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Is there a role for placental histopathology in predicting the recurrence of preterm birth?

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Abstract

Purpose Spontaneous preterm birth (sPTB) is a major cause of neonatal morbidity and mortality with a relatively high rate to recurrence. Our aim was to study the role of placental histopathology in predicting recurrence of sPTB.

Methods We conducted a retrospective cohort study. The medical records and placental pathologic reports of all women with sPTB (gestational age $23^{0/7}$–$36^{6/7}$ weeks), during 2008–2015, were reviewed. Only women who had a subsequent delivery were included. Multiple pregnancies and women with known uterine anomalies were excluded. Placental histopathology lesions were classified into maternal and fetal vascular malperfusion lesions, acute maternal and fetal inflammatory responses lesions, and chronic inflammatory lesions. Placental lesions were compared between patients with and without recurrent sPTB on their subsequent pregnancies.

Results Maternal characteristics, gestational age, birthweight, and the rate of preterm rupture of membrane at index delivery were similar between the recurrent sPTB ($n=72$) and the non-recurrent sPTB ($n=167$) groups. The incidence of placental vascular malperfusion lesions, or inflammatory lesions did not differ between the study groups. However, on multivariate logistic regression analysis, the presence of only acute inflammatory response lesions was associated with recurrence of early sPTB (< 34 weeks) (adjusted OR 3.16; 95% CI 1.22–8.18).

Conclusion The presence of isolated placental acute maternal or fetal inflammatory response in index sPTB may be associated with recurrence of early sPTB.

Keywords Pathology · Placenta · Prediction · Preterm birth

Introduction

Preterm birth (PTB) is the leading cause of neonatal morbidity and mortality [1]. Surviving premature infants may still develop long-term sequelae, including cerebral palsy, impaired learning, visual disorders, and other chronic diseases in adulthood [2]. Globally, 15 million babies are born preterm each year, which is approximately 11% of all deliveries. Despite large preventive efforts, the incidence of PTB appears to increase in most countries [3].

Spontaneous preterm birth (sPTB) is regarded as a syndrome caused by multiple pathologic processes [4]. Chorioamnionitis is a precursor in many spontaneous preterm births [5], while poor utero-placental perfusion and abnormal placentation play a role in up to third of cases [6, 7]. Other causes of sPTB include disruption of maternal–fetal tolerance, decline in progesterone action, and uterine overdistension [4]. Placental histopathology provides important insights into the different subtypes of preterm birth [7–9].

In case of preterm labor, effective interventions are available, such as the administration of tocolysis, corticosteroids, and magnesium sulfate for neuroprotection, when appropriate [1, 10, 11]. However, it is challenging to identify those women who will eventually give birth preterm. Identifying women at risk for recurrent PTB is motivating, as it may improve their prenatal management.

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Women at risk for recurrent sPTB can be offered prophylactic progesterone supplements, low-dose aspirin, cervical cerclage, or cervical length monitoring.

Recently, we demonstrated the role of placental histopathology in predicting the recurrence of preeclampsia [12] and fetal growth restriction [13], which together with sPTB, constitute diseases of the placental bed, also known as the "Great Obstetrical Syndromes" [14]. Our hypothesis is that underlying maternal factors, resulting the development of sPTB and abnormal placental histopathology, may still be present in subsequent pregnancies, contributing to the recurrence of sPTB. Only few have studied the association between placental histopathology and the risk of recurrent sPTB [15, 8]. In the current study, we aimed to investigate the role of placental histopathology in predicting recurrence of sPTB while using the updated definitions of placental histopathology lesions [16].

Materials and methods

A retrospective cohort study was performed, examining all PTBs at a single, university affiliated, tertiary medical center, between January 2008 and December 2015. According to our departmental protocol, we perform placental histopathologic analysis in all PTBs. Data of all singleton spontaneous PTBs ($23^{0/7}$–$36^{6/7}$ weeks of gestation) were extracted from the computerized database. This included preterm labor and preterm premature rupture of membranes (PPROM). Women who had a subsequent delivery were included. Exclusion criteria were multiple pregnancies, labor induction, intrauterine fetal demise, pregnancy termination, known uterine anomalies, and missing data. Women with PPROM were managed expectantly up to 34 week gestation and were administered antibiotics according to the American College of Obstetricians and Gynecologists (ACOG) guidelines [17]. In all participants, gestational age was confirmed by first-trimester ultrasonography. The study was approved by the Local Ethics Committee at the Edith Wolfson Medical Center (Registry No. 0120–17-WOMC). Informed consent was not required, since patients' data were reviewed retrospectively and were de-identified.

