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Management of abnormal serum markers in the absence of aneuploidy or neural tube defects

William T. Schnettler^{1,2,3}, Michele R. Hacker^{2,3}, Rachel E. Barber², and Sarosh Rana^{1,2,3}

¹Division of Maternal Fetal Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

²Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA, USA

³Harvard Medical School, Boston, MA, USA

Abstract

Objective—Few guidelines address the management of pregnancies complicated by abnormal maternal serum analytes (MSAs) in the absence of aneuploidy or neural tube defects (NTDs). Our objective was to gather preliminary data regarding current opinions and management strategies among perinatologists in the US.

Methods—This survey of Maternal Fetal Medicine (MFM) physicians and fellows used a secure electronic web-based data capture tool.

Results—A total of 545 potential participants were contacted, and 136 (25%) responded. The majority were experienced academic physicians with robust practices. Nearly all (97.7%) respondents reported a belief in an association between abnormal MSAs and adverse pregnancy outcomes other than aneuploidy or NTDs. Plasma protein A (PAPP-A) and α -fetoprotein (AFP) were most often chosen as markers demonstrating a strong association with adverse outcomes. Most (86.9%) respondents acknowledged that abnormal MSAs influenced their counseling approach, and the majority (80.1%) offered additional ultrasound examinations. Nearly half started at 28 weeks and almost one-third at 32 weeks. Respondents acknowledging a relevant protocol in their hospital or practice were more likely to offer additional antenatal testing ($p = 0.01$).

Conclusions—Although most perinatologists were in agreement regarding the association of MSAs with adverse pregnancy outcomes, a lack of consensus exists regarding management strategies.

Keywords

Adverse; analytes; maternal; outcomes; pregnancy

Introduction

The correlation between maternal serum levels of certain proteins and fetal anomalies, such as aneuploidy and neural tube defects (NTDs), was first realized in the mid-1980s [1-4]. Today, such markers include plasma protein A (PAPP-A), free β human chorionic gonadotropin (β hCG), α -fetoprotein (AFP), hCG, unconjugated estriol (UE3) and inhibin A.

Specific patterns of protein concentrations suggest elevated risk for aneuploidy or NTDs [5]. However, abnormal values often do not confer elevated risk for aneuploidy or NTDs – creating a management dilemma for the clinician.

Evidence supports an association between these maternal serum analyte (MSA) abnormalities and adverse pregnancy conditions and outcomes such as intrauterine growth restriction (IUGR), hypertensive disorders of pregnancy and embryonic or fetal demise [6-14]. A proposed mechanism for the association is abnormal placental invasion early in gestation [7,8]. However, measurement of MSAs has not proven useful in screening for such adverse pregnancy outcomes [14,15]. In addition, a lack of consensus exists regarding management strategies for pregnancies complicated by abnormal MSAs. Our objective was to gather preliminary data regarding the variability in current national opinions, knowledge and management of abnormal MSAs in the absence of aneuploidy or NTDs.

Materials and methods

Study population

This was a cross-sectional study of Maternal Fetal Medicine (MFM) physicians within academic departments with accredited MFM fellowship programs in the US. We used a sample of convenience by obtaining a list of all accredited fellowship programs from the Society for MFM's public website and identifying potential participants from each program's public website. All faculty members and fellows within each department's MFM division were sent an e-mail asking them to complete an anonymous survey via a secure online website. A statement explaining the purpose and anonymous nature of the survey was presented to each individual entering the survey. The study was approved by the Committee on Clinical Investigations at Beth Israel Deaconess Medical Center, Boston, MA.

Survey design/data acquisition

Data were collected using research electronic data capture (REDCap), which is a secure, web-based electronic data capture tool [16]. Questions were designed to assess respondents' level of experience, familiarity with the current literature regarding the study question and opinions regarding management. The survey was pilot tested at the authors' institution, and the resulting suggestions were incorporated to generate the final version of the survey. A second e-mail request was distributed 3 weeks after the initial e-mail, and data collection concluded 6 weeks after the initial e-mail.

Data analysis

All analyses were performed using SAS 9.2 (SAS institute Inc., Cary, NC, USA). Data are presented as proportions, and comparisons were made with the χ^2 or Fisher's exact test, as appropriate. *p* values <0.05 were considered statistically significant.

Results

Survey response rate

Of 682 potential participants, we obtained valid e-mail addresses for 545. A total of 136 participants provided complete responses, yielding a response rate of 25%. All participants provided complete responses.

Respondents' characteristics

Three (2.2%) respondents were not physicians and were excluded from the analysis. Nearly all of the remaining respondents were either attending MFM specialists or fellows in

training, and greater than 80% of them had more than 10 years of experience in obstetrics. Few practiced outside of academic or university-based centers, the predominant practice setting was urban or mixed and almost half cared for more than 300 prenatal patients yearly. While half of respondents reported that more than 75% of their patients undergo serum screening for aneuploidy or NTDs, more than 10% reported that fewer than half of their patients chose screening. Respondents' training and practice characteristics are detailed in Table I.

