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First trimester maternal serum AFP and total hCG in aneuploidies other than trisomy 21

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Total human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) were measured in maternal serum at 10–14 weeks of gestation from 53 pregnancies affected by trisomy 18, 42 cases with trisomy 13, 46 with Turner's syndrome and 13 with other sex aneuploides. The only significant association was the finding of reduced levels of total hCG in cases of trisomy 18 and 13. The association of increased levels of AFP in cases of trisomy 18 with ventral wall defects and the slight increase in AFP in cases of sex chromosomal anomalies other than Turner's syndrome was found. AFP and total hCG are not likely to replace the markers free β-hCG and PAPP-A in first trimester screening for chromosomal anomalies. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS: trisomy 18; trisomy 13; turner's syndrome; free β-hCG; PAPP-A; first trimester screening

INTRODUCTION

In second trimester trisomy 21 pregnancies maternal serum alpha-fetoprotein (AFP) is reduced (on average 0.70 MoM) and total hCG is increased (on average 2.00 MoM) (Wald *et al*., 1997). In trisomy 18 pregnancies, both total human chorionic gonadotropin (hCG) and AFP levels are reduced (Canick *et al*., 1990; Barkai *et al*., 1993; Palomaki *et al*., 1995). In cases when the trisomy 18 fetus is also associated with a neural tube defect the AFP is invariably increased but not so in cases with a Ventral Wall Defect (VWD). In Turner's syndrome the marker patterns are less distinct but in cases with fetal hydrops AFP is reduced (0.83 MoM) and total hCG is increased (5.90 MoM), whilst in non-hydropic Turner's syndrome AFP is reduced (0.69 MoM) but total hCG is near normal (0.90 MoM) (Ruiz *et al*., 1999). In trisomy 13 no clear pattern has been observed (Saller *et al*., 1999).

In the first trimester the only biochemical markers of any value for use in screening for trisomy 21 are free β-hCG and pregnancy associated plasma protein-A (PAPP-A), and in a large series of 210 cases we have demonstrated low levels of PAPP-A (0.51 MoM) and raised levels of free β-hCG (2.15 MoM) (Spencer *et al*., 1999). In contrast, AFP and total hCG are poor markers of trisomy 21 (Spencer *et al*., 2000d). In this study we examine the value of AFP and total hCG in the other chromosomal abnormalities and compare these to previously reported values of PAPP-A and free β-hCG (Tul *et al*., 1999; Spencer *et al*., 2000a, b, c).

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METHODS

From 1994 onwards maternal serum samples were collected at the Harris Birthright Research Centre from women prior to chorionic villus sampling carried out because of advanced maternal age or increased risk for chromosomal abnormality after nuchal translucency measurement at 10–14 weeks. Serum was stored at -20°C. Maternal age, weight, duration of pregnancy based on last menstrual period, and crown–rump length (CRL), along with all relevant ultrasound findings, were registered in a database. After karyotyping, the details were added to the records in the fetal database. Examination of these records was made to retrieve as many non-trisomy 21 aneuploidies as possible. Nine hundred and forty-seven control samples with maternal and gestational age-matching were retrieved from women having a normal karyotype or the birth of a baby without abnormalities. This control set have been part of previous studies (Spencer *et al*., 1999; Tul *et al*., 1999; Spencer *et al*., 2000a, b, c).

In total 53 cases of trisomy 18, 42 cases of trisomy 13, 46 cases of Turner's syndrome and 13 other sex chromosome anomalies (47XXX, 47XXY, 47XYY) were available for study. These sets of chromosome abnormalities have been part of previous studies (Spencer *et al*., 1999; Tul *et al*., 1999; Spencer *et al*., 2000a, b, c).

Maternal serum AFP and total hCG were measured with the Kryptor analyser—a rapid random access immunoassay analyser using immunofluorescent immunoassays (CIS UK Ltd, High Wycombe, Bucks, UK). The samples were measured over a period of five days. The between-day precision of these assays has been previously reported (Spencer *et al*., 2000d).

