First-Trimester Biochemical Markers and Small-for-Gestational-Age Infants

Marcadores Bioquímicos do Primeiro Trimestre e Recém-Nascidos Leves para Idade Gestacional

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ABSTRACT

Introduction: Several studies suggested an association between first trimester biochemical markers (PAPP-A and β-HCG) and infants below 10th percentile. Our goal was to describe this relationship of biochemical markers with small-for-gestational-age fetuses in our population.

Material and Methods: Retrospective analytic study of 2 035 pregnant women that underwent first-trimester screening in the period between March 2009 and September 2011. Small-for-gestational-age infants below 10th percentile were compared with control group (term newborn with birth weight above 10th percentile). Infants below 3rd percentile and control group were also compared. Multiple and logistic regression analysis were done with PAPP-A, β-HCG (multiples of the expected normal median) and demographic maternal characteristics (ethnicity, weight and smoker status).

Results: This study demonstrated an independent contribution of PAPP-A, maternal weight and smoker status in predicting small-for-gestational-age infants. For PAPP-A, the odds ratio for small-for-gestational age below 10th and 3rd percentile was 2.41 and 3.41, respectively ($p < 0.01$). For β-HCG, odds ratio below 10th percentile was 1.70 ($p = 0.03$) and for birth weight below the 3rd percentile, the odds ratio was 3.22 ($p < 0.01$).

Conclusions: Low levels of PAPP-A and β-HCG (values below 5th percentile of the study population) were associated with an increased risk of small-for-gestational-age infants in the pregnant population included in this study.

Keywords: Biological Markers; Infant, Small for Gestational Age; Pregnancy Trimester, First; Prenatal Diagnosis; Portugal.

RESUMO

Introdução: Estudos anteriores mostram uma relação dos marcadores bioquímicos do 1º trimestre, proteína plasmática A associada à gravidez e subunidade β da gonadotrofina coriónica, com o nascimento de recém-nascidos com peso abaixo do percentil 10. O nosso objectivo foi descrever a relação entre estes marcadores bioquímicos com os recém-nascidos leves para a idade gestacional, na nossa população.

Material e Métodos: Estudo retrospectivo analítico de 2 305 grávidas que realizaram o rastreio combinado do primeiro trimestre entre Março 2009 e Setembro de 2011. Comparação entre o grupo dos recém-nascidos abaixo do percentil 10 e o grupo controlo (recém-nascidos de termo com peso acima do percentil 10) e os recém-nascidos abaixo do percentil 3 e o grupo controlo. Foi realizado uma análise de regressão múltipla e logística com a utilização dos valores de proteína plasmática A associada à gravidez e subunidade β da gonadotrofina coriónica (em múltiplos da mediana) e as características demográficas maternas como etnia, peso e *status* tabágico.

Resultados: O estudo revelou uma contribuição independente da proteína plasmática A associada à gravidez, do peso materno e dos hábitos tabágicos para os recém-nascidos abaixo do percentil 10. Na regressão logística para o marcador proteína plasmática A associada à gravidez, o risco relativo abaixo do percentil 10 foi de 2,41 e abaixo do percentil 3 de 3,41 ($p < 0,01$). No caso da subunidade β da gonadotrofina coriónica, o *odds ratio* determinado para percentil inferior a 10 foi de 1,70 ($p = 0,03$) e para o percentil inferior a 3 foi de 3,22 ($p < 0,01$).

Conclusões: Baixos níveis da proteína plasmática A associada à gravidez e de subunidade β da gonadotrofina coriónica (valores inferiores ao percentil 5 da população estudada) estiveram relacionados com aumento do risco do nascimento de recém-nascidos leves para a idade gestacional na população de grávidas abrangidas pelo estudo.

Palavras-chave: Diagnóstico Prenatal; Marcadores Biológicos; Portugal; Primeiro Trimestre da Gravidez; Recém-nascido Leve para a Idade Gestacional.

