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Maternal Serum Placental Growth Factor in Prospective Screening for Aneuploidies at 8–13 Weeks' Gestation

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Key Words
First-trimester screening · Placental growth factor · Nuchal translucency · Free β-human chorionic gonadotropin · Pregnancy-associated plasma protein A

Abstract
Objective: To investigate whether measurement of maternal serum placental growth factor (PLGF) can improve the performance of first-trimester combined screening for trisomy-21 by fetal nuchal translucency (NT) thickness and serum free β-human chorionic gonadotropin (β-hCG) and PAPP-A. ***Methods:*** In singleton pregnancies attending for routine care, serum PLGF, free β-hCG and PAPP-A were measured at 8^{+0}–13^{+6} weeks' gestation, and fetal NT was measured at 11^{+0}–13^{+6} weeks. The population included 12,154 normal and 44 trisomy-21 pregnancies. We examined the effect of adding PLGF on the performance of screening by the combined test. ***Results:*** In the trisomy-21 pregnancies the median multiple of the normal median PLGF, adjusted for gestational age, maternal weight, racial origin, smoking status and method of conception, was significantly reduced (0.6070, 95% CI 0.5543–0.6648), and this did not change significantly with gestational age. Adding PLGF to combined testing with a risk cut-off of 1 in 100 reduced the false positive rate from 2.7% (95% CI 2.5–3.0) to 2.6% (95% CI 2.4–2.8) and increased the detection rate from 85% (95% CI 75–93) to 88% (95% CI 78–95). ***Conclusions:*** Inclusion of serum PLGF improves the performance of the first-trimester combined test in screening for trisomy-21.

Introduction

Placental growth factor (PLGF) is a member of the vascular endothelial growth factor family and is implicated in angiogenesis and trophoblastic invasion of the maternal spiral arteries [1–3]. Maternal serum levels of PLGF at 11–13 weeks' gestation are decreased in pregnancies with impaired placentation resulting in preeclampsia and delivery of small for gestational age (SGA) neonates [4, 5]. Case-control studies have reported that maternal serum PLGF at 11–13 weeks is also decreased in fetal trisomy-21, but there is contradictory evidence concerning levels in affected pregnancies at 8–10 weeks [6–9].

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Effective first-trimester screening for aneuploidies is provided by a combination of maternal age, fetal nuchal translucency (NT) thickness and maternal serum free β-human chorionic gonadotropin (free β-hCG) and pregnancy-associated plasma protein A (PAPP-A). Such combined screening identifies about 90% of fetuses with trisomies 21, 18 or 13, at a false positive rate of 5% [10, 11].

The objective of this prospective study is to investigate whether measurement of serum PLGF can improve the performance of first-trimester combined screening for trisomy-21 provided by fetal NT and serum free β-hCG and PAPP-A.

Methods

Study Population

This was a prospective screening study designed to examine the performance of maternal serum PLGF in screening for aneuploidies in singleton pregnancies attending for routine pregnancy care at University College Hospital, King's College Hospital and Medway Maritime Hospital, UK. In the first hospital visit, which was held at 8^{+0}–13^{+6} weeks' gestation, maternal characteristics and medical history were recorded and a blood sample was analysed within 10 min of collection for measurement of serum PAPP-A, free β-hCG and PLGF using automated machines that provide reproducible results (Delfia Xpress® System; PerkinElmer Life and Analytical Sciences, Waltham, Mass., USA).

In cases presenting at 11^{+0}–13^{+6} weeks, an ultrasound scan was also carried out in the same visit to, firstly, determine gestational age from the measurement of the fetal crown-rump length (CRL), secondly, to measure fetal NT thickness as part of screening for aneuploidies, and thirdly to examine the fetal anatomy for the diagnosis of major fetal defects [12–15]. Women presenting before 11 weeks were given another appointment for the 11^{+0}–13^{+6} weeks' ultrasound scan and provided another blood sample for repeat measurement of serum PAPP-A, free β-hCG and PLGF. The risk for aneuploidies was derived for the measurements of fetal NT and serum free β-hCG and PAPP-A at 11^{+0}–13^{+6} weeks. The measurements of serum PAPP-A, free β-hCG and PLGF at 8^{+0}–10^{+6} weeks and serum PLGF at 11^{+0}–13^{+6} weeks were part of a research study which was approved by the appropriate Hospital Ethics Committee.

