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Risk factors for neonatal death in an inland region in the State of São Paulo Brazil

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Abstract *The main objective of this study was to identify risk factors for neonatal death in an inland region of the State of São Paulo. A case-control study was conducted using a case group of 162 child deaths that occurred in 2009 in the state's VI Regional Health Department – Bauru. The control group consisted of 324 children selected from the Live Births Information System database who shared the same birth date and city of residence. Univariate and hierarchical multiple logistic regression analyses were performed to identify the factors associated with neonatal death by calculating crude odds ratios adjusted for potential confounders and respective 95% confidence intervals.* Results: *The likelihood of neonatal death was greater among women who had had a history of infant death (OR = 24.97, CI = 12.20 to 51.10) and who had had only up to three antenatal appointments (OR = 11.40, CI = 5, 92 to 21.93), and among infants born at less than 28 weeks of gestation (OR = 168.00, CI = 49.63 to 568.66). The influence of birth weight was also observed among newborns weighing under 1,500g.* Conclusions: *This study identified five independent risk factors for neonatal death, the most notable of which is maternal history of neonatal death, which has not been properly acknowledged as a risk factor by previous studies.*
Key words *Infant mortality, Epidemiology, Antenatal care, Childbirth*

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Introduction

Data released by the World Health Organization (WHO) reveal that the number of child deaths declined from 12.7 million in 1990 to an estimated 5.9 million in 2015. Despite these advances, the number of preventable deaths remains high, especially those that occur during the neonatal period, which account for approximately 45% of child deaths. It is estimated that almost one million neonatal deaths occur on the day of birth and that close to two million infants die in the first week of life. Among the main causes of death are prematurity, pneumonia, and childbirth-related complications[1].

Over recent decades in Brazil, the infant mortality rate has decreased at a rate well above the global average, from 51 deaths per 1,000 live births in 1990 to 15 per 1,000 live births in 2015. As in the rest of the world, the neonatal period accounts for the largest proportion of child deaths in the country, with a rate of nine deaths per 1,000 live births in 2015[1].

Child mortality, divided into its neonatal and post neonatal components, is associated with various social, behavioral, biological and other factors that act in a hierarchical fashion. A study exploring risk factors for neonatal death showed that theoretical and conceptual models are useful for understanding health outcomes because they allow researchers to explore the relationships between different factors. The authors used a four-level model: one made up of distal factors, two intermediate levels, and one comprising proximal factors[2].

Distal factors associated with child mortality, such as level of schooling and maternal age, are social in nature and act according to their capacity to influence others involved in the long causal chain of neonatal mortality. Multiparity, birth order and interval, and under six antenatal appointments are among some of the intermediate determinants, while low birth weight and an Apgar score under seven are considered proximal risk factors[3].

Exploring and understanding the processes that result in infant mortality is critical to ensuring the delivery of high quality, effective child and maternal health care. Considering the inter and intra-regional variations in mortality rates[4], it is important to examine context-specific determinants in order to inform preventative strategies and children's health care policies and interventions, thus warranting regional studies. The present study therefore aims to identify the risk factors for neonatal death in an inland region of the State of São Paulo. The study focuses especially on intermediate risk factors related to previous pregnancy outcomes, obstetric situations, and antenatal care, which, despite requiring health service interventions, have received limited research attention at national level.

Methods

This case-control study encompassed the 68 municipalities that make up the VI Regional Health Department - Bauru (*Departamento Regional de Saúde – DRS VI, Bauru*) of the State of São Paulo, Brazil.

The DRS VI has two Epidemiological Surveillance Groups (*Grupos de Vigilância Epidemiológica* – GVE) and each municipality provides pregnancy, childbirth, and postpartum care to women with low-risk pregnancies. Specialist antenatal, childbirth and neonatal care however is limited to the municipalities that host the five Regional Health Management Teams (*Colegiados de Gestão Regional*): Avaré, Bauru, Botucatu, Jaú, and Lins.

The case group consisted of 162 neonatal deaths, which accounted for 84.8% of the deaths (191 cases) occurring in DRS VI in 2009, while the control group was made up of 324 newborns born in the same municipalities in the same year. The control group was composed by selecting the first two babies registered on the Live Births Information System (*Sistema de Informações de Nascidos Vivos* – SINASC) immediately after each case. Since the number of cases was predetermined, this inclusion criterion was employed to increase the statistical power of the study. The resulting sample size had a statistical power of 80% to detect an odds ratio of 2.5 or greater with a 0.05 significance level for exposure factors with frequencies ranging between 20 and 80%.

