Second-Trimester Maternal Serum Beta-Human Chorionic Gonadotropin and Lipid Profile as a Predictor of Gestational Hypertension, Preeclampsia, and Eclampsia: A Prospective Observational Study

Abstract

**Background:** Hypertensive disorders of pregnancy are important complications of pregnancy and are associated with high maternal and perinatal mortality and morbidity. Early diagnosis may improve maternal and perinatal outcome by ensuring appropriate management. **Aim:** Our aim is to assess the serum beta-human chorionic gonadotropin (hCG) and serum lipid profile in the early and late trimesters of at-risk mothers and to analyze whether these parameters can be used to predict pregnancy-induced hypertension (PIH) and its time of onset. **Materials and Methods:** A prospective observational study was conducted in the Department of Obstetrics and Gynecology, Tata Main Hospital, Jamshedpur, India. Two hundred antenatal women were screened for serum beta-hCG and lipid profile in their early (14–18 weeks) and late (24–28 weeks) second trimesters. All patients were followed up till delivery and observed for the development of PIH. Results were evaluated and analyzed statistically. **Results:** The incidence of PIH in our study was 14.67% (n = 27). Most of the patients had late-onset PIH (88.89%, n = 27), whereas 11.12% (n = 3) had an early onset of the disease. Of 27 patients, 6 patients developed preeclampsia and none had eclampsia. The mean beta-hCG level in the study population at the early second trimester was 91,723.97, whereas in the late second trimester, it was 22,456.25. In PIH patients, a significant increase in the level of serum cholesterol, triglyceride, and very-low-density lipoprotein was noted in both the early and late second trimesters. **Conclusion:** This study showed that serum beta-hCG and lipid profile in the second trimester are useful indicators to identify women who are likely to develop PIH, preeclampsia, or eclampsia.

**Keywords:** Beta-human chorionic gonadotropin, lipid profile, pregnancy-induced hypertension

Introduction

Hypertensive disorders of pregnancy constitute an enigmatic and clinically challenging group of pregnancy complications that are responsible for a substantial burden of illness in both industrialized and less industrialized countries. According to June 2014 meta-analysis by the WHO, hypertensive disorders of pregnancy account for 14% of all maternal deaths. The incidence of pregnancy-induced hypertension (PIH) ranges from 5% to 15% in India. Hypertensive disorders of pregnancy included chronic hypertension, gestational hypertension, preeclampsia, chronic hypertension with superimposed preeclampsia, and eclampsia. The exact cause and onset of hypertensive disorder of pregnancy is still unresolved, and several theories have been put forward regarding the etiopathogenesis of PIH. Research is still continuing to identify an ideal marker which can predict the future development of PIH so that these mothers can be grouped as high risk and close monitoring and necessary management can be instituted. Several tests have been proposed to predict hypertension in pregnancy including biochemical and hormonal assay, so that timely intervention may be instituted, but till this day, no single test has achieved that purpose.

In PIH, there is a mid-trimester surge of beta-human chorionic gonadotropin (hCG) level due to the overwhelming secretory response of the immunologically modified trophoblast. Furthermore, there is a 2–3 times rise in serum triglyceride (TG) concentration which is likely to get accumulated in the uterine spiral arteries contributing to endothelial activation and damage.

**How to cite this article:** Murmu S, Dwivedi J. Second-trimester maternal serum beta-human chorionic gonadotropin and lipid profile as a predictor of gestational hypertension, preeclampsia, and eclampsia: A prospective observational study. Int J App Basic Med Res 2020;10:49-53.

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Access this article online

Website: www.ijabmr.org
DOI: 10.4103/ijabmr.IJABMR_271_19

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It has been proposed that instead of a single investigation, a combination of antenatal tests could predict the occurrence of PIH with more specificity and sensitivity. With this aim in mind, we considered evaluating maternal beta-hCG levels and lipid profile in the second trimester of pregnancy as predictors of PIH and its time of onset for our study.

