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Maternal serum screening marker levels in women with a previous aneuploidy pregnancy

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Objective To re-evaluate in a larger cohort of patients if the maternal serum biochemical markers used in first trimester aneuploidy screening have the same marker distributions in pregnancies with a previous history of aneuploidy compared with those that have no previous history.

Methods Information related to previous pregnancy history is routinely recorded as part of first trimester screening in three centres King George, Kings College and Fetal Medicine Centre, London. From the database, records were extracted for women who had a previous pregnancy diagnosed with trisomies 13, 18 or 21. For each woman with a previous aneuploidy, five unaffected pregnancies in women of the same maternal age and with no previous aneuploidy pregnancy were selected as controls. A comparison was made between the marker distributions for pregnancy associated plasma protein-A (PAPP-A) and free β-human chronic gonadotrophin (β-hCG) amongst the cases and controls using nonparametric statistical tests.

Results A series of 8240 controls were compared against group of 1032 cases with a previous trisomy 21, 293 with a previous trisomy 18 and 158 with a previous trisomy 13. Cases with multiple previous trisomies were excluded. There were no significant differences in the level of free β-hCG; however, in cases of trisomy 21 and trisomy 13 the levels of PAPP-A were increased by 5 and 16%, respectively.

Conclusion Risk calculation algorithms may need to take account of the increased PAPP-A levels in women with a previous trisomy 21 or trisomy 13. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS: PAPP-A; free β-hCG; first trimester; Down's syndrome; trisomy

INTRODUCTION

Calculation of risk for trisomy 21 or either of the other major aneuploidies (trisomy 13 or 18) is usually performed by modifying the *a priori* risk of the aneuploidy by a likelihood ratio derived from the marker profile. In most instances the *a priori* risk is based on the maternal age, but in a small proportion of cases a previous pregnancy with a specific aneuploidy needs to be taken into account in addition to the age-related background risk. Current practice is that the age-related background risk is modified by a fixed percentage usually of the order of 0.75% in the first trimester for trisomy 21 (Cuckle and Arbuzova, 2004) and trisomies 13 and 18 (Nicolaides *et al*., 1999).

Until recently, it has been assumed that the distribution of marker levels in women with a previous aneuploidy pregnancy was the same as in those without a previous affected pregnancy. In 2005, we reported preliminary evidence that this may not be the case and found significantly increased levels of both free β-human chronic gonadotrophin (β-hCG) and PAPP-A (Cuckle *et al*., 2005). In this present study, we look to extend this assessment of whether marker distributions are different in pregnancies after a previous aneuploidy.

METHODS

Information on previous aneuploidy pregnancies is routinely sought either on the first trimester screening request form or during the patient consultation in the screening centres at King George Hospital, Goodmayes (formerly at Harold Wood Hospital, Romford), at Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London and at the Fetal Medicine Centre, London. In all three centres, all relevant clinical information is recorded in a foetal database (PIA Fetal Database, ViewPoint, Wessling, Germany) along with ultrasound information and the biochemical parameters measured as part of a first trimester screening program. At King George Hospital and at the Fetal Medicine centre the biochemical markers were measured by time-resolved amplified cryptate emission using the Brahms Kryptor system (Brahms AG, Hennigsdorf, Germany), whilst at King's College the markers were measured by time-resolved fluorescence using the DelfiaXpress system (PerkinElmer Life Sciences, Turku, Finland).

An SQL query of the databases at the three sites was set up to extract relevant data in all cases in which the patient had a history of a previous aneuploid pregnancy.

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Table 1—Summary of median maker MoMs in controls and cases with previous aneuploidy pregnancies

Group	n	Median MoM	95% CI	IQR	p Mann–Whitney test	p median test
Control free β-hCG	8240	0.983	0.966–0.998	0.826	—	—
Trisomy 21 free β-hCG	1032	0.976	0.922–1.033	0.773	0.3225	0.8172
Trisomy 18 free β-hCG	294	0.993	0.920–1.105	0.869	0.8105	0.0951
Trisomy 13 free β-hCG	158	0.946	0.876–1.119	0.844	0.3544	0.8096
Control PAPP-A	8240	1.000	0.987–1.011	0.701	—	—
Trisomy 21 PAPP-A	1032	1.050	1.010–1.086	0.730	0.0003	0.0159
Trisomy 18 PAPP-A	294	1.009	0.944–1.090	0.835	0.0498	0.6329
Trisomy 13 PAPP-A	158	1.161	1.027–1.296	0.837	0.0011	0.0299

β-hCG, β-human chronic gonadotrophin; CI, confidence interval; IQR, interquartile range; MoM, multiple of the median.

For each case, five pregnancies of the same maternal age (+/−1 year) and tested at the same period (+/−2 days) were selected as controls.

For each case and controls, the raw analytical value for free β-hCG and PAPP-A was converted to multiples of the appropriate gestation [multiple of the medians (MoMs)] and corrected for maternal weight, ethnicity, smoking status, parity, IVF pregnancy and measuring instrument as outlined in Kagan *et al*. (2008) and which forms the basis of the FMF 2008 risk algorithm.

In cases when women had more than one different type of aneuploidy in previous pregnancies, these cases were excluded from further analysis. The marker levels in those women with a previous trisomy 21, previous trisomy 13 and previous trisomy 18 were each compared with the control group using nonparametric Mann-Whitney tests and the median test.

RESULTS

In total, 1648 women were identified with a previous aneuploidy pregnancy. Of these, 165 had multiple pregnancies with more than one type of aneuploidy. A total of 1032 women had a previous pregnancy with trisomy 21, 293 with trisomy 18 and 158 with trisomy 13. The control group included 8240 women without a previous aneuploidy pregnancy.

The median marker MoMs in the control group and aneuploidy group are shown in Table 1 along with the p values derived from both the Mann-Whitney test and the median test of cases versus controls. Free β-hCG levels were not found to be significantly different between controls and any previous aneuploidy; however, for PAPP-A there was a significantly high median MoM of 5% in cases with a previous trisomy 21 and 16% in cases with a previous trisomy 13 but not for trisomy 18.

The spread of the log MoM in each group was similar for free β-hCG being 0.261 in controls and 0.255, 0.279 and 0.278 in the trisomy 21, trisomy 18 and trisomy 13 groups, whilst that for PAPP-A was similar in controls, trisomy 21 and trisomy 13 cases (0.231, 0.227, 0.229) but higher in the trisomy 18 cases (0.271).

DISCUSSION

The results of this study confirm that levels of PAPP-A in pregnancies with a previous history of trisomy 21 or trisomy 13 are increased between 5 and 16%, respectively, but not increased in trisomy 18. This is in agreement with our previous data (Cuckle *et al*., 2005). However, we could find no evidence for any elevation of free β-hCG, contrary to our earlier study in 2005 (Cuckle *et al*., 2005). In the earlier study, no correction of marker MoMs were made for smoking, ethnicity, parity or IVF pregnancy and whilst an attempt to adjust for parity was made by matching cases to controls of the same maternal age (and hence likely parity). In this study, we have controlled directly for all of these variables in the adjustment of the marker MoMs and chosen an age-matched control group also.

The level of difference we have seen in this study is smaller than we reported before. Whether the size of the difference we report (5–16%) is significant and worth correcting for is probably debatable. An artificially increased PAPP-A is likely to lead to some small decrease in detection amongst those women with a previous trisomy (21 or 13); however, set aside the very small incidence of pregnancies with a previous affected pregnancy population detection rates will not improve if correction is made.

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