Considering the source of information, it is important to scrutinize the quality of data. With a view to generating reliable data, national information systems are undergoing constant improvements both in terms of coverage and quality[5,6] and SINASC has obtained significant improvements in terms of its data quality. A study published in 2015 found that the completeness rate for data concerning the Southeast Region data was 99%[6]. Data for the DRS VI is not available and it was not possible to assess data quality for all the variables used in the present study. However, the fact that the proportion of missing

data is low, particularly since almost all births in the region occur in hospital settings, suggests that the quality of data is generally high.

Also with respect to data quality, a recent study that assessed the recording of perinatal deaths in one the host municipalities of the DRS VI's Regional Management Center (*Pólo de Gestão Regional*) on the Mortality Information System (*Sistema de Informações sobre Mortalidade* – SIM) found that the concordance rate between system data and independently obtained data was 80%. Although it focused on the SIM, the findings of this study suggest that the quality of SINASC data used by the present study is also high since the same teams input data into both systems[7].

It should be highlighted that, before 2008, there was no standard instrument for investigating neonatal deaths in the DRS VI and no coordination between municipal and regional child and maternal health care services. As a result, coverage of investigation of cases, which itself was often partial, was only 53%. In 2008, the government initiated a continuing education program that aimed to train professionals working in the epidemiological surveillance services to conduct effective death investigations, standardize investigation forms, and widen investigation to encompass the whole maternal and child health network, thus resulting in significant improvements in investigation practices and widening coverage.

The data used for this study was collected in 2010 drawing on child death investigation forms from 2009 provided by the GVE and from the SINASC database. The data was inputted using the software Access and analyzed using the Statistical Package for the Social Sciences (SPSS) version 15.0.1.

We explored the association between neonatal mortality (dependent variable) and the following explanatory variables: maternal schooling (up to seven years; eight years and over); maternal age (up to 19 years; 20 to 34 years; 35 years and over); presence of a partner (yes, no); maternal history of neonatal death (no, yes); number of living children (none; one to three; four or more); type of pregnancy (simple, multiple); number of antenatal appointments (zero to three; four to six; seven or more,); type of delivery (vaginal or caesarian); gestational age at birth in weeks (< 28; 28 to 36; 37 and over); birth weight in grams (< 1,500; 1,500 to 2,499; 2,500 and over); and Apgar score in the first minute of life (zero to three; four to six; seven or over).

Univariate and hierarchical multiple logistic regression analyses were performed to calculate the crude and adjusted odds ratios (and respective 95% confidence intervals) for potential confounders. Multiple regression was guided by a theoretical model of determination (Figure 1) developed for the present study based on a model proposed by Lima et al.[2] employed in a study conducted in the Northeast Region of Brazil[8]. The model is made up of four blocks of variables: block one (distal factors), containing sociodemographic variables (level of schooling and maternal age); block two, comprising variables related to previous pregnancy outcomes (previous neonatal death and number of living children); block three, containing variables relating to obstetric situations and antenatal care (type of pregnancy, number of antenatal appointments, type of delivery, maternal age at the time of delivery);

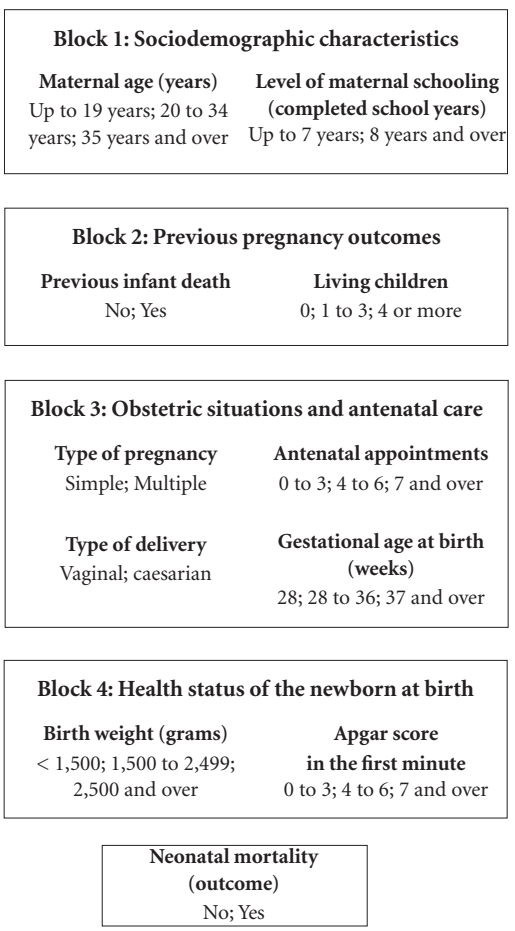

Figure 1. Theoretical model used to analyze the determinants of neonatal mortality.

and block four, comprising variables concerning the health status of the newborn at birth (birth weight and Apgar score in the first minute of life).

