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Role of first trimester screening test in predicting the perinatal outcomes in low risk term pregnancies

Gökçe Turan[1], Ezgi Turgut[1], Halis Özdemir[2], Roujin Akbarihamed[1], Sibel Konca[1], Deniz Karcaaltıncaba[1], Merih Bayram[1]

[1]Department of Obstetrics & Gynecology, School of Medicine, Gazi University, Ankara, Turkey
[2]Department of Obstetrics & Gynecology, Malatya Training and Research Hospital, Malatya, Turkey

Abstract

Objective: This study aims to investigate the relationship between the nuchal translucency (NT) values measured in the first trimester and the well-being of the newborn.

Methods: The study was planned as a retrospective cross-sectional study and was conducted between January 2018 and January 2020. A total of 2394 patients who had a combined test and delivered at our university hospital were included in the study. The demographic data of the pregnant women were recorded. NT MoM values, PAPP-A and β-hCG MoM values, birth weight, gender, need for neonatal intensive care (NICU), and Apgar scores were evaluated.

Results: It was found that NT (MoM) values were similar among the SGA, AGA, and LGA groups (p=0.159). PAPP-A (MoM) values were similar in the SGA group compared to AGA and LGA infant groups (p=0.947). It was also found that β-hCG (MoM) values were similar in the AGA group compared to SGA and the LGA infant groups (p=0.694). When compared with those with NICU and non-NICU, the NT, PAPP-A, β-hCG, and birth weight values were again not found to be statistically significant (p>0.05). The NT, PAPP-A, β-hCG, and male gender factors were evaluated in the Binary Logistic Regression Analysis, in which being an SGA baby was considered as a risk. It was found that a 1 mm increase in NT values increased the risk of having an SGA baby 2.63 times at a statistically significant level (OR=2.636, p=0.009, 95% CI: 1.277–5.440). PAPP-A, β-hCG levels, and having a male gender were not related to the risk of having an SGA baby. Furthermore, NT, PAPP-A, β-hCG levels, and having a male gender were not associated with the risk of NICU hospitalization.

Conclusion: In conclusion, we could not predict the birth weight with increased NT MoM values that were detected in the first trimester combined test in this study; however, we found that the risk of having an SGA fetus increases with a weak rise in NT value.

Keywords: Apgar, birthweight, nuchal translucency, prenatal screening.

Introduction

The first-trimester risk assessment test for trisomy is a risk calculation test using a combination of ultrasound examination and biochemical tests. This screening test was described by Nicolaides[1,2] and posteriorly validated in large prospective studies.[3,4] In this screening test for aneuploidies, the risk is assessed at 11 weeks to 13 weeks + 6 days of gestation. With a combination of maternal age, nuchal translucency (NT), and maternal serum free β-hCG and pregnancy-associated plasma protein-A (PAPP-A) levels, this test is called "the Combined First-Trimester Test by the Fetal Medicine Foundation (FMF)".

NT is defined as the subcutaneous fluid located under the skin at the back of the fetal neck measured between 11 weeks and 13 weeks + 6 days of gestation, regardless of whether it covers only the head or whole body, or presents septations.[5] The main mechanisms suggested for increased NT are a change in the composition of the extracellular matrix, heart, great artery anomalies, and impaired or delayed lymphatic development.[3] Fetuses with increased NT are at high risk for

Correspondence: Gökçe Turan, MD. Department of Obstetrics & Gynecology, School of Medicine, Gazi University, Beşevler, Ankara, Turkey.
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ORCID ID: G. Turan 0000-0002-2443-1927; E. Turgut 0000-0002-5509-7888; H. Özdemir 0000-0002-9194-8504; R. Akbarihamed 0000-0003-0380-2722; S. Konca 0000-0002-9253-3909; D. Karcaaltıncaba 0000-0001-5276-9303; M. Bayram 0000-0003-1299-2433

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chromosomal, structural, and genetic anomalies, and generally, it is accepted as a non-specific sign of fetal abnormality.[6,7] For this reason, abnormal results detected in NT values may affect the weight of the fetus or may help us to predict other adverse outcomes. Therefore, according to the literature, ultrasound markers and biochemical markers used in the first-trimester screening test are not only used in aneuploidy risk calculation but have also been shown to predict adverse pregnancy outcomes since the first trimester of pregnancy.[6]

The aim of this study was to investigate the relationship between NT values measured in the first trimester and maternal serum free β-hCG and PAPP-A levels with term birth weight and well-being of the newborn.

