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"Abnormal Analyte Preeclampsia": Do the second trimester maternal serum analytes help differentiate preeclampsia subtypes?

Agatha S CRITCHFIELD, MD[1], **Jessica K PAULUS, ScD**[2], **Rahmouna FAREZ, MD**[3], and **Adam C URATO, MD**[1,3]

[1]Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Tufts Medical Center, Boston, Massachusetts

[2]Tufts Clinical and Translational Science Institute, Tufts University, Boston, Massachusetts

[3]MetroWest Medical Center, Framingham, Massachusetts.

Abstract

Objective—To determine if serum screen analytes identify preeclamptic patients at risk for small-for-gestational-age newborns, maternal laboratory abnormalities and preterm delivery (<37 weeks gestation).

Study Design—Using a retrospective cohort of 102 preeclamptic patients, associations between serum screen analytes and newborn birth-weight percentile, gestational age (GA) at delivery and maternal pre-delivery laboratory abnormalities were evaluated using correlation coefficients and local polynomial regression.

Results—Inhibin-A and MS-AFP were inversely correlated with newborn birth weight %ile (-0.27, p=0.006; -0.35, p=0.00004) and delivery GA (r = -0.42, p<0.0001; r = -0.26, p = 0.008) and positively correlated with pre-delivery AST (r = 0.22, p=0.03; r=0.21, p=0.04) and LDH (r=0.33, p=0.0007; r= 0.29, p=0.004). A positive correlation was noted between both second trimester β-HCG and Estriol and maternal pre-delivery creatinine (0.28, p=0.004; 0.4, p < 0.0001, respectively).100% of patients with ≥2 abnormal analytes delivered prior to 37 weeks gestation.

Conclusions—Preeclamptic patients with abnormal serum screen analytes are more likely to have SGA newborns, deliver preterm and have pre-delivery laboratory abnormalities.

Keywords

serum screen; hypertension; small-for-gestational age

Corresponding Author: Agatha S. Critchfield, MD. Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Tufts Medical Center, 800 Washington Street, Box 360, Boston, MA 02111. Acritchfield@tuftsmedicalcenter.org. Fax: (617) 636-4202. Phone: (617) 636-4625 (work), (401) 952-8701 (home).

Declaration of Interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Introduction

Preeclampsia is a heterogeneous disorder affecting 3 – 5 % of all pregnancies (1). It is defined as persistent hypertension (systolic blood pressure ≥ 140mmHg and/or diastolic blood pressure ≥ 90mmHg) diagnosed after 20 weeks of gestation accompanied by proteinuria (2). The exact etiology of preeclampsia remains a mystery but is likely associated with abnormal placentation and subsequent vascular and endothelial dysfunction (3). Traditionally, preeclampsia has been categorized as either *mild* or *severe* disease, with severe preeclampsia including a variety of signs and symptoms of evolving endothelial dysfunction and worsening maternal and/or fetal morbidity. More recent reports indicate that there may be varying subtypes of preeclampsia beyond the traditional designations of mild or severe disease (4 – 8). Many of these studies have focused on preterm versus term subtypes of preeclampsia, with those fetuses born preterm more likely to be of lower birth weight percentile and mothers more likely to be young, current smokers, to have diabetes and evidence of end organ injury (4 - 6).

Abnormal first and second trimester serum screen analytes (Pregnancy Associated Plasma Protein A (PAPP-A), Beta Human Chorionic Gonadotropin (β-HCG), Inhibin-A, Estriol, Maternal Serum Alpha Fetoprotein (MS-AFP)) are associated with the later development of obstetrical morbidity, including fetal growth restriction, intrauterine fetal demise, preterm labor and preeclampsia (9 – 16). It is hypothesized that these later pregnancy complications may be a result of abnormal placentation that manifests itself in the first or second trimester as abnormal serum screen analytes. However, few studies have addressed the association between abnormal second trimester serum screen analytes and particular preeclampsia subtypes.

In this study, we sought to determine if abnormalities in the second trimester serum screen analytes are associated with a subset of preeclampsia characterized by poor fetal growth (indicative of placental injury) and preterm delivery (< 37 weeks gestation). We hypothesize that, among a retrospective cohort of women with singleton gestations diagnosed with preeclampsia, those with abnormal second trimester serum screen analytes will be more likely to have a small-for-gestational-age newborn (a marker of placental dysfunction) when compared to those patients without abnormal second trimester serum screen analytes. In addition, we hypothesize that these patients will also have evidence of more severe maternal end organ disease (abnormal pre-delivery laboratory values). Our hypothesis is that such “abnormal analyte preeclampsia” will be characterized by more severe disease with lower newborn birth-weights, preterm delivery and maternal laboratory abnormalities.

