PRENATAL DIAGNOSIS
Prenat Diagn 2000; **20**: 491–494.

The influence of ethnic origin on first trimester biochemical markers of chromosomal abnormalities

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In a first trimester study of 5422 Caucasian women, 752 Afro-Caribbean women and 170 Asian women we have shown that the median maternal serum marker MoMs for free β-hCG and PAPP-A were 19% and 48% higher in Afro-Caribbean women and 19% higher and 35% higher in Asian women, compared to Caucasian women. Correcting for maternal weight made very little difference to the effect in Afro-Caribbeans (21% and 57% higher after weight correction) but reduced the effect in Asians (4% and 17% higher after weight correction). It is estimated that correcting for maternal weight and ethnicity overall would increase the detection rate by a modest 1.4%. However, the effect on an individual's risk could result in as much as a two-fold increase in the patient specific risk for trisomy 21. The impact of ethnic origin seems to be greater than that observed with second trimester biochemical markers and larger studies are required in order to develop robust algorithms for correcting for ethnic origin in the first trimester. Copyright © 2000 John Wiley & Sons, Ltd.

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

INTRODUCTION

In the second trimester of pregnancy screening for trisomy 21 using a combination of maternal age and maternal serum biochemical markers is now an accepted procedure in many developed countries. As more data on screening are gathered, the possibility of refining the risk algorithms leading to improved detection efficiency has become possible by taking into account a variety of factors such as multiple pregnancy, maternal weight, insulin dependent diabetes mellitus, previous pregnancy results and maternal smoking. Correction for these factors seeks to reduce the between patient variance, leading to reductions in the false positive rate. Another factor known to have an impact on biochemical marker levels is that of ethnic origin. Although some of the published data in the second trimester are confounded by the fact that correction for maternal weight was not applied, it is clear that for Afro-Carribbean women AFP and total hCG are 15–20% higher than in white women (Johnson, 1985; Baumgarten, 1986; Wald and Cuckle, 1987; Canick *et al*., 1990; Simpson *et al*., 1990; Muller and Boue, 1990; Bogart *et al*., 1991; Burton and Nieb, 1991; Kulch *et al*., 1993; Watt *et al*., 1996; O'Brien *et al*., 1997). Similarly in South Asian women, AFP is 5% lower and total hCG 5% higher than in white women (Muller *et al*., 1994; Watt *et al*., 1996) and in orientals AFP, total hCG and free β-hCG are higher than in white women (Onda *et al.*, 1996; Hseih *et al*., 1995). Correction for ethnic origin can be carried out by two different methods. The first method involves the construction of racial specific medians, requiring a significant number of cases at each gestational week for each race (Bryant-Greenwood *et al*., 1998). The second method is an indirect method of adjusting the measured MoM in any one ethnic group back to that equivalent in a white individual (Watt *et al*., 1996). Although in population terms the improvement in the false positive or detection rate is small, making allowance for ethnic origin can make a significant difference to an individual's risk.

Screening for trisomy 21 is now poised to move into the first trimester when a combination of nuchal translucency thickness (NT) and maternal serum free β-hCG and pregnancy associated plasma protein-A (PAPP-A) have been shown both retrospectively (Spencer *et al*., 1999) and prospectively (Spencer *et al*., 2000) to achieve detection rates of 85–90% at a 5% false positive rate. In this study we analyse the impact of ethnic origin on biochemical marker levels.

METHODS

All pregnant women attending for maternity care at Harold Wood Hospital and at King's College Hospital are offered screening for chromosomal abnormalities by a combination of fetal nuchal translucency thickness and maternal serum free β-hCG and PAPP-A in a one stop clinic (OSCAR) (Spencer *et al*., 2000). Free β-hCG and PAPP-A are measured by a KRYPTOR analyser — a random continuous access immunoassay analyser, using time-resolved amplified cryptate emission (TRACE) technology, which provides results within 20 min of sampling. The performance of this system has been described before (Spencer *et al*., 1999). Demographic data, ultrasound findings and the results of biochemical testing are logged onto a

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Received: 8 December 1999
Revised: 8 February 2000
Accepted: 20 February 2000

networked fetal database at the time of assessment and from this information individual patient-specific risks are produced.

A search was made of the databases at each site to identify all singleton pregnancies which had first trimester biochemical testing from the onset of the service and for which a normal pregnancy outcome unaffected by chromosomal abnormalities was confirmed and for which ethnic group and maternal weight information was also recorded.