Methods

The study included 2394 patients who had combined screening tests between January 2018 and January 2020 at the Department of Obstetrics & Gynecology, Gazi University Medical School and who gave birth in the same hospital. The study was planned cross-sectional retrospectively after the approval of the ethics committee of our hospital (Ethics Committee Number: 2020/463). All participants gave informed consent. The inclusion criteria were: *(i)* singleton pregnancy, *(ii)* gestational age being between 11 and 13 weeks 6 days based on fetal crown-rump length, sonographic measurement in the first trimester, and *(iii)* pregnant women who gave birth in our hospital at term delivery week.

Multiple pregnancies, aneuploidy, neural tube defect, abdominal wall defect or other severe anatomical defects, diabetes mellitus, pregnancy-induced hypertension, preeclampsia, premature rupture of membranes, and pre-existing maternal medical diseases (such as chronic hypertension, heart disease, pregestational overt diabetes, renal disease, etc.) and patients with in vitro fertilization (IVF), patients receiving exogenous progesterone in the first trimester, those with evidence of intrauterine infections, patients who gave birth before 37 weeks of gestation and those whose data could not be obtained were excluded from the study.

The scans were done by transabdominal ultrasonography, and transvaginal ultrasonography was used when necessary. NT and CRL were measured in millimeters (mm) on the mid-sagittal level under sonography between 11 weeks and 13 weeks and 6 days of gestation. The mm measurements of the NT values were recorded as MoM (multiple of the median) (they were given in MoM value to standardize the NT values) for age, weight, and week of gestation. All examinations were performed by five perinatologists (M.B., D.K., H.O., E.T., and G.T.) working in line with the FMF protocols. Age, maternal body mass index (BMI), smoking status, gravida, and parity values of the pregnant women were obtained for the combined test. We recorded birth weight, gender, delivery type, 1- and 5-minute Apgar scores, birth week, need for the neonatal intensive care unit (NICU), NT value (MoM) in the first-trimester screening test, CRL measurements (mm), PAPP-A (MoM), and maternal serum free β-hCG (MoM) values from hospital records. Also, the newborn's well-being was accepted as NICU needs and non-NICU needs.

Small for gestational age (SGA) was defined as a birth weight less than 2500 g, large for gestational age (LGA) was defined as a birth weight more than 4000 g, and newborn in between was defined as appropriate for gestational age (AGA).

Statistical analysis

The continuous variables were expressed as median (min–max), and the categorical data as numbers and percentages. The normality analyses of continuous variables were done by Shapiro-Wilk test and Kolmogorov-Smirnov goodness of fit test. Since the continuous variables did not fit the normal distribution, the comparisons between the SGA, AGA, and LGA were made by Kruskal-Wallis test (Post hoc: Bonferroni corrected Mann-Whitney U test). The comparisons between the NICU / Non-NICU were made by Mann-Whitney U test. The binary logistic regression was used to predict the effects of the variables on SGA, and the need for NICU. The Hosmer-Lemeshow test was used for model fit. The analyses were done by IBM SPSS Package Program version 22.0 (IBM Corporation, Armonk, NY, USA). Statistical significance level was considered $p<0.05$.

Results

The records of 3177 patients who gave birth in our clinic between January 2018 and January 2020 were reviewed. Ultimately, 2394 patients who met the study criteria and had a combined screening test were included in the study. The demographic data of the patients and their parameters regarding pregnancy and newborns are listed in **Table 1**.

It was found that NT (MoM) values were similar among the SGA [0.87 (0.39–1.94)], AGA [0.81 (0.08–2.87)] and LGA [0.81 (0.09–1.17)] groups (p=0.159). Similarly, PAPP-A (MoM) values were similar in the SGA group [1.13 (0.35–6.06)] compared to AGA [1.07 (0.13–6.75)] and LGA infant groups [1.03 (0.29–2.82)] (p=0.947). It was also found that β-hCG (MoM) values were similar in the AGA group [1.01 (0.13–11.5)] compared to SGA [0.93 (0.21–3.86)] and the LGA infant group [0.89 (0.25–5.04)] (p=0.694). Also, the NT, PAPP-A and β-hCG, and CRL values were not significant among the SGA, AGA, and LGA groups in the first trimester (**Table 2**).

When compared with those with NICU and non-NICU, the NT, PAPP-A, β-hCG, and birth weight values were again not found to be statistically significant (p>0.05) (**Table 3**).

