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First-trimester biochemical markers of placentation in screening for gestational diabetes mellitus

Argyro Syngelaki [a], Reena Kotecha [a], Alice Pastides [a], Alan Wright [b], Kypros H. Nicolaides [a,*]

[a] Harris Birthright Research Centre of Fetal Medicine, King's College Hospital, London, UK
[b] Institute of Health Research, University of Exeter, Exeter, UK

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ABSTRACT

Objective. To investigate whether first-trimester biochemical markers of placentation, including pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PLGF), are altered in women that subsequently develop gestational diabetes mellitus (GDM) and to examine their potential value in improving the performance of screening for GDM by maternal characteristics and medical history.

Methods. The study population of 31,225 singleton pregnancies, including 787 cases that developed GDM, was drawn from women undergoing routine prospective screening for pregnancy complications at 11–13 weeks' gestation. Maternal serum PAPP-A and PLGF were measured and the levels were expressed as multiples of the median (MoM) after adjustment for maternal characteristics and medical history. The performance of screening for GDM by maternal factors and MoM values of PAPP-A and PLGF was evaluated by receiver operating characteristic (ROC) curves.

Results. In the GDM group, compared to the unaffected group, the median PAPP-A was reduced (0.949, 95% CI 0.913–0.987 MoM) ($p = 0.0009$) and median PLGF was increased (1.053, 95% CI 1.023–1.083 MoM) ($p = 0.004$). The performance of screening for GDM by maternal factors was not improved by the addition of PAPP-A and/or PLGF.

Conclusions. First trimester maternal serum PAPP-A and PLGF are not useful in screening for GDM.

1. Introduction

Maternal serum pregnancy associated plasma protein-A (PAPP-A) and placental growth factor (PLGF) at 11–13 weeks' gestation are reduced in pregnancies with fetal trisomies 21, 18 and 13 and in those that subsequently develop preeclampsia and in those that deliver small for gestational age (SGA) neonates [1–4]. The measurements of serum PAPP-A and PLGF are affected by several maternal and pregnancy characteristics, including gestational age at sampling, maternal racial origin, weight, smoking status, method of conception and diabetes mellitus type 1 or 2, and these are taken into account in the calculation of multiple of the median (MoM) values [5,6]. In pregnant women with diabetes mellitus type 2 treated

Abbreviations: PAPP-A, pregnancy associated plasma protein-A; PLGF, placental growth factor; MoM, multiple of the median; GDM, gestational diabetes mellitus; SGA, small for gestational age; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic; DR, detection rate; FPR, false positive rate; IQR, interquartile range; SD, standard deviation; AUROC, area under receiver operating characteristic curve; CI, confidence interval.

* *Corresponding author at:* Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS. Tel.: +44 2032998256; fax: +44 2032993898.
E-mail address: kypros@fetalmedicine.com (K.H. Nicolaides).

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with insulin, serum PAPP-A is decreased by about 20% and PLGF by 13%; in those treated with diet or metformin PAPP-A is reduced by about 10%, but PLGF is not significantly different from unaffected pregnancies [5,6].

Gestational diabetes mellitus (GDM) and type 2 diabetes mellitus are mainly caused by insulin resistance and insulin deficiency and they are both associated with obesity, advanced age and non-white racial origin [7]. Some studies that examined first-trimester serum PAPP-A in women who subsequently developed GDM reported that the levels were reduced, but other studies reported that the levels were not significantly altered [8–15]. In contrast, two case–control studies that examined first-trimester serum PLGF reported that in women who developed GDM the levels were increased [15,16].

The aim of this prospective screening study is to investigate whether first-trimester maternal serum PAPP-A and PLGF are altered in women who subsequently develop GDM and to examine their potential value in improving the performance of screening for GDM by maternal characteristics and medical history [17].