Statistical analysis

All analyte measurements were converted to multiple of the median values (MoM) using the median values derived from previous studies of unaffected pregnancies and gestations (GA) calculated from CRL and expressed in decimal weeks. The regression formulae used to derive the medians were as follows:

Free β-hCG median (IU/l) = 10^((0.005885 × GA^3) − (0.2399 × GA^2) + (3.1245 × GA) − 11.523

PAPP-A median (IU/l) = 10^((−0.0226 × GA^2) + (0.7362 × GA) − 5.163)

MoM values were calculated with and without correction for maternal weight. MoM values were corrected for maternal weight by dividing the observed MoM value by the MoM value expected for maternal weight. The weight correction formula was derived solely from Caucasian women using the reciprocal correction procedure (Neveux *et al.*, 1996).

We used the method of Watt *et al.*, 1996) using our measured parameters to correct for ethnicity in Afro-Caribbean women and in Asian women. To estimate the effect of allowing for ethnicity on the false positive and detection rates when screening for trisomy 21 in the first trimester we used standard statistical modelling techniques (Royston and Thompson, 1992), We used the population parameters for unaffected and affected pregnancies from our previous study (Spencer *et al.*, 1999) the age related risk for trisomy 21 in the first trimester (Snijders *et al.*, 1995) and a population with the maternal age distribution of pregnancies in England and Wales (OPCS, 1986–1994). We simulated three populations, one composed of only Caucasian women, one containing 50% Afro-Caribbean women and 50% Caucasian women and another containing 50% Asian and 50% Caucasian women. For each group 15 000 free β-hCG and PAPP-A analyte MoMs were picked at random from the gaussian distributions of the analytes in unaffected and affected pregnancies. For the mixed populations 50% of the analyte values were picked at random and adjusted by the difference between the Caucasian median and the Afro-Caribbean or Asian median MoM. These values were used to calculate the likelihood ratios for the populations with and without ethnicity correction, which in turn were used to generate detection rates and false positive rates in the population model.

RESULTS

The study population comprised of 5422 Caucasians, 752 Afro-Caribbeans and 170 Asians. The median maternal weights in the three groups (and the 10th to 90th centiles) were 65.0 kg (53.0–86.0) for Caucasian women, 68.85 kg (53.0–92.0) for Afro-Caribbean women and 57.8 kg (46.5–76.2) for Asian women. In the Caucasian group, the concentration of both free β-hCG and PAPP-A increased with the reciprocal of maternal weight (Figure 1). The slope of the increase in marker MoM with reciprocal maternal weight was similar for all three ethnic groups.

Table 1 shows that in Afro-Caribbean women the

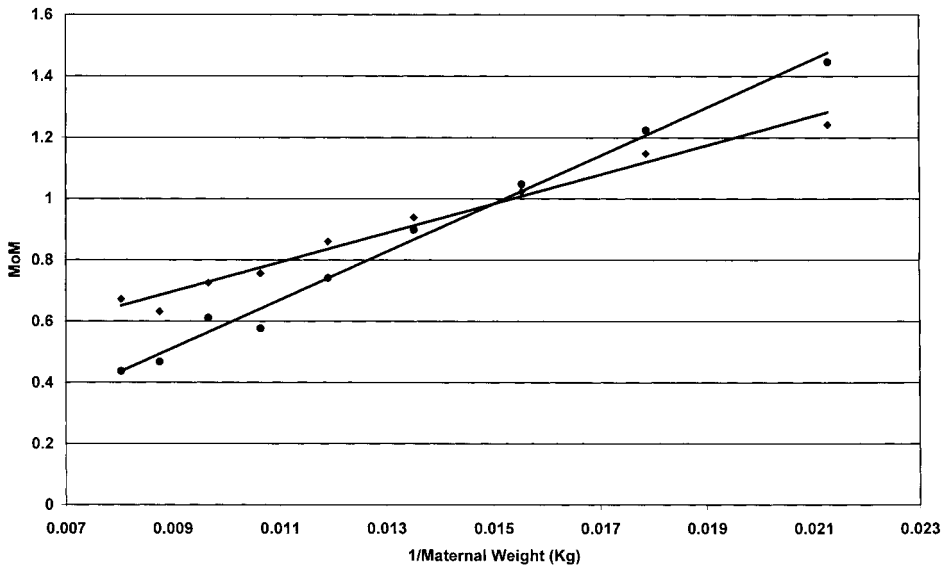

Figure 1—Regression of the reciprocal of maternal weight and median marker MoM for free β-hCG (◆) and PAPP-A (●) in 5422 Caucasian women. The regression equation for free β-hCG being Y = 47.815X + 0.2661 (r^2 = 0.9794) and that for PAPP-A being Y = 78.604X − 0.1956 (r^2 = 0.9902)

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Table 1—Marker values (as MoM) in Afro-Caribbean women and Caucasian women with and without maternal weight adjustment

Marker	No. of Caucasian women	No. of Afro-Caribbean women	Ratio of median MoM Afro-Caribbean/ Caucasian (95% CI)		Ratio of weight adjusted: non-weight corrected MoM
			Non-weight corrected	Weight corrected	
Free β-hCG	5422	752	1.19 (1.13–1.31)	1.21 (1.14–1.31)	1.02
PAPP-A	5422	752	1.48 (1.39–1.56)	1.57 (1.49–1.65)	1.06

Note: CI, confidence interval.

