ISSN: 2377-9004

Benítez et al. Obstet Gynecol Cases Rev 2017, 4:109
DOI: 10.23937/2377-9004/1410109
Volume 4 | Issue 2
Open Access

Obstetrics and Gynaecology Cases - Reviews

RESEARCH ARTICLE

Ultrasound and Biochemical First Trimester Markers as Predictive Factors for Intrauterine Growth Restriction

Benítez Martín A*, Vargas Pérez M and Manzanares Galán S

Hospital Universitario Virgen de las Nieves, Granada, Spain

***Corresponding author:** *Benítez Martín A, Hospital Universitario Virgen de las Nieves, Granada, Spain, E-mail: adarabm@gmail.com*

Abstract

Introduction: Intrauterine Growth Restriction (IUGR) occurs in about 10% of pregnancies and it is considered the most common and complex problem in modern obstetrics.

The aim of this study was to investigate the relationship between first trimester biochemical (PAPP-A and free b-hCG) and ultrasound (Crown-rump length; CRL and Nuchal translucency; NT) screening tests and the risk of IUGR.

Methods: This was a retrospective cohort study of 16788 singleton pregnancies attending between January 2009 and December 2016. Sample was divided in percentiles by weight at birth and women were assigned to two groups: Normal pregnancy group (birth weight at or above the 10th percentile for gestational age) and SGA group. The SGA group was classified into three subgroups per birth weight below the 10th, 5th and 3rd percentile for gestational age.

Results: In SGA pregnancies and severe IUGR, the median PAPP-A MoM, free β-hCG MoM and CRL measurements were significantly lower than that in the normal group, but the median NT was not statistically significantly different from normal. A multivariate model analysis was performed with the method of selecting successive steps, obtaining the variables able to predict SGA and severe IUGR.

Discussion: After analyzing our results, we ascertained that some variables were protective, and others were risk factors for SGA, however a multivariate model established to predict SGA indicates that these were not good predictors of SGA (AUC = 0.65). When analyzing the data by comparing the normal group to severe IUGR, we conclude that the model including MoM PAPP-A, MoM β-hCG, CRL, maternal weight, smoker status, hypertension conditions and parity, was a good model for predicting the risk of IUGR severe (AUC 0.703).

Keywords

Early fetal growth, Free β-human chorionic gonadotropin, Low birth weight, Pregnancy-associated plasma protein-A, SGA

Introduction

Intrauterine Growth Restriction (IUGR) is defined as the pathologic inhibition of intrauterine fetal growth and the failure of the fetus to achieve its growth potential [1]. It occurs in about 10% of pregnancies [2] and considered by the American College of Obstetricians and Gynecologists "the most common and complex problem in modern obstetrics" [3]. A healthy fetus with estimated weight or birth weight below the 10th percentile per population standards is commonly defined as Small for Gestational Age (SGA) [4]. Pathological SGA is known as Intrauterine Growth Restriction (IUGR) or Fetal Growth Restriction (FGR).

IUGR is associated with increased fetal and neonatal mortality and morbidity. It has been linked to immediate perinatal adverse events (prematurity, cerebral palsy, intrauterine fetal death, neonatal death) and also to adult pathologic conditions (obesity, hypertension, type-2 diabetes) [5,6].

Early recognition of fetuses at increased risk of IUGR enables more appropriate surveillance, thereby optimizing management, which has been shown to reduce the risk of adverse fetal outcome [7].

Several studies have linked low first-trimester maternal serum levels of Pregnancy Associated Plasma Protein-A (PAPP-A) and free β-human Chorionic Gonadotropin (β-hCG) with an increased risk of SGA [8-10] and others [11] have found a relationship between Crown Rump Length (CRL) measurement in the first trimester of pregnancy and delivery of a SGA fetus.

