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Environmental risk factors and perinatal outcomes in preterm newborns, according to family recurrence of prematurity

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Abstract

Objective—We analyzed the role of environmental risk factors, socio-demographic characteristics, clinical characteristics, and reproductive history in preterm births and their associated perinatal outcomes in families classified according to their histories of preterm recurrence among siblings.

Study Design—A retrospective study was conducted at “Nuestra Señora de la Merced” Maternity Hospital in the city of Tucumán, Argentina. A total of 348 preterm, non-malformed, singleton children born to multipara women were reviewed. The family history score described by Khoury was applied, and families were classified as having no, medium or high genetic aggregation.

Results—Families with no familial aggregation showed a higher rate of short length of cohabitation, maternal urinary tract infections during the current pregnancy and maternal history of miscarriage during the previous pregnancy. Families with a high level of aggregation had a significantly higher incidence of pregnancy complications, such as diabetes, hypertension and immunological disorders.

Conclusion—Reproductive histories clearly differed between the groups, suggesting both a different response to environmental challenges based on genetic susceptibility, and the activation of different pathophysiological pathways to determine the duration of pregnancy in each woman.

Keywords

preterm birth; familial aggregation; pregnancy

1. Introduction

Preterm birth (PTB) is a complex and heterogeneous trait, resulting from the interplay of several genetic and environmental factors^{1–2}. The hypothesis that both maternal and fetal genetic backgrounds contribute to PTB appears to be supported by the evidence from familial studies^{3–10}, twin heritability studies^{11–12}, cross generational and sibling analyses^{13–24}, racial disparities^{3, 25–29}, and case-control genetic association studies designed to identify candidate genes^{30–33}.

A history of preterm delivery is the strongest predictor for premature delivery in future gestations³. The role of other proposed predictors such as maternal, genetic, or environmental factors remains unknown³⁴.

In addition, different phenotypes can be expressed in families with multiple preterm births for two reasons: 1) PTB is common (~10% or more in most populations) and 2) multiple pathological pathways likely underlie this phenomenon^{34–37}.

An event with a complex inheritance, such as PTB, often demonstrates familial aggregation because the relatives of the index case are more likely to share the same gene-gene and gene-environment interactions with the proband. Consanguinity can also increase the contribution of genetic factors, and sub-phenotypes of PTB, such as early gestational age or PPRM (preterm premature rupture of membranes), may have more specific genotype correlations³⁸. Non-genetic factors and genetic modifiers, which may vary among individuals, can also contribute to diseases; consequently, related parents who share disease-predisposing genotypes at relevant loci may still be discordant for a given phenotype³⁹.

Familial aggregation notwithstanding, the complex interplay between multiple traits results in different phenotypes despite a common genotype³⁰. Numerous studies have described a wide range of potentially interacting risk factors for prematurity, and these factors may be common to different subtypes^{40–41}. However, evidence of non-homogeneity has also been reported³⁷.

To explore the heterogeneity between preterm newborns and the degree of familial aggregation, we analyzed the role of environmental risk factors, socio-demographic characteristics, clinical characteristics, and reproductive history in preterm births and their associated perinatal outcomes in families classified according to their histories of preterm recurrence among siblings.

2. Methods

2.1. Study Population

This retrospective, observational study was conducted in multiparous women who delivered preterm, singleton, live-born children without malformations at the “Nuestra Señora de la Merced” Maternity Hospital in Tucumán province, northwestern Argentina, between July 2005 and December 2007. This study is part of an international collaborative project aimed at elucidating the etiological genetic factors in PTB through candidate gene evaluation and DNA sequencing²³.

More than 80% of all newborns in Tucumán are delivered at “Nuestra Señora de la Merced.” The premature delivery rate in the general population was 10.3% during the study. The sample was composed primarily of individuals of South American Amerindian heritage (98.7%).

Premature babies delivered at less than 37 weeks of gestational age were identified using the daily delivery room records, on which births were registered within 24 hours.

Mothers who delivered multiple births, mothers under 16 years of age, or children born with congenital malformations were excluded from the study.

