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Prenatal screening in twin pregnancies

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Summary

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Prenatal screening intends to identify women at risk for carrying a fetus with a certain anomaly. Prenatal testing for trisomy 21 (Down syndrome=DS) has become part of routine obstetric care in the Netherlands. The current test of choice for singleton pregnancies is the first trimester combined test. This combined test estimates the individual risk of a woman for a trisomy 21 affected pregnancy based on maternal age, ultrasound measurement of the fetal nuchal translucency (NT) and the maternal serum biochemical markers, free beta human chorionic gonadotropin (free β -hCG) and pregnancy associated plasma protein-A (PAPP-A).

Fetal anomaly screening in twin pregnancies is more complex than in singletons. Fetuses can either be discordant (only one affected) or concordant (both affected/unaffected) for a certain anomaly. In DS screening both 'fetus specific' markers, i.e. NT measurements, and 'pregnancy specific', i.e. maternal serum markers, have to be taken into consideration for twin pregnancies. Moreover, twin pregnancies are at increased risk for adverse pregnancy outcome compared with singletons.

In this thesis we evaluated the screening options for aneuploidy and structural anomalies in twin pregnancies, including new screening markers and screening for adverse pregnancy outcome. Maternal serum and fetal ultrasound markers, both old and new in the first trimester of pregnancy are evaluated.

Chapter 1 contains a brief general introduction on twin pregnancies and prenatal screening. Further it describes the outline and aim of this thesis.

In **Chapter 2** we assessed whether first trimester maternal serum markers in twin pregnancies currently used for DS screening should be corrected for twin chorionicity. The data of 200 euploid twins were used for setting up reference values for free β -hCG and PAPP-A. Significantly lower first trimester free β -hCG and PAPP-A levels in monochorionic twins ($n=37$, 1.53 and 1.59 MoM) compared with dichorionic twins ($n=163$, 2.11 and 2.40 MoM) were found. This study strengthened the need to make a distinction between mono- and dichorionic twins for DS screening, since biochemical markers are significantly lower in monochorionic.

A Disintegrin And Metalloprotease 12s (ADAM12s) is suggested to be a potential first trimester serum marker for fetal trisomy and adverse pregnancy outcome in singletons.

In **Chapter 3** the processing effects and storage conditions on ADAM12s for usage in the routine clinical chemistry laboratory are evaluated. We demonstrated that ADAM12s is stable when stored at -20°C for at least 25 days and at 4°C for at least 4 days. The ADAM12s concentration is not influenced by multiple freeze/thaw cycles and specimens can be stored for 96 hours at 4°C prior to centrifugation. This stability allows a widely spread application of ADAM12s measurement in obstetric practice.

In **Chapters 4, 5** and **6** ADAM12s was evaluated as screening marker for fetal trisomy and adverse pregnancy outcome in both singleton and twin pregnancies.

In **Chapter 4** the screening performance of ADAM12s as marker for fetal trisomy was evaluated in singleton pregnancies. The results of ADAM12s in 218 singleton cases of trisomy 21, in 62 trisomy 18 and in 29 trisomy 13 compared with matched controls are described. The median ADAM12s was 1.00 MoM in controls, and in the trisomy 21 cases at 8, 9, 10, 11, 12, 13 weeks of gestation it was 0.45 ($n=3$), 0.73 ($n=22$), 0.74 ($n=53$), 0.85 ($n=37$), 0.92 ($n=7$), 1.06 ($n=32$) MoM, respectively. The median for trisomy 18 was 0.85 MoM and for trisomy 13 0.63 MoM. The ADAM12s MoM values were reduced in early first trimester for all trisomies. However, the screening performance for Down syndrome is not greatly improved by adding ADAM12s. ADAM12s could be an additional biochemical marker for first trimester screening for trisomies other than Down syndrome.

In **Chapter 5** maternal serum ADAM12s and Placental Protein 13 (PP13) were studied as screening markers for adverse pregnancy outcome in singletons pregnancies. In a retrospective case control study 17 cases of preeclampsia (PE), 30 cases of gestational hypertension (GH) and 8 cases of small for gestational age (SGA) fetus matched with 165 control cases were included. Median MoM values for ADAM12s were 0.90, 0.77 and 0.88 for PE, GH and SGA cases respectively. Median MoM values for PP13 were 0.77, 0.95 and 0.89 respectively. ROC analysis yielded areas under the curve for ADAM12s and PP13 of 0.63 and 0.59 for PE, 0.68 and 0.57 for GH and 0.59 and 0.62 for SGA, respectively. Combined ADAM12 and PP13 did not improve the area under the curve. If specificity was set at 0.80, the corresponding sensitivity of ADAM12s was 52% for GH. Decreased first trimester levels of ADAM12s may be useful in early prediction of GH, although the predictive value was limited. Decreased levels of PP13 were not significantly correlated with adverse pregnancy outcome. Combining ADAM12s and PP13 in this study did not improve screening performance.