The NT, PAPP-A, β-hCG, and male gender factors were evaluated in the binary logistic regression analysis, in which being an SGA baby was considered as a risk. It was found that a 1 mm increase in NT values increased the risk of having an SGA baby 2.63 times at a statistically significant level (OR=2.636, p=0.009, 95% CI: 1.277–5.440). PAPP-A (OR=1.048, p=0.762, 95% CI: 0.773–1.421) and β-hCG (OR=0.917, p=0.543, 95% CI: 0.695–1.211) levels, and having a male gender (OR=0.996, p=0.984, 95% CI: 0.642–1.545) were not related to the risk of having an SGA baby. Furthermore, NT (respectively, OR=0.906, p=0.584, 95% CI: 0.636–1.291), PAPP-A (OR=1.107, p=0.090, 95% CI: 0.984–1.245), β-hCG levels (OR=0.986, p=0.777, 95% CI: 0.894–1.087), and having a male gender (OR=1.022, p=0.797, 95% CI: 0.865–1.208) were not associated with the risk of NICU hospitalization (**Table 4**).

Table 1. Patients' demographic data, pregnancy, and neonatal parameters.

Variable	Median (min–max)
Age (year)	29.50 (18.00–50.00)
Pre-pregnancy BMI	22.37 (14.70–33.29)
Gravida	1.00 (1.00–11.00)
Pregnancy week during screening	12.60 (11.00–13.87)
Week of birth	39.42 (37.01–41.85)
NT (MoM)	0.81 (0.08–2.87)
CRL (mm)	59.00 (45.1–87.00)
PAPP-A (MoM)	1.07 (0.13–6.75)
Free beta β-hCG (MoM)	1.01 (0.13–11.52)
Form of delivery (n, %)	
NVD	833 (34.8%)
CS	1561 (65.2%)
Smoking (n, %)	
Yes	672 (28.1%)
No	1722 (71.9%)
Birth weight of the newborn (g)	3070.00 (2400–4720)
Birth height of the newborn (cm)	49.00 (34.00–66.00)
Head circumference of the newborn (cm)	34.50 (27.50–52.00)
1-minute Apgar score	9.00 (1.00–10.00)
5-minute Apgar score	10.00 (1.00–10.00)
Need for NICU (n, %)	
Yes	880 (36.8%)
No	1514 (63.2%)
Sex of the newborn (n, %)	
Female	1243 (51.9%)
Male	1151 (48.1%)

β-hCG: human chorionic gonadotropin; **BMI:** body mass index; **CRL:** crown-rump-length; **CS:** cesarean section; **MoM:** multiples of the median; **NICU:** neonatal intensive care unit; **NT:** nuchal translucency; **NVD:** normal vaginal delivery; **PAPP-A:** pregnancy-associated plasma protein A.

Discussion

In the present study, we investigated the relations between the parameters evaluated in a dual screening test and pregnancy outcomes. We detected no differences in NT, PAPP-A, and β-hCG values among SGA, LGA, and AGA groups. Also, there were no significant

Table 2. Comparison of NT, PAPP-A, and β-hCG between SGA, AGA, and LGA infants.

	SGA (n=83)	AGA (n=2279)	LGA (n=32)	p-value
NT (MoM)	0.87 (0.39–1.94)	0.81 (0.08–2.87)	0.81 (0.09–1.17)	0.159*
PAPP-A (MoM)	1.13 (0.35–6.06)	1.07 (0.13–6.75)	1.03 (0.29–2.82)	0.947*
β-hCG (MoM)	0.93 (0.21–3.86)	1.01 (0.13–11.5)	0.89 (0.25–5.04)	0.694*
CRL (mm)	60.0 (45.0–82.0)	59.0 (38.8–87.0)	56.5 (45.0–77.0)	0.739*

*Kruskal-Wallis test (Post hoc: Bonferroni corrected Mann-Whitney U test). p<0.05 presence of statistical significance. **AGA:** appropriate for gestational age; **β-hCG:** human chorionic gonadotropin; **LGA:** large for gestational age; **MoM:** multiples of the median; **NT:** nuchal translucency; **PAPP-A:** pregnancy-associated plasma protein A; **SGA:** small for gestational age.

Table 3. Relationship of newborn well-being with birth weights, and biochemical markers.