Citation: Benítez MA, Vargas PM, Manzanares GS (2017) Ultrasound and Biochemical First Trimester Markers as Predictive Factors for Intrauterine Growth Restriction. Obstet Gynecol Cases Rev 4:109. doi.org/10.23937/2377-9004/1410109

Received: October 20, 2017: **Accepted:** December 04, 2017: **Published:** December 06, 2017

The aim of this study was to investigate the relationship between first trimester biochemical (PAPP-A and free b-hCG) and ultrasound (CRL and NT) and the risk of SGA.

Methods

This was a retrospective cohort study of 16788 singleton pregnancies attending the first-trimester combined screening program in a Virgen de las Nieves University Hospital, Granada, Spain, between January 2009 and December 2016. The prenatal program is free of charge and includes a combined biochemistry at 8-13 + 6 weeks, and ultrasound screening test for chromosomal abnormalities at 11 to 13 + 6 weeks of gestation, according to the protocols of the Fetal Medicine Foundation (FMF).

Maternal serum free β-hCG and PAPPA-A were measured using the Elecsys analyzer (Roche®, Roche Farma S.A. Spain). These values were converted to Multiples of the Medium (MoM) values by expressing the absolute concentration relative to the median value for the gestational age at the day of blood sampling using the FMF® module of the Astraia® computer system [12].

An ultrasound examination (Voluson ProV) was performed to measure the fetal CRL and NT. Gestation was determined using the date of the last menstrual period in women with at least 3 regular cycles before pregnancy, or by measurement of crown-rump length in the first trimester if a discrepancy of more than 7 days between menstrual dating and sonographic assessment was found.

We excluded pregnancies affected by chromosomal abnormalities, structural abnormalities or intrauterine death. Sample was divided in percentiles by weight at birth and women were assigned to two groups. Normal singleton pregnancy was defined as those pregnancies in which a live baby was delivered after 37 complete weeks of gestation with a birth weight at or above the 10th percentile for gestational age. The SGA group was classified into three subgroups according to birth weight below the 10th, 5th and 3rd percentile for gestational age.

Data were analyzed by both linear and logistic regression. CRL, NT, PAPP-A and free β-hCG in relation to birth weight for gestational age are presented as Odds Ratios (OR) with 95% Confidence Intervals (CI's). Maternal demographic characteristics were compared between cohorts using unpaired two tailed Student´s t test for continuous variables, Yates´ corrected X^2 and Fisher exact test for categorical variables.

Data were processed using Microsoft Excel® and statistical analysis was performed using SPSS 21.0. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 16788 women with a singleton pregnancy met the inclusion criteria and were included in the study. There were 182 cases of spontaneous miscarriage (1.1%) and 210 cases of stillbirth (1.3%). Outcome could not be traced in 137 cases. Therefore, a total of 16259 cases was included in the analysis. The normal group comprised 14764 pregnancies (90.8%) and the SGA group comprised 1495 pregnancies (9.2%). In 748 cases (4.6%) the birth weight was between the 10th to 5th percentile, in 341 cases (2.1%) the birth weight was between the 5th to 3rd percentile and 406 cases (2.5%) it was below the 3rd percentile.

Table 1: Maternal characteristics of normal pregnancy group and SGA group.

Parameter	Weight	
	> 10th percentile	> 10th percentile
n	14952	1517
Maternal age (years)	30.29 (± 5.6)	29.8 (± 5.8)
Maternal weight (kg)	66.05 (± 13.8)	63.07 (± 13.3)
Maternal height (cm)	163 (± 6.2)	161.4 (± 5.9)
Maternal BMI	24.89 (± 5.04)	24.24 (± 4.9)
Cigarette smoker (%)	14.36	25
Primiparous (%)	49	60
Ethnicity (%)		
Arab	94.4	5.6
Asian	94.6	5.4
Caucasian	89.4	10.6
Ecuadorian	81.8	18.2
East Asian	96.5	3.5
Hispanic American	95.4	4.6
Black	88.4	11.6
Diabetes (%)	6.4	5.15
Hypertension (%)	2.49	5.4
Conception (%)		
Spontaneous	96.12	96.86
Oocyte donation	0.29	0.13
IVF-ICSI	2.6	2.6
AID-AIC	0.6	0.34

IVF: *In Vitro* Fertilization; ICSI: Intracytoplasmic Sperm Injection; AID: Artificial Insemination Donor; AIC: Artificial Insemination Conjugal.