Materials and Methods

This hospital-based prospective study was conducted over a period of 1 year at Tata Main Hospital, Jamshedpur, India. The study was approved by the Institutional Ethical Committee. All pregnant women between 13 and 18 weeks of gestation with single uncomplicated pregnancy with systolic blood pressure (BP) <140 mmHg and diastolic BP <90 mmHg who were willing to follow up and deliver in our hospital were included in our study. The women included in the study were told about the potential significance of the test and its benefit in detail in their own language, and informed consent was obtained. Women with hypertension diagnosed before 20 weeks of gestation, multiple pregnancy, diabetes mellitus, and history of PIH in previous pregnancy and pregnant women with renal parenchymal disease or with any medical disease which may alter lipid profile, thyroid disease, and congenital anomaly proved with ultrasound were excluded from the study.

All patients were investigated for serum beta-hCG and lipid profile for two occasions, once in the early second trimester (14–18 weeks) and another at the late second trimester (24–28 weeks). Serum beta-hCG level was measured by chemiluminescence immunoassay. Total cholesterol (TC), TG, and high-density lipoprotein (HDL) were evaluated using diagnostic kits, whereas low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) were calculated using the Friedewald formula. The values were tabulated and analyzed based on the standard normal values mentioned for their corresponding period of gestation. The patients were followed till delivery to assess whether they developed hypertension at any stage of pregnancy. The final maternal outcome obtained thereafter was also recorded, tabulated, and analyzed.

Statistical analysis

Data were summarized by routine descriptive studies such as mean, median, standard deviation, and quartiles for numerical variables and counts and percentages for categorical variables. Univariate analysis was done by comparing beta-hCG and individual lipid profile parameters between patients with PIH and those without PIH. Student’s t-test was employed to differentiate between two means, and statistical analysis was done using the Chi-square test.

Results

Of 200 women, 184 women completed the study, whereas 4 underwent MTP and the rest 12 were lost to follow-up. Of 184 patients followed, 27 women developed PIH constituting 14.67% of the study population. Thus, the incidence of PIH was 14.67% in our study. When further subdivided, the incidence of preeclampsia was 22.22% of the PIH cohort (n = 6) [Table 1]. Of these 6 preeclamptic patients, 3 women had early-onset preeclampsia (onset before 34 weeks), whereas the rest 3 had late-onset disease. Most of the patients (88.88%) had late-onset PIH (after 34 weeks), whereas the incidence of early-onset PIH (before 34 weeks) was only 11.12%. The incidence of PIH was slightly higher in the age group of 25–30 years and lowest in the age group of 20–25 years. In the PIH group, 55.55% of the patients had normal body mass index (BMI), 29.6% were overweight, and 14.8% were obese. We found that the incidence of PIH in a particular population rises with BMI. Of total 184 women, 33 (17.93%) women delivered preterm. About 40.7% had preterm delivery in the PIH group compared to 14.01% in the normotensive group. Sixty-five percent of the total study population underwent LSCS. The incidence of LSCS in the PIH group was 74% in comparison to 63% in case of normotensive patients. Descriptive statistics of the numerical variables of entire study population are shown in Table 2. On receiver operating characteristic (ROC) curve analysis, it was found that at a cutoff level of 67750 mIU/ml, beta-hCG at 14–18 weeks can predict PIH with 51.85% sensitivity (95% confidence interval [CI] = 31.9–71.3) and 88.54% specificity (95% CI = 82.5–92.1) [Figure 1]. Similarly, serum beta-hCG above 23180 mIU/ml at 24–28 weeks can predict PIH/preeclampsia with 62.96% sensitivity (95% CI = 42.4–80.6) and 72.61% specificity (95% CI = 64.9–79.4) [Figure 2]. In both the early and late second trimesters, serum cholesterol, TG, and VLDL levels were significantly raised in PIH population compared to the normotensive group (P < 0.05). Serum LDL level is significantly increased in the late second trimester in PIH patients but not in the early second trimester [Table 3].

