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Maternal serum activin A and inhibin A in trisomy 18 pregnancies at 10–14 weeks

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In 45 cases of trisomy 18 and 493 control pregnancies at 10–14 weeks of gestation, maternal serum inhibin A, total activin A, free β-hCG and PAPP-A were measured. In the trisomy 18 pregnancies the median values were 0.74 MoM for inhibin A, 1.23 MoM for activin A, 0.38 MoM for free β-hCG and 0.16 MoM for PAPP-A. The degree of deviation from normal in the levels of inhibin and activin is small in comparison with free β-hCG and PAPP-A and they are therefore unlikely to be of value in improving the sensitivity of 90% for a 1% false-positive rate achieved by screening with fetal nuchal translucency and maternal serum free β-hCG and PAPP-A. Copyright © 2001 John Wiley & Sons, Ltd.

KEY WORDS: inhibin; activin; free β-hCG; PAPP-A; nuchal translucency; trisomy 18; first trimester; aneuploidy; prenatal screening

INTRODUCTION

Trisomy 18 is the second most common autosomal trisomy. During the second trimester screening algorithms have been developed based on the observation of low levels of maternal serum α-fetoprotein (AFP), total human chorionic gonadotrophin (hCG), free β-hCG and unconjugated oestriol (Canick *et al*., 1990; Barkia *et al*., 1993; Spencer *et al*., 1993). These algorithms allow a detection of 60% of trisomy 18 pregnancies for a false-positive rate of 0.2–0.7% (Palomaki *et al*., 1995; Spencer, 1999). In the first trimester, levels of maternal serum pregnancy associated plasma protein-A (PAPP-A) and free β-hCG are also reduced and in conjunction with fetal nuchal translucency thickness (NT) algorithms have been developed which identify 90% of cases for a 1% false-positive rate (Tul *et al*., 1999). Unlike in cases of trisomy 21, PAPP-A levels continue to be reduced in cases of trisomy 18 across the second trimester although the practical usefulness of this observation in screening has yet to be realised. In recent years much interest and debate has focussed on the value of adding inhibin A measurement into second trimester screening protocols for trisomy 21, although this has no value in the first trimester (Wald *et al*., 1996; Noble *et al*., 1997; Spencer *et al*., 2001a), and limited data suggest that inhibin A is unable to discriminate for trisomy 18 aneuploidy in the second trimester (Aitken *et al*., 1996; Lambert-Messerlian *et al*., 1998; Cuckle *et al*., 1999a). In the second trimester, activin has been found in various small studies to be a poor discriminator for trisomy 21 (Lambert-Messerlian *et al*., 1996a,b; Cuckle *et al*., 1999b), and Spencer *et al*. (2001b) came to a similar conclusion when studying 45 cases of trisomy 21 in the first trimester.

In the present study we evaluate whether maternal serum levels of inhibin A and total activin A are altered in the first trimester of pregnancies affected by trisomy 18 and whether either may be of value in first trimester screening.

MATERIALS AND METHODS

At the Harris Birthright Research Centre and at Harold Wood Hospital maternal serum samples were collected at 10–14 weeks of gestation as part of screening for trisomy 21 and other chromosomal anomalies by a combination of maternal age, fetal NT and maternal serum free β-hCG and PAPP-A (Spencer *et al*., 1999, 2000). All serum was aliquoted and stored at -20°C within 1 h of collection. Institutional research ethics approval had been granted for further research on stored excess clinical material.

From the stored sample bank, 45 cases of trisomy 18 and 493 control pregnancies were selected for analysis. These samples have not formed any part of previous studies of trisomy 18 (Tul *et al*., 1999). Maternal serum inhibin A and total activin A were measured in all samples in duplicate using quantitative enzyme immunoassay techniques (Serotec, Kidlington, UK). The performance of these assays has been described previously (Spencer *et al*., 2001a,b). Maternal serum PAPP-A and free β-hCG were re-measured using the Kryptor system as previously described (Spencer *et al*., 1999). All samples were analysed blinded to the assessor.

