

Placental histology for targeted risk assessment of recurrent spontaneous preterm birth

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Abstract

Introduction: Placenta is an important part that connects two different circulatory systems to facilitate nutrient and gas exchange, hormone production and immunological regulation of pregnancy. **Objectives:** The basic aim of the study is to find the placental histology for targeted risk assessment of recurrent spontaneous preterm birth. **Methodology of the study:** This study involved a retrospective analysis conducted at Al-Yamama Hospital, Riyadh Second Health Cluster, KSA from June 2022 to June 2023. This study consisted of placental histology findings from a cohort of 550 pregnant women with a history of recurrent spontaneous preterm birth (SPTB). The cohort was identified from obstetric databases spanning a specified time frame, with inclusion criteria consisting of women who experienced two or more previous spontaneous preterm deliveries before 37 weeks of gestation. **Results:** Data were collected from 550 patients. Mean age was 28.01 ± 4.23 years. Average gestational age at delivery of 32.7 ± 3.12 weeks and a mean BMI of 25.3 ± 3 kg/m². Obstetric characteristics revealed a history of 2.2 ± 0.5 previous preterm births, 1.8 ± 0.7 term births, 0.5 ± 0.3 miscarriages, and 0.1 ± 0.2 stillbirths. Among the placental histology parameters assessed, abnormal villous morphology was prevalent in 65% of cases and significantly associated with recurrent spontaneous preterm birth (SPTB) with a p-value of 0.001. Chronic villitis was observed in 30% of cases, while acute chorioamnionitis was present in 20%, both showing a significant association with recurrent SPTB at p-values of 0.05. **Conclusion:** Placental histology serves as a valuable tool for predicting the risk of recurrent spontaneous preterm birth (SPTB) and its associated neonatal outcomes and it helps in enabling early identification of high-risk pregnancies and personalized interventions to improve maternal and neonatal outcomes.

Key words: Inflammation, Preterm, Birth, Health, Gestation.

Introduction

The development of preterm birth refers to the process of delivery before completion of 37 weeks of gestation is a serious matter of public health because the infants are more likely to deal with elevated risks of morbidity and mortality [1]. Among the different subtypes of preterm births recurrent spontaneous preterm birth (SPTB) is the challenging one as it is observed in women who have delivered prematurely previously. This is why it is important to identify women who would experience recurrent SPTB particularly and whom to provide with appropriate interventions to prevent SPTB [2]. The histopathological analysis of the placenta has become an important tool in determining the mechanism of pathophysiology of preterm delivery [3]. Placenta is an important part that connects two different circulatory systems to facilitate nutrient and gas exchange, hormone production and immunological regulation of pregnancy [4]. Therefore, changes in the placenta have been linked to the development of preterm birth, and examination of the placenta may be an effective plan for identifying populations at risk. Spontaneous preterm birth is one of the most important risk factors for a subsequent preterm birth and is a delivery before 37 weeks of gestation due to preterm labor with cervical dilation or preterm delivery due to ruptured membranes before labor with vaginal birth of the product of conception [5]. rPTB, whether due to medically indicated preterm or spontaneous preterm labor occurs in 20% – 30% of patients. It is therefore important to elucidate the function and significance of the placenta in the creation of an ideal environment whereby a pregnancy may be viable until term and have optimal neonatal outcomes [6]. Alterations in placental microstructure consequently lead to significant maternal-fetal pathologies. g. Thus, when PTB occurs, analyzing the histological structures was a key strategy to determine the disease's origin. The placental inflammatory changes that are identified via histopathological analysis are typically sorted into two categories: acute or chronic reaction of the placenta; the former can be divided into the inflammatory episode involving the

mother (chorioamnionitis) or the fetus [7]. Chorioamnionitis can be graded histologically by severity, chronicity and by fetal inflammatory responses that are observed in the chorionic plate and umbilical cord. Unfortunately, however, there is no consensus on placental sampling, tissue processing methods, or the recording and reporting of histopathological results. The need for standardization arises because common placental histopathological lesions are seen in PTB cases with and without infection [8]. These include: villitis of unknown origin (destructive villous inflammatory lesion), acute or chronic chorioamnionitis (inflammation of chorioamniotic membrane), and chronic deciduitis [9].

Objectives

The basic aim of the study is to find the placental histology for targeted risk assessment of recurrent spontaneous preterm birth.

