Predicting complications of pregnancy with first-trimester maternal serum free-βhCG, PAPP-A and inhibin-A

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Objective  To find whether free βhCG, PAPP-A and inhibin-A levels in maternal serum or fetal nuchal translucency (NT) thickness at the first-trimester screening for trisomy 21 (T21) might detect women at high risk for adverse pregnancy outcomes.

Methods  A retrospective analysis of 1136 women with singleton pregnancy between 10 and 14 weeks. Women with pregnancy complications were allotted to five subgroups: small for gestational age (SGA), large for gestational age (LGA), gestational diabetes (GDM), hypertensive disorders, preterm delivery; women with normal pregnancy represented the control group. NT, maternal serum free βhCG, PAPP-A and inhibin-A were measured. Mann–Whitney test was used for the comparison of free βhCG, PAPP-A, inhibin-A and NT between a subgroup of a certain pregnancy complication and the control group. Multivariate logistic regression models were built to explore the relationship among different variables and the occurrence of pregnancy complications.

Results  PAPP-A values were significantly lower in women who delivered SGA babies (n = 51, 0.76 MoM; p = 0.002) and significantly higher in women who delivered LGA babies (n = 120, 1.12 MoM; p = 0.036). In women with GDM (n = 27), free βhCG, PAPP-A and inhibin-A were insignificantly lower than in controls, whereas in women with hypertensive disorders (n = 56) no significant differences between the groups were found. In women with a preterm delivery (<34 weeks) (n = 17), inhibin-A levels were significantly higher (1.25 MoM; p = 0.015).

Conclusion  Low PAPP-A level is associated with the delivery of an SGA baby and high PAPP-A with the delivery of an LGA baby. High inhibin-A is associated with preterm delivery before 34 weeks. Fetal placental products in the first trimester do not prove to be useful as a screening tool for predicting pregnancy complications. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS: prenatal screening; free βhCG; PAPP-A; inhibin-A; trisomy 21; small for gestational age; large for gestational age; adverse outcome

INTRODUCTION

Increased risk for adverse outcome of pregnancies with false-positive results on second-trimester biochemical screening for trisomy 21 (T21) was already noted in the early period of screening (Beekhuis et al., 1992; Pergament et al., 1995). The correlations of certain complications of pregnancy and abnormal values of single markers for T21 such as alpha-fetoprotein (AFP), human chorionic gonadotrophin (hCG) and unconjugated oestriol (uE3) in the second trimester were noted even earlier (Wald et al., 1977; Walters et al., 1985; Gonen et al., 1992; Lieppman et al., 1993; Muller et al., 1993). Numerous studies investigating second-trimester markers for T21 as markers of various pregnancy complications have been published since; yet the results are conflicting. The reasons for conflicting results might be due to differences in study designs or small sample sizes (Spencer, 2000). In two large studies with 28700 and 26500 women included, respectively, the relationships of abnormal serum marker values in the second trimester and adverse outcomes of pregnancies were confirmed, their conclusions being that this is of little clinical value in the prediction of pregnancy complications (Walton et al., 1999; Spencer, 2000).

Studies of the usefulness of first-trimester biochemical markers as predictors of pregnancy complications have shown that low levels of free beta-hCG (fβhCG) and pregnancy associated plasma protein-A (PAPP-A) at 10 to 14 gestational weeks were associated with subsequent development of pregnancy complications (Pedersen et al., 1995; Ong et al., 2000; Smith et al., 2002) and increased inhibin-A levels with pre-eclampsia (Sebire et al., 2000). In contrast, the study of Morssink et al. (1998) has shown that the levels of PAPP-A and fβhCG in the first trimester is not associated with subsequent fetal growth retardation or preterm delivery.

