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Placental villous hypermaturation is associated with idiopathic preterm birth

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Abstract

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Declaration of Interest

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Objective—Pregnancy complications such as intra-amniotic infection, preeclampsia, and fetal intrauterine growth restriction (IUGR) account for most cases of preterm birth (PTB), but many spontaneous PTB cases do not have a clear etiology. We hypothesize that placental insufficiency may be a potential cause of idiopathic PTB.

Methods—Secondary analysis of 82 placental samples from women with PTB obtained from a multicenter trial of repeat versus single antenatal corticosteroids. Samples were centrally reviewed by a single placental pathologist masked to clinical outcomes. The histopathologic criterion for infection was the presence of acute chorioamnionitis defined as neutrophils marginating into the chorionic plate. Placental villous hypermaturation (PVH) was defined as a predominance of terminal villi (similar to term placenta) with extensive syncytial knotting. Idiopathic PTB comprised a group without another known etiology such as preeclampsia, IUGR or infection.

Results—Acute chorioamnionitis was observed in 33/82 (40%) cases. Other known causes of PTB were reported in 18/82 (22%). The remaining 31/82 (38%) were idiopathic. The frequency of PVH in idiopathic PTB (26/31=84%) was similar to cases with IUGR or preeclampsia (16/18=89%), but significantly more common than PVH in the group with acute chorioamnionitis (10/33=30%) ($p<0.001$).

Conclusions—PVH, which is a histologic marker of relative placental insufficiency, is a common finding in idiopathic PTB.

Keywords

Chorioamnionitis; histology; idiopathic preterm labor; placenta; Tenney-Parker change

Introduction

Spontaneous preterm birth (PTB) is a leading cause of perinatal morbidity and mortality [1]. Although some preterm deliveries are associated with intra-amniotic infection [2–4], many spontaneous PTB cases lack a defined etiology (idiopathic).

The causes of spontaneous PTB are likely multifactorial [5,6]. Depending on the gestational age studied and techniques utilized, evidence of intra-amniotic infection is reported in 15–60% of the cases [2–4]. This wide range may be one reason that treatments targeted against infection are sometimes ineffective [7]. One underappreciated cause of idiopathic PTB may be placental insufficiency. Placental insufficiency is a clinical term [8] essentially used to describe our ignorance [9], but placental findings appear to be related to oxidative stress [10–12]. The underlying cause may be abnormal uterine spiral artery remodeling [13–22], leading to abnormal uteroplacental blood flow [10,23,24].

Placental insufficiency is associated with characteristic placental pathology [25–30]. So-called pre-placental injury is related to abnormal uteroplacental blood flow and is diagnosed by the presence of reduced placental weight, placental infarctions, accelerated chorionic villous maturation, conspicuous syncytial knotting (Tenney-Parker change) and perivillous fibrin deposition [8,12,25–27,30]. The combination of accelerated villous maturation [12,30] and Tenney-Parker changes [12,25–27], which we call placental villous hypermaturation (PVH), may be used as histologic evidence of placental insufficiency, because it is

associated with severe preeclampsia [25,26] and late onset intrauterine growth restriction (IUGR) [26]. In contrast, severe early-onset IUGR shows a different histologic pattern, so-called distal villous hypomaturity [12,29], which is a developmental deficit in terminal villous differentiation [12]. Nonetheless, studies performed by specialized placental pathologists suggest the overall histologic impression of placental insufficiency is reproducible (kappa statistic 0.68) [29]; and, although pathologists may have difficulty precisely dating the gestational age of the placenta [31], they can reasonably agree on whether the placenta has preterm or term villous maturation (kappa statistic 0.58) [32].

We hypothesize that similar to preeclampsia and late onset IUGR, idiopathic spontaneous PTB may also be associated with placental histologic features of insufficiency. To test this hypothesis, cases of intra-amniotic infection should be identified and analyzed as a separate group. Ideally, microbiologic cultures and PCR would be used to test amniotic fluid for infection [2,4], but in the absence of this gold standard, studies may employ placental histology. Placental histology has a high negative predictive value (97%) and reasonable positive predictive value (79%) for intra-amniotic infection compared with fluid cultures [4]. Therefore, in the absence of acute chorioamnionitis, intra-amniotic infection is unlikely [4]. In this study, we compared the frequency of PVH in idiopathic PTB with the frequency in a group of cases positive for histologic evidence of intra-amniotic infection and a third group of cases known to cause PTB (i.e. preeclampsia and IUGR).