Maternal characteristics of the normal pregnancy group and the SGA group are summarized in Table 1. Multiple regression analysis demonstrated significant independent contributions in predicting SGA from PAPP-A, free β-hCG, CRL, as well as maternal age, weight, height and BMI, smoking, ethnic origin, hypertension and parity.

In SGA pregnancies, the median PAPP-A MoM, free β-hCG MoM and CRL was significantly lower than that in the normal group, but the median NT was not statistically significantly different from normal (Table 2). Maternal age, weight, height and Body Mass Index (BMI) was significantly lower in SGA pregnancies with respect to the normal group (Table 3). There was an increased incidence of maternal smoker status, hypertension, primiparity and Caucasian ethnicity resulting in SGA pregnancies. Diabetes status and conception type were not significantly different between the two groups (Table 1).

A multivariate model analysis was performed with the method of selecting successive steps, obtaining the variables able to predict SGA. The PAPP-A MoM (OR = 0.63, 95% CI 0.56-0.71), free β-hCG MoM (OR = 0.87, 95% CI 0.56-0.71), CRL (OR = 0.99, 95% CI 0.98-0.99) and maternal BMI (OR = 0.96, 95% CI 0.95-0.98) were protective factors for SGA, while smoker status (OR = 1.98, 95% CI 1.68-2.35), hypertension (OR = 2.42, 95% CI 1.74-3.37) and primiparity (OR = 1.56, 95% CI 1.38-1.83) were risk factors for SGA.

The Area Under the Curve (AUC) for this model was 0.650 (Figure 1) indicating that the ability of the multivariate model analysis to predict fetuses with estimated birth weight below the 10th percentile was low. For this reason, a multivariate model analysis was performed comparing the normal group (n = 14952) and the SGA group with birth weight below the 3rd percentile (severe IUGR, n = 408).

In the severe IUGR group, the median PAPP-A MoM, free β-hCG MoM and CRL were significantly lower than that in the normal group, but the median NT was not significantly different from normal. The maternal weight and height was significantly lower in severe IUGR pregnancies with respect to the normal group (Table 3). The smoker maternal status, hypertension and primiparity were significantly different in severe IUGR pregnancies compared to normal.

A multivariate model analysis was performed with the method of selecting successive steps, obtaining the variables able to predict severe IUGR. The PAPP-A MoM (OR = 0.77, 95% CI 0.63-0.93), free β-hCG MoM (OR = 0.56, 95% CI 0.45-0.71), CRL (OR = 0.99, 95% CI 0.98-0.99), maternal weight (OR = 0.99, 95% CI 0.98-0.99) and maternal height (OR = 0.95, 95% CI 0.94-0.98) were protective factors for severe IUGR (Table 4). While smoker status (OR = 0.46, 95% CI 0.35-0.61), hypertension (OR = 4.85, 95% CI 3.10-7.55) and primiparity (OR = 1.48, 95% CI 1.15-1.90) were risk factors for severe IUGR.

The Area Under the Curve (AUC) for this model was 0.703 (Figure 2). Therefore, the ability of the multivariate model analysis to predict fetus with estimated

Table 2: Median Multiples of the Median (MoM) for free β-hCG, PAPP-A, CRL and NT in pregnancies with SGA infants and normal group.

	Fetal weight (percentile)	Median	SD	P value
free β-hCG (MoM)	> 10th	1.26	0.86	< 0.001
	< 10th	1.13	0.82	
PAPP-A (MoM)	> 10th	1.12	0.81	< 0.001
	< 10th	0.92	0.72	
CRL (percentile)	> 10th	58.74	21.45	< 0.001
	< 10th	54.12	21.76	
NT (percentile)	> 10th	92.71	17.63	0.682
	> 10th	92.51	17.61	

Table 3: Median of maternal age (years), maternal weight (kg), maternal height (cm) and maternal BMI in pregnancies with SGA infants compared to normal group.