2. Methods

2.1. Study Population

This study was drawn from a large prospective observational study for early prediction of pregnancy complications in women attending for their routine first hospital visit in pregnancy at King's College Hospital, London, UK. This visit, which is held at 11^{+0} to 13^{+6} weeks' gestation, included recording of maternal characteristics and medical history, ultrasound examination to confirm gestational age from the measurement of the fetal crown–rump length [18] and diagnose any major fetal abnormalities [19] and measurement of maternal serum PAPP-A and PLGF. Maternal serum samples were analyzed by automated biochemical analyzers within 10 min of blood sampling using the DELFIA Xpress system (PerkinElmer Life and Analytical Sciences, Waltham, USA) or the Cobas e411 system (Roche Diagnostics, Penzberg, Germany). The women were screened between February 2010 and June 2013 and gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

Details of maternal characteristics and the findings of the assessment at 11–13 weeks were recorded in our database. Data on pregnancy outcome were obtained from the maternity computerized records or the general medical practitioners of the women and were also recorded in our database.

The inclusion criteria for this study on screening for GDM were singleton pregnancy delivering a phenotypically normal neonate at ≥30 weeks' gestation. We excluded pregnancies with diabetes mellitus type 1 or 2, those ending in termination, miscarriage or delivery at <30 weeks because they may not have had screening and diagnosis of GDM.

2.2. Maternal History and Characteristics

Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, African, South Asian, East Asian and mixed), cigarette smoking during pregnancy (yes or no), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), medical history including diabetes mellitus type 1 or 2, family history of diabetes mellitus (first, second or third degree relative with diabetes mellitus type 1 or 2) and obstetric history. The questionnaire was then reviewed by a doctor together with the patient. The maternal weight and height were measured. For the purpose of this study women were classified as parous or nulliparous with no previous pregnancies at or beyond 24 weeks and if parous we recorded whether any of the previous pregnancies were complicated by GDM or resulted in the delivery of a macrosomic neonate, defined as birthweight above the 95th percentile [20].

2.3. Outcome Measure

Screening for GDM in our hospital is based on a two-step approach. In all women random plasma glucose is measured at 24–28 weeks' gestation and if the concentration is ≥6.7 mmol/L, a 75 g oral glucose tolerance test (OGTT) is carried out within the subsequent 2 weeks. The diagnosis of GDM is made if the fasting plasma glucose level is ≥6 mmol/L or the plasma glucose level 2-h after the oral administration of 75 g glucose is ≥7.8 mmol/L [21].

2.4. Statistical Analysis

In each patient the measured serum PAPP-A and PLGF concentration was converted to MoM as previously described [5,6]. Mann Whitney-U test was used to compare the median MoM values of PAPP-A and PLGF between the GDM and unaffected groups. The *a priori* risk for GDM was estimated from an algorithm derived from multivariable logistic regression analysis of maternal characteristics and medical history in 75,161 singleton pregnancies including 1827 (2.4%) that developed GDM [17]. Bayes theorem was applied to combine the *a priori* risk of GDM with maternal serum PAPP-A and PLGF MoM values. To assess the performance of the markers in the prediction of GDM, detection rates (DRs) for various false positive rates (FPRs) were calculated, receiver operating characteristic (ROC) curves were produced and area under the curves (AUROC) calculated. The AUROCs were compared using DeLong's test.

The statistical software package R was used for all data analyses [22].

2.5. Literature Search

We searched MEDLINE and EMBASE in March 2015 without any time limits to identify English-language articles reporting on first-trimester maternal serum PAPP-A and/or PLGF in pregnancies complicated by GDM.

3. Results

3.1. Screening Population

During the period, the entry criteria were fulfilled by 31,225 singleton pregnancies, including 787 (2.5%) that developed GDM. In the GDM group, 280 cases were treated by dietary

intervention, 144 received metformin and 363 were treated with insulin. The maternal and pregnancy characteristics of the GDM and unaffected groups are presented in Table 1. In the GDM group, women tended to be older, heavier and shorter; there were higher proportions of women of African, South Asian and East Asian racial origin, conceptions with ovulation drugs, history of first or second degree relative with diabetes, and previous pregnancies complicated by GDM and deliveries of macrosomic neonates.

