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Estimating Combined Maternal Serum Homocysteine And Uterine Artery Doppler In 18-22 Weeks Of Pregnancy To Predict Adverse Pregnancy Outcome : An Observational Study

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Abstract

Introduction: The main objective of antenatal care is to identify and manage high-risk pregnancies and their associated complications. Abnormal placentation due to vascular changes can increase adverse outcomes. Elevated maternal homocysteine levels are linked to placenta-related disorders, often caused by vascular damage and placental insufficiency. Uterine artery Doppler is a non-invasive tool to assess uteroplacental blood flow, where a high pulsatility index indicates impaired placentation. This study evaluates the combined role of maternal serum homocysteine and uterine artery pulsatility index in the second trimester to predict unfavorable fetal outcomes.

Methodology : This prospective cohort study included 63 pregnant women between 18–22 weeks with singleton pregnancies at SMS Medical College, Jaipur. Serum homocysteine and uterine artery Doppler assessments were performed with defined cutoff values.

Results : Among the 63 patients, 11.1% developed hypertensive disorders, 4.7% experienced fetal growth restriction (FGR), and 1.58% had spontaneous preterm births. A strong association was seen when combining tHcy and utA PI for predicting FGR ($p = 0.001$), with 100% sensitivity and specificity. Individually, utA PI showed 100% sensitivity and 96.7% specificity for FGR, while tHcy demonstrated 67% sensitivity and 88% specificity. Both parameters combined were significant for predicting pregnancy-induced hypertension ($p = 0.003$), with tHcy showing stronger predictive value ($p = 0.0005$) than utA PI ($p = 0.08$).

Conclusion : Combined assessment of uterine artery Doppler PI and serum homocysteine appears promising for predicting adverse pregnancy outcomes. Further studies on populations larger in number with proper randomization are required to validate these findings.

Keywords: Fetal growth restriction, Serum homocysteine, uterine artery Doppler, pulsatility index, second trimester

Introduction

[1]The practice of obstetrics is concerned with human reproduction. Its importance is reflected by use of maternal and neonatal outcomes as an index of quality of health and life among nations and is used as a yardstick to measure the level of medical care in a country. Hence by taking cautious and informed steps and timely assessing factors which may predict good or bad obstetrics outcome, we can identify and manage high risk pregnancies and their complications.

[5]In most developed countries, pregnancies are planned, complications are few and outcomes are generally favorable for both mother and infant. Adverse outcomes are far more frequent in the developing world.[6] The most severe adverse outcome of pregnancy is the death of the mother and/or her offspring. Even if both the mother and infant survive, pregnancy complications or problems at delivery or during the neonatal period can lead to severe maternal or infant morbidity.[7] Vasculature related pregnancy complications are a major cause of these adverse maternal and fetal outcomes. The origin is thought to be related to early placentation, a process that involves trophoblast invasion and angiogenesis, but that is also dependent on vascular and endothelial function.[8]

[2] Any disturbance in placentation or implantation over an altered vascular territory increases the risk of early miscarriage and other complications like pre eclampsia, abruptio placenta, intrauterine fetal death or fetal growth restriction. Several biochemical markers and imaging modalities have been studied to help in early prediction of adverse pregnancy outcome. Few of which are PAPP-A, SFLT-2, PLGF, activin, inhibin-A, homocysteine, uterine artery doppler, nuchal fold thickness, etc. Of these here we are focusing on two parameters – Serum homocysteine and uterine artery doppler pulsatility index in second trimester.

[2] Homocysteine(tHcy) is a thiol containing amino acid produced by intracellular demethylation of methionine. Its levels in a normal pregnancy show a decreasing trend. [3]Based on evidence supporting the role of homocysteine in endothelial dysfunction and as a risk factor for cardiovascular diseases, elevated maternal homocysteine is hypothesized to play a role in placenta mediated pregnancy complications described earlier. All have been linked to abnormal placental vasculature, share a common pathophysiology and have an increased risk to reoccur.

