Revista Médica del
Hospital General de México

PERMANYER

Check for updates

ORIGINAL ARTICLE

Perinatal morbidity in gestations with pathological combined first trimester screening for aneuploidies and normal karyotype

Carmen M. Migdan[1] and Diego Lerma-Puertas[2]*

[1]Department of Obstetrics and Gynecology, Hospital Universitario Miguel Servet; [2]Department of Perinatal Medicine, Hospital Universitario Clínico. Zaragoza, Spain

Abstract

Objective: *Positive Combined First Trimester Screening and by risk groups: 0-50, 51-100, 101-150, 151-200, 201-250, and normal karyotype relate with negative screening for adverse perinatal results.* **Method:** *Retrospective study of cases and controls in single pregnancies, with predictive analysis using multivariate logistic regression.* **Results:** *3,791 screenings were performed at our unit in 2012, with a screening/number of deliveries ratio of 89.9%. There is a greater likelihood of the newborn being underweight (AOR = 2.6, 95% CI 1.2 – 5.7), premature (OR = 2.2, 95% CI 1.03 – 4.5), admitted to the ICU (OR = 7.4, CI 95% 1.5 – 34.6) or admitted to the Neonates department (AOR = 8.1, 95% CI 1.7 – 37.7) in the case group.* **Conclusion:** *Combined first trimester screening is a predictive method for pregnant women with a higher risk of adverse perinatal outcomes.*

Keywords: *PAPP-A. β-HCG. Adverse perinatal outcomes. Aneuploidies.*

Introduction

The early diagnosis of any congenital defect in the fetus is of vital importance, as it enables the implementation of the most appropriate measures, both during pregnancy and during childbirth, as a means of preventing unnecessary risks to the mother and child and of attempting to improve the prognosis of the newborn after birth[1].

All pregnant women in the first trimester are offered prenatal aneuploidy screening, which estimates the individual risk of chromosomopathy, combining the *a priori* risk due to the mother´s age with the biochemical analysis of PAPP-A and maternal blood and free β-HCG fraction and with an ultrasound measurement of Nuchal Translucency (NT)[2,3].

Previous studies have revealed that the biochemical and ultrasound markers of first-trimester combined screening, abnormal PAPP-A, βHCG and NT in pregnancies without aneuploidy can be predictive of adverse perinatal outcomes[4-6].

Elevated NT with normal karyotype is associated with fetal structural anomalies and several genetic syndromes, including heart defects, Noonan syndrome, Smith-Lemli-Opitz syndrome and skeletal dysplasias of the achondroplastic type and thanatophoric displasia[7-12].

Low PAPP-A is associated with placental defects and has been associated with abortions, antepartum fetal death, restricted intrauterine growth, hypertensive disease of pregnancy, prematurity, and low birth weight.

Moreover, due to the association with abnormal placentation, high elevated βHCG is associated with preeclampsia, restricted intrauterine growth, antepartum fetal death and prematurity[13-16].

Correspondence:
*Carmen M. Migdan
E-mail: mig_mihaela@yahoo.es

Date of reception: 24-10-2021
Date of acceptance: 20-01-2022
DOI: 10.24875/HGMX.21000096

Available online: 09-08-2022
Rev Med Hosp Gen Mex. 2022;85(3):114-119
www.hospitalgeneral.mx

The aim of our study is to find out if there are any significant differences in adverse obstetric and perinatal outcomes in pregnant women with positive combined screening and normal karyotype in the group of cases, by risk group (0-50, 51-100, 101-150, 151-200, 201-250), comparing them with the control group.

Material and methods

Using the medical records database, we conducted a retrospective study of cases and controls in pregnant women that underwent combined screening in the first trimester in the prenatal diagnosis section of the department of obstetrics and gynecology at Miguel Servet University Hospital, Zaragoza, in the period from January to December 2012, both months included.

The following inclusion criteria were used: single pregnancies subjected to combined first-trimester screening and follow-up of pregnancy and delivery at our hospital, whereby the following were excluded from the study: twin pregnancies with aneuploidy and/or fetal malformations, and cases with an absence of data related to the mother and/or newborn.

To determine biochemical free β-HCG and PAPP-A, all the pregnant women were scheduled for blood collection between 9+0]-10+0] weeks, and for an ultrasound measurement of nuchal translucency between 11+0] -13+6 weeks and with a skull-caudal length (LCC) of between 45 and 84 mm.

