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**Title:**

# PAPP-A, free β-hCG and early fetal growth in relation to adverse pregnancy outcome and neonatal disease

## English summary

Adverse pregnancy outcomes such as preterm delivery and fetal growth restriction are major determinants of perinatal mortality and morbidity and much routine antenatal care involves identifying pregnant women at high risk of these outcomes. However, the conditions often are not detected until the pathological processes have become too advanced to facilitate optimal management. As we have become aware that complications of late pregnancy may be established in the first half of pregnancy, it seems reasonable to focus on this period in an attempt to identify women at increased risk of poor outcomes. Early identification of high-risk pregnancies would make it possible to target appropriate surveillance, intervention and possibly treatment at these high-risk pregnancies, hopefully before irreversible damage occurs, thereby improving the outcome. This thesis focuses on the placenta-derived serum markers, PAPP-A and free β-hCG, and ultrasound measures of fetal growth in the first half of pregnancy. These biomarkers are available in women participating in the prenatal screening program offered to all pregnant women in Denmark, and it would be favorable if they could be used in early identification of pregnancies at increased risk of subsequent poor outcomes.

The main purpose of this thesis was to investigate if adverse pregnancy outcome and neonatal disease are associated with first-trimester maternal levels of PAPP-A and free β-hCG, and early fetal growth, evaluated as the ratio between the observed versus the expected increase in fetal size, measured by ultrasound in gestational weeks 12 and 20.

We investigated these associations using data on the serum markers and the ultrasound measures from the Astraia Database; data regarding pregnancy and delivery including any complications from the Aarhus Birth Cohort, and data about the newborn as well as information about admission to neonatal intensive care unit (NICU) and diseases during the hospital stay from The Neobase.

In the first study (N = 8,347), we found first-trimester low levels of PAPP-A to be significantly associated with slow early fetal growth. This finding is consistent with the known biological function of PAPP-A, as PAPP-A is involved in the control of the insulin-like growth factor (IGF) system, and the IGF plays a role in placentation and in placental growth and function. In the second study (N = 9,450), low levels of PAPP-A and free β-hCG, and fast early fetal growth were found to be associated with an increased risk of preterm delivery, and the combination of slow early fetal growth and low PAPP-A revealed a further increased risk. The findings suggest two different mechanisms leading to preterm delivery, as the association of fast early fetal growth may have a mechanical explanation, whereas the combination of low PAPP-A and slow early fetal growth may indicate that a suboptimal intrauterine environment leads to both growth restriction and preterm delivery. The third study (N = 9,450) showed that slow early fetal growth and low levels of PAPP-A and free β-hCG were associated with an increased risk of SGA, and the combination of low PAPP-A and slow early fetal growth further increased this risk. These results suggest that fetal growth restriction may be established early in pregnancy. The restriction may reflect either a placentation defect because the intrauterine environment is affected by the same factors both early and later in pregnancy, or a suboptimal first-trimester environment which permanently affects the fetus by restricting its growth potential. Study four (N = 9,450) demonstrated that low levels of PAPP-A and free β-hCG were associated with an increased risk of neonatal admission to the NICU, irrespective of what could be expected as a consequence of preterm delivery or SGA. A possible explanation could be that these serum markers are actually better indicators of the newborn deviating from its genetic growth potential than is a low birth weight. Furthermore, PAPP-A was associated with neonatal hypoglycaemia, icterus and a low Apgar score, and low free β-hCG with hypoglycaemia.

The overall conclusion of this thesis is that the first-trimester serum markers, PAPP-A and free β-hCG, and early fetal growth measured by ultrasound in week 12 and 20 are early predictors of complications of late pregnancy and diseases in the neonatal period. The biomarkers studied in this thesis are only a few of many biomarkers identified as early risk factors of poor pregnancy outcomes, but, unfortunately, none of these markers have separately proved useful as screening tests in early pregnancy. However, combining different biomarkers may be clinically expedient, and the challenge is in the future to further research the optimum choice of biomarkers and strategies to obtain the best predictive model. In addition, to determine which approaches are effective in improving maternal and neonatal outcome when screening in early pregnancy, future studies should explore diverse management strategies, such as increased surveillance, early intervention or treatment for high-risk pregnancies.