INTRODUCTION

In the last few years, first trimester biochemical markers have been increasingly used as evidence for adverse gestational outcomes, including Small for Gestational Age (SGA) infants, preterm births, intrauterine fetal death, miscarriages and pre-eclampsia.[1-10] Early detection capability of increased risk of foetal morbidity and mortality has major clinical implications and is required to optimize prenatal surveillance.[1,11]

Pregnancy-associated plasma protein A (PAPP-A) is a trophoblast-derived protein acting as a protease in insulin-like growth factor binding and is theoretically responsible for placental growth factor stimulation.[12,13] Previous studies have shown that a low PAPP-A concentration is related as an independent factor to an increased risk of SGA [1-3,5,11,14] i.e. with a birth weight less than the 10th percentile. A low concentration of β-subunit of human chorionic gonadotropin (β-hCG) is also related to SGA in the first trimester of pregnancy.[1,3,5,11,14]

Our study aimed to show the capacity of PAPP-A and β-hCG measurements in the first trimester of pregnancy to predict SGA infants.

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MATERIAL AND METHODS

A retrospective cohort study of the clinical record of all pregnant women completing the combined first-trimester screening has been carried out in our Foetal Medicine Unit at the *Centro Hospitalar Tondela-Viseu*, between March 2009 and September 2011.

The combined first trimester screening included blood sampling between 9th and 13th weeks of pregnancy in order to obtain PAPP-A and β-hCG levels, followed by foetal ultrasound obtained between 11th and 13th weeks of pregnancy, in order to assess crown-rump length (CRL), nuchal translucency (NT) and additional risk markers, when appropriate.[15]

Serum PAPP-A and β-hCG levels were converted in multiples of the median (MoM) adjusted for gestational age, ethnicity, maternal weight and smoking habit.[16] In statistical analysis, PAPP-A and β-hCG variables were related not only with continuous dichotomous variables, but also with cut-off values corresponding to the 5th percentile of our group of patients (0.439 MoM for PAPP-A and 0.313 MoM for β-hCG).

Demographic data (maternal age and parity) and clinical data (smoking and maternal weight) obtained in the first medical appointment as well as neonatal outcome data (gestational age of delivery, birth weight) were recorded in a restricted-access database (PIA-Fetal *Database*, ViewPoint, Webling, Germany). Maternal age (in years), parity (nulliparous or not) and weight (in kg) were recorded at the time of blood sampling. Smoking habits were classified as 'smokers' and 'non-smokers' regardless of the daily number of cigarettes consumed at the time of blood sampling. Data regarding deliveries occurring outside our hospital and respective newborns were obtained through telephone contact with mothers.

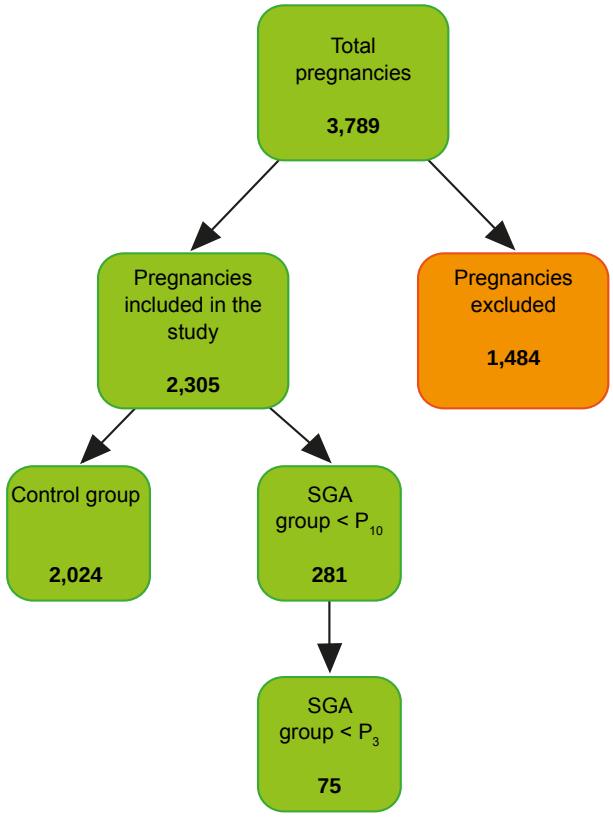

Figure 1 – Descriptive flowchart of the number of patients included in the study. (SGA – small for gestational age; P_{10} – 10th percentile; P_3 – 3rd percentile)

Multiple pregnancies, major structural or chromosomal foetal disorders with gestational age at or lower than 25 weeks, premature foetus with weight above the 10th percentile and incomplete data records were excluded from the study.