The IMMULITE® 2000 automatic analyser (Siemens Healthcare Diagnostics) was used for the measurement of the biochemical parameters. The PAPP-A values in mIU/L and β-HCG values in ng/ml (with the equivalence ng/ml = IU/L), were converted into MoM, dividing the individual value of the marker by the value of the population median for the gestational age expressed in days.

The same plane as for the LCC was used to measure Nuchal Translucency (NT), with the fetus in a neutral position in accordance with the Fetal Medicine Foundation (FMF) standard https://fetalmedicine.org/education/the-11-13-weeks-scan.

A median of MoM NT of between 0.90 - 1.10 MoM, or the standard deviation of the log10 MoM NT, of between 0.08-0.13, was regarded as adequate. Prisca software version 639 – 0106 2012 was used to calculate the risk.

All the pregnant women with positive combined screening, risk >1/250 and normal karyotype were selected from the case group, who were divided into risk groups: 1-50, 51-100, 101-150, 151-200, 201-250 and the pregnant women with normal combined screening, risk < 1/14000 in the control group. Data on maternal backgrounds, delivery characteristics and neonatal morbidity was collected.

The gestational age of newborns was measured in days and was calculated through an ultrasound performed in the first trimester of pregnancy, or based on the date of the last period in which the gestational age did not changed by more than two standard deviations (< 6 days).

Preterm birth refers to births that occurred spontaneously or were induced before 36[6] weeks of gestation (≤ 259 days)[17].

The weight of newborns was calculated in grams (g) at the time of delivery. The following category variables were taken into account: Low weight: Percentile (p < 10), Normal weight: Percentile: P10 – 90 and Large for gestational age (LGE): Percentile: p > 90. Weight according to gestational age was estimated using the Spanish tables of neonatal weights of the Spanish Society of Obstetrics and Gynecology (SEGO).

The SPSS programme was used for the statistical analysis of data. The description of the quantitative variables was carried out using mean and standard deviation. The chi-square test or Fisher's exact test was used to analyse the qualitative variables. Multivariate logistic regression analysis was used to assess the prediction in the case group and by risk group, in addition to the control group of the outcome variables. $p < 0.05$ was regarded as significant.

Only pregnant women that gave their consent to perform combined screening in the first trimester participated in the study, pursuant to the standards of the Society of Gynecology and Obstetrics (SEGO) and our hospital´s quality commission.

Results

4,217 deliveries and 3,791 first-trimester combined screenings (FTCS) were performed at our hospital in 2012, with an FTCS/number of deliveries ratio of 89.9%. Of the total number of FTCS performed, 3515 FTCS were negative (92.7%) and 276 FTCS were positive (7.3%). Of the population screened in the year 2012, there were 30 true positives (TP), 246 false positives (FP), 3514 true negatives (TN) and 1 false negative (diagnosis through out-of-hospital amniocentesis). The sensitivity and specificity of FTCS in our sample were 96.8% and 93.5% respectively, with a false positive rate of 6%.

Table 1. Logistic regression analysis of the characteristics of the newborns, in the case and control group

Newborn Characteristics	Cases				Controls	
	OR	p	AOR	p	AOR	p
	IC 95%		IC 95%		IC 95%	
Premature ≤ 366 weeks	2,17	0,041	-	-	-	-
	1,03-4,56					
Weight RN < P10	1,9	0,018	2,6	0,013	-	-
	1,12-3,48		1,22-5,7			
Term gestation	-	-	-	-	2,26	0,036
					1,05-4,86	
					1,06-40,36	

Source: Prenatal diagnosis section 2012.
OR: odds ratio; AOR: adjusted odds ratio; CI: confidence interval; NB: newborn; P: percentile; p: level of statistical significance.

There were 219 (39.9%) pregnant women with positive combined screening and normal karyotype in the study period. A control group from the same period was selected with 330 (15.7%) pregnant women with similar demographic characteristics.

Of the 549 single pregnancies included in the study, 30 (5.7%) were born prematurely and 54 (10.2%) were born with low birth weight (percentile <10). There was a greater likelihood in the case group of newborns with low birth weight (AOR = 2.642, p = 0.013) and of prematurity (OR = 2.170, p = 0.041) and in the full-term newborn control group (AOR = 2.265). By risk group, births with low weight were more likely in the 1-50 group (AOR = 2.269, p = 0.036) and in the 100-150 group (AOR = 3.291, p = 0.008) (Table 1).