A p-value of < 0.20 was adopted for the multivariate analysis for potential confounding variables in the same block or in blocks lower down in the hierarchy, except in the case of level of schooling, which was maintained in the model regardless of the value to reflect socioeconomic status, regarded as the most distal determinant of the outcome under study. A variable was considered a risk factor for neonatal death when the p-value was < 0.05 using the Wald test after adjusting for factors from the same and preceding blocks.

This study was approved by the Research Ethics Committee of the Botucatu Faculty of Medicine and complied with all ethical principles that govern research involving human subjects.

Results

Table 1 shows the characteristics of the cases and controls and the results of the univariate analyses. Pregnancies were more likely to result in neonatal death among women who had a history of neonatal death (OR = 24.97, IC = 12.20-51.10), had attended up to three (OR = 11.40, IC = 5.92-21.93) or between four and six (OR = 4.77, IC = 2.90-7.58) antenatal appointments, and where gestational age was under 28 weeks (OR = 168.00, IC = 49.63-568.66) and between 28 and 36 weeks (OR = 9.85, IC = 5.63-17.24). With respect to the health status of the newborn at birth, there was an association between neonatal death and birth weight — between 1,500 and 2,499 grams (OR = 5.34, IC = 2.99-9.54) and under 1,500 grams (OR = 103.35, IC = 42.33-252.34) — and Apgar score in the first minute of life — between zero and three (OR = 47.18, IC = 23.00-96.77) and four and six (OR = 27.07, IC = 12.78-57.32).

There was a 29-fold increase in the likelihood of neonatal death (IC = 13.77-61.67) among women who had a history of neonatal death, regardless of level of schooling and number of living children. Furthermore, when adjusted for the preceding blocks and type of delivery, having had less than six antenatal appointments led to an 11 to 15-fold increase in the likelihood of neonatal death. The risk of neonatal death among extremely premature babies (born at less than 28 weeks of gestation) was extremely high (OR = 261; IC 95% = 52.26-1310.10), while there was a six-fold increase in the likelihood of neonatal death among babies born at between 28 and 36 weeks of gestation. Similarly, the proximal variables very low birth weight (under 1,500 grams) and an Apgar score in the first minute of life below seven (Table 2) had an effect on the likelihood of neonatal mortality that was independent of the preceding factors.

Discussion

The present study reveals the factors associated with neonatal mortality in a large region of the State of São Paulo. Five factors were associated with a greater likelihood of neonatal death, three of which are from the block representing intermediate factors in the theoretical model utilized for the analysis: history of neonatal death, number of antenatal appointments, and prematurity. Although fixed, the effects of the first of these three factors may be attenuated by quality of antenatal care and should be used as a risk marker for specialist antenatal care. The other two are susceptible to health interventions during gestation and are also related to the quality of care provided during this period. Proximal risk factors were low birth weight, which is intimately associated with prematurity and a low Apgar score in the first minute of life, which in turn is related to quality of care during labor and birth. These findings suggest that, with a view to preventing infant mortality, improving the quality of antenatal and childbirth care should be a priority for health resource allocation in the region.

The most important risk factor for neonatal mortality was prematurity, confirming the findings of earlier research. This is a worldwide problem: a recent systematic literature review showed that preterm birth was the leading cause of death among neonates and under-fives, ahead of pneumonia, which formerly occupied this position[9]. Similarly, a national prospective cohort study conducted in Holland showed that neonatal mortality was closely associated with gestational age, ranging between 546 deaths per 1,000 births at 25 weeks and 18 per 1,000 births at 31 weeks[10].

Though the fact that prematurity is the main cause of neonatal mortality is not entirely a novelty, it is important to highlight that the situation in Brazil is far from comfortable: Brazil ranks among the 10 countries with the highest rate of preterm births[11], the majority of which are preventable with appropriate care during pregnancy[12]. The prevention of premature births requires investment in women's and maternal health, the

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Table 1. Crude association between neonatal deaths and socioeconomic variables related to previous pregnancy outcomes, obstetric situations, and health status of the newborn at birth. DRS VI- Bauru/São Paulo, Brazil, 2009.

