Biomarkers for Adverse Pregnancy Outcomes in Rheumatic Diseases

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KEYWORDS

• Adverse pregnancy outcomes • Preeclampsia • Growth restriction
• Soluble fms-like tyrosine kinase-1 • Placental growth factor • SLE
• Cardiovascular disease • Endothelial damage

KEY POINTS

- Adverse pregnancy outcomes are more common in women with rheumatic diseases, and the pathophysiology is likely multifactorial; hence, sole reliance on biomarkers to predict preterm delivery or other adverse outcomes may not be possible or advisable.
- Preterm (or classic) preeclampsia is a manifestation of placental insufficiency, which may also lead to fetal growth restriction, placental abruption, and stillbirth: collectively known as maternal-placental syndrome (MPS).
- Pregnancy is a delicate balance of circulating angiogenic factors of which antiangiogenic factors, for example, soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) predominate when there is MPS.
- Commercially available biomarkers, such as placental growth factor, sFlt-1, and sEng have the same diagnostic accuracy and prognostic significance in women with rheumatic diseases and chronic kidney disease as in healthy pregnant women.
- In the long term, the effect of these antiangiogenic biomarkers and the inflammatory cascade triggered by MPS, combined with preexisting metabolic risk factors, is likely contributory to the accelerated cardiovascular disease seen in young women with rheumatic diseases, especially systemic lupus erythematosus.

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DEFINITIONS OF ADVERSE OUTCOMES IN PREGNANCY

Most autoimmune rheumatic diseases disproportionately affect women of childbearing ages, and when pregnant, these women are at an increased risk of adverse pregnancy outcomes. Much of the published literature focuses on preeclampsia, a heterogeneous disorder identified by a common phenotype of hypertension and proteinuria. The crux of the disorder is the placenta, a highly vascular structure, and it is placental ischemia and insufficiency that gives rise to the recognized clinical manifestations. Therefore, future vascular disease is likely to initially manifest with clinical features of placental dysfunction or insufficiency. These features include the following:

i. Preeclampsia: new-onset hypertension and proteinuria in excess of 0.3 g/24 hours or $\geq$30 mg/mL on a spot urinary protein:creatinine urine sample after 20 weeks' gestation. It affects 3% to 5% of all pregnancies.[1]
ii. Fetal growth restriction: slowing or cessation of fetal growth while in utero.
iii. Small-for-gestational age (SGA) neonates: neonatal weight is lower than the 10th percentile of that expected for the population.
iv. Placental abruption: pathologic separation of the placenta from the uterus.
v. Stillbirth.

These features are often collectively known as maternal-placental syndrome (MPS). The individual features are not exclusive to MPS but also can occur for a variety of reasons, such as fetal chromosomal abnormalities or multiple pregnancies. Nevertheless, women with underlying rheumatic disease have a much higher incidence of these complications.[2]

Risk factors for preeclampsia and subsequent development of placental insufficiency are summarized in **Box 1**.

Box 1
Common risk factors for preeclampsia and subsequent placental insufficiency

- Nulliparity
- Extremes of maternal age younger than 18 years or older than 35 years
- Immunologic:
  - Multiparous women who have changed partner from previous pregnancies
  - Short interval between first coitus and conception
  - "Dangerous" father: man who has previously fathered preeclamptic pregnancies in a different woman.
  - Artificial reproductive therapy, especially with donor ovum
- Genetic: "familial clustering": inheritability of preeclampsia in twin studies is 22% to 47%
- Metabolic and vascular risk factors: for example, diabetes, obesity, chronic hypertension, renal dysfunction
- Thrombophilias, especially antiphospholipid syndrome
- Underlying autoimmune inflammatory diseases; for example, systemic lupus erythematosus, scleroderma
- Past factors:
  - Previous severe early-onset preeclampsia
  - Maternal preterm delivery
  - Maternal low birth weight
- Hypoxia:
  - Multifetal gestation
  - High altitude
  - Prolonged gestation: placental growth outstrips the vascular supply