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Adverse Pregnancy Outcomes after Abnormal First Trimester Screening for Aneuploidy

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Abstract

Women with abnormal first trimester screening but with a normal karyotype are at risk for adverse pregnancy outcomes. A nuchal translucency >3.5mm is associated with an increased risk of subsequent pregnancy loss, fetal infection, fetal heart abnormalities and other structural abnormalities. Abnormal first trimester analytes are also associated with adverse pregnancy outcomes but the predictive value is less impressive. As a single marker, PAPP-A <1st%ile has a good predictive value for subsequent fetal growth restriction. Women with PAPP-A <5th%ile should undergo subsequent risk assessment with routine MSAFP screening with the possible addition of uterine artery PI assessment in the midtrimester.

Keywords

First trimester screening; congenital heart disease; intrauterine growth restriction; intrauterine fetal demise

Introduction

Although the primary aim of first trimester screening is to identify pregnancies at risk of aneuploidy, first trimester findings may give insight into other adverse pregnancy outcomes. The following pages outline a practical approach to interpreting abnormal first trimester findings and review what further testing may be indicated. Abnormalities discussed will include: 1) A thickened nuchal translucency 2) abnormal fetal anatomy detected at first trimester screening and 3) Abnormal serum analytes.

Thickened Nuchal Translucency

A thickened nuchal translucency (NT) was originally described as an NT >95th%ile for a given crown rump length (CRL). However more recent data has suggested that adverse outcomes are much more common with an NT that exceeds a set threshold of 3.5mm (i.e. $\geq 3.5\text{mm}$), a measurement that essentially represents $\geq 99^{\text{th}}$ %ile throughout the gestational age window for first trimester screening.^{1–3} Given that it can be difficult to distinguish between a thickened NT and a cystic hygroma, all NTs $\geq 3.5\text{mm}$ will be grouped together whenever

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possible. In some investigations, cystic hygromas were excluded and this will be noted where appropriate.

A thickened NT has been associated with a myriad of syndromes, however most of these have only been reported once or twice in the literature.⁴ Therefore, unless a specific family history is present that points to an increased likelihood of a specific disorder, it is unlikely to be clinically feasible to counsel patients regarding all these rare possibilities. Further, in most cases it is not certain whether or not the finding of a thickened NT are specifically associated with the syndrome or if the association was incidental. Therefore we will focus on the most likely risks and abnormalities associated with this finding. Given the strong association between thickened NT and abnormal karyotype, this chapter presumes that definitive diagnosis for chromosomal abnormalities has been offered and/or performed. The following sections pertain to management of thickened NT where a normal karyotype has been determined. In cases where karyotype determination has been declined, risks of adverse pregnancy outcome are likely to be increased given the 20 to 60% risk superimposed by undetected chromosomal abnormalities.

Miscarriage or Fetal Death—A thickened NT has been associated with an increased risk of miscarriage or fetal death. The risk increases with increasing NT thickness (Table 1). Counseling in the setting of thickened NT should include an increased risk of miscarriage or fetal loss both prior to chorionic villus sampling or amniocentesis and again once a normal karyotype is established. In the majority of cases, fetal loss occurs prior to 20 weeks and is heralded by progressive fetal hydrops. Therefore, perinatal management should include some surveillance for fetal miscarriage prior to 20 weeks. However, given that further anatomic and cardiac evaluation of fetuses with thickened NT is warranted, additional sonographic evaluation for the primary aim of detecting inevitable fetal loss is redundant (see below).

