Iran J Public Health, Vol. 52, No.4, Apr 2023, pp.695-702

Original Article

The Correlation between the First Trimester Combined Test Results and Thyroid Stimulating Hormone Levels as Well as Its Effect on Pregnancy Outcomes

Ezgi Ozsoz Kolsuz [1], Dilek Uysal [2], *Aysegul Gulbahar [2]

1. *Department of Obstetrics and Gynecology, Kutahya University of Health Sciences, Evliya Celebi Training and Research Hospital, Kutahya, Turkey*
2. *Department of Obstetrics and Gynecology, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkey*

***Corresponding Author:** Email: draysegulgulbahar@gmail.com

(Received 10 Nov 2022; accepted 19 Jan 2023)

Abstract

Background: Determining the pregnancy outcomes with independent prognostic factors in the first trimester combined screening test and thyroid stimulating hormone (TSH) is a concern for practitioners. We aimed to evaluate the correlation between TSH and first trimester combined screening test levels and examine their effects on pregnancy outcomes in healthy pregnant women.

Methods: A total of 349 pregnant women in Izmir Ataturk Training and Research Hospital,Turkey with normal TSH values in the first trimester between 2015 and 2020 were enrolled. Patients were divided into two groups as 274 and 75 patients according to TSH values with 2,5 as cut-off value; their birth weights and weeks were compared. Patients were also divided into three groups according to gestational weeks; their TSH values and combined tests were compared.

Results: When grouped based on the TSH threshold value (2.5uIU/ml), no significant relationship was found between the combined test parameters and TSH levels. In the combined test, after grouping according to the week of gestation, a negative correlation was observed between free beta-human chorionic gonadotropin (β-hCG) and TSH measured at 11 weeks (P=0.040, r=-0.189). A significant negative correlation was found between free β-hCG and newborn birth weight (P=0.032, r=-0.199), TSH and delivery time (P=0.011, r=-0.235).

Conclusion: Free β-hCG and TSH levels could guide practitioners for birth weight and early delivery, respectively. Postponing the combined test for patients with elevated serum TSH levels to between the 12th and 13th weeks of gestation may reduce false positives.

Keywords: Thyroid stimulating hormone; Combined test; Newborn birth weight

Introduction

Thyroid hormone promotes development of human body and fetus by stimulating metabolism in all tissues. Fetal thyroid tissue matures functionally between the 18th and 20th weeks of gestation. Many studies have shown a strong association between fetal and maternal thyroid functions, but there is insufficient information regarding thyroid function during early pregnancy (1,2).

Birth weight is an important indicator of fetal growth and development, which reflects adaptation of the fetus to the intrauterine environment (3). High thyroid-stimulating hormone (TSH) levels in early and late pregnancy are associated with a higher risk of low birth weight, therefore, small gestational age (SGA) (4,5).

In early pregnancy, free beta-human chorionic gonadotropin (β-hCG) is produced by differentiated syncytiotrophoblasts, and is necessary for pregnancy continuation. β-hCG has the same alpha subunit as TSH and may show thyrotropic activity in the first trimester (6). Some studies have shown significant association between low levels of β-hCG and adverse pregnancy outcomes, such as fetal loss, intrauterine growth restriction, and low birth weight (7). Pregnancy-associated plasma protein-A (PAPP-A) is a placental glycoprotein (8). In the first trimester, low serum PAPP-A level is associated with placental dysfunction and poor pregnancy outcomes (7,9,10). Therefore, fetal growth disorders must be considered when the first-trimester serum PAPP-A level is less than 0.4 MoM (5th percentile) (11). Additionally, previous studies have focused on adverse pregnancy outcomes due to thyroid dysfunction and abnormal changes in combined screening test markers in pregnant women. However, studies showing the extent to which these markers affect each other in the follow-up of healthy pregnancies and their effects on pregnancy outcomes are limited.

We aimed to evaluate the correlation between serum TSH levels in the first trimester with serum PAPP-A, free β-hCG, nuchal translucency (NT), and crown-rump length (CRL) measurements, which are independent prognostic factors in the first trimester combined screening test, and examine their effects on pregnancy outcomes in healthy pregnant women.

