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Maternal Serum Screening Markers and Adverse Result: A New Perception

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Abstract – There have been a number of studies evaluating the association of aneuploidy serum markers with adverse pregnancy outcome. More recently, the development of potential treatments for these adverse outcomes as well as the introduction of cell-free fetal DNA (cffDNA) screening for aneuploidy necessitates a re-evaluation of the benefit of serum markers in the identification of adverse outcomes. Analysis of the literature indicates that the serum markers tend to perform better in identifying pregnancies at risk for the more severe but less frequent form of individual pregnancy complications rather than the more frequent but milder forms of the condition. As a result, studies which evaluate the association of biomarkers with a broad definition of a given condition may underestimate the ability of such markers to identify pregnancies that are destined to develop the more severe form of the condition. Consideration of general population screening using cffDNA solely must be weighed against the fact that traditional screening using serum markers enables detection of severe pregnancy complications, not detectable with cffDNA, of which many may be amenable to treatment options.

Keywords: Aneuploidy Screening; Preeclampsia; IUGR; Preterm Birth; Fetal Loss; Placenta Accreta; Open Neural Tube Defects.

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INTRODUCTION

More recently, there have been new developments that need to be considered when evaluating aneuploidy screening markers for other adverse outcomes. Evaluation of cell-free fetal DNA (cffDNA) in maternal blood offers the opportunity to significantly improve the detection of Down syndrome while substantially reducing false positive rates (Macri, Weiss, 1982). This new technology can also be used to detect trisomy 18, 13 and sex chromosome abnormalities (Kupferminc, *et. al.,* 1993). albeit at somewhat lower detection rates than for trisomy 21. Based on the initial studies, the American Congress of Obstetricians and Gynecologists cffDNA-based testing could be offered to pregnancies at high risk for aneuploidy including those with advanced maternal age. Before it can be determined whether or not cffDNA testing should be applied to a low risk population a number of factors need to be considered. First, the cost of the technology is significant and at presents the cost of providing cffDNA testing to the entire population is substantially greater than that of current screening protocols even after factoring in the savings due to improved detection (Krantz, *et. al.,* 1996). The cffDNA approach is highly focused on the specific genetic disorders tested for and therefore, at present cffDNA testing cannot detect the significant percentage of atypical abnormal karyotype results which are associated with abnormal l serum or nuchal translucency values. Furthermore, cffDNA testing does not appear to be useful in the identification of other adverse perinatal outcomes which can lead to severe perinatal morbidity and mortality such as preeclampsia, preterm birth and small for gestational age neonates (Askie, *et. al.,* 2007). Indeed, the incidence of severe morbidity, mortality and NICU admission exceeds the incidence of the genetic disorders that can be identified by cffDNA testing. The ability to reduce the incidence of severe morbidity and mortality lies in the early identification and treatment of asymptomatic pregnancies.

REVIEW OF LITERATURE:

Several studies have evaluated first trimester free β human chorionic gonadotropin (free hCGβ) and pregnancy associated plasma protein A (PAPP-A) as markers for preeclampsia (Orlandi, *et. al.,* 1997). In general, these studies did not show an association of preeclampsia with free hCGβ but did show an association with low PAPP-A resulting in detection rates of 8%–15% at a false positive rate of 5%.

Morris *et al.* performed a systematic meta-analysis of cohort studies evaluating second trimester markers and preeclampsia. There was significant variation among studies in the threshold used to identify patients at high-risk as well as significant variation in screening performance. The most effective thresholds were 2.0 multiples of the median (MoM) for alpha-fetoprotein (AFP) resulting in a positive likelihood ratio (LR) of 2.36 and a negative likelihood ratio of 0.96; 2.0 MoM for hCG resulting in a positive LR of 2.45 and a negative LR of 0.89; 0.5 MoM for unconjugated estriol (uE3) resulting in a positive LR of 1.50 and a negative LR of 0.99 and 2.79 MoM for inhibin (dimeric inhibin A) resulting in a positive LR of 19.5 and a negative LR of 0.30. Similarly, Kang *et al.* found a significant association between inhibin and preeclampsia but not AFP and uE3. In a 3 marker protocol including PAPP-A, inhibin and HCG, the detection rate was 40% at a 5% false positive rate. The FASTER trial (Krantz, *et. al.,* 2000) also showed an association between preeclampsia and inhibin with a detection rate of 17% at a false positive rate of 3% but detection was not improved with additional markers. Among preeclampsia pregnancies, approximately 70% of perinatal deaths and 60% of cases of severe neonatal morbidity occur in early onset (<34 weeks) preeclampsia even though these cases represent only about 10% of all preeclampsia cases. As a result, a significant positive impact on perinatal morbidity and mortality can be achieved with effective screening programs for the early-onset form of the disease.

1- Intrauterine Growth Restriction:

Until recently, the terminology used to describe intrauterine growth restriction (IUGR) has been inconsistent and confusing (Wapner, *et. al.,* 2003). and the term small for gestational age (SGA) has been used interchangeably with IUGR. An estimated fetal weight below the tenth percentile can alert the clinician to small fetal size but does not effectively differentiate between those fetuses who are small for pathological reasons and those that are constitutionally small but healthy. The authors found that those pregnancies more likely to have adverse pregnancy outcome or NICU admissions had estimated fetal weight <3rd percentile or abnormal umbilical artery (UA) Doppler compared to those pregnancies with normal UA Doppler and estimated fetal birth weight between the 3rd and 10th percentiles.

