PRENATAL DIAGNOSIS
Prenat Diagn 2000; **20**: 792–794.

The influence of parity and gravidity on first trimester markers of chromosomal abnormality

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We have studied changes in first trimester fetal nuchal translucency (NT) and maternal serum free β-hCG and PAPP-A with gravidity and parity in 3252 singleton pregnancies unaffected by chromosomal abnormality or major pregnancy complications. We have shown that gravidity and parity is associated with a small but progressive decrease in fetal NT and a small but progressive increase in free β-hCG and PAPP-A. None of these small changes with increasing gravidity or parity are statistically significant and hence correction for these variables is not necessary when considering first trimester screening for chromosomal abnormalities. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS: free β-hCG; PAPP-A; nuchal translucency; trisomy 21; prenatal screening; Down syndrome; chromosomal abnormality

INTRODUCTION

In the second trimester of pregnancy both maternal serum total human chorionic gonadotrophin (hCG) and free β-hCG have been shown to decrease with an increasing number of pregnancies (gravidity) or an increasing number of previous births (parity) (Daniel *et al.*, 1994; Spencer, 1995; Haddow *et al.*, 1995; Mooney *et al.*, 1995; Wald and Watt, 1996). The observed effect (after taking into account an increased maternal weight with increasing number of pregnancies) is quite small — less than a 6% difference between primigravid and multigravid women. Correction for such a small change is not considered worthwhile when screening for trisomy 21 in the second trimester.

In the first trimester maternal serum biochemical markers and ultrasound markers are now being used routinely in some centres to screen for chromosomal abnormalities. A combination of maternal serum free β-hCG, pregnancy associated plasma protein-A (PAPP-A) and fetal nuchal translucency thickness (NT) at 10–14 weeks of gestation has been shown to identify 90% of cases of trisomy 21 at a 5% false positive rate (Spencer *et al.*, 1999), and this method can also identify about 90% of other major chromosomal abnormalities (Tul *et al.*, 1999; Spencer *et al.*, 2000a; 2000b; 2000c).

In this study we examine the effect of parity and gravidity on first trimester maternal serum levels of free β-hCG and PAPP-A and on fetal NT in a group of normal pregnancies.

METHODS

All pregnant women attending for maternity care at Harold Wood Hospital are offered screening for chromosomal abnormalities by a combination of fetal NT and maternal serum free β-hCG and PAPP-A in a One Stop Clinic for Assessment of Risks (OSCAR) (Spencer *et al.*, in press). Free β-hCG and PAPP-A are measured by a KRYPTOR analyser (CIS UK, High Wycombe, Bucks, UK) — a random continuous access immunoassay analyser, using time resolved amplified cryptate emission technology (TRACE), which provides results within 20 min of sampling. The performance of this system has been described before (Spencer *et al.*, 1999). Fetal NT is measured using standard ultrasound procedures by sonographers trained and audited by the Fetal Medicine Foundation (Snijders *et al.*, 1998). Demographic data, ultrasound findings and the results of biochemical testing are logged onto a networked fetal database at the time of assessment and from this information patient-specific risks are produced. Outcome follow up of all pregnancies is obtained from maternity and delivery room records.

A search was made of the database to identify all singleton pregnancies which had first trimester screening and for which a normal pregnancy outcome unaffected by chromosomal abnormality, fetal death, pregnancy induced hypertension, fetal growth restriction or structural abnormalities and for which parity, gravidity and maternal weight information were recorded. In total, data from 3252 singleton pregnancies were available for analysis with 259 cases excluded. The exclusions were necessary since chromosomal abnormalities and pregnancy complications are known to influence marker levels and if not excluded these could have been a confounding variable.

Statistical analysis

All analyte and NT measurements were converted to multiple of the median values (MoM) using the median values derived from previous studies of

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Received: 11 April 2000
Revised: 8 June 2000
Accepted: 17 June 2000

unaffected pregnancies and gestational age calculated from fetal crown–rump length. MoM values for biochemical markers were calculated with and without correction for maternal weight using the reciprocal weight procedure of Neveux *et al.* (1996) and locally derived parameters (Spencer *et al.*, 2000d). Statistical analysis of data was performed with Analyse-It (Smart Software, Leeds, UK) a statistical software add-in for Microsoft Excel 7.