For the purpose of the study, clinical characteristics and placental histopathology lesions in index pregnancies were compared between women with and without recurrent sPTB. Data regarding pregnancy outcome in subsequent pregnancy were obtained from our computerized database as well. For women who did not give birth at our institute in their subsequent pregnancy, a telephone survey was performed to obtain relevant information.

Data collection

The following data were extracted from the medical files: age, gestational age (GA) at delivery, parity, pre-pregnancy body mass index (BMI kg/m^2), time interval between deliveries, pre-gestational diabetes mellitus, gestational diabetes mellitus, thrombophilia (defined as any thrombophilia, inherited or acquired, which necessitated thromboprophylaxis), gestational hypertension, preeclampsia, and smoking.

Placental pathology

As part of our departmental protocol, in every case of pregnancy complication, such as preterm birth, placentas are sent for histopathological evaluation. Placental pathology examinations were performed using our standard protocol by a single pathologist (author L.S). Placental lesions were classified according to the updated criteria adopted by the Society for Pediatric Pathology [16], and as previously reported by us [12, 13, 18]. Briefly, placental weight was determined 24 h after delivery untrimmed and fixed. It should be noted that placental weight might be subject to bias because of our fixation method, due to the formaldehyde stored in the placentas, and possible differences in cord length and size [19].

From each placenta, six tissue samples were embedded in paraffin blocks for microscopic assessment: One role of the free membranes was taken from the rupture edge to the placental margin (chorion and amnion with attached decidua capsularis), one at the cord insertion, one from central tissue that appeared abnormal on gross examination, two from normally appearing central tissue, and one at the margin visible abnormal areas on gross examination. In addition, two sections of the umbilical cord were sampled. Placental lesions were divided into four main groups [16]:

1. Maternal vascular malperfusion (MVM) lesions, including placental hemorrhages (marginal and retroplacental), vascular lesions (acute atherosis, mural hypertrophy, and decidual arteriopathy), and villous changes (increased syncytial knots, villous agglutination, increased intervillous fibrin deposition, distal villous hypoplasia, and villous infarcts).
2. Fetal vascular malperfusion (FVM) lesions, including vascular lesions (thrombosis of the chorionic plate and stem villous vessels) and villous changes (villi with stromal vascular karyorrhexis and avascular villi).
3. Acute inflammatory lesions: maternal inflammatory response (MIR) was divided into three stages: stage 1—

acute subchorionitis or chorionitis; stage 2—acute chorioamnionitis: polymorphonuclear leukocytes extended; and stage 3—necrotizing chorioamnionitis: karyorrhexis of polymorphonuclear leukocytes, amniocyte necrosis. Fetal inflammatory response (FIR) was also divided into 3 stages: stage 1—umbilical phlebitis; stage 2—involvement of the umbilical vein and one or more umbilical arteritis; and stage 3—necrotizing funisitis.

4. Chronic inflammatory lesions: villitis of unknown etiology (VUE) or chronic villitis was defined as lymphohistiocytic inflammation localized to the stroma of terminal villi but often extending to the small vessels of upstream villi. Immunohistochemistry studies were performed to identify T-cell infiltration using an antibody against CD3 (rabbit monoclonal SP7, Thermo-Scientific) in all cases suspected of VUE after H&E staining. Cases in which an etiology was identified, such as CMV infection were excluded. High grade VUE was defined as the presence of multiple foci, on more than one section, at least one of which shows inflammation affecting more than 10 contiguous villi. Chronic deciduitis (CD) was diagnosed by the presence of lymphocytes and plasma cells in the basal plate.

Finally, the following macroscopic pathologies of the umbilical cord were examined: marginal (< 1 cm from the nearest margin) and velamentous insertions, hypercoiling (> 3 coils per 10 cm) and hypocoiling (< 1 coil per 10 cm).

Figure 1 depicts several placental histopathology lesions.

Statistical analysis

Data were analyzed using SPSS software version 23.0 (IBM Inc. Chicago, USA). Continuous variables were compared by Student's *t* test, and categorical variables were compared by Chi-square test, or Fisher's exact test, as appropriate. A multivariate logistic regression analysis was performed to study the association between the different pathology lesions and recurrent sPTB, after controlling for confounders. The variables included in the multivariate analysis were age and gestational age, as these are associated with certain placental histopathology lesions, and parity, as it may affect the incidence of sPTB. First, each individual histopathologic lesion served as an independent variable (MVM, FVM, MIR, FIR, VUE, and CD). Second, we analyzed combinations of lesions as an independent variable (Any pathologic lesion, MVM and/or FVM, MIR and/or FIR, and isolated lesions as further described). Isolated acute inflammatory response was defined as the presence of MIR and/or FIR without coexisting vascular malperfusion lesions. Isolated malperfusion lesions was defined as the presence MVM and/or FVM lesions without coexisting inflammatory lesions.