To correct for marker variation with gestational age each value was converted to MoMs from the

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Table 1—Mean (range) maternal age, gestation, crown–rump length (CRL) and storage time for the study population and the control population

	Controls ($n=947$)	Trisomy 18 ($n=53$)	Trisomy 13 ($n=42$)	Turner's ($n=46$)	Other sex aneuploidy ($n=13$)
Maternal age (years)	35 (15–47)	35 (18–46)	36 (26–45)	36 (15–47)	32 (26–43)
Gestation (days)	85 (72–94)	86 (79–94)	85 (77–96)	86 (76–95)	87 (75–93)
CRL (mm)	60 (38–85)	53 (36–71)	56 (44–75)	56 (40–78)	61 (47–72)
Storage time (days)	546 (102–1811)	813 (32–1395)	1011 (0–2330)	768 (53–1382)	1025 (25–1380)

Table 2—Median AFP and total hCG MoM with $\log_{10}$ SD and the statistical significance of any difference from the control group as measured by Mann–Whitney U tests

	Median AFP	*p* value	$\log_{10}$ SD	Total hCG	*p* value	$\log_{10}$ SD
Trisomy 18 (all cases)	0.910	0.5327	0.4833	0.379	<0.0001	0.2686
Trisomy 18 (VWD only)	2.905	<0.0001	0.5942	0.261	<0.0001	0.2311
Trisomy 18 (excluding VWD)	0.813	0.3922	0.2687	0.385	<0.0001	0.2818
Trisomy 13	0.924	0.4089	0.3544	0.379	<0.0001	0.2656
Turner's	1.138	0.1856	0.3711	0.801	0.2678	0.2562
Other sex anomalies	1.356	0.0026	0.3464	1.120	0.3705	0.1629

respective median marker levels in unaffected pregnancies of the same gestational age derived in a previous study (Spencer *et al.*, 2000d). Statistical analysis of data was performed using Excel and Analyse-It (Smart Software, Leeds, UK), a statistical software 'add-in' for Excel 97.

RESULTS

Table 1 summarizes the data for the control group and the various chromosomally abnormal groups. Table 2 summarizes the median MoMs observed in each chromosomal group. In the cases of trisomy 18 the

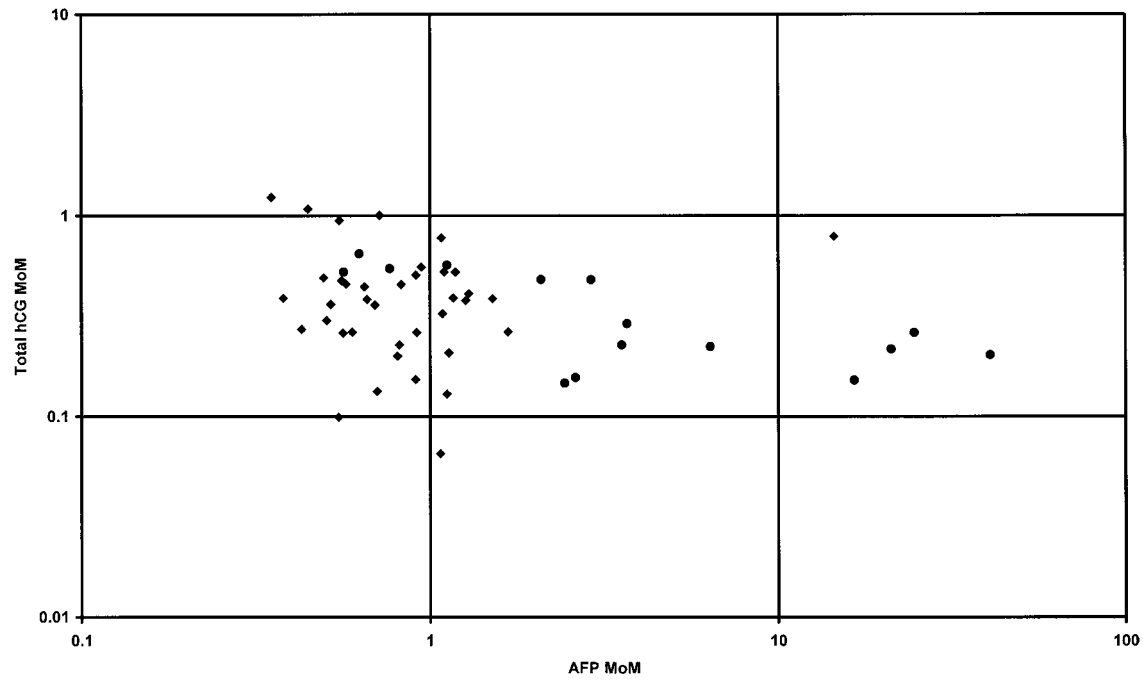

Figure 1—AFP and total hCG MoM in cases of trisomy 18 (● = cases with VWD)