	Fetal weight (percentile)	Median	SD	P value
Maternal age (years)	> 10th	30.29	5.65	0.002
	< 10th	29.82	5.86	
Maternal weight (kg)	> 10th	66.05	13.88	< 0.001
	< 10th	63.07	13.32	
Maternal height (cm)	> 10th	163	6.2	< 0.001
	< 10th	161.39	5.9	
Maternal BMI	> 10th	24.89	5.04	< 0.001
	< 10th	24.24	4.99	

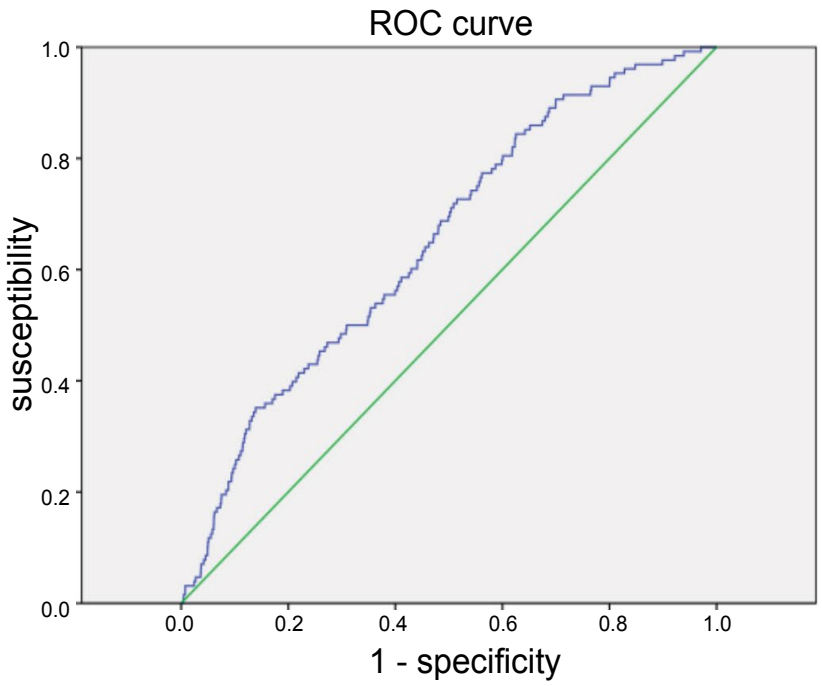

Figure 1: The ability of this model to predict SGA with birth weight below 10th is low, AUC = 0.650.

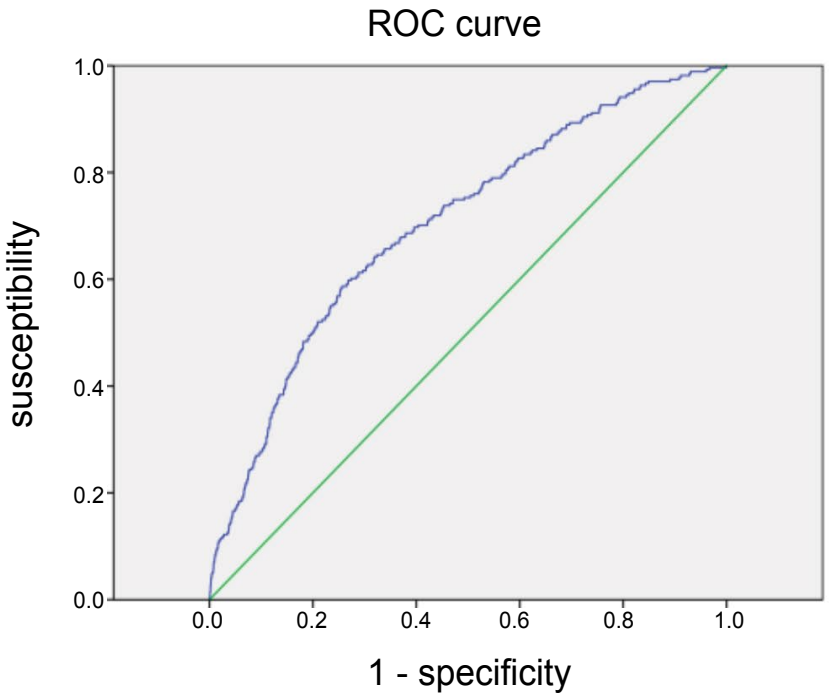

Figure 2: The ability of this model to predict IUGR with birth weight below 3rd is acceptable, AUC = 0.703.