In **Chapter 6** ADAM12s was determined in first trimester serum of uncomplicated and complicated twins. Maternal serum of 215 twin pregnancies was compared with a population of singletons. Median ADAM12s MoM in euploid twins is significantly increased (1.61 MoM, $n=209$) compared with singletons, however, not doubled like other first trimester markers such as free β -hCG and PAPP-A. Monochorionic twins have significantly lower median ADAM12s MoM than dichorionic twins, namely 1.36 MoM ($n=4$) versus 1.67 MoM ($n=168$). Statements about the screening performance of ADAM12s in twin trisomy cases are not possible at this stage since too few cases have been studied so far. In twin pregnancies ADAM12s is not a sufficient potential marker for predicting adverse pregnancy outcome. Median ADAM12s MoMs are not significantly different in twins complicated by hypertensive disorders or small for gestational age fetus compared with uncomplicated twins.

Twin pregnancies are at increased risk for adverse pregnancy outcome compared with singletons. In monochorionic twins the risk of adverse outcome is also determined by the existence of Twin-to-Twin Transfusion syndrome (TTTS), complicating approximately 9-15% of all monochorionic twin pregnancies. Timely diagnosis of TTTS is beneficial for treatment options and outcome of the fetuses.

In **Chapter 7** the use of nuchal translucency (NT) discordance as predictor of subsequent Twin-to-Twin Transfusion syndrome (TTTS) in monozygotic twins has been investigated. In 61 monozygotic diamniotic twins NT and crown-rump-length (CRL) discordance was calculated as the percentage of delta NT and CRL (absolute difference NT/CRL fetus 1 and fetus 2 of the largest measurement, and correlated with subsequent development of TTTS. NT discordance of more than 20% in monozygotic diamniotic twins was associated with an increased risk for subsequent development of TTTS, and earlier presentation of symptoms.

114

In **Chapter 8** the use of first trimester trisomy 21 serum markers was described in relationship to subsequent TTTS development in monozygotic (MZ) twins. Serum of 56 MZ twins was evaluated for first trimester free β -hCG and PAPP-A and correlated for outcome. In MZ twins later developing TTTS, we found a trend towards higher values of first trimester free β -hCG and PAPP-A. Larger studies are needed to confirm our data whether assessment of first trimester free β -hCG and PAPP-A will be of diagnostic or prognostic value for individual patients.

In **Chapter 9** the outcome of multiple pregnancies complicated by a single anomalous fetus is described. Ultrasound and outcome data were evaluated for multiples with a single fetus (major/minor) anomalous. In our population 38 twin fetuses demonstrated anomalies, predominantly central nervous system (n=5), skeletal (n=7), urinary tract (n=6) and cord anomalies (n=5) and four cases had multiple congenital anomalies. Median gestational age at delivery was not significantly different for twins without structural anomalies and twins with one anomalous fetus managed expectantly. In this cohort we report on a tendency towards expectant management on request of the pregnant women and their partners of those twins discordant for major (lethal) anomalies. Fetocide was only opted in a small number of cases with severe but non-lethal anomalies in DC twins.

In **Chapter 10** this thesis finally describes a general discussion and perspectives.

In conclusion, prenatal screening in twins is complex. Overall, it is advised to report on a fetus specific risk rather than on a pregnancy specific risk for both mono- and dichorionic twins. In general first trimester screening is advocated above second trimester screening and in any case above screening based on maternal age only. Single NT screening is a sufficient screening program in multiple pregnancies with comparable performance as in singletons. However, first trimester combined testing is reported to reduce false positive rates. For the future, screening programs need to incorporate the between-fetus correlation coefficient for NT measurements. Shifting from single NT measurements towards first trimester combined screening requires implementation of serum chorionicity correction factors. Additionally, other co-variables such as gestational age, conception mode and ethnicity need to be further evaluated in twin pregnancies and adjusted to tailor-made individual risk estimation. Likewise additional first trimester ultrasound markers will need to be evaluated for aneuploidy screening in twin pregnancies, since these markers allow calculating even more specific risk per fetus.

Moreover, we think that calculation of NT discordance should be standardized in monozygotic twins so that predictive values can be calculated in an unselected population. Finally, the current serum screening markers of the first trimester combined test and new serum screening markers need to be further evaluated as predictors of adverse pregnancy outcome in twin pregnancies.

115