An index preterm, live birth was defined as a newborn providing a cluster of siblings (family) that could be used to determine whether these relatives had an excess frequency of the same disease when compared to an appropriate reference population ⁴².

All of the enrolled subjects signed an informed consent form that, together with the protocol, was approved by the CEMIC (Centro de Educación Médica e Investigaciones Clínicas) Ethics Committee (IRB 00001745 – IORG 0001315) and the IRB (protocol 200411759) of the University of Iowa.

2.2. Data source and collection procedures

Mothers who agreed to participate were personally interviewed by a qualified team from a large South American, hospital-based network ⁴³ with expertise in epidemiological data.

The information collected was recorded on standardized antenatal, obstetrics, and neonatal clinical research forms. The forms included the standardized clinical perinatal record ⁴⁴, the ECLAMC clinical records ⁴³, and a structured questionnaire designed to collect socio-demographic, clinical and behavioral data, maternal reproductive history, obstetrical complications, and neonatal outcomes.

All coded records were reviewed by the pediatricians and obstetricians involved in the study. In cases of doubt, disagreement or missing data, the local monitor reviewed the clinical research forms or contacted the patient to ensure the accuracy of the records.

2.3. Outcome definition and ascertainment

2.3.1. Preterm delivery—Preterm delivery was defined as a live birth at less than 37 weeks of gestation ⁴⁵. The gestational age was estimated from the date of the last menstrual period (LMP). If the date of the LMP was uncertain, an ultrasound examination was performed before 22 weeks of estimated gestation to establish the gestational age ⁴⁶. When an ultrasound was not available, the case was excluded. In the event of a difference greater than seven days between the ultrasound result and the LMP, the former was used as the gold standard.

2.3.2. Clinical subtypes—Three clinical subtypes were identified in accordance with recently developed research guidelines for conducting genetic epidemiologic studies of PTB ^{41, 47–50}:

1. preterm labor leading to PTB, called idiopathic PTB (PTB-I)
2. preterm premature rupture of membranes (PTB-PPROM)
3. medically indicated iatrogenic PTB (PTB-M)

The first two subtypes, PTB-I and PTB-PPROM, were grouped together and called spontaneous PTB. The third subtype, PTB-M, was classified according to whether the cause was maternal or fetal.

Data on the onset of labor were registered in the clinical perinatal record by the obstetrician. Based on this categorization, preterm deliveries at the hospital were classified by researchers as the following:

- a. PTB-I: preterm labor leading to PTB (idiopathic), when diagnosed as cervical change (dilation and effacement) due to regular uterine activity. A rupture of membranes was only included in this category when the rupture occurred during active labor.
- b. PTB-PPROM: preterm premature rupture of the membranes, diagnosed by pelvic examination or by obvious leakage of fluid from the cervix into the posterior fornix. In unclear cases, either a sample of fluid was examined by microscopy looking for “arborization” or an ultrasound was performed, searching for oligohydramnios. Membrane rupture had to occur before the onset of labor regardless of the means of delivery.
- c. PTB-M: medically indicated, in which the maternal (PTB-MM) or fetal condition (PTB-MF) required a premature delivery at less than 37 weeks gestation.

PTB-MM was considered when the etiology leading to premature delivery was a maternal condition, such as preeclampsia, diabetes, or antiphospholipid syndrome. PTB-MF was considered when the premature delivery was due to fetal or placental causes, such as growth restriction, abnormal fetal surveillance, or placenta previa.

Preterm births were classified by two independent researchers. When there was a disagreement between them, the case was reviewed by the principal investigator.

2.4. Definition of Variables

Sociodemographic characteristics of the parents—The following characteristics of the mother were analyzed: age, level of education (defined as zero to seven years of school), marital status (single, married, or living together), length of cohabitation with current male partner (including no cohabitation or less than one year of cohabitation), and change of sexual partner between current and last pregnancy. The age of the father, when available, was included.

Clinical characteristics of the mother—The following clinical characteristics were analyzed: number of previous pregnancies and time elapsed between current and previous pregnancy (in months).