Materials and Methods

The participants were selected from a total of 505 pregnant women who are in the first trimester and admitted to Izmir Ataturk Training and Research Hospital's outpatient clinic for routine obstetrics examinations between January 2015 and December 2020.

Our exclusion criteria were; thyroid disease or thyroid surgery; bad obstetrics history (gestational diabetes, preeclampsia, intrauterine growth retardation, hypertension, fetal death); in vitro fertilization and multiple pregnancies; children with congenital anomalies; risks associated with abdominal wall, neural tube defect or other chromosomal abnormalities in current pregnancy; smoking, alcohol, and drug use (antiepileptic, antihypertensive, insulin, etc).

Pregnant women diagnosed with thyroid dysfunction during the first-trimester screening, even without history of thyroid disease, were referred to the Endocrine Clinic. Only patients without prescribed medication were included. They demonstrated normal TSH values in the second and third trimesters. In total, 349 patients were included.

First trimester TSH and combined screening test results (CRL, NT, PAPP-A, free β-hCG, gestational weeks in which the test was performed, current gestational age, maternal weight) and demographic characteristics (age, last menstrual period, gravida, parity, delivery method, drug use during pregnancy, personal and family history) of included participants were retrospectively obtained.

Maternal serum TSH value was measured by the quantitative diagnostic method using the ADVIA Centaur and ADVIA Centaur XP systems (Siemens Healthineers, Erlangen, Germany). Serum and heparinized plasma PAPP-A values and maternal serum free β-hCG were measured by the quantitative in vitro diagnostic method with IMMUNITE 2000 systems analyzers (Siemens Healthineers).

From combined screening test components, CRL and NT were measured in millimeters and MoM, respectively. Serum levels of PAPP-A and free β-hCG were measured in mlU/ml and ng/ml, respectively, and their MoM values were calculated.

TSH level of 2.5uIU/ml, recognized as the upper limit according to the reference range for serum

TSH in the first trimester, was considered the cutoff point.

Patients were grouped based on TSH levels: Group 1 (TSH<2.5uIU/ml) with 274 patients and Group 2 (TSH≥2.5uIU/ml) with 75 patients. Numerical and MoM values of combined screening test results (NT, CRL, PAPP-A, and free β-hCG), birth week, and birth weights of existing pregnancies were compared between groups.

Patients were grouped based on gestational weeks in which combined tests were performed: Group 1 (11th week), Group 2 (12th week), and Group 3 (13th week). Serum TSH levels in the first trimester and the numerical and MoM values of NT, CRL, free β-hCG, and PAPP-A were compared between groups.

Of 349 included patients whose full pregnancy follow-up and delivery were performed in our hospital, those with poor perinatal and intrapartum results (SGA, LGA, preterm birth, preeclampsia, ablatio placenta, etc.) were excluded. A total of 117 pregnant women with term pregnancies at 37–42 weeks and newborn birth weight in the normal range (2500-4500 gr) were included in the analysis. The correlations between birth-week and newborn birth weight, serum TSH level in the first trimester, and the numerical and MoM values of NT, CRL, free β-hCG, and PAPP-A were examined.

The study was approved by the review board of X university (date:22/01/2021;approval number:1124) and conducted according to the principles of the Declaration of Helsinki. Due to the retrospective nature of the investigation, informed consent was not required.

Statistical Analysis

Analyses were performed using SPSS V22.0 Software (IBM®, NY, USA). Categorical data are presented as numbers and percentages. Continuous data was shown as mean±standard deviation. Chi-square test was used to compare categorical data. Normality of distributions was examined using Kolmogorov–Smirnov and Shapiro-Wilk tests. T-test and Mann-Whitney U test were used for normal and non-normal distributed variables. Pearson's correlation analysis was used to determine the relationship between two continuous variables. Statistical significance was set at $P<0.05$.

Results

Demographic characteristics and laboratory findings of 349 patients included in the study are given in Table 1.

