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A first trimester trisomy 13/trisomy 18 risk algorithm combining fetal nuchal translucency thickness, maternal serum free β-hCG and PAPP-A

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This study examines 45 cases of trisomy 13 and 59 cases of trisomy 18 and reports an algorithm to identify pregnancies with a fetus affected by trisomy 13 or 18 by a combination of maternal age fetal nuchal translucency (NT) thickness, and maternal serum free β-hCG and PAPP-A at 11–14 weeks of gestation. In this mixed trisomy group the median MoM NT was increased at 2.819, whilst the median MoMs for free β-hCG and PAPP-A were reduced at 0.375 and 0.201 respectively. We predict that with the use of the combined trisomy 13 and 18 algorithm and a risk cut-off of 1 in 150 will for a 0.3% false positive rate allow 95% of these chromosomal defects to be identified at 11–14 weeks. Such algorithms will enhance existing first trimester screening algorithms for trisomy 21. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS: prenatal screening; aneuploidy; trisomy 13; trisomy 18; nuchal translucency; free β-hCG; PAPP-A

INTRODUCTION

Trisomies 18 and 13 are the second and third most common autosomal trisomies after trisomy 21. In the first trimester of pregnancy trisomy 21 occurs at a frequency eight times that of trisomy 13 and three times that of trisomy 18. Ultrasonographic features of trisomies 13 and 18 in the first trimester include increased fetal nuchal translucency thickness (NT) (Sherod *et al*., 1997; Snijders *et al*., 1999), as is also the case with trisomy 21. However, unlike cases with trisomy 21, levels of maternal serum free β-hCG and pregnancy associated plasma protein-A (PAPP-A) are both reduced (Tul *et al*., 1999; Spencer *et al*., 2000a), and it is not possible to devise a specific algorithm which will differentiate between cases of trisomy 13 and trisomy 18. In order to enhance our first trimester screening programme we have sought to derive an algorithm which will provide a combined risk of trisomy 13 or trisomy 18 and to assess the likely detection rate using such an approach.

METHODS

Individual fetal NT and maternal serum free β-hCG and PAPP-A results for 42 cases with trisomy 13 and 50 cases with trisomy 18 were available from previous studies (Spencer *et al*., 2000a; Tul *et al*., 1999). These cases were supplemented with data from an additional three cases of trisomy 13 and nine cases of trisomy 18 which were identified during prospective first trimester screening in the OSCAR clinic at Harold Wood Hospital (Spencer *et al*., 2000b). In all cases fetal NT was measured under standardised conditions (Snijders *et al*., 1998) by sonographers certified by the Fetal Medicine Foundation. All biochemical measurements were performed using the Kryptor analyser (Brahms Diagnostica GmbH, Berlin) and the performance of this system has been previously described (Spencer *et al*., 1999a). Population parameters for the unaffected population were obtained from previous studies (Nicolaides *et al*., 1998; Spencer *et al*., 1999a).

Statistical analysis

All marker measurements were converted to MoMs using medians derived from normal pregnancies at the same gestation (Spencer *et al*., 1999a). Correction of free β-hCG and PAPP-A MoM for maternal weight was also performed using the reciprocal-linear regression weight correction procedure of Neveux *et al*. (1996) with locally derived parameters (Spencer *et al*., 2000c).

Assessment of the combined risk algorithm as a potential screening procedure was examined using standard statistical modelling techniques (Royston and Thompson, 1992). We used previously identified parameters for PAPP-A and free β-hCG for unaffected pregnancies (Spencer *et al*., 1999a) and similarly data for nuchal translucency from 95 476 unaffected pregnancies (Nicolaides *et al*., 1998; Snijders *et al*., 1998). For trisomy 13 and trisomy 18 affected pregnancies we used the combined population parameters from this analysis. Using these population parameters, a series of 15 000 random MoM values were selected for each marker from within the Gaussian distributions of the affected and unaffected pregnancies. These values were then used to calculate a likelihood ratio (Reynolds and Penney, 1990) for the combination of the three markers. These likelihood ratios were then used, together with the derived combined age related risk for trisomy 13 or trisomy 18 in the first

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trimester from the data of Snijders *et al*. (1995), to calculate the expected detection rate of affected pregnancies at a fixed false positive rate in a population with the maternal age distribution of pregnancies in England and Wales (Office of National Statistics, 2000)

RESULTS

Table 1 identifies the risk of trisomies 13 and 18 at 12 weeks of gestation for different maternal ages and also shows the combined risk of either trisomy occurring in an individual pregnancy.