Beliefs and management strategies

Nearly all (97.7%) respondents reported that they believed there was an association between abnormal MSAs and adverse pregnancy outcomes other than aneuploidy and NTDs; only these respondents' data were used for the analysis regarding the management of pregnancies complicated by abnormal MSAs (Table II). Of those 130 respondents, only 3 (2.3%) felt that the literature in particular did not support the association between abnormal MSAs and adverse pregnancy outcomes. PAPP-A and AFP were most often chosen as the markers that demonstrated a strong association with adverse pregnancy outcomes, while AFP was most commonly selected as the single marker having the strongest association.

Eighty-seven percent of respondents stated that knowledge of abnormal MSAs, not indicative of aneuploidy or NTDs, influenced their counseling approach to the affected pregnancy; however, there was substantial variability in physicians' management approaches with regard to the methods, timing and initiation of antenatal testing (Table II). Most (80.1%) respondents offered additional ultrasound examinations for the sole indication of abnormal MSAs, but the initiation of these examinations varied, with nearly half starting at 28 weeks and almost one-third at 32 weeks. The proportion (40.8%) of respondents who offered repeat ultrasound examinations for follow-up of fetal growth only with a diagnosis of IUGR was similar to the proportion that offered repeat ultrasound examinations every 4 weeks. Just over 45% of physicians began additional antenatal testing (with nonstress testing or biophysical profiles) at 32 weeks, but the remainder initiated testing across a wide range of gestational ages (Table II). Very few (3.1%) reported that they would offer early delivery by induction or cesarean section for women with abnormal MSAs not indicative of aneuploidy or NTDs.

We also evaluated whether either having a research interest in the association between MSAs and adverse pregnancy outcomes or the presence of a hospital/practice-based protocol regarding the management of pregnancies complicated by abnormal MSAs influenced the responses. Fifty-nine participants (45.4%) acknowledged a research interest in this area. Although there were no statistically significant differences, respondents with a research interest were more likely to offer twice weekly compared with weekly antenatal testing (Figure 1) and were more likely to offer additional ultrasounds to estimate fetal weight or interval growth for women with abnormal MSAs not indicative of NTDs or aneuploidy. When stratifying by whether the respondent's hospital or practice had a relevant protocol in place ($n = 37$; 28.5%), respondents with such a protocol were more likely to offer additional antenatal testing for all women with abnormal MSAs without aneuploidy or NTDs ($p = 0.01$).

Discussion

We present data from a survey of MFM specialists and fellows that illustrates the opinions, knowledge and varied management approaches toward abnormal MSAs in the absence of aneuploidy or NTDs. This experienced cohort of physicians was nearly unanimous (97.7%) in the belief that the existing evidence supports an association between abnormal MSAs and adverse pregnancy outcomes. Respondents also tended to agree on the MSAs with the

strongest association and their importance in pregnancy counseling. However, management approaches were quite variable, and the presence of a hospital/practice-based protocol appeared to diminish this variability.

The utility of a protocol to guide clinical management hinges upon the screening effectiveness of the test and the availability and efficacy of further diagnostic studies or therapies. While protocol-driven clinical management has been shown to be associated with improved patient outcomes in other medical specialties [17], little evidence exists supporting an optimal fetal surveillance protocol, even for fetuses with such confirmed risks as fetal growth restriction or placental abruption [18,19]. Proposals for such a protocol include costly adjuncts, such as targeted ultrasound examination and uterine artery Doppler studies, but the evidence to support such additional testing is lacking [20-24]. Despite the strength of association between MSAs and adverse pregnancy outcomes, there exists no evidence to support maternal serum screening solely for the identification or prevention of adverse pregnancy outcomes. Studies are needed to evaluate whether increased antenatal surveillance prompted by abnormal MSAs can modify pregnancy outcomes.

There are limitations to this study that warrant mention. First, the survey was designed to address the broad issue of abnormality in maternal serum analyte levels as it relates to obstetric management. The definition of abnormal varies among clinicians, and some may direct antepartum management differently based upon the degree of deviation from the normal range. Rather than specifying cutoffs to define abnormal within the survey, we left this to the discretion of each respondent. Similarly, the survey did not differentiate between management in the setting of a single abnormal analyte versus multiple abnormal analytes. Finally, we developed the survey instrument specifically for this study as we were unable to identify an existing validated instrument that met our study objective. Aside from the face validity assessment during the pilot testing, we did not validate the instrument.