Uterine artery Doppler is the primary surveillance tool for monitoring pregnancies with FGR. [2] It is a simple, non invasive and effective screening test in pregnancy that is widely used to study the pattern of uteroplacental circulation that can help to identify a range of clinical complications that may be attributed to placental disease. It provides a measure of uteroplacental perfusion. [5]There has been much research regarding uterine artery pulsatility index (UtA PI) to predict FGR. It is a ratio that combines vascular impedance of both fetal and maternal sides of the placenta. [4]Pulsatility index (PI) is defined as the difference between the peak systolic flow and minimum diastolic flow velocity divided by mean velocity recorded throughout the cardiac cycle.

Prediction, prevention, early diagnosis and treatment and providing optimal health care to all patients are necessary to achieve the millennium developmental goals. [2]The role of early detection of adverse pregnancy outcomes and appropriate management is to reduce both maternal and neonatal morbidity and mortality. This study primarily aims to investigate the possible role of combined screening with two such investigations-maternal total serum homocysteine (tHcy) and second trimester uterine artery Doppler Pulsatility Index (UA PI) to predict adverse fetal outcomes and hence help in early identification and management of adverse outcome.

Methodology

A prospective cohort study which involved 63 women between 18 to 22 weeks of gestation with singleton pregnancy attending the outpatient of department of Obstetrics and Gynaecology in SMS Medical College, Jaipur from November 2022 to November 2023 were included in the study after taking written informed consent and fulfilling the inclusion and exclusion criteria

Inclusion Criteria

1. Women with uncomplicated, singleton pregnancy with spontaneous conception.
2. Women between gestational age 18-22 weeks
3. Women aged between 20 and 35 years who understand the study and are willing to give written and informed consent and women not being included in other studies.

Exclusion Criteria

Volume 9, Issue 3; May-June 2026; Page No 05-11

1. Mothers on any form of thromboprophylaxis.
2. Maternal medical illness such as chronic hypertension, multiple gestation, diabetes mellitus, SLE, thrombophilias or other bleeding disorders, severe anaemia, pre-existing cardiovascular or renal diseases.
3. Fetal anomalies and chromosomal abnormalities.
4. Patients with bad obstetric history, previous pregnancy loss.

Informed consent was obtained from study participants and under aseptic precautions, 2 ml blood was drawn for serum Homocysteine (tHcy) estimation between 18-22 weeks of gestation. Uterine artery Doppler Pulsatility Index (utA PI) a non-invasive routine study was done as a part of targeted second trimester anomaly scan (18-22 weeks) at the Department of Radiology in institution. Since there is no standard nomogram for tHcy value in second trimester, we have taken 95th centile = 12 µmol/l) as cutoff for this study. The uterine artery PI is considered to be abnormal if it is above the 90th centile (>1.59) for gestational age.

The patients were followed up till their delivery in order to assess the main maternal and fetal outcome measures namely the development of hypertension, FGR and pre-term birth, Gestational age at delivery, birth weight of the baby at delivery and APGAR score at birth were the neonatal outcomes considered. The relationship between mid-trimester tHcy levels and utA PI with adverse pregnancy outcomes was assessed.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 20.0 software.

Chi-square test and other diagnostic measures such as sensitivity and specificity were calculated wherever required.