Cardiac Defects—Multiple reports have described an association between fetal cardiac defects and a thickened NT. This association is likely due to the effects of reduced diastolic cardiac function; although this finding may not be present in all fetuses with a thickened NT and a cardiac defect. Table 2 presents the risk of cardiac defects in the setting of a thickened NT. For simplification, studies were only included where sample size exceeded 100 and where specific data could be abstracted for nuchal translucency ≥ 3.5 mm. In manuscripts where outcomes were reported as >99 th%ile, this cutoff was used as equivalent to 3.5 mm. Currently, the American College of Obstetricians and Gynecologists (ACOG) recommends offering a fetal echocardiogram following a nuchal translucency of ≥ 3.5 mm.¹² The cost effectiveness of offering fetal screening echocardiography at NT measurements of 2.5 to 3.4 mm has not been established. However, consideration should be given to referring patients with an NT between 2.5 and 3.4 mm for a level II anatomic ultrasound at a referral center. While some authors have reported diagnosing fetal heart defects on transvaginal ultrasound at the time a thickened NT is identified, caution should be used in counseling patients based on these results.¹³ The false positive rate in one study was 33% (i.e. 1 in 3 of suspected abnormalities later was found to have normal fetal heart structure). Others have described an increased risk of cardiac anomalies with the finding of an absent or reversed A-wave in the ductus venosus.¹⁴

Fetal Infections—A thickened NT has been associated with parvovirus infection^{15–18} but not with other TORCH infections.¹⁹ The finding of thickened NT in the setting of first trimester parvovirus infection is associated with an adverse outcome in 20% of cases. However the accuracy of this rate is likely to be poor due small numbers and to the lack of prospective studies evaluating parvovirus status in all women with a thickened NT. If there is a history of an affected contact or maternal symptoms then it is reasonable to evaluate

maternal quantitative IgG and IgM for parvovirus. If thickened NT progresses to signs of fetal hydrops at 20–22 weeks, parvovirus screening is recommended as well as consideration of evaluation for the standard infections associated with fetal hydrops such as toxoplasmosis and CMV.

Other Fetal Abnormalities—Fetal abnormalities that have a significant number of reports associating them with a thickened NT are listed in Table 3. This list is by no means exhaustive; however it serves to focus additional testing as needed and to provide additional guidance for subsequent targeted ultrasound examinations and or genetic testing. Attention should be given to potential genetic sources of severe fetal anemia. If anomalies are found on subsequent sonographic evaluation that are associated with other known syndromes, they should prompt additional counseling, evaluation and/or testing. Conversely, some of the genetic disorders in Table 3 have variable rates of abnormal findings on prenatal ultrasound. Therefore, the absence of sonographic markers may not be sufficient to exclude the presence of a genetic syndrome. Few studies have evaluated long term developmental outcomes in neonates born following a NT measurement of $\geq 3.5\text{mm}$. The optimal timing of follow-up sonographic evaluations is also not well established. Some have suggested a targeted sonographic evaluation at 14 to 16 weeks for preliminary evaluation of the fetal anatomy and to evaluate whether or not the thickened NT has resolved.⁷² Resolution is associated with a more favorable prognosis while progressive hydrops is associated with a poor prognosis. Subsequent evaluation at 20 to 22 weeks can be performed to complete the anatomic evaluation as needed and to evaluate the fetal cardiac anatomy. These recommendations are based on expert opinion and do not reflect any systematic prospective comparison of the utility of various strategies. Therefore, the exact schedule of evaluation should be based on a combination of factors including provider preference, patient preference and maternal body habitus. If fetal karyotype is normal and anatomic evaluation is normal at 20 to 24 week, then patients can be reassured that the likelihood of a positive pregnancy outcome has been reported as 96% (95%CI; 94–98%).⁷³ Further, the one controlled study examining developmental outcome following isolated NT thickening reported no significant increase in rates of developmental delay.⁷⁴

Abnormal First Trimester Anatomy

Although a complete fetal anatomic survey is not feasible in fetuses between 11 and 13/7 weeks' gestation, detection of some structural abnormalities is possible, especially using a transvaginal approach.^{75–76} Studies in this gestational age range report sensitivities in the detection of fetal anatomic abnormalities ranging from 16 to 65%, although some of these studies included cystic hygroma as one of the abnormalities, boosting detection rates.^{75–79}

Table 4 provides a list of some of the abnormalities that can be detected in the first trimester. While some of these abnormalities may be associated with a thickened NT (Table 3), many are not. Fetal abnormalities identified concurrent with a thickened NT, especially suspected cardiac defects, increase the risk of chromosomal abnormality. It is reasonable to attempt evaluation of a the fetal anatomy transvaginally following the finding of a thickened NT. While any anatomic abnormalities that are detected at the time of nuchal evaluation should be incorporated into patient counseling, early evaluation of fetal heart anatomy and other structural abnormalities is probably most efficient at 14 to 16 weeks.