Materials and Methods

Study population

After obtaining IRB approval (IRB # 9416), we retrospectively assembled a cohort of women with preeclampsia admitted to our institution (Tufts Medical Center, a tertiary care referral center located in Boston, MA) between January 2008 and July 2011 with available second trimester serum screens. Patients with preeclampsia were identified either at the time of admission to the hospital or by ICD-9 code (642.4 – 642.7). Preeclampsia diagnosis was

confirmed by medical record review by the principal investigators. Preeclampsia was defined as those women at > 20 weeks 0 days gestation with incident hypertension (defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least two occasions six hours apart) and proteinuria (300 mg protein excreted over 24 hours, 2+ protein on urine dipstick or a urine protein:creatinine ratio ≥ 0.3). Women with chronic hypertension, known renal disease, multiple gestations, severe fetal anomalies or known fetal chromosomal abnormalities were excluded.

Data collection

Maternal demographic data including age, gravidity, parity, race, gestational age at delivery and mode of delivery were collected from the medical record (either electronic record or paper chart). Maternal second trimester serum screen analyte multiples of the median (MoMs) (Inhibin-A, MS-AFP, β-HCG and Estriol), immediate pre-delivery laboratory values (hematocrit, platelets, creatinine, aspartate aminotransferase (AST), uric acid, lactate dehydrogenase (LDH)) and newborn data including gender, birth weight and birth weight percentile were collected from the medical record. Birth weight percentile was determined by fetal growth calculator using the Hadlock growth curve. The following were used to define serum screen analytes as abnormal: Inhibin – A ≥ 2 MoMs, MS-AFP ≥ 2 MoMs, βHCG ≥ 2 MoMs or Estriol ≤ 0.5 MoMs. In addition, pre-delivery AST > 42 IU/L, platelets < 150K/μL, Creatinine > 1.0 mg/dL, uric acid > 6.0 mg/dL and LDH > 175 IU/L were considered abnormal in our patient population.

Statistical analysis

Demographic and clinical characteristics were summarized for the cohort using means and proportions and corresponding measures of variability. Pearson and Spearman correlation coefficients were calculated to estimate the associations between analytes and clinical outcomes. Plots between individual serum analytes and birth weight percentile and gestational age at delivery were created with a smoother fit using local polynomial regression. The graphical association between gestational age at delivery and birth weight percentile was plotted in the same way.

In order to evaluate if there was a trend between the number of abnormal second trimester serum screen analytes, newborn birth weight percentile and preterm delivery, we created a score variable (“Analyte Score”) that was equal to the sum of the number of significant abnormal serum screen analyte test results. An Analyte Score was calculated for each participant.

Statistical analyses used the SAS statistical package, version 9.2 (SAS Institute, Cary, NC) and R (version 2.15.1). All *p*-values are 2-sided.

Results

A total of 124 women with preeclampsia and available serum screens were identified. Twenty two were excluded due to inability to confirm preeclampsia diagnosis upon medical record review, yielding a total of 102 patients with confirmed preeclampsia *and* available second trimester serum screens admitted to our institution between January 2008 and July

2011. The mean patient age was 29.7 years (SD 6.4) and they delivered at a mean of 34.8 weeks gestation. Sixty three percent of patients met criteria for Severe Preeclampsia or HELLP Syndrome (Table 1). Among the cohort, 36 (35%) had ≥ 1 abnormal second trimester serum screen analyte. Twenty three (23%) had a second trimester Inhibin-A ≥ 2 MoM, 6 (6%) had a MS -AFP ≥ 2MoM, 18 (18%) had a β-HCG ≥ 2MoM and 8 (9%) had an Estriol ≤ 0.5MoM.

A significant inverse correlation was noted between second trimester Inhibin-A and MS-AFP and both newborn birth weight percentile ($r = -0.27$, $p=0.006$; $r = -0.35$, $p=0.0004$ respectively) and gestational age at delivery ($r = -0.42$, $p<0.0001$; $r = -0.26$, $p = 0.008$ respectively) (Table 2).

All four maternal serum screen analytes were associated with abnormal maternal pre-delivery laboratory values (Table 2). Significant positive correlations were noted between Inhibin A ≥ 2 MoMs and maternal pre-delivery AST ($r = 0.22$, $p=0.03$) and LDH ($r=0.33$, $p=0.0007$). MS-AFP was also positively associated with maternal pre-delivery AST ($r=0.21$, $p=0.04$) and LDH ($r= 0.29$, $p=0.004$). In addition, a significant positive correlation was noted between both second trimester β-HCG and Estriol and maternal pre-delivery creatinine (0.28, $p=0.004$; 0.4, $p < 0.0001$, respectively).