Variables	Controls Nº (%)	Cases Nº (%)	p	OR (CI 95%)
Block I: Sociodemographic				
Level of maternal schooling				
8 years or over	243 (75.0)	102 (77.9)		1.00
Up to 7 years	81 (25.0)	29 (22.1)	0.520	0.85(0.52-1.38)
Maternal age (years)				
20 to 34	213 (65.8)	89 (65.9)		1.00
Up to 19	72 (22.2)	31 (23.0)	0.904	1.03(0.63-1.67)
35 and over	39 (12.0)	15 (11.1)	0.801	0.92(0.48-1.75)
Block II: Previous pregnancy outcomes				
History of neonatal death				
No	290 (96.7)	72 (53.7)		1.00
Yes	10 (3.3)	62 (46.3)	< 0.001	24.97(12.20-51.10)
Living children				
1 to 3	177 (56.5)	67 (50.0)		1.00
None	123 (39.3)	63 (47.0)	0.152	1.35(0.85-2.04)
4 or more	13 (4.2)	4 (3.0)	0.725	0.81(0.26-2.58)
Block III: Obstetric situations				
Type of pregnancy				
Simple	314 (96.9)	126 (96.9)		1.00
Multiple	10 (3.1)	4 (3.1)	0.996	0.99(0.30-3.23)
Antenatal appointments				
7 or more	228 (70.6)	35 (28.0)		1.00
4 to 6	75 (23.2)	55 (44.0)	< 0.001	4.77(2.90-7.85)
0 to 3	20 (6.2)	35 (28.0)	< 0.001	11.40(5.92-21.93)
Type of delivery				
Vaginal	147 (45.4)	72 (52.9)		1.00
Caesarian	177 (54.6)	64 (47.1)	0.138	0.73(0.49-1.10)
Gestational age (weeks)				
37 and over	279 (86.1)	31 (23.3)		1.00
28 to 36	42 (13.0)	46 (34.6)	< 0.001	9.85(5.63-17.24)
< 28	3 (0.9)	56 (42.1)	< 0.001	168.00(49.63-568.66)
Block IV: Health status of the newborn				
Weight (grams)				
2,500 or more	278 (85.8)	39 (25.0)		1.00
1,500 to 2,499	40 (12.3)	30 (19.2)	< 0.001	5.34(2.99-9.54)
< 1,500	6 (1.9)	87 (55.8)	< 0.001	103.35(42.33-252.34)
1 minute Apgar score				
7 or over	297 (92.6)	32 (25.0)		1.00
4 to 6	12 (3.7)	35 (27.3)	< 0.001	27.07(12.78-57.32)
0 to 3	12 (3.7)	61 (47.7)	< 0.001	47.18(23.00-96.77)

effective implementation of actions directed at family planning, and improvements in the quality of care delivered before, during, and after pregnancy, while the survival of premature babies depends on the quality of perinatal care: almost three-quarters of deaths due to preterm birth complications could be prevented through simple actions such as keeping babies warm, breastfeeding support, and basic care for infections and breathing difficulties provided by health care professionals who are adequately trained and equipped to provide the necessary care.

Table 2. Association between neonatal mortality and variables related to previous pregnancy outcomes (Block II), obstetric situations (Block III), and health status of the newborn (Block IV) considering the adjusted odds ratio values. DRS VI - Bauru/São Paulo, Brazil, 2009.

Variables	p	OR (CI 95%)
Block II: Previous pregnancy outcomes*		
History of neonatal death		
No		1.00
Yes	< 0.001	29.14 (13.77-61.67)
Living children		
1 to 3		1.00
None	0.092	1.54 (0.93-2.57)
4 or more	0.312	0.43 (0.08-2.19)
Block III: Obstetric situations†		
Antenatal appointments		
7 or more		1.00
4 to 6	< 0.001	11.40 (3.95-32.87)
0 to 3	< 0.001	15.45 (4.29-55.65)
Type of delivery‡		
Vaginal		1.00
Caesarian	0.686	1.88 (0.51-2.74)
Gestational age (weeks)		
37 and over		1.00
28 to 36	< 0.001	6.78 (2.74-16.78)
< 28	< 0.001	261.67(52.261310.10)
Block IV: Health status of the newborn		
Weight (grams)		
2,500 or more		1.00
1,500 to 2,499	0.980	0.98 (0.20-4.77)
< 1,500	0.032	11.34 (1.23-103.81)
1 minute Apgar score		
7 or more		1.00
4 to 6	< 0.001	11.65 (2.66-50.88)
0 to 3	< 0.001	46.06 (11.30187.77)

* Block II: adjusted for level of schooling and variables from the same block. †Block III: adjusted for level of schooling, variables from block II, and variables from the same block. ‡Variable not included in the adjustments for Block IV.

