Risk Factors Associated with Prematurity Other than Infectious Causes: A Prospective Multicenter Cohort Study in the Colombian Northeast

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ABSTRACT

Introduction: Prematurity causes great morbidity and mortality in childhood, which is why the identification and prevention of risk factors is essential.

Objective: To identify the association of non-infectious risk factors with prematurity in two reference centers in northeastern Colombia.

Patients and Methods: Multicenter prospective cohort study carried out between January 2019 and March 2020. A non-probabilistic convenience sampling was carried out in pregnant women with a single pregnancy, greater than 20 weeks who were then followed up monthly until the moment of birth. Preterm birth was considered as an outcome variable, after the normality analysis, based on Shapiro-Wilk Test; Chi2 or Fisher tests were performed for qualitative variables, and t-test or Wilcoxon test for quantitative variables, $p < 0.05$ was considered significant and OR was calculated by regression logistics.

Results: 559 pregnant women were studied, with 63 preterm births. An association was found between prematurity and gestational obesity (OR 2.71; 95% CI 1.52-4.81), hypertensive disorder associated with pregnancy (OR 3.88; 95% CI 2.18-6.90), premature rupture of membranes (OR 3.86 95% CI 1.60-9.29) and previous preterm labor in the current pregnancy (OR 17.39 95% CI 9.57-31.51).

Conclusions: Prematurity is significantly associated with gestational obesity, pregnancy-associated hypertensive disorder, premature rupture of membranes, and previous preterm labor in current pregnancy. Further studies would be needed to support these findings.

Keywords (MeSH)

Risk Factors, Premature newborn, Maternal Obesity, Premature rupture of membranes, Gestational diabetes, Gestational Hypertension, Pregnancy-Induced Hypertension, Premature Labor.

Introduction

The World Health Organization (WHO) defines premature as any birth that occurs before 37 weeks of gestation or 259 days after the first day of the last reliable menstruation. Prematurity can be classified as: late (birth between 34 and 36.6 weeks), moderate (32 to 33.6 weeks), very premature (28 to 31.6 weeks) and extremely premature (<28 weeks) [1].

Around the world, an estimated 15 million premature babies are born each year, which are responsible for 75-80% of perinatal mortality (40% of these deaths occur in children under 32 weeks) and for most neurological and respiratory complications shown by neonates. This entity is a serious public health problem, positioned as the leading cause of death in newborns and the second leading cause of death after pneumonia in children under 5 years of age [1-3].

Similarly, for infants who manage to survive the neonatal stage, there is greater long-term morbidity related to learning problems, social adaptation, disorders of the sense organs which may present language, vision and hearing compromise, among others; This limits the quality of life of patients and generates significant health, education and general care expenses [1,2].

There are multiple classifications on the cause of preterm birth, within which classifications have been proposed according to maternal and fetal pathologies, including placental damage, although are little-used due to their limited clinical utility. One of the most accepted classifications when conducting preterm birth studies is the division between spontaneous prematurity (secondary to the onset of spontaneous preterm labor with or without premature rupture of membranes) or induced (labor induction or cesarean section per medical instructions without triggering labor) [4-6]. The literature often cites a relative proportion of 70% of spontaneous preterm births and 30% of induced preterm births, however, the percentage of each varies according to the region studied [4].

Among the main causes of induced preterm births are perinatal (hypertensive disorders associated with pregnancy, placental abruption and placenta previa) or fetal (Intrauterine Growth Restriction - IUGR or acute fetal distress) [7].

The literature reports that ascending bacterial infection and chorioamnionitis cause at least 40% of all spontaneous preterm births, and their pathophysiology is the only one that has demonstrated a strong causal relationship. Patients with Preterm Labor (PL) and intact membranes present positive cultures of amniotic fluid in 12.8%, this percentage rises to 32.4% in those

with Preterm Premature Rupture of Membranes (PPROM) [8,9]. Similarly, 60% of preterm births have positive fetal cultures compared to 20% of those at term. In relation to these findings, many pregnant women usually present a subclinical infection, becoming asymptomatic; This led to the standardization of an infectious screening for all pregnant women with PL without a known cause [10].