Table 2—Marker values (as MoM) in Asian women and Caucasian women with and without maternal weight adjustment

Marker	No. of Caucasian women	No. of Asian women	Ratio of median MoM Asian/ Caucasian (95% CI)		Ratio of weight adjusted: non-weight corrected MoM
			Non-weight corrected	Weight corrected	
Free β-hCG	5422	170	1.19 (1.08–1.31)	1.04 (0.95–1.16)	1.03
PAPP-A	5422	170	1.35 (1.19–1.47)	1.17 (1.03–1.27)	1.15

Note: CI, confidence interval.

median marker MoMs for both free β-hCG and PAPP-A before weight correction were significantly higher than in Caucasian women, with free β-hCG being 19% higher and PAPP-A being 48% higher. Similarly, Table 2 shows that in Asian women the median marker MoMs before weight correction were also significantly higher than in Caucasian women, with free β-hCG being 19% higher and PAPP-A some 35% higher.

After weight correction the Afro-Caribbean/Caucasian difference was not significantly altered, suggesting that maternal weight difference did not account for the increased free β-hCG and PAPP-A output in Afro-Caribbean women. In Asian women, although weight correction did bring the median marker MoMs closer to those of Caucasian women, free β-hCG was still 4% higher and PAPP-A 17% higher in Asian women. When the maternal weight corrected log MoMs for each ethnic group were compared with the Caucasian group using unpaired t-tests (of unequal variance), for Asian women the difference for free β-hCG and PAPP-A did not reach statistical significance with $p = 0.284$ and 0.077 respectively. However for the Afro-Caribbean group the difference for free β-hCG and PAPP-A was highly significant with $p < 0.001$ for both markers.

The overall impact of correcting for ethnicity in populations containing 50% Caucasian and 50% Afro-Caribbean or 50% Asians in shown in Table 3. The population impact of correction is small in that detection rates would increase by only 1.4%.

DISCUSSION

In the second trimester of pregnancy it is well documented that ethnic differences in biochemical markers levels exist for Afro-Caribbean, South Asian, Oriental and Hispanic women, and that these differences compared to Caucasian women cannot be explained solely by differences in maternal weight (Watt *et al.*, 1996; Bryne *et al.*, 1997; Bryant-Greenwood *et al.*, 1998).

In our study of the first trimester biochemical markers, free β-hCG and PAPP-A, we have shown that in Afro-Caribbean women these markers levels are significantly higher than in Caucasians and that weight correction does not account for these differences. Also, in Asian women the marker values are increased, some of which can be accounted for by weight correction. The marker most significantly affected appears to be PAPP-A, with levels (after weight correction) of 17 to 35% higher. Such sizeable increases in marker levels need to be taken into account in first trimester screening algorithms. Whilst doing so will not have a significant impact on overall detection rates, it is very important with respect to an individual's risk, which could alter by up to two-fold. For example, in a 67 kg, 25-year-old Afro-Caribbean, with an uncorrected free β-hCG of 2.10 MoM and a PAPP-A of 0.65 MoM, the risk of trisomy 21 without correction would be 1 in 540. After correction the free β-hCG MoM is 1.73 and the PAPP-A MoM is 0.41 with a corrected risk of 1 in 260.

Table 3—Effect of correcting for ethnicity on the overall detection rate for trisomy 21 in the first trimester with maternal age, free β-hCG and PAPP-A at a standardized 5% false postitive rate

Ethnic mix 50 : 50	Without correction	With correction
Caucasian: Afro-Caribbean	65.9%	67.3%
Caucasian: Asian	65.8%	67.2%

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Further larger data sets are required to develop robust methods of correcting for ethnic origin and to assess the biological significance of such differences in marker production between various ethnic groups.

ACKNOWLEDGMENTS

We acknowledge the support of CIS (UK) Ltd in providing funding for the biochemical portion of the OSCAR clinic at Harold Wood Hospital. The work at the Harris Birthright Research Centre is supported by a grant from the Fetal Medicine Foundation (Charity no. 1037116).

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