OBSTETRICS AND GYNAECOLOGY
CLINICAL PRACTICE GUIDELINE

Low PAPP-A or raised nuchal translucency with normal chromosomes

Scope (Staff):	WNHS Obstetrics and Gynaecology Directorate staff
Scope (Area):	Obstetrics and Gynaecology Directorate clinical areas at KEMH and OPH

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Aims

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

Key points

1. All women should be offered first trimester aneuploidy screening with adequate pre-test and post-test counselling. Options include no screening, the combined first trimester screen, and cell-free DNA screening (non-invasive prenatal testing).
2. Women who have a low PAPP-A on first trimester screening should be counselled by the medical practitioner ordering the test about the possible risk of complications of pregnancy associated with low PAPP-A, although emphasis should be centred around screening for maternal risk factors.
3. All fetuses with NT measurement ≥3.5mm should be referred for Maternal Fetal Medicine (MFM) review due to the association of NT thickening with aneuploidy, subchromosomal copy number variation, and structural anomalies.
4. Women with abnormalities detected at the anatomy scan must be referred for MFM review.

5. A low PAPP-A (<0.4 MoM) is associated with placental-mediated pregnancy complications and should be taken into account when determining optimal timing of birth.

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 fetus, 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, fetal growth restriction (FGR), preterm birth and pre-eclampsia in chromosomally normal fetuses, whilst a raised nuchal translucency is associated with specific structural abnormalities and genetic syndromes[2].

PAPP-A

A low PAPP-A is defined as a maternal serum PAPP-A value <0.4MoM (5th percentile) in the first trimester, with increased frequency of adverse obstetrical outcomes noted below this level[3].

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 mineralisation and angiogenesis. A low PAPP-A is therefore descriptive of poor early placentation resulting in complications such as fetal growth restriction, fetal demise, preterm birth and pre-eclampsia in the third trimester.

Although current evidence does suggest an association between a low PAPP-A level and poor placentation, the performance characteristics of PAPP-A as a stand-alone screening test suggest that it is insufficient in the prediction of adverse perinatal outcomes on its own. Nonetheless, the likelihood of an adverse outcome does increase as the PAPP-A level decreases, with extremely low levels of PAPP-A having high positive predictive value,[5] as follows:

- <0.4 MoM (5th percentile)
  - 1 to 4% risk of pregnancy loss before 20 weeks
  - increased risk of intrauterine growth restriction, positive predictive value 14% (OR 2.7, 95% CI 1.9-3.9)
  - increased risk of preterm delivery before 34 weeks (OR 2.3, 95% CI 1.1-4.7)
- <0.2 MOM (1st percentile)
  - significantly increased risk of intrauterine growth restriction, with positive predictive values of 24% (OR 5.4, 95% CI 2.8-10.3)[6]

The clinical meaning of low PAPP-A detected, in the context of a low probability fetal aneuploidy screen, remains under debate, and there is no strong evidence to justify

ongoing ultrasound surveillance. Emphasis on screening for adverse perinatal outcomes should be on women with **risk factors** that might contribute to placental damage:

- Women with pre-existing risk factors for placental insufficiency, such as chronic renal disease, autoimmune disease, pre-existing hypertension, advanced maternal age (>40), pre-existing diabetes and high BMI.
- Other risk factors including previous obstetric history that may increase the risk of placental insufficiency, previous IUGR, previous mid-trimester loss due to APH, abruption, previous delivery prior to 34 weeks due to PET or IUGR.

PAPP-A can be measured in the first trimester as part of a formal screening test for early-onset preeclampsia. This test also incorporates maternal history, blood pressure, and uterine artery doppler velocimetry. This test is not currently recommended by RANZCOG but it is actively being considered.

There is no known relationship between high PAPP-A levels and adverse outcome.[7]

Ultrasounds

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 ≥95th centile (≥3.5mm) are at increased risk, with this risk rising exponentially as the measurement increases[1].

The majority of structural anomalies are amenable to ultrasound detection, and as such detailed anatomical ultrasound examination is recommended[1], 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[1].

Abnormal growth and normal dopplers on mid trimester scan

- These women are at increased risk of early onset FGR and fetal demise. They should be managed in conjunction with the MFM department.

Third trimester

Low PAPP-A is a risk factor for third trimester fetal growth restriction. As clinical examination is poorly sensitive in detecting growth restriction, third trimester ultrasound (around 34 weeks) should be offered to women with PAPP-A <0.4MoM.

References

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Related WNHS policies, procedures and guidelines

WNHS Obstetrics and Gynaecology Guideline: Small for Gestational Age (SGA) & Intrauterine Growth Restriction (IUGR): Management of

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Version history

Version number	Date	Summary
1	Feb 2012	First version. Titled 'Management of Women with a Low PAPP-A or Raised Nuchal Translucency, with Normal Chromosomes' (B1.12).
2	Aug 2015	• All women should be offered first trimester screening between 9 and 14 weeks. • Women who have a low PAPP-A on first trimester screening should be counselled by the medical practitioner ordering the test about the risk of complications of pregnancy associated with low PAPP-A. • Abnormal growth and normal dopplers on mid trimester scan: These women are at increased risk of early onset IUGR and fetal demise. They should be managed in conjunction with the MFM department.
3	Nov 2018	• Low threshold for IOL at 40 weeks, in context of PAPP-A < 5th centile • Low PAPP-A defined as <0.4MoM. • No strong evidence to justify ongoing ultrasound surveillance with low PAPP-A in the context of a low probability fetal aneuploidy screen. Screen women with risk factors that may contribute to placental damage.
4	Nov 2022	• Aneuploidy screening options include no screening, the combined first trimester screen, and cell-free DNA screening (non-invasive prenatal testing). • All fetuses with NT ≥3.5mm should be referred for MFM review due to association of NT thickening with aneuploidy, subchromosomal copy number variation, and structural anomalies. • Low PAPP-A (<0.4 MoM) is associated with placental-mediated pregnancy complications and should be considered when determining optimal timing of birth. • PAPP-A can be measured in the first trimester as part of a formal screening test for early-onset preeclampsia. • Third trimester ultrasound (around 34 weeks) should be offered to women with PAPP-A <0.4MoM.

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