Maternal weight and height, measured at the time of the scan, demographic characteristics, ultrasonographic measurements and biochemical results were recorded in computer databases. Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, African, South Asian, East Asian and mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs or in vitro fertilization), cigarette smoking during pregnancy (yes or no), preexisting diabetes mellitus (type 1, type 2 or no) and obstetric history including parity. The questionnaire was then reviewed by a doctor together with the patient.

Women were given their estimated individual risk for trisomies 21, 18 and 13 and those considering their risk to be high were offered chorionic villus sampling or amniocentesis for fetal karyotyping. Karyotype results and details on pregnancy outcomes were added into the database as soon as they became available. The definition of preeclampsia was that of the International Society for the Study of Hypertension in Pregnancy [16]. The birth weight percentile for gestation at delivery was calculated using a reference range derived from our population and the neonate was considered to be GA if the birth weight was below the 5th percentile [17].

Statistical Analysis

This analysis focuses on the data from the first serum sample. Serum PLGF was logarithmically transformed to obtain a symmetric distribution of residuals with approximately constant standard deviation. This was assessed by inspecting histograms and probability plots. Gross outliers beyond the 99.99th centile were removed. In the normal pregnancy outcome group, multiple regression analysis of log-transformed values was carried out to determine the maternal characteristics that provide a significant contribution to the measured concentration of PLGF and to derive the estimates of parameters required to produce log multiple of the median (MoM) PLGF. Prior to performing the multiple regression analysis, continuous variables were centred by subtracting the mean from each measured value (69 from maternal weight in kilogrammes and 30 from maternal age in years) and gestational age was centred by subtracting 77 from gestational age in days.

Each measured value in the normal and aneuploid pregnancies was expressed as a MoM after adjustment for those characteristics found to provide a substantial contribution to the log-transformed value. Taking previously published parameter estimates for PAPP-A and free β-hCG [18], trivariate gaussian distributions were obtained for the joint distribution of log MoM values for PLGF, PAPP-A and free β-hCG. Mann-Whitney test was used to determine the significance of differences in the median MoM between each aneuploidy and the normal group. Pearson correlation analysis was used to examine the intercorrelation between $\log_{10}$ PLGF MoM, $\log_{10}$ PAPP-A MoM and $\log_{10}$ free β-hCG in the aneuploid and normal groups. Similarly, the measured NT was expressed as a difference from the expected normal mean for gestational age (Δ value) and regression analysis was then used to determine the significance of association between PLGF MoM and ΔNT [19].

Standardized detection rates were computed by obtaining the likelihood ratios for biochemistry alone or biochemistry and fetal NT for trisomy-21 pregnancies in the sample and then applying these to each year of maternal age from 12 to 50 to estimate the age-specific detection rates. These were then weighted according to the maternal age distribution of trisomy-21 pregnancies in England and Wales in 2000–2002. Similarly, standardized false positive rates were computed by obtaining the likelihood ratios for biochemistry and NT, as appropriate, in normal pregnancies in the sample and then applying these to each year of maternal age from 12 to 50 to estimate the age-specific false positive rates. These were then weighted according to the maternal age distribution of unaffected pregnancies in England and Wales in 2000–2002 [20]. Confidence intervals (CI) and p values (two-sided) were obtained by bootstrapping. The statistical software package R [21] was used for data analyses.