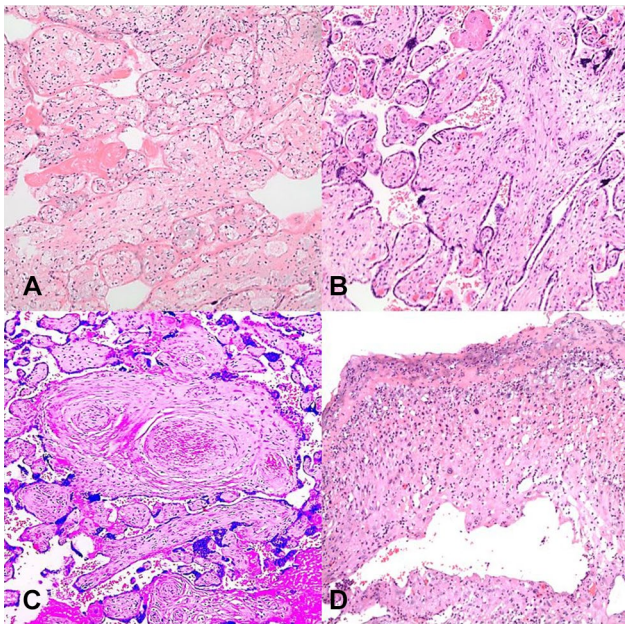

Fig. 1 Examples of placental histopathology lesions. **a** Scattered old and intermediate aged infarcts (maternal vascular malperfusion); **b** avascular villi (fetal vascular malperfusion); **c** thrombi in fetal vessels of stem villi (fetal vascular malperfusion); **d** neutrophils infiltration (maternal inflammatory response)

Results

During the study period, out of 24,378 deliveries, 1821 (7.46%) women had a sPTB (< 37 week gestation). Of those, 239 (13%) had a subsequent delivery and met the inclusion criteria. In their subsequent delivery, 72 (30.1%) women gave birth preterm and 167 (69.9%) women gave birth at term. Twenty-eight women (11.7%) gave birth at other hospitals in their subsequent pregnancy and data regarding their outcome were obtained by a telephone survey.

Maternal and obstetric characteristics of the study groups are presented in Table 1. There were no between-group differences with regard to maternal age, maternal BMI, parity, gestational age in index pregnancy, incidence of PPROM, time interval between deliveries, hypertensive disorders, thrombophilia, or smoking. Gestational age in subsequent pregnancy was 38.7 ± 1.0 weeks in the no-recurrence group and 33.9 ± 3.3 weeks in the recurrence sPTB group (< 0.001). Women in the recurrent sPTB group were more likely to undergo cervical cerclage or be treated with progesterone supplements in their subsequent pregnancy. Placental histopathology analysis in index pregnancy is presented in Table 2. The incidence of the different histopathology lesions and umbilical cord anomalies did not differ between the study groups. We observed high incidence of vascular malperfusion lesions and inflammatory lesions in both study groups. There were only two cases of high grade VUE, one

Table 1 Maternal and obstetric characteristics of women with and without recurrence of spontaneous preterm birth (sPTB)

	No recurrence of sPTB ($n=167$)	Recurrent sPTB ($n=72$)	p value
Maternal age in index pregnancy, years	27.5 ± 4.6	28.7 ± 5.5	0.08
BMI before index pregnancy, Kg/m^2	22.9 ± 4.6	23.9 ± 4.7	0.30
Parity in index pregnancy	0.65 ± 0.95	0.85 ± 1.0	0.16
Gestational age, weeks			
In index pregnancy	34.2 ± 2.9	33.5 ± 3.2	0.12
In subsequent pregnancy	38.7 ± 1.0	33.9 ± 3.3	< 0.001
Birthweight, g			
In index pregnancy	2222 ± 610	2224 ± 730	0.98
In subsequent pregnancy	3084 ± 402	2355 ± 768	< 0.001
PPROM in index pregnancy			
< 37 weeks	95 (56.9)	39 (54.2%)	0.69
< 34 weeks	29 (17.4)	16 (22.2)	0.37
Time interval between deliveries, months	33.5 ± 15.6	30.1 ± 17.3	0.13
Cerclage in subsequent pregnancy	2 (1.2%)	12 (16.7)	< 0.001
Progesterone in subsequent pregnancy	16 (9.6)	14 (19.4)	0.035
Gestational hypertension or preeclampsia	2 (1.2)	4 (5.6)	0.069
Thrombophilia	4 (2.4)	4 (5.6)	0.24
Smoking	14 (8.4)	7 (9.7)	0.73

Data are presented as mean ± SD, or *n* (%)

BMI Body mass index, *PPROM* preterm premature rupture of membranes

in the recurrent sPTB and one in the no-recurrence group. There were no cases of velamentous cord insertion.