In the unaffected group, the median PAPP-A and PLGF were 1.0 MoM (95% CI 0.994–1.006) and 1.0 MoM (95% 0.995–1.005), respectively. In the GDM group, compared to the unaffected group, the median PAPP-A was reduced (0.949 MoM, 95% CI 0.913–0.987) (p = 0.0009) and PLGF was increased (1.053 MoM, 95% CI 1.023–1.083) (p = 0.004); in the subgroup of GDM treated by insulin the alteration in serum PAPP-A and PLGF was greater than in all cases of GDM (Table 2).

3.2. *Estimated Performance of Screening for GDM*

The DRs of all GDM and GDM treated with insulin, at fixed FPR of 10% and 20%, in screening by maternal factors, PAPP-A and PLGF are given in Table 3 and illustrated in Fig. 1. In the prediction of GDM, the AUROCs for maternal characteristics with PAPP-A, PLGF or their combination were not significantly different than the AUROCs for maternal factors alone (p = 0.9819; p = 0.9336; p = 0.7217).

3.3. *Literature Search*

The data from previous studies comparing maternal serum PAPP-A and PLGF levels in normal pregnancies and pregnancies that developed GDM are summarized in Supplementary Table 1.

4. Discussion

4.1. *Main Findings of the Study*

The study has demonstrated that in women who develop GDM maternal serum PAPP-A at 11–13 weeks' gestation is decreased by about 6% and serum PLGF is increased by 5%. The differences between GDM and unaffected pregnancies were greater in cases of GDM requiring treatment with insulin, rather than diet or metformin. However, the addition of PAPP-A MoM, PLGF MoM or their combination does not improve the performance of screening of GDM by maternal factors alone.

4.2. *Strengths and Limitations*

The major strengths of the study are firstly, prospective examination of a large number of pregnancies and secondly, the use of Bayes theorem to combine the *a priori* risk for GDM

Table 1 – Maternal and pregnancy characteristics of the study population.

Variables	Unaffected (n = 30,438)	GDM all (n = 787)	GDM on diet (n = 280)	GDM on metformin (n = 144)	GDM on insulin (n = 363)
Maternal age in years, median (IQR)	30.6 (26.0–34.4)	33.2 (29.4–36.9) *	33.1 (29.3–36.2) *	33.4 (29.9–37.1) *	33.3 (29.6–37.5) *
Maternal weight in kg, median (IQR)	66.8 (59.0–77.4)	77.2 (65.1–167.0) *	72.3 (62.3–88.5)	75.3 (65.3–92.3) *	81.0 (68.0–93.5) *
Maternal height in cm, median (IQR)	165 (160–169)	163 (158–167) *	163 (157–167) *	163 (158–166) *	163 (159–167) *
Gestation at sampling (days), median (IQR)	89 (86–92)	89 (86–92)	89 (86–91)	89 (86–92)	89 (86–91)
Fetal crown–rump length in mm, median (IQR)	63.1 (58.0–68.8)	63.2 (58.1–68.4)	63 (58–68)	63.8 (58.2–69.8)	63.0 (58.0–68.0)
Racial origin					
Caucasian, n (%)	22,784 (74.8)	446 (56.6)	188 (67.1)	77 (53.4)	181 (49.8)
Afro-Caribbean, n (%)	5182 (17)	212 (26.9) *	49 (17.5)	40 (27.7) *	123 (33.8) *
South Asian, n (%)	1177 (3.8)	73 (9.2) *	23 (8.2) *	20 (13.8) *	30 (8.2) *
East Asian, n (%)	582 (1.9)	41 (5.2) *	14 (5) *	4 (2.7)	23 (6.3) *
Mixed, n (%)	713 (2.3)	15 (1.9)	6 (2.1)	3 (2)	6 (1.6)
Cigarette smokers, n (%)	3230 (10.6)	53 (6.7)	20 (7.1)	7 (4.8)	26 (7.1)
Conception					
Spontaneous, n (%)	29,498 (96.9)	754 (95.8)	265 (94.6)	136 (94.4)	353 (97.2)
Ovulation induction drugs, n (%)	304 (0.9)	14 (1.7)	8 (2.8) *	0	6 (1.6)
In vitro fertilization, n (%)	636 (2)	19 (2.4)	7 (2.5)	8 (5.5) *	4 (1.1)
Family history of diabetes, n (%)					
1st degree	3962 (13)	248 (31.5) *	75 (26.7) *	44 (30.5) *	129 (35.5) *
2nd degree	2777 (9.1)	92 (11.6) *	31 (11)	14 (9.7)	47 (12.9) *
3rd degree	708 (2.3)	22 (2.7)	7 (2.5)	2 (1.3)	13 (3.5) *
Chronic hypertension, n (%)	401 (1.3)	46 (5.8) *	8 (2.8)	11 (7.6) *	27 (7.4) *
Parity					
Nulliparous, n (%)	15,076 (49.5)	320 (40.6)	129 (46)	51 (35.4)	140 (38.5)
Parous with previous GDM, n (%)	156 (0.5)	222 (28.2) *	82 (29.2) *	36 (25) *	104 (28.6) *
Parous with previous LGA, n (%)	1012 (3.3)	77 (9.7) *	22 (7.8) *	19 (13.1) *	36 (9.9) *
Gestation at delivery in weeks, median (IQR)	40.1 (39.0–40.9)	38.6 (38.1–39.3) *	39.1 (38.3–40.0)	38.6 (38.1–39.2) *	38.4 (37.9–39.0) *
Birth weight in grams, median (IQR)	3400 (3068–3730)	3320 (2992–3680)	3355 (3044–3750)	3300 (2981–3600)	3310 (2968–3650)