52 newborns (9.8%) were admitted and observed, with 36 newborns (17.6%) in the case group and 16 newborns (4.9%) in the control group (p < 0.001). Of the total admissions, 11 newborns (2.1%) were admitted to the ICU, 17 (3.2%) were admitted due to prematurity, 12 (2.3%) were admitted due to low weight and 5 (3%) were admitted due to prematurity-related complications. The prematurity-related complications observed in the newborns in question were: wet lung/lung maladaptation, hyaline membrane, bronchopulmonary dysplasia, retinopathy of prematurity and retinal hemorrhage.

We found a greater likelihood of admission to the ICU in the case group (OR = 7.4, p = 0.011) and to the Neonates department (AOR = 8.120, p = 0.008), the most likely causes of admission being prematurity (OR = 3.979, p = 0.011), low weight (OR = 18.371, p = 0.005), jaundice (OR = 4.808, p = 0.002), and respiratory distress (OR = 4.808, p = 0.001). Admission due to perinatal infection was more likely in the control group (AOR = 6.554) (Table 2).

The likelihood of the hospitalisation of newborns by risk group was: 1-50 group admission to the Neonates department (OR = 2.472, p = 0.019), due to prematurity (OR = 4.13, p = 0.01), due to prematurity-related complications (OR = 6.333, p = 0.046), due to low weight (AOR = 6.322, p = 0.049) and due to respiratory distress (OR = 4.8, p = 0.001); in the 50-100 segment admission due to jaundice (AOR = 3.278, p = 0.035), in the 100-150 group, admission to the neonates unit (OR = 2.704, p = 0.028), due to low weight (OR = 2.704, p = 0.015) and perinatal infection (AOR = 5.505, p = 0.029); in the 150-200 group, due to respiratory distress (AOR = 5.813, p = 0.01) and in the 200-250 group, admission to the ICU (AOR = 16.8, p = 0.034) and due to respiratory distress (OR = 3.125, p = 0.048) (Table 3).

Discussion

The "Inversion of the antenatal control pyramid" concept is a model of prenatal care in which, gathering epidemiological, clinical, biophysical, ultrasound and analytical data between 11 and 14 weeks of gestation enables us to individualise the risk of each pregnant woman for a wide spectrum of pathological conditions (fetal death and spontaneous abortion, premature birth, preeclampsia, gestational diabetes, fetal growth restriction, macrosomia), thereby establishing preventive measures and, in some cases, therapeutic measures[18-20].

Table 2. Logistic regression analysis of neonatal morbidity, in the case and control group

Neonatal morbidity	Cases				Controls	
	OR	p	AOR	p	AOR	p
	IC 95%		IC 95%		IC 95%	
ICU admissions	7,4	0,011	-	-	-	-
	1,58-34,67					
Neonatal admissions	4,1	0,001	8,1	0,008	-	-
	2,21-7,63		1,74-37,73			
Admission for Prematurity	3,9	0,011	-	-	-	-
	1,38-11,46					
Underweight Income	18,3	0,005	-	-	-	-
	2,35-143,4					
Admission for jaundice	4,1	0,002	-	-	-	-
	1,67-10,08					
Admission for respiratory distress	4,8	0,001	-	-	-	-
	1,86-12,41					
Admission for perinatal infection	-	-	-	-	6,55	0,043
					1,06-40,36	

Source: Prenatal Diagnostic Section, HUMS, 2012.
OR: odds ratio; AOR: adjusted odds ratio; CI: confidence interval; NB: newborn; P: percentile; p: significance level.

Prematurity has major health implications due to high fetal morbidity and mortality, particularly at extreme gestational ages. Prematurity is the most frequent cause of perinatal mortality (2/3) and can cause significant long-term morbidity due to neurological, gastrointestinal and respiratory disorders[21,22].

The prevalence of prematurity in Spain is 9.5%[17,] with the rate of late prematurity (34 to 36 weeks of gestation) being far more prevalent both in Europe and in the USA, where it can vary from 50% to 75%[23,24].