Further, a significant positive correlation was observed between gestational age at delivery and newborn birth weight percentile ($r = 0.34$, $p = 0.0005$). In addition, gestational age at delivery was positively correlated with maternal pre-delivery platelet counts ($r =0.21$, $p = 0.03$) and negatively correlated with pre-delivery AST ($r = -0.28$, $p= 0.004$) and LDH ($r = -0.38$, $p = 0.0001$) (Table 2).

Individual serum screen analytes were plotted against both birth weight percentile and gestational age at delivery (Figures 1 and 2, respectively). Those fetuses with elevated Inhibin-A and MS-AFP were delivered at earlier gestational ages and had lower birth-weight percentiles. While this trend in birth-weight percentile was not seen with β-HCG, those patients with elevated β-HCG did deliver at earlier gestational ages (Figure 2). In addition, a clear association was seen between birth-weight percentile and gestational-age at delivery, with growth restricted fetuses being delivered at earlier gestational ages (Figure 3).

Twenty three (23%) patients had elevated values for either Inhibin-A (≥ 2 MoM) or MS-AFP (≥ 2 MoM), with 74% of these patients delivering an infant with birth weight percentile < 10 (Table 3). Three (3%) patients had elevated values for both Inhibin-A and MS-AFP (Analyte Score = 2), and 100% of these patients delivered infants with birth weight percentiles < 10 (Table 3). In addition, a significant trend was noted between Analyte Score and gestational age at delivery, with 45% of patients with no abnormal serum screen analytes delivering prior to 37 weeks gestation, in contrast to 100% of patients with both an abnormal Inhibin-A and MS-AFP ($p = 0.0001$) (Table 3).

Discussion

In this study, we found that those women with preeclampsia who have higher second trimester Inhibin-A and MS-AFP levels had pregnancies associated with both lower birth

weight percentiles and an earlier gestational age at delivery. It is notable that this trend was quite strong among the subgroup of preeclamptic patients with elevated values for both Inhibin-A (≥ 2MoM) and MS-AFP (≥ 2MoM) – with 100% of these patients delivering small for gestational age newborns and at less than 37 weeks gestation. Further, we found that those women with abnormal second trimester serum screen analytes were more likely to display pre-delivery laboratory abnormalities (another indicator of more severe disease).

Abnormal second trimester serum screen analytes have been strongly associated with obstetrical morbidity, including but not limited to preeclampsia and low birth-weight (15). However, it is clear that preeclampsia itself is an extremely heterogeneous disorder ranging from very mild late-term disease to extremely severe disease often occurring at earlier gestational ages and accompanied by significant maternal and fetal morbidity. Our work is consistent with recent investigations (4 – 8) suggesting that, in fact, there may be different preeclampsia subtypes. We confirm here the previously reported finding that those women with more severe disease (as indicated by fetal growth restriction and maternal lab abnormalities) are, not surprisingly, delivered at earlier gestational ages. This association between preterm gestational age at delivery and more severe preeclampsia has led some to suggest that preeclampsia types are best understood as term versus preterm. We feel that differentiating preeclampsia based on term versus preterm is valuable, but that using the serum analytes may be a more accurate approach. While many preeclamptic patients with abnormal serum screen analytes may be delivered preterm, the abnormal serum screen analyte characterization takes into account the underlying placental pathophysiology. Abnormal placentation may manifest early in the pregnancy as abnormal second trimester serum screen analytes and later as preeclampsia characterized by poor fetal growth and an increased likelihood of maternal end organ disease. Our data suggests that preeclampsia associated with abnormal second trimester analytes (“abnormal analyte preeclampsia”) may represent a way to more finely distinguish between preeclampsia subtypes than “term versus preterm”.

The strength of this study is that it includes all women with confirmed preeclampsia and available second trimester serum screens admitted from 2008 – 2011 at a tertiary care referral center, giving us a relatively large patient population. Additionally, we confirmed preeclampsia diagnoses through medical record review and were able to abstract a wide array of variables related to maternal and fetal outcomes. Finally, the primary outcomes of interest: birth weight percentile, gestational age at birth, and maternal laboratory values were ascertained using objective measures that are unlikely to depend on serum analyte levels.