Methods

Patient samples

This study was approved by the Oregon Health & Science University Institutional Review Board. We performed a retrospective secondary analysis of placental samples collected from women with intact membranes who presented with an increased risk for PTB. Cases were collected during the NICHD MFMU Network multicenter trial to study the effects of single versus weekly courses of antenatal corticosteroids in a tightly controlled randomized fashion [33]. These women gave ethical consent for the use of their placental samples and clinical data. Placental histologic sections were available from 82 cases of spontaneous PTB. The effect of single versus multiple courses of antenatal corticosteroids had previously been shown in this cohort to have no effect on placental histology [34]. However, we controlled for this confounder in our multivariate analysis, because others have suggested steroids may cause histologic features similar to PVH [35]. Idiopathic PTB was defined as cases not associated with other known causes of PTB, such as histologic evidence of intra-amniotic infection (including 16 cases of preterm premature rupture of membranes (PPROM) with acute chorioamnionitis), or a third eclectic group composed of preeclampsia ($n=2$), IUGR ($n=6$), abruption ($n=1$), preterm PPRM negative for acute chorioamnionitis ($n=7$) and insulin-dependent diabetes ($n=2$). These exclusion criteria yielded 31 cases of idiopathic PTB, 33 cases associated with histologic evidence of intra-amniotic infection and 18 cases with other known causes of PTB without infection that are often associated with placental insufficiency.

Placental histologic examination

Multiple histologic sections were available for each case, including two sections of the umbilical cord, a section of placental membranes, and at least two representative sections of placental parenchyma. Gross placental weights were not available for analysis. Histologic examination of the 82 cases was performed by a single placental pathologist (TKM) while blinded to gestational age, steroid treatment group and clinical outcomes. Routine hematoxylin & eosin (H&E)- stained sections were scored for pathologic findings defined based on descriptions in *Pathology of the Human Placenta* by Drs Benirschke and Kaufmann [30] and numerous peer-reviewed studies [18–29]. Briefly, placental sections were scored as positive for PVH if the finding were diffusely present (multiple 10× objective fields in multiple histologic sections) in preterm samples (<37 weeks) and characterized by a “predominance of terminal villi. . . usually found in pregnancy at 38–41 weeks” [30] with conspicuous syncytial knotting (Figure 1E). Distal villous hypoplasia [29] was not observed in our cohort, perhaps because there were no cases of severe early onset IUGR [12]. Sections were scored as positive for acute chorioamnionitis if there was at least “acute chorionitis” (so-called grade 1 chorioamnionitis (Figure 1)), which requires multiple clusters of maternal neutrophils marginating into the placental chorionic plate [4]. Only cases negative for acute chorioamnionitis were considered negative for infection.

Statistical analysis

Statistical analysis was conducted using SAS software (SAS Institute, Cary, NC). Categorical variables were compared using the chi-square or Fisher’s Exact tests. Continuous variables were compared using the Wilcoxon Rank-Sum test or Kruskal–Wallis test. Multivariate analysis was performed on PTB cases to examine the relationship between PVH and idiopathic PTB, compared with acute chorioamnionitis, and other known causes of PTB. Covariates included in the model were single versus repeat antenatal steroids, parity, and gestational age at delivery. A nominal two-sided $p < 0.05$ was considered significant.

Results

The mean gestational age was 33 weeks $\pm$ 3.0 [range 26–37 weeks] and was not significantly different between the three groups, although cases with acute chorioamnionitis did deliver about 2 weeks earlier than the other two groups. Maternal race was evenly distributed between pregnancy outcome groups (approximately 43% black, 39% white, 18% Hispanic) and there was no difference in the distribution of steroid treatment number.

Histologic evidence of acute chorioamnionitis was identified in 33/82 (40%) cases. Inflammation involving the amnion was observed in 24/33 and funisitis was seen in 25/33 of these cases. Acute chorioamnionitis was diagnosed in 16/23 (70%) cases of PPROM. The remaining seven negative PPROM cases were not considered idiopathic, but instead were included in the group of PTB cases often associated with placental insufficiency (e.g. preeclampsia, IUGR, abruption, diabetes). This group comprised 18/82 (22%) preterm deliveries in our study. Therefore, our study isolated 31/82 (38%) cases of idiopathic spontaneous PTB.