	NICU (n=880)	Non-NICU s(n=1514)	p-value
NT (MoM)	0.81 (0.08–2.87)	0.81 (0.12–2.87)	0.661*
PAPP-A (MoM)	1.08 (0.13–6.36)	1.06 (0.16–6.75)	0.355*
β-hCG (MoM)	1.0 (0.22–6.1)	1.01 (0.13–11.5)	0.671*
Birthweight (gram)	3070 (2400–4590)	3067.5 (2400–4720)	0.325*

*Mann-Whitney U test. p<0.05 presence of statistical significance. **AGA:** appropriate for gestational age; **β-hCG:** human chorionic gonadotropin; **LGA:** large for gestational age; **MoM:** multiples of the median; **NT:** nuchal translucency; **PAPP-A:** pregnancy-associated plasma protein A; **SGA:** small for gestational age.

differences in NT, PAPP-A, and β-hCG values in the groups with and without NICU need. NICU need was not significant in predicting NT, PAPP-A, β-hCG, and gender. Although we could not predict birth weight with increased NT MoM values detected in the first trimester combined test, the risk of having an SGA fetus increased with a weak rise in NT value. Although it was accepted previously that birth weight was predictable from the second half of the second trimester, recently, it has been accepted that the changes in fetal weight occur as of the first trimester.[8] Although increased PAPP-A and NT values in the first trimester have been previously associated with adverse pregnancy outcomes and especially with IUGR,[8] it was reported that there might be correlational relations between NT and birth weight in cases if there were no adverse pregnancy outcomes.[9]

Another study conducted in 2012 reported that birth weight was associated with NT, PAPP-A, β-hCG, and uterine artery Doppler findings, which suggested that these findings could cause early recognition of LGA infants.[10] The same study concluded that LGA newborns, PAPP-A, and NT thickness were significantly increased and UtA-PI was significantly decreased.[10]

Weismann-Brenner et al. previously reported that there was a correlation between NT and LGA newborns.[11] As a result of the study, "The median NT in LGA neonates was found to be significantly higher than in the non-LGA neonates".[11] Similarly, Boucoiran et al. reported that there was a correlation between NT MoM and LGA and SGA infants and birth weights.[12] They found that NT was significantly lower in SGA newborns, and NT was considerably higher in the LGA group.[12] Again, similarly, Timmerman et al. also identified a positive correlation between NT MoM and birth weight and concluded that the increase in NT was associated with macrosomia.[13]

Although Rinat et al. reported that NT measurements were correlated with the birth weight of babies in the LGA and SGA in the general population,[14] other researchers reported that there were no such correlations between AGA babies and birth weight.[13] Poon et al. reported that not only NT MoM values were effective in predicting macrosomia but also the combination of parameters and maternal characteristics that were used in the screening of aneuploidies were effective in predicting birth weight.[15] In another study conducted by the same author, it was reported that there was a linear relation between decreased NT and SGA.[16] In the present study, on the contrary, we found no differences between the NT measurements and birth weights of SGA, AGA, and

Table 4. The relation of SGA and NICU need with NT, PAPP-A, and β-hCG.

	Variables in the equation					
	SGA			NICU hospitalization		
	Exp (B)	P-value*	95% CI	Exp (B)	P-value*	95% CI
NT	**2.636**	**0.009**	**1.277–5.440**	0.906	0.584	0.636–1.291
PAPP-A	1.048	0.762	0.773–1.421	1.107	0.090	0.984–1.245
β-hCG	0.917	0.543	0.695–1.211	0.986	0.777	0.894–1.087
Male gender	0.996	0.984	0.642–1.545	1.022	0.797	0.865–1.208

*Binary logistic regression (Backward: LR) (Hosmer-Lemeshow test for SGA, and NICU need = 0.452, 0.611, respectively). p<0.05 presence of statistical significance. **β-hCG:** human chorionic gonadotropin; **NICU:** neonatal intensive care unit; **NT:** nuchal translucency; **PAPP-A:** pregnancy-associated plasma protein A.

LGA babies. However, we found in the binary regression analysis that there may be an increase in the risk of SGA with a weak rise in the NT value.

In the literature, some studies reported that birth weight might be associated with fetal gender. Spencer et al. reported that NT was 3.4% lower in female fetuses,[17] and Weismann-Brenner et al. found that NT was higher in the male gender, and the relations between NT and birth weight were independent of gender.[11] A total of 48.1% of the fetuses were male in our study. In the regression analysis that included male gender and dual screening test parameters, having male gender was not effective in predicting SGA and determining NICU needs. The explanation of the gender difference in NT values might be that the late maturation of the cardiovascular system in male fetuses might cause moderately increased accumulation of nuchal fluid, or in other words, increased NT values.