Table 1. Characteristics of the study groups in the screening population

Maternal characteristics	Normal outcome (n = 11,414)	Trisomy-21 (n = 44)	Trisomy-18 (n = 18)
Median maternal age, years (IQR)	31.4 (27.1–35.0)	38.9 (35.2–40.2)	40.4 (35.8–41.6)
Median maternal weight, kg (IQR)	65.5 (58.4–75.5)	69.3 (61.6–77.4)	63.5 (56.5–72.0)
Median gestational age of fetus, days (IQR)	88 (85–91)	88 (85–90)	84 (80–87)
Racial origin			
Caucasian, n (%)	8,731 (76.5)	36 (81.8)	9 (50.0)
Afro-Caribbean, n (%)	1,518 (13.3)	7 (15.9)	7 (38.9)
South Asian, n (%)	561 (4.9)	0	1 (5.6)
East Asian, n (%)	353 (3.1)	1 (2.3)	0
Other (%)	251 (2.2)	0	1 (5.6)
Cigarette smoker, n (%)	910 (8.0)	0	2 (11.1)
Mode of conception			
Spontaneous, n (%)	10,995 (96.3)	42 (95.5)	17 (94.4)
In vitro fertilization, n (%)	312 (2.7)	2 (4.5)	1 (5.6)
Ovulation drugs, n (%)	107 (0.9)	0	0
Parity			
Nulliparous, n (%)	6,053 (53.0)	18 (40.9)	11 (61.1)
Multiparous, n (%)	5,361 (47.0)	26 (59.1)	7 (38.9)
Diabetes mellitus			
Type 1	43 (0.4)	–	–
Type 2	31 (0.3)	–	–

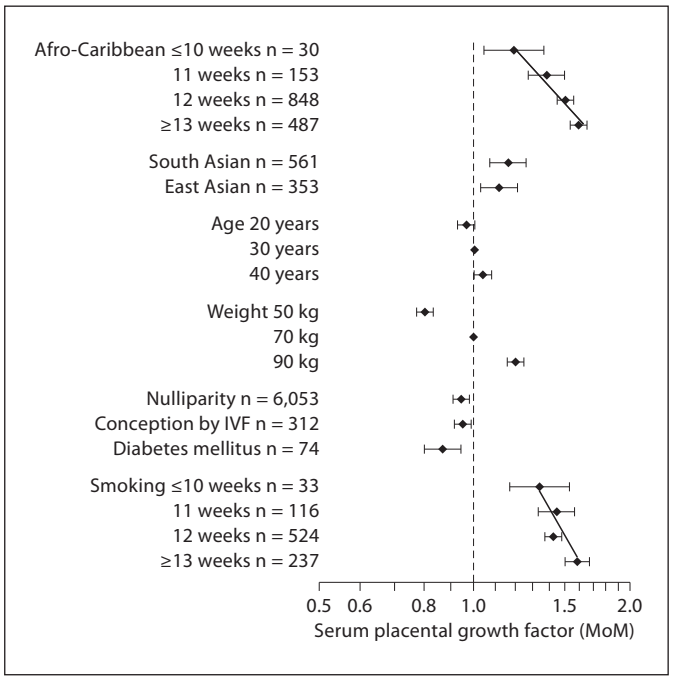

Fig. 1. Estimated effects on serum PLGF of different racial groups relative to Caucasian, of smokers relative to non-smokers, of ovulation induction drugs relative to spontaneous conception, and of women with preexisting diabetes mellitus relative to those without diabetes. Effects are shown with 95% CI.

Results

Characteristics of the Study Population

During the study period (July 2009 to February 2011), we examined 12,715 singleton pregnancies. We excluded 476 (3.7%) cases because they had missing outcome data (n = 318) or the fetal karyotype was not known and the pregnancies resulted in termination, miscarriage or stillbirth (n = 158).

In the study population of 12,239 cases there were 12,154 (99.3%) with normal fetal karyotype or the birth of a phenotypically normal neonate (euploid group) and 85 (0.7%) cases with prenatal diagnosis of fetal trisomy-21 (n = 44), trisomy-18 (n = 18) or other aneuploidy (trisomy-13, n = 3; Turner syndrome, n = 8; triploidy, n = 3; sex chromosome aneuploidies, mosaicisms, deletions or translocations, n = 9). The observed number of trisomies 21 and 18 was not significantly different from the expected on the basis of maternal age and gestational age at the time of screening (trisomy-21 expected 43.1, p = 0.89; trisomy-18 expected 17.7, p = 0.94).

