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ORIGINAL ARTICLE

Bridging the Gaps Between the Histopathological and Demographic Risk Factors of Preterm Birth in a Unique Miami Inner-City Population

Muthu Kumar Veerapen,[1] Liset Pelaez,[2] JoNell Efantis Potter,[3] Lunthita Duthely,[3] Rhea Birusingh,[2] Evadnie Rampersaud,[1] Olaf A. Bodamer,[1] and Maria Matilde Rodriguez[2]

[1]Department of Human Genetics, University of Miami, Miami, FL, USA; [2]Department of Pathology, University of Miami, Holtz Children's Hospital, Miami, FL, USA; [3]Department of Obstetrics and Gynecology, University of Miami, Miami, FL, USA

We aim to identify the link between placental histological findings and obstetric reports to determine possible risk factors of spontaneous preterm birth (SPTB). We prospectively ascertained birth records and outcomes from all deliveries in our hospital in 1 year. Records were used to determine and stratify for either full-term or preterm [spontaneous or indicated (I)] deliveries. We analyzed for risk factor association using χ^2 tests and common odds ratio estimates (SPSS v21.0). Our cohort totaled 6088 deliveries: 236 IPTB, 43 SPTB, and 5809 term births. Largely Hispanic, we determined race, parity, prenatal care access, preeclampsia, gestational diabetes, and BMI to be highly associated with SPTB ($p < 0.01$). Histologically, placentas of women with SPTB were twice as likely to have chronic villitis. We found that chronic villitis is associated with SPTB. Results of this study can be used in increasing the understanding of SPTB.

Keywords: chronic villitis, obstetrics, premature, placenta, spontaneous preterm birth

ABBREVIATIONS

CI: confidence interval;
GW: gestational weeks;
IPTB: indicated preterm birth;
OR: odds ratio;
PTB: preterm birth;
SPTB: spontaneous preterm birth;
TB: term birth

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Muthu Kumar Veerapen and Liset Pelaez contributed equally to this work.
Address correspondence to Dr Maria Matilde Rodriguez, MD, Department of Pathology, University of Miami, Holtz Children's Hospital, 1611 NW 12 Avenue, Miami, FL 33136 USA. E-mail: mmrod@miami.edu

INTRODUCTION

The recent National Birth Statistics reported a 15-year low in the rates of preterm birth (PTB) in the United States of America: 11.53% [1]. This prevalence can be further stratified on the basis of ancestry where African-Americans have the highest (16.53%), followed by Native-Americans (13.25%) and Latin Americans (11.58%). Despite the overall nationwide drop in prevalence, the March of Dimes (MOD) 2013 PTB report card has deemed Florida a grade "D," having one of the highest prevalence (13.7%) of PTB in the United States [2]. This could be due to the highly diverse population found in Florida and a lack of clear public policies which could improve these rates [3].

PTB is defined by the World Health Organization (WHO) as live births prior to the completion of 37 gestational weeks (GW), based on the mother's last menstrual cycle [4]. Currently, PTB accounts for up to 75% and 80% of perinatal morbidity and mortality, respectively, [5]. Of the worldwide 8 million infant deaths a year, approximately 17–34% are attributable to PTB [6]. There is a group of women at risk for SPTB [7]. From the total infants that survive after being delivered prematurely, about 10–15% are significantly disabled. Preterm infants are born with multiple short- and long-term health complications including bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, cognitive impairment, and an increased risk for adult onset diseases such as hypertension and diabetes [8, 9, 10]. Another less well known complication is that when infants are born preterm, there is an interruption of normal renal organogenesis involving the vascular tree and kidney branching increasing the susceptibility of the surviving infants to develop hypertension and renal disease as adults [11]. Considering the vast amount of health conditions associated with PTB, a considerable amount of money is invested in the care of preterm infants in the USA which totals approximately $26 billion per year [12]. The MOD reports that the average cost of care for a preterm infant is 10 times greater than for a full-term (FT) infant.