As the dilemma about abnormal levels of the first-trimester markers in anticipating pregnancy complications remains, we designed this study to explore whether the levels of fβhCG, PAPP-A and inhibin-A in maternal serum, or fetal nuchal translucency (NT) thickness at the first-trimester screening for T21 might detect the women at high risk for adverse outcome of pregnancy.
METHODS

In Ljubljana, first-trimester screening for T21 by nuchal translucency has been offered since November 1997. NT is measured according to the Fetal Medicine Foundation (FMF) guidelines (Snijders et al., 1998), the data are analysed by an FMF computer programme for risk calculation and the risk is reported to the woman. After appropriate counselling and informed consent, the women attending the screening between February 1999 and August 2001 were asked for a blood sample for the purpose of this study. The samples were sent to the laboratory where sera were frozen and stored at −20°C. Later, maternal serum fβhCG and PAPP-A were measured by the Kryptor analyser (Brahms AG, Berlin)—a rapid random access immunoassay analyser using time-resolved amplified cryptate emission (TRACE) technology. Inhibin-A was measured using DSL-10-28 100 Active Inhibin-A ELISA (DSL, Texas, USA), an enzyme-amplified two-step sandwich-type immunoassay. Demographic data, maternal weight, smoking status, obstetric history and the results of the NT scan were entered into a database. Outcomes of pregnancies were collected from a short follow-up questionnaire given to patients immediately after the NT scan and obtained from them after the end of pregnancy, or from hospital records or by telephone interviews with the women. The data on the course of pregnancy, gestational age at delivery, birthweight, sex and presence of anomalies of the baby were entered in the database.

Most frequent pregnancy complications, that is, small or large for gestational age babies, gestational diabetes mellitus (GDM), hypertensive disorders and preterm delivery, were the criteria for the formation of subgroups, whereas women without complications in pregnancy served as the control group.

Babies born with birthweight below the 10th centile for gestational age (according to Slovene reference standards) were included in the ‘small for gestational age’ (SGA) group, those born above the 90th centile in the ‘large for gestational age’ (LGA) group and all others in the ‘appropriate for gestational age’ (AGA) group. The Slovene reference standards for weight were used (Verdenik, 2000).

Gestational diabetes mellitus was diagnosed using a 3-h 100-g oral glucose tolerance test.

Pregnancy-induced hypertension (diastolic blood pressure ≥90 mm Hg) with or without proteinuria and pre-eclampsia were allotted to the group of hypertensive disorders.

The preterm delivery group was split into the very preterm group (delivery between 24 and <34 weeks) and preterm delivery (34 to <37 gestational weeks).

The study was approved by the national medical ethics committee.

Statistical analysis

Gestational age was calculated for each case from the crown-rump length (CRL). Regression analysis was done to derive the relationship between fβhCG, PAPP-A, inhibin-A, NT and gestational age, then the expected values of fβhCG, PAPP-A, inhibin-A and NT were calculated for each case, and the measured values were converted to multiples of medians (MoM). Correction of MoMs for maternal weight was performed using the reciprocal linear regression weight correction (Neveux et al., 1996).

The distributions of markers were tested using the Kolmogorov–Smirnov test of fit. Pearson correlation coefficients were computed for determination of correlation between markers, and maternal age and weight. Mann–Whitney test was used for comparison of MoMs of fβhCG, PAPP-A, inhibin-A and NT between the subgroups of women with a certain complication of pregnancy, and the control group of women without complications. Multivariate logistic regression models were built to explore the relationships among different variables and the occurrence of different complications later in pregnancy. Odds ratios with a 95% confidence interval (CI) were calculated. For the analysis, complications of pregnancy were defined as dichotomous variables (present = yes, absent = no). Smoking in pregnancy was also defined as a dichotomous variable.

Analyses were performed using SPSS 10.0 for Windows statistical package.

RESULTS

In the study group, 1293 women with singleton pregnancies were enrolled. Pregnancy outcomes were obtained from 1253 (96.9%) cases, but only 1136 women with known maternal weight were considered for further analysis. The women in whom some variables were occasionally missing (e.g. smoking) were excluded from the specific analyses only.