Table 1: Demographic and laboratory findings of patients

Variables	*Mean±SD*
Maternal Age (yr)	27.74±5.89
Mother Weight (kg)	65.81±12.99
Gravida	2.27±0.70
Parite	0.97±1.12
Gestational Week	12.29±0.67
Newborn Birth Weight	3279.13±404.41
CRL (mm)	73.02±5.45
NT (MoM)	0.87±0.20
TSH (uIU/ml)	1.79±1.40
PAPP-A (MoM)	1.04 ± 0.59
PAPP-A (mIU/ml)	3.05 ± 2.06
Free β-hCG (MoM)	1.12±0.76
Free β-hCG (ng/ml)	44.73±31.43

CRL, crown-rump length; NT, nuchal translucency; TSH, thyroid stimulating hormone; PAPP-A, pregnancy-associated plasma protein-A; hCG, human chorionic gonadotropin; SD, standard deviation

Patients were divided into two groups based on TSH values. A total of 274 patients had TSH values within the normal range (1.25±0.66 uIU/ML) in the first trimester; 75 patients had TSH values higher than the normal range (3.72±1.65uIU/ML). Table 2 shows the evaluation results according to the combined test results between the groups.

Table 2: Comparison of the patient groups with normal and high serum TSH levels in the first trimester with combined test parameters

Variables	***TSH < 2,5 (uIU/ml) (n= 274)***	***TSH ≥ 2,5 (uIU/ml) (n= 75)***	
	Mean±SD	Mean±SD	*P*
PAPP-A (MoM)	1.02±0.57	1.07±0.6	0.656
PAPP-A (mIU/ml)	3.08±2.11	2.95±1.87	0.807
Free β-hCG (MoM)	1.15±0.68	1.03±0.68	0.204
Free β-hCG (ng/ml)	45.63±32.02	41.41±29.16	0.226
NT (MoM)	0.86±0.2	0.91±0.21	0.071
CRL (mm)	60.30±9.08	59.65±8.98	0.849

CRL, crown-rump length; NT, nuchal translucency; TSH, thyroid stimulating hormone; PAPP-A, pregnancy-associated plasma protein-A; hCG, human chorionic gonadotropin; SD, standard deviation

Patients were divided into three groups according to the week in which their combined tests were performed, and a correlation analysis was performed between TSH values in the first trimester and the combined test results according to these weeks (Table 3).

Table 3: Correlation Analysis of Combined Test Results by Weeks with TSH Values in the First Trimester

Variables	***TSH(11th week) (n= 119)***		***TSH (12th week) (n= 158)***		***TSH (13th week) (n= 72)***	
	r	*P*	*r*	*P*	*r*	*P*
PAPP-A (MoM)	-0.006	0.952	0.020	0.799	0.56	0.638
PAPP-A (mIU/ml)	0.006	0.951	-0.050	0.535	-0.56	0.639
Free β-hCG (MoM)	-0.189	0.040*	-0.129	0.107	-0.057	0.637
Free β-hCG (ng/ml)	-0.188	0.040*	-0.111	0.167	-0.218	0.66
NT (MoM)	0.071	0.446	0.075	0.351	-0.158	0.185
CRL (mm)	0.080	0.387	-0.070	0.384	-0.002	0.988

CRL, crown-rump length; NT, nuchal translucency; TSH, thyroid stimulating hormone; PAPP-A, pregnancy-associated plasma protein-A; hCG, human chorionic gonadotropin. * = $P < 0.005$

A statistically significant negative correlation was found between TSH of the group that underwent a combined test between the 11th week of gestation and their values of free β-hCG (MoM) and free β-hCG (ng/ml).

One hundred and seventeen pregnant women, whose newborn birth weight and gestational week were within normal range, gave birth at our institution. When we evaluated the combined test serum markers and TSH values in the first tri-

mester and their effect on delivery method, we found no statistically significant difference between normal delivery and cesarean section. We examined the effects of isolated serum TSH values on birth week and birth weight; the birth week showed statistically significant difference between patients with normal (39.31±1.19) and high (38.82±1.24) TSH values (*P*=0.039). Birth weight did not significantly differ between normal (3299.61±374.67g) and high (3226.84±478.87g) TSH groups (*P*=0.258).

Correlation of TSH values in the first trimester with birth week and newborn birth weight were r=-0.235 (*P*=0.011) and r=-0.131 (*P*=0.743), respectively.

A negative correlation between values of free β-hCG (MoM and ng/ml) and newborn birth weight was observed (Table 4).