Beta et al. conducted a predictive model of preterm delivery with the biochemical markers of the 1st trimester, maternal characteristics and obstetric history and conclude that preterm delivery could be detected with a rate of 20% in nulliparous women and 38% in women with a history of preterm delivery ≥ 16 weeks, with 10% false positives[25]. *Spencer* et al. conclude that low PAPP-A increases the risk of prematurity, but the same does not apply to βHCG. The lower the PAPP-A, the greater the risk of prematurity, even so the detection rate for low PAPP-A does not exceed 10%[26]. *Dugoff* et al, in the FASTER study, found a statistical association of PAPP-A < P5 with prematurity[5]. Prematurity was found in 6% of pregnancies in our study, with a greater probability in the case group (OR = 2).

Several studies report higher morbidity[27] and perinatal mortality in newborns with low birth weight < P10[28].

Morris et al. found an association between low weight < P10 and PAPP-A < P5 with a likelihood OR 2.08 (CI 1.89-2.29), with a prediction rate of 13%, for 7% of false positives[29].

Peterson et al. conclude that PAPP-A is positively correlated with birth weight, with a higher risk of low weight for gestational age with PAPP-A < 0.57 MoM[30].

A study conducted by *Spencer* et al. concludes that fetuses with a low weight for their gestational age are associated with lower medians of PAPP-A[26].

In our study, 2% of newborns weighing less than the 10th percentile were identified, being more likely in the case group (AOR = 2.642) and in the *1 to 50* (AOR = 2.269) and *100 to 150* (AOR = 3.291) risk groups.

With regard to morbidity in newborns, *Kirkegaard* et al. associate low levels of PAPP-A < 4 MoM and βHCG with a higher rate of admissions to neonatal

Table 3. Logistic regression analysis of neonatal morbidity, in the risk range of 1 to 50, 50 to 100, 100 to 150, 150 to 200, 200 to 250

Neonatal morbidity	Segment 1-50		Segment 50-100	Segment 100-150		Segment 150-200	Segment 200-250	
	OR	AOR	AOR	OR	AOR	AOR	OR	AOR
	IC 95%	IC 95%	IC 95%	IC 95%	IC 95%	IC 95%	IC 95%	IC 95%
ICU admissions	-	-	-	-	-	-	5,5*	16,87
							1,39-21,79	1,23-231,18
Neonatal admissions	2,4*	-	-	2,7*	-	-	-	
	1,15-5,27			1,11-6,57				
Admission for Prematurity	4,1*	-	-	-	-	-	-	-
	1,39-12,23							
Underweight Income	7,1*	6,3	-	5,4*	5,6*	-	-	-
	2,18-23,43	1,009-39,6		1,39-21,07	1,16-27,88			
Admission for jaundice	-	-	3,27*	-	-	-	-	-
			1,08-9,9					
Admission for respiratory distress	4,8*	-	-	-	-	5,8*	3,12	-
	1,86-12,41					1,5-22,3	1,01-9,7	
Admission due to prematurity complications	6,3	-	-	-	-	-	-	-
	1,03-38,8							
Admission for perinatal infection	-	-	-	5,4*	5,5*	-	-	-
				1,39-21,07	1,19-25,46			

Source: Prenatal Diagnostic Section, HUMS, 2012.
OR: odds ratio; AOR: adjusted odds ratio; CI: confidence interval; NB: newborn; P: percentile.
*Significant association.

intensive care units (ICU), regardless of gestational age and low weight[31].

In our study, there was a greater probability of hospitalisation in the neonates unit and the ICU in the case group and in the *1 to 50* and *50 to 100* risk groups, with the most likely cause of admission being prematurity (OR = 4.13), prematurity-related complications (OR = 6.333) and low birth weight (AOR = 6.322). Several studies have followed up on adverse obstetric outcomes and the relationship with biochemical and ultrasound parameters in the 1st trimester, but in general they have all been used on an isolated basis and therefore have less sensitivity and predictive value.

Our study has the major advantage of having used combined 1st trimester screening as a predictive method of adverse obstetric outcomes during pregnancy, which increases the likelihood of detecting pregnant women with a higher risk of developing pathologies, which may enable us to act from the beginning of pregnancy, modifying the risk (for example, the administration of aspirin in platelet dysfunction) or conducting a close follow-up procedure with predictable action.