In the euploid group there were 11,414 (93.9%) cases with normal pregnancy outcome (normal group) and 740 (6.1%) that developed preeclampsia and/or delivered SGA neonates. The characteristics of the euploid group and

Table 2. Fitted regression model for maternal serum PLGF in the normal pregnancy outcome group from the screening population

Coefficient	log_{10} scale		MoM scale	
	estimate	95% CI	estimate	95% CI
Constant	1.273900	1.266307 to 1.281493	18.788834	18.463195 to 19.120216
Maternal age (– mean 30 years)	0.001824	0.001257 to 0.002391	1.004208	1.002898 to 1.005521
Gestational age (– mean 77 days)	0.012619	0.012113 to 0.013126	1.029483	1.028283 to 1.030685
Weight (– mean 69 kg)	–0.001578	–0.001793 to –0.001362	0.996374	0.995879 to 0.996868
Racial origin				
Afro-Caribbean: constant	0.114621	0.092971 to 0.136272	1.302031	1.238713 to 1.368586
– mean 77 days	0.006109	0.004431 to 0.007786	1.014165	1.010256 to 1.018090
East Asian	0.043682	0.025719 to 0.061646	1.105814	1.061008 to 1.152512
South Asian	0.073149	0.059019 to 0.087279	1.183447	1.145564 to 1.222583
Smoking: constant	0.130434	0.106343 to 0.154526	1.350313	1.277446 to 1.427336
– mean 77 days	0.004114	0.002154 to 0.006075	1.009518	1.004971 to 1.014086
Conception by IVF	–0.029505	–0.048458 to –0.010552	0.934319	0.894420 to 0.975997
Parity: nulliparous	–0.017371	–0.023860 to –0.010882	0.960792	0.946543 to 0.975255
Diabetes mellitus	–0.057885	–0.095191 to –0.020579	0.875215	0.803172 to 0.953721

Table 3. Distributional characteristics of log_{10} MoM PLGF values in normal and aneuploid pregnancies in the screening population

Parameter	Normal		Trisomy-21		Trisomy-18	
	estimate	95% CI	estimate	95% CI	estimate	95% CI
Mean	0	–	–0.2144	–0.2660 to –0.1628	–0.2827	–0.3657 to –0.1997
Standard deviation	0.1690	0.1669 to 0.1713	0.1249	0.1032 to 0.1583	0.2098	0.1562 to 0.3193
Correlation with PAPP-A log MoM	0.3124	0.2957 to 0.3289	0.3802	0.1257 to 0.1618	0.3969	–0.1035 to 0.7370
Correlation with free β-hCG log MoM	0.1438	0.1257 to 0.1618	0.2169	–0.0855 to 0.4837	0.5808	0.1389 to 0.8298
Correlation with NT log MoM	0.0277	0.0093 to 0.0561	–0.0880	–0.4087 to 0.1762	–0.0375	–0.4957 to 0.4370

Distributional characteristics of log_{10} MoM PLGF values in normal and aneuploid pregnancies in the screening population.

the cases of trisomy-21 and trisomy-18 are presented in table 1.

Normal Pregnancy Outcome

Maternal serum PLGF concentration increased with maternal age and gestational age, decreased with maternal weight, was higher in women of Afro-Caribbean, South Asian and East Asian racial origin than in Caucasians, it was increased in cigarette smokers and decreased in pregnancies conceived by in vitro fertilization, in nulliparous women and those with preexisting diabetes mellitus (fig. 1). The effect of Afro-Caribbean race and smoking increased with gestational age. The regression model for the fitted mean log_{10} PLGF concentration is summarized in table 2.

In the study population the median free β-hCG MoM was 0.9808 (IQR 0.6719–1.5063), the median PAPP-A MoM was 1.0301 (IQR 0.7184–1.4701) and the media ΔNT was 0.18 (IQR –0.04 to 0.42).