IQR = interquartile range. Comparison between outcome groups by Mann Whitney U-test for continuous variables and χ^2 test for categorical variables.
* P < 0.05 in comparisons to the unaffected group.

Table 2 – Median and 95% confidence limits, for maternal serum pregnancy-associated plasma protein-A and placental growth factor.

Marker	Unaffected (n = 30,438)	All GDM (n = 787)	GDM on diet (n = 280)	GDM on metformin (n = 144)	GDM on insulin (n = 363)
PAPP-A MoM	1.000 (0.994, 1.006)	0.949 (0.913, 0.987) *	1.0155 (0.950, 1.085)	0.962 (0.883, 1.048)	0.896 (0.846, 0.949) *
PAPP-A IU/L	2.618 (2.598, 2.638)	2.250 (2.142, 2.364) *	2.408 (2.223, 2.609)	2.393 (2.143, 2.673)	2.084 (1.933, 2.246) *
PLGF MoM	1.000 (0.995, 1.005)	1.053 (1.023, 1.083) *	1.041 (0.99434, 1.089)	1.0291 (0.961, 1.102)	1.071 (1.025, 1.120) *
PLGF pg/ml	35.188 (34.974, 35.404)	37.898 (36.496, 39.354) *	36.427 (34.316, 38.669)	38.048 (34.681, 41.742)	39.12 (6.865, 41.284) *

GDM = gestational diabetes mellitus; PAPP-A = Pregnancy-associated plasma protein A; PLGF = Placental growth factor; MoM = multiple of the median.
* $P < 0.05$ in comparisons to the unaffected group.

based on maternal factors with serum PAPP-A and PLGF MoM values. We examined more than 30,000 women with singleton pregnancies within a narrow gestational age range at 11–13 weeks, asked specific questions to identify known factors associated with GDM and measured maternal weight and height. Measurement of PAPP-A and PLGF was carried out prospectively by automated machines that provide reproducible results within 40 min of blood collection.

A limitation of the study relates to the method of identifying the GDM affected pregnancies. The diagnostic OGTT was not carried out in all pregnancies, as recommended by the international association of diabetes and pregnancy study groups [23], but only in those with risk factors as recommended by NICE [24] or abnormal results of a random blood glucose level at 24–28 weeks' gestation. It is therefore possible that some of the women included in our non-GDM group actually had GDM and the performance of screening of our method was overestimated.