Extremes of First Trimester Maternal Serum Analytes and Adverse Pregnancy Outcomes

First trimester analytes are thought to reflect in part on placental function. Therefore, it is logical that abnormalities would be associated with an increased risk of pregnancy complications related to placental function. This section with review the associations between depressed values of pregnancy associated plasma protein A (PAPP-A) and elevated

levels of the free β subunit of human chorionic gonadotrophin (HCG) and adverse pregnancy outcomes related to abnormal first trimester placentation including: miscarriage, stillbirth, and intrauterine growth restriction. The association between abnormal first trimester analytes and other pregnancy complications that may also be related to first trimester placentation, namely preeclampsia and preterm birth, will also be reviewed. Finally, we will review a possible association between abnormal analytes and other abnormalities. While the exact multiple of the median (MOM) cut off for PAPP-A < the 1st and 5th%iles varies slightly by study; this value can easily be obtained from the reference lab used in each clinical center.

Early Fetal Loss—Multiple large cohort studies have established a relationship between depressed levels of PAPP-A and early pregnancy loss. Table 5 reviews the screen positive rates and positive predictive values (PPVs) for PAPP-A levels below the 5th and 1st %iles. Overall, the positive predictive value of PAPP-A is relatively low as the majority of pregnancy loss precedes first trimester screening. HCG <1st%ile has also been associated with a 2.8–4.1% PPV for early fetal loss.^{82–83} Combining depressed PAPP-A with maternal characteristics, maternal serum alpha-fetoprotein (MSAFP), and unconjugated estriol levels increases the detection rate of early loss to 39%.⁸⁶ However, ultrasound examination to evaluate the fetal anatomy is already planned between 16 (in cases of abnormal overall first trimester screening) and 18–20 weeks (in cases of normal testing) in most cases. Therefore, no additional intervention is indicated in the asymptomatic patient. The maternal risks of a short delay in diagnosis of fetal loss are low as disseminated intravascular coagulation following early pregnancy loss is rare. Further, since there are no proven effective interventions to prevent pre-viable pregnancy loss related to poor placentation; the cost-effectiveness of repeated screening to detect pregnancy loss is likely to be poor. Given that normal first trimester testing is associated with rates of pregnancy loss of 0.36%, clinicians should use normal first trimester as an opportunity to reassure patients regarding subsequent risk of miscarriage.⁸²

Late Fetal Loss—Table 5 reviews the screen positive rates and positive predictive values (PPVs) for PAPP-A levels below the 5th and 1st %iles for stillbirth or late fetal loss. Even at PAPP-A levels <1st%ile, the PPV for stillbirth is only 0.84 to 2.0%. Depressed levels of HCG are not significantly related to the risk of stillbirth.⁸³ In one report, 7 of the 8 stillbirths that occurred in women with PAPP-A <5th%ile were related to signs of abnormal placentation: i.e. placental abruption or growth restricted fetuses. Given that PAPP-A<1st %ile is a strong predictor of growth restriction (see below), it is likely that screening strategies to detect small for gestational age fetuses (SGA) will identify the fetuses at highest risk of stillbirth following a depressed PAPP-A. While regular fetal surveillance in this population is likely to be accompanied by some reduction in the risk of stillbirth; the ability of fetal surveillance in a population with normal fetal growth to prevent unexplained stillbirth or fetal demise associated with placental abruption is far from certain.

Intrauterine Growth Restriction—Multiple studies have established a correlation between abnormal first trimester analyte levels, especially PAPP-A, and birth weight. One strength of the research in this area is that first trimester screening ensures accurate pregnancy dating. In contrast, many reports are weakened by a poor definition of growth restriction. A definition of growth restriction based on an overall birth weight of <10th%ile for gestational age is likely to include a large proportion of constitutionally small neonates that do not have a significantly increased risk of adverse outcome. The most robust studies include a more extreme definition of growth restriction (SGA <5th%ile); therefore studies with growth restriction defined as SGA<10th%ile are only included as related to PAPP-A levels <1st%ile (Table 5.)