Aneuploidies

Distributional parameters for PLGF in aneuploid and normal pregnancies are given in table 3. The estimated mean log MoM in trisomy-21 pregnancies of –0.2144 (95% CI –0.2660 to –0.1628) corresponds to a median MoM of 0.6104 (95% CI 0.5420–0.6876). The respective values for trisomy-18 were –0.2827 (95% CI –0.3657 to –0.1997) and 0.5216 (95% CI 0.4308–0.6314) MoM.

The median PLGF MoM in trisomy-21 and trisomy-18 did not change significantly with gestational age (r =

Table 4. Findings for the normal outcome group and the trisomy-21 and trisomy-18 pregnancies from the referred population and for the trisomy-13, Turner syndrome and triploidy pregnancies from the combined data of the screening study and the referred population

	Normal	Trisomy-21	Trisomy-18	Trisomy-13	Turner	Triploidy
Median maternal age, years (IQR)	35.6 (30.9–38.8)	37.9 (34.5–40.0)	38.9 (36.4–41.0)	33.5 (24.2–41.1)	28.5 (22.6–30.9)	29.2 (25.3–37.5)
Median gestational age (IQR)	13.1 (12.6–13.6)	13.6 (12.7–13.8)	12.1 (11.7–12.7)	12.5 (12.2–13.1)	12.4 (11.9–13.2)	12.4 (11.6–12.9)
Median fetal ΔNT (IQR)	0.55 (0.15–1.12)	2.48 (1.56–4.67)	3.19 (1.06–5.31)	3.77 (1.48–5.63)	7.83 (4.71–9.38)	0.46 (0.14–1.95)
Median serum free β-hCG MoM (IQR)	1.41 (0.81–2.27)	2.55 (1.71–3.97)	0.20 (0.12–0.45)	0.43 (0.23–0.68)	0.69 (0.47–1.41)	0.28 (0.11–8.17)
Median serum PAPP-A MoM (IQR)	0.78 (0.56–1.31)	0.69 (0.43–0.93)	0.19 (0.13–0.30)	0.26 (0.19–0.39)	0.44 (0.33–0.59)	0.10 (0.06–0.64)
Median serum PLGF MoM (IQR)	1.00 (0.78–1.33)	0.62 (0.53–0.87)	0.57 (0.43–0.78)	0.48 (0.24–0.66)	0.54 (0.50–0.66)	0.52 (0.28–0.62)

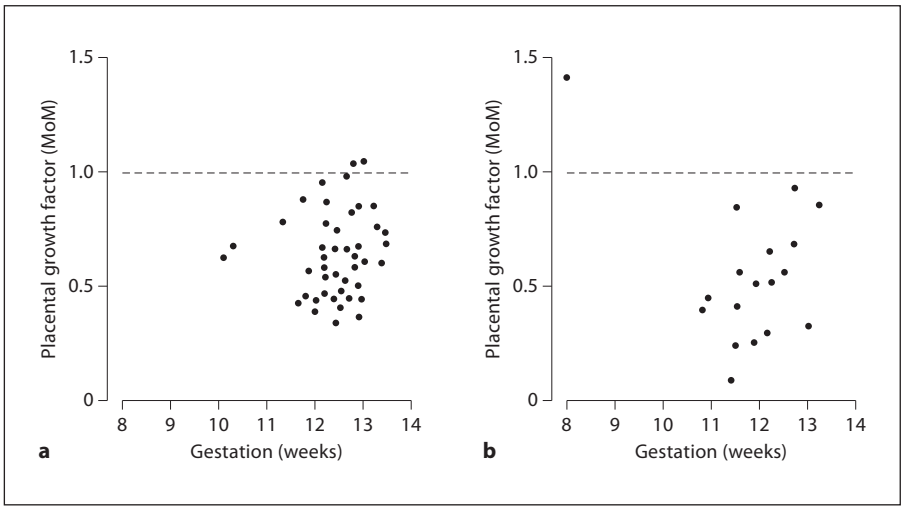

Fig. 2. Relationship between the median PLGF MoM and gestational age in trisomy-21 (**a**) and trisomy-18 (**b**) pregnancies.