The frequency of PVH in the idiopathic PTB group (26/ 31=84%) was significantly greater than in cases with acute chorioamnionitis (10/33=30%) ($p < 0.001$). This association was independent of the infection diagnostic category (funisitis, acute chorionitis [grade 1] [4], and acute amnionitis). The frequency of PVH in the idiopathic group was similar to that observed in our preeclampsia/IUGR group (16/ 18=89%) (Table 1). There were no significant associations between PVH and parity, (nulligravida PVH frequency [55%], compared with multigravida [67%]; $p=0.31$), or corticosteroid administration (single course PVH frequency [58%], compared with repeat courses [68%]; $p=0.33$). Multivariate analysis did not reveal a statistically significant relationship between PVH and race, or gestational age, but there appeared to be an increased frequency of acute chorioamnionitis delivering before 34 weeks (Figure 2).

Discussion

We report that PVH is common in idiopathic spontaneous PTB similar to pregnancy complications like preeclampsia and IUGR, which are thought to be associated with placental insufficiency. This placental finding is significantly less common in PTB cases positive for histologic evidence of intra-amniotic infection. Our data are consistent with the working hypothesis that placental insufficiency may be a cause of idiopathic spontaneous PTB.

The placental samples used for this analysis were derived from women with threatened PTB who participated in a tightly controlled multicenter clinical trial comparing the effects of single versus multiple courses of antenatal steroids. Sawady *et al.* [34] had reported that placental weight may be affected by repeated steroid therapy, but not placental histologic features in this case series [34]. This finding differed from Ghidini *et al.* [35], who showed an association between the increased number of steroid doses and villous fibrosis [35]. Regardless, even if antenatal steroids do affect placental histology, there was no difference in the frequency of single versus multiple doses between our three PTB study groups (idiopathic, histologic infection, and other); so, this potential confounder is less likely to influence our data.

Given the significance of intra-amniotic infection in PTB, it is important to point out that the frequency of acute chorioamnionitis in our study was within the reported range of 15–60% [2–4]. Most of the cases positive for acute chorioamnionitis in our study delivered before 34 weeks' gestation, which is similar to the results by Watts *et al.* [36] who reported an inverted relationship between positive amniotic fluid cultures and gestational age [36].

PVH was common in idiopathic PTB (84% of cases) and it was more likely to occur after 34 weeks gestation. Other causes of PTB such as preeclampsia and IUGR were also more likely to deliver later in gestation in our study and had a similarly high frequency of PVH (89%). It is therefore possible that the pathologic diagnosis of PVH may be biased the closer delivery is to 37 weeks. This potential bias has been studied by Khong *et al.* [35] who have shown that the magnitude and direction of error when assessing placental maturity is actually less after 31 weeks gestation than earlier, with a relative *underestimation* of gestational age in later preterm deliveries [31]. Gestational age was tightly controlled in our case series [33]

and the pathologist's diagnosis was made while blinded to gestational age, which is important to reduce bias [31].

Notably, we did not observe distal villous hypoplasia in our series, which has been associated with severe early-onset IUGR, but not isolated preeclampsia [12]. There were six cases of IUGR in our series, but none showed distal villous hypoplasia as defined by Kaufmann's group [12] or the Society for Pediatric Pathology [29]. The absence of distal villous hypoplasia in idiopathic PTB suggests that similar to preeclampsia and later onset IUGR, the mechanism may be related to oxidative stress rather than developmental pathology [10–12].

We defined PVH as premature maturation of terminal chorionic villi (resembling term, greater than 38 weeks gestation) with conspicuous syncytial knotting (Tenney- Parker changes) in *preterm placentas*. Our specific definition requiring that the PVH diagnosis be made only in preterm deliveries should make this study more reproducible, because pathologists can reliably distinguish mature term from preterm villous architecture [32]. This is important because although others have reported significant differences in placental villous architecture associated with PTB [25–30], the reproducibility of these associations has been questioned [31]. Our strict preterm definition, together with our evaluation for distal villous hypoplasia, and the strength of our tightly controlled multicenter trial, reinforces prior studies from the 1990s [20,27], suggesting that placental insufficiency may cause idiopathic PTB. Moreover, emphasizing the potential significance of the role of placental insufficiency in idiopathic PTB is timely provided differences in blood flow [23,24], novel genetic signatures [5] and serum proteomics [6].