In general, prematurity is a complex entity that involves multiple pathophysiological mechanisms, for which in recent years various risk factors that could contribute to it have been studied, such as: teenage pregnancy, short birth interval, inadequate weight before and during pregnancy (underweight or obesity), chronic diseases (diabetes and / or high blood pressure), substance abuse (tobacco and high alcohol consumption) and mental health disorders (stress and depression). Nowadays, it is suggested that there are still many risk factors that have not been determined and that could be associated with socio-demographic, genetic and environmental variables that have not been studied [11].

The pathophysiology of prematurity is broad and sometimes the causes overlap. It is essential to define in daily clinical practice, the interventions for risk factors, classify according to gestational age and consider possible complications derived from it since there are many unfavorable outcomes generated by prematurity. In general, prevention continues to be the most important objective, the various associated pregnancy conditions must be identified, which, in turn, must be studied when carrying out a comprehensive approach in order to intervene in a timely manner, so that they impact on the reduction of neonatal mortality and morbidity [12].

Given that the pathophysiology of intrauterine infection has been well studied, the objective of the present study is to identify the association of socio-demographic risk factors, maternal characteristics, and gestational comorbidities other than infectious ones related to prematurity in two reference centers in northeastern Colombia.

Materials and Methods

Prospective multicenter cohort study based on the medical records of pregnant women who ended their pregnancy at the “*Clínica Materno Infantil San Luis*” (CMISL) and the “*Hospital Universitario de Santander*” (HUS) between January 2019 and March 2020 as well as their newborns’ medical records.

The study had the approval of the Ethics Committees of the CMISL, the HUS, and the “*Universidad Industrial de Santander*” (UIS). All pregnant women who accepted to participate received thru explanation of the aim and methodology of the study and filled out the informed consent, and the underage ones the informed assent.

A non-probabilistic convenience sampling was carried out. Pregnant women with a single pregnancy who consulted for any reason after the 20th week of gestational age were included, and the medical records were monitored monthly until delivery.

Exclusion criteria were pregnant women who had a decision to end the gestation period due to trauma or by voluntary termination of pregnancy, pregnant women with chorioamnionitis or infections associated with pregnancy, cervical incompetence, and multiple pregnancies. Neonates with life limiting congenital anomalies and those who died at birth without a definite cause were also excluded.

Several variables were registered, including: Sociodemographic maternal variables-(Place of origin, age, anthropometric parameters and number of pregnancies), maternal comorbidities (obesity, Hypertensive Disorder Associated with Pregnancy (HDAP) and diabetes), perinatal variables (PL and PPRM) and neonatal variables (gender, anthropometric parameters, type of delivery and early neonatal hypoglycemia).

The nutritional status of the pregnant women was defined according to the Rosso-Mardones curve based on the Weight/Height relationship according to gestational age [13]. HDAP was defined as: 1) Gestational hypertension: blood pressure levels above 140 / 90mm of Hg, after the 20th week of gestation, in a previously normotensive patient, without proteinuria, with return to normality in the postpartum period. 2) Preeclampsia: gestational hypertension associated with proteinuria greater than 0.3 g / 24 hours. 3) Chronic hypertension: preexisting hypertension in pregnancy or diagnosed before the 20th week of gestation, which persists for up to 12 weeks after delivery. 4) Chronic hypertension with superimposed preeclampsia: proteinuria onset greater than 0.3 g / 24 h in a pregnant woman after week 20 with chronic hypertension and registering normal proteinuria [14].

The diagnostic criteria for gestational diabetes were: pregnant women with one or more altered values of the oral glucose tolerance curve with a load of 75 gr (fasting> 92mg/dL, first hour> 180mg/dL, second hour> 153mg/dL) or all patient with O'Sullivan's test> 200mg/dL [15].

Preterm premature rupture of membranes (PPROM) was defined as premature rupture of membranes (PROM) that occurs before 37 weeks of pregnancy [16].