Results

1. Mean maternal age of the participants was found to be 27±4 years. Out of 63 samples, 22 cases (34.9%) were primigravidas.
2. During the course of pregnancy, only 9 cases (14.3%) out of 63 had a higher serum homocysteine level, i.e. >12 umol/L; 4 cases (6.3%) had a higher uterine artery pulsatility index, i.e. >1.59 and 3 cases had both Uterine artery PI and serum homocysteine raised. Amongst these, 2 cases (3.1%) who had both Uterine artery PI and serum homocysteine raised underwent LSCS for FGR and one underwent vaginal deloivery. 1 case (1.6%) with only Uterine artery PI raised underwent LSCS for FGR. Out of cases with only Serum homocysteine raised, 1 case underwent LSCS for meconium stained liquor while another 1 case underwent LSCS for Previous LSCS (with refusal for TOLAC).
3. Statistically speaking, p value of Serum homocysteine in predicting FGR is 0.129 which was non significant. Sensitivity is 67% and specificity is 88%. P value of uterine artery PI in predicting FGR is 0.004 which is significant. Sensitivity is 100% and specificity is 96.7%. P value of combined uterine artery PI and serum homocysteine in predicting FGR is <0.001 which is very significant. Sensitivity is 100% and specificity is 100%.
4. When analysis of APGAR scores was done, out of 3 cases (4.8%) with both investigations abnormal, 2 cases (3.1%) had an APGAR of <7 while 1 case (1.6%) had an APGAR of >7. While 7 cases (11.1%) had either of the investigation abnormal out of which 2 cases (3.1%) had an APGAR of <7 while 5 cases (7.9%) had an APGAR of >7. Rest 53 cases (84.1%) had both investigations normal out of which 2 cases (3.1%) had an APGAR of <7

In our study, out of 7 patients who developed hypertension during pregnancy, 3 (42.9%) patients had only Serum homocysteine raised (p value =0.0005), while no patient had only Uterine artery PI raised (p value =0.08). While 2 (28.5%) patients had both Uterine artery PI and Serum homocysteine raised (p value =0.003), while 2 (28.5%) patients had both investigations within normal limits.

Discussion

In the modern day where we have solutions to most problems just a click away, modern medicine is also evolving and improving towards providing the best healthcare facilities. A big step towards it is improving antenatal care and managing any foreseen complications. The ability to predict adverse outcomes like development of hypertension, FGR, etc. go a long way towards being better prepared and provide the best care possible.

Volume 9, Issue 3; May-June 2026; Page No 05-11

In this study, the pregnant women with elevated tHcy and abnormal utA PI were associated with adverse outcomes like hypertensive disorders and FGR. Independently, tHcy was able to better predict development of hypertension while utA PI was better able to predict FGR and not vice versa.

In a study conducted by Ramesh P et al (2022) 2 they found that statistically significant association was found when tHcy and UA PI were used together for the prediction of FGR (p = 0.003) with a specificity of 83.4%. Both elevated tHcy and abnormal UA PI used in combination predicted adverse pregnancy outcome like FGR but with a low sensitivity of 14.3% and high specificity of 98.9%. However, when used independently these markers predicted FGR with a better sensitivity (tHcy- 28.6% and UA PI- 44.4%).

While in another study conducted by Maged AM et al (2017)9 tHcy was measured at 15-19 weeks, and then, Ut-A Doppler was performed at 18-22 weeks of pregnancy. They found that tHcy and Ut-A resistance index were significantly higher in women who developed PE, IUGR, and other complications when compared to controls. The use of both tHcy assessment and Ut-A Doppler improved the sensitivity of prediction of PE relative to the use of each one alone (85.2 relative to 73.33 and 60%, respectively). They concluded that the use of elevated homocysteine and uterine artery Doppler screening are valuable in prediction of preeclampsia, IUGR, and poor placentation disorders.

With regards to hypertensive disorders of pregnancy, in a study conducted by Ramesh P et al (2022)2 they found that with regard to PIH, both parameters were found to be statistically significant only when used independently (p = 0.001) but not when used in combination (p = 0.17)

While in another study conducted by Shinde T et al (2021) 11 they found that the predictability of uterine artery mean pulsatility index (PI) at 11–14 weeks for hypertensive disorders of pregnancy was significantly high with sensitivity (89.3%) and specificity (95.8%).

In a study conducted by Wu H et al (2018) 10 they found that overall, there was a positive association between tHcy concentrations and SBP or DBP levels. Significantly higher SBP levels were found in those with tHcy concentrations of ≥15 μmol/L (p for trend <0.001). Consistently, significantly higher DBP levels were found in participants with tHcy concentrations of ≥15 μmol/L (p for trend <0.001).