results are also identified according to the presence ($n=15$) or absence ($n=38$) of a ventral wall defect. Of the markers from the various anomalies, only the following reached any statistical significance: the reduced levels of total hCG in cases of trisomy 18 (with or without ventral wall defect); the increased levels of AFP in cases of trisomy 18 with a ventral wall defect; the increased levels of AFP in the other sex anomaly group; and the reduced levels of total hCG in cases of trisomy 13. The finding of increased levels of AFP in cases of trisomy 18 associated with ventral wall defects is at odds with the findings of normal levels in the second trimester in the small series reported by Palomaki *et al.* (1995).

Figures 1–4 show the results and the distributions for each anomaly group.

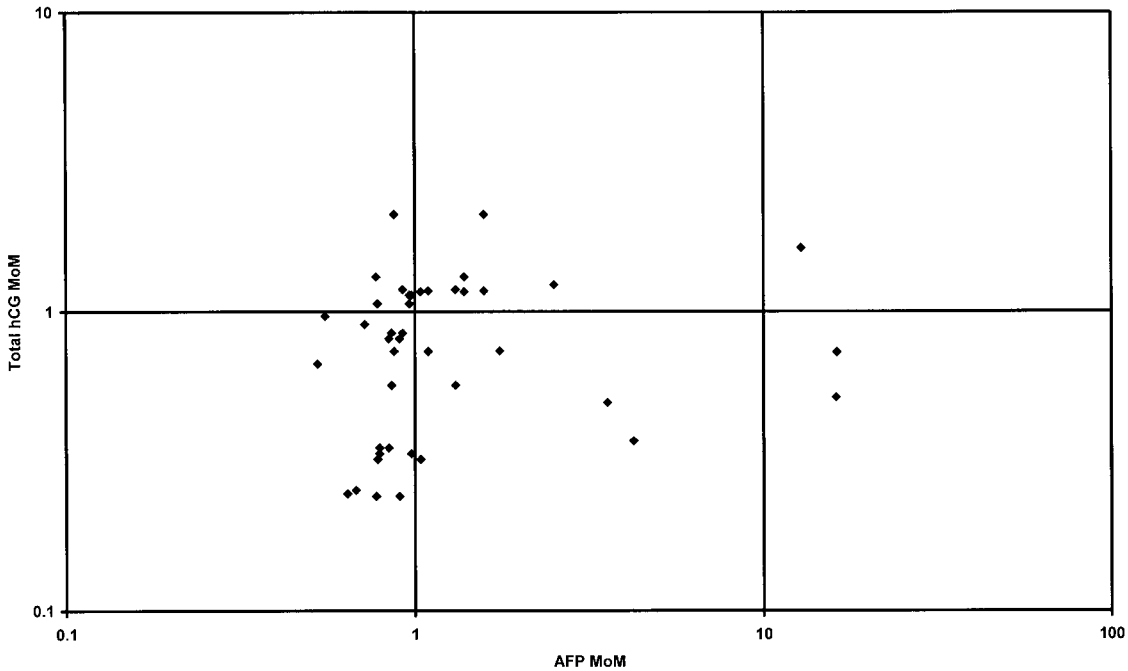

Figure 2—AFP and total hCG MoM in cases of trisomy 13

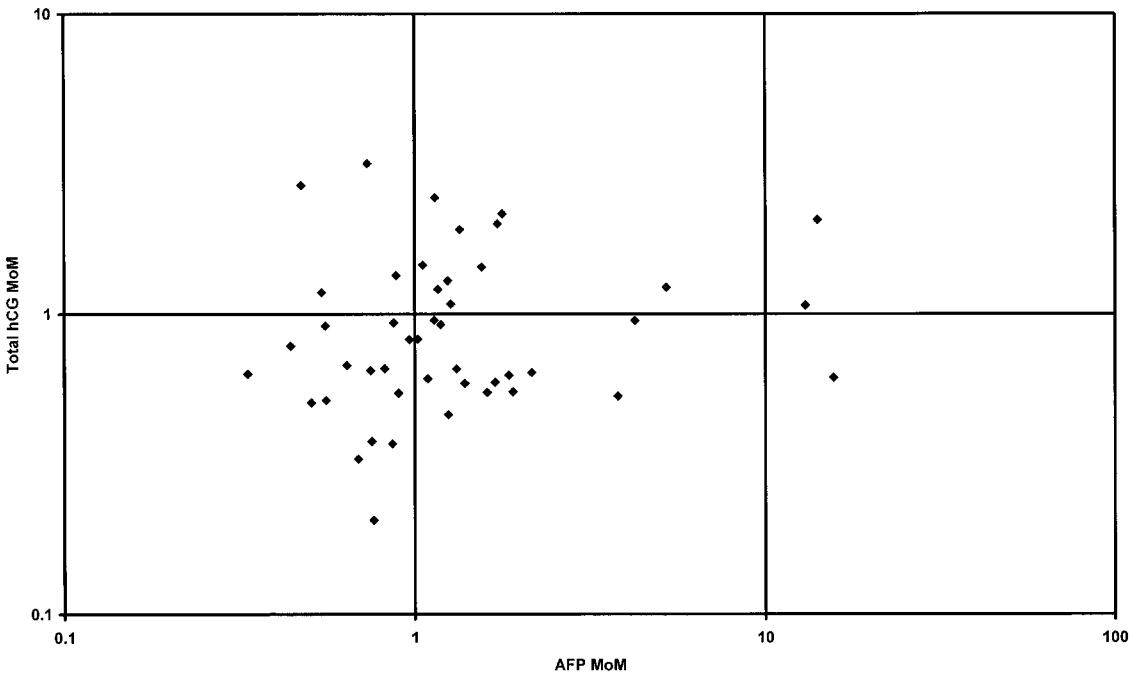

Figure 3—AFP and total hCG MoM in cases of Turner's syndrome

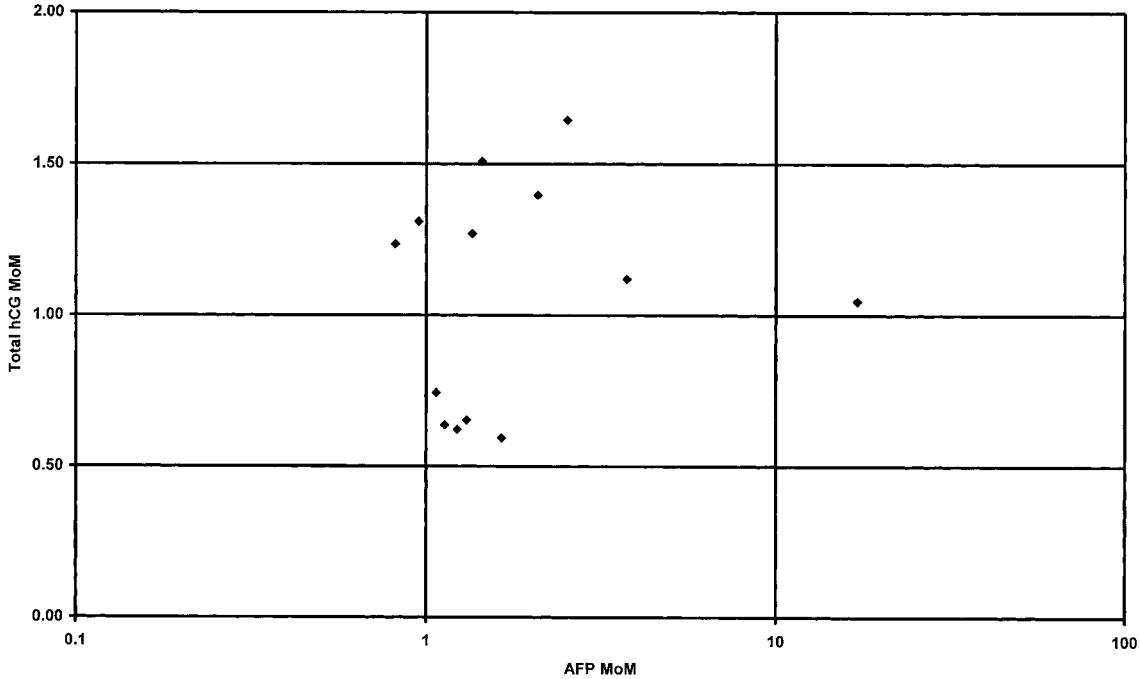

Figure 4—AFP and total hCG MoM in cases of other sex chromosomal anomalies

Table 3—Median marker levels (MoMs) in first trimester aneuploidies

	AFP	Total hCG	Free β-hCG	PAPP-A
Trisomy 21	0.82	1.31	2.12	0.51
Trisomy 18	0.91	0.38	0.28	0.18
Trisomy 13	0.92	0.74	0.51	0.25
Turner's	1.14	0.80	1.11	0.49
Other sex aneuploidy	1.36	1.12	1.07	0.88
Triploidy	2.14	3.13	4.59	0.12

DISCUSSION

