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The influence of maternal insulin-dependent diabetes on fetal nuchal translucency thickness and first-trimester maternal serum biochemical markers of aneuploidy

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Objective To evaluate the influence of maternal insulin dependent diabetes mellitus (IDDM) on maternal serum free β-hCG, PAPP-A and fetal nuchal translucency (NT), thickness at 11 to 13^{+6} weeks of gestation in a large cohort of women screened prospectively for chromosomal anomalies.

Methods Information on maternal IDDM status, maternal serum biochemical marker levels and fetal NT were collected from the prenatal screening computer records in two first-trimester screening centres. In total the control group included 33 301 pregnancies of which 16 366 had NT and maternal serum biochemistry results and 16 305 with NT only. The IDDM group included 195 pregnancies of which 79 had NT and maternal serum biochemistry results and 127 with NT only. The median maternal weight corrected free β-hCG and PAPP-A, expressed as multiple of the median (MoM), and fetal NT, expressed as delta values, in the IDDM and non-IDDM groups were compared.

Results There were no significant differences between the IDDM and non-IDDM groups in median maternal weight corrected free β-hCG (IDDM 0.87 MoM, 95% Confidence Interval 0.75 to 1.16 MoM, non-IDDM 1.00 MoM), median maternal weight corrected PAPP-A (IDDM 1.02 MoM, 95% Confidence Interval 0.83 to 1.05 MoM, non-IDDM 1.01 MoM), or mean delta NT (IDDM 0.0358 mm, non-IDDM 0.0002 mm).

Conclusions In pregnancies with maternal IDDM, first-trimester screening for chromosomal defects does not require adjustments for the measured fetal NT. However, more data are required before the possible reduction in maternal serum free β-hCG and the reduction of PAPP-A suggested by the published world series can be considered sufficiently important to take into account in the calculation of risks for chromosomal defects.

KEY WORDS: prenatal screening; trisomy 21; nuchal translucency; free β-human chorionic gonadotrophin; pregnancy associated plasma protein-A

INTRODUCTION

In women with insulin dependent diabetes mellitus (IDDM), the levels of second-trimester maternal serum biochemical markers of trisomy 21 are on the whole reduced, although considerable variation exists in the published literature. This variation is partly due to the fact that in some of the earlier literature correction for maternal weight differences was not applied—IDDM women tend to be around 6 kg heavier than unaffected controls (Sancken and Bartels, 2001). Also it is possible that the extent of the reduction of marker levels is dependent on the adequacy of diabetic control since an inverse relationship has been established between high levels of glycosylated haemoglobin (indicating poor diabetic control) and levels of Alpha fetoprotein (AFP) (Reece *et al*., 1987; Baumgarten and Robinson, 1988; Martin *et al*., 1990). The latest meta analysis of the published literature (taking into account weight correction) still shows a significant reduction of around 8% for AFP and around 6% for unconjugated oestriol, but no significant difference for Total hCG or free β-hCG (Huttly *et al*., 2004).

Screening for aneuploidy is now moving away from the second trimester with a greater focus on the use of fetal nuchal translucency (NT) thickness and the maternal serum biochemical markers free β-hCG and Pregnancy Associated Plasma Protein-A (PAPP-A) between the 11th week and 13 weeks 6 days (Spencer *et al*., 1999). At this time, retrospective and prospective studies have shown that detection rates of 90% for trisomy 21 can be achieved for a 5% false-positive rate and additionally for a further 1% false-positive rate, 90% of cases of other aneuploides can be detected (Spencer *et al*., 2000, 2003; Bindra *et al*., 2002; Spencer and Nicolaides, 2002; Nicolaides *et al*., 2005).

The aim of the present study is to investigate whether in women with IDDM fetal NT and levels of maternal serum PAPP-A and free β-hCG are altered.

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METHODS

In Harold Wood Hospital (Essex), all pregnant women are offered screening for trisomy 21 by a combination of fetal NT thickness and maternal serum free β-hCG and PAPP-A in an One Stop Clinic for Assessment of Risk (OSCAR) (Spencer *et al*., 1999, 2000, 2003a). Free β-hCG and PAPP-A are measured by a KRYPTOR Analyzer—a random access immunoassay analyser, using time-resolved amplified cryptate emission (TRACE) technology, which provides an accurate and highly reproducible result within 30 min. Fetal NT and crown-rump length are measured by standardised techniques (Snijders *et al*., 1998) by sonographers who had completed the certificate of competence in the first-trimester scan issued by the Fetal Medicine Foundation (FMF). Demographic characteristics, ultrasound findings and the results of biochemical testing are entered into a computer database at the time of assessment. Data on pregnancy outcome are obtained from the maternity unit and are also entered into the database. A search was made of the database to identify normal singleton pregnancies that had first-trimester combined screening and additionally those in which the mother had IDDM. In total a series of 16 366 normal non-IDDM pregnancies were identified along with 79 normal pregnancies from mothers who had IDDM.