Overall as a single marker, PAPP-A<1st%ile has a strong PPV for SGA <5th%ile (15.8%)⁸³ and SGA<10th%ile (24.1–26.3%)^{83,85,90} and appears to be sufficient indication as a single marker to recommend subsequent sonographic evaluation of fetal growth. Further the cost effectiveness is likely to be favorable as few women would require screening ($\leq 1\%$), but 1 in 6 women screened would have a fetus with SGA<5th%ile and 1 in 4 would have a fetus with SGA<10th%ile.

The strength of PAPP-A<5th%ile as a single marker is less certain as the observed rates of SGA<5th%ile are only 1.5 to 2 fold higher than expected. Therefore many researchers have used PAPP-A<5th%ile in combination with other indicators of increased risk of SGA to increase the sensitivity and specificity of testing. One approach is use parameters obtained at routine second trimester ultrasound evaluations including: fetal growth parameters (routinely obtained) and uterine artery Doppler measurements (not routinely obtained at all centers). Another approach is to combine first trimester measures with second trimester maternal serum alpha fetoprotein (MSAFP) measurements that are routinely obtained after 15 weeks to screen for neural tube defects. A third approach is to combine first trimester screening with maternal risk factors.

Of these methods, combining MSAFP values is the most straightforward and reproducible. Smith et al evaluated this approach in a cohort of 8483 women.⁹¹ In this cohort, PAPP-A<5th%ile was associated with a 10.9% rate of SGA while MSAFP>95%ile was associated with a 4.9% rate of SGA. Surprisingly there was no association between a test result of PAPP-A<5th%ile and a subsequent MSAFP>95%ile. Of the small proportion of women with both a PAPP-A<5th%ile and MSAFP>95%ile the subsequent rate of SGA was 32.1%. Therefore it seems reasonable to perform surveillance for SGA in women where both test results are outside the usual bounds. This study also reported an increased risk of stillbirth in women with both abnormal test values; however it was not clear how many of these stillbirths occurred in the absence of growth restriction.

The utility of second trimester ultrasound markers is less clear. Fox et al.⁹² reported that 10.5% of women with PAPP-A<5th%ile have evidence of fetal growth disturbances defined as: a) estimated fetal weight <25%ile b) a greater than 7 day growth discrepancy with established dates or c) a measurement of >90th%ile for head or abdominal circumference. In this group, the rate of birth weight <10th%ile was 47.8% and the rate of birth weight<5th%ile was 21.7%. While these results are provocative, the study was relatively small and these rates are based on only 25 fetuses with both PAPP-A<5th%ile and second trimester ultrasound growth disturbances. Cooper et al.⁹³ performed uterine artery Doppler examination at 18 and 22 weeks on all women with a PAPP-A <0.4 MOM (n=289). In pregnancies with a pulsatility index (PI) of >1.45, the subsequent incidence of SGA was 36% at 18 weeks and 64% at 22 weeks. Further prospective studies are need to evaluate this exploratory cutoff for PI to determine if measuring PI at the mid-trimester is an effective strategy. Others have investigated the addition of maternal serum placental growth factor (PIGF) at 11 to 13+6 weeks to increase the sensitivity and specificity of first trimester analytes in the prediction of SGA;⁹⁴ however this work is preliminary. Depressed levels of HCG<1st%ile were related to an increased risk of SGA<10th%ile in one report (PPV 14.3%)⁹⁰ but were not related to an increased risk of SGA <5th%ile in another report.⁸³