One limitation of our study is that the relevance of the predictive values is limited due to the fact it is a case-control study. Nevertheless, we have been able to clearly illustrate the importance of first-trimester combined screening as a model for predicting adverse perinatal outcomes, such as prematurity, low weight and admissions to the ICU and neonates unit.

Conclusion

Performing prenatal screening for aneuploidy, from 9+0] to 13+6 weeks of gestation, is of paramount importance, not only in screening for Down syndrome, but also for the early prediction of pregnant women at a high risk of developing adverse fetal events such as:

prematurity, low weight for gestational age and neonatal admissions.

Aknowledgments

The authors thank for the excellent assistance in conducting this review of Dr. José Luis Bartha Rasero, head of the Obstetrics Department at La Paz University Hospital, and I would also like to thank the Miguel Servet University Hospital Prenatal Diagnosis Unit for providing with the appropriate information.

Funding

There was no funding for this article.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments have been performed on humans or animals for this research.

Data confidentiality. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Maiz N, Burgos J, Barbazán MJ, Recio V, Martínez-Astorquiza T. Maternal attitude towards first trimester screening for fetal abnormalities. Prenat Diagn. 2016;36(5):449-455. doi:10.1002/pd.4802
2. Souka AP, Von Kaisenberg CS, Hyett JA, Sonek JD, Nicolaides KH. Increased nuchal translucency with normal karyotype. Am J Obstet Gynecol. 2005;192(4):1005-1021. doi:10.1016/j.ajog.2004.12.093
3. Atzei A, Gajewska K, Huggon IC, Allan L, Nicolaides KH. Relationship between nuchal translucency thickness and prevalence of major cardiac defects in fetuses with normal karyotype. Ultrasound Obstet Gynecol. 2005;26(2):154-157. doi:10.1002/uog.1936
4. Krantz D, Goetzl L, Simpson JL, et al. 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. 2004;191(4):1452-1458. doi:10.1016/j.ajog.2004.05.068
5. Dugoff L, Hobbins JC, Malone FD, et al. 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. 2004;191(4):1446-1451. doi:10.1016/j.ajog.2004.06.052
6. Ong CY, Liao AW, Spencer K, Munim S, Nicolaides KH. First trimester maternal serum free beta human chorionic gonadotrophin and pregnancy associated plasma protein A as predictors of pregnancy complications. BJOG. 2000;107(10):1265-1270. doi:10.1111/j.1471-0528.2000.tb11618.x
7. Guterman S, Beneteau C, Redon S, et al. Prenatal findings in 1p36 deletion syndrome: New cases and a literature review. Prenat Diagn. 2019;39(10):871-882. doi:10.1002/pd.5498
8. Alamillo CML, Fiddler M, Pergament E. Increased nuchal translucency in the presence of normal chromosomes. Curr Opin Obstet Gynecol. 2012;24(2):102-108. doi:10.1097/GCO.0b013e3283505b25
9. Achiron R, Heggesh J, Grisaru D, et al. Noonan syndrome: a cryptic condition in early gestation. Am J Med Genet. 2000;92(3):159-165. doi:10.1002/(sici)1096-8628(20000529)92:3<159:aid-ajmg1>3.0.co;2-2
10. Carvalho MHB, Brizot ML, Lopes LM, Chiba CH, Miyadahira S, Zugaib M. Detection of fetal structural abnormalities at the 11-14 week ultrasound scan. Prenat Diagn. 2002;22(1):1-4. doi:10.1002/pd.200
11. Hyett JA, Clayton PT, Moscoso G, Nicolaides KH. Increased first trimester nuchal translucency as a prenatal manifestation of Smith-Lemli-Opitz syndrome. Am J Med Genet. 1995;58(4):374-376. doi:10.1002/ajmg.1320580415
12. Markov D, Jacquemyn Y, Leroy Y. Bilateral cleft lip and palate associated with increased nuchal translucency and maternal cocaine abuse at 14 weeks of gestation. Clin Exp Obstet Gynecol. 2003;30(2-3):109-110. http://www.ncbi.nlm.nih.gov/pubmed/12854855