All patients included were Caucasians. The mean maternal age was 30.4 years (range 18–44 years), 284 (22%) were 35 or more years old. The mean maternal weight was 63.5 kg (range 40–110 kg), 1015 (80%) were nulliparous and 382 (35.1%) were primigravid. In 48 (4.2%) cases, the combined risk for T21 was greater than 1/300. All the babies were born without obvious signs of chromosomal abnormalities. The mean CRL was 63.9 mm (range 38–84 mm).

fβhCG, PAPP-A and inhibin-A MoMs all fitted a Gaussian distribution after correction for maternal weight and logarithmic transformation with Kolmogorov–Smirnov test showing linearity at the 0.01 probability level. In smokers, PAPP-A was significantly reduced (0.89 MoM) and inhibin-A was significantly increased (1.09 MoM) in comparison with non-smokers (1.02 MoM and 0.97 MoM, p = 0.004 and p = 0.031, respectively).

SGA babies

The birthweight of 51 (4.5%) babies was below the 10th centile for gestational age according to Slovene reference standards (Verdenik, 2000). PAPP-A values were lower in women who delivered SGA babies.
(0.76 MoM, controls with AGA babies 1.01 MoM, p = 0.002), PAPP-A \leq 0.5 MoM was present in 19.6% (10/51) of women who delivered an SGA baby and in 8.3% (79/953) of women with an AGA baby.

One fourth of the women with an SGA baby were smokers and their PAPP-A level was low (0.75 MoM), but PAPP-A level was also low in non-smokers with an SGA baby (0.82 MoM) and only slightly reduced in smokers with an AGA baby (0.91 MoM). PAPP-A level was normal in non-smokers with an AGA baby (1.02 MoM). In a multivariate model, a low PAPP-A level and the presence of hypertensive disorders were significant variables for predicting the delivery of an SGA baby (Table 1). The predictive value of PAPP-A became a weaker marker when the model was adjusted for smoking (Table 2). The risk for an SGA baby was 3.4 (95% CI 1.67–6.97) times greater among smokers than non-smokers (Table 2).

LGA babies

The birthweight of 120 (10%) babies was above the 10th centile for gestational age. PAPP-A values were significantly higher in the women who delivered an LGA baby (1.12 MoM, controls 1.01 MoM, p = 0.036). Of the 120 women, 9 (7.5%) were smokers. The levels of markers did not differ between smokers and non-smokers with an LGA baby. Five (4.2%) LGA babies of markers did not differ between smokers and non-smokers (Table 2).

In our multivariate model, feto-placental markers observed in the first trimester were not useful in detecting the women at risk for GDM when adjusted for maternal age, weight, smoking, parity and gravidity. Hypertension in pregnancy increased the risk of developing GDM also by 3.52 times. 63% (17/27) of the women with GDM also by 3.52 times. 63% (17/27) of the women who developed pre-eclampsia and delivered an SGA baby at 37.5 gestational weeks, the levels of markers were very low (0.31, 0.49 and 0.74 MoM for MoM hCG, PAPP-A, inhibin-A and NT respectively). In the five mothers out GDM, these values were 0.99, 1.01 and 0.99 MoM for MoM hCG, PAPP-A and inhibin-A respectively.

In the women who delivered an LGA baby at 37.4 gestational weeks, fβhCG was high (2.39 MoM), PAPP-A was 1.07 MoM, inhibin-A was 0.86 MoM for fβhCG, PAPP-A and inhibin-A respectively). For women without GDM, these values were 0.99, 1.01 and 0.99 MoM for fβhCG, PAPP-A and inhibin-A respectively.

Strong statistical correlations between GDM and hypertensive disorders (r = 0.092, p = 0.001), and GDM and maternal weight (r = 0.087, p = 0.004) were observed. Five women developed both GDM and hypertension in the current pregnancy.

In our multivariate model, feto-placental markers observed in the first trimester were not useful in detecting the women at risk for GDM when adjusted for maternal age, weight, smoking, parity and gravidity. Hypertension in pregnancy increased the risk of developing GDM also by 3.52 times. 63% (17/27) of the women with GDM were nulliparous.