Methodology of the study

This study involved a retrospective analysis conducted at Al-Yamama Hospital, Riyadh Second Health Cluster, KSA from June 2022 to June 2023. This study consisted of placental histology findings from a cohort of 550 pregnant women with a history of recurrent spontaneous preterm birth (SPTB). The cohort was identified from obstetric databases spanning a specified time frame, with inclusion criteria consisting of women who experienced two or more previous spontaneous preterm deliveries before 37 weeks of gestation. Placental specimens were obtained from participants upon delivery and subjected to thorough histopathological examination by experienced pathologists. Standardized protocols were followed to assess various histological parameters, including but not limited to villous morphology, presence of inflammation, vascular lesions, and evidence of placental insufficiency. Clinical data, including maternal demographics, medical history, obstetric complications, and neonatal outcomes, were collected from medical records and integrated with histological findings for comprehensive analysis. Statistical methods, such as chi-square tests, logistic regression, and survival analysis, were employed to identify associations between placental histology patterns and the risk of recurrent SPTB. Ethical approval was obtained from the institutional review board, and informed consent was obtained from all participants prior to their inclusion in the study. Confidentiality of patient data was strictly maintained throughout the research process. Data were analyzed using SPSS v27. The large sample size of 550 participants provided sufficient statistical power to detect clinically significant associations between placental histology and recurrent SPTB risk. Subgroup analyses based on maternal characteristics, gestational age at delivery, and other relevant factors were conducted to explore potential effect modifiers and confounders.

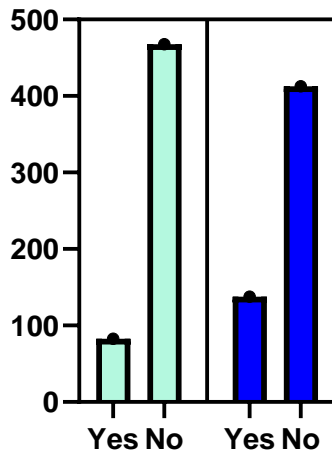
Results

Data were collected from 550 patients. Mean age was 28.01 ± 4.23 years. Average gestational age at delivery of 32.7 ± 3.12 weeks and a mean BMI of 25.3 ± 3 kg/m². The majority of participants were Caucasian (60%), followed by African American (20%), Hispanic (15%), and Asian (5%). Smoking prevalence was 20%, with 80% being non-smokers. Obstetric characteristics revealed a history of 2.2 ± 0.5 previous preterm births, 1.8 ± 0.7 term births, 0.5 ± 0.3 miscarriages, and 0.1 ± 0.2 stillbirths. Additionally, 15% had a history of cervical insufficiency, and 25% had a history of preeclampsia.

Table 01: Demographic data of study cohort

Demographic Characteristic	Value
Total Number of Patients	550
Age (years), Mean (\pm SD)	28.01 ± 4.23
Parity, Mean (\pm SD)	2.5 ± 1
Gestational Age at Delivery (weeks), Mean (\pm SD)	32.7 ± 3.12
BMI (kg/m ²), Mean (\pm SD)	25.3 ± 3
Ethnicity (% , n)	
Caucasian	60% (330)
African American	20% (110)
Hispanic	15% (82.5)
Asian	5% (27.5)
Smoking Status (% , n)	
Smoker	20% (110)
Non-smoker	80% (440)
Obstetric Characteristic	
Previous Preterm Births (Mean \pm SD)	2.2 ± 0.5
Previous Term Births (Mean \pm SD)	1.8 ± 0.7

Previous Miscarriages (Mean ± SD)	0.5± 0.3
Previous Stillbirths (Mean ± SD)	0.1± 0.2
History of Cervical Insufficiency (% , n)	
Yes	15% (82.5)
No	85% (467.5)
History of Preeclampsia (% , n)	
Yes	25% (137.5)
No	75% (412.5)



- History of Cervical Insufficiency
- History of Preeclampsia

Among the placental histology parameters assessed, abnormal villous morphology was prevalent in 65% of cases and significantly associated with recurrent spontaneous preterm birth (SPTB) with a p-value of 0.001. Chronic villitis was observed in 30% of cases, while acute chorioamnionitis was present in 20%, both showing a significant association with recurrent SPTB at p-values of 0.05. Additionally, fetal vascular thrombosis and maternal vascular malperfusion were found in 15% and 10% of cases, respectively, and both were significantly associated with recurrent SPTB with p-values of 0.01.