Based on GW, PTB can be categorized into extreme (< 28 GW), very (28–32 GW), and moderate/late preterm (32–37 GW) [13]. The rate of infant survival increases in proportion to the GW, the infant is delivered [14, 15]. In addition, it has also been shown that GW is independent of increased childhood mortality [16]. PTB is a multifactorial condition that can be caused by environmental stress such as maternal smoking [17] and body mass index (BMI) [18]; parity and preterm parity as one of the best outcome predictors [19]; racial disparities [20]; a history of *in vitro* fertilization (IVF), especially in multiparous women [21]; socioeconomic differences and access to healthcare [22]; infection and inflammation e.g. bacterial vaginosis and vaginal infections [23, 24]; and genetic variability [25, 26]. Obstetric presentations allow the categorization of PTB into either indicated (IPTB) or spontaneous (SPTB). IPTB is defined as deliveries that are indicated because a continuation of pregnancy could lead to complications in mother and/or infant. In these cases, the mother is either induced into labor or a cesarean section is performed. Generally, SPTB is defined as vaginal, live, spontaneous birth, and a preterm premature rupture of membranes (PPROM) that accounts for up to 70% of total PTB. Women undergoing SPTB tend to have minimal obstetric complications such as preeclampsia, hypertension, visible infections, and maternal-fetal distress [27, 28]. However, true SPTB are characterized by intact membranes with some vascular complications such as uteroplacental ischemia or hemorrhage, that accounts for approximately 40–45% of all PTB [29].

The classification of PTB is important for clinical research and in elucidating the cause of PTB, notably SPTB. It has been shown that clinicians are more likely to categorize PTB as IPTB [30]. The histological evaluation of the placenta shed light on the etiopathogenesis of PTB and can assist neonatologists in further management of these very ill neonates guiding them about administering or not antibiotics

depending on the presence or absence of acute villitis, chorioamnionitis, and chronic intervillositis that are indicative of infection/inflammation [31]; and hematomas, infarctions, decidual vasculopathy, and uteroplacental vascular lesions are often associated with preeclampsia, hypertension, and intrauterine growth restrictions (IUGR) [32]. Goldenberg, Andrews [33], studying the differences between SPTB and IPTB placental reports, concluded that women with SPTB are more likely to suffer from acute inflammation; whereas, women with IPTB have an increased chance of mononuclear infiltrations, decidual leukocytoclastic necrosis, and vascular insufficiencies.

Previously, a retrospective study over an 11-year period was conducted at the University of Miami on birth outcomes, which focused on the obstetric report comparisons between minority populations. They concluded that Hispanics have the lowest PTB rate when compared to non-Hispanic whites and blacks [34]. In this study, our objective is to identify a link between the obstetric reports and placental histological findings into determining possible causes of SPTB in all live births reported in a tertiary care hospital in Miami, FL.

METHODS

Retrospectively, birth records and outcomes were reviewed from prospectively collected data from all women who delivered at Jackson Memorial Hospital (JMH) in the year 2007. We searched clinical data from a total of 6102 deliveries. This dataset was extracted and matched on the basis of singleton deliveries and study variables by our database manager. We then evaluated obstetric and pathological reports in order to determine PTBs (<37 GW) and subsequently, distinguish between SPTB and IPTB.

Upon cleaning the dataset for missing and duplicate data, analysis was performed using IBM SPSS Statistics for Windows, Version 21.0.0.0 (Armonk, NY: IBM Corp). For continuous variables, frequencies and means were obtained and tested for normality using the Brown–Forsythe test and compared using a one-way ANOVA, correcting for multiple testing using Bonferroni for equal variances and Tamhane's T2 for unequal variances. For dichotomous variables, we employed the χ^2 test where we performed a Monte-Carlo permutation of 1000 sampling with replacement (99% confidence interval) and reported 2-tailed significance values based on the permutations and counts. To report association of a study variable to SPTB, we utilized Cochran's and Mantel–Haenszel statistics to generate common odds ratio (OR). Some variables that we deemed appropriate for dichotomy were filtered using Receiver Operating Characteristic (ROC) curves. We performed bootstrapping ($n = 1000$) to increase the reliability of results while reducing the impact of outliers. This research was performed upon approval by the institutional review board (IRB), University of Miami Miller School of Medicine (IRB#20120096).

RESULTS AND DISCUSSION

A total of 6102 individual delivery data points were obtained from the year 2007. We cleaned up the dataset for missing and duplicate data to yield 6088 data points. Of the 6088 deliveries, 279 are PTB (4.58%) including 236 IPTB (85.59%) and 43 SPTB (15.41%). These results differ from reports [27] of other study populations probably due to a strict filter of GW and pathological findings to classify PTB utilized at JMH. Table 1 illustrates the different study variables (demographics and obstetrics) analyzed in our study. From the comparisons of the IPTB, SPTB, and full-term deliveries, we found race, maternal age, birth weight, preterm parity, access to prenatal care, and obesity to be risk factors for PTB ($p < 0.05$). Notably, our cohort consists largely of Hispanics

Table 1. Study variables characterized from our cohort.