Lifestyle features—The following lifestyle characteristics were analyzed: smoking during pregnancy (number of cigarettes), alcohol consumption (yes/no), coffee intake (yes/no), maternal employment status during pregnancy (yes/no), physical recreational activities during pregnancy (yes/no), and stress from severe life events classified as described in Khashan et al.⁵¹.

Pregnancy care and complications—The following details were analyzed: number of prenatal visits, use of corticosteroids, vaginal bleeding, low pre-pregnancy maternal body mass index ($BMI < 18.5 \text{ kg/m}^2$), difficulty with conception (some treatment required to become pregnant), urinary and periodontal infections, chorioamnionitis, diabetes, hypertension-related disorders, immunological disorders, placental disorders, and fetal health disorders.

Reproductive history—Information on all previous pregnancies was classified as either pregnancy loss (miscarriage or stillbirth) or live birth (term or preterm newborn). The reproductive history of the adverse outcome was based on the patient’s self-report and, in 70% of the cases, was confirmed by the mother’s clinical records.

Perinatal outcomes—We retrieved neonatal outcome data, including gestational age, birth-weight, adequacy of weight for gestational age, gender, type of delivery, admission to the neonatal intensive care unit, neonatal morbidity (sepsis, respiratory distress, retinopathy), and early neonatal mortality.

2.5. Statistical analysis

To evaluate familial aggregation, familial preterm birth recurrence was estimated from the proportion of all previous preterm births in siblings. The familial relative risk (FRR) was defined as the ratio between the PTB rate in siblings and the PTB rate of the population⁵². The incidence of PTB in the hospital was assumed to be the same as in the general population. The aggregation heterogeneity was evaluated by estimating the family history score (FHS) of each family⁴². The FHS for each family was calculated using the formula $Z_i = (\sum O_i - \sum E_i) / (\sum E_i)^{1/2}$, in which the value observed (O_i) was the number of preterm siblings in each family. $E_i = 1 - \exp(-\sum \lambda T_i)$ was the expected value for each family, λ was estimated based on the rate of incidence in the general population (10.3% in Tucumán), and T_i was the number of pregnancies for each family. The Z_i distribution was then taken as the proxy for the familial genetic aggregation and was classified as FHS: 1) with no genetic aggregation ($z < 0$), 2) with medium aggregation ($0 \leq z < 1.64$), and 3) with high genetic aggregation ($Z \geq 1.64$).

The ordered logit model (for ordinal dependent variables: with no, medium and high familial aggregation) was used to evaluate the non-linear probability model between the independent variables and familial aggregation. The independent variables included the parental sociodemographic characteristics, clinical characteristics, lifestyle features, pregnancy care and complications as defined above. In addition, an ordered logit model was used to evaluate the characteristic phenotype in accordance with familial aggregation. In both approaches, the Huber method for estimating robust standard errors was used for outlier (adjusted) data⁵³.

3. Results

During the study period, 1,043 preterm live-born children were identified. Of these children, 103 were excluded because they could not be traced (9.8%). Also excluded were 155 (14.9%) cases of malformed, preterm, live-born children: 117 (11.2%) cases of multiple births; and 14 (1.3%) preterm births from mothers younger than 16 years of age.

Of the 654 eligible cases, 556 (85%) mothers agreed to participate in the study, and 348 (62.6%) preterm, singleton, non-malformed, live-born infants from mothers with one or more previous pregnancies were included in the sample to analyze familial aggregation (the remaining 108 preterm newborns were delivered by nulliparous women).

The preterm rate for the general population at the hospital was 10.3%, and the preterm rate in this sibling sample was 23.1% (238 preterm siblings and 1,029 total gestations). The FRR was 20% for cases with one previous PTB and 33% for those families with two previous preterm births.