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Table 1—Characteristics of the control and trisomy 18 pregnancies

	Controls ($n=493$)	Trisomy 18 ($n=45$)
Maternal age (years)	28.1 (SD 5.2)	35.00 (SD 5.65)
Maternal weight (kg)	68.0 (SD 13.6)	61.8 (SD 8.5)
Caucasian (%)	430 (87.2%)	38 (84.4%)
Cigarette smokers (%)	78 (15.8%)	8 (17.8%)
Primigravidae (%)	240 (48.7%)	13 (28.9%)
Gestational age (weeks)	12 (SD 0.8)	12 (SD 0.9)

Table 2—Weight-corrected median MoM values for maternal serum analytes in 45 trisomy 18 pregnancies together with their distributions

	Median MoM	Cases below the 5th centile or above the 95th centile (%)
Inhibin A	0.74	<5th centile 11 (24%)
Activin A	1.23	>95th centile 6 (13%)
Free β-hCG	0.38	<5th centile 25 (55%)
PAPP-A	0.16	<5th centile 35 (78%)

Statistical analysis

All inhibin A and total activin A measurements, both in the trisomy 18 group and the unaffected pregnancies, were expressed as multiples of the median (MoM) from previously established regressed median analysis (Spencer *et al.*, 2001a,b). Similarly, weight-corrected MoM values were established for all markers using reciprocal regression models. Analyse-It software (Smart Software, Leeds, UK) was used for statistical analysis and normality of the distributions was examined using the Kolmogorov–Smirnov test. Significance of marker levels in the trisomy 18 group was established by *t*-test of unequal variance with confirmed Gaussian distributions.

RESULTS

The characteristics of the trisomy 18 and the control groups are shown in Table 1. The weight-corrected median values for total activin A, inhibin A, free β-hCG and PAPP-A in the trisomy 18 pregnancies are shown in Table 2, together with the proportion of affected pregnancies above or below the 95th or 5th centile for unaffected pregnancies. Log_{10} transformation of the marker MoMs allowed normalisation of the data to a Gaussian distribution. The mean log_{10} inhibin A MoM in the trisomy 18 group was significantly lower (-0.086, $p=0.029$) with a log_{10} SD of 0.2601 compared with 0.001 and 0.1936, respectively, in the unaffected group. The mean log_{10} activin A MoM in the trisomy 18 group was not significantly different (0.064, $p=0.112$) with a log_{10} SD of 0.2396 compared with 0.007 and 0.1657, respectively, in the unaffected group. Figures 1 and 2 show the individual results for inhibin A and activin A. For free β-hCG and PAPP-A the log_{10} distributions in cases of trisomy 18 were significantly lower ($p<0.001$) than in the control group, with mean log_{10} MoMs of -0.4959 (SD $=0.2843$) for free β-hCG and -0.8109 (SD $=0.2715$) for PAPP-A.

Table 3 shows the level of correlation between the various markers in the unaffected and trisomy 18 groups. Highly significant correlation was observed between free β-hCG and activin, free β-hCG and inhibin, and between inhibin and activin in the trisomy 18 group.