We propose that idiopathic PTB may be part of a continuum of placental insufficiency phenotypes in the spectrum of preeclampsia and IUGR. Terminal villous formation accelerates exponentially in the third trimester of pregnancy so that by term the placental surface area available for nutrient exchange reaches 13 m² [37]. This increase in the number of terminal villi and surface area is important to nourish the rapidly growing fetus. Indeed, terminal villous differentiation appears to accommodate the 10-fold increase in fetal weight from 20 weeks gestation to term [12]. If we accept the hypothesis that there may be abnormal uteroplacental blood flow leading to oxidative stress in preeclampsia, late onset IUGR, and some cases of spontaneous PTB, then PVH may be either a compensatory mechanism to increase nutrient transfer surface area, or it may be a histologic marker of oxidative damage. We did not measure surface area in our study and this metric was not required for a diagnosis of PVH. However, future studies could test this hypothesis by directly comparing uteroplacental blood flow with placental stereometry [37] and pregnancy outcomes.

The shared mechanism leading to abnormal uteroplacental blood flow may be abnormal spiral artery remodeling. Pregnancy-induced vascular remodeling of the uterine spiral arteries is key to a successful pregnancy [13–15] and there are numerous reports correlating abnormal remodeling with PTB [18–22]. Variations in spiral artery remodeling between women may be related to differences in placental invasion, or differences in maternally mediated responses [10]. Significant variations in remodeling may be detected as early as

the first trimester [38,39] and they are maintained until term [17]. Starzyk *et al.* (1997) reported using placental bed biopsies that there is a distribution of spiral artery changes from normal to abnormal independent of pregnancy outcome [17]. However, the distribution is weighted toward more and smaller-caliber thick-walled spiral arteries in women with preeclampsia compared with normal controls [17]. Variations in spiral artery remodeling within and between women raise the possibility that various pregnancy complications associated with placental insufficiency may be pleiotropic manifestations of a shared underlying process.

The weaknesses of our study include a modest sample size and the absence of culture/PCR data to confirm the presence of intra-amniotic infection. Our retrospective analysis was dependent on available histologic sections from a tightly controlled multicenter clinical trial designed to test the effects of antenatal steroids in women with threatened PTB [33]. Although the sample size is modest, the strength of this study is strict inclusion/exclusion criteria and uniform sample collection. It was a randomized multicenter trial, which addresses potential selection bias related to patient populations and sample collection. Unfortunately, placental weight measurements were not obtained, but it is important to recognize that small for gestational age placentas are associated with IUGR and not spontaneous PTB [26].

In conclusion, our data suggest a potential relationship between PVH and idiopathic PTB. The precise role of placental insufficiency in the development of idiopathic preterm labor in humans remains unknown, but this hypothesis may be tested once methods are developed to accurately measure placental blood flow in women.

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Figure 1.

Histologic features of intra-amniotic infection and placental insufficiency. (A) Funisitis is a specific indicator of infection and is defined by the presence of fetal neutrophils marginating into the blood vessel wall. (B–C) Acute chorioamnionitis is a sensitive sign of infection and is defined by maternal neutrophils marginating into the placental chorionic plate. PVH is characterized by term-appearing terminal chorionic villi with conspicuous syncytial knotting in preterm samples. (D) Normal villous maturation before 37 weeks gestation (this case is at 32 weeks) shows a predominance of intermediate villi with fewer numbers of terminal villi and only inconspicuous perivillous fibrin and syncytial knots. (E) In contrast, PVH is readily diagnosed in many cases of idiopathic PTB (this case too was at 32 weeks), because the chorionic villi resemble preterm preeclampsia, IUGR or placental sections from term (F). Bar is 100 μm (A–F).

Figure 2.

PVH in PTB related to gestational age. The frequency of acute chorioamnionitis (empty bars), idiopathic PTB (black filled in bars), and other known covariates (e.g. preeclampsia/gestational hypertension, IUGR, abruption, PPROM, diabetes) suggests infection may be the most common cause of PTB before 32 weeks and less common after 34 weeks.

Table 1

PVH is Common in Idiopathic PTB.

	Acute chorioamnionitis (n=33)	Other complications (n=18)	Idiopathic PTB (n=31)
Normal villous maturation	23/33 (70%)	2/18 (11%)	5/31 (16%)
PVH	10/33 (30%)	16/18 (89%)	26/31 (84%) *

Compared to PTB with histologic evidence of infection, idiopathic PTB had significantly more PVH, even when controlled for covariants such as gestational age, steroid treatment group, and other known causes of PTB (preeclampsia/gestational hypertension, IUGR, PPROM without infection, abruption, diabetes).

*
 $p < 0.001$.