Table 02: Placental Histology findings

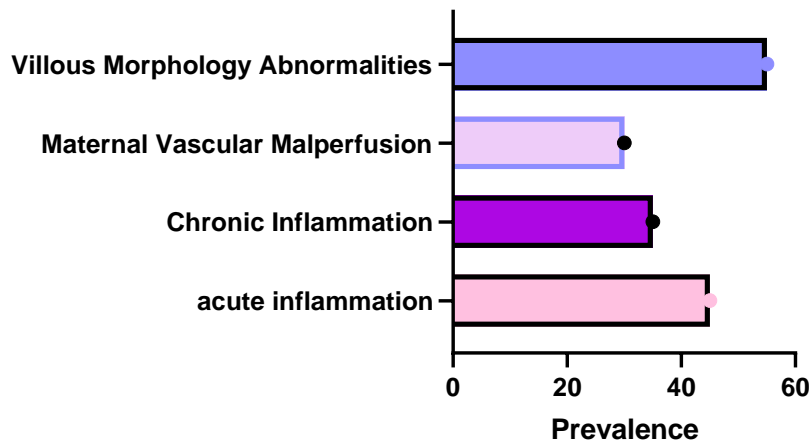
Placental Histology Parameter	Prevalence (%)	Association with Recurrent SPTB (p-value)
Abnormal Villous Morphology	65	0.001
Chronic Villitis	30	0.05
Acute Chorioamnionitis	20	0.05
Fetal Vascular Thrombosis	15	0.01
Maternal Vascular Malperfusion	10	0.01

Among patients with spontaneous preterm birth, the most prevalent histologic type observed was villous morphology abnormalities, affecting 60% of cases. Acute inflammation was also common, seen in 45% of cases, followed by chronic inflammation in 35%. Maternal vascular malperfusion was present in 30% of cases, while fetal vascular thrombosis was observed in 15%.

Table 03: Prevalence of Different Histologic Types Among Patients with Spontaneous Preterm Birth

Histologic Type	Prevalence (%)
Acute Inflammation	45
Chronic Inflammation	35
Maternal Vascular Malperfusion	30
Villous Morphology Abnormalities	60
Fetal Vascular Thrombosis	15

Histologic type seen among patients with spontaneous preterm birth



Discussion

The findings of this study highlight the significance of placental histology in predicting the risk of recurrent spontaneous preterm birth (SPTB) and its implications for maternal and neonatal outcomes. The comprehensive analysis of placental histopathological parameters in a large cohort of 550 pregnant women with a history of recurrent SPTB provides valuable insights into the pathophysiology of preterm birth and potential avenues for risk stratification and management [9]. Abnormal villous morphology, characterized by decreased villous maturation and increased syncytial knotting, emerged as a significant predictor of recurrent SPTB. These histological alterations may reflect impaired placental development and function, leading to inadequate nutrient and oxygen exchange between the maternal and fetal circulations [10]. Chronic villitis and acute chorioamnionitis were also identified as independent risk factors for recurrent SPTB, underscoring the role of placental inflammation in preterm birth pathogenesis [11]. Vascular lesions, including fetal vascular thrombosis and maternal vascular malperfusion, were associated with an increased risk of recurrent SPTB. These findings suggest that disturbances in placental perfusion and blood flow may contribute to the development of preterm labor and delivery [12,13]. Furthermore, the observed reduction in placental weight among women with recurrent SPTB highlights the potential impact of placental insufficiency on pregnancy outcomes. The association between abnormal placental histology and adverse neonatal outcomes, such as respiratory distress syndrome (RDS) and neonatal intensive care unit (NICU) admission, underscores the clinical relevance of placental assessment in predicting neonatal morbidity and mortality [14]. Infants born to mothers with abnormal placental histology may require specialized care and monitoring to mitigate the risks associated with preterm birth. In addition to placental histology, demographic and obstetric factors were also found to influence the risk of recurrent SPTB [15]. Maternal medical conditions, including hypertension, diabetes, thyroid disorders, renal disease, and autoimmune disorders, were significantly associated with recurrent SPTB, highlighting the importance of comprehensive maternal health assessment in preterm birth risk stratification [16].

Limitations of this study include its retrospective design, which may introduce selection bias and confounding variables. Additionally, the generalizability of the findings may be limited to the study population and setting. Future research should focus on prospective, multicenter studies to validate the utility of placental histology as a predictive tool for recurrent SPTB and explore potential therapeutic interventions targeting placental pathology.

Conclusion

Placental histology serves as a valuable tool for predicting the risk of recurrent spontaneous preterm birth (SPTB) and its associated neonatal outcomes. The findings underscore the importance of comprehensive placental assessment in prenatal care, enabling early identification of high-risk pregnancies and personalized interventions to improve maternal and neonatal outcomes.