RESULTS

In order to confirm that maternal age would not be a confounding factor in the analysis of parity/gravidity data the individual marker MoMs were examined with respect to maternal age. The individual $\log_{10}$ MoMs for each marker (weight corrected in the case of free β-hCG and PAPP-A) were regressed against maternal age. There was no significant association between maternal age and fetal NT ($r=0.024$), free β-hCG ($r=0.006$) and PAPP-A ($r=0.034$).

The median MoM marker values (weight corrected in the case of free β-hCG and PAPP-A) for pregnancies classified by gravidity and parity are shown in Tables 1 and 2. The trend of each median marker MoM with gravidity or parity was examined using linear regression, weighted by the number of pregnancies in each group. There appeared to be a significant negative association between NT and increasing gravidity ($r=-0.472$) or parity ($r=-0.410$), with NT MoM decreasing by 1.3% for an increase in parity of 1. For free β-hCG there appeared to be a significant positive association with increasing gravidity ($r=0.733$) or parity ($r=0.686$), with free β-hCG MoM increasing by 2% for an increase in parity of 1. For PAPP-A there appeared to be also a positive association with increasing parity ($r=0.325$) and to a lesser extent with gravidity ($r=0.173$) with PAPP-A MoM increasing by 0.2% for an increase in parity of 1. Although these trends showed some association with changing gravidity or parity, when the individual $\log_{10}$ MoMs were regressed against gravidity (or parity) the correlation was not significant (r for NT, free β-hCG and PAPP-A where 0.00, -0.01 and $+0.01$, respectively). When the individual $\log_{10}$ MoM distributions were compared between primigravid and multigravid women and between nulliparous and multiparous women using t-tests of equal variance no significant differences could be found for NT ($p=0.297$ and 0.315), free β-hCG ($p=0.226$ and 0.261) or PAPP-A ($p=0.445$ and 0.148).

DISCUSSION

The initial study of gravidity and its impact on second trimester maternal serum total hCG levels (Daniel *et al.*, 1994) which found a 20% reduction was partly flawed by the fact that maternal weight correction had not been applied. Subsequent studies of both free β-hCG (Spencer, 1995; Wald and Watts, 1996) and total hCG (Haddow *et al.*, 1995; Mooney *et al.*, 1995; Wald and Watts, 1996) have shown that, after weight correction, the difference between hCG levels in primigravid and multigravid or nulliparous and parous women are small, of the order of 3–6% lower and that the levels of the decline increases with increasing number of births. In the first trimester it appears that gravidity or parity is associated with a small but progressive decrease in fetal NT and a small

Table 1—Median marker values in pregnancies classified by gravidity

Gravidity	*n*	Maternal age (years)	Weight (kg)	Median NT (MoM)	Median free β-hCG (MoM)	Median PAPP-A (MoM)
1	1023	27.25	63.50	1.02	1.00	1.00
2	1103	29.43	65.20	1.00	0.98	1.00
3	599	30.41	65.60	1.00	1.01	1.01
4	292	31.91	67.40	1.01	1.06	0.98
5	137	32.92	69.60	1.01	1.07	1.03
>5	98	33.07	66.50	0.97	0.96	1.03
>1	2229	30.30	66.00	1.00	0.98	1.01

Table 2—Median marker values in pregnancies classified by parity

Parity	*n*	Maternal age (years)	Weight (kg)	Median NT (MoM)	Median free β-hCG (MoM)	Median PAPP-A (MoM)
0	1372	27.38	63.60	1.02	0.99	1.01
1	1124	29.84	66.00	0.99	1.00	0.98
2	499	31.36	66.60	1.01	1.00	1.01
3	165	33.04	66.20	1.02	1.01	1.06
4	57	33.85	68.00	0.97	1.12	1.05
>4	34	35.66	73.75	0.97	0.86	1.07
>0	2879	30.58	66.40	1.00	1.00	1.00

but progressive increase in free β-hCG and PAPP-A. None of these small changes with increasing gravidity/parity are statistically significant. The effect on the performance of Down syndrome screening in the first trimester is small. At a 5% false positive rate the detection rate would be increased by less than 0.1% and hence correction for these minor changes is not necessary when considering first trimester screening for chromosomal abnormalities. Recently, in a small study of around 1000 cases, de Graaf *et al*. (2000), have suggested that PAPP-A levels increase with increasing gravidity, our results are consistent with these findings. Whether an increased risk of Down syndrome is really associated with increased parity (Schimmel *et al.*, 1997) or not (Kallen and Masback, 1988; Kallen, 1997; Haddow and Palomaki, 1994) remains to be confirmed and its impact on screening assessed.