Table 4: Correlation Analysis of the combined test serum markers with the birth week and newborn birth weight of the TSH in the first trimester

Variables	***Birth Week (n= 117)***		***Newborn Birth Weight (n= 117)***	
		P	*r*	*P*
PAPP-A (MoM)	0.038	0.681	0.034	0.716
PAPP-A (mIU/ml)	0.048	0.610	0.127	0.173
Free β-hCG (MoM)	-0.116	0.212	-0.199	0.032*
Free β-hCG (ng/ml)	-0.110	0.238	-0.228	0.014*
TSH (uIU/ml)	-0.235	0.011*	-0.131	0.743

CRL, crown-rump length; NT, nuchal translucency; TSH, thyroid stimulating hormone; PAPP-A, pregnancy-associated plasma protein-A; hCG, human chorionic gonadotropin. * = $P < 0.005$

Discussion

Research on the effect of the relationship between TSH and free β-hCG levels on first-trimester aneuploidy screening results is ongoing. Studies have shown the reliability of the combined test performed in pregnant women with thyroid dysfunction (12,13). Some studies associate high TSH levels in the first trimester with adverse pregnancy outcomes, contradictingly, there are also several studies that do not make this association (14-16). An association between low free β-hCG in the first trimester and intrauterine fetal growth retardation and low birth weight has been shown (17).

This study examined the relationship between TSH levels in the first trimester in healthy, low-risk pregnant women without a history of thyroid disease, drug use, and combined test markers. When grouped according to the week of combined testing, there was a significant negative correlation between free β-hCG and TSH values in the 11th week of gestation.

It has been reported that maternal thyroid hormones do not affect free β-hCG and PAPP-A secretion, thereby not affecting double screening test results (13). However, in our study, a significant negative correlation was found between free β-hCG and TSH in the 11th week. β-hCG peak stimulates TSH receptors and causes suppression of TSH in the hypothalamo-hypophyseal axis in the first trimester. This supports the idea that β-hCG and TSH have the same alpha subunit structure (6). We believe this mechanism may have affected the combined test results, especially between the 11th and 12th weeks of gestation. Therefore, we suggest postponing the time of the combined test for patients with a history of high serum TSH levels in the first trimester to between 12th and 13th weeks of gestation may be the right approach for reducing false positives. Further studies are needed to obtain additional significant results.

Lee et al. associated maternal TSH levels (>4mIU/l) with an increased risk of premature birth and neonatal respiratory distress syndrome

(RDS). Increased RR (2.14) was found for low birth weight in pregnancies with maternal serum TSH levels (>4mIU/L), although the difference was not statistically significant (16). Örgül et al. evaluated the association between TSH values in the first trimester and combined screening test parameters and concluded that combined test markers were not affected by TSH levels. Therefore, NT, free β-hCG, and PAPP-A could be safely used for prenatal screening in pregnant women with thyroid dysfunction (12). When we grouped the participants according to TSH values in the first trimester, no significant association was found between TSH and combined screening test markers. Although there was no significant association between the group with high serum TSH levels in the first trimester and free β-hCG values, we believe that this may be due to the small number of patients, average TSH values of existing patients being high (3.72±1.65uIU/ml), but not above the reference limit in non-pregnant women, and normal TSH values observed during the follow-up of pregnant women.

Karagiannis et al. found that regardless of the possible effect of thyroid hormones on placentation, thyroid function did not significantly affect the prevalence of SGA newborns in women without a history of thyroid disease, and no abnormal maternal thyroid function resulting in SGA infants was recognized between the 11th and 13th weeks of gestation (17). Similarly, our study included pregnant women who did not have thyroid dysfunction that required euthyroid or drug therapy, and no significant association was discovered between the birth weight of these pregnant women's newborns and TSH.

PAPP-A potentially affects fetal growth and well-being[8]. Low maternal serum PAPP-A levels in the first trimester have been found to be predictive indicators for adverse pregnancy outcomes linked to poor placental function in previous meta-analyses (11,18,19). In addition, studies have shown that thyroid hormones regulate the expression of insuline-like growth factor (IGF) and IGF binding protein (IGFBP), suggesting that poor obstetric outcomes in pregnant women with thyroid dysfunction can occur in ways similar to the function of PAPP-A (13).