Table 2 summarises the distribution parameters for the unaffected population and for the combined trisomy 13 and trisomy 18 populations. As reported in our previous studies (Spencer *et al*., 1999a) in the unaffected population there was no significant correlation between $\log_{10}$ MoMs for NT and free β-hCG ($r = -0.057$) and between the $\log_{10}$ MoMs for NT and PAPP-A ($r = 0.000$). There was a small significant correlation between $\log_{10}$ MoMs for free β-hCG and PAPP-A ($r = 0.160$). In the combined trisomy 13 and 18 group there was a small significant correlation between $\log_{10}$ MoMs for NT and free β-hCG ($r = 0.152$) but not between $\log_{10}$ MoMs for NT and PAPP-A ($r = 0.068$), or between $\log_{10}$ MoMs for free β-hCG and PAPP-A ($r = 0.105$). The median MoM free β-hCG, PAPP-A and NT in the combined trisomy group was 0.375, 0.201 and 2.819 respectively.

When the observed statistical parameters were used in the mathematical model of a population with the maternal age distribution of pregnancies in England and Wales the detection rate and false positive rates that would be achieved at different risk cut-offs are shown in Table 3.

Table 1—Risk of trisomy 13 and trisomy 18 at 12 weeks' gestation at various maternal ages and the combined risk for either trisomy in any one individual pregnancy

Maternal age	Risk of T13	Risk of T18	Risk of either T13 or T18
15	7890	2545	1924
16	7860	2535	1917
17	7825	2524	1909
18	7780	2510	1898
19	7720	2490	1883
20	7640	2465	1863
21	7535	2431	1838
22	7405	2389	1806
23	7235	2334	1765
24	7020	2265	1712
25	6755	2179	1648
26	6430	2074	1568
27	6040	1948	1473
28	5595	1805	1365
29	5090	1642	1241
30	4545	1466	1109
31	3980	1284	971
32	3415	1102	833
33	2870	926	700
34	2370	765	578
35	1920	619	468
36	1535	495	374
37	1210	390	295
38	945	305	230
39	730	235	178
40	560	181	137
41	425	137	104
42	325	105	79
43	245	79	60
44	185	60	45
45	140	45	34
46	105	34	26
47	75	24	18
48	55	18	13
49	40	13	10
50	30	10	7

Table 2—Distribution parameters for the combined trisomy 13/18 and unaffected populations

	Free β-hCG	PAPP-A	NT
Log_{10} mean MoM unaffected	0.0040	−0.0040	0.0000
Log_{10} SD unaffected	0.2558	0.2431	0.1200
Log_{10} mean MoM affected	−0.4262	−0.6976	0.4500
Log_{10} SD affected	0.3165	0.3000	0.2521

Table 3—Trisomy 13/18 detection rates and false positive rate for the combined NT and maternal serum biochemistry marker combinations modelled against the age distribution of pregnancies in England and Wales

Risk cut off	False positive rate %	Detection rate %
1 in 50	0.10	93.15
1 in 100	0.20	94.61
1 in 150	0.30	95.35
1 in 200	0.39	95.83
1 in 250	0.47	96.19
1 in 300	0.54	96.47

DISCUSSION

Although the birth prevalence of trisomies 13 and 18 are considerably lower than that for trisomy 21 (1 in 5000 versus 1 in 650), the relative incidences at the 11 to 14 week ultrasound examination are considerably higher (1 in 800 versus 1 in 400) (Snijders *et al*., 1995). Thus at the time of first trimester screening it would be advantageous to be able to identify such cases at risk from those that have increased nuchal translucency as a result of trisomy 21 or other causes. It is well established that the biochemical pattern in pregnancies affected by trisomies 13 or 18 are different from that of trisomy 21 in that free β-hCG levels are reduced and that the low levels of PAPP-A are carried through into the second trimester (Spencer *et al*., 1999b). It is therefore not

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possible to create an algorithm which will distinguish between trisomies 13 and 18. However, the construction of a combined algorithm would allow clear identification of at-risk pregnancies. Using our combined algorithm we predict that at a 1 in 150 risk cut-off 95% of cases could be identified for an invasive testing rate of 0.3%. This compares well with the 90% detection for a 5% false positive rate achieved retrospectively (Spencer *et al*., 1999a) and prospectively (Spencer *et al*., 2000b) for trisomy 21. We believe this simple algorithm would benefit and enhance screening procedures in the first trimester.

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