Discussion

PIH and preeclampsia syndrome remain one of the intriguing topics even in modern-day obstetrics. Even

Table 1: Distribution of pregnancy-induced hypertension cohort into pregnancy-induced hypertension and preeclampsia

| Group                | Number of patients | Percentage |
|----------------------|--------------------|------------|
| PIH                  | 21                 | 77.77      |
| Preeclampsia         | 6                  | 22.22      |
| Onset <34 weeks      | 3                  | 50 of patients with preeclampsia |
| Onset >34 weeks      | 3                  | 50 of patients with preeclampsia |

PIH: Pregnancy-induced hypertension
though complications associated with PIH have been observed from ancient times and various treatment modalities have been suggested, till now early prediction remains beyond our reach. Novel investigative tools applicable preferably during early gestation when there is time for therapeutic modification are needed. In this context, we studied the maternal serum beta-hCG and lipid profile in the early second trimester (14–18 weeks) and the late second trimester (24–28 weeks) for prediction of PIH/preeclampsia and its time of onset. One hundred and eighty-four antenatal women carrying singleton pregnancy and fulfilling all inclusion and exclusion criteria were included in our prospective observational study. Two venous samples were collected from each patient for beta-hCG and lipid profile at 14–18 weeks and then at 24–28 weeks. All relevant patient data and investigations were analyzed statistically.

Most of the patients in the study population were in the age group of 20–25 years, comprising about 54.34%. The mean age for the PIH group was 25.6 years, and in case of the normotensive group, it was 24.6 years. These values were analyzed using unpaired t-test, and it was found that $P = 0.126$, which was statistically insignificant. Majority of the women who developed PIH were primigravida (about 74%) were in accordance with studies by other authors. Only 26% of the hypertensive women were multipara. Redman suggested that in later pregnancies, there is development of protective immunologic mechanisms against paternal antigens.[6] In an overview by Zuspan, PIH occurs mainly in primiparous women (85%) who have 4–5 times higher risk than multiparous women.[7] When the weight-specific incidence of PIH was studied, it was noted that the incidence rises with rising BMI. It is well documented that obese women have a higher incidence of

### Table 2: Descriptive statistics of numerical variables - whole Cohort ($n=184$)

| Variable | Valid n | Mean   | Median | Minimum | Maximum | Lower quartile | Upper quartile | SD      | SE      |
|----------|---------|--------|--------|---------|---------|----------------|----------------|---------|---------|
| Age      | 184     | 24.72  | 24.50  | 18.00   | 35.0    | 23.00          | 26.00          | 3.192   | 0.235   |
| BMI      | 184     | 23.66  | 23.35  | 17.50   | 32.4    | 22.20          | 25.8           | 3.085   | 0.227   |
| Time of onset | 27 | 250.52 | 253.00 | 211.00 | 269.0   | 247.00         | 258.00         | 12.008  | 2.311   |
| Beta-hCG1 | 184   | 91,723.97 | 76,520.00 | 10,800.00 | 566,400.00 | 49,400.00     | 113,420.00     | 73,221.418 | 5397.955 |
| Beta-hCG2 | 184   | 22,456.25 | 12,365.00 | 2340.00 | 112,980.00 | 9670.0         | 32,155.0       | 19,908.520 | 1467.676 |
| TC1      | 184     | 175.65 | 176.00 | 146.00  | 220.0   | 168.00         | 181.5          | 12.113  | 0.893   |
| TC2      | 184     | 203.97 | 202.00 | 162.00  | 265.0   | 195.50         | 213.0          | 16.482  | 1.215   |
| TG1      | 184     | 127.36 | 124.00 | 105.00  | 186.0   | 118.00         | 133.5          | 12.008  | 0.893   |
| TG2      | 184     | 147.28 | 143.00 | 118.00  | 210.0   | 132.00         | 152.0          | 16.482  | 1.215   |
| LDL1     | 184     | 89.60  | 86.40  | 52.40   | 80.8    | 79.00          | 93.3           | 12.113  | 0.893   |
| LDL2     | 184     | 106.28 | 106.00 | 64.00   | 159.2   | 96.80          | 116.7          | 16.482  | 1.215   |
| VLDL1    | 184     | 27.04  | 24.80  | 2.00    | 346.0   | 23.30          | 26.5           | 12.008  | 0.893   |
| VLDL2    | 184     | 29.45  | 28.60  | 22.40   | 44.0    | 24.60          | 30.4           | 12.008  | 0.893   |
| HDL1     | 184     | 64.45  | 65.00  | 51.00   | 80.0    | 58.50          | 70.0           | 12.008  | 0.893   |
| HDL2     | 184     | 68.18  | 69.00  | 54.00   | 87.0    | 63.00          | 74.0           | 12.008  | 0.893   |

hCG: Human chorionic gonadotropin; TC: Total cholesterol; TG: Triglyceride; LDL: Low-density lipoprotein; VLDL: Very LDL; HDL: High-density lipoprotein; SD: Standard deviation; SE: Standard error; BMI: Body mass index

