OBSTETRICS

A low angiogenic index-1 (placental growth factor/soluble vascular endothelial growth factor receptor-1 ratio) at 24-28 weeks of gestation is a biomarker to identify the patient at risk for subsequent fetal death

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OBJECTIVE: We sought to determine if maternal plasma concentrations of angiogenic and antiangiogenic factors measured at 24-28 weeks of gestation can predict subsequent fetal death.

STUDY DESIGN: A case-cohort study was designed to include 1000 randomly selected subjects and all remaining fetal deaths (cases) from a cohort of 4006 women with a singleton pregnancy, enrolled at 6-22 weeks of gestation, in a pregnancy biomarker cohort study. The placentas of all fetal deaths were histologically examined by pathologists who used a standardized protocol and were blinded to patient outcomes. Placental growth factor, soluble endoglin, and soluble vascular endothelial growth factor receptor-1 concentrations were measured by enzyme-linked immunosorbent assays. Quantiles of the analyte concentrations (or concentration ratios) were estimated as a function of gestational age among women who delivered live neonates but did not develop preeclampsia or deliver small-for-gestational-age newborns. A positive test was defined as analyte concentrations (or ratios) <2.5th and 10th centiles (placental growth factor, placental growth factor/soluble vascular endothelial growth factor receptor-1 [angiogenic index-1] and placental growth factor/soluble endoglin) or >90th and 97.5th centiles (soluble vascular endothelial growth factor receptor-1 and soluble endoglin). Inverse probability weighting was used to reflect the parent cohort when estimating the relative risk.

RESULTS: There were 11 fetal deaths and 829 controls with samples available for analysis between 24-28 weeks of gestation. Three fetal deaths occurred <8 weeks and 8 occurred ≥28 weeks of gestation. The rate of placental lesions consistent with maternal vascular underperfusion was 33.3% (1/3) among those who had a fetal death <28 weeks and 87.5% (7/8) of those who had this complication ≥28 weeks of gestation. The maternal plasma angiogenic index-1 value was <10th centile in 63.6% (7/11) of the fetal death group and in 11.1% (92/829) of the controls. The angiogenic index-1 value was <2.5th centile in 54.5% (6/11) of the fetal death group and in 3.7% (31/829) of the controls. An angiogenic index-1 value <2.5th centile had the largest positive likelihood ratio for predicting fetal death >24 weeks (14.6; 95% confidence interval, 7.7—27.7) and a relative risk of 29.1 (95% confidence interval, 8.8—97.1), followed by soluble endoglin >97.5th centile and placental growth factor/soluble endoglin <2.5th, both with a positive likelihood ratio of 13.7 (95% confidence interval, 7.3—25.8) and a relative risk of 27.4 (95% confidence interval, 8.2—91.2). Among women without a fetal death whose plasma angiogenic index-1 concentration ratio was <2.5th centile, 61% (19/31) developed preeclampsia or delivered a small-for-gestational-age neonate; when the 10th centile was used as the cut-off, 37% (34/92) of women had these adverse outcomes.

CONCLUSION: (1) A maternal plasma angiogenic index-1 value <2.5th centile (0.126) at 24-28 weeks of gestation carries a 29-fold increase in the risk of subsequent fetal death and identifies 55% of subsequent fetal deaths with a false-positive rate of 3.5%; and (2) 61% of women who have a false-positive test result will subsequently experience adverse pregnancy outcomes.

Key words: endoglin, maternal vascular underperfusion, placenta, placental growth factor, preeclampsia, preterm delivery, small for gestational age, soluble fms-like tyrosine kinase-1, soluble vascular endothelial growth factor receptor-1

Introduction

Fetal death is an obstetrical syndrome[1,2] caused by multiple etiologies rather than the end stage of a single disease process.[3-6]

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This syndrome affected 23,595 pregnancies in the United States[7] in 2013, and according to the World Health Organization, an estimated 2.6 million fetal deaths occurred globally during the third trimester.[8,9] The most common type of fetal death is unexplained stillbirth,[10-13] which comprises a progressively larger proportion of all fetal deaths as pregnancy advances. This category of fetal death accounts for approximately 20% of all cases just >20 weeks of gestation and for about 40% of all cases at term,[10-15] while infection and congenital anomalies cause most early fetal deaths (<28 weeks of gestation).[16-19] Placental causes leading to fetal death are more frequent >26 weeks of gestation[14] including placental vascular underperfusion, resulting in an impaired supply of nutrients to the fetus,[20-35] abruptio placentae,[36-38] and placental senescence that has been implicated as a mechanism of fetal death at term.[22]

The term "placental malperfusion" (formerly called "maternal vascular lesions of underperfusion") refers to a group of vascular lesions, including