REFERENCES

Daniel RG, Reynolds T, Penney MD. 1994. Calculation of Down's syndrome risk. *Lancet* **343**: 490

de Graaf IM, Cuckle HS, Pajkrt E, Leschot NJ, Bleker OP, van Lith JMM. 2000. Co-variables in first trimester maternal serum screening. *Prenat Diagn* **20**: 186–189.

Haddow JE, Palomaki GE. 1994. Multiparity and Down's syndrome. *Lancet* **344**: 956

Haddow JE, Palomaki GE, Knight GJ. 1995. Effect of parity on human chorionic gonadotrophin levels and Down's syndrome screening. *J Med Screening* **2**: 28–30.

Kallen K. 1997. Parity and Down syndrome. *Am J Med Genet* **70**: 196–201.

Kallen B, Masback A. 1988. Down syndrome: seasonality and parity effects. *Heriditas* **109**: 21–27.

Mooney RA, Arvan DA, Saller D, French CA, Peterson CJ. 1995. Decreased maternal serum hCG levels with increasing gravidity and parity. *Obstet Gynecol* **86**: 900–905.

Neveux LM, Palomaki GE, Larivee DA, Kinght GJ, Haddow JE. 1996. Refinements in managing maternal weight adjustment for prenatal screening results. *Prenat Diagn* **16**: 1115–1119.

Schimmel MS, Eidelman AI, Zadka P, Kornbluth E, Hammerman C. 1997. Increased parity and risk of trisomy 21 — review of 37 110 live births. *Br Med J* **314**: 720–721.

Snijders RJM, Noble P, Sebire N, Souka A, Nicolaides KH. 1998. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation. *Lancet* **351**: 343–346.

Spencer K. 1995. The influence of gravidity on Down's syndrome screening with free beta hCG. *Prenat Diagn* **15**: 87–89.

Spencer K, Souter V, Tul N, Snijders R, Nicolaides KH. 1999. A rapid screening program for trisomy 21 at 10–14 weeks using fetal nuchal translucency, maternal serum free β-hCG and PAPP-A. *Ultrasound Obstet Gynecol* **13**: 231–237.

Spencer K, Ong C, Skentou H, Liao AW, Nicolaides KH. 2000a. Screening for trisomy 13 by fetal nuchal translucency and maternal serum free beta hCG and PAPP-A at 10–14 weeks of gestation. *Prenat Diagn* **20**: 411–416.

Spencer K, Tul N, Nicolaides KH. 2000b. Maternal serum free beta hCG and PAPP-A in fetal sex chromsome defects in the first trimester. *Prenat Diagn* **20**: 390–394.

Spencer K, Liao AWJ, Skentou H, Cicero S, Nicolaides KH. 2000c. Screening for triploidy by fetal nuchal translucency and maternal serum free β-hCG and PAPP-A at 10–14 weeks of gestation. *Prenat Diagn* **20**: 495–499.

Spencer K, Harding CE, Power M, Moakes A, Nicolaides KH. OSCAR — One Stop Clinic for Assessment of Risk for fetal anomalies: a report of the first year of prospective screening for chromosomal anomalies in the first trimester. *Br J Obstet Gynaecol* (in press).

Spencer K, Ong CYT, Liao AWJ, Nicolaides KH. 2000d. The influence of ethnic origin on first trimester biochemical markers of chromosomal abnormalities. *Prenat Diagn* **20**: 491–494.

Tul N, Spencer K, Noble P, Chan C, Nicolaides KH. 1999. Screening for trisomy 18 by fetal nuchal translucency and maternal serum free beta hCG and PAPP-A at 10–14 weeks of gestation. *Prenat Diagn* **19**: 1035–1042.

Wald NJ, Watts HC. 1996. Serum markers for Down's syndrome in relation to number of previous births and maternal age. *Prenat Diagn* **16**: 699–703.