Limitations Of The Study

Though the strength of this study is its prospective nature, the small sample size and the very small number of patients with elevated tHcy and abnormal second-trimester UA PI could have contributed to be insignificant in a few results when compared to other studies with significant results. Larger population studies are therefore required.

In the present study, only UA PI was used as the parameter of choice, compared to many of the previous studies where RI and diastolic notching have also been used to denote abnormal Doppler patterns thereby improving the sensitivity of prediction of adverse outcome.

Conclusion

Early identification and management of high-risk pregnancies and their complications is an important and essential element of providing good antenatal care.

There are a number of tools (PAPP-A, SFLT-2, PLGF, etc.) that can be used to predict adverse pregnancy outcome. However, these investigations are either not easily accessible or are very expensive to be used in routine screening for antenatal patients. The present study shows that fetuses with raised combined uterine artery pulsatility index and serum homocysteine are at an increased risk of subsequent intrapartum fetal compromise with a sensitivity and specificity of 100%. Also, this combined test is able to predict the development of hypertension in pregnancy with a highly significant value (p value = 0.003). Although more studies are required to prove the same, these results suggest that this combined test may have a very strong potential clinical application in normal pregnancies in second trimester itself. Such stratification would allow a more targeted approach for intrapartum monitoring as well as more informed decisions to be made regarding the mode and place of delivery. Homocysteine although expensive, is a good tool with pulsatility index to add to routine second trimester investigations, especially in high risk population like increased age, history of smoking, alcohol consumption, obesity, previous bad obstetric history, etc. Hence combined uterine artery pulsatility index and serum homocysteine could be used as an

Volume 9, Issue 3; May-June 2026; Page No 05-11

essential complementary tool to the routine doppler studies to increase sensitivity to predict poor neonatal outcomes.

Compliance With Ethical Standards

Institutional review board and ethical committee clearance were obtained for this study.

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Volume 9, Issue 3; May-June 2026; Page No 05-11