Preterm Birth—Overall the ability of PAPP-A to predict spontaneous preterm birth prior to 34 weeks is low (Table 5). Some of the risk of preterm delivery associated with low levels of PAPP-A is likely due to indicated preterm birth due to the association between PAPP-A and SGA. Therefore the likelihood that PAPP-A can be used to identify a clinical population who are good candidates for preterm birth interventions is low. The sensitivity of PAPP-A <5th%ile for preterm delivery ≤ 32 weeks is 9.4%.^{83,90} Therefore, if additional tests could

increase the sensitivity and specificity, it would be of interest. It is also not known if preterm births associated with depressed levels of PAPP-A would be reduced by currently available treatments such as 17-OH progesterone. Depressed or elevated levels of HCG are not associated with an increased risk of preterm delivery.^{83,90}

Preeclampsia—Overall, PAPP-A <5th or 1st%ile as a single marker has a poor PPV for preeclampsia. Given the low rates of preeclampsia in a population with depressed PAPP-A and the lack of effective preventative strategies in women at relatively low risk; it is unlikely that first trimester analytes used to screen for aneuploidy are useful at this time. In women with abnormal uterine artery Doppler in the second trimester; the retrospective addition of first trimester serum analytes appears to have only a small impact on ROC curves (area under the curve 0.818 vs. 0.853).⁹⁶ However active research is ongoing regarding other potential first trimester markers of preeclampsia including the addition of first trimester uterine artery PI,⁹⁷ maternal plasma inhibin A at 11–13 weeks,⁹⁸ and a combination of uterine artery PI and maternal serum placental protein 13 (PP-13).⁹⁹

Most recently, Poon et al¹⁰⁰ have proposed a multivariate prediction model for early onset preeclampsia that includes maternal parity, history of prior preeclampsia, uterine artery PI at 11–13 weeks, maternal mean arterial pressure, PAPP-A and PIGF. At a 5% false positive rate, 93% of preeclampsia prior to 34 weeks was detected. Limitations include a very low rate of overall preeclampsia (2%) in the population used to derive the model, the cumbersome nature of the model, and the fact that the model for early onset preeclampsia was based on only 34 cases. Prospective evaluation of this model will be needed in US population, as well as the availability of effective interventions, before this model can be adopted into clinical practice.

Other Abnormalities—A recent report from Hoffman et al¹⁰¹ links inhibin A ≥ 2.0 MOM with structural abnormalities including multicystic dysplastic kidney (MCDK) and two vessel umbilical cord. HCG ≥ 2.0 MOM was associated with MCDK and hydrocele, and PAPP-A ≥ 2.0 MOM was associated with hydrocele. This report is largely of interest due to questions it raises about the mechanism through which certain structural abnormalities might interact with maternal serum analytes. MCDK and a 2-vessel cord are easily detected on ultrasound examination, and hydrocele is generally not clinically significant. Uccella et al.¹⁰² have recently linked a PAPP-A of <0.52 MOM to an increased risk of cesarean delivery for non reassuring fetal status in labor. While this result has some biologic plausibility, this information should not be incorporated into clinical practice until this exploratory cutoff is validated.

Summary

A thickened NT in the setting of a normal karyotype is associated with adverse pregnancy outcomes. At first trimester screening, as detailed an anatomic survey as feasible should be performed and definitive diagnosis for aneuploidy should be offered. Patients should be counseled regarding the increased risk of fetal loss prior to amniocentesis or chorionic villus sampling. Once a normal karyotype has been established screening for parvovirus and/or targeted genetic testing should be offered if appropriate. An early anatomic survey should be offered at 14 to 16 weeks, followed by repeat ultrasound with fetal echocardiogram at 20 to 22 weeks. Counseling regarding absence of any identified abnormalities and with resolution of the thickened NT. Progression to fetal hydrops is associated with a poor prognosis.

Women with PAPP-A <1st%ile are at high risk for growth restriction, and should undergo subsequent evaluation. Those fetuses with suspected intrauterine growth restriction should undergo further evaluation with serial umbilical artery Doppler examinations as well as

surveillance for fetal well being. This stepwise strategy is likely to identify those pregnancies at highest risk for stillbirth in women with PAPP-A<1st%ile. Women with a PAPP-A <5th%ile in combination with a MSAFP>95%ile should also undergo subsequent screening for IUGR. It is reasonable to consider adding uterine artery PI to the midtrimester anatomic ultrasound in women with a PAPP-A<5th%ile. Women with normal first trimester testing should be reassured that their risk of subsequent pregnancy loss is very low and that their risk of other adverse pregnancy outcomes is reduced.