Table 4: Median Multiples of the Median (MoM) for free β-hCG and PAPP-A, CRL, NT, maternal weight and height in the IUGR group (birth weight below the 3rd centile) compared to the normal group.

	Fetal weight (percentile)	Median	SD	P value
free β-hCG (MoM)	> 10th	1.26	0.86	< 0.001
	< 3rd	1.06	0.75	
PAPP-A (MoM)	> 10th	1.12	0.81	< 0.001
	< 3rd	0.85	0.66	
CRL (percentile)	> 10th	58.74	21.45	0.001
	< 3rd	55.04	21.25	
NT (percentile)	> 10th	92.71	17.63	0.821
	< 3rd	92.92	16.61	
Maternal weight (kg)	> 10th	66.05	13.88	0.014
	< 3rd	64.19	14.79	
Maternal height (cm)	> 10th	163	6.2	< 0.001
	< 3rd	161.06	6	

weight or birth weight below the 3rd percentile was acceptable.

Discussion

The main finding of the present study is that a combination of biochemical (PAPP-A and β-hCG) and ultrasonography (NT and CRL) markers in the first trimester combined with maternal characteristics (maternal age, weight, height, BMI, ethnicity, hypertension, smoker status and parity) allows us to predict those fetuses which will be SGA at delivery.

Recent publications relate low maternal levels of PAPP-A and β-hCG with poor obstetric outcomes [7,11,12]. One of the current aims of obstetric research is to find a method of screening for intrauterine growth restriction in the first trimester, starting from the premise that the main etiology is a placentation failure that occurs in the early stages of pregnancy. Furthermore, it has been shown that early identification of fetuses at risk of SGA improves the outcome four-fold, resulting in a decrease in the risk of adverse pregnancy outcome [13].

Low serum PAPP-A indicates impaired placentation [14]. Certainly, a plausible hypothesis to explain how low PAPP-A can reflect poor placental function and lead to potential SGA is the role of PAPP-A as an Insulin-Like Growth Factor Binding Protein (IGFBP) 4 and 5 protease [15]. It is believed to be of importance in increasing local bioavailability of insulin-like growth factor II (IGF-II), which is important for the trophoblast invasion and fetal growth [16]. In accordance with this role, lowered levels of PAPP-A would have less of a protease effect on IGFBPs leading to higher levels of bound (biologically inactive) IGF-I and II and thus reduced fetal growth.

β-hCG is not directly related to fetal growth, but may be reduced due to placental insufficiency. The extent of β-hCG reduction in SGA fetuses is controversial as some studies show a relation and other do not [8,17-19]. The data from this study confirm a relationship between low levels of β-hCG and SGA ($p < 0.001$).

After analyzing our results, we ascertained that some variables were protective and others risk factors for SGA, but a multivariate model established for predicting SGA indicates that they were not good predictors of SGA (AUC = 0.65). When analyzing the data by comparing the normal group to severe IUGR, we conclude that the model including MoM PAPP-A, MoM β-hCG, CRL, maternal weight, smoker status, hypertension and parity, was a good model for predicting the risk of severe IUGR (AUC 0.703).