Although the main purpose of the screening tests is to predict the probability of trisomy, it was found that abnormal maternal serum screening results were associated with some adverse pregnancy results such as IUGR, stillbirth, preterm birth, preeclampsia, etc. as well as increased risk for other chromosomal and anatomical abnormalities.[17] In the literature, it was reported that inadequate placentation in the first-trimester causes low PAPP-A and β-hCG MoM values in the maternal serum.[18] This abnormal course of the serum markers was explained with the probable mechanism implying that the low values in the first trimester occurred due to insufficient placentation, and the high values in the second trimester occurred due to increased production of hormones in response to hypoperfusion.[17]

A study conducted by Kierkegaard et al. reported that low PAPP-A and β-hCG values were associated with the 5-minute Apgar score being below 7, which was not associated with preterm birth or neonatal infections.[19] Also, in the same study, it was reported that fetuses with low PAPP-A and β-hCG values were associated with NICU need, and PAPP-A activates the insulin-like growth factor, cell reproduction, and perhaps carbohydrate metabolism in the fetus. This can be explained by low PAPP-A, increased neonatal hypoglycemia, and increased NICU needs.[19] It was reported in a previous study that free β-hCG levels were measured by hydrogen peroxide (H_2O_2) and may be associated with oxidative stress.[20] In the present study, we detected no significant changes in PAPP-A and β-hCG values of all groups. The reason for this may be that the patient group was at term in terms of the birth week in our study, different from the studies in the literature. Also, since negative conditions such as preterm, preeclampsia, and diabetes that may cause placental insufficiency were excluded in the study, PAPP-A and β-hCG values may have been similar in all 3 groups.

There were some limitations in our study. The first one was that not all newborns were karyotyped, and we did not have long-term neurodevelopmental data. The second one was that the study had a retrospective design. These limitations made our analysis difficult because of the challenges in accessing some data.

As far as we are concerned, there are few studies evaluating fetal weight and the well-being of the fetus with first-trimester NT measurements.[5] The number of patients was lower in previous studies when compared to the present study. We believe that the study contributes to the literature because the number of patients was significantly higher, and it is one of the few studies in the literature. Furthermore, we consider that the strength of our study was the fact that all newborns from patients included were evaluated by a perinatologist before the mother was discharged from the hospital. Another strength of the present study was the evaluation of poor gestational outcomes with the model that was created with regression analysis.

Conclusion

In conclusion, we found no differences in NT, PAPP-A and β-hCG values between SGA, LGA and AGA groups. Also, there was no significant difference in NT, PAPP-A, and β-hCG values in the groups with and without NICU needs, and NICU need was not significant in predicting NT, PAPP-A, and β-hCG values and gender. Although we could not predict birth weight with increased NT MoM values detected in the first trimester combined test, the risk of having an SGA fetus increases with a weak rise in NT value. Prospective and long-term studies with more patients are needed to better understand the effects of 11–14-week screening on the fetus and newborn in the last trimester.