At King's College Hospital, pregnant women are screened in the first trimester using fetal NT alone by sonographers or obstetricians who have completed the FMF certificate of competence in the first-trimester scan. Demographic characteristics and ultrasound findings are similarly stored in a fetal database along with relevant pregnancy history, maternal history and pregnancy outcome. A search of this database revealed a further 127 cases of IDDM and an additional 16 305 normal pregnancies.

In total the non-IDDM control group included 33 301 pregnancies of which 16 366 had both fetal NT and maternal serum biochemistry results and 16 305 with fetal NT only. The IDDM group included 195 pregnancies of which 79 had fetal NT and maternal serum biochemistry results and 127 with fetal NT only.

Statistical analysis

The database contained the weight corrected median MoM's for the biochemical markers used routinely in risk calculation. The median levels of free β-hCG and PAPP-A for the interval between 73 and 97 gestational days were determined from a previous study (Ong *et al*., 2000) and multiple of the median values (MoM) were calculated for each subject after taking into account maternal weight (Spencer *et al*., 2003b). The median MoM values for each clinical group were calculated. Log_{10} transformed values were compared between the IDDM and non-IDDM control groups using t-test for independent samples with unequal variance.

To take account of gestational variation in NT, we expressed the measured fetal NT as the difference from the normal median NT at the measured crown-rump length (CRL) established in a large multicentre study (Snijders *et al*., 1998). This difference, the Delta NT, has been shown to be a more statistically appropriate way of dealing with NT gestational age variation than the MoM approach (Spencer *et al*., 2003c). Comparison of Delta NT in the IDDM group and the controls was by use of Z tests.

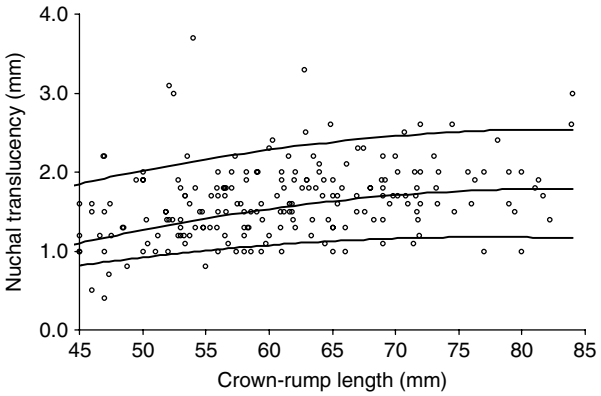

Figure 1—Fetal nuchal translucency thickness in pregnancies with insulin dependent diabetes mellitus (IDDM) plotted on the normal range for fetal crown-rump length (median, 95th centile and 5th centile) derived by Snijders *et al*. (1998)

RESULTS

The median and average maternal weight in the control group was 66.80 and 69.34 Kg, whilst in the IDDM group the median and average weight was 68.60 and 73.15 Kg. The median maternal weight corrected free β-hCG in cases with IDDM was 0.87 (95% confidence interval 0.75–1.16) compared with the 1.00 MoM in the non-IDDM controls. The median maternal weight corrected PAPP-A in cases with IDDM was 1.02 (95% Confidence Interval 0.83–1.05) compared with 1.01 MoM in the non-IDDM controls. When the $\log_{10}$ MoM of the IDDM cases were compared against the control population using unpaired t-tests of unequal variance there was no statistically significant difference (free β-hCG, $p = 0.52$ and PAPP-A, $p = 0.36$). The mean delta NT in the IDDM group was not significantly different from that in the non-IDDM controls (0.0358 mm vs 0.0002 mm, $p = 0.418$; Figure 1) as was the median delta NT (0.0351 mm vs 0.0000 mm).

DISCUSSION

This study has shown that in pregnancies with maternal IDDM, fetal NT thickness and maternal serum free β-hCG and PAPP-A are not significantly different from normal. In contrast, two previous studies including 34 and 79 diabetic pregnancies have reported that the levels of PAPP-A may be reduced by as much as 20% (Pedersen *et al*., 1998; Ong *et al*., 2000) and the levels of free β-hCG may be reduced by 25% (Ong *et al*., 2000). In the combined data from this and the previous studies,

the median MoM for free β-hCG in 114 cases was 0.82, some 18% lower than in an unaffected population and the median MoM for PAPP-A in 193 cases was 0.89, some 11% lower than in an unaffected population.

Our finding that in pregnancies with maternal IDDM the thickness of fetal NT is not altered is compatible with the results of a previous a study of 74 women with IDDM, which reported that there was no significant association between fetal NT thickness and length or diabetes, insulin dosage, glycosylated haemoglobin concentration or level of glycemic control (Bartha *et al*., 2003). In that study, fetal NT was not compared to values in non-IDDM pregnancies.

In conclusion, when screening for chromosomal defects by fetal NT and maternal serum free β-hCG and PAPP-A at 11 to 13^{+6} weeks in pregnancies with maternal IDDM it is not necessary to make adjustments for the measured fetal NT. However with regard to the biochemical markers, more data are required before the possible reduction in free β-hCG, and PAPP-A in IDDM can be considered sufficiently important to take into account the calculation of risks for chromosomal defects.

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