References

1. Mandruzzato G, Antsaklis A, Botet F, Chervenak FA, Figueras F, et al. (2008) Intrauterine restriction (IUGR). J Perinat Med 36: 277-281.
2. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, et al. (2013) Optimizing the definition of intrauterine growth restriction: The multicenter prospective PORTO Study. Am J Obstet Gynecol 208: 290.e1-290.e6.
3. American College of Obstetricians and Gynecologists (2013) ACOG Practice bulletin no. 134: fetal growth restriction. Obstet Gynecol 121: 1122-1133.
4. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M (1997) A United States national reference for fetal growth. Obstet Gynecol 87: 163-168.
5. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A (2013) Maternal and fetal risk factors for stillbirth: Population based study. BMJ 346: 108.
6. Mayer C, Joseph KS (2013) Fetal growth: a review of terms, concepts and issues relevant to obstetrics. Ultrasound Obstet Gynecol 41: 136-145.
7. Kirkegaard I, Henriksen TB, Uldbjerg N (2011) Early fetal growth, PAPP-A and free β-hCG in relation to risk of delivering a small-for-gestational age infant. Ultrasound Obstet Gynecol 37: 341-347.
8. Spencer K, Cowans NJ, Avgidou K, Molina F, Nicolaides KH (2008) First-trimester biochemical markers of aneuploidy and the prediction of small-for-gestational age fetuses. Ultrasound Obstet Gynecol 31: 15-19.
9. Goetzinger KR, Singla A, Gerkowicz S, Dicke JM, Gray DL (2009) The efficiency of first-trimester serum analytes and maternal characteristics in predicting fetal growth disorders. Am J Obstet Gynecol 201: 412.e1-412.e6.
10. Poon LC, Maiz N, Valencia C, Plasencia W, Nicolaides KH (2009) First trimester maternal serum pregnancy associated plasma protein-A and preeclampsia. Ultrasound Obstet Gynecol 33: 23-33.
11. Leung TY, Sahota DS, Chan LW, Law LW, Fung TY, et al. (2008) Prediction of birth weight by fetal crown-rump length and maternal serum levels of pregnancy-associated plasma protein-A in the first trimester. Ultrasound Obstet Gynecol 31: 10-14.
12. Habayeb O, Daemen A, Timmerman D, De Moor B, Hackett GA, et al. (2010) The relationship between first trimester fetal growth, pregnancy-associated plasma protein A levels and birthweight. Prenat Diagn 30: 873-878.
13. Lindqvist PG, Molin J (2005) Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? Ultrasound Obstet Gynecol 25: 258-264.
14. Lawrence JB, Oxvig C, Overgaard MT, Sottrup-Jensen L, Gleich GJ, et al. (1999) The insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease secreted by human fibroblast is pregnancy-associated plasma protein-A. Proc Natl Acad Sci U S A 96: 3149-3153.
15. Laursen LS, Overgaard MT, Soe R, Boldt HB, Sottrup-Jensen L, et al. (2001) Pregnancy-associated plasma protein-A (PAPP-A) cleaves insulin-like growth factor binding protein (IGFBP)-5 independent of IGF: implications for the mechanism of IGFBP-4 proteolysis by PAPP-A. FEBS Lett 504: 36-40.
16. Prefumo F, Canini S, Casagrande V, Pastorino D, Venturini PL, et al. (2006) Correlation between first-trimester uterine artery Doppler indices and maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein A. Fertil Steril 86: 977-980.
17. Smith GC, Stenhouse EJ, Crossley JA, Aitken DA, Cameron AD, et al. (2002) Early pregnancy levels of pregnancy-associated plasma protein-A and the risk of intrauterine growth restriction, premature birth, preeclampsia and stillbirth. J Clin Endocrinol Metab 87: 1762-1767.
18. Dugoff L, Hobbins J, Dugoff L, Hobbins JC, Malone FD, et al. (2004) First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial). Am J Obstet Gynecol 191: 1446-1451.
19. Krantz D, Goetzl L, Simpson JL, Thom E, Zachary J, et al. (2004) Association of extreme first-trimester free human chorionic gonadotropin-beta, pregnancy-associated plasma protein A, and nuchal translucency with intrauterine growth restriction and other adverse pregnancy outcomes. Am J Obstet Gynecol 191: 1452-1458.