Characteristic	IPTB (%) ($n = 236$)	SPTB (%) ($n = 43$)	TB (%) ($n = 5809$)	Total population (%) ($n = 6088$)	p-Value
Race					<0.001
Black, non-Hispanic	30.6	18.6	15.7	16.3	
White	5.1	4.7	4.3	4.4	
Hispanic	39.6	53.5	55.6	55.0	
Haitian	8.5	7.0	11.8	11.7	
Asian	0.9	2.3	1.5	1.4	
Caribbean	5.1	4.7	3.7	3.8	
Other	10.2	9.3	7.3	7.5	
Maternal age (years)					0.07
<20	12.3	25.6	10.9	11.0	
20–30	51.3	53.5	53.5	55.2	
31–34	16.9	14.0	16.3	16.3	
≥35	19.5	7.0	17.7	17.7	
Maternal age (years) ± SD	27.74 ± 6.83	24.53 ± 6.93	27.63 ± *6.64*	27.61 ± *6.66*	0.01
Gestational age (GW)			—		0.005
<28	27.1	9.3	—	24.4	
28–32	31.8	32.5	—	31.9	
33–36	41.1	58.1	—	43.7	
Gestational age (GW) ± SD	30.9 ± 4.1	32.2 ± 3.0	—		0.017
Birth weight (g)					0.05
<2500	86.4	78.0	12.4	15.7	
≥2500	13.6	22.0	87.6	84.3	
Birth weight (g) ± SD	1695.2 ± 795.1	2087.6 ± 648.8	3179.9 ± 733.5	3114.9 ± 793.8	0.005
Gender					0.115
Male	54.7	51.2	52.2	52.3	
Female	44.5	48.8	47.7	47.6	
Ambiguous	0.8	0	0.1	0.1	
Preterm parity					<0.001
No	79.2	88.4	92.6	92.1	
Yes	20.8	11.6	11.6	7.9	
Parity					0.041
0	44.9	58.1	42.1	42.3	
≥1	55.1	41.9	56.1	55.9	
Education (grade)					0.094
$\leq 12^{th}$	34.6	51.2	35.3	35.4	
>12th	65.4	48.8	64.7	64.6	
Prenatal care					<0.001
None	10.0	4.8	2.9	3.2	
1st Trimester	72.7	71.4	71.6	71.6	
2nd Trimester	13.4	21.4	21.0	20.7	
3rd Trimester	3.9	2.4	4.5	4.4	
Preeclampsia					<0.001
No	86.9	100	95.1	94.8	
Yes	13.1	0	4.9	5.2	
Gestational hypertension					<0.001
No	74.2	100	87.6	87.2	
Yes	25.8	0	12.4	12.2	

(Continue on next page)

Table 1. Study variables characterized from our cohort. *(Continued)*

Characteristic	IPTB (%) ($n = 236$)	SPTB (%) ($n = 43$)	TB (%) ($n = 5809$)	Total population (%) ($n = 6088$)	p-Value
BMI (kg/m^2)					
17.00–19.70	0.9	2.7	0.2	0.2	0.002
19.80–26.09	32.7	21.6	19.6	20.1	
26.10–28.99	15.9	37.8	21.9	21.8	
≥29.00	50.5	37.8	58.2	57.8	
Pre-gestational diabetes					0.934
No	98.7	100	573398.7	98.7	
Yes	1.3	0	761.3	1.3	
Gestational diabetes					0.182
No	95.3	100	95.3	94.0	
Yes	4.7	0	6.1	6.0	

[a]Data are stratified by either indicated (IPTB), spontaneous (SPTB), or full-term births (TB).
[b]The three groups are analyzed by for differences using either χ^2 or one-way ANOVA. Odds-ratio (OR) are calculated only between SPTB and IPTB.