Only one woman with pre-pregnancy diabetes mellitus type 2 was included in our study; the levels of all markers were very low (0.31, 0.49 and 0.74 MoM for MoM hCG, PAPP-A and inhibin-A respectively). She was 27 years old and her combined risk for T21 was low.

Hypertensive disorders

No statistically significant differences were found by comparing MoMs of fβhCG, PAPP-A, inhibin-A and NT between women who developed hypertensive disorders and controls. When adjusted for fβhCG, PAPP-A, NT, maternal age, weight, smoking, parity and gravidity, inhibin-A was found to be important in predicting hypertensive disorders (p = 0.001, odds ratio 2.01, 95% CI 1.32–3.05). Only two women with pre-gestational hypertension were included in our study; therefore, we could not include them in the multivariate model for predicting hypertensive disorders of pregnancy. One of them developed pre-eclampsia and delivered an SGA baby at 37.5 gestational week, the levels of markers were reduced (0.58, 0.44, 0.39 and 0.97 MoM for MoM hCG, PAPP-A, inhibin-A and NT respectively). The other had an uncomplicated pregnancy and delivered an AGA baby at 37.4 gestational week, fβhCG was high (2.39 MoM), PAPP-A was 1.07 MoM, inhibin-A was 1.49 MoM and NT was 0.96 MoM.

Table 1—Results of multivariate logistic regression model for predicting delivery of an SGA baby; other included variables (MoM hCG, MoM inhibin-A, MoM NT, maternal age, smoking, gravidity, GDM) did not reach statistical significance

<table>
<thead>
<tr>
<th>p</th>
<th>Odds ratio</th>
<th>95% CI</th>
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<tr>
<td>p &lt; 0.05</td>
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<tr>
<td>Maternal age</td>
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<td>MoM PAPP-A</td>
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Table 2—Results of multivariate logistic regression model 2 with the variable ‘smoking’ included for predicting delivery of an SGA baby; other included variables (MoM hCG, MoM inhibin-A, MoM NT, maternal age, weight, parity, gravidity, fetal sex) did not reach statistical significance

<table>
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<th>p</th>
<th>Odds ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
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<tr>
<td>Hypertensive disorders</td>
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<td>MoM PAPP-A</td>
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<td>0.529</td>
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Preterm delivery

The mean gestational age at the end of pregnancy was 39.6 weeks (range 14.4–42.8 weeks). Three pregnancies (0.3%) ended before 22 gestational weeks. The causes of these miscarriages were not found, chromosomal analysis was performed only in one case providing a normal karyotype. Seventeen women (1.5%) delivered between 22 and 33.9 weeks, 41 (3.6%) between 34 and 37 weeks and 1075 (94.6%) after the completed 37th gestational week. No statistically significant difference was found comparing MoMs of $f_{\beta}$hCG, PAPP-A, inhibin-A and NT of 58 women who delivered before the completed 37th gestational week with 1078 of those who delivered after 37 gestational weeks. The women who delivered before the completed 34th week had a significantly higher level of inhibin-A (1.25 MoM vs. 0.98 MoM in women who delivered after the completed 34th week, $p = 0.015$). The levels of $f_{\beta}$hCG and PAPP-A were also higher in this group but not significantly (1.06 and 1.10, respectively). Inhibin-A reached statistical significance ($p = 0.007$, odds ratio 2.98, 95% CI 1.36–6.53) when adjusted for $f_{\beta}$hCG, PAPP-A, NT, maternal age, smoking, invasive test in pregnancy, hypertensive disorders, first-trimester bleeding, parity and gravidity.

DISCUSSION

We consider the most interesting finding of our study to be the association between low maternal serum PAPP-A at 10 to 14 gestational weeks and delivery of SGA babies, and between high PAPP-A level and delivery of LGA babies. To our knowledge, this is the first study to demonstrate correlations between low PAPP-A levels and SGA babies, and high PAPP-A levels and LGA babies in the same population.