An analysis of the parental socio-demographic and lifestyle *characteristics* showed no significant association with the probability of familial aggregation. Only the couples in the group with no familial clustering showed a higher rate of short-length cohabitation and urinary infections (Table 1). Compared with mothers with long-length cohabitation (LLC: N = 270), those mothers with short-length cohabitation (SLC: N = 78) were more frequently single (LSC = 41.0%, LLC = 2.6% $p < 0.001$), with higher frequencies of changing paternity (LSC = 65.4%, LLC = 27.4%, $p < 0.001$) and high frequency of mothers under 19 years of

age (SLC = 23.1%, LLC = 7.4%, $p < 0.001$). Mothers with SLC also had more previous miscarriages (SLC = 36.4%, LLC = 21.1%, $p = 0.017$), greater consumption of alcohol (SLC = 37.2, LLC = 20.8%, $p = 0.018$), and a higher frequency of neonatal complications (SLC = 96.7%, LLC = 90.3%, $p = 0.049$).

Families with a higher level of aggregation had a significantly higher frequency of pregnancy complications, such as diabetes, hypertension, and immunological disorders compared with the others groups. In the no aggregation group, the frequency of placental or fetal disorders was higher (Table 1).

No significant difference was observed in the respective vaginal delivery rates of the groups (high, medium, and no familial aggregation: 47.6%, 39.1%, and 46.5, respectively; ($\chi^2_{df=2} = 0.123$, $p = 0.245$).

Spontaneous PTB represented 67.8% of the sample, while the remaining births (32.2%) were medically indicated. The rates of PTB-I, PTB-PROM, PTB-MM, and PTB-MF were 24.4%, 43.4%, 21.3%, and 10.9%, respectively. Familial aggregation levels showed significant differences ($\chi^2_{df=6} = 22.78$, $p < 0.001$) between the clinical subtypes. PTB-MM showed inverse trends compared to PTB-MF. While the latter decreased with familial aggregation, the former increased and was the leading cause of preterm delivery in the group with a high degree of recurrence (Table 1). PTB-PPROM was the most common subtype found among families with no or medium recurrence, and idiopathic PTB accounted for approximately one quarter of the cases in each group (Table 1).

When we analyzed the reproductive history in the last pregnancy before the index case according to the degree of aggregation, we observed an increase in the rate of miscarriage and a decrease in the recurrence rate of prematurity. In families with no history of recurrence, the miscarriage rate was high (37.5%) when compared with the other groups (medium and high aggregation, 15.7% and 8.5%, respectively). This trend was statistically significant (Z trend: -5.1, $p < 0.001$). The opposite trend was observed in stillbirths, where the rate increased proportionately with familial aggregation (Z trend: 3.5, $p < 0.001$). We also found that the frequency of live births increased with the level of familial aggregation (Table 2).

In families with high familial aggregation, siblings of the index cases were live births in 84.7% of cases but only 7% of them were < 37 weeks (Table 2).

The same distribution was observed when all siblings were analyzed (Table 3). High familial aggregation for prematurity was associated with a 62% reduction in the probability of a previous miscarriage (OR: 0.38, 95% CI [0.24, 0.60]) and medium familial aggregation was associated with a 40% reduction in risk (OR: 0.60, 95% CI [0.42, 0.85]) when both were compared to families without familial aggregation.

Conversely, families with high and medium familial aggregation had an increased risk for stillbirth (OR: 2.57, 95% CI [1.95, 3.41] and OR: 5.40, 95% CI [1.95, 17.2], respectively).

Families with a high preterm recurrence had an almost four-fold greater likelihood of stillbirth than those families with no aggregation (OR: 4.64 95% CI [1.72, 14.5], but only 12% of these births were term infants (Table 3).

With respect to neonatal clinical characteristics and outcomes, no significant differences were found between the familial aggregation groups (Table 4).

4. Discussion

We found a strong familial aggregation in PTB, which is consistent with previous studies ^{3–10}.

We investigated several phenotypic features and risk factors that may explain the observed familial clustering ³⁴. We were unable to find any statistical differences between the groups with regard to environmental exposure, sociodemographic characteristics or lifestyle risk factors such as alcohol/coffee consumption or smoking. These risk factors have been analyzed in previous studies using term live-birth control groups, while our study only compared preterm newborns. Only the length of cohabitation with a male partner and the rate of urinary tract infection showed statistically significant differences in the group with no familial aggregation. The higher frequency of urinary tract infections in this group is consistent with a larger number of idiopathic preterm births ^{54–55}.