0.129, p = 0.405 and r = –0.363, p = 0.138, respectively; fig. 2a, b).

Referred Population

During the study period, in addition to screening in our population, we examined fetal NT and serum free β-hCG, PAPP-A and PLGF in 403 singleton pregnancies which were referred to our centre for CVS because after combined screening in their hospital the estimated risk for aneuploidies was increased. These included 315 euploid cases, 37 with trisomy-21, 23 with trisomy-18, and 28 with other aneuploidies (trisomy-13, n = 7; Turner syndrome, n = 9; triploidy, n = 6; sex chromosome aneuploidies, mosaicisms, deletions or translocations, n = 6). The median PLGF MoM values in the euploid and aneuploid pregnancies in this referred population were similar to those observed in our screening population (table 4).

Trisomy-13, Turner Syndrome and Triploidy

The data on trisomy-13, Turner syndrome and triploidy from the screening and referred populations were pooled because the individual number of cases in each group was too small for meaningful analyses to be carried out. In total there were 10 cases of trisomy-13, 17 cases of Turner syndrome and 9 of triploidy and the median PLGF MoM was 0.4786 (IQR 0.2412–0.6551), 0.5437 (IQR 0.5015–0.6611) and 0.5190 (IQR 0.2809–0.6238), respectively.

Performance of Screening for Trisomy-21

Estimated standardized detection and false positive rates in screening by serum free β-hCG and PAPP-A and fetal NT, with and without inclusion of serum PLGF, are given in table 5. Adding PLGF to biochemical testing with a risk cut-off of 1 in 100 reduced the false positive rate from 4.7 to 4.3% ($p < 0.001$) and increased the detection rate from 62 to 69% (p = 0.002). In combined biochemical

Table 5. Estimated detection rates and false positive rates, with 95% CI, in first trimester screening for fetal trisomy-21

Method of screening	Risk cut-off 1 in 50		Risk cut-off 1 in 100		Risk cut-off 1 in 200		Risk cut-off 1 in 300	
	FPR	DR	FPR	DR	FPR	DR	FPR	DR
PLGF	2.2 (2.0–2.4)	45 (35–55)	4.9 (4.6–5.2)	58 (48–68)	9.9 (9.6–10.3)	71 (61–79)	14.4 (13.9–14.9)	79 (70–86)
PAPP-A and free β-hCG	2.4 (2.2–2.6)	51 (40–62)	4.7 (4.4–5.0)	62 (51–72)	8.6 (8.2–9.0)	73 (63–82)	11.9 (11.4–12.4)	79 (70–86)
PLGF and PAPP-A	2.2 (2.0–2.4)	45 (35–55)	4.9 (4.6–5.2)	58 (48–68)	8.9 (8.5–9.3)	73 (65–80)	14.4 (13.9–14.9)	79 (70–86)
PLGF and free β-hCG	2.4 (2.2–2.6)	47 (37–56)	4.8 (4.5–5.1)	59 (50–68)	8.9 (8.5–9.3)	73 (63–82)	12.4 (12.0–12.9)	82 (74–88)
PLGF, PAPP-A, and free β-hCG	2.4 (2.2–2.6)	59 (48–70)	4.3 (4.0–4.6)	69 (58–78)	7.5 (7.1–7.9)	79 (69–86)	10.1 (9.7–10.6)	84 (76–91)
NT, PAPP-A and free β-hCG	1.5 (1.3–1.7)	80 (69–89)	2.7 (2.5–3.0)	85 (75–93)	4.8 (4.5–5.2)	89 (80–96)	6.6 (6.2–7.0)	91 (83–97)
NT, PAPP-A, free β-hCG and PLGF	1.5 (1.3–1.7)	84 (73–92)	2.6 (2.4–2.8)	88 (78–95)	4.4 (4.1–4.7)	92 (83–97)	5.9 (5.5–6.3)	93 (86–98)

Rates are standardized so that they relate to the population of England and Wales 2000–2002 . FPR = False positive rates; DR = detection rates.

and fetal NT testing, addition of PLGF reduced the false positive rate from 2.7 to 2.6% (p = 0.03) and increased the detection rate from 85 to 88% (p = 0.09).