FIGURE 1: Combined association of tHcy and UtA PI with APGAR score at birth

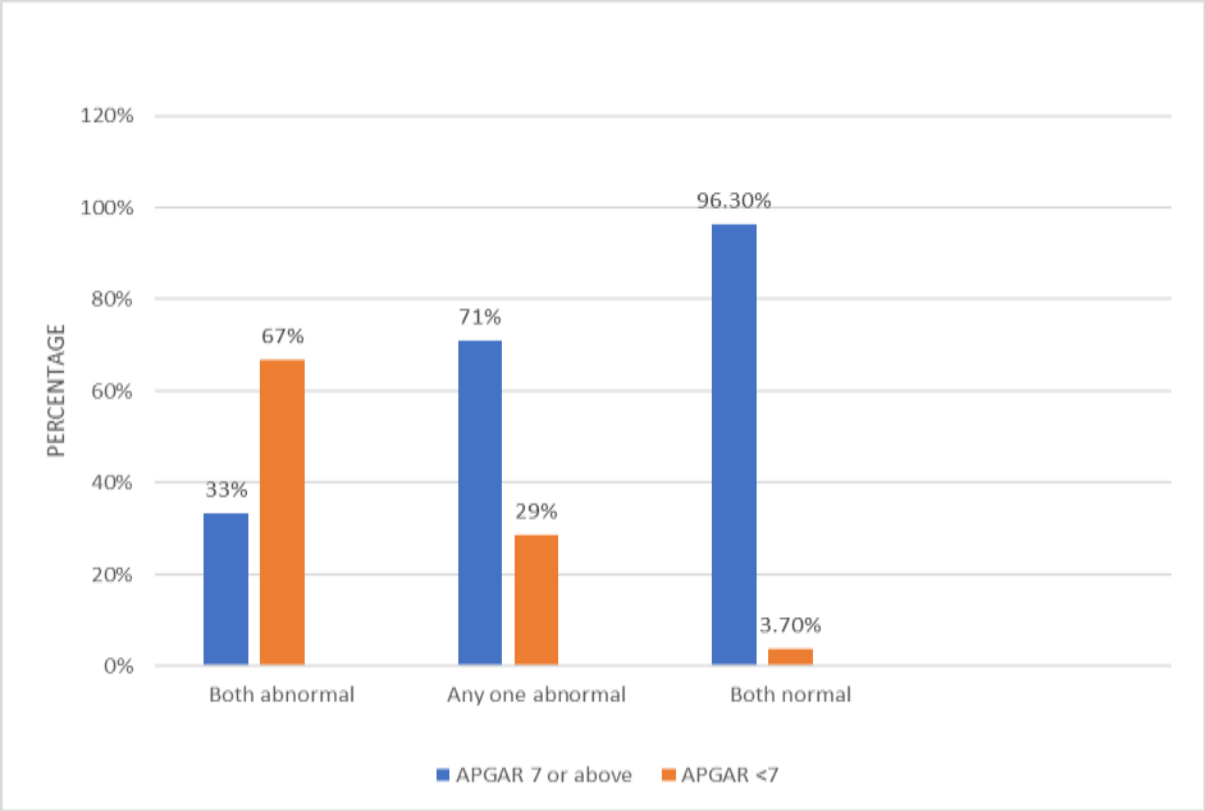
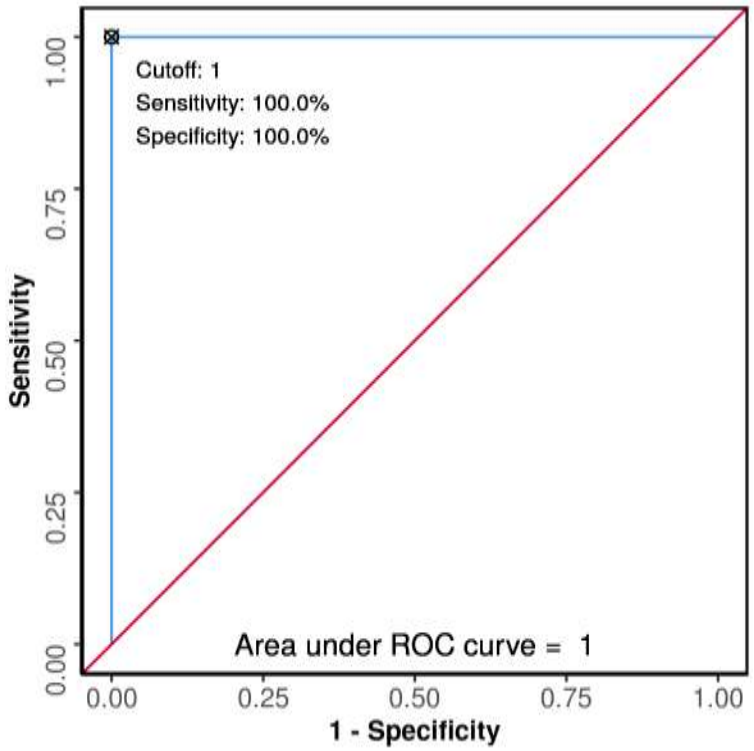


FIGURE 2: ROC Curve Analysis Showing Diagnostic Performance of S. Homocystine (µmol/L)+UtA PI in Predicting FGR: Yes vs FGR: No (n = 63)



Volume 9, Issue 3; May-June 2026; Page No 05-11

TABLE 1 : Sensitivity And Specificity Of Parameters For Fgr

Predictor	P value	Sensitivity	Specificity
S. Homocystine (µmol/L)	0.129	67%	88%
UtA PI	0.004	100%	96.7%
S. Homocystine (µmol/L) + UtA PI	<0.001	100%	100%

TABLE 2: Correlation between Hypertension and Serum homocysteine and Uterine artery PI

Investigations	No. of patients with Hypertension
Only Serum homocysteine raised	3 (42.9%)
Only Uterine artery PI raised	0 (0%)
Both Uterine artery PI and Serum homocysteine raised	2 (28.5%)
Normal investigations	2 (28.5%)

Volume 9, Issue 3; May-June 2026; Page No 05-11