Preterm labor (PL) was defined as the onset of regular uterine activity that leads to cervical changes in position, consistency, length and/or cervix dilation causing cervix effacement greater than 50% and a dilation of 4 cm or more before the 37th week of gestation [17].

Intrauterine growth restriction (IUGR) was defined as: 1. Fetal growth below the 10th percentile for gestational age, associated with signs of fetal compromise (abnormalities of the feto-placental circulation identified by Doppler), 2. Weight less than the 3rd percentile for gestational age 3. Deviation from the growth pattern with flattening of the growth curve outside the lane and slowing down, regardless of whether it was above the 10th percentile [18].

Macrosomia and low weight for gestational age were defined as birth weight above the 90th percentile and below the 10th percentile, respectively, according to the Fenton-growth charts [19].

Transient neonatal hypoglycemia was defined as blood glucose <50 mg/dL in the first 48 hours or <60 mg/dL in the 48-72 hours [20].

Preterm delivery was considered as an outcome variable. Gestational age was calculated according to the most reliable data found in the medical records in the following order: first trimester ultrasound, date of last reliable menstrual period and neonatal physical examination.

The information collected was stored using two databases typed by two researchers. Afterward, we checked the agreement of both databases; in case of disagreement, a third researcher introduced the data to make sure it was reliable.

For this statistical analysis, the categorical, nominal and ordinal variables are presented as proportions with their confidence intervals (95% CI). The quantitative variables are presented with measures of central tendency and dispersion (average and their standard deviations [SD] or Interquartile range [IQR] in the event that their distribution is not normal). A normality analysis was performed using the Shapiro Wilk test. Subsequently, a group comparison analysis was performed using the Chi2 or Fisher test for qualitative variables and the t-test or Wilcoxon test for quantitative variables according to their distribution. Any difference where the test performed showed $p < 0.05$ was considered significant. OR were calculated using logistic regression to estimate the association between the variables and prematurity. All analysis were performed with Stata 16.1 (College Station, Texas, USA, 2019).

Results

In the present study, five hundred fifty-nine (559) pregnant women were included, of which 161 (28.80%) belonged to the HUS and 398 (71.20%) belonged to the CMISL. This distribution occurred randomly (Figure 1).

Regarding births, there were 496 (88.7%) term births and 63 (11.2%) preterm births, of which the majority: 55 (87.4%) were late preterm.

Concerning socio-demographic and maternal variables, the average weight of pregnant women with premature births was greater (80,2 kg) compared to pregnant women with term deliveries (75,5 kg); it was the only variable with statistical significance ($p = 0.04$). There were no significant differences between the two study groups regarding the origin, maternal age, maternal height, and previous pregnancies (Table 1).

Figure 1: Selection and distribution of the population.

Table 1: Socio-Demographic and maternal variables.

Variable	Premature (n=63)	Non-premature (n=496)	P value
Urban origin	n (%)	n (%)	0,59
	52 (82,54%)	422 (85,08%)	
Maternal age	M (IQR)	M (IQR)	0,174
	26 (22-29)	27 (23-32)	
Maternal age <20 years	n (%)	n (%)	0,79
	9 (14,29%)	65 (13,10%)	
Maternal age 20-35 years	n (%)	n (%)	0,73
	47 (74,60%)	360 (72,58%)	
Maternal age >35 years	n (%)	n (%)	0,58
	6 (9,52%)	59 (11,9%)	
Maternal Weight in Kg	M (IQR)	M (IQR)	0,04
	80,20 (60-87)	75,50 (69-83)	
Maternal height in Cm	m (SD)	m (SD)	0,52
	158,26 (5,2)	158,75 (5,85)	
Primiparous	n (%)	n (%)	0,29
	18 (28,57%)	175 (35,28%)	
Multigestant with 3 or more pregnancies (including the current one)	n (%)	n (%)	0,20
	20 (31,75%)	121 (24,4%)	

SD: Standard Deviation, IQR: Interquartile range

Table 2: Variables associated with maternal pathology.