women (55.0%), where race is a risk factor for PTB ($p < 0.001$). Hispanics are the largest minority group in the United States and represent one of the largest ethnic groups in Miami [35]. Hispanics are also the third most prevalent race in PTB. Upon stratifying for blacks and Hispanics in our study, Hispanic women are twice as likely to have a SPTB as compared to blacks (OR = 2.26). Overall, women with SPTB were younger [OR = 0.50 (95%CI = 0.25–1.02), $p = 0.06$], present at more advanced gestational age [OR = 2.41 (95%CI = 1.64–4.93), $p = 0.013$], and tend to have less visible complications (preeclampsia and hypertension). A bias was introduced to this variable because when phenotyped for SPTB, women were selected on the basis of minimal indications of infections and complications such as preeclampsia and hypertension. Infant gender did not show significant differences despite recent findings that indicated a higher prevalence of male preterm infants [36]. Parity and history of preterm parity showed an

Table 2. Histological findings and the association to spontaneous preterm birth.

Characteristic	IPTB (%)	SPTB (%)	Total (%)
Chorioamnionitis			
None	62.3	65.1	62.7
Present	37.7	34.9	37.3
Chronic villitis			
None	95.8	90.7	95.0
Present	4.2	9.3	5.0
Decidual necrosis			
None	94.9	97.7	95.3
Present	5.1	2.3	4.7
Hematoma			
None	89.0	95.3	90.0
Present	11.0	7.1	10.0
Infarcts			
<10%	95.3	95.3	95.3
≥10%	4.7	4.7	4.7
Umbilical cord vasculitis			
None	88.1	88.4	88.2
Present	11.9	11.6	11.8

increased likelihood to being born preterm ($p < 0.05$) when compared among groups, but upon stratification for IPTB and SPTB, neither variable showed significance ($p > 0.1$). Socioeconomic differences is a known risk factor for PTB [22]. In our study, this was only observed upon stratifying for IPTB and SPTB [OR = 0.51 (95%CI = 0.26–0.99), $p = 0.045$] indicating lower education levels to be associated with SPTB. On the contrary, higher educational levels tend to be associated with IPTB. Access to prenatal care is important as it was shown to be a strong risk factor to PTB compared to TB ($p < 0.001$). However, no difference was observed in women with either SPTB or IPTB [OR = 2.12 (95%CI = 0.50–9.57)].

In Table 2, we summarized the histological findings in women with IPTB and SPTB. Women with SPTB were twice as more likely to have chronic villitis during the histologic examination of theirs placentas. Chronic villitis, defined by the presence of a lymphohistiocytic infiltrate in chorionic villi, is associated to preterm delivery, fetal growth restriction, and recurrent pregnancy loss. A recent study by Rudzinski, Gilroy [37], demonstrated that chronic villitis may represent host-versus-graft rejection by the mother. This finding points toward a possible role of the maternal immune system in the SPTB. In our cohort, chronic villitis was present in 4.2% of IPTB, 9.3% of SPTB suggesting a tendency to happen in spontaneous preterm labor when the placentas had chronic villitis. The remainder of the studied variables was not significant, even upon stratifying for minority populations (*data not shown*).

CONCLUSION AND FUTURE DIRECTIONS

It is important to obtain quality phenotype data and characterize deliveries based on clinical and histological findings (Clayton, Sappenfield et al. 2012). Our study confirms that race is an important risk factor in PTB. Considering that Hispanics have the highest birth rates and are the fastest growing population in the United States, the lower rates of morbidity and mortality indicate an interesting epidemiological paradox [1, 34]. It would therefore be of interest to further characterize this population by deep phenotyping or high throughput genotyping methods to elucidate this paradox in Hispanics.

Another promising theory is the immunological reaction depicted in some preterm placentas with chronic villitis of unknown etiology since the fetus has a mixed genetic makeup from the father and the mother and the chronic inflammation in chorionic villi and sometimes in the decidua can represent a maternal immunological response to paternal antigenic stimulation.

Limitations in this study include the low number of samples being analyzed due to restrictions to collect prospective data maintained by the IRB. We could increase statistical power by increasing the number of years for retrospective sampling, but could not collect prospective maternal information. It would be interesting to replicate the findings of this paper in either accumulating multiple years of birth outcomes of tertiary care centers in South Florida. Another limitation includes the vast socioeconomic and ancestry admixture in our studied cohort which were possibly confounding factors for determining significant associations.

In conclusion, we found some demographic and physiological risk factors associated with PTB and histologically, the spontaneous preterm birth group had twice as many cases of chronic villitis as the induced preterm birth group suggesting an immunological maternal response to fetal paternal antigens.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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