Until 1999, the function of PAPP-A was unknown, when Lawrence et al. (1999) found that PAPP-A is a protease for an insulin-like growth factor–binding protein-4 (IGFBP-4). Following cleavage, the affinity of IGFBPs for insulin-like growth factor-I (IGF-I) and IGF-II is reduced. Variables that regulate the amount of proteolysis regulate the action of the IGFs (Clemmons, 1998). Locally synthesized IGFs promote cellular mitosis and differentiation, and are probably important both in embryogenesis and in regulation of fetal and placental growth (Clemmons, 1998; van Kleffens et al., 1998). At term, cord blood concentrations of IGF-I are positively correlated, and concentrations of IGFBP-1 are inversely correlated with birthweight (Giudice et al., 1995). The level of PAPP-A in maternal serum might reflect the local level of PAPP-A and availability of IGFs. Low level of PAPP-A might indicate low levels of IGFs and poorer fetal and/or placental growth. At present, it is not known whether poor fetal growth is a consequence of poor placental function, or whether they are poorer because of the influence of the same factors (e.g. low levels of growth factors such as IGFs).

The association between low PAPP-A levels in the first half of pregnancy and fetal intra-uterine growth restriction has been reported previously (Westergaard et al., 1983; Pedersen et al., 1995; Ong et al., 2000; Smith et al., 2002; Yaron et al., 2002).

In our study, the median of PAPP-A in women who delivered babies with birthweight below the 10th centile for gestational age was 0.76 MoM. The odds ratio for an SGA baby was 2.7 (95% CI 1.3–5.5) if PAPP-A was ≤0.5 MoM (Se = 19.6%, Sp = 91.7%, PPV = 11%, NPV = 93.5%). However, two studies failed to demonstrate the association between PAPP-A levels and SGA babies (Morssink et al., 1998; Johnson et al., 1993). In one of them, only the women following fertility treatment were enrolled, which could be the reason for discrepancy in results (Johnson et al., 1993).

In our multivariate model for predicting the delivery of an SGA baby, low PAPP-A level at 10 to 14 gestational weeks and the presence of hypertensive disorders in pregnancy were significant variables after adjustment for $f_{\beta}$hCG, inhibin-A, NT, maternal age, weight, parity, gravidity and fetal sex. The predictive value of PAPP-A proved weaker when this model was adjusted for smoking. One fourth of women with SGA babies were smokers with low PAPP-A levels (0.75 MoM), but PAPP-A was reduced also in non-smokers with SGA babies (0.82 MoM) and slightly reduced in smokers with AGA babies (0.91 MoM).

The reduced level of PAPP-A in smokers has been reported previously (Spencer, 1999; de Graaf et al., 2000), the explanation being that smoking inhibits apoptosis of the syncytiotrophoblast and the consequence is disturbed feto-placental exchange (de Graaf et al., 2000). Additionally, the direct influence of smoking on reduced PAPP-A production may cause low levels in maternal serum and, probably more importantly, in intra-uterine PAPP-A levels. It is well known that smoking negatively affects the placental vessels and nutrient supply to the fetus affecting also PAPP-A production and lowering IGFs that may have synergistic effects on fetal growth.

On the other hand, in women delivering LGA babies, the PAPP-A level at 10 to 14 gestational weeks was significantly higher in comparison to the women delivering AGA babies. In the multivariate model, PAPP-A level, maternal weight, parity and male fetal sex were significant variables for predicting the delivery of an LGA baby after adjustment for $f_{\beta}$hCG, inhibin-A, NT, maternal age, smoking, gravidity and gestational diabetes mellitus. To our knowledge, no report on the correlation between LGA babies and high PAPP-A levels in maternal serum at 10 to 14 gestational weeks has been published.