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Table 1Risk of Miscarriage in the Setting of Thickened NT ¹⁻⁴

Nuchal Translucency	Fetal Death *	Live Birth without Abnormality **
3.5–4.4mm	2.7%	70%
4.5–5.4mm	3.4%	50%
5.6–6.4mm	10.1%	30%
>6.5mm	19.0%	15%

* Fetal death in the absence of chromosomal abnormalities

** Residual rate excluding fetal death, major abnormalities, or chromosomal abnormalities

Table 2

Incidence of Cardiac Abnormalities with Thickened NT

Study	≥ 3.5 (all)	3.5–4.4mm	> 4.5mm
Hyett et al, 1997 ⁵	18/287	5/188	13/99
Hyett et al, 1999 ⁶	20/315	6/208	14/107
Ghi et al, 2001 ⁷	42/597	12/384	30/213
Aztei et al, 2005 ⁸	64/1087	23/654	41/423
Simpson et al, 2007 ^{9*}	12/310		
Clur et al 2008 ^{10**}	28/374	6/199	22/175
Zosmer et al, 1999 ¹¹	19/398		
Totals	203/3368	52/1633	120/1017
Rates (95% CI)	6.0% (5.2–6.8%)	3.2% (2.3–4.1%)	11.8% (9.8–13.8%)

* Cystic hygromas excluded. >99.4th%ile (2.5MOM) reported as ≥ 3.5mm category

** Calculated from data presented in another format

Table 3**Abnormalities Associated with Thickened NT with Normal Karyotype**

Abnormality	Defect	Potential Ultrasound Findings
Dandy Walker ^{2,20}	Developmental	Cerebellar Hypoplasia
Holoprosencephaly ^{2,21–22}	Developmental	Alobar: Monoventricle, fused thalami
Facial Cleft ^{2,23–26}	Developmental	Facial Cleft
Diaphragmatic Hernia ^{2,22,27–31}	Developmental	Cardiac axis shift, viscera in thorax
Omphalocele ^{2,22–23,25,28–29,32–37}	Developmental	Abdominal wall defect
Megacystitis ^{2,28,38–44}	Developmental	Bladder >7mm at <14 weeks
Multicystic dysplastic kidneys ^{2,22–23,27,33,41,45}	Developmental	Enlarged, cystic kidneys, oligohydramnios
Achondrogenesis ^{46–49}	Autosomal Recessive	Severe Limb Shortening Hypomineralization
Jarcho-Levin Syndrome ^{2,50–53}	Autosomal Recessive	Scoliosis/Spine Disorganization
Fetal Akinesia Deformation sequence ^{2,22–24,54}	Autosomal Recessive	Arthrogryposis
Spinal muscular atrophy ^{2,20,42,55–57}	Autosomal Recessive	Decreased fetal activity
Mucopolysaccharidosis type VII ^{58–60}	Autosomal Recessive	Hydrops, Ascites, hepatomegaly
Smith-Lemli Opitz Syndrome ^{2,22,61–63}	Autosomal Recessive	Polydactyly, cardiac defects, ambiguous genitalia in males
Zellweger syndrome ^{20, 64–66}	Autosomal Recessive	Hypertelorism, cardiac defects, brain defects, hepatomegaly, growth restriction
Body Stalk anomaly ^{2,22,67–69}	Developmental	Large abdominal wall defect, kyphoscoliosis
Noonan Syndrome ^{2,20,32,38–39,41,45,70–71}	Autosomal Dominant	Pulmonary Stenosis, hypertrophic cardiomyopathy, polyhydramnios, hydrothorax, skin edema