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villous infarcts, syncytial knots, villous agglutination, increased intervillous fibrin deposition, villous hypoplasia, persistent muscularization of the basal plate arteries, and mural hypertrophy of the decidual arterioles, as well as acute atherosis of the basal plate and decidual arteries.[39-43] The frequency and burden of placental vascular lesions of malperfusion is reflected in the maternal plasma by an imbalance between the concentration of angiogenic (placental growth factor [PlGF]) and antiangiogenic (soluble vascular endothelial growth factor receptor [sVEGFR]-1 and soluble endoglin [sEng]) factors.[44]

Several investigators[45-47] have characterized the changes in the plasma concentrations of angiogenic and antiangiogenic factors in women who subsequently had a fetal death, demonstrating that, from ≥20 weeks of gestation, these patients had a lower maternal plasma PlGF and higher sEng and sVEGFR-1 concentrations than women with a normal pregnancy.[45] Additionally, a maternal plasma PlGF/sVEGFR-1 concentration ratio (angiogenic index-1) of <0.12 multiples of the median at 30-34 weeks of gestation in normal pregnancy—which corresponds to the 5th-6th centile of the distribution—identified 4 of 5 fetal deaths that occurred later in pregnancy.[48] Given that an imbalance in angiogenic and antiangiogenic factors reflects the presence and burden of placental vascular lesions[44] of malperfusion that have been proposed to be the leading cause of fetal death in the late second and third trimesters until term,[14] we sought to validate and extend these findings by determining whether plasma angiogenic index-1 at 24-28 weeks of gestation could be used as a biomarker to identify patients at risk for a subsequent fetal death.

Materials and Methods

Study design and participants

This was a case-cohort study. We randomly selected 1000 patients from a cohort of 4006 pregnant women enrolled in a longitudinal study previously reported by our group.[44] The remaining women in the original cohort who had a fetal death, but were not selected in the random sample of 1000 women, were subsequently added to the case cohort. Women who had multiple gestations or any of the following conditions at the time of enrollment were excluded from this study: active vaginal bleeding; severe maternal morbidity (ie, renal insufficiency, congestive heart disease, and chronic respiratory insufficiency); chronic hypertension requiring medication; asthma requiring systemic steroids; requirement of antiplatelet or nonsteroidal antiinflammatory drugs; active hepatitis; or fetal chromosomal abnormalities and congenital anomalies. All study participants provided written informed consent and were followed up until delivery. The use of clinical data and biological specimens obtained from these women for research purposes was approved by the institutional review boards of Wayne State University and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, and US Department of Health and Human Services.

Clinical definitions

The following definitions were used in this study:

1) Fetal death: diagnosed as the death of the fetus >20 weeks of gestation and confirmed by ultrasound examination.[49]
2) Preeclampsia: diagnosed by the presence of systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on at least 2 occasions, 4 hours to 1 week apart, and of proteinuria ≥300 mg in a 24-hour urine collection or by 1 dipstick with ≥1+.[50,51] We have used this definition after analysis from the Collaborative Perinatal Project, which was reported in detail by Friedman and Neff,[52] and the reasons described by one of the authors.[53] Moreover, the definition outlined above was the one used in our center to collect outcome information when the patients were recruited and delivered.
3) Small-for-gestational-age (SGA) neonate: a birthweight <10th centile for gestational age at delivery according to a US reference population.[54]
4) Preterm delivery: a delivery occurring <37th week of gestation.

Sample collection and immunoassays

Patients were scheduled to donate maternal plasma in EDTA tubes at enrollment, then every 4 weeks until the 24th week of gestation, and biweekly thereafter until delivery. Samples were centrifuged and stored at −70°C. Maternal plasma concentrations of sVEGFR-1, PlGF, and sEng were measured by immunoassays (R&D Systems, Minneapolis, MN) as previously described.[55] The interassay and intraassay coefficients of variation of the assays were 1.4% and 3.9% for sVEGFR-1, 2.3% and 4.6% for sEng, and 6.02% and 4.8% for PlGF, respectively. The sensitivity of each assay was 16.97 pg/mL for sVEGFR-1, 0.08 ng/mL for sEng, and 9.52 pg/mL for PlGF. Laboratory personnel performing the assays were blinded to the clinical information.

Histologic placental examination

Placentas were examined according to standardized protocols by perinatal pathologists blinded to clinical diagnoses and obstetrical outcomes. Placental lesions consistent with maternal vascular lesions of underperfusion (now known as placental malperfusion) were diagnosed using criteria established by the Perinatal Section of the Society for Pediatric Pathology[56] and were classified as the following: (1) villous changes, which are further subdivided into abrupt onset (remote villous infarcts, recent villous infarcts), gradual onset with intermediate duration (increased syncytial knots, villous agglutination, increased intervillous fibrin), or gradual onset with prolonged duration (decreased placental weight/increased fetoplacental weight ratio, distal villous hypoplasia); and (2) vascular lesions (persistent muscularization of the basal plate arteries, mural hypertrophy of the decidual arterioles, acute atherosis of the basal plate arteries and/or the decidual arterioles).[40]

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