13. Zygmunt M, Herr F, Münstedt K, Lang U, Liang OD. Angiogenesis and vasculogenesis in pregnancy. Eur J Obstet Gynecol Reprod Biol. 2003;110 Suppl: S10-8. doi:10.1016/s0301-2115(03)00168-4
14. Fitzgerald B, Levytska K, Kingdom J, Walker M, Baczyk D, Keating S. Villous trophoblast abnormalities in extremely preterm deliveries with elevated second trimester maternal serum hCG or inhibin-A. Placenta. 2011;32(4):339-345. doi:10.1016/j.placenta.2011.01.018
15. Paulesu L, Rao CV, Ietta F, Pietropolli A, Ticconi C. hCG and Its Disruption by Environmental Contaminants during Human Pregnancy. Int J Mol Sci. 2018;19(3):914. doi:10.3390/ijms19030914
16. Turco MY, Gardner L, Kay RG, et al. Trophoblast organoids as a model for maternal-fetal interactions during human placentation. Nature. 2018;564(7735):263-267. doi:10.1038/s41586-018-0753-3
17. Sego GAP, Perinatal M. Parto Pretérmino. Guía de Asistencia Práctica actualizada en febrero de 2020 Índice. SEGO, Guía Asist Práctica, Med Perinat. Published online 2020:1-62. www.prosego.com.
18. Nicolaides KH. A model for a new pyramid of prenatal care based on the 11 to 13 weeks' assessment. Prenat Diagn. 2011;31(1):3-6. doi:10.1002/pd.2685
19. Nicolaides KH. Turning the Pyramid of Prenatal Care. Fetal Diagn Ther. 2011;29(3):183-196. doi:10.1159/000324320
20. Sonek JD, Kagan KO, Nicolaides KH. Inverted Pyramid of Care. Clin Lab Med. 2016;36(2):305-317. doi:10.1016/j.cll.2016.01.009
21. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84. doi:10.1016/S0140-6736(08)60074-4
22. Spong CY. Prediction and prevention of recurrent spontaneous preterm birth. Obstet Gynecol. 2007;110(2 Pt 1):405-415. doi:10.1097/01.AOG.0000275287.08520.4a
23. Torchin H, Ancel P-Y. [Epidemiology and risk factors of preterm birth]. J Gynecol Obstet Biol Reprod (Paris). 2016;45(10):1213-1230. doi:10.1016/j.jgyn.2016.09.013
24. Howson CP, Kinney M V, McDougall L, Lawn JE, Born Too Soon Preterm Birth Action Group. Born too soon: preterm birth matters. Reprod Health. 2013;10 Suppl 1:S1. doi:10.1186/1742-4755-10-S1-S1
25. Beta J, Akolekar R, Ventura W, Syngelaki A, Nicolaides KH. Prediction of spontaneous preterm delivery from maternal factors, obstetric history and placental perfusion and function at 11-13 weeks. Prenat Diagn. 2011;31(1):75-83. doi:10.1002/pd.2662
26. Spencer K, Cowans NJ, Molina F, Kagan KO, Nicolaides KH. First-trimester ultrasound and biochemical markers of aneuploidy and the prediction of preterm or early preterm delivery. Ultrasound Obstet Gynecol. 2008;31(2):147-152. doi:10.1002/uog.5163
27. Smith NA, Bukowski R, Thomas AM, Cantonwine D, Zera C, Robinson JN. Identification of pathologically small fetuses using customized, ultrasound and population-based growth norms. Ultrasound Obstet Gynecol. 2014;44(5):595-599. doi:10.1002/uog.13333
28. Vasak B, Koenen S V, Koster MPH, et al. Human fetal growth is constrained below optimal for perinatal survival. Ultrasound Obstet Gynecol. 2015;45(2):162-167. doi:10.1002/uog.14644
29. Morris RK, Bilagi A, Devani P, Kilby MD. Association of serum PAPP-A levels in first trimester with small for gestational age and adverse pregnancy outcomes: systematic review and meta-analysis. Prenat Diagn. 2017;37(3):253-265. doi:10.1002/pd.5001
30. Peterson SE, Simhan HN. First-trimester pregnancy-associated plasma protein A and subsequent abnormalities of fetal growth. Am J Obstet Gynecol. 2008;198(5):e43-5. doi:10.1016/j.ajog.2007.12.026
31. Kirkegaard I, Uldbjerg N, Henriksen TB. PAPP-A and free β-hCG in relation to admission to neonatal intensive care unit and neonatal disease. Prenat Diagn. 2011;31(12):1169-1175. doi:10.1002/pd.2858