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RESEARCH ARTICLE

Role of gestational age and maternal biological factors in early term neonatal morbidity

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Abstract

Background: *The morbidity of early-term newborns (ETNBs) is associated with the immaturity of their organs and maternal biological factors (MBF). In this study, we determined the relationship between MBF and early-term birth. In addition, we assessed the role of gestational age (GA) and MBF in the morbidity of ETNBs compared with full-term newborns (FTNBs).* **Methods:** *This retrospective cohort included ETNBs and FTNBs. The frequency of morbidities was compared between groups stratified by GA with the X^2 test or Fisher's exact test. The association of MBF with GA and morbidity was calculated using binomial regression models between the variables that correlated with the morbidity of the ETNBs using Spearman's correlation. A significance level of 5% was estimated for all analyses.* **Results:** *The probability of morbidity at birth for ETNBs was 1.9-fold higher than for FTNBs (37.5% vs. 19.9%), as they required more admission to the neonatal unit and more days of hospitalization; the most frequent pathology was jaundice. The MBF associated with early term birth were hypertensive disorders of pregnancy (aRR = 1.4, 95% confidence interval (CI): 1.3–1.6), intrauterine growth restriction (aRR = 1.5, 95%CI: 1.3–1.6), and chronic hypertension (aRR = 1.6, 95%CI: 1.4–1.8). No association was found between MBF and morbidity at 37 and 38 weeks.* **Conclusions:** *The morbidity among ETNBs is related to physiological immaturity. The adverse MBF favor a hostile intrauterine environment, which affects fetal and neonatal well-being.*

Keywords: *Newborn. Morbidity. Biological factors. Gestational age.*

Rol de la edad gestacional y factores biológicos maternos en la morbilidad del neonato a término temprano

Resumen

Introducción: *La morbilidad de los recién nacidos a término temprano (RNTT) se asocia con la inmadurez de sus órganos y factores biológicos maternos (FBM). En este estudio se determinó la relación entre FBM y el nacimiento a término temprano. Además, se evaluó el papel de la edad gestacional (EG) y los FBM en la morbilidad de los RNTT comparados con los recién nacidos a término completo (RNTC).* **Métodos:** *Este estudio de cohorte retrospectivo incluyó RNTT y RNTC. La frecuencia de morbilidades se comparó entre grupos estratificados por EG con la prueba de X^2 o la prueba exacta de Fisher. La asociación de FBM con EG y morbilidad se calculó mediante modelos de regresión binomial entre variables correlacionadas con morbilidad de ETNB mediante la correlación de Spearman. Se estimó un nivel de significación del 5% para todos los análisis.* **Resultados:** *Los RNTT presentaron una probabilidad 1.9 veces mayor de morbilidad al nacer*

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comparado con los RNTC (37.5% vs 19.9%), ya que requirieron mayor admisión a la unidad neonatal y más días de hospitalización; la patología más frecuente fue la ictericia. Los FBM asociados con el nacimiento a término temprano fueron los: trastornos hipertensivos gestacionales, restricción del crecimiento intrauterino e hipertensión crónica. No se encontró asociación entre factores biológicos maternos y la morbilidad a las 37 y 38 semanas. **Conclusiones:** *La morbilidad del RNTT se relaciona con la inmadurez fisiológica. Los FBM adversos favorecen un medio intrauterino hostil afectando el bienestar fetal y neonatal.*

Palabras clave: *Recién nacido. Morbilidad. Factores biológicos. Edad gestacional.*

Introduction

In 2012, multiple international organizations, including the World Health Organization (WHO), defined a term pregnancy according to weeks of gestation[1]. By 2017, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (ACOG), in their perinatal care guidelines, classified term newborns into subgroups, considering the differences in their morbidity and mortality: (i) early-term newborns (ETNBs), between 37 weeks and 0 days to 38 weeks and 6 days; (ii) full-term newborns (FTNBs), between 39 weeks and 0 days to 40 weeks and 6 days; and (iii) late-term newborns (LTNBs), between 41 weeks and 0 days to 41 weeks and 6 days[2]. Early-term births are estimated to account for 15%–30% of all births worldwide, with a higher incidence in low and middle income countries[3-11]. This increase has been attributed to medical indications for delivery, such as adverse maternal factors that can lead to early-term deliveries vaginally or through cesarean section[12], and no medically indicated delivery, such as cervical ripening, inductions of labor and cesarean delivery before 39 0/7 weeks of gestation[13].