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References

1. Nicolaides KH, Syngelaki A, Poon LC, Gil MM, Wright D. First-trimester contingent screening for trisomies 21, 18 and 13 by biomarkers and maternal blood cell-free DNA testing. Fetal Diagn Ther 2014;35:185–92. [PubMed] [CrossRef]
2. Wright D, Syngelaki A, Bradbury I, Akolekar R, Nicolaides KH. First-trimester screening for trisomies 21, 18 and 13 by ultrasound and biochemical testing. Fetal Diagn Ther 2014;35:118–26. [PubMed] [CrossRef]
3. Kagan KO, Wright D, Nicolaides KH. First-trimester contingent screening for trisomies 21, 18 and 13 by fetal nuchal translucency and ductus venosus flow and maternal blood cell-free DNA testing. Ultrasound Obstet Gynecol 2015;45:42–7. [PubMed] [CrossRef]
4. Nicolaides KH, Spencer K, Avgidou K, Faiola S, Falcon O. Multicenter study of first-trimester screening for trisomy 21 in 75 821 pregnancies: results and estimation of the potential impact of individual risk-oriented two-stage first-trimester screening. Ultrasound Obstet Gynecol 2005;25:221–6. [PubMed] [CrossRef]
5. Hendrix MLE, Bons JAP, Snellings RRG, Bekers O, Van Kuijk SMJ, Spaanderman MEA, Al-Nasiry S. Can fetal growth velocity and first trimester maternal biomarkers improve the prediction of small-for-gestational age and adverse neonatal outcome? Fetal Diagn Ther 2019;46:274–84. [PubMed] [CrossRef]
6. Kalem Z, Ellibeş Kaya A, Bakırarar B, Namlı Kalem M. Fetal nuchal translucency: is there an association with birthweight and neonatal wellbeing? Turk J Obstet Gynecol 2019;16:35–40. [PubMed] [CrossRef]
7. Khan J, Stafstrom M, Martines JC. Feeding of low birth weight newborns in tertiary care hospitals in Pakistan: do they follow the world health organization latest guidelines? J Coll Physicians Surg Pakistan 2015;25:583–7. [PubMed]
8. Pardo J, Peled Y, Yogev Y, Melamed N, Ben-Haroush A. Association of crown-rump length at 11 to 14 weeks' gestation and risk of a large-for-gestational-age neonate. J Ultrasound Med 2010;29:1315–9. [PubMed] [CrossRef]
9. Kelekci S, Yilmaz B, Savan K, Sonmez S. Can increased nuchal translucency in the first trimester of pregnancy predict gestational diabetes mellitus. J Obstet Gynaecol 2005;25:579–82. [PubMed] [CrossRef]
10. Plasencia W, González Dávila E, Tetilla V, Padrón Pérez E, García Hernández JA, González González NL. First-trimester screening for large-for-gestational-age infants. Ultrasound Obstet Gynecol 2012;39:389–95. [PubMed] [CrossRef]
11. Weissmann-Brenner A, Weisz B, Lerner-Geva L, Gindes L, Achiron R. Increased nuchal translucency is associated with large for gestational age neonates in singleton pregnancies. J Perinat Med 2011;39:305–9. [PubMed] [CrossRef]
12. Boucoiran I, Djemli A, Taillefer C, Rypens F, Delvin E, Audibert F. First-trimester prediction of birth weight. Am J Perinatol 2013;30:665–71. [PubMed] [CrossRef]
13. Timmerman E, Pajkrt E, Snijders RJM, Bilardo CM. High macrosomia rate in healthy fetuses after enlarged nuchal translucency. Prenat Diagn 2014;34:103–8. [PubMed] [CrossRef]
14. Hackmon R, Librach C, Burwick R, Rodrigues N, Farine D, Berger H. Do early fetal measurements and nuchal translucency correlate with term birth weight? J Obstet Gynaecol Canada 2017;39:750–6. [PubMed] [CrossRef]
15. Poon LCY, Karagiannis G, Stratieva V, Syngelaki A, Nicolaides KH. First-trimester prediction of macrosomia. Fetal Diagn Ther 2011;29:139–47. [PubMed] [CrossRef]
16. Poon LCY, Karagiannis G, Staboulidou I, Shafiei A, Nicolaides KH. Reference range of birth weight with gestation and first-trimester prediction of small-for-gestation neonates. Prenat Diagn 2011;31:58–65. [PubMed] [CrossRef]
17. Spencer K, Ong CYT, Liao AWJ, Papademetriou D, Nicolaides KH. The influence of fetal sex in screening for trisomy 21 by fetal nuchal translucency, maternal serum free beta-hCG and PAPP-A at 10–14 weeks of gestation. Prenat Diagn 2000;20:673–5. [PubMed] [CrossRef]
18. Krantz D, Goetzl L, Simpson JL, Thom E, Zachary J, Hallahan TW, et al.; First Trimester Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening (BUN) Study Group. Association of extreme first-trimester free human chorionic gonadotropin-β, pregnancy-associated plasma protein A, and nuchal translucency with intrauterine growth restriction and other adverse pregnancy outcomes. Am J Obstet Gynecol 2004;191:1452–8. [PubMed] [CrossRef]
19. 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;31:1169–75. [PubMed] [CrossRef]
20. Kharfi A, Giguère Y, De Grandpré P, Moutquin JM, Forest JC. Human chorionic gonadotropin (hCG) may be a marker of systemic oxidative stress in normotensive and preeclamptic term pregnancies. Clin Biochem 2005;38:717–21. [PubMed] [CrossRef]