JAMA Network Open

Invited Commentary | Obstetrics and Gynecology

Spontaneous Preterm Birth Phenotyping Based on Cervical Length and Immune-Mediated Factors

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Cervical length (CL) screening by ultrasonographic measurement is an established tool widely implemented in the clinical protocols of preterm birth (PTB) prediction and prevention. Growing evidence has shown immune-mediated factors in the etiology of spontaneous PTB (sPTB), with robust biological plausibility supporting deep interrelationships with progressive cervical shortening. We explore a retrospective cohort study that examined the sequential measurement of CL and leucocyte markers in both singleton and twin pregnancies.[1] The study's objective was to identify the clinical presentations associated with sPTB in relation to variations in these parameters.[1] Progressive CL shortening was associated with higher rates of sPTB in both singletons (4.1% vs 2.7%) and twins (41.9% vs 18.2%) as compared with cases with stable CL. In addition, in singleton pregnancies, individuals in the early preterm birth subgroup with a shortened or stable CL had elevated total white blood cell count, neutrophil count, and neutrophil-to-lymphocyte ratio, along with a reduced lymphocyte-to-monocyte ratio, in comparison with individuals in the full-term birth subgroup. However, in twins, similar changes were exclusive to those with a shortened cervix. Finally, the study quantified the association between immune-related indicators and risk of sPTB, incorporating CL. In singleton pregnancies, an increase in the white blood cell count and neutrophil count was associated with early sPTB for both stable and shortened CL. Conversely, in twins, there was a significantly higher white blood cell count, neutrophil count, and monocyte count only in the subgroup with shortened CL.

This study[1] offers an interesting and original perspective, proposing a novel combined method for approaching the characterization and investigation of sPTB by looking at different clinical presentations of patients: those with or without cervical shortening and those with or without signs of systemic inflammation. This study found 2 distinct potential mechanisms of sPTB for twins and singletons. In singleton pregnancies, maternal immune response was found to be associated with sPTB irrespective of whether the woman had a shortened or stable CL. However, for twin pregnancies, maternal immune response was only associated with sPTB in women with a shortened CL and not in those with a stable cervix. On this basis, the authors concluded that the mechanism of sPTB may be different in singletons and twins; in twin pregnancy with stable CL, sPTB appears to be unassociated with immunological factors.

The major merit of the study[1] is to attempt to move toward a better assessment of the risk of sPTB by including multiple clinically relevant markers encompassing simple established measurements of anatomy (ie, CL) and novel indicators of pathophysiology (ie, markers of inflammation). In addition, the work responds, albeit partially, to the need to generate new predictive multiparametric models for sPTB, relying not on a single univariate (and static) cutoff of CL and its percentile for gestational age but on longitudinal measures of the same, introducing a more relevant analysis design for the clinical and anatomical natural history of sPTB.

The major limitations are related to lack of information on medications, including progesterone, tocolytics antibiotics, and steroids; lack of assessment of any infectious etiology; and exclusion of severe preterm birth before 28 weeks' gestation. The article does not provide an explanation for the identification of distinct mechanisms underlying sPTB in singleton pregnancies compared with twin pregnancies, especially regarding why immune factors seem to be associated with sPTB exclusively in twin pregnancies with a shortened CL. Retrospective studies may involve risk of selection bias

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since it is more common to perform longitudinal measurements in higher-risk cases. However, the authors correctly discussed most of these limitations, which were partly due to the regulation and current practice accepted in China, and stated that longitudinal CL is performed routinely at their center.

Extensive research on PTB phenotypes indicates a move away from solely relying on gestational age thresholds for defining PTB.[2,3] Instead, there is a push to incorporate factors such as clinical presentation, features, and the type of PTB initiation to pursue a deeper understanding of PTB etiology. This recommendation stems from the recognition that these aspects significantly influence infant outcomes for up to 2 years of age, with different extents in different PTB phenotypes, at fixed gestational ages.[3] In twin pregnancies, representing a clearly separate phenotype, uterine distension plays a central role in the pathophysiology of cervical shortening, which in fact appears here[1] unrelated to immune factors. Conversely, in singleton pregnancies cervical shortening may occur following different mechanisms. Recent evidence demonstrated the establishment of a novel taxonomy of obstetrical disorders informed by placental pathology, which enhances the identification and utilization of placental biomarkers.[4] An abnormal placental growth factor–soluble fms-like tyrosine kinase-1 (PlGF–sFlt-1) ratio at 28 to 32 weeks of gestation was associated with sPTB, especially when maternal vascular malperfusion placental lesions are present.[4] This knowledge reinforces the concept of a subclinical or clinically manifest placental dysfunction as a potential precursor of sPTB. Additionally, a recent study[5] found that individuals at an elevated risk of preterm preeclampsia after first trimester combined screening by the Fetal Medicine Foundation method tend to give birth earlier and face an increased likelihood of spontaneous delivery, be it at full term or preterm (without preeclampsia).[5] This study indicates that as the first-trimester risk for preeclampsia increases, pregnancy duration shortens, implying the potential involvement of subclinical placental dysfunction in the initiation of birth, at full term or preterm, possibly serving as a mechanism for human parturition.[5] However, despite both studies cited previously[4,5] supporting the concept of placental dysfunction as a possible initiator of sPTB, prophylaxis with low dose aspirin has had contradictory results, with a recent major work on this topic failing to show a significant effect for reduction in either sPTB or iatrogenic preterm birth without preeclampsia.[6]