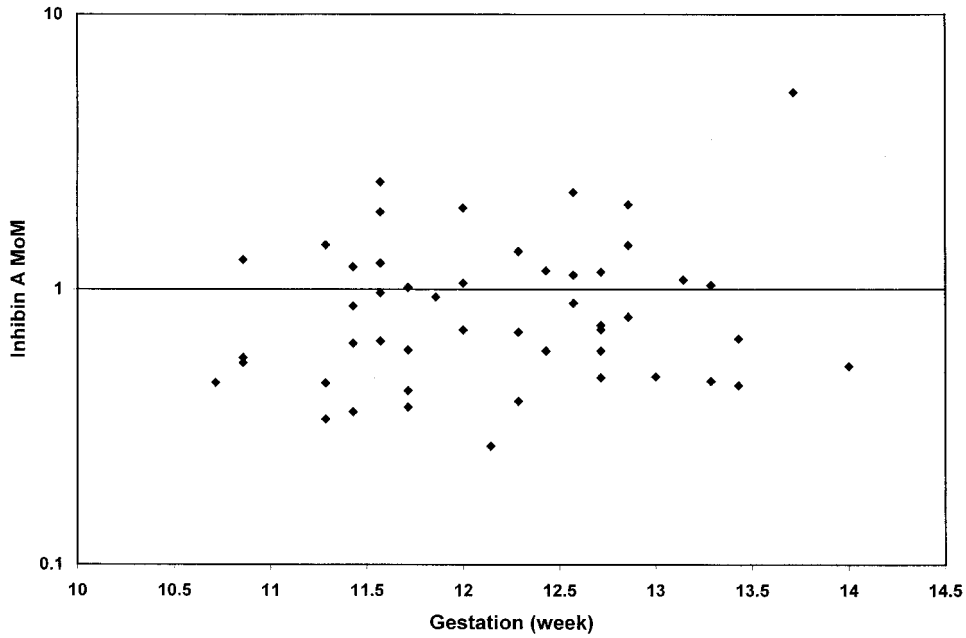

Figure 1—Variation of inhibin A MoM with gestation in 45 cases of trisomy 18

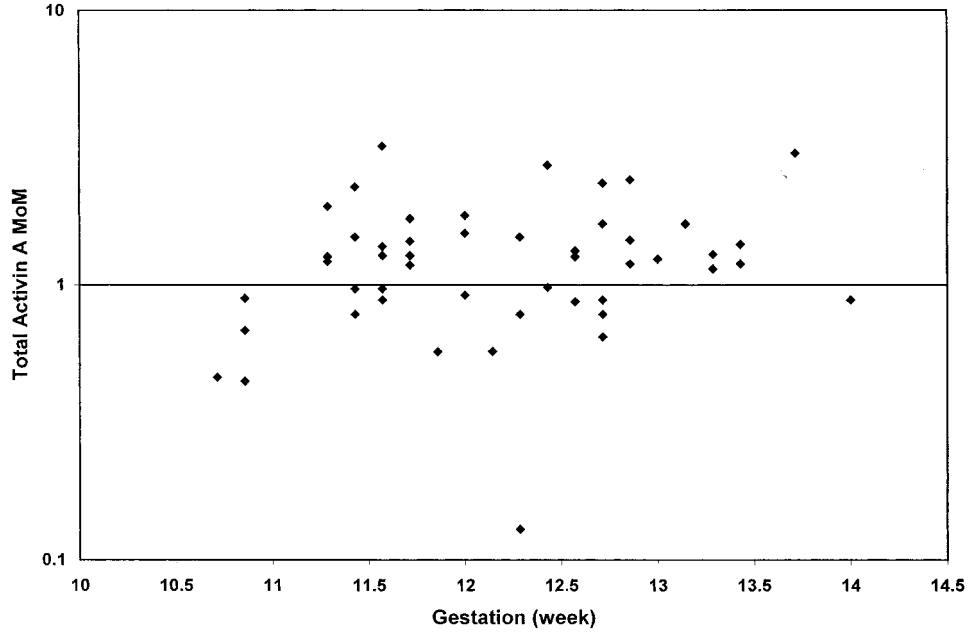

Figure 2—Variation of activin A MoM with gestation in 45 cases of trisomy 18 Maternal serum activin A and inhibin A in trisomy 18 pregnancies at 10–14 weeks

Table 3—Correlation between the various markers in the unaffected and trisomy 18 groups

Markers	Unaffected cases	Trisomy 18 cases
Free β-hCG and PAPP-A	+0.2190	+0.2087
Free β-hCG and inhibin	+0.2429	+0.5931
Free β-hCG and activin	+0.1205	+0.3627
PAPP-A and inhibin	+0.0764	+0.1523
PAPP-A and activin	+0.2091	+0.0917
Inhibin and activin	+0.1636	+0.6055

DISCUSSION

The findings of the present study demonstrate that in trisomy 18 pregnancies at 10–14 weeks of gestation maternal serum inhibin A levels are reduced but activin A is not significantly different from normal. Furthermore, this new dataset confirms our previous observation of an association between trisomy 18 and very much reduced levels of free β-hCG and PAPP-A (Tul *et al.*, 1999).

Our finding of low inhibin A, with a median MoM of 0.74, is compatible with two previous reports. Thus, Aitken *et al.* (1996) and Cuckle *et al.* (1999a) each examined four trisomy 18 pregnancies in the first trimester and reported median MoMs of 0.3 and 0.88, respectively. This reduction in levels of inhibin is small in comparison with free β-hCG and PAPP-A. This observation, coupled with the high degree of correlation between free β-hCG and inhibin (and activin), make either marker unlikely to be of value in improving the sensitivity of 90% for a 1% false-positive rate achieved by screening with fetal NT and maternal serum free β-hCG and PAPP-A (Tul *et al.*, 1999).

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