We recognize several limitations to this study including the retrospective nature of the design. However, information on serum screen analytes was recorded in the medical record before clinical outcomes occurred. Therefore, misclassification of analyte levels is likely to be non-differential in nature and would not result in an attenuation of effect estimates. In addition, while this study was performed at a single institution with consecutive patients, we are a tertiary care referral center and therefore a large portion of our study population was transferred to our institution for antepartum care. The high acuity nature of a tertiary care center population may also explain the relatively high percentage of patients with severe preeclampsia among our study cohort. Our population was further restricted to patients with

available second trimester serum screens. Collecting data on second trimester screens was more difficult in the case of patients that received the bulk of their prenatal care at outside facilities. It is unclear why patients transferred from outside facilities were less likely to have had serum screens performed – perhaps they presented to care at a later gestational age or were more likely to decline serum screening. We are not aware of how they would differ systematically from patients with available serum screens. However, if the availability of second trimester serum screens is related to the risk of clinical outcomes, our results may be limited by selection bias. In addition, data on maternal smoking status was not collected and we acknowledge the possibility that smoking may be a confounding variable. Furthermore, our results may only be generalizable to births that are referred to tertiary care centers for antepartum care if the association between abnormal analytes and birth weight varies by this referral status. Lastly, our study was limited to those women diagnosed with preeclampsia. As our objective focused on subtypes of preeclampsia, we did not examine women with abnormal serum analytes who did not develop preeclampsia.

In summary, we have found that those women with preeclampsia who have high Inhibin-A and MS-AFP values on their second trimester serum screen are more likely to have pregnancies associated with lower birth-weight percentile, earlier gestational age at delivery and more likely to have maternal pre-delivery laboratory abnormalities. Our data suggest that women with preeclampsia who have abnormal second trimester analytes should be recognized as a higher risk subset that is more likely to manifest fetal effects and maternal end organ involvement. The findings of this study may help to better characterize patients with preeclampsia and advance our understanding of the pathophysiologic distinctions of preeclampsia subtypes. Future research may include a prospective evaluation of those women who have abnormal second trimester serum screen analytes in order to develop this finding as a clinically applicable predictive tool that may be useful for ongoing pregnancy surveillance and management.

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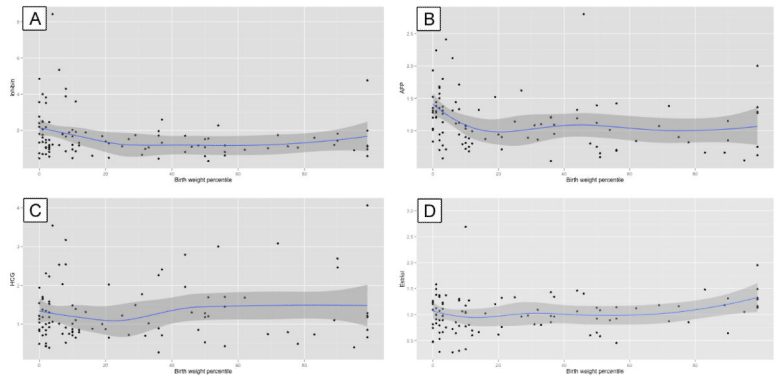

Figure 1.

Individual serum screen analytes (A: Inhibin-A (MoM); B: MS-AFP (MoM); C: β-HCG (MoM); D: Estriol (MoM) plotted against birth-weight percentile (as calculated by Hadlock scale).

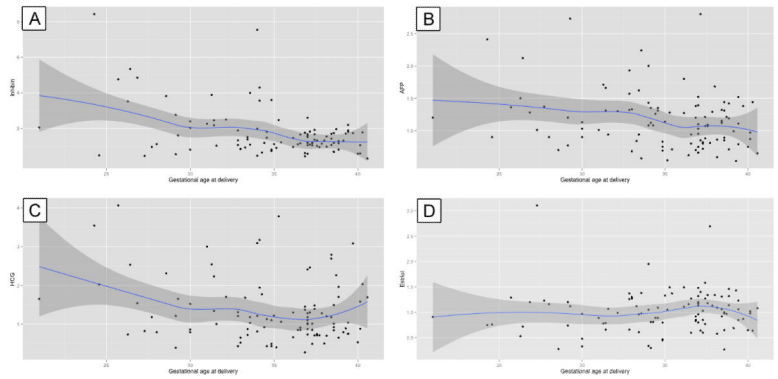

Figure 2.