Also, in our study the women with SGA babies had lower $f_{\beta}$hCG, and the women with LGA higher $f_{\beta}$hCG levels than the women with AGA babies. These differences were smaller than differences in PAPP-A
levels, and were not statistically significant. Inhibin-A was insignificantly lower in both SGA and LGA groups. An insignificantly lower level of inhibin-A in women that delivered babies with birthweight below the 5th centile has been reported by Sebire et al., 2000. We agree with the observation of Smith et al., 2002 that differences in the levels of fβhCG and PAPP-A reflect a specific property of PAPP-A in the physiological regulation of trophoblast function, and that the control of IGF system in the first trimester may play a key role in determining the subsequent pregnancy outcome (Smith et al., 2002). Birthweight and gestational age at delivery may be related to placental development or function during the first trimester (Johnson et al., 1993). Placental function may be assessed by its products.

The levels of the three analysed feto-placental products were lower in women who developed GDM, but none was statistically significant. Also, in the multivariate model, feto-placental markers did not prove to be significant in detecting women at risk for GDM. Low fβhCG and PAPP-A levels at 10 to 14 gestational weeks in women with pre-existing diabetes mellitus and with GDM were noted by Ong et al., 2000, and low PAPP-A levels in pre-existing diabetes mellitus were noted by Pedersen et al., 1998. In the second trimester, AFP, uE3 and hCG were reduced in women with insulin-dependent diabetes; for the purpose of screening for T21, the corrections for some markers are necessary (Wald et al., 1992), although some have argued that the improved quality of diabetic care renders correction now inappropriate. In our study, only one woman with pre-existing diabetes mellitus was included; her markers were low, and she delivered an LGA baby. Also, in the five women with GDM who delivered an LGA baby, PAPP-A levels were low (median 0.65 MoM). On the other hand, PAPP-A in non-diabetic mothers of LGA babies was high (1.12 MoM). LGA babies of diabetic mothers are different from LGA babies of non-diabetic mothers: they have increased adiposity, muscle mass and organomegaly. In contrast, their head circumference is not above average because brain growth is normal. In babies of diabetic mothers, the total body water is decreased in comparison to controls of a similar birthweight. Reduction in the total body water is more pronounced in LGA babies, since less intracellular water may be found in cells that have increased fat content (Brans et al., 1983). According to Pedersen, the periods of maternal hyperglycaemia result in fetal hyperglycaemia, stimulating fetal insulin release. Fetal hyperinsulinaemia results in macrosomia, and also contributes to the increased risk of intra-uterine death, respiratory distress syndrome, hypoglycaemia and other morbidity seen in neonates of diabetic mothers. The mother’s nutrients appear to play the major role in inducing excessive fetal growth in diabetic pregnancies (Landon and Gabbe, 2000).

Since non-diabetic mothers with LGA babies had high PAPP-A in the first trimester, we suppose this to be an important reason for increased fetal growth. PAPP-A increases IGF levels; IGFs are important in placental transport of nutrients to the fetus (Kniss et al., 1994) and promote synchronous fetal and placental growth, resulting in a healthy LGA baby. On the other hand, mothers with pre-existing diabetes or GDM delivering an LGA baby had low levels of PAPP-A; therefore we suppose that PAPP-A cannot be responsible for increased fetal growth, and increased fetal growth is very likely due to maternal hyperglycaemia. Thus, due to growth promoting factors different in diabetic and non-diabetic mothers, their LGA babies are different, and the morbidity encountered is higher in the former. Unfortunately, the number of included women was small and further studies are needed to confirm this hypothesis. In two other studies, low PAPP-A levels in diabetic pregnancies were reported (Ong et al., 2000; Pedersen et al., 1998), yet the data on the birth of LGA babies is missing. In women with GDM, and probably also in those with pre-existing diabetes, PAPP-A levels do not seem to be useful in predicting LGA babies because of decreased PAPP-A levels in GDM women.

In the group of pregnant women with hypertensive disorders, only inhibin-A was increased (1.07 MoM), reaching a statistical significance in the multivariate model after adjustment for fβhCG, PAPP-A, NT, maternal age, weight, smoking, parity and gravidity, but not in the univariate analysis. This might be the consequence of a small number of women, but it also indicates that the differences between hypertensive and normotensive women regarding inhibin-A levels are small. Sebire and co-workers found a significantly higher inhibin-A level (1.4 MoM) in nine women who developed pre-eclampsia (Sebire et al., 2000). Petraglia (1997) proposed the theory that the trophoblast increases the production of inhibin-A as an adaptive response to pathological conditions. Impaired placental perfusion and/or placental damage may be followed by a regenerative process with increased synthesis of placental products, but the spillage into maternal circulation as a consequence of placental damage after impaired placenta would also be the reason for increased levels of markers (Sebire et al., 2000).