The morbidity of ETNBs is higher than that of FTNBs and LTNBs[14] because of physiological immaturity. The development of organs is a continuous process that takes place at different rhythms to fulfill specific functions in extrauterine life; even in ETNBs with positive pulmonary maturation tests, the risk of adverse birth outcomes is not low[15]. In addition to gestational age (GA), other variables also affect the degree of maturation impairment[16]. Adverse maternal biological factors, such as infection or inflammation, hypoxia or ischemia, gestational diabetes, preexisting diabetes mellitus, maternal obesity, polyhydramnios, or oligohydramnios, may cause an unfavorable intrauterine environment, which compromises fetal well-being and can independently accelerate delivery.

A study[17] conducted in the U.S.A. indicated that during 1998–2003, antepartum hemorrhage and hypertensive disorders showed the greatest risk of morbidity at early-term birth. A Canadian study by Brown et al. (2015) identified maternal chronic diseases as the most common medical indication for early-term birth[18]. In 2017, Younes et al. in Qatar[5] reported that advanced maternal age, pregestational diabetes, fertility assistance, and a history of preterm delivery are independent risk factors for preterm or early-term deliveries.

Although studies from middle and low income countries have assessed the incidence and morbidity of ETNBs, few have explored the maternal biological factors that can affect the morbidity of ETNBs. Here, we determined, the relationship between maternal factors and early-term birth. In addition, we compared the role of GA and maternal biological factors in the morbidity of ETNBs and full-term newborns (FTNBs) in Colombia, a middle income country.

Methods

We conducted a descriptive, exploratory, retrospective follow-up cohort study in the Maternal and Infant Unit of the Hospital Militar Central, a highly complex hospital in Bogotá, Colombia. We included ETNBs and FTNBs born in 2020 given the expected proportion of early-term births (22.5%–33.8%) and the frequency of ETNB morbidity, with a power of 80%, an alpha of 0.05 using the X^2 test for the proportions of two independent samples, a minimum sample size of 180 ETNBs was estimated to calculate relative risk.

Medical records were identified with numbers provided by the epidemiology department of the institution and chosen by date of admission of the mothers from the beginning of 2020 until the desired sample size was obtained. Relevant data were obtained from the institution's electronic medical records. The inclusion criteria were neonates born in the institution in 2020 with GA between 37 weeks 0 days to 40 weeks 6 days, whose GA was established using the last menstrual period and first-trimester obstetric ultrasound, and for whom all data were available. The exclusion criteria were GA diagnosis by neurological or physical maturity

scales, twins, stillbirth, congenital malformations, and newborns admitted to the neonatal unit after a referral from another institution because transportation can increase the risk of neonatal morbidity.

Data on maternal biological factors that might cause preterm birth were collected. These factors were identified based on previous studies[19]. Type of birth (vaginal or cesarean) was also included as a variable. Other birth-related variables included the type of adaptation at birth (spontaneous, conducted with positive pressure ventilation (PPV), or induced with PPV plus chest compressions and adrenaline), 5-min Apgar score (<7), admission to the neonatal care unit, admission to the neonatal intensive care unit, days of hospitalization, and the morbidities for which they were admitted to the neonatal care, including respiratory diseases, infection, jaundice, feeding problems, and perinatal asphyxia. The diagnoses were obtained by reviewing the International Classification of Diseases 10th revision (ICD-10) codes in the medical records. Other variables evaluated were supplemental oxygen requirement, invasive or noninvasive ventilation, and discharge with home oxygen.

Statistical analysis

Categorical variables were presented as percentages, and continuous variables as means and standard deviations. For association analysis, infants whose mothers had any of the adverse factors were considered as exposed, and the dependent variable was the early term birth or morbidity.