Low PAPP-A levels in the first trimester were associated with poor pregnancy outcomes but had poor predictive value (20). Similarly, in our study, no statistically significant outcomes were observed regarding the association of serum PAPP-A levels and MoM values with birth weight, birth week, and delivery method. In our study, only low-risk pregnant women who delivered during an average gestational period and within normal birth weight ranges according to gestational age were examined. This is a strength of our study as findings apply to the general population.

Sanz et al. reported that decreased PAPP-A levels in the first trimester were associated with low birth weight, whereas elevated serum TSH levels were not significantly associated with this adverse outcome. They found that low PAPP-A or high TSH levels helped predict low birth weight (21.1% sensitivity and 85.7% specificity, respectively), and suggested that with the combination of both indicators, a 7.8% decrease in sensitivity, but an increased association with low birth weight prediction was observed (21). Zhang et al. examined the association between maternal thyroid function and birth weight in early and late pregnancy. The study reported that high TSH and free T4 concentrations or low T3 concentrations in the first and third trimesters were associated with low birth weight (14). Contrary to these findings, our study showed that PAPP-A and serum TSH values in the first trimester were not statistically significant in independently predicting newborn birth weight.

Sirikunalai et al. examined the relationship between serum free β-hCG values and pregnancy outcomes at 11th–14th and 14th–18th weeks of gestation. They found an association between abnormally low and high free β-hCG levels and adverse pregnancy outcomes. Furthermore, they suggested that high levels of free β-hCG in the first trimester could indicate a risk of preterm delivery (17). In our correlation analysis between combined test serum markers of the first trimester and delivery method, birth week, and

newborn birth weight, a negative correlation was found between the values of free β-hCG (MoM) and free β-hCG (ng/ml) and newborn birth weight. Nevertheless, this marker was not significantly associated with the delivery method or birth week.

Prior et al. examined PAPP-A and free β-HCG levels and conducted prenatal fetal and maternal evaluations and 48-hour postnatal follow-up. β-hCG and PAPP-A levels were reported to have no significant association between groups when compared according to the delivery method (19). Similarly, our study concluded that combined screening test markers did not predict the delivery method. However, a history of cesarean delivery or uterine surgery is among the indications for performing a cesarean delivery. Our study included not only emergency cesarean deliveries but also elective ones; this is a crucial limitation of the study, and more accurate results will be achieved with exclusion of these participants.

Other limitations of our study include a retrospective design, small sample size, and use of single-center data. Additionally, we could not evaluate some patients' pregnancy outcomes, although they already had first-trimester records, because they did not give birth at our hospital. Moreover, recurrent planned cesarean deliveries in patients with a history of cesarean or uterine surgery were not excluded when examining the participants' delivery methods. These issues create a limitation in considering delivery method specific to current pregnancies.

Conclusion

Combined test serum markers in the first trimester were not affected by TSH levels. A negative correlation found between free β-hCG and TSH in the 11th week of gestation suggests that postponing the time of the combined test for patients with a history of elevated serum TSH levels in the first trimester to between the 12th and 13th weeks of gestation may help to reduce false positives. Additionally, free β-hCG levels showed a negative correlation with birth weight. In our study, a high TSH value led to earlier deliveries. We believe prospective, multicenter studies encompassing a large number of patients will be more influential in predicting these outcomes.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

This research received no external funding.

Conflicts of interest

All authors have no conflicts of interest to declare.

References

1. Korevaar TI, Chaker L, Jaddoe VW, Visser TJ, Medici M, Peeters RP (2016). Maternal and birth characteristics are determinants of offspring thyroid function. *J Clin Endocrinol Metab*, 101: 206–213.
2. Shields BM, Knight BA, Hill A, Hattersley AT, Vaidya B (2011). Fetal thyroid hormone level at birth is associated with fetal growth. *J Clin Endocrinol Metab*, 96: E934–E938.
3. Koller-Smith LI, Shah PS, Ye XY, et al (2017). Comparing very low birth weight versus very low gestation cohort methods for outcome analysis of high-risk preterm infants. *BMC Pediatr*, 17:166.
4. Monen L, Kuppens SM, Hasaart TH, et al (2015). Maternal thyrotropin is independently related to small for gestational age neonates at term. *Clin Endocrinol (Oxf)*, 82:254–259.
5. Nishioka E, Hirayama S, Ueno T, et al (2015). Relationship between maternal thyroid-stimulating hormone (TSH) elevation during pregnancy and low birth weight: a longitudinal study of apparently healthy urban