Mothers with one year of cohabitation with their partners were mostly young and single, with a greater alcohol intake and a higher rate of previous miscarriages.

There are several related reasons why this group may be at increased risk for PTB. Single mothers face more economic constraints than married mothers ^{56–58}. Both depression and lack of social or emotional support during pregnancy have been associated with an increased risk of preterm delivery ⁵⁹. In South America, the percentage of unintended pregnancies has remained at approximately 70% since the 1970s ⁶⁰. If the relative risk of preterm mothers observed with SLC is 1.5, then given a SLC cohabitation rate of 40% of the mothers in Tucumán, Argentina, the estimated attributable risk is approximately 5%. Consequently, medical and social policies aimed at reducing the rate of unwanted pregnancies could prevent a significant number of preterm births in young and single women.

As expected, families with a higher recurrence of preterm delivery had the highest incidence of obstetric complications. An increased risk of recurrence was previously reported for hypertension ³⁴, diabetes ^{61–62}, and antiphospholipid syndrome ⁶³. Placental disorders such as abruptio placentae ^{34, 64} or placenta previa ^{65–66} have also been associated with a higher degree of recurrence, but we failed to find an association with these characteristics in our sample.

The distribution of clinical subtypes was different from that described in the literature. While the frequency of iatrogenic PTB was similar to the previously published frequency, a large proportion of PROM was observed in the group of spontaneous preterm births ^{40–41}.

Discrepancies between the current study population and other populations may be due to a different ethnic mixture. The expected distribution may have also been modified by the exclusion of primiparous women, malformations, and multiple preterm pregnancies (representing 25% of the sample).

This factor was clearly different in the three groups, whether in the pregnancy immediately prior to the index case or for all siblings of the index case.

The reference group showed a high frequency of pregnancy loss and unexpectedly high rates of spontaneous abortion: 37.5% in the preceding pregnancy and 28.4% in all of the siblings, a finding that is noteworthy because these mothers were all young.

Although the frequency of stillbirth increased with familial aggregation, the overall pregnancy loss rate decreased.

These findings suggest that some pregnancies may have ended at different stages of gestation and that families with lower PTB recurrence were those families with the worst perinatal outcomes because their pregnancy loss rate was unusually high. Thus, as a result of the high rate of miscarriage in this population and based on competitive risk, only a few pregnancies would have resulted in preterm newborns. The mechanisms responsible for preterm birth are likely to be associated with stillbirth in many cases⁶⁷, and those mechanisms that determine the completion of pregnancy may be weaker or activated later. Therefore, families with a greater degree of familial aggregation had, by definition, a high risk of prematurity but were most likely to have a live newborn. This probability was 82.7%, while the probability of preterm birth was 80%.

Despite the discrepant distribution of etiologies leading to preterm delivery, neonatal outcomes were similar in the three aggregation groups.

Gestational age, birth weight and frequency of growth restriction were similar. No differences were observed in the need for hospitalization in intensive care or the frequency of complications. Only a slightly higher death rate at discharge, which was not statistically significant, was observed in the group with no aggregation.

The family history score was used to evaluate genetic heterogeneity. Cases were classified into three familial aggregation groups: no, medium, and high aggregation, according to the number of previous preterm births in the sibling proband. Estimates of relative risk for familial disease are quite useful for research studies on disease etiology. They have been used to determine disease clusters in certain families and to assess genetic heterogeneity^{68–70}. Familial history scores have been described and validated in other studies of chronic diseases and suggest familial genetic heterogeneity⁴². Thus, it is reasonable to suspect the existence of clues to a genetic-environmental interaction. A negative history score indicates that the familial reproductive history shows fewer preterm births than expected, while a positive score shows more preterm births than expected⁷¹. Strengths and Weaknesses: Several methodological limitations should be considered when interpreting these findings. First, the results are restricted to singleton, non-malformed, preterm births in a single maternity hospital. Newborns with malformations and multiple deliveries were excluded to avoid bias related to this premature clustering. Another limitation is associated with the extrapolation of these findings to all preterm children. A sample obtained from a single hospital favors the social and ethnic homogeneity in the population (internal validity) but adversely affects any extrapolation of its results to other populations (external validity). The sample size for some preterm subtypes could be too small (e.g., high familial aggregation) to identify true differences.

