CLINICAL PRACTICE GUIDELINE

Low PAPP-A or raised nuchal translucency with normal chromosomes

This document should be read in conjunction with this Disclaimer

Purpose

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

Key points

1. All women should be offered combined first trimester screening between 9 and 14 weeks, with adequate pre-test and post-test counselling.
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 or ≥95th 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 pregnancy1.
4. Any woman returning an abnormal anatomy scan must be referred for MFM review.
5. Normal scan: routine care – no further follow up necessary.
6. Low threshold for IOL at 40 weeks, in the context of PAPP-A < 5th centile.

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, intrauterine growth restriction (IUGR), preterm birth and pre-eclampsia in chromosomally normal foetuses, 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) on first trimester screen, 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 mineralization 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, there is no strong evidence to suggest an association between low PAPP-A levels and adverse perinatal outcomes[4]. Furthermore, the performance characteristic of PAPP-A alone, is insufficient in the prediction of adverse perinatal outcomes. Nonetheless, 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:

<0.4 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)[5]

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.

There is no known relationship between high PAPP-A levels and adverse outcome[6].

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 Maternal Fetal Medicine department.

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 and echocardiography 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].

References

1. Bilardo CM, Timmerman E, Pajkrt E, van Maarle M. Increased nuchal translucency in euploid fetuses - what should we be telling the parents? **Drenatal Diagnosis**. 2010;30(2):93-102.
2. Proctor LK, Toal M, Keating S, Chitayat D, Okun N, Windrim RC, et al. Placental size and the prediction of severe early-onset intrauterine growth restriction in women with low pregnancy-associated plasma protein-A. **Ultrasounds in Obstetrics & Gynecology,** . 2009;34(3):274-82.
3. Gagnon A, Wilson RD, Audibert F, Allen VM, Blight C, Brock JA, et al. Obstetrical complications assoicated with abnormal maternal serum marker analytes. **Journal of Obstetrics and Gynaecology Canada**. 2008;30(10):918-49.
4. DynaMed Plus [Internet]. Measurement of pregnancy associated plasma protein A concentration. 2018. Available from: http://www.dynamed.com.kelibresources.health.wa.gov.au/topics/dmp~AN~T907057/Measurement-of-pregnancy-associated-plasma-protein-A-concentration.
5. Spencer K, Cowans NJ, Chefetz I, Tal J, Meiri H. First-trimester maternal serum PP-13, PAPP-A and second-trimester uterine artery Doppler pulsatility index as markers of pre-eclampsia. **Ultrasounds in Obstetrics & Gynecology**. 2007;29(2):128-34.
6. Jacob A, Canick JA, Messerlian GM, Farina A, Lockwood CJ, Wilkins-Haug L, et al. Pregnancy outcomes predicted by serum markers assayed in Down syndrome screening. **Up To Date**. 2010 (June).

Related WNHS policies, procedures and guidelines

Useful resources (including related forms)

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