In first trimester trisomy 21 pregnancies maternal serum free β-hCG is increased and PAPP-A is decreased (Spencer *et al.*, 1999). In trisomy 18 and trisomy 13 pregnancies both PAPP-A and free β-hCG are decreased (Tul *et al.*, 1999; Spencer *et al.*, 2000a). In Turner's syndrome free β-hCG is normal whilst PAPP-A is reduced, and in other sex aneuploidies both markers are near normal (Spencer *et al.*, 2000b). In triploidy overall levels of free β-hCG are high and PAPP-A levels are reduced but the pattern is dependent upon the triploidy phenotype with type I having supra low free β-hCG and supra low PAPP-A and type II having elevated free β-hCG and marginally reduced PAPP-A (Spencer *et al.*, 2000c).

The findings of this study of first trimester maternal serum AFP and total hCG demonstrate that only reduced levels of total hCG in trisomy 18 and 13 cases are significantly different from normal, and when the median MoMs are compared with the other markers both AFP and total hCG are inferior (Table 3). The findings are comparable to those in trisomy 21 and triploidy where AFP and total hCG have been shown to be poor discriminators in comparison with free β-hCG and PAPP-A (Spencer *et al.*, 2000c, d). Therefore, during the first trimester of pregnancy the markers of choice for all chromosomal abnormalities are maternal serum free β-hCG and PAPP-A.

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REFERENCES