![Figure 1: Receiver operating characteristic curve analysis for predicting pregnancy-induced hypertension on the basis of beta-human chorionic gonadotropin 1 (14–18 weeks)](image1)

![Figure 2: Receiver operating characteristic curve analysis for predicting pregnancy-induced hypertension on the basis of beta-human chorionic gonadotropin 2 (24–28 weeks)](image2)
PIH. Ehrentha et al.\cite{10} reported in 2010 that the risk of PIH rises with maternal prepregnancy BMI.

The number of participants who had preterm delivery was 33 which accounts for 17.93%. This is similar to the study done by Slattery and Morrison\cite{9} where the incidence was found to be 8%–15%. About 40% of the women belonging to the PIH group had preterm delivery compared to 14% in case of the normotensive group. These values were tabulated and analyzed using Fisher’s exact test two-tailed, and the $P$ value was statistically significant. A prospective study done by Ye et al.\cite{10} in China showed that PIH leads to preterm delivery and iatrogenic prematurity caused due to the necessity to terminate pregnancy. The rate of LSCS in the PIH group was found to be 74.07% in comparison to the normotensive group where it was about 63%. Tuffnell et al.\cite{11} and Sibai\cite{3} reported LSCS rate of 72.4% and 32.4%, respectively. However, the incidence in our institute was higher. Results obtained were analyzed using Chi-square test, and the $P$ value was found to be 0.4645 which was statistically insignificant.

From ROC curve analysis, it was found that for an early second-trimester beta-hCG value above 67,750 mIU/ml, sensitivity was 51.85% and specificity was 88.54% with a positive likelihood ratio of 4.52 and a negative likelihood ratio of 0.54. This is similar to findings by Vidyabati et al.\cite{12} in 2010 that second-trimester serum beta-hCG levels increased significantly in those women who developed PIH and it has a predictive value. More recently, a California-based study conducted by Towner et al.\cite{13} and Taché et al.\cite{14} in 2014 showed that adverse pregnancy outcome in terms of PIH/preeclampsia is more in women with elevated values although no specific cutoff values have been mentioned in either study. Davidson et al.\cite{15} in a retrospective case–control study in 2003 noted small but significant elevations in the concentrations of beta-hCG in the second-trimester serum of women who subsequently developed pregnancy-induced hypertension and preeclampsia.

When we compared the mean value of serum TC in the normotensive and PIH groups, we found that for both early and late second-trimester TC estimations, the $P$ value was statistically significant ($<0.05$). Vidyabati et al.\cite{12} and Yadav et al.\cite{16} have also reported similar findings. However, no significant alteration in TC level could be observed in the third trimester by De et al.\cite{5} When we compared the mean value of serum LDL cholesterol in the normotensive and PIH groups, we noted that there was no statistically significant difference between early trimester LDL cholesterol in the PIH and normotensive groups but $P < 0.05$ for late second-trimester LDL cholesterol. This finding in our study differed from other studies by Vidyabati et al.\cite{12} and Cekmen et al.\cite{17} but was supported by De et al.\cite{5} We compared the mean value of serum VLDL cholesterol in the normotensive and PIH groups and found that for both early and late second-trimester VLDL cholesterol estimations, the values were higher in PIH patients than the normotensive group, $P < 0.05$. Similar findings have been reported by Yadav et al.,\cite{16} Vidyabati et al.,\cite{12} and De et al.\cite{5} We also compared the mean value of serum HDL cholesterol in the normotensive and PIH groups. We found that there was a statistically insignificant variation in both the early and late second-trimester VLDL cholesterol estimations, the values were higher in PIH patients than the normotensive group, $P < 0.05$. Similar findings have been reported by Yadav et al.,\cite{16} Vidyabati et al.,\cite{12} and De et al.\cite{5} We also compared the mean value of serum HDL cholesterol in the normotensive and PIH groups. We found that there was a statistically insignificant variation in both the early and late second-trimester values of HDL cholesterol in the PIH and normotensive groups. Vidyabati et al.\cite{12} and Yadav et al.\cite{16} had similar findings. However, other authors like De et al.\cite{5} and Cekmen et al.\cite{17} noted that plasma HDL levels were significantly lower in PIH patients than controls. A meta-analysis done in 2014 by Spracklen et al.\cite{18} also showed that preeclampsia was associated with elevated TC, non-HDL cholesterol, and TG levels and with lower levels of HDL cholesterol in the third trimester.