The frequency of morbidities was compared between groups stratified by GA with the X^2 test or Fisher's exact test when the expected frequency was < 5. The association of maternal biological factors with GA and morbidity was calculated using binomial regression models between the variables associated with the morbidity of the ETNBs in bivariate analysis.

A significance level of 5% was estimated for all analyses. All analyses were performed using Stata 16 statistical software. The study was approved by the institution's research ethics committee (No. 2021-051).

Results

In 2020, 686 births occurred in the institution, with 12% preterm, 44% early-term, 40% full-term, and 4% late-term births. Of them, 398 infants met the inclusion criteria and were included in the study: 197 ETNBs (49.5%) and 201 FTNBs (50.5%).

Cesarean sections were more frequent in ETNBs (47.7%) than in FTNBs (42.7%). Admission to the neonatal care unit was 32% for ETNBs compared to 17% for FTNBs. Admission to the neonatal intensive care unit was 1.75 times higher in ETNBs (21%), than in FTNBs (12%).

Overall morbidity was 1.9 times higher in ETNBs (37.5%) than in FTNBs (19.9%). ETNB required more admission to the neonatal unit (aRR 1.3, 95% confidence interval (CI): 1.2-1.5, p = 0.0001) and more days of hospitalization (aRR 3.8, 95%CI: 3.8-3.9, p = 0.0001). Due to the low prevalence of individual pathologies, other morbidities were grouped for analysis based on a related condition: respiratory (transient tachypnea of the newborn and pneumonia), perinatal asphyxia, jaundice, and feeding problems (difficulty in breastfeeding, sucking and swallowing disorders, and hypernatremic dehydration). No statistically significant differences were detected between ETNBs and FTNBs, except for jaundice, which was higher in ETNBs (71.2%) than FTNBs (28.7%) (p = 0.0001) (Table 1).

The maternal biological factors associated with early-term birth were hypertensive disorders of pregnancy (aRR = 1.4, 95%CI: 1.3-1.6), chronic hypertension (aRR = 1.6, 95%CI: 1.4-1.8), and intrauterine growth restriction (aRR = 1.5, 95%CI: 1.3-1.6). No association was found between maternal biological factors and morbidity at 37 and 38 weeks of GA, nor between GA and delivery route. However, a higher frequency was found between induced labor (aRR 1.3 95%CI: 1.1-1.5) and emergency cesarean section (aRR 1.3 95% CI: 1.3-1.4) (Table 1).

Discussion

These results revealed that the most frequent cause of ETNB morbidity was jaundice, consistent with other studies[6,7]. A 2019 study from India by Menon et al. observed that phototherapy was more frequent in ETNBs (53.7%) than FTNBs (46.3%; odds ratio [OR]: 17.73)[7]. Maisels and Kring[20] reported that neonates discharged with GA ≤ 38 weeks showed an OR of > 7 for re-hospitalization for jaundice. Battersby et al.[21] also stated that jaundice was the most frequent pathology in term neonates and described the effectiveness of home phototherapy treatment in decreasing neonatal hospitalization. In this study, birth at 39 and 40 weeks was a protective factor. It is noteworthy that feeding problems were 2.5 times more frequent in the ETNB, most likely related to immaturity.

No significant difference in respiratory morbidity was observed between ETNBs and FTNBs, independently of the route of delivery. This result is likely related to the

Table 1. Association analysis of gestational age and maternal biological factors and neonatal morbidity in early-term and full-term neonates

