ignored	2	0.63	0	0.00	.	.	.
Congenital birth defect							
Yes	155	49.05	23	7.28	63.90	27.32 - 149.48	< 0.001
No	161	50.95	293	92.72	1.00	Reference	

Source: Authors.

notes are often written after the professional has seen the patient, resulting in recall bias or meaning that the information is not noted down. Another limitation is that the study was undertaken in a university hospital that receives patients with high-risk pregnancies, resulting in potential skewness in the data and higher prevalence of risk in the control group than in the general population, reducing the chance of confirming that this factor is a risk for perinatal death.

It can be concluded that preterm birth, low birth weight, and having congenital birth defects were the primary risk factors for perinatal death in the study sample, indicating that variables related to fetal viability are determining factors for this outcome. Despite the poor quality of patient records, the results suggest that adequate antenatal care is an important protective factor. The findings also show an association between ABO blood types, especially those with B antigens on the red blood cells, and perinatal death. However, further investigation is needed, including molecular research, to ascertain the relationship between the presence of B antigens and adverse pregnancy outcomes.

Collaborations

CC Szyhta contributed to the conception and design of the study, collection, analysis and interpretation of data, writing and critical review of the final article. ZP Silva contributed to the analysis and interpretation of data and critical review of the final article. GP Alencar contributed to the conception and design of the study and in the critical review of the final article. MF Almeida contributed to the conception and design of the study, analysis and interpretation of data and writing of the article.

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