Abnormal second-trimester serum analytes are more predictive of preterm preeclampsia

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OBJECTIVE: We sought to determine the association of abnormal second-trimester serum analytes with early preterm preeclampsia.

STUDY DESIGN: We conducted a retrospective study of 7767 subjects undergoing second-trimester serum aneuploidy screening. Values of maternal serum α-fetoprotein (AFP), β-human chorionic gonadotropin (hCG), and inhibin (INH) were calculated as multiples of the median (MoM) and evaluated by gestational age at delivery and occurrence of preeclampsia.

RESULTS: Of 459 (6.5%) cases of preeclampsia, 65 (14%) delivered <34 weeks and 394 (86%) delivered >34 weeks. Elevated AFP, hCG, and INH >2 MoM were associated with preeclampsia, and the odds ratio was higher for the development of preeclampsia <34 weeks than >34 weeks (odds ratio, 8.04 vs 2.91 for AFP, 3.6 vs 2 for hCG, and 4.17 vs 3.08 for INH, $P < .001$ for all). The higher the MoM for each analyte the greater the likelihood of preeclampsia.

CONCLUSION: Elevated AFP, hCG, and INH levels >2 MoM are associated with developing early preeclampsia, and the more elevated they are, the higher the likelihood.

Key words: α-fetoprotein, abnormal analytes, human chorionic gonadotropin, inhibin, preterm preeclampsia

Cite this article as: Olsen RN, Woelkers D, Dunsmoor-Su R, et al. Abnormal second-trimester serum analytes are more predictive of preterm preeclampsia. Am J Obstet Gynecol 2012;207:228.e1-7.

Preeclampsia is a disease that continues to be a leading cause of morbidity and mortality to both mothers and fetuses in 5-8% of pregnancies, of which up to 11% end in preterm deliveries.[1,2] Preterm preeclampsia, in particular that occurring <34 weeks, has more significant associations with fetal growth abnormalities (10-25%), placental abruption (1-4%), perinatal death (1-2%), and neonatal complications.[2-4]

Many studies have evaluated new models and pathways for better predicting who is at highest risk of developing preeclampsia to offer improved pregnancy surveillance.[5-8] Since preeclampsia is linked with abnormal placental development and function, efforts have focused on identifying placental biomarkers that correlate with pathophysiological changes seen with defective early trophoblastic invasion to evaluate risk.[9]

Since the introduction of multiple marker screening for Down syndrome, several other adverse pregnancy outcomes have been correlated with abnormal levels of maternal serum analyte levels.[5,10-12] α-Fetoprotein (AFP), a glycoprotein produced from the yolk sac and fetal liver and gastrointestinal tract, is transported to the maternal serum through the placenta, through diffusion across membranes, or at the time of fetal-maternal bleeding.[13-16] An AFP multiples of the median (MoM) >2.5 has been correlated with an overall odds ratio (OR) of 3.8 for developing any preeclampsia.[7,17] Elevated levels of human chorionic gonadotropin (hCG), a hormone secreted by syncytiotrophoblast cells to maintain the decidual spiral arteries and vascular supply of the pregnancy, has been associated with an OR of 5.9 for development of preeclampsia when the second-trimester MoM is ≥3.[18] Elevated inhibin (INH) A, a chemical produced by the syncytiotrophoblasts to regulate cell growth and immunologic recognition, is a marker of placental function and has been similarly linked to elevated risk of preeclampsia.[19] Some authors have found it to be one of the most strongly associated markers among hCG, INH, AFP, and estriol.[6] These studies have not consistently delineated between early- and late-onset preeclampsia.

In addition to serum markers for Down syndrome screening, several other maternal serum levels have shown promise as predictive tools for preeclampsia, such as elevated levels of placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and soluble endoglin (sENG), or low pregnancy-associated plasma protein A (Papp-A) and placental protein 13 (PP13) levels.[5,8,20,21] Uterine artery Doppler studies have also been increasingly used to help identify at-risk patients.[22]

While many markers have been associated with a diagnosis of preeclampsia, given the greater morbidity associated with preeclampsia <34 weeks, we sought to determine whether abnormally elevated second-trimester serum analytes would correlate more strongly with early variants of preeclampsia than later variants, and thereby identify the patients at greatest risk for the poorest outcomes.

Materials and Methods

This was a retrospective cohort study of pregnant women who had been evalu-

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Received Mar. 12, 2012; revised Apr. 27, 2012; accepted June 5, 2012.

The authors report no conflict of interest.

Presented as a poster at the 32nd annual meeting of the Society for Maternal-Fetal Medicine, Dallas, TX, Feb. 6-11, 2012.