Variables	Early-term cohort (n = 197) n (%)	Full-term cohort (n = 201) n (%)	Bivariate analysis RR (95% CI)	Final model** (95% CI)
Intrapartum variables				
Vaginal birth (total)	103 (52.2)	115 (57.2)	1.0 (0.8-1.3) p = 0.46	
Spontaneous vaginal birth	94 (47.7)	106 (52.7)	0.8 (0.7-1.0) p = 0.19	
Induction of labor	9 (4.6)	9(4.5)	1.3 (1.0-1.8) p = 0.02	1.3 (1.1-1.5) p = 0.0001
CS+ (total)	93 (47.7)	85 (42.7)	1.06 (0.8-1.2) p = 0.56	
Elective CS++	6 (3)	12 (6)	0.56 (0.24-1.30) p = 0.18	
CS due to complication during pregnancy	13 (6.6)	10 (4.9)	1.15 (0.79-1.67) p = 0.45	
CS due to maternal illness	8 (4.0)	0	1	
CS due to previous CS	14 (7.1)	28 (14.4)	0.63 (0.4-0.9) p = 0.04	
Iterative CS +++	16 (8.1)	14 (6.9)	1 (0.76-1.53)	
Emergency CS++++	36 (18)	21 (10.4)	1.35 (1.08-1.69) p = 0.008	1.36 (1.3-1.4) p = 0.0001
Type of adaptation: spontaneous	180 (91.3)	183 (91.0)	1.0 (0.71-1.45) p = 0.9	-
Type of adaptation: conduced or induced &	17 (8.6)	18 (10)	1.0 (0.37-2.7) p = 0.98	
Apgar > 7	196 (99.5)	198 (98.5)	0.88 (0.5-1.4) p = 0.65	
Apgar < 7	1	3	0.5 (0.9-2.75) p = 0.42	
Morbidity				
Days of hospitalization	1.07 ± 2.7*	0.6 ± 1.7*	1.0 (1.02-1.03) p = 0.0001	3.8 (3.8-3.9) p = 0.0001
Admission to the neonatal care unit	63 (32)	28 (17)	1.03 (1.0-1.0) p = 0.0001	1.3 (1.2-1.5) p = 0.0001
Admission to the neonatal intensive care unit	21 (21.0)	12 (12.5)	1.7 (0.9-1.8) p = 0.05	-
Respiratory morbidity	16 (16.0)	16 (16.4)	1.0 (0.7-1.4)	-
Oxygen requirement (includes high-flow, low-flow cannula, CPAP, invasive ventilation)	22 (22.1)	31 (32.1)	0.8 (0.4-1.3) p = 0.37	-
Noninvasive ventilation (CPAP, high-flow, low-flow cannula)	20 (20.1)	33 (37.7)	0.7 (0.2-2.2) p = 0.33	-
Invasive ventilation	2 (2.0)	3 (3.13)	0.8(0.2-2.3) p = 0.69	-
Home oxygen	2 (2.0)	1 (0.69)	1.35 (0.6-3.04) p = 0.45	-
Perinatal asphyxia	1 (0.9)	1 (0.6)	1.0 (0.25-4.05) p = 0.98	-
Jaundice	139 (71.2)	57 (28.7)	1.5 (1.3-1.9) p = 0.0001	1.64 (1.44-1.86) p = 0.0001
Feeding problems	5 (5.0)	2 (2.4)	1.45 (0.9-2.34) p = 0.12	-
Congenital malformation	3 (1.5)	2 (1)	1.21 (0.59-2.5) p = 0.596	-
Biological factors				
Maternal systemic infection	2 (2.1)	0	1	-
Intrauterine infection	4 (4.0)	5 (5.6)	0.89 (0.42-1.8) p = 0.77	-
Bacterial vaginosis	21 (20.9)	23 (18)	0.95 (0.69-1.33) p = 0.80	-
Premature rupture of membranes	13 (13.1)	10 (10.2)	1.15 (0.79-1.67) p = 0.45	-

(Continues)

Table 1. Association analysis of gestational age and maternal biological factors and neonatal morbidity in early-term and full-term neonates (*continued*)