Variable	Premature (n=63)	Non-premature (n=496)	P value	OR (CI 95%)
Gestational obesity	45 (71,43%)	238 (47,98%)	<0,001	2,71 (1,52-4,81)
HDAP	23(36,51%)	64 (12,9%)	<0,001	3,88 (2,18-6,90)
Gestational Diabetes	6 (9,52%)	48 (9,68%)	0,96	

Table 3: Perinatal Variables.

Variable	Premature (n=63)	Non-premature (n=496)	P value	OR (CI 95%)
PROM	16 (25,4%)	213 (42,94%)	0,001	3,86 (1,60-9,29)
Previous PL	41 (65,08%)	48 (9,68%)	<0,001	17,39 (9,57-31,51)

Table 4: Neonatal variables.

Variable	Premature (n=63)	Non-Premature (n=496)	P value	OR (CI 95%)
Female sex	28 (44,44%)	249 (50,2%)	0,38	
Low newborn weight for gestational age	19 (30,16%)	82 (16,53%)	0,008	2,18 (1,21-3,92)
IUGR	4 (6,35%)	11 (2,22%)	0,05	
Fetal Macrosomy	12 (19,05%)	59 (11,9%)	0,10	
Transient neonatal hypoglycemia	11 (17,46%)	14 (2,82%)	<0,001	7,28 (3,14-16,86)
Cesarean delivery	47 (74,60%)	283 (57,06%)	0,009	2,21 (1,22-4)

Table 5: Causes of preterm birth.

Cause of preterm birth	n = 63
PL with no documented infection	45 (71,42%)
Preeclampsia	11 (17,46%)
PPROM + oligohydramnios	2 (3,7%)
IUGR	2 (3,7%)
Placental accreta	1 (1,58%)
Intrahepatic cholestasis	1 (1,58%)
Maternal cholecystitis	1 (1,58%)

Regarding the variables associated with maternal pathology, pregnant women with obesity had 2.71 times the risk of having a premature birth, and pregnant women with any Hypertensive Disorder Associated with Pregnancy (HDAP) had 3.88 times the risk of presenting this outcome. There was no statistically significant association between gestational diabetes and preterm birth (Table 2).

When analyzing perinatal variables, pregnant women who presented PPRM had 3.86 times the risk of preterm birth. If the pregnant woman had threatened preterm labor (TPL) at any stage of pregnancy, even if successfully controlled, the risk of premature birth was 17.39 times higher than pregnant women who did not have this finding. This variable had the most significant statistical association found in this study (Table 3).

The analysis of neonatal variables showed no difference between the mean distribution of newborn gender among the preterm and the full-term. The preterm group was associated with a 2.18 higher risk of having low birth weight according to the Fenton curves, as well as 7.28 times the risk of presenting transient neonatal hypoglycemia and 2.21 times the risk of cesarean delivery; there were no statistically significant differences between the groups related to IUGR and macrosomia (Table 4).

Table 5 shows the causes that led to the preterm birth of 63 patients. Of these preterm births, 71.42% began with a PL without a clear cause (not associated with active maternal infection), which is defined as spontaneous preterm birth, and the remaining 28.58% of preterm births were medically indicated due to the presence of perinatal pathology, referred to in the literature as induced preterm birth (preeclampsia, PPRM + oligohydramnios, IUGR, placenta accreta spectrum disorders (PAS), intrahepatic cholestasis, and maternal cholecystitis) [4].

Discussion

The present study found a prevalence of prematurity of 11.20%, and 87.40% corresponded to late prematurity, similar to worldwide statistics [21]. In the analysis by logistic regression models, four variables were identified as statistically significant risk factors for preterm birth: gestational obesity (RR 2.71, 95% CI 1.52-4.81), HDAP (RR 3.88 CI95 % 2.18-6.90), PROM (RR 3.86 CI95% 1.60-9.29) and PL at any stage of pregnancy, even if it had been controlled (RR 17.39, 95% CI 9.57- 31-51). PL was the variable with the highest statistical association found in our study. Additionally, it was related to the group of premature babies with the highest proportion of cesarean births (RR 2.21 95% CI 1.22-4), low birth weight (RR 2.18 95% CI 1.21-3.92), and transient neonatal hypoglycemia (RR 7.28 95% CI 3.14-16.86).