Our database recorded 2,305 pregnancies, which were divided in two major groups: one control group including full-term newborns (over 37 weeks) with weights in the 10th percentile or above. The study group – including SGA newborn babies, included every newborn baby weighing below the 10th percentile at birth.[17] The SGA group was still subdivided in another group with babies weighing below the 3rd percentile for gestational age at birth (Fig. 1).

Multiple regression analysis was used in order to determine the independent contribution of individual biochemical markers (expressed as MoM) in SGA determination, as well as other variables like maternal weight, maternal ethnicity and smoking. In addition to this analysis, a logistic regression was also carried out in order to assess the relative risk of PAPP-A and β-hCG for the 10th and 3rd percentile in SGA. A *p* value below 0.05 was considered statistically significant. The statistical analysis was carried out using SPSS for Windows software (version 18.0, Chicago, IL, USA).

RESULTS

Our study included 2,305 pregnant women after 1,484 were excluded due to foetal structural and chromosomal disorders, multiple pregnancies, gestational ages below 25 weeks, premature babies weighing above 10th percentile and incomplete data. The control group included 2,024 newborn babies (87.8%) and the remaining 281 newborn (12.2%) corresponded to the group including newborn babies weighing below the 10th percentile, from which 75 babies were born weighing below the 3rd percentile (3.3%). Maternal demographic characteristics, gestational age at delivery, newborn weight at birth and mean level of biochemical markers for each group are shown in Table 1. PAPP-A mean level was significantly lower in the SGA group, born below the 10th percentile [PAPP-A = 1.04 ± 0.67; $p < 0.01$] as well as below the 3rd percentile [PAPP-A = 0.92 ± 0.48; $p = 0.01$]. There were no significant differences between both groups regarding β-hCG average levels in SGA group [β-hCG = 0.90 ± 0.63; $p = 0.97$]. With the exception of maternal age, all remaining studied clinical variables (Table 1) were statistically significant in both groups – maternal weight, smoking, nulliparity, gestational age and weight at birth.

The multiple regression analysis showed an independent contribution of PAPP-A, maternal weight and smoking for SGA prediction [R^2 0.025; $p < 0.01$] (Table 2). In contrast,

Table 1 - Maternal demographic and gestational characteristics and biochemical markers

Variable	Small for Gestational Age (SGA) (*n* = 281)	Control (*n* = 2,024)	*P value*
Maternal age (years). mean	29.0 (± 5.4)	30.0 (± 5.0)	0.11
Maternal weight (kg). mean	62.0 (± 12.1)	65.7 (± 11.8)	< 0.01
Smokers (%)	15.7	7.1	< 0.01
Nulliparous (%)	64.8	52.3	< 0.01
PAPP-A (MoM), mean	1.04 (± 0.7)	1.16 (± 0.6)	< 0.01
β-hCG (MoM), mean	0.90 (± 0.6)	1.00 (± 1.2)	0.97
GA at delivery (weeks). mean	38.0 (± 2.0)	39.0 (± 1.0)	< 0.01
Weight at birth (kg). mean	2.6 (± 0.4)	3.4 (± 0.4)	< 0.01

The values are presented as mean ± standard deviation. GA – gestational age. PAPP-A – pregnancy-associated plasma protein A; β-hCG – β-subunit of the human chorionic gonadotropin; kg – kilogram; MoM – multiples of the median

Table 2 – Multiple regression for the prediction of SGA newborn (*n* = 2,305)

	Small for Gestational Age (SGA)	
Variables	**OR (95% CI)**	***P***
PAPP-A	-0.033 (-0.012; -0.054)	**< 0.01**
β - hCG	-0.007 (0.004; -0.018)	0.231
Maternal Weight	-0.003 (-0.002; -0.004)	**< 0.01**
Ethnicity	0.000 (0.081; -0.082)	0.988
Smoking	0.120 (0.072; 0.169)	**< 0.01**

OR – *odds ratio*; CI – confidence interval

Table 3 – Logistic regression for the comparison of mean MoM of PAPP-A and β-hCG levels in SGA newborn

	PAPP-A			**β - hCG**		
SGA	MoM	*P*	OR	MoM	*P*	OR
< P10	1.037	0.000	2.41	0.902	0.028	1.70
< P3	0.916	0.000	3.41	0.870	0.001	3.22

Odds ratio in SGA below P10 and below P3 (PAPP-A = 0.44 MoM and β-HCG = 0.31 MoM corresponding to the 5th percentile).

