



## Low PAPP-A level

First trimester screening for aneuploidy (abnormal chromosomes) can have some benefits for detecting potential complications of pregnancy other than certain chromosomal abnormalities. For example, a widened nuchal translucency (NT) has also been correlated with risk for having a baby with a cardiovascular malformation, even when that fetus is confirmed to be chromosomally normal. In a similar vein, an abnormal Doppler waveform in the first trimester, showing reverse end-diastolic velocity in the fetal ductus venosus, presumably secondary to tricuspid regurgitation, has also been correlated with both cardiovascular malformations and aneuploidy.

There is an association between 'abnormal' levels of the maternal serum markers, PAPP-A and hCG, used in the screening assessment, and pregnancy outcome. The 'composite' first trimester screening result can be reassuring with regard to risk for a chromosomally abnormal baby, but one of the maternal serum markers, PAPP-A (pregnancy-associated plasma protein-A), is "low" at 0.25 MoM (multiples of the median), there can be other fetal issues. First trimester screening does not help to detect ALL chromosomal abnormalities – it is most reliable for trisomies 21 (Down syndrome), 18, and 13. Secondly, whether the baby is chromosomally normal or not, a 'reassuring' screen does not rule out the possibility of other fetal abnormalities – physical or developmental or abnormalities of placentation. In other words, a 'normal' screen does not ensure a normal baby or pregnancy outcome, although it does increase the probability of both!

PAPP-A is produced by the placental trophoblasts, especially, by the extravillous cytotrophoblasts. It is a 'protease' for insulin-like growth factor (IGF) binding proteins 4 and 5. This means it has the ability to help release IGF from these binding proteins so that it is free to interact with its cell receptor. IGF is thought to play an important role in trophoblast invasion and hence the early development and vascularization of the placenta and the placental bed. These early events in the formation of the placenta are critical to pregnancy outcome and, when abnormal, are associated with miscarriage, intrauterine growth restriction (IUGR) of the baby, pregnancy-induced hypertensive disorders, fetal death in utero, premature delivery, and even cesarean section for indications of fetal or maternal compromise. It has been postulated that low levels of PAPP-A, resulting in less release of IGF, could be a pathway by which placentation abnormalities occur that culminate in these poor pregnancy outcomes.

Recent studies would support this association between low PAPP-A levels in first trimester and risk for poor pregnancy outcome. The odds ratios for fetal loss before 24 weeks, at or above 24 weeks, and at any gestational age was about a three-fold risk of losing a baby with low PAPP-A levels. There is an association between low PAPP-A and low for gestational age birth weight babies as well. A linear relationship between the severity of growth restriction and the decrease in PAPP-A levels – in other words, the lower the PAPP-A, the smaller the babies at any gestational age.

Low PAPP-A levels are not only associated with certain fetal chromosomal abnormalities, but also with an increased risk for a poor pregnancy outcome. **BUT**, despite this association, the positive predictive value of a low PAPP-A for one of these outcomes is still relatively **low**. That means the chance of one of these events is higher with a low PAPP-A, but **you shouldn't panic** at the outset that something bad is going to happen.

Additional surveillance for this situation includes:

- 1) A screen for MSAFP at 16 weeks
- 2) a 'targeted' ultrasound to carefully evaluate the baby's anatomy and growth;
- 3) Doppler flow velocimetry of the uterine arteries at the time of the 'targeted' ultrasound to look for increased resistance to maternal-placental perfusion (indicative of an abnormality of placentation);
- 4) Serial assessment of fetal growth, and;
- 5) Doppler flow studies on the fetal umbilical cord and middle cerebral arteries to look for evidence of increased resistance to fetal-placental perfusion (again, indicative of abnormal placental vascularization) and fetal blood flow redistribution (suggestive of preservation of brain at the expense of perfusion of less 'essential' organs), respectively.

None of these will accurately predict outcome, but if they are abnormal, can justify more intensive antepartum fetal surveillance so that chances of delivering a healthy baby, regardless of the gestational age, are improved.