LOW PAPP-A, OR RAISED NUCHAL TRANSLUCENCY, WITH NORMAL CHROMOSOMES: MANAGEMENT OF

AIMS

1. To provide information on potential adverse outcomes associated with these abnormal results.
2. To appropriately refer women with abnormal results for appropriate antenatal management.
3. To implement adequate antenatal surveillance to prompt early identification and management of potential adverse outcomes.
4. To ultimately reduce maternal and fetal morbidity and mortality, where possible.

KEY WORDS
Low PAPP-A in pregnancy, Raised Nuchal Translucency, Plasma protein-A, first trimester screening,

BACKGROUND INFORMATION
Abnormalities in maternal analyte levels and fetal measurements obtained during first trimester screening can be a marker not only for certain chromosomal disorders and anomalies in the foetus, but for specific pregnancy complications. In particular, low maternal serum pregnancy associated plasma protein-A (PAPP-A), at 11-13 weeks’ gestation is associated with stillbirth, infant death, intrauterine growth restriction (IUGR), preterm birth and pre-eclampsia in chromosomally normal fetuses, whilst a raised nuchal translucency is associated with specific structural abnormalities and genetic syndromes.

PAPP-A
A low PAPP-A is defined as a maternal serum PAPP-A value <0.4MoM, with increased frequency of adverse obstetrical outcomes noted below this level.

PAPP-A is a large glycoprotein produced by the placenta and decidua thought to have several functions, including prevention of recognition of the fetus by the maternal immune system, matrix mineralization and angiogenesis. A low PAPP-A is therefore descriptive of poor early placentation resulting in complications such as foetal growth restriction, fetal demise, preterm birth and pre-eclampsia in the third trimester.
A low PAPP-A level is poorly sensitive, as although these associations exist at the lower end of the PAPP-A distribution, the majority of patients with these adverse outcomes do not have a low PAPP-A. In addition, it has a low positive predictive value as few patients with a low PAPP-A actually have an adverse outcome\(^3\). However, the likelihood of an adverse outcome does increase as the PAPP-A level decreases, with extremely low levels of PAPP-A having very high positive predictive value, as follows:

\(<0.45\) MoM \((5^{th}\) percentile\)  
- 1 to 4% risk of pregnancy loss before 20 weeks  
- increased risk of intrauterine growth restriction, positive predictive value 14% \((\text{OR} 2.7, 95\% \text{ CI} 1.9-3.9)\)  
- increased risk of preterm delivery before 34 weeks \((\text{OR} 2.3, 95\% \text{ CI} 1.1-4.7)\)

\(<0.29\) MoM \((1^{st}\) percentile\)  
- significantly increased risk of intrauterine growth restriction, with positive predictive values of 24\% \(^4\) \((\text{OR} 5.4, 95\% \text{ CI} 2.8-10.3)\) \(^5\)

Studies have shown that in combination with a low PAPP-A level, second trimester monitoring of fetal growth, placental size and Doppler indices can help to identify women at high risk of adverse obstetric outcomes \(^1\), \(^2\), \(^5\), \(^6\), \(^7\), and improve accuracy. In addition, a normal ultrasound examination does not rule out an adverse pregnancy outcome \(^6\).

There is no known relationship between high PAPP-A levels and adverse outcome \(^3\).

**KEY POINTS**

All women should be offered first trimester screening between 11 and 14 weeks, including measurement of PAPP-A level, with adequate pre-test counselling.

1. Should a woman return a low PAPP-A result \((<0.4\text{MoM})\), a referral should be made to a specialist O&G/ or specialist O&G service by 20 weeks gestation with assessment regarding the need for closer maternal and fetal surveillance.
2. Routine anatomy scan with Doppler assessment at 18 – 20 weeks.
4. Assessment of BP and urinalysis for presence of proteinuria at each antenatal visit.

**NUCHAL TRANSLUCENCY**

Raised nuchal translucency between 11 and 14 weeks’ gestation is a strong marker for adverse pregnancy outcome, and in the chromosomally normal fetus is associated with miscarriage, intrauterine death, and numerous other structural (especially cardiac) defects. Fetuses with NT measurement \(\geq 95^{th}\) centile \((\geq 3.5\text{mm})\) are at increased risk, with this risk rising exponentially as the measurement increases \(^8\), \(^9\).

The majority of structural anomalies are amenable to ultrasound detection, and as such detailed anatomical ultrasound examination and echocardiography is recommended \(^8\), should the nuchal translucency be elevated. The majority of babies who achieve a normal scan will have an uneventful outcome with no increased risk for developmental delay or other defects when compared to the general population \(^8\).
KEY POINTS

1. All women should be offered first trimester screening between 11 and 14 weeks, including measurement of nuchal translucency, with adequate pre-test counselling.
2. CVS/amniocentesis as appropriate.
3. All fetuses with NT measurement $\geq 3.5\text{mm}$ or $\geq 95^{th}$ centile should be referred for tertiary level detailed anatomy scan by an experienced operator to assess presence or absence of any fetal anomaly, including echocardiography. This should be done at approximately 19 weeks gestation to allow for early detection, time for additional investigations and, where appropriate, discussion and arrangement of termination of pregnancy.
4. Any woman returning an abnormal anatomy scan must be referred for MFM review.
5. Normal scan: routine care – no further follow up necessary.

REFERENCES