In our study, no statistically significant difference was found in the levels of fβhCG, PAPP-A, inhibin-A and NT of 58 women who delivered before the completed 37th gestational week compared to 1078 women who delivered after 37 weeks, which is in agreement with two other studies (Ong et al., 2000; Morssink et al., 1998). But, in our group of ‘very preterm delivery’ (before 34 gestational weeks), all markers were increased. Inhibin-A levels were increased the most (1.25 MoM) reaching a statistical significance in the uni- and the multivariate model. This is consistent with the hypothesis that the pathophysiology of extreme premature delivery may be different from moderately premature delivery (Novy et al., 1995). Smith et al. (1998) were looking at fetal growth in the first trimester by measuring CRL. Suboptimal growth (smaller-than-expected CRL) was related to low birthweight and extremely premature delivery (24–32 gestational weeks), but not with a moderately premature delivery. They concluded that suboptimal intra-uterine environment in the first trimester limits fetal growth for the remainder of pregnancy and can be the cause for extremely preterm delivery.

Inhibin-A in maternal serum significantly (by 4–7%) improves detection rates of T21 in the second (Aitken et al., 1996), but not in the first trimester (Spencer et al.,
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2001). The increase in inhibin-A concentration in pregnancies affected by T21 occurs after 13 weeks of gestation (Aitken et al., 1996), and the difference between affected and unaffected pregnancies increases with gestation (Spencer et al., 2001). Inhibin-A is produced mainly by syncytiotrophoblast and also by decidua and amnion, and suppresses hCG release; this suppression is gestation-dependent with no effect in the first trimester (Mersol-Barg et al., 1990). Inhibin-A levels decrease with gestation after the completed 10 weeks (Spencer et al., 2001). Regulation of placental expression of inhibin-A is not clear; however, it has been shown that hCG, prostaglandins, epidermal growth factor and transforming growth factor α (TGF-α) stimulate, whereas the activin and TGF-β suppress placental inhibin production (Jackson and Dudley, 1998). We observed an increased inhibin-A level in the group of very preterm delivery and in the group of hypertensive disorders.

Placental development and function during the first trimester appears to affect the development of hypertension in pregnancy, and birthweight and gestational age at delivery. An altered placental function and regulation of synthesis and/or secretion of placental products in different pregnancy complications may possibly be the reason for abnormal levels of placental products. However, most cases of abnormal serum markers remain unexplained. Genetic predisposition with or without deleterious effects may be important, which is in agreement with the observations that in different pregnancies in the same woman, significant correlations between fβhCG and PAPP-A in the first trimester, and also between AFP, hCG and uE3 in the second trimester, were noted (Spencer, 2002; Holding and Cuckle, 1994; Spencer, 1997). To our knowledge, no study comparing biochemical markers and complications in different pregnancies in the same woman has been published.

PAPP-A, fβhCG and inhibin-A are the products of the trophoblast. We noted only weak correlations between these three markers in our population. Different associations of markers with maternal smoking and with complications in pregnancy suggest that they have different regulations of synthesis and different mechanisms of transport to maternal circulation. They are not simply related to the volume of the trophoblast, although the volume of the trophoblast affects their levels as well.

CONCLUSION

Low PAPP-A level is associated with the delivery of an SGA baby, and high PAPP-A level with the delivery of an LGA baby. High inhibin-A is associated with preterm delivery before 34 gestational weeks. Fetal-placental products in the first trimester do not prove to be useful as a screening tool for predicting complications of pregnancy. Abnormal values noted at screening for T21 may warn the clinician to take special care of women, and to seek more carefully for early signs of pregnancy complications.

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