Barkai G, Goldman B, Ries L, Chaki R, Zer T, Cuckle H. 1993. Expanding multiple marker screening for Down's syndrome to include Edward's syndrome. *Prenat Diagn* **13**: 843–850.

Canick JA, Palomaki GE, Osthanondh R. 1990. Prenatal screening for trisomy 18 in the second trimester. *Prenat Diagn* **10**: 546–548.

Palomaki GE, Haddow JE, Knight GJ, Wald NJ, Kennard A, Canick JA, Saller DN, Blitzer MG, Dickerman LH, Fisher R, Hansmann D, Hansmann M, Luthy DA, Summers AM, Wyatt P. 1995. Risk-based prenatal screening for trisomy 18 using alpha-fetoprotein, unconjugated oestriol and human chorionic gonadotropin. *Prenat Diagn* **15**: 713–723.

Ruiz C, Lamm F, Hart PS. 1999. Turner syndrome and multiple marker screening. *Clin Chem* **45**: 2259–2261.

Saller DN, Cnick JA, Blitzer MG, Palomaki GE, Schwartz S, Blakemore KJ, Haddow JE. 1999. Second trimester maternal serum analyte levels associated with fetal trisomy 13. *Prenat Diagn* **19**: 813–816.

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 β-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 β-hCG and PAPP-A in fetal sex chromosome 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**: 495–500

Spencer K, Berry E, Crossley JA, Aitken DA, Nicolaides KH. 2000d. Is maternal serum total hCG a marker of trisomy 21 in the first trimester of pregnancy. *Prenat Diagn* **20**: 311–317

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

Wald NJ, Kennard A, Hackshaw A, McGuire A. 1997. Antenatal screening for Down's syndrome. *J Med Screen* **4**: 181–246.