Further research upon the pathophysiologic mechanisms contributing to the association between MSA abnormalities and adverse pregnancy outcomes is warranted. This understanding will help elucidate the optimal role MSAs may have, in conjunction with other screening and diagnostic methods to assign risk to a given pregnancy and potentially generate therapeutic targets. Of equal importance are studies designed to evaluate whether increased surveillance in these fetuses will result in improved pregnancy outcomes. Despite such limitations in our current knowledge, a consensus guideline that raises practitioners' awareness of these risks and proposes a standardized level of antenatal monitoring may result in more evidence-based practice and uniformity in management strategies.

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Figure 1.
Method of antenatal testing.

Table I

Respondent training and practice characteristics.

Characteristic	All respondents (n = 133) n (%)
Level of training	
Maternal Fetal Medicine specialist	97 (72.9)
Maternal Fetal Medicine fellow	34 (25.6)
Generalist in obstetrics/gynecology	2 (1.5)
Years of experience (including residency and fellowship)	
<5 years	22 (16.5)
6–10 years	29 (21.8)
11–20 years	38 (28.6)
>20 years	44 (33.1)
Practice type	
Academic/university based	128 (96.2)
Community	5 (3.8)
Annual number of prenatal patients	
<100	14 (10.5)
100 to 200	33 (24.8)
201–300	22 (16.5)
301–400	15 (11.3)
>400	49 (36.8)
Setting of patient population	
Urban	58 (43.6)
Suburban	11 (8.3)
Rural	2 (1.5)
Mixed	62 (46.6)
Percentage of patient population that undergoes maternal serum based risk assessment for aneuploidy or neural tube defects	
<25%	2 (1.5)
26–50%	13 (9.8)
51–75%	51 (38.4)
>75%	67 (50.4)

Table II

Management strategies and beliefs among respondents.

Characteristic	<i>n</i> = 130 <i>n</i> (%)
In your clinical opinion, does the current literature support an association between abnormal maternal serum analyte markers and adverse pregnancy outcomes such as IUGR, pre-eclampsia or IUFD?	
Yes	127 (97.7)
No	3 (2.3)
In your clinical opinion, which markers have demonstrated the strongest association to adverse pregnancy outcomes (excluding aneuploidy or neural tube defects)? (You may select more than one) ^a	
PAPP-A	85 (65.4)
Free β hCG	16 (12.3)
α fetoprotein	115 (88.5)
hCG	32 (24.6)
Unconjugated estriol	10 (7.7)
Inhibin	25 (19.2)
In your clinical opinion, which marker has demonstrated the strongest association to adverse pregnancy outcomes (excluding aneuploidy or neural tube defects)?	
PAPP-A	33 (25.4)
Free β hCG	3 (2.3)
α fetoprotein	75 (57.7)
hCG	6 (4.6)
Unconjugated estriol	0 (0.0)
Inhibin	7 (5.4)
Missing	6 (4.6)
In your daily practice, does the knowledge of an abnormal maternal serum screening result (not indicative of aneuploidy or neural tube defect) impact your management plan or counseling approach to the pregnancy in any way?	
Yes	113 (86.9)
No	17 (13.1)
Do you offer additional ultrasound examinations with estimation of fetal weight for women with abnormal serum analyte results and no other indication?	
Yes, starting near 28 weeks	60 (46.2)
Yes, starting near 32 weeks	41 (31.5)
Yes, starting near 34 weeks	3 (2.3)
Yes, starting near 36 weeks	1 (0.8)
No	25 (19.2)
Do you offer repeat ultrasound examinations to follow interval growth for women with abnormal serum analyte results and no other indication?	
Yes, but only if IUGR was diagnosed	53 (40.8)
Yes, every 2 weeks	1 (0.8)
Yes, every 3 weeks	2 (1.5)
Yes, every 4 weeks	49 (37.7)

Characteristic	<i>n</i> = 130 <i>n</i> (%)
No	14 (10.8)
Unknown	11 (8.5)
Which methods of antenatal testing do you typically use to monitor these patients? ^a	
Once weekly NST	30 (23.1)
Once weekly modified biophysical profile	13 (10.0)
Once weekly full biophysical profile	28 (21.5)
Twice weekly NST	32 (24.6)
Twice weekly modified biophysical profile	23 (17.7)
Twice weekly full biophysical profile	6 (4.6)
None of the above	12 (9.2)
When do you initiate the additional antenatal testing?	
Near 28 weeks	15 (11.5)
Near 32 weeks	59 (45.4)
Near 34 weeks	9 (6.9)
Near 36 weeks	11 (8.5)
None of the above	24 (18.5)
Unknown	12 (9.2)
Do you offer early delivery by induction of labor, or cesarean section (if indicated), for women with abnormal serum analyte results but no other indication?	
Yes	4 (3.1)
No	126 (96.9)

IUFD, intrauterine fetal demise; IUGR, intrauterine growth restriction; NST, nonstress testing; PAPP-A, plasma protein A.

^aProportions may sum to more than 100%, because respondents could choose more than one answer.