First trimester markers of trisomy 21 and the influence of maternal cigarette smoking status

Maternal cigarette smoking is associated with alterations in maternal serum analytes used in screening for trisomy 21 during the second trimester of pregnancy. Thus, serum free β-hCG levels in women who smoke are reduced by 11–14% in unaffected pregnancies (Spencer, 1998; Ferriman *et al*., 1999) and by 16% in pregnancies affected by trisomy 21 (Spencer, 1998). The consequence of this reduction in serum free β-hCG levels is that in cigarette smokers there is a 10% decrease in sensitivity for trisomy 21 and a 50% reduction in the false positive rate. Although correcting for smoking status improves the detection rate by only 1–2%, the increase in accuracy of the estimated risk for an individual patient is considerable.

There is now interest in moving screening for chromosomal abnormalities to the first trimester of pregnancy (Grudzinskas and Ward, 1997). Combining maternal serum pregnancy associated plasma protein – A (PAPP-A) and free β-hCG with fetal nuchal translucency thickness (NT) can identify about 90% of pregnancies affected by trisomies 21, 18 and 13, triploidy and sex chromosome aneuploidies for a false positive rate of about 5% (Spencer *et al*., 1999, 2000a,b,c; Tul *et al*., 1999).

In an earlier study of 2887 unaffected pregnancies (Spencer, 1999) we observed that levels of maternal serum free β-hCG were not altered in the first trimester of pregnancy, whilst PAPP-A levels were reduced by 15%. We have now had the opportunity to examine the effect of self-reported maternal cigarette smoking status on first trimester maternal serum levels of free β-hCG and PAPP-A and fetal NT in normal and trisomy 21 pregnancies.

For NT in the unaffected group we used NT data from the 2887 previously reported (Spencer, 1999) unaffected pregnancies screened in our OSCAR clinic (Spencer *et al*., in press). For pregnancies affected by trisomy 21 we used available information from our previous study of NT and maternal serum biochemical marker levels from 204 of the 210 cases (Spencer *et al*., 1999), supplemented with a further series of 20 cases identified during prospective screening in our OSCAR clinics. All biochemical measurements were performed using the CIS Kryptor system and all markers were expressed a MoMs corrected for maternal weight when appropriate (Spencer *et al*., 1999).

The median maternal age, weight and gestation in the trisomy 21 and unaffected pregnancies according to cigarette smoking status are shown in Table 1. In the unaffected population the median NT MoM in smokers was identical to that in non-smokers—0.996 (95% confidence interval 0.975–1.017) versus 1.000 (0.990–1.010)—with a $\log_{10}$ MoM SD of 0.1086 in smokers and 0.1155 in non-smokers. The $\log_{10}$ MoM distributions in the two groups were compared by *t*-tests assuming equal variance and no significant difference ($p=0.244$) was observed. In trisomy 21 pregnancies the median MoM NT in the smokers was again similar to that in non-smokers—2.539 (CI 2.07–3.17) versus 2.607 (CI 2.44–2.80)—with a $\log_{10}$ MoM SD of 0.2025 in smokers and 0.1918 in non-smokers. The $\log_{10}$ MoM distributions in the two groups were compared by *t*-tests assuming equal variance and no significant difference ($p=0.334$) was observed.

In trisomy 21 pregnancies the median weight corrected MoM free β-hCG in the smokers was 13% lower than in non-smokers—1.787 (CI 1.09–2.24) versus 2.048 (CI 1.88–2.26)—with a $\log_{10}$ MoM SD of 0.2648 in smokers and 0.2784 in non-smokers. The $\log_{10}$ MoM distributions in the two groups were compared by *t*-tests assuming equal variance but this difference did not reach statistical significance ($p=0.198$). The median weight corrected MoM PAPP-A in the smokers was 6% higher in the smokers than in non-smokers—0.556 (CI 0.36–0.72) versus 0.526 (CI 0.45–0.56)—with a $\log_{10}$ MoM SD of 0.2720 in smokers and 0.2821 in non-smokers. The $\log_{10}$ MoM distributions in the two groups were compared by *t*-tests assuming equal variance but no significant difference ($p=0.279$) was observed.

The findings of this study in the first trimester suggest that maternal cigarette smoking does not affect fetal NT in either trisomy 21 or unaffected pregnancies. Furthermore, the data suggest that in trisomy 21 pregnancies cigarette smoking is associated with a 13% decrease in maternal serum free β-hCG concentration, which is similar to the previously reported 16% decrease in affected pregnancies in the second trimester (Spencer, 1998). In unaffected pregnancies cigarette smokers have an 11–14% reduction in free β-hCG levels during the second trimester (Spencer, 1998; Ferriman *et al*., 1999), but the levels are not altered in the first trimester of pregnancy (Spencer, 1999). The consequence of these findings would be a decrease in the detection of trisomy 21 in cigarette smokers.

In trisomy 21 pregnancies cigarette smoking is

Table 1—Median maternal age, weight and gestation in trisomy 21 and unaffected pregnancies according to cigarette smoking status

	Trisomy 21		Unaffected	
	Smoker $n=27$	Non-smoker $n=197$	Smoker $n=600$	Non-smoker $n=2287$
Age (years)	36	38	26.5	29.4
Weight (kg)	68.0	63.0	65.0	65.4
Gestation (days)	87	87	84	84

associated with a 6% increase in maternal serum PAPP-A concentration. In contrast, in unaffected pregnancies smoking is associated with a 15% reduction in serum levels (Spencer, 1999). The consequence of these findings on first trimester screening for trisomy 21 would be an increase in the false positive rate and a decreased detection of trisomy 21 amongst the smoking group.

The data suggest that maternal cigarette smoking status is associated with alterations in maternal serum free β-hCG and PAPP-A concentrations which could potentially decrease the sensitivity and increase the false positive rate in screening for trisomy 21 during the first trimester of pregnancy amongst the smoking group.

The incidence of smoking in the unaffected population (20.8%) was similar to that found in a previous study (Spencer, 1998) in which an age-related variation in smoking incidence was confirmed. The incidence of smoking amongst women having a pregnancy affected by trisomy 21 was 12%—considerably lower than the overall pregnant population. However, this incidence of smoking does need to be adjusted for the fact that cases with trisomy 21 on average occur more often in an older population whose incidence of smoking is also less (Chen *et al*., 1999). Using the age distribution of cases of trisomy 21 and the incidence of smoking in various age bands from a previous study (Spencer, 1998) we predict that in our 224 cases of trisomy 21 we would expect to see 36 cases amongst women who smoked. The fact that we observed only 27 cases (a deficit of 25%) lends support to other observations of a deficit of smokers amongst women who had pregnancies associated with trisomy 21 and the negative association between trisomy 21 births and maternal cigarette smoking (Kline *et al*., 1981, 1993; Shiono *et al*., 1986; Hook and Cross, 1985, 1998; Christianson and Torfs, 1988; Chen *et al*., 1999). If these results and observations are confirmed by further studies it would be necessary to make some correction to *a priori* age risks and marker distributions in order to provide accurate risks for women who smoked.

The biochemical marker changes described are also consistent with findings of changes in placental morphology in the early first trimester (Jauniaux and Burton, 1992) in which synctiotrophoblastic necrosis is increased in the placenta of smokers which may result in decreased synthesis of placental proteins (such as PAPP-A and free β-hCG) and increased permeability to fetal products such as alpha-feto protein (AFP). Such findings may be an explanation for the change in maternal serum marker levels in women who smoke.

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