Maternal serum ADAM12s in the late first trimester of pregnancies with Trisomy 21

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INTRODUCTION

A disintegrin And Metalloprotease (ADAM12s) (Gilpin et al., 1998) has been shown to have proteolytic activity against insulin-like growth factor binding proteins 3 and 5 (Loechel et al., 2000; Shi et al., 2000) and is thought to be part of a mechanism controlling fetal growth during pregnancy (Cowans and Spencer, 2007). In pregnancies with Trisomy 21, reduced levels of ADAM12s have been found in the early first trimester (Laigaard et al., 2003, 2006a,b) with levels increasing above normal in the second trimester (Christiansen et al., 2007). Similar patterns have been observed for Trisomy 18 (Laigaard et al., 2005a, 2006a; Spencer and Cowans, 2007) and also with other rare aneuploides (Spencer et al., 2007). It was concluded that ADAM12s may have a ‘window of uselessness’ in terms of clinical discrimination located somewhere between 11 and 13 weeks of pregnancy (Christiansen et al., 2007). In this present study, we explore further ADAM12s in cases with Trisomy 21 between 11 and 13 weeks of gestation.

MATERIALS AND METHODS

Screening for Down syndrome and other chromosomal anomalies by a combination of fetal nuchal translucency (NT) thickness and maternal serum-free β-hCG and Pregnancy Associated Plasma Protein-A (PAPP-A) at 11+0 to 13+6 weeks was offered to all women booked for maternity care at Harold Wood Hospital, Essex (between June 1998 and December 2004), King George Hospital, Goodmayes (between July 2001 and December 2004), Kent and Canterbury Hospital, Canterbury (between July 2002 and December 2004), William Harvey Hospital, Ashford (between July 2002 and December 2004) and Queen Elizabeth The Queen Mother’s Hospital, Margate (between July 2002 and December 2004). An ultrasound examination was carried out to measure the fetal NT and crown-rump length (CRL) and to diagnose any major structural defects. All scans were carried out by sonographers who had obtained the Fetal Medicine Foundation certificate of competence in the 11–14 weeks’ scan (www.fetalmedicine.com). The maternal serum-free β-hCG and PAPP-A were measured using the Kryptor analyser (Brahms AG, Berlin) and the performance of this assay has been described previously (Spencer et al., 1999). Patient-specific risks were calculated by a multivariate approach using population parameters established in large-scale retrospective studies and prospective studies (Snijders et al., 1998; Spencer et al., 1999) and the maternal age and gestational-related risk of Trisomy 21 at the time of screening (Snijders et al., 1999) or for Trisomy 13/18 (Spencer and Nicolaides, 2002). Women with a risk of greater than 1:300 for Trisomy 21 or 1:100 for Trisomy 13/18 were offered invasive testing to determine the fetal karyotype. Data on pregnancy outcome were obtained from the cytogenetics laboratories, the National Chromosomal Anomaly

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Cytogenetic Register, and the maternity units in which the pregnancy was delivered. In total, from this routine screening program, 46 samples collected as part of routine prospective screening and which had not previously had ADAM12s measured were selected for further analysis. Of the cases, 13 of 46 resulted in live-born infants with Trisomy 21, and of the 13 live-born, 8 cases were missed by the screening program with the remaining 3 declining invasive testing, and 2 continuing with the pregnancy.

As a control group we used gestational age-matched data from the 414 first-trimester samples published as part of a previous study (Cowans and Spencer, 2007) and which were analyzed in the same batches as these Trisomy 21 cases. In all first-trimester cases, gestational age at sample collection (median controls = 85 days; median cases = 88.9 days) was determined by CRL measurement. Samples had on average been frozen and thawed as aliquots once (range 0–2). The control group had a median maternal age of 29.5 years whilst that for the group of cases was 37 years. The maternal weight of the two groups was similar (median controls = 65.0 kg; median cases was 66.5 kg). The group was predominantly of Caucasian origin (85% in the controls and 83% in the cases). All samples were obtained as part of routine screening services for which patients gave written consent for excess diagnostic material to be used for research purposes.

Serum ADAM12s was measured blind to clinical outcome, using a newly developed manual DELFIA assay (PerkinElmer Life & Analytical Sciences, Turku, Finland) which was based on previously described ELISA and AutoDELFIA assays (Laigaard et al., 2003, 2005b) as previously described (Cowans and Spencer, 2007).

ADAM12s marker concentrations were converted into multiples of the median (MoM) by dividing each result by the expected median marker level from the control pregnancies at the same gestational age as derived from the equations in a previous study (Cowans and Spencer, 2007) and corrected for maternal weight as also described in the previous study.

RESULTS

The overall median ADAM12s MoM was 0.977 (95% confidence interval 0.724–1.082) across the gestational range of 11–13 weeks. At 11 completed weeks it was 0.914 (n = 7), at 12 completed weeks it was 0.896 (n = 23) and at 13 completed weeks it was 1.032 (n = 16). Correlation of ADAM12s and PAPP-A in the cases had a Pearson’s r of 0.28 (p = 0.063), whilst the correlation of ADAM12s with free β-hCG gave an r of −0.13 (p = 0.394), and with delta NT it was r = 0.01 (p = 0.452). In the controls the correlation with PAPP-A, free β-hCG and NT were 0.324, 0.062 and 0.110, respectively.

DISCUSSION

In this study we have shown that maternal serum ADAM12s concentrations are relatively close to normal between the narrow gestational window of 11–13 weeks with some limited evidence of an increasing pattern across this time period. These results are in general agreement with the study of Laigaard et al. (2006a) on a smaller series of 16 cases spread across the period 9–12 weeks, and the larger series of 218 cases spread across the period 10–13 weeks (Laigaard et al., 2006b). The earlier study of Laigaard et al. (2003) showed a potential value of reduced levels of maternal serum ADAM12s in pregnancies with Trisomy 21 examined in particularly early gestation (prior to 10 weeks). Other studies (Christiansen et al., 2007) have shown elevated levels of ADAM12s in the second trimester and there now appears a demonstrated temporal pattern for this marker with very reduced levels as early as 7 weeks to relatively normal levels around 12 weeks (Laigaard et al., 2006b) to increased levels at 15–18 weeks (Christiansen et al., 2007).

Combining data from all the published series (Laigaard et al., 2003, 2006a, b) with the current series gives median values as shown in Table 1. From this, there is a period at the end of the first trimester—probably after the 11th or 12th week when ADAM12s is unlikely to play a major part in future first-trimester screening developments although there is considerable variation between the three main studies done at this time period. This may partly be a reflection of the small numbers in the earlier study, or possible bias in sample selection. Also, the current data was generated using a new format of the ADAM12s assay (albeit, using the same monoclonal antibody pair), and it is possible that the two assays are not directly comparable.

Table 1.—Median maternal serum ADAM12s MoMs in the first trimester of pregnancies with Trisomy 21 at different completed gestational weeks by metanalysis (log median in each study weighted by the number of cases).

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The low levels of ADAM12s in early first trimester have still only been demonstrated in one study containing 13 cases prior to 10 weeks. It remains still to be seen if the very low levels of ADAM12s in cases with Trisomy 21 in early first trimester seen in the early Laigaard et al. (2003) study can be replicated.

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REFERENCES