This study does not include a full-term control group. Its objective, however, was to determine whether particular environmental factors could explain the different aggregation of families with preterm children, rather than to see whether these families differed from those families whose newborns were at term. Thus, the goal of the study was to shed light on the interaction between genetic heterogeneity and environmental factors.

For exposure factors with a minimal prevalence of 10%, the sample size is adequate for detecting a high risk factor (3 times the risk in exposed cases) but not for the identification of those risk factors with a medium impact on premature delivery.

The probability of missing or misclassified data is low. Our study data were collected at a single center over a two-year period. Personal interviews were conducted by a qualified and experienced team from a large South American, hospital-based network⁴³. This design permitted a better assessment of maternal and neonatal characteristics, outcomes, and complications by minimizing the impact of temporal changes, especially those changes

related to obstetrical interventions⁷². Nevertheless, we cannot rule out maternal recall bias, especially in miscarriage reports. We believe, however, that there is no reason to suspect that families with no recurrence for prematurity systematically reported a higher miscarriage rate than other groups and vice versa, especially because the sociodemographic and clinical characteristics were similar. It was not possible for us to determine the effect of elective pregnancy interruption because this procedure is illegal in Argentina. However, there was no reason to assume differences between the groups.

5. Conclusion

Only a few environmental risk factors were associated with a higher probability of clustering in families whose last pregnancy was a live, preterm newborn. This result suggests that genetic factors may have played a major role in the observed recurrence.

The maternal reproductive history differed between groups, suggesting either a different genetic response to similar environmental factors or the activation of different pathophysiological pathways involved in determining the length of pregnancy in each woman. Miscarriage, stillbirth, and PTB may all represent the same outcome with different degrees of severity. Hence, if the risks are competitive, a woman who miscarried may never deliver a preterm baby.

Families without aggregation had the worst prognosis when considered from a biological and reproductive standpoint of view. However, families with higher levels of aggregation are at the highest risk from the perspective of the health system and in terms of the impact of prematurity on neonatal mortality and morbidity. Moreover, in light of the improvements in neonatal survival and maternal genetic effects on the etiology of prematurity, this trend may help to explain part of the increase of this disorder over the last few decades³⁰.

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Table 1

Phenotype characteristics by familial aggregation level

Sociodemographic characteristics of the parents	Familial aggregation level			
	No n=208	Moderate n=69	High n=71	B* p
Mother's age (years) X±SD	26.4 ± 6.4	29.9 ± 6.2	26.4 ± 5.6	0.020 0.278
Father's age (years) X±SD	28.6 ± 7.5	33.1 ± 8.5	29.9 ± 7.1	0.013 0.345
Mother's level of education (years) (median)	4	4	4	-0.088 0.324
Mother's level of education (years) (median)	4	4	4	-0.067 0.345
N° of previous pregnancies (median)	3	5	4	
More than 3 previous pregnancies n (%)	72 (34.6)	48(68.1)	34(47.9)	0.356 0.133
Unmarried n(%)	27 (13.0)	6 (9.2)	7 (9.1)	0.062 0.891
Length of cohabitation <1 year n(%)	59 (28.4)	9 (13.0)	10 (14.1)	-0.861 0.024
Changing paternity n (%)	77(37.0)	32 (46.4)	16 (22.5)	-0.105 0.664
Length of time between births (months) (median p10–p90)	67.50 27.3–21.2	70.37 28.7–173.1	64.66 26.7–133.1	0.002 0.564
Age of mother at the first pregnancy (median p10–p90))	18.46 15.3–24.2	18.39 15.4–23.2	18.76 15.5–25.8	0.236 0.113
Lifestyle features				
Smoking during pregnancy NO n(%)	164(78.8)	61 (88.4)	52 (73.2)	
1–10 n(%)	42 (20.2)	7 (10.1)	18 (25.4)	-0.104 0.534
10 n(%)	2 (1.0)	1 (1.4)	1 (1.4)	
Alcohol consumption during pregnancy n (%)	53 (25.4)	18 (26.5)	14 (19.7)	0.027 0.920
Coffee intake during pregnancy n (%)	118(56.7)	34 (50.0)	35 (49.3)	-0.037 0.781
Work outside the home n(%)	62 (29.9)	17 (24.6)	12 (16.9)	-0.478 0.084
Physical activities during pregnancy n (%)	9 (4.5)	2 (2.9)	3 (4.2)	-0.107 0.342
Severe life events. n (%)	106(51.5)	38 (55.1)	37 (52.1)	0.169 0.453
Pregnancy care and complications				
Prenatal visits < 4 n(%)	66 (31.7)	27 (39.1)	27(38.0)	-0.017 0.742
No ultrasound examinations. n(%)	23 (11.1)	8 (11.6)	9 (12.7)	0.215 0.065
Use of corticosteroid. n(%)	141 (67.8)	45 (64.3)	48 (68.6)	0.124 0.356
Vaginal bleeding n(%)	105(50.5)	28 (40.6)	28 (39.4)	-0.444 0.069
Difficulty in conceiving n(%)	36 (17.3)	9 (13.1)	7 (9.9)	-0.471 0.160
Urinary infections n(%)	91 (44.2)	22 (31.9)	20 (28.6)	-0.568 0.022