4.3. *Comparison with Findings from Previous Studies*

Five previous studies reported that in GDM serum PAPP-A was reduced by 9%–42% [8,10,12–14], but in another three studies there were no significant differences between GDM and unaffected pregnancies [9,11,15]. Such differences may be the consequence of the small number of cases of GDM in most studies and possible differences in the methods of screening and diagnosis of GDM. Our results are similar to those of the largest previous study of 20,926 pregnancies, including 870 cases of GDM, which reported that in GDM serum PAPP-A was reduced by about 9% [13]. Only one of the previous studies examined the potential impact of including serum PAPP-A in the prediction of GDM and reported that addition of PAPP-A improved the prediction provided by maternal factors alone from about 37% to 52%, at FPR of 25% [12].

Two case–control studies reported that in pregnancies which develop GDM serum PLGF at 11–13 weeks' gestation is increased by about 20% [15,16]. One of the studies estimated that addition of serum PLGF to maternal factors would increase the prediction of GDM from 54% to 63%, at FPR of 20% [15].

5. Conclusion

Screening for GDM at 11–13 weeks' gestation can predict 58% and 72% of cases, at FPR of 10% and 20%, respectively. Such performance of screening is not improved by the addition of serum PAPP-A and/or PLGF.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.metabol.2015.07.015.

Authors' Contribution

AS and KN planned study design; AS, AW and KN prepared, drafted and revised the manuscript; AS and AW performed and revised statistical analysis; AS, RK and AP contributed in data collection.

Disclosure Statement

The authors have no conflict of interest to disclose.

Table 3 – Estimated detection rates of gestational diabetes mellitus, at false positive rates of 10% and 20%.

Screening test	All GDM irrespective of treatment			GDM treated with insulin		
	AUROC	Detection rate with 95% CI (%)		AUROC	Detection rate with 95% CI (%)	
		FPR 10%	FPR 20%		FPR 10%	FPR 20%
Maternal factors	0.8409	58 (57.5–58.5)	72 (71.5–72.5)	0.8662	63 (62.5–63.5)	75 (74.5–75.5)
Maternal factors plus						
PAPP-A	0.8409	58 (57.5–85.5)	72 (71.5–72.5)	0.8662	64 (63.5–64.5)	77 (76.5–77.5)
PLGF	0.8410	57 (56.5–57.5)	72 (71.5–72.5)	0.8670	65 (64.5–65.5)	76 (75.5–76.5)
PLGF and PAPP-A	0.8415	58 (57.5–58.5)	70 (69.5–70.5)	0.8685	65 (64.5–65.5)	77 (76.5–77.5)

GDM = gestational diabetes mellitus; CI = confidence interval; FPR = False positive rate; AUROC = area under receiver operating characteristic curve; PAPP-A = Pregnancy-associated plasma protein A; PLGF = Placental growth factor.

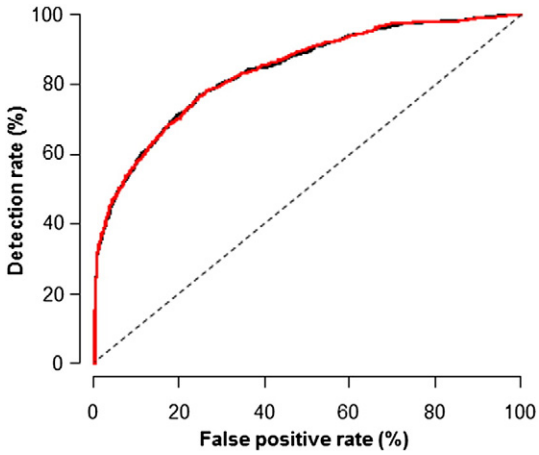

Fig. 1 – Receiver operating characteristic curves for prediction of all gestational diabetes mellitus based on maternal factors (black curve) and maternal factors in combination with pregnancy-associated plasma protein A and placental growth factor (red curve).

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