There is the need to summarize and clarify the mechanisms and processes leading to sPTB as well as their etiologies, and this cannot be done outside of the comprehensive, generalized framework of PTB phenotyping, as presented previously.[2,3] As far as the complex potential links between placental dysfunction and inflammation are concerned, extensive research has also been developed.[7] Both infection or sterile inflammation mechanisms of immune origin (including maternal antifetal rejection) may lead to infiltration of the placenta by lymphocytes, plasma cells, and/or macrophages, leading to chronic placental inflammatory lesions, which may be responsible for both abnormal placental function and perhaps alterations in maternal white blood cell distributions, as shown in the study by Wu et al.[1,7]

The new knowledge presented in this study represents a small but important step toward the overarching goal of understanding sPTB phenotyping and etiology related to differences in CL. Upcoming research will need to clarify the extent to which cervical shortening may be the promoter of inflammation (and possible subclinical activation of ripening, myometrial contractility, membrane activation, and others) or if it is instead the consequence of inflammation (due to other causes such as suboptimal placental function, membrane competence, infection, and others) promoting cervical shortening via different mechanisms. Future studies on PTB phenotypes will need to further elucidate the intricate links between infection, sterile inflammation, immune-mediated factors, and placental abnormalities or dysfunction, potentially leading to initiation of birth at full term or preterm.

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Published: April 11, 2024. doi:10.1001/jamanetworkopen.2024.4559

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Conflict of Interest Disclosures: None reported.

REFERENCES

1. Wu T, Li S, Gong X, et al. Longitudinal cervical length measurements and spontaneous preterm birth in singleton and twin pregnancies. *JAMA Netw Open*. 2024;7(4):e244592. doi:10.1001/jamanetworkopen.2024.4592

2. Barros FC, Papageorghiou AT, Victora CG, et al; International Fetal and Newborn Growth Consortium for the 21st Century. The distribution of clinical phenotypes of preterm birth syndrome: implications for prevention. *JAMA Pediatr*. 2015;169(3):220-229. doi:10.1001/jamapediatrics.2014.3040

3. Villar J, Restrepo-Méndez MC, McGready R, et al. Association between preterm-birth phenotypes and differential morbidity, growth, and neurodevelopment at age 2 years: results from the INTERBIO-21st Newborn Study. *JAMA Pediatr*. 2021;175(5):483-493. doi:10.1001/jamapediatrics.2020.6087

4. Romero R, Jung E, Chaiworapongsa T, et al. Toward a new taxonomy of obstetrical disease: improved performance of maternal blood biomarkers for the great obstetrical syndromes when classified according to placental pathology. *Am J Obstet Gynecol*. 2022;227(4):615.e1-615.e25. doi:10.1016/j.ajog.2022.04.015

5. Cavoretto PI, Farina A, Salmeri N, Syngelaki A, Tan MY, Nicolaides KH. First trimester risk of preeclampsia and rate of spontaneous birth in patients without preeclampsia. *Am J Obstet Gynecol*. Published online January 18, 2024. doi:10.1016/j.ajog.2024.01.008

6. Nicolaides KH, Syngelaki A, Poon LC, et al. First-trimester prediction of preterm pre-eclampsia and prophylaxis by aspirin: Effect on spontaneous and iatrogenic preterm birth. *BJOG*. 2024;131(4):483-492. doi:10.1111/1471-0528.17673

7. Kim CJ, Romero R, Chaemsaithong P, Kim JS. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. *Am J Obstet Gynecol*. 2015;213(4)(suppl):S53-S69. doi:10.1016/j.ajog.2015.08.041

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