Sociodemographic characteristics of the parents	Familial aggregation level			B*	p
	No n=208	Moderate n=69	High n=71		
Periodontal infections n(%)	99 (47.6)	34 (50.0)	31 (43.7)	-0.197	0.389
Choriomnionitis n(%)	23 (11.0)	8 (11.6)	7 (9.9)	-0.111	0.743
Diabetes n(%)	3 (1.4)	2 (2.9)	4 (5.6)	1.720	0.085
Hypertensive disorders n (%) [†]	23 (11.1)	15 (21.7)	18 (25.4)	0.543	0.043
Immunological disorders. n (%) [‡]	2 (1.4)	1 (1.4)	4 (4.3)	0.412	0.023
Placental disorders n (%) [§]	13 (6.3)	5 (7.3)	2 (2.8)	-0.235	0.032
Fetal health disorders. n(%) ^{//}	19 (9.1)	2 (2.9)	2 (2.8)	-0.212	0.021
Vaginal delivery. n(%)	99 (47.6)	27 (39.1)	33 (46.5)	0.123	0.245
BMI < 18.5 kg/m ²	22.66%	22.39%	22.32%		
Clinical subtypes					
Spontaneous PTB					<0.001
PTB-I. n(%)	50 (24.0)	14 (20.3)	21 (29.6)	1.292	0.020
PTB-PPROM n(%)	97 (46.7)	35 (50.7)	19 (26.8)	-0.953	0.065
PTB-M					
Maternal causes. n(%)	33 (15.8)	14 (20.3)	27 (38.0)	1.978	<0.001
Fetal or placental causes. n(%)	28 (13.5)	6 (8.7)	4 (5.6)	-1.327	0.015

BMI: body mass index; PTB: preterm birth; PTB-I: idiopathic preterm birth; PTB-PPROM: preterm premature rupture of membrane; PTB-M: medically indicated preterm birth.

* B: correlation coefficient in an ordinal logistic regression

[†] Hypertensive disorders: includes chronic hypertension (n=5), gestational hypertension (n=26), preeclampsia (n=22), help syndrome (n=2), and eclampsia (n=1).

[‡] Maternal immunological disorders: Includes antiphospholipid syndrome (n = 4) Rh sensitization (n = 3) and Lupus (n = 1)

[§] Placental disorders: includes abruption placentae (n=13), placenta previa (n=6), and accretismo (n=1)

^{//} Fetal health disorders: includes non reassuring fetal monitoring (n=3), pathological Doppler (n=4), abnormal amniotic fluid (n=3), hydrops fetalis (n=1), and growth restriction (n=12)

Table 2

Reproductive outcomes in the last previous pregnancy by familial aggregation level

