Low PAPP-A: what are the clinical implications?

Abstract

Ultrasound and pulsed Doppler can assist in confirming impaired placentation looking at fetal biometry and umbilical artery Dopplers. The authors recommend confirmation of fetal wellbeing at 28–30 weeks with a PAPP-A level below the first centile.

Keywords: maternal serum, PAPP-A.

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Introduction

Recent evidence has shown that low levels of Pregnancy-associated plasma protein A (PAPP-A) at the first trimester screening test can be an independent risk factor for certain adverse pregnancy outcomes such as intrauterine fetal death after 24 weeks, spontaneous fetal loss before 24 weeks, preterm birth, gestational hypertension, preeclampsia and low birth weight.[1–5]

It remains unclear however, if low serum PAPP-A levels should be used as a screening tool for adverse outcomes, and if so, what cut-off values should be used? Data suggest the positive predictive values for the individual outcomes and sensitivity is low, reducing the value as a screening test, despite reports of statistically significant associations.

In this case review, two women presented to our maternity unit in the same week with very similar first trimester serum PAPP-A levels (<1st percentile) but had entirely different clinical outcomes.

The first woman had an uncomplicated but anxious antenatal course, satisfactory growth ultrasounds at 30 and 38 weeks gestation and a healthy birth after an induction of labour (patient request) at 39 weeks. The second patient presented with a massive placental abruption at 34 weeks, requiring an emergency caesarean section. The baby was stillborn with severe intrauterine growth restriction. This woman was a smoker, poorly compliant, with a previous history of IUGR and preeclampsia.

PAPP-A is a large zinc glycoprotein produced by placental trophoblasts, particularly the extravillous cytotrophoblasts.[6] It belongs to the alpha-macroglobulin plasma protein group and is a metalloproteinase (enzyme that specifically cleaves proteins). It can connect to a range of cytokines and modulates their activity.[6] Haaning, *et al.* discovered that full-length pre PAPP-A contains over 1500 amino acids.[6]

PAPP-A molecules tend to cleave insulin-like growth factor (IGF) binding proteins 4 and 5.[6] This means it can help release IGF from these binding proteins enabling it to interact with its cell receptor.[2] It is suggested that IGF has a critical role in trophoblast invasion, affecting early development and vascularisation of the placenta and the placental bed.[7,8]

Maternal serum PAPP-A levels are first detected around 28 days post implantation. This is often followed by a rapid rise (levels doubling every 3–4 days) and then a gradual increase until term.[9]

PAPP-A is found in the ovarian follicles, luteal cells and fallopian tubes of non-pregnant women. In men it is present in seminal fluid. PAPP-A is present in unstable atherosclerotic plaques circulating levels are elevated in acute coronary syndromes.[10]

Serum PAPP-A levels are significantly reduced in pregnancies conceived with assisted reproductive techniques (ART). A recent study by Amor, *et al.* reported average PAPP-A multiples of the median (MoM) of 0.83 in these women vs. 1.00 MoM for sponateous conceptions. The authors suggested that the low PAPP-A levels could be because of a less than optimal early implantation process in some forms of ART.[11]

Westergaard, *et al.* reported complete absence of PAPP-A in both maternal blood and placental tissue from a pregnancy with Cornelia de Lange syndrome.[12] Serum PAPP-A has been used in combination with free beta human chorionic gonadotropin (B-hCG) and nuchal translucency as an effective first-trimester screening marker for pregnancies including trisomies 13, 18, and 21. Nicolaides reported that the combination of first trimester serum biochemical analyses with nuchal translucency measurements detected about 90% of fetuses with Down syndrome with a false positive rate of 5%. It can be further improved by the inclusion of other ultrasound makers (like the presence nasal bone) and Doppler parameters. This, in combination with early biochemical testing around 9–10 weeks can improve detection rates of Trisomy 21 up to 94%.[13,14] The well known

PAPP – A MoM	Percentile
0.45-2.07	5th – 95th
< 0.29	< 1st
< 0.44	< 5th
> 2.08	> 95th
> 3.92	> 99th

Table 1: Serum PAPP-A MoM levels with population percentile.

Case 1	Case 2
38 yo PAPP-A 0.27 MoM G5P3 (2.4, 2.8, 2.4 kg) BMI 28 Previous preeclampsia, Gestational Diabetes Mellitus Smoker Poor antenatal compliance 28 wk ultrasound – no abnormality detected EFW on 15th centile. Did not attend subsequent ultrasound as requested Antepartum Haemorrhage at 34/40, code 1 LSCS Stillborn male 1390 g Postnatal thrombophilia screen -negative Desires further fertility	39 yo PAPP-A 0.26 MoM G2P1 (3.1kg) BMI 30 Uncomplicated pregnancy Fetal anomaly scan – no abnormality detected 30 & 38wk USS satisfactory growth, no abnormality detected 39+1 wks Favourable cervix Induction of labour for low PAPP-A (Patient anxiety/ request) 6 hr labour, live female infant, birth weight 3100 g Newborn Apgars 9[1] & 9[5]

Table 2: Clinical details. The two sides of the clinical coin increased anxiety during an otherwise low risk pregnancy versus an adverse outcome resulting in stillbirth.

aneuploidies have each a specific biochemical pattern.

Data from the First and Second Trimester Evaluation of Risk for Fetal Aneuploidy (FASTER) trial[11] reported an association between low PAPP-A levels (≤ 5th percentile) and significantly higher rates of spontaneous fetal loss ≤ 24 weeks, preeclampsia, low birth weight and preterm birth. A multicentre, prospective cohort study of 7934 women found that most of the increase in risk of stillbirth was attributed to placental dysfunction associated with placental abruption or intrauterine growth restriction.[3] The contrast in outcomes between the two women in our case study with similar PAPP-A levels illustrates how difficult it can be to predict adverse outcome because of a low PAPP-A alone. The important difference between the two pregnancies are the vastly different histories (smoking, previous IUGR, previous pre-eclampsia, poor socio-economic status) and should therefore always be taken into account when formalising a management plan. Consideration should be given to the possible need for other tests (e.g. thrombophilia sceeen) or interventions (e.g. low does aspirin).

What level of PAPP-A should be used to screen at risk women? PAPP-A levels of less than the fifth percentile were shown in some studies to have a high specificity but low positive predictive value for adverse pregnancy outcomes.[15,16] The First Trimester Maternal Serum Biochemistry and Ultrasound Fetal Nuchal Translucency Study (BUN) found PAPP-A levels less than the 1st percentile had a high positive predictive value for IUGR.[16] Therefore, it would be more appropriate to use a lower PAPP-A level for a more cost effective screening program for adverse pregnancy outcomes.[17–19]

Conclusion

Biochemical markers like PAPP-A can be a useful tool to screen for impaired placentation associated with fetal growth restriction, fetal death in-utero, pre-eclampsia and abruption placentae. Ultrasound and pulsed Doppler are diagnostic modalities that can assist in confirming impaired placentation looking at fetal biometry and umbilical artery Dopplers. We recommend confirmation of fetal wellbeing at 28–30 weeks with a serum PAPP-A level below the 1st centile.

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