Japanese women at very low risk. *Early Hum Dev,* 91:181–185.
6. Hershman JM (2004 Jun). Physiological and pathological aspects of the effect of human chorionic gonadotropin on the thyroid. *Best Pract Res Clin Endocrinol Metab*, 18(2):249-65.
7. 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*, 191:1446-51.
8. Lawrence JB, Oxvig C, Overgaard MT, et al (1999). The insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease secreted by human fibroblasts is pregnancy-associated plasma protein-*A. Proc Natl Acad Sci U S A*, 96:3149-53.
9. Barrett SL, Bower C, Hadlow NC (2008). Use of the combined first-trimester screen result and low PAPP-A to predict the risk of adverse fetal outcomes. *Prenat Diagn*, 28:28-35.
10. Spencer CA, Allen VM, Flowerdew G, et al (2008). Low levels of maternal serum PAPP-A in early pregnancy and the risk of adverse outcomes. *Prenat Diagn*, 28:1029-36.
11. Royal College of Obstetricians and Gynaecologists. The Investigation and Management of the Small for Gestational Age Fetus Green-top Guideline NO. 31 [Internet]. *RCOG*, 2014 [updated Feb 2014; cited Jan 2013]. Available from https://www.rcog.org.uk/media/t3lmjhnl/gtg_31.pdf
12. Örgül G, Doğan R, Portakal O, Beksaç MS (2018). Relationship between first-trimester maternal TSH levels and Down syndrome screening tests. *Cukurova Med J*, 43:94-99.
13. Aytan H, Caliskan AC, Demirturk F, Sahin S, Erdogan F, Kuzu Z (2013). Relationship between maternal thyroid hormones and the biochemical markers of the first-trimester aneuploidy screening. *Arch Gynecol Obstet*, 287:1125–1129.
14. Zhang C, Yang X, Zhang Y, et al (2019). Association Between Maternal Thyroid Hormones and Birth Weight at Early and Late Pregnancy. *J Clin Endocrinol Metab*, 104:5853–5863.
15. Karagiannis G, Ashoor G, Maiz N, Jawdat F, Nicolaides KH (2011). Maternal thyroid function at eleven to thirteen weeks of gestation and subsequent delivery of small for gestational age neonates. *Thyroid*, 21:1127–1131.
16. Lee SY, Cabral HJ, Aschengrau A, Pearce EN (2020). Associations Between Maternal Thyroid Function in Pregnancy and Obstetric and Perinatal Outcomes. *J Clin Endocrinol Metab*,105:e2015-e2023.
17. Sirikunalai P, Wanapirak C, Sirichotiyakul S, et al (2016). Associations between maternal serum free beta human chorionic gonadotropin (β-hCG) levels and adverse pregnancy outcomes. *J Obstet Gynaecol*,36:178-182.
18. Bilagi A, Burke DL, Riley RD, Mills I, Kilby MD, Katie Morris R (2017). Association of maternal serum PAPP-A levels, nuchal translucency and crown-rump length in first trimester with adverse pregnancy outcomes: retrospective cohort study. *Prenat Diagn*,37:705-711.
19. Prior T, Mullins E, Bennett P, Kumar S (2014). Are 1st-trimester β-human chorionic gonadotrophin and pregnancy-associated plasma protein A levels predictive of intrapartum fetal compromise in a selected normal population?. Aust N Z J Obstet Gynaecol;54:418-423.
20. Morris RK, Bilagi A, Devani P, Kilby MD (2017).Association of serum PAPP-A levels in the first trimester with small for gestational age and adverse pregnancy outcomes: systematic review and meta-analysis. *Prenat Diagn*,37:253-265.
21. Caballero Sanz S, Nozaleda Pastor G, Garcia-Tizon Larroca S (2018). First-Trimester Biochemical Screening For Low Birth Weight: Clinical Effectiveness of Low Pregnancy-Associated Plasma Protein-A and High Thyroid-Stimulating Hormone. *Clin Lab*,64:1501-1508.