Intimately related to gestational age at birth, low birth weight can generally be addressed through actions directed at preventing preterm birth. The findings of the present study show that birth weight was a relevant independent factor when under 1,500 grams. The lack of an independent negative effect of birth weight between 1,500 and 2,499 grams is probably due to technological advances in recent years that have increased babies' chances of survival.

The main contribution of this study was the identification of history of neonatal death as an independent risk factor for neonatal mortality. Pregnancies in women who have had a history of neonatal death should be considered high-risk and therefore require special attention. However, with respect to previous pregnancy outcomes, only history of stillbirth or perinatal death are considered high-risk pregnancy factors in Brazil[13]. It is therefore suggested that the conception of previous loss should be widened to include previous history of child loss regardless of age and that this should be a criterion for recommending referral and at least one examination in a specialized service and classification as a high-risk pregnancy to ensure appropriate antenatal interventions.

A reduced number of antenatal appointments is an independent factor that may be influenced by health services, particularly through the following actions: early identification of all pregnant women in a given area; ensuring return visits at specified intervals[13]; active searches for women who miss antenatal appointments; checking whether referred cases are receiving care at the respective referral centre; and the extinction of "antenatal discharge", which should be considered effectively completed only after a final check-up before delivery. Such actions should be implemented or strengthened in the antenatal care services in the region studied.

However, despite the importance of regular antenatal care, it is recognized that it is not enough to quantify the number of antenatal appointments[13]. The present study is limited because it only assessed the number of appointments, rather than the quality of antenatal care. It is therefore suggested that further research should explore the association between quality of antenatal care and risk of neonatal death using indicators such as the detection and early treatment of intrauterine growth retardation and congenital syphilis during pregnancy and Rh isoimmunization by giving the mother immune globulin at the right time.

This study shows that an Apgar score in the first minute of life of less than seven is an independent risk factor for death during the neonatal period. Despite questions regarding its sensitivity, specificity and capacity for predicting morbidity and mortality in the short and long term[14], this indicator is widely used to assess newborn health status in the first few minutes after birth and the

degree of neonatal depression[15,16]. The findings of the present study confirm that the Apgar score is an effective indicator of newborn vulnerability.

Other national and international studies[17,18] have found an association between a low Apgar score and neonatal mortality. A study carried out in São José dos Campos in the State of São Paulo using data from statements of live births and death certificates showed that the likelihood of neonatal death was three times greater among newborns with an Apgar score of less than seven, while a population study conducted in Scotland using data from over one million births found that there was a strong association between low Apgar scores (0-3) in the fifth minute of life and risk of neonatal and child death.

Further research into the quality of childbirth and newborn care should be carried out to support actions aimed at preventing neonatal mortality in the region concentrating, for example, on the following aspects of care: the use of demonstrably useful child birth technology in maternity centers; whether the antenatal and childbirth health care provided by the health service network and Regulation Center (*Central de Regulação*) is tailored to meet the needs of each specific case; whether women in labor are provided with care in a welcoming environment in the first maternity center that they go to; whether women are effectively informed about their and their baby's health status and the procedures.

One of the limitations of case-control studies tends to be the temporal analysis of associations. However, in the case of the present study, all the variables associated with neonatal death were related to events that took place before the outcome and the associations observed in the analyses were not due to recall bias. One limitation that should be highlighted however is the use of different information sources for the cases and controls, given that case data was obtained from investigation forms, while the information on the controls obtained from SINASC constituted secondary data. Regarding the data quality, as described above, the information was collected straight after the implementation of an education program aimed precisely at training teams to conduct effective child death investigations. Furthermore, the teams that inputted data into the SINASC had recently received training and were adequately overseen. Therefore, despite the fact that no specific study has been conducted in the region to validate the data, an assumption may be made that the data is of adequate quality.

Conclusions

This study observed five independent risk factors for neonatal mortality in the DRS VI – Bauru: prematurity and low birth weight, especially in extreme situations (being born at less than 28 weeks of gestation and birth weight under 1,500 grams); Apgar score, where the magnitude of the effect on neonatal mortality of a score between zero and three was four times greater than a score of between four and six; and antenatal care and previous pregnancy outcomes, suggesting that pregnant women who have had a history of neonatal death should receive special attention given the strong association between this factor and neonatal mortality.

Collaborations

FCM Sleutjes and CMGL Parada worked on the design and design or the analysis and interpretation of the data and final preparation, MABL Carvalhaes and MJ Temer acted in the writing of the article or in its critical revision.

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