Since beta-hCG was not normally distributed, its correlation with time of onset of PIH/preeclampsia was analyzed by means of Spearman’s correlation coefficient. The coefficient rho was 0.0971, whose $P = 0.6301$ and 95% CI for rho was $0.294–0.460$, which does not indicate good correlation between early second-trimester beta-hCG and time of onset.

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**Table 3: Comparison of numerical variables between pregnancy-induced hypertension and nonpregnancy-induced hypertension - Student’s unpaired $t$-test**

|                          | Mean PIH | Mean non-PIH | $t$  | df  | $P$  | SD PIH | SD non-PIH |
|--------------------------|----------|--------------|------|-----|------|--------|------------|
| Age                      | 25.59    | 24.57        | 1.53837 | 182 | 0.126 | 3.608  | 3.103      |
| TC1                      | 192.11   | 172.82       | 9.23835 | 182 | 0.000 | 12.933 | 9.450      |
| TC2                      | 228.04   | 199.83       | 10.31157 | 182 | 0.000 | 13.819 | 13.012     |
| TG1                      | 154.30   | 122.73       | 14.51953 | 182 | 0.000 | 14.631 | 9.560      |
| TG2                      | 183.93   | 140.97       | 18.35251 | 182 | 0.000 | 12.857 | 10.939     |
| LDL1                     | 95.37    | 86.61        | 0.59185  | 182 | 0.555 | 15.719 | 58.857     |
| LDL2                     | 121.24   | 103.70       | 5.91045  | 182 | 0.000 | 15.068 | 14.104     |
| VLDL1                    | 42.37    | 24.40        | 3.73531  | 182 | 0.000 | 60.745 | 2.646      |
| VLDL2                    | 36.86    | 28.17        | 17.98615 | 182 | 0.000 | 2.750  | 2.237      |
| HDL1                     | 65.19    | 64.32        | 0.61655  | 182 | 0.538 | 7.077  | 6.632      |
| HDL2                     | 70.48    | 67.78        | 1.97318  | 182 | 0.050 | 7.531  | 6.387      |

TC: Total cholesterol; TG: Triglyceride; LDL: Low-density lipoprotein; VLDL: Very LDL; HDL: High-density lipoprotein; SD: Standard deviation; PIH: Pregnancy-induced hypertension
Similarly, for late second-trimester beta-hCG, the coefficient rho was −0.0468, whose $P = 0.8167$ and 95% CI for rho was −0.419–0.339, indicating no correlation. Kang et al.[19] conducted a retrospective cohort study on 32 women with preeclampsia and 3044 controls to estimate the combined screening performance of first and early second-trimester serum markers which included beta-hCG, for the development of preeclampsia, and analyze the correlation among marker levels, week of onset, and severity of the disease. They too could not find any correlation between hCG levels and week of onset of disease.

However, Taché et al.[14] in 2014 noted that with high beta-hCG levels, the risk increases, and this was especially true for early-onset severe preeclampsia, indicating the placental dysfunction. In our study, we were unable to demonstrate any correlation between serum levels of different lipids and time of onset of PIH/preeclampsia. This might be owing to very small number ($n = 27$) of PIH patients that we got in our study population.

In previous studies of plasma lipids of preeclamptic women, the distinction between early- and late-onset diseases has not been made. A study done by Clausen et al.[20] reports that hypertriglyceridemic dyslipidemic pattern of nonfasting plasma lipids at 18 weeks of gestation is associated with the increased risk of developing early but not late-onset preeclampsia.

**Conclusion**

Hypertensive disorders in pregnancy are one of the major causes of maternal morbidity and mortality. An ideal predictor of the disease, the application of which could significantly alter the associated morbidity and mortality, remains elusive. Serum beta-hCG may be used as a predictor of PIH, but the sensitivity of the test is low. It might be of help if this test is provided to women who have risk factors for developing PIH. Maternal lipid profile in the second trimester may also be a good, noninvasive, reproducible, and economical test for prediction of PIH.