On multivariate logistic regression analysis, after controlling for maternal age, parity, and gestational week at index pregnancy, the presence of each individual histopathologic lesion was not associated with recurrent sPTB < 34 or < 37 weeks of gestation. When examining combinations of lesions (Table 3), the presence of isolated placental acute inflammatory response lesions (MIR and/or FIR) was associated with recurrent early sPTB (< 34 weeks of gestation). Other combinations of inflammatory or vascular lesions were not associated with recurrent sPTB.

Discussion

In the current study, we found that in pregnancies complicated by sPTB, the presence of placental acute inflammatory response as a sole finding was associated with increased risk of recurrence of early sPTB (less than 34 weeks). Other placental histopathology lesions were not found to be associated with recurrent sPTB in subsequent pregnancy.

The "common pathway" of labor involves three clinical events: increased uterine contractility, cervical dilatation, and rupture of the membranes. In cases of sPTB, several pathologic processes may activate one or more of these components preterm, while the exact etiology occasionally cannot be identified [4]. In the current study, placental histopathology examination revealed high prevalence of vascular malperfusion lesions and inflammatory response lesions. Maternal vascular malperfusion lesions were found in 40% of placentas. This finding is in agreement with previous reports [4, 6, 20]. Yet, in the current study, vascular lesions were not found to be associated with recurrence of sPTB, as opposed to their association with recurrence of preeclampsia [12] and fetal growth restriction [13]. Similarly, another investigator [21] could not demonstrate an association between placental intervillous thrombi (placental lesion related to MVM) in index sPTB and recurrent PTB.

Accumulating evidence establishes the association between inflammatory processes and sPTB. The transition of the myometrium from a quiescent to a contractile state is accompanied by a shift in signaling between anti-inflammatory and pro-inflammatory pathways, including chemokines (IL-8) and cytokines (IL-1 and 6). Membrane activation also involves increased expression of inflammatory cytokines, such as TNF-alpha and LI-1 [22, 23]. In the current study, acute inflammatory lesions were observed in 52% of placentas. Interestingly, after controlling for confounders, the presence of isolated placental acute inflammatory response, MIR or FIR, was associated with recurrence of early sPTB (< 34 weeks) with an adjusted OR of 3.16 (CI 95% 1.22–8.18). This finding suggests that sPTB originating from inflammatory processes tends to reoccur, as opposed to sPTB due to other etiologies. Similarly, Hackney et al. [21] have found that funisitis at the time of sPTB

Table 2 Placental and umbilical cord histopathology in index pregnancy, in women with and without recurrence of spontaneous preterm birth

	No recurrence of PTB ($n=167$)	Recurrent PTB ($n=72$)	p value
Placental weight, g	381 ± 87.2	391 ± 97.6	0.42
Birthweight to placental weight ratio	5.8 ± 1.3	5.6 ± 1.2	0.32
Umbilical cord anomalies			
Hypercoiling	22 (13.2)	12 (16.7)	0.47
Hypocoiling	25 (15.0)	10 (13.9)	0.82
Marginal cord insertion	32 (19.2)	13 (18.1)	0.84
Maternal vascular malperfusion (MVM) lesions			
Placental hemorrhage	10 (6.0)	5 (6.9)	0.77
Vascular lesions related to MVM	21 (12.6)	9 (12.5)	0.98
Villous lesions related to MVM	49 (29.3)	16 (22.2)	0.25
Any MVM lesion	69 (41.3)	25 (34.7)	0.33
Fetal vascular malperfusion (FVM) lesions			
Vascular lesions related to FVM	6 (3.6)	6 (8.3)	0.19
Villous lesions related to FVM	2 (1.2)	3 (4.2)	0.16
Any FVM lesion	8 (4.8)	7 (9.7)	0.15
Acute maternal inflammatory response (MIR) lesions			
MIR stage 1	26 (15.6)	8 (11.1)	0.36
MIR stage 2	18 (10.8)	13 (18.1)	0.12
MIR stage 3	5 (3.0)	3 (4.2)	0.70
Any MIR lesion, stages 1–3	49 (29.3)	23 (31.9)	0.68
Acute fetal inflammatory response (FIR) lesions			
FIR stage 1	8 (4.8)	4 (5.6)	0.75
FIR stage 2	10 (6.0)	5 (6.9)	0.77
FIR stage 3	0	0	
Any FIR lesion, stages 1–3	18 (10.8)	9 (12.5)	0.70
Chronic inflammatory lesions			
Villitis of unknown etiology (VUE)	7 (4.2)	2 (2.8)	0.72
Chronic deciduitis (CD)	12 (7.2)	6 (8.3)	0.75
Combinations of lesions			
Any vascular malperfusion lesion (MVM and/or FVM)	76 (45.5)	29 (40.3)	0.45
Any inflammatory response lesion (MIR and/or FIR)	18 (10.8)	9 (12.5)	0.70
Any chronic inflammatory lesion (VUE and/or CD)	18 (10.8)	7 (9.7)	0.80