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0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2012.06.006

TABLE 1
Maternal demographics, n = 7978

Demographic	Mean (SD)
Maternal age, y	28.88 (6.0)
Gestational age, wk	16.8 (3.2)
Race, n (%)	
Black	751 (9.4)
White, non-Hispanic	4010 (50.2)
American Indian	73 (0.9)
Asian	1019 (12.8)
Hispanic	683 (8.5)
Unknown	1455 (18.2)
Gravidity, n (%)	
1	2606 (32.6)
2-5	4506 (56.3)
>5	498 (6.3)
Missing	381 (4.8)

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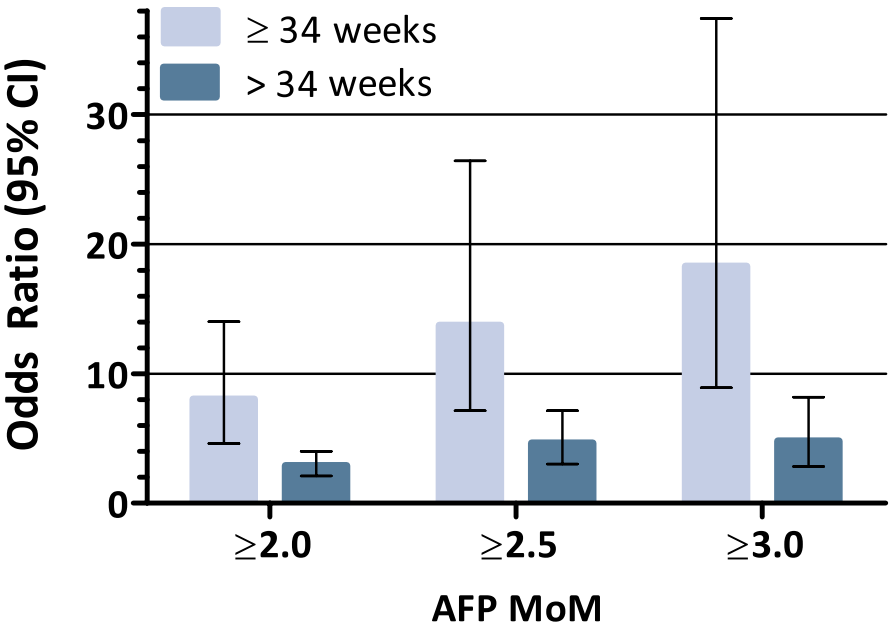
FIGURE 1
Risk of preeclampsia and early delivery as function of AFP



Odds ratio for early preeclampsia is greater than for late preeclampsia in women with elevated AFP, and increases with advancing cutoffs of AFP.

AFP, α-fetoprotein; *CI,* confidence interval; *MoM,* multiples of median.

Olsen. Serum analytes and preeclampsia. Am J Obstet Gynecol 2012.

ated with second-trimester maternal serum aneuploidy screening (AFP, INH, and hCG levels) performed at a single institution from 1995 through 2010 (as identified by *Current Procedural Terminology* codes 82105, 82677, 84702, and 86336). Institutional review board approval was obtained prior to data collection. Maternal serum samples were drawn between 15-22 completed weeks of gestation. First-trimester serum samples were not included in our study as they were introduced more recently to our clinical care. Analytes, including serum INH, hCG, and AFP, were measured by specific immunoassay and expressed as MoM by use of day-specific medians for gestational age, correcting as well for maternal diabetes, smoking status, and in vitro fertilization status. Estriol was not evaluated as prior studies have shown that it is not associated with elevated risk of preeclampsia.[10] Gestational age was provided by the referring physician based on last menstrual period, ultrasound dating, or a combination of both. If incorrect dating was later discovered, analyte values were recalculated based on correct dating.

Data from an institutional review board–approved institutional perinatal database were used to find variables including gestational age at time of measurement of serum analytes, last menstrual period, pregnancy history, maternal age at delivery, maternal race, preeclampsia, abnormal placentation (eg, placenta previa, abruption, or placenta accreta), delivery type, gestational age at delivery, Apgar scores, and birthweight. The perinatal database is compiled from formal clinical abstraction sheets completed by providers caring for the patients at prenatal intake, time of delivery, and time of discharge. A database coordinator was responsible for data entry and identifying discrepancies that were then addressed by the clinical provider and at monthly quality assurance meetings. If necessary, a chart review was performed by the quality assurance committee.

Definition of preeclampsia was by usual clinical criteria, including blood pressure of >140 mm Hg systolic and/or 90 mm Hg diastolic on ≥2 occasions, proteinuria of ≥300 mg during a 24-hour period, 3+ protein on urine dipstick, or urine protein-creatinine ratio of >0.3 in a patient with previously normal urinalysis and blood pressure.[1] The perinatal database did not include enough variables to identify with certainty all variants of preeclampsia.

Pregnancies electively terminating <24 weeks' gestational age were excluded, as were multiples and fetuses with known chromosomal and major fetal anomalies. Pregnancies were separated into those with and without preeclampsia, as well as those delivered <34 weeks and >34 weeks. Statistics were performed using descriptive statistics and χ^2 analysis. Logistic regression was used to estimate OR and exponential 95% confidence intervals. Given that the exposure variables were already controlled for age, body mass index (BMI), race, in vitro fertilization, diabetes, and smoking status, these were not included in the model. The variables of placenta previa and abruption were excluded from the regression model as they did not change the primary association. Data regarding variables such as progesterone or steroid use were not available and therefore were not analyzed.

OR for each analyte were calculated for MoM 2, 2.5, and 3, comparing risk of