Maternal weight was the only variable with statistical significance among the socio-demographic variables associated with prematurity in the present study. Previous cohort studies [22,23] identified other associated variables, such as maternal age, particularly for those under 18 and those over 40 years of age, where the risk of prematurity is up to 1.2 times higher. A 2013 meta-analysis [24] with data based on developing countries found a positive association between maternal height <150cm and prematurity (OR 1.1-1.4) and a slightly increased risk of prematurity among women in their first-pregnancy (OR 1.1 95% CI 1.0-1.2) and grand multiparity defined as parity ≥ 3 (OR 1.2 95% CI 1.1-1.4).

In the present study, gestational obesity was a risk factor for prematurity, with an OR similar to other studies such as a Swedish cohort [25] that included 1,857,822 pregnant women and their newborn babies. The Swedish cohort found an OR of 2.71 for the association between gestational obesity and preterm delivery. A meta-analysis [26] on maternal body mass index and preterm birth included 39 studies (3 case-control studies and 36 cohort studies) with 1,788,633 pregnant women with pregestational obesity and their products. The association between these two variables was not statistically significant. Although, when performing subgroup analysis, patients with grade II and III pregestational obesity had a higher risk of having preterm births (ORa 1.33, 95% CI: 1.12-1.57 and ORa 1.83, 95% CI 1.62– 1.07 respectively).

In another prospective cohort study in more than 80,000 Norwegian pregnant women, the risk of premature birth was higher in obese maternal mothers with an OR of 2 (95% CI 1.48-2.71) [27]. Similar results to those obtained in a cohort of more than 60,000 Danish women, obese women had a risk ratio of 1.5 for spontaneous

premature birth with premature rupture of membranes compared to women with normal nutritional status [28].

Among the main findings of this study, we highlight the association of previous PL at any stage of the current pregnancy, even if controlled. Pregnant women also had a 17.39 times higher risk of recurrent preterm labor and consequently preterm birth, which is why it should be a significant risk factor when monitoring pregnant women.

Additionally, obese pregnant women had 2.71 times the risk of preterm delivery than pregnant women with normal nutritional status. Pregnant women with obesity without a diagnosis of HDAP or diabetes had an OR of 2.43 (95% CI 1.27-4.65). These results are concordant with the lipoinflammation theory, where obesity without the context of a metabolic syndrome represents a significant risk factor for adverse perinatal outcomes; such as prematurity, and pregnant women who gain weight rapidly have a higher proinflammatory status compared to those who have chronic obesity with mature adipocytes [29]. However, we consider that new evidence is required to solidify this theory. In the future, we believe it is necessary to carry out studies based on non-infectious placental inflammatory changes and their relationship with obesity and prematurity.

In the present study, it was impossible to identify the onset of gestational obesity or its occurrence in a pregestational stage. All these aspects might have stemmed from sociocultural factors or shortcomings in the unification of medical records in the healthcare system and follow-up of patients. Thus, we consider it is vitally important to prioritize a generalized strategy to monitor the nutritional status of women beginning in the pregestational stage.

Among the strengths of this study, it is a prospective cohort with data collection in two tertiary care centers that attend pregnant women in northeastern Colombia. We had an acceptable sample size considering that it was focused on premature births. Additionally, with the monthly follow-up, it was possible to associate the risk factors of pregnant women and the outcomes of premature infants.

This study leaves a significant precedent that broadens the analysis of variables possibly related to prematurity other than infectious causes in pregnant women in northeastern Colombia. Although, it would be necessary to carry out new studies that evaluate other additional risk factors related to genetic and environmental variables.

Ethical considerations

The study was performed with the prior approval of the ethics committee of the CMISL, the HUS, and the *Universidad Industrial de Santander* (UIS). The purpose and methodology of the research were explained to all pregnant women invited to participate in this study, and those who accepted to participate signed written informed consent or assent if they were underage.

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