Data are presented as mean ± SD, or n (%)

Table 3 Association between placental histologic findings and recurrence of spontaneous preterm birth

Placental histologic findings	aOR (95% CI)[a] for recurrent sPTB < 37 weeks	aOR (95% CI)[a] for recurrent sPTB < 34 weeks
Any pathological placental lesion (vascular malperfusion lesion and/or inflammatory lesion)	0.80 (0.42–1.55)	1.87 (0.50–6.97)
Isolated vascular malperfusion lesions	1.04 (0.57–1.90)	1.05 (0.39–2.83)
Isolated acute inflammatory response lesions (MIR and FIR)	1.49 (0.76–2.93)	3.16 (1.22–8.18)
Isolated chronic inflammatory lesions	0.88 (0.34–2.29)	1.33 (0.31–5.64)

aOR adjusted odds ratio, *CI* confidence interval

[a]Adjusted for maternal age, parity, and gestational week at index pregnancy

significantly increased the risk of recurrent early PTB (OR 3.38, $p=0.016$). However, after adjustment for gestational age in index sPTB, they found only a non-significant trend ($p=0.08$) towards an association between funisitis and recurrent sPTB.

These findings imply that some women may have sustained risk factors predisposing them to develop recurrent preterm births. Focusing on acute inflammatory response lesions, without coexisting vascular malperfusion lesions, allowed us to study a specific group of women with presumed susceptibility to ascending infection, which may reoccur in subsequent pregnancies. Further research is needed to address the question of individual susceptibility to infection or even to look at the placental microbiome as the etiology for this tendency [24]. Early recognition of this group of women may facilitate early intervention and preventive treatments.

Our initial hypothesis was that placental histopathology could aid us predicting which woman would have a recurrent PTB, and implying an individual preventive method accordingly. However, we did not observe a significant association between any of the placental histopathology lesions and recurrent sPTB (< 37 weeks). The high incidence of maternal vascular malperfusion and inflammatory response lesions supports recent evidence that aspirin treatment may in some degree prevent preterm births [11]. Interestingly, among the 14 patients who had a cervical cerclage in their subsequent pregnancy, only two delivered at term. The low success rate of cervical cerclage in these patients is probably due to a markedly higher risk of PTB. Among patients who received progesterone, we observed a higher rate of term deliveries (16/30). Finally, it should be noted that many women who had vascular or inflammatory placental lesions in their first sPTB, delivered at term in their subsequent pregnancy. Hence, placental histopathology cannot serve as the only tool for predicting recurrent sPTB or for deciding whether a preventive method should be used.

The current study has several strengths. First, as opposed to the previous studies [8, 25], we followed a cohort of patients with spontaneous PTB to their subsequent births. Second, all placental histopathology analyses were performed by a single investigator, who naturally was blinded to the results of subsequent pregnancies at that time. Third, we analyzed placental lesions using the recent definitions adopted by the Society for Pediatric Pathology [16].

Several limitations, however, must be acknowledged. First, the study may be subject to bias due to its retrospective design. Second, there is a relatively small sample of patients with recurrent PTB. Third, data from 11.7% of cases were obtained by a telephone survey, which could introduce a recall bias. Fourth, the study included patients with PPROM who were managed expectantly up to 34 weeks of gestation and received antibiotics. This may affect their placental histopathology by disguising signs of acute infection. Moreover, antibiotics may alter placental membrane microbiome resulting dysbiosis, which is associated with PTB [26]. Fifth, placental histopathology examinations are not available in every medical center, limiting the generalizability of this significant tool.

In conclusion, the presence of isolated placental acute inflammatory response lesions in pregnancies complicated by spontaneous preterm birth is associated with an increased risk of recurrence of early sPTB (less than 34 weeks). Validating our results on larger prospective studies may yield a prediction model combining clinical and histopathological factors to better manage these high-risk pregnancies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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