Variables	Early-term cohort (n = 197) n (%)	Full-term cohort (n = 201) n (%)	Bivariate analysis RR (95% CI)	Final model** (95% CI)
Urinary tract infection	27 (27.3)	37 (34.3)	0.8 (0.6-1.1) p = 0.22	-
Hypertensive disorders of pregnancy	59 (59.1)	28 (26.2)	1.5 (1.2-1.8) p = 0.0001	1.4 (1.3-1.6) p = 0.0001
Chronic hypertension	6 (5.78)	2 (1.39)	1.5 (1.0-2.3) p = 0.04	1.6 (1.4-1.8) p = 0.04
Intrauterine growth restriction	25 (24.0)	5 (3.47)	1.7 (1.4-2.1) p = 0.0001	1.5 (1.3-1.6) p = 0.0001
Placenta previa	3 (2.98)	1 (0.6)	1.5 (0.8-2.7) p = 0.15	-
Placenta abruption	1 (0.9)	0	1	-
Bleeding in the second half of pregnancy	1 (0.9)	0	1	-
Gestational diabetes	15 (14.8)	14 (9.72)	1.0 (0.7-1.5) p = 0.79	-
Preexisting diabetes	3 (2.8)	0	1	-
Maternal obesity	52 (53.1)	50 (54.3)	1.0 (0.8-1.3) p = 0.7	
Oligohydramnios	9 (9.2)	6 (5.26	1.2 (0.7-1.8) p = 0.35	
Polyhydramnios	3 (3.11)	1 (0.6)	1.52 (0.8-2.7) p = 0.15	

+CS: cesarean section; ++ Before the start of labor by decision of the mother or the obstetricians; +++ Cesarean section performed after 2 cesarean sections; ++++ For failure to progress or no reassuring fetal status
*Mean ± standard deviation. ** Adjusted by Chronic hypertension; Hypertensive disorders, intrauterine growth restriction.
& Conducted: need positive pressure ventilation. Induced: need chest compressions with or without epinephrine.
CI: confidence interval; CPAP: continuous positive airway pressure; CS: cesarean section; RR: relative risk.

low frequency of respiratory morbidity in the sample size. Studies have concluded that respiratory morbidity is more frequent in ETNBs and is associated with cesarean delivery, especially elective cesarean. Several studies have indicated that elective cesarean section and male sex are risk factors for respiratory distress[22-25].

Although no association was found between cesarean section and newborn morbidity, the percentage of cesarean sections in both ETNBs (47.7%) and FTNBs (42.7%) was higher than the WHO recommendation of 10%–15%[26], a situation that has been occurring in high, medium, and low income countries[27]. As cesarean section impairs the prognosis of ETNBs[28,29], some countries have implemented strategies to reduce deliveries before 39 weeks[30] with good results; for example, not performing any indicated deliveries (both induction of labor and cesarean) before 39 weeks in uncomplicated pregnancies. In 2021, the ACOG and the U.S. Maternal Fetal Medicine Society updated the medical and obstetric indications for defining the time of delivery, considering that, in some cases, deferring birth until 39 weeks may increase the risk for both mother or fetus.

In this study, ischemic hypoxia (including intrauterine growth restriction, hypertensive disorders of pregnancy, and chronic hypertension) was the cause of early-term birth, consistent with the findings of Brown et al.[16]. In a systematic review, Boskabadi et al.[31] (2020) reported that hypertensive disorders, diabetes, maternal infection, and vaginal bleeding were maternal factors associated with neonatal jaundice. In this study, FTNBs with adverse maternal factors did not show a higher risk of morbidity than ETNBs with similar factors; however, these maternal factors may have affected neonatal outcomes by triggering labor before adequate maturation[19].

Preterm birth rates continue to increase worldwide[32]; countries with higher preterm rates also have higher rates of early-term births[33], indicating common factors between both conditions. Identifying the modifiable factors can help decrease morbidity and mortality in preterm newborns and ETNBs. Future studies should attempt to develop strategies or innovative interventions that identify treatable factors early to decrease short- and long-term consequences of preterm and early-term birth.

This study found that the frequency of early-term births continues to be high, with higher morbidity than FTNBs, and that certain adverse maternal biological factors can contribute to early birth or morbidity. However, this study has some limitations. First, it was a retrospective study.

Second, although the sample size was sufficient, there were too few morbidity events to draw statistically significant associations. Future studies should include a larger sample size to validate our results.

In conclusion, the morbidity among ETNBs is related to physiological immaturity; the adverse maternal biological factors favor a hostile intrauterine environment, which affects fetal and neonatal well-being.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. This study involved a retrospective review of medical records, for which approval was obtained from a formally constituted review board (Institutional Review Board or Institutional Ethics Committee).

Conflicts of interest

The authors declare no conflicts of interest.

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