Table 4

Structural Abnormalities that may be seen in the First Trimester

Abnormality	Ultrasound Finding
Acrania-anencephaly sequence	Absent cranial vault, echogenic amniotic fluid ⁸⁰
Holoprosencephaly	Single ventricle
Cerebellar defects	Ventriculomegaly
Hydranencephaly	Fluid filled cranium
Encephalocele	Cranial defect, usually posterior
Spina Bifida	Irregularities of the bony spine, bulging posterior contour of the fetal back
Body Stalk Abnormality	Large abdominal wall defect, kyphoscoliosis
Omphalocele	Bowel herniation beyond 12 weeks gestation
Gastrochesis	Bowel herniation lateral to cord insertion
Cleft Lip	Cleft Lip
Cardiac Abnormalities	Various, abnormal ductus venosus flow
Prune Belly Syndrome	Megacystitis
Diaphragmatic Hernia	Mediastinal shift, stomach visible in chest
Skeletal Abnormalities	Absent long bones, significantly decreased calcification, joint contractures

Table 5**Adverse Pregnancy Outcomes with Low Levels of PAPP-A**

Outcome	PPV <5th%ile *	Screen+Rate	PPV <1st%ile *	Screen+Rate
<u>Pregnancy Loss <20–24 Weeks</u>				
Ong (n=5297) ⁸¹	1.4%	5.3%		
Goetzl (n=7,932) ⁸²	1.4%	5.1%	2.7%	1.05%
Dugoff(n=34,271) ⁸³	2.2%	5.1%	4.5%	1.03%
Brameld (n=22125) ⁸⁴	0.6%	4.1%		
Scott (n=44535) ⁸⁵			8.0%	0.44%
<u>Stillbirth (>20–24)</u>				
Smith (n=7934) ⁸⁷	2.0%	5.0%		
Brameld (n=22125) ⁸⁴	1.3%	4.1%		
Smith (n=8839) ⁸⁸	0.9%	5.2%		
Dugoff(n=34,271) ⁸³	0.6%	.58%	0.84%	1.06%
Scott (n=44535) ⁸⁵			2.0%	0.44%
<u>Birth weight <5th%ile</u>				
Ong (n=5297) ⁸¹	7.9%	5.3%		
Smith (n=8839) ⁸⁸	10.0%	5.2%		
Spencer (n=46262) ⁸⁹	9.7–12.2% *	4–5.0% *		
Dugoff(n=34,271) ⁸³	9.5%	4.8%	15.8%	0.9%
<u>Birth weight<10%ile</u>				
Krantz (n=8012) ⁹⁰			24.1%	0.8%
Dugoff(n=34,271) ⁸³			26.3%	0.8%
Scott (n=44535) ⁸⁵			25.0%	0.44%
<u>Preterm Birth<32 weeks</u>				
Brameld (n=22125) ⁸⁴	4.3%	4.1%		
Smith (n=8839) ⁸⁸	2.6%	5.2%		
Dugoff(n=34,271) ⁸³	1.4%	5.1%	2.4%	1.0%
Scott (n=44535) ⁸⁵			10.0%	0.44%
<u>Preterm Birth <34 weeks</u>				
Ong (n=5297) ⁸³	2.5%	5.3%		
Krantz (n=8012) ⁹⁰	2.5%	4.6%	2.8%	0.9%
Spencer (n=54722) ⁹⁵	2.2–2.8% *	4–5.0% *		
<u>Preeclampsia</u>				
Ong (n=5297) ⁸¹	5.4%	5.3%		
Brameld (n=22125) ⁸⁴	7.9%	4.2%		
Smith (n=8839) ⁸⁸	7.6%	5.2%		

Outcome	PPV <5th%ile*	Screen+Rate	PPV <1st%ile*	Screen+Rate
Dugoff(n=34,271) ⁸³	3.5%	5.2%	4.2%	1.05%

PAPP-A 5th%ile cutoffs where reported: 0.4 MOM^{84,87}, 0.45 MOM^{82,90}; 0.42 MOM^{83, 89}

PAPP-A 1st%ile cutoffs where reported: 0.29 MOM^{82,90}, 0.28 MOM⁸³

MOM of 0.2 reported as approximation of PAPP-A at 1st%ile⁸⁵

* Screen positive rates were not reported in this study; we estimated a screen positive rate of 4 to 5.0% and then calculated a range of possible PPV as reported.