Individual serum screen analytes (A: Inhibin-A (MoM); B: MS-AFP (MoM); C: β-HCG (MoM); D: Estriol (MoM)) plotted against gestational age (weeks) at delivery

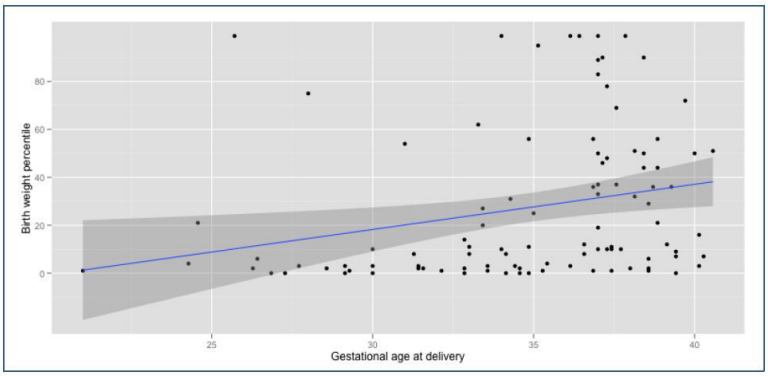

Figure 3.
Birth-weight percentile (as calculated by Hadlock scale) plotted against gestational age (weeks) at delivery

Table 1

Demographic and Clinical Characteristics of Patients and Newborns

Variable		**Total (N = 102)**
Maternal age at admission (years), mean (SD)		29.7 (6.4)
Gravidity, median (range)		2 (1-11)
Parity, median (range)		0 (0-5)
Gestational age at delivery (weeks), mean (range)		34.8 (21.0 – 40.6)
Preeclampsia diagnosis, n (%)		
	Severe/HELLP	64 (63)
	Mild	38 (37)
Birth-weight (grams), mean (range)		2316.7 (545 – 5000)
Birth Weight < 10th%ile, n (%)		50 (49)
Mode of delivery, n (%)		
	Cesarean Section	56 (55)
	Vaginal Delivery	46 (45)
Fetal Gender, n (%)		
	Male	51 (50)
	Female	51 (50)
2nd Trimester Analyte Abnormalities, n (%)		
	Inhibin-A ≥ 2MoM	23 (23)
	MSAFP ≥ 2MoM	6 (6)
	βHCG ≥ 2MoM	18 (18)
	Estriol ≤ 0.5MoM	8 (9)

MS-AFP: Maternal Serum Alpha Fetoprotein; βHCG: Beta Human Chorionic Gonadotropin; MoM: Multiples of the Median

Table 2

Correlation between Second Trimester Analytes, Gestational Age at Delivery, Newborn Birth-weight Percentile and Maternal Pre-delivery Laboratory Values

	Inhibin-A	MS-AFP	β-HCG	Estriol	Gestational age at delivery (weeks)
Birthweight %ile	**-0.27** (0.006)	**-0.35** (0.0004)	0.10 (0.34)	0.13 (0.18)	**0.34088** (0.0005)
Gestational age at delivery (weeks)	**-0.42** (<.0001)	**-0.26** (0.008)	**-0.23** (0.02)	0.06 (0.58)	***
Hematocrit (%)	-0.05 (0.64)	0.11 (0.25)	-0.14 (0.16)	0.03 (0.78)	0.07 (0.46)
Platelets (K/uL)	-0.10 (0.31)	-0.10 (0.33)	0.06 (0.58)	-0.06 (0.57)	**0.21** (0.03)
Uric Acid (Mg/DL)	0.12 (0.22)	0.10 (0.34)	0.09 (0.37)	0.16 (0.11)	0.03 (0.79)
AST (IU/L)	**0.22** (0.03)	**0.21** (0.04)	0.23 (0.81)	-0.14 (0.17)	**-0.28** (0.004)
Creatinine (Mg/DL)	0.06 (0.57)	0.01 (0.90)	**0.28** (0.004)	**0.40** (<0.0001)	0.04 (0.68)
LDH (IU/L)	**0.33** (0.0007)	**0.29** (0.004)	0.11 (0.28)	-0.17 (0.08)	**-0.37947** (0.0001)

Results expressed as correlation coefficient (p-value)

MS-AFP: Maternal Serum Alpha Fetoprotein;

βHCG: Beta Human Chorionic Gonadotropin

AST: Aspartate Aminotransferase

LDH: Lactate Dehydrogenase

Table 3

Association between Abnormal Inhibin-A and MS-AFP, Birth-weight < 10th%ile and Preterm Delivery

Abnormal Inhibin and AFP Score*	Number of patients, n (%)	Birth-weight < 10th%ile, n (%)	Preterm birth: <37.0 weeks, n (%)
0	76 (75)	31 (41)	34 (45)
1	23 (23)	17 (74)	20 (87)
2	3 (3)	3 (100)	3 (100)
		p = 0.001**	p = 0.0001**

*Score calculated by adding number of individual abnormal analytes for Inhibin (≥ 2 MoM) and AFP (≥ 2 MoM)

**p value from the Cochrane-Armitage Trend Test