Familial aggregation level				
Outcome	No n=208	Moderate n=69	High n=71	Z trend (p)
Spontaneous Abortion				
N (%)	78 (37.5)	11 (15.9)	6 (8.5)	-5.1
OR* (1C [†] 95%)	1.00	0.42 [0.18, 0.74]	0.23 [0.07, 0.41]	(<0.001)
Pregnancy loss				
Stillbirths				
N (%)	3 (1.4)	9 (13.1)	7 (9.9)	3.5
OR (1C 95%)	1.00	9.28 [2.04, 29.9]	7.07 [1.27, 20.5]	(<0.001)
Preterm birth				
N (%)	0 (0.0)	22 (31.9)	53 (74.6)	14.3
OR (1C 95%)	-	1.00	2.37 [1.42, 4.1]	(<0.001)
Livebirth				
Term livebirth				
N (%)	127 (61.1)	27 (39.1)	5 (7.0)	-8.07
OR (1C 95%)	1.00	0.63 [0.23, 0.70]	0.11 [0.06, 0.14]	(<0.001)

* OR: Odds ratio,

[†] IC 95%: Confidence interval of 95%

Wilcoxon rank-sum test for trends (Cuzik et al)

Table 3

Reproductive outcomes in all previous pregnancies by familial aggregation level

Familial aggregation level				
Outcome	No n=507	Moderate n=291	High n=219	Z trend (p)
Spontaneous Abortion				
N (%)	144 (28.4)	50 (17.2)	24 (11.0)	− 3.2
OR* (IC [†] 95%)	1.00	0.60 [0.42, 0.83]	0.38 [0.24, 0.60]	(<0.001)
Pregnancy loss				
Stillbirths				
N (%)	6 (1.2)	16 (5.5)	14 (6.4)	4.1
OR (IC 95%)	1.00	4.64 [1.72, 14.5]	5.40 [1.95, 17.2]	(<0.001)
Preterm birth				
N (%)	0	80 (27.5)	155 (70.8)	17.6
OR (IC 95%)	-	1.00	2.57 [1.95, 3.41]	(<0.001)
Livebirth				
Term livebirth				
N (%)	357 (70.4)	145 (49.8)	26 (11.9)	−9.0
OR (IC 95%)	1.00	0.71 [0.58, 0.86]	0.17 [0.11, 0.25]	(<0.001)

* OR: Rate ratio,

[†] IC 95%: Confidence interval of 95%

Wilcoxon rank-sum test for trends (Cuzik et al)

Table 4

Neonatal outcomes by familial aggregation level

Neonatal Characteristics	Familial aggregation level			B*	p
	No	Moderate	High		
Gestational age X±SD	32.7±2.9	33.1±2.8	33.0±2.7	0.067	0.238
Birthweight (grams) X±SD	1817.1±580.4	1805.2±565.8	1834.1±600.7	-0.001	0.957
IUGR n (%)	30 (15.2)	13 (21.0)	13 (20.3)	0.025	0.842
Male n (%)	106 (51.0)	39 (56.5)	29 (40.8)	-0.224	0.375
Death at discharge n (%)	18 (9.7)	5 (7.7)	5 (7.7)	0.051	0.923
Neonatal death				0.188	0.640
At birth	1 (5.5)	0 (0.0)	1 (20.0)		
< 12 hs	6 (33.3)	1 (20.0)	0 (0.0)		
< 7 days	4 (22.2)	2 (40.0)	3 (60.0)		
< 24 days	7 (38.9)	2 (40.0)	1 (20.0)		
Hospitalized n (%)	196 (95.2)	63 (91.3)	68 (97.1)	0.532	0.564
Complications n (%)	184 (92.5)	59 (89.4)	65 (94.2)	-0.697	0.420
Respiratory distress n (%)	177 (89.8)	60 (90.9)	63 (91.3)	0.462	0.524
Retinopathy n (%)	19 (10.0)	4 (6.0)	4 (6.1)	-0.673	0.195
Sepsis n (%)	30 (15.5)	16 (23.9)	12 (18.2)	0.503	0.114
Persistent ductus arteriosus n (%)	23 (11.8)	7 (10.4)	7 (10.4)	0.451	0.274

Number of cases and percentage: N(%)

* B: correlation coefficient in an ordinal logistic regression