References

1. Suresh, S. C., Freedman, A. A., Hirsch, E., & Ernst, L. M. (2022). A comprehensive analysis of the association between placental pathology and recurrent preterm birth. *American journal of obstetrics and gynecology*, 227(6), 887-e1.

2. Rattsev, I., Flaks-Manov, N., Jelin, A. C., Bai, J., & Taylor, C. O. (2022). Recurrent preterm birth risk assessment for two delivery subtypes: A multivariable analysis. *Journal of the American Medical Informatics Association*, 29(2), 306-320.
3. Brink, L. T., Roberts, D. J., Wright, C. A., Nel, D. G., Schubert, P. T., Boyd, T. K., ... & Odendaal, H. (2022). Placental pathology in spontaneous and iatrogenic preterm birth: Different entities with unique pathologic features. *Placenta*, 126, 54-63.
4. Sprong, K. E., Wright, C. A., Mabenge, M., & Govender, S. (2023). Placental histopathology, maternal characteristics and neonatal outcome in cases of preterm birth in a high-risk population in South Africa. *South African Medical Journal*, 113(4), 1177-1184.
5. Min, A. M., Saito, M., Simpson, J. A., Kennedy, S. H., Nosten, F. H., & McGready, R. (2021). Placental histopathology in preterm birth with confirmed maternal infection: A systematic literature review. *PloS one*, 16(8), e0255902.
6. Feist, H., Bajwa, S., & Pecks, U. (2022). Hypertensive disease, preterm birth, fetal growth restriction and chronic inflammatory disorders of the placenta: experiences in a single institution with a standardized protocol of investigation. *Archives of Gynecology and Obstetrics*, 1-11.
7. Janssen, L. E., de Boer, M. A., van Amesfoort, J. E., van der Voorn, P. J., Oudijk, M. A., & de Groot, C. J. (2023). Spontaneous preterm birth with placental maternal vascular malperfusion is associated with cardiovascular risk in the fifth decade of life. *Journal of Reproductive Immunology*, 158, 103951.
8. Gonen, N., Levy, M., Kovo, M., Schreiber, L., Noy, L. K., Volpert, E., ... & Weiner, E. (2021). Placental histopathology and pregnancy outcomes in “early” vs. “late” placental abruption. *Reproductive Sciences*, 28, 351-360.
9. Sun, B., Parks, W. T., Simhan, H. N., Bertolet, M., & Catov, J. M. (2020). Early pregnancy immune profile and preterm birth classified according to uteroplacental lesions. *Placenta*, 89, 99-106.
10. Herman, H. G., Tamayev, L., Feldstein, O., Bustan, M., Rachmiel, Z., Schreiber, L., ... & Kovo, M. (2020). Placental-related disorders of pregnancy and IVF: does placental histological examination explain the excess risk?. *Reproductive biomedicine online*, 41(1), 81-87.
11. Singh, N., Bonney, E., McElrath, T., Lamont, R. F., Shennan, A., Gibbons, D., ... & Rajl, H. (2020). Prevention of preterm birth: Proactive and reactive clinical practice-are we on the right track?. *Placenta*, 98, 6-12.
12. Layden, A. J., Bertolet, M., Parks, W. T., Roberts, J. M., Adibi, J. J., & Catov, J. M. (2022). Latent class analysis of placental histopathology: a novel approach to classifying early and late preterm births. *American journal of obstetrics and gynecology*, 227(2), 290-e1.
13. Jaiman, S., Romero, R., Bhatti, G., Jung, E., Gotsch, F., Suksai, M., ... & Kadar, N. (2022). The role of the placenta in spontaneous preterm labor and delivery with intact membranes. *Journal of perinatal medicine*, 50(5), 553-566.
14. Cornish, E. F., McDonnell, T., & Williams, D. J. (2022). Chronic inflammatory placental disorders associated with recurrent adverse pregnancy outcome. *Frontiers in Immunology*, 13, 825075.
15. Polnaszek, B. E., Clark, S. L., & Rouse, D. J. (2022). Pathologic assessment of the placenta: evidence compared with tradition. *Obstetrics & Gynecology*, 139(4), 660-667.
16. Ernst, L. M., Basic, E., Freedman, A. A., Price, E., & Suresh, S. (2023). Comparison of Placental Pathology Reports From Spontaneous Preterm Births Finalized by General Surgical Pathologists Versus Perinatal Pathologist: A Call to Action. *The American Journal of Surgical Pathology*, 47(10), 1116-1121.