β–hCG did not show any significant contribution ($p > 0.05$).

In the logistic regression, when PAPP-A level corresponded to the 5th percentile of our group of patients, the relative risks for SGA below the 10th percentile and the 3rd percentile were 2.41 (OR 2.41; 95% CI, 1.6 – 3.7) and 3.41 (OR 3.41; 95% CI, 1.8 – 6.5) respectively, with $p < 0.01$. We also found statistically significant differences in β-hCG values for the 5th percentile of our group of patients, with a relative risk of 1.70 (OR 1.70; 95% CI, 1.1 – 2.7) for a percentile below 10 ($p = 0.03$) and 3.22 (OR 3.22; 95% CI, 1.7 – 6.3) for a percentile below 3 ($p = 0.00$) (Table 3).

DISCUSSION

Our study showed an increased SGA incidence in smoking mothers and an inverse correlation between SGA incidence and maternal weight, placing mothers with less weight at a higher risk of having SGA babies. In addition, the study showed an association between low serum PAPP-A levels in the first trimester and SGA newborn, arguing for a hypothesis of placental failure in these newborn babies, weighing below the 10th percentile.

The β-hCG results were less consensual, as there was no statistically significant difference in the mean value of this marker between both groups in the descriptive analysis. Nevertheless, we found an association of this marker, as

an independent factor, with SGA newborn babies, although with a lower statistical strength than PAPP-A. The low number of pregnancies included in the study may explain these results which, although conflicting, are in line with previously published studies.[3,5,6,14]

The increase in the use of biochemical markers in the first trimester led to the increase of scientific publications showing a similar relation of these markers with SGA newborn babies, mainly for PAPP-A.[1-5,11-14] Table 4 shows the data published in some of these studies regarding the value of biochemical markers and the obtained odds ratio.

Although concordant, the odds ratios are low, meaning that, although increasing the probability of an SGA newborn, the presence of low levels of these markers is not equivalent to SGA. However, the higher the odds, the lower the weight percentile associated.

In addition to their relation with SGA newborn, these markers have been studied as predictive factors for other obstetric complications. Low PAPP-A concentrations are also related with preterm delivery,[5-7] foetal death,[8,9] pre-eclampsia and other hypertensive disorders[5,10] and spontaneous miscarriages.[5] Although this association is clear, most pregnancies with such outcomes do not present low PAPP-A levels, revealing the low sensitivity of this marker. In addition, it has a low positive predictive value, as few pregnant mothers with low PAPP-A levels present these obstetric complications. Other obstetric complications related with low β-hCG levels have been studied, as the increased risk of SGA newborn and spontaneous miscarriages.[5]

CONCLUSION

We found that low PAPP-A and β-hCG levels were related with an increased risk of SGA newborn babies in our group of patients. Nevertheless, further studies are required in order to optimize obstetric complications screening. The results are in line with increasing evidence that first trimester biochemical markers will become useful tools to be included in this screening model.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

FINANCIAL SOURCES

There were no external financial sources in the writing of this manuscript.

Table 4 - Published studies on the relationship of PAPP-A and β-hCG with SGA newborn

Studies	Total	Percentile	*PAPP-A*		β-hCG	
			Mean value (MoM)	OR	Mean value (MoM)	OR
Goetzinger et al[1]	2,153	< P_{10}		2.6		1.1
Kirkegaard et al[2]	9,450	< P_5		2.4		1.8
Ranta et al[4]	2,844	< P_{10}	0.79	2.6	0.90	1.7
Spencer et al[11]	49,801	< P_{10}	0.82	2.7	0.98	1.4
		< P_3	0.75	3.7	0.98	1.7
Dugoff et al[5]	33,395	< P_{10}		2.5		1.6
Our study	2,305	< P_{10}	1.04	2.4	0.90	1.7
		< P_3	0.92	3.4	0.87	3.2

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