Finally, as recent literature shows, the time of onset of preeclampsia is now considered to be a surrogate indicator of the disease severity and etiology. Although in this study correlation between serum beta-hCG and lipid profile and time of onset was not demonstrated, more exhaustive research in a larger population is needed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, *et al*. Global causes of maternal death: A WHO systematic analysis. Lancet Glob Health 2014;2:e323-33.
2. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, van Look PF. WHO analysis of causes of maternal death: A systematic review. Lancet 2006;367:1066-74.
3. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol 2003;102:181-92.
4. Hsu CD, Chan DW, Iriye B, Johnson TR, Hong SF, Repke JT. Elevated serum human chorionic gonadotropin as evidence of secretory response in severe preeclampsia. Am J Obstet Gynecol 1994;170:1135-8.
5. De J, Mukhopadhyay A, Saha PK. Study of serum lipid profile in pregnancy induced hypertension. Indian J Clin Biochem 2006;21:165-8.
6. Redman CW, Sargent IL. Immunology of pre-eclampsia. Am J Reprod Immunol 2010;63:534-43.
7. Zuspan FP. New concepts in the understanding of hypertensive diseases during pregnancy. An overview. Clin Perinatol 1991;18:653-9.
8. Ehrenthal DB, Jurkovitz C, Hoffman M, Jiang X, Weintraub WS. Prepregnancy body mass index as an independent risk factor for pregnancy-induced hypertension. J Womens Health (Larchmt) 2011;20:67-72.
9. Slatterry MM, Morrison JJ. Preterm delivery. Lancet 2002;360:1489-97.
10. Ye RW, Liu YH, Ma R, Ren AG, Liu JM. Association between pregnancy-induced hypertension, cesarean delivery and perinatal mortality: A prospective study. Zhonghua Liu Xing Bing Xue Za Zhi 2009;30:891-4.
11. Tuffnell DJ, Jankowicz D, Lindow SW, Lyons G, Mason GC, Russell IF, *et al*. Outcomes of severe pre-eclampsia/eclampsia in Yorkshire 1999/2003. BJOG 2005;112:875-80.
12. Vidyabati RK, Hijam D, Singh NK, Singh WG. Serum beta hCG and lipid profile in early second trimester as predictors of pregnancy induced hypertension. J Obstet Gynecol India 2014;60:44-50.
13. Towner D, Gandhi S, El Kady D. Obstetric outcomes in women with elevated maternal serum human chorionic gonadotropin. Am J Obstet Gynecol 2006;194:1676-81.
14. Taché V, Baer RJ, Currier RJ, Li CS, Towner D, Waetjen LE, *et al*. Population-based biomarker screening and the development of severe preeclampsia in California. Am J Obstet Gynecol 2014;211:377.e1-8.
15. Davidson EJ, Riley SC, Roberts SA, Shearing CH, Groome NP, Martin CW. Maternal serum activin, inhibin, human chorionic gonadotrophin and alpha-fetoprotein as second trimester predictors of pre-eclampsia. BJOG 2003;110:46-52.
16. Yadav K, Aggarwal S, Verma K. Serum βhCG and lipid profile in early second trimester as predictors of pregnancy-induced hypertension. J Obstet Gynaecol India 2014;64:169-74.
17. Cekmen MB, Erbagci AB, Balat A, Duman C, Maral H, Ergen K, *et al*. Plasma lipid and lipoprotein concentrations in pregnancy induced hypertension. Clin Biochem 2003;36:575-8.
18. Spracklen CN, Smith CJ, Saftlas AF, Robinson JG, Ryckman KK. Maternal hyperlipidemia and the risk of preeclampsia: A meta-analysis. Am J Epidemiol 2014;180:346-58.
19. Kang JH, Farina A, Park JH, Kim SH, Kim JY, Rizzo N, *et al*. Down syndrome biochemical markers and screening for preeclampsia at first and second trimester: Correlation with the week of onset and the severity. Prenat Diagn 2008;28:704-9.
20. Clausen T, Djurovic S, Henriksen T. Dyslipidemia in early second trimester is mainly a feature of women with early onset pre-eclampsia. BJOG 2001;108:1081-7.