Discussion

The findings of this prospective screening study demonstrate that in trisomy-21 pregnancies maternal serum PLGF at 8–13 weeks' gestation is reduced and measurement of this placental product improves the performance of first-trimester combined screening for this aneuploidy.

In normal pregnancy, serum PLGF concentration is affected by maternal age, gestational age, maternal weight, racial origin, cigarette smoking and method of conception, and these factors must be taken into account before comparing normal with pathological pregnancies. Serum PLGF increases with maternal age by about 4% every 10 years and since the maternal age in trisomy-21 pregnancies is higher than in euploid pregnancies failure to correct for this effect of age would tend to overestimate the MoM values in the trisomy-21 pregnancies and consequently reduce the detection rate. In women of Afro-Caribbean racial origin, serum PLGF is substantially higher than in Caucasians and this difference increases with gestational age being about 20% at less than 10 weeks and 60% at 13 weeks. Similarly in women of Afro-Caribbean racial origin, serum PAPP-A and free β-hCG are increased by about 60 and 10%, respectively [18]. Consequently, in biochemical screening of women of this racial origin, failure to take into account these changes would result in a substantial underestimate of the true risk of trisomy-21. The effect of smoking is similar to that of racial origin, being higher than in non-smokers and increasing from about 30% at less than 10 weeks to 60% at 13 weeks. The effect of smoking on PLGF is opposite to that of PAPP-A and free β-hCG where the levels at 11–13 weeks are reduced by about 15 and 5%, respectively [18]. Smoking is also associated with increased serum AFP at 11–13 weeks by about 10% [22].

The finding that in trisomy-21 pregnancies serum PLGF at 11–13 weeks' gestation is reduced is compatible with the results of previous case-control studies [6–9]. In a few of our cases of trisomy-21 examined before 11 weeks, the levels of PLGF were also lower than in euploid pregnancies and the PLGF MoM in trisomic fetuses did not change significantly with gestational age between 8 and 13 weeks. Two recent studies reporting in trisomy-21 pregnancies at 8–10 weeks reported contradictory results. Koster et al. [8], who examined 151 cases of trisomy-21 at 8–13 weeks, including 60 at 8–10 weeks, found that the median PLGF MoM was 0.8 and this did not change significantly with gestational age, whereas Cowans et al. [9] reported that the median MoM in 37 affected cases was increased to 1.3. A possible explanation for the findings of Cowans et al. [9] is that the concentration of PLGF increases with storage time, because their samples from the trisomy-21 pregnancies were stored for up to 9 years, whereas the controls were assayed within 1 year of collection. In our prospective study, all samples were assayed within 10 min of collection.

In both the euploid and trisomy-21 pregnancies there was a significant association between serum levels of PLGF and PAPP-A, which presumably reflects the postulated roles of these peptides in placental development and/or their common origin from trophoblast. However, in the case of PAPP-A, unlike PLGF, the deviation in levels between trisomic and euploid pregnancies was inversely related to gestational age. Addition of PLGF to free β-hCG and PAPP-A was associated with a substantial improvement in the performance of first-trimester

biochemical screening for trisomy-21. At an estimated risk cut-off of 1 in 100 there was a simultaneous reduction in false positive rate from 4.7 to 4.3% and a major increase in detection rate from 62 by 69%.

The level of serum PLGF in pregnancies with fetal trisomy-18, trisomy-13, Turner syndrome and triploidy was lower than in pregnancies with euploid fetuses and lower than in those with trisomy-21. Measurement of serum PLGF can be performed by the same automated machines used for free β-hCG and PAPP-A at little extra cost. It is therefore anticipated that a beneficial consequence of incorporating PLGF in first-trimester combined screening for trisomy-21 would be the detection of a high proportion of the other major aneuploidies.

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