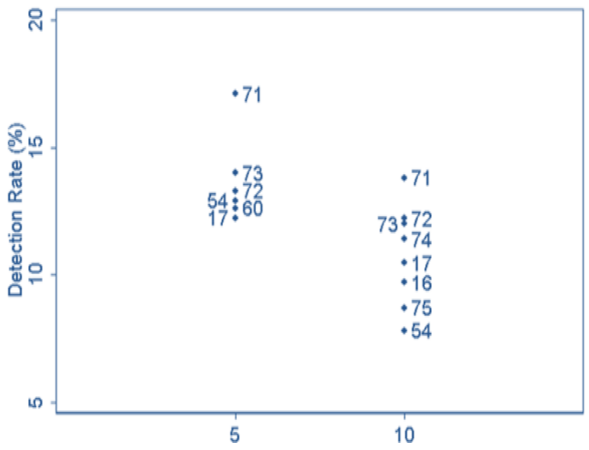

Figure- Detection Rate of IUGR using PAPP-A the numbers indicate the associated references

As a follow-up to the FASTER trial, Dug off *et al.* evaluated the effectiveness of the serum markers in identifying IUGR, defined either as below the tenth percentile or below the fifth percentile for birth weight (Goetzinger, Odibo, 2014). Table 1 show that PAPP-A, AFP, HCG, uE3 and inhibin identify a greater percentage of pregnancies with birth weight below the fifth percentile than those with birth weight below the tenth percentile. Since the below the tenth percentile group contains all of the pregnancies below the fifth percentile the difference between the two percentile cut-offs may not appear as significant.

Marker	Birth Weight Percentiles			*p*-Value *
	≤5th	≤10th	6th–10th	
PAPP-A	12.2	10.5	9.1	0.006
AFP	7.2	4.9	3.1	<0.001
hCG	11.9	10.7	9.7	0.06
uE3	2.7	2.2	1.8	0.104
Inhibin	13.1	10.5	8.5	<0.001

Table 1- Detection rate (%) at a 5% false positive rate based on definition of IUGR using Birth Weight Percentiles

2- Preterm Birth:

In 2012, 9.9% of singleton births were preterm (<37 weeks) including 2.8% which were early preterm (<34 weeks) (Spencer, Nicolaides, 2002). Identification of pregnancies at high risk for preterm birth based on short cervix can identify approximately one third of preterm births. Recent randomized control trials have indicated that treatment with progesterone (Goetzl, 2010). or cervical circulate can significantly reduce preterm birth. Since only one third of early preterm births (<34 weeks) have short cervix below 1.5 cm the addition of biochemical and other biophysical markers may lead to reduction in incidence of preterm birth and by extension a reduction in perinatal morbidity and mortality. Several studies have evaluated the association of PAPP-A with preterm birth. Table shows that PAPP-A is more strongly associated with early preterm birth than with preterm birth. At a 5%

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false positive rate, early preterm birth was identified in 9%–15% of cases compared to 5%–9% in preterm birth. The positive likelihood ratio of PAPP-A below the fifth percentile ranged from 2 to 3 for early preterm birth. (Cicero, *et. al.,* 2001). evaluated PAPP-A at a 10% false positive rate and contrary to the other studies actually had higher detection in the preterm birth group (24%) compared to the early preterm birth group (20%). However, when maternal characteristics (African American race, Body Mass Index, Prior preterm birth, history of chronic hypertension, history of pre-gestational diabetes) were factored in, the detection rate was the same (38%) in both groups.

3- Open Neural Tube Defects:

The concept of prenatal screening began with the use of AFP for the detection of open neural tube defects (ONTDs) and evolved so that the main focus of serum marker screening is now chromosomal abnormalities (Davenport, Macri, 1983). Current advances in non-invasive cffDNA testing are not directed at the identification of pregnancies affected by ONTDs. A first trimester ultrasound is effective in identifying anencephaly but less so in identifying open spina bifida although newer techniques may improve detection. A second trimester anatomy scan can be effective in identifying neural tube defects in specialized centers focused on high risk pregnancies; however, it has been demonstrated to be less effective in general practice focused on low risk pregnancies (Katz, *et. al.,* 1990). Therefore, ACOG recommends that maternal serum AFP screening be offered to all pregnant women and that those found to be at high risk for ONTD may be offered specialized ultrasound examination to identify the defect. The importance of prenatal screening and detection of such defects may be even more relevant now that fetal surgery offers the promise of improved outcome in certain cases of open Spina bifida. The serum screen for open neural tube defects is straightforward with labs using either a 2.0 MoM or 2.5 MoM cut-off the detection rate of open Spina bifida is approximately 10 percentage points greater with a 2 MoM rather than a 2.5 MoM cutoff (Gross, *et. al.,* 1994). In addition, there have been significant improvements in AFP assays since screening was first introduced with radioimmunoassay in the 1970s. As a result the distribution of AFP is much narrower and thus the use of a 2.0 MoM can result in false positive rates of 2% or less.

CONCLUSION:

Preterm birth the clinical presentation may vary widely with respect to maternal/fetal morbidity and mortality. The more severe form of these adverse outcomes has significantly higher rates of severe morbidity and mortality. The information presented in this review indicates that there is improved performance of serum markers with respect to the more severe form of various pregnancy complications. Moreover, the most severe cases tend to occur less frequently than the milder forms of these conditions. As a result, studies which evaluate the association of biomarkers with a broad definition of a given condition may underestimate the ability of such markers to identify pregnancies that are destined to develop the more severe form of the condition. Therefore, more effort should be made to narrowly define specific adverse outcomes which may be identified by maternal serum markers. Additionally, refinements to the risk based on follow-up assessments after the completion of serum screening could further improve the process.

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