



## Original Research Article

## To determine the efficacy of uterine artery pulsatility index and pregnancy associated plasma protein-a in the first trimester as a predictor of gestational hypertension- A prospective observational cohort study

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## ABSTRACT

Hypertensive disorders complicates 5-10% of all pregnancies. WHO has found that 16% of maternal deaths worldwide are due to gestational hypertension.

**Aim:** To determine the efficacy of uterine artery pulsatility index (UA-PI) and Pregnancy associated plasma protein A (PAPP-A) done in the first trimester as a predictor of gestational hypertension (GHT) and adverse fetal outcomes like fetal growth restriction, Small for gestational age babies, Preterm deliveries.

**Materials and Methods:** This is a prospective observational cohort study of 287 antenatal women, whose 1<sup>st</sup> trimester UA-PI and PAPP-A MoM values were obtained.

**Results:** Of the total 287 women, 68 (23.7%) developed GHT and 31 women developed adverse fetal outcomes.

28 women (9.8%) had an abnormal UA-PI ( $\geq 2.70$ ) and 11 (3.8%) women had an abnormal PAPP-A value ( $< 0.5$  MoM). Of the 28 women who had abnormal UA-PI value, 24 developed gestational hypertension. The sensitivity of UA-PI for prediction of GHT was 35.29%, specificity-98.17%, accuracy-66.73% and p-value-0.0005 which is statistically significant. Of the 11 women who had abnormal PAPP-A MoM value, 3 developed GHT. The sensitivity of PAPP-A for the prediction of GHT was 4.41%, specificity- 96.35% , and p-value was 0.925 which is statistically insignificant.

**Conclusion:** The study shows that 1<sup>st</sup> trimester UA-PI levels can be considered as a good predictor of GHT, while PAPP-A- was not reliable predictor for GHT. Both UA-PI and PAPP-A value, were not found to be useful markers in the prediction of adverse fetal outcomes in my study.

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### 1. Introduction

Hypertensive disorders complicate 5-10% of all pregnancies, and together they are one member of the deadly triad-along with hemorrhage and infection-contributing greatly to maternal morbidity and mortality. The WHO has systematically reviewed maternal deaths and found that 16% of maternal deaths worldwide are due to hypertensive disorders.<sup>1</sup> The diagnosis of gestational hypertension is made if a previously normotensive women develops hypertension for the first time in pregnancy after 20 weeks of gestation which is more than or equal to 140mm Hg

systolic and / or 90 mm Hg diastolic, atleast 2 readings taken 6 hours apart.<sup>2</sup>

### 2. Etiology of Gestational Hypertension

#### 2.1. Abnormal placental implantation

According to Ramsey and Donner, uteroplacental vessel development occurs in 2 stages. The first wave of trophoblastic invasion and modification of spiral arteries up to the border between the decidua and the myometrium occurs at 12 weeks. The second wave is between 12-16 weeks and involves some invasion into intramyometrial segments of spiral arteries. This remodeling convert the

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narrow lumen muscular spiral arteries into dilated, low resistance uteroplacental vessels. Normal trophoblastic invasion increases the spiral artery lumen from 15-20mm to 300-500 mm thus reducing impedance to flow and optimizing fetomaternal exchange. Faulty trophoblastic invasion of spiral arteries results in diminished placental perfusion and upstream increased uterine artery resistance. Increased uterine artery resistance in the first two trimesters provide indirect evidence of this process and serve as a predictor of GHT.<sup>3</sup>

## 2.2. Immune maladaptation to maternal and fetal tissues

There is loss of the maternal tolerance to paternally derived placental and fetal antigens leads to dysregulation of the production of blocking antibodies. This occurs in first pregnancy, when the mother is exposed to paternal antigens for the first time or in molar pregnancies where they are exposed to the double dose of paternal antigens. Increase in antigen load leads to increase in the production of inflammatory mediators and increased Th1 (T1 helper) cell response, which can cause damage to placenta leading to hypoxia.<sup>4</sup>

GHT is found to be a disorder of polygenic and multifactorial inheritance.<sup>5</sup>

GHT can present with varied presentation ranging from late onset gestational hypertension with an average size baby at term to early onset preeclampsia leading to preterm deliveries complicated by fetal growth restriction, Oligohydramnios.<sup>6,7</sup>

Research is approaching towards the combination of predictive modalities that might be helpful in better prediction of GHT. Two among them are UA -PI and PAPP-A levels in first trimester.

The reference standard values for UA-PI was given by a large study conducted by Gomez et al.<sup>8,9</sup>

Gall and Helbert in 1972 first identified PAPP-A as one of four proteins in the plasma of pregnant women, and, accordingly, given the name 'pregnancy-associated plasma protein A'. During pregnancy, PAPP-A is produced by placental syncytiotrophoblasts and secreted into the maternal circulation where its concentration increases until term.<sup>10</sup> In 1999, this IGF-dependent proteolytic activity was identified by Lawrence *et al.*<sup>11</sup> as PAPP-A. IGF -insulin like growth factors 1 and 2 which are polypeptides with high similarity in the sequence to insulin, that promote cell growth, differentiated function and survival in diverse tissues. Maternal serum levels of PAPP-A have long been known to be depressed in the first trimester of down's syndrome pregnancies. Other chromosomal abnormalities and adverse pregnancy outcomes, e.g. preeclampsia, intrauterine growth restriction are also associated with depressed levels of PAPP-A as is low birth weight babies.<sup>12</sup> Thus, there are compelling data for PAPP-A regulation of

IGF action during fetal development, folliculogenesis and aging, as well as in normal and abnormal growth of bone, skeletal muscle and vascular tissue.

## 3. Aim

To determine the efficacy of uterine artery pulsatility index (UA-PI) and Pregnancy associated plasma protein A (PAPP-A) done in the first trimester as a predictor of gestational hypertension (GHT) and adverse fetal outcomes like fetal growth restriction (FGR), Small for gestational age (SGA) babies, Preterm deliveries

## 4. Materials and Methods

### 4.1. Study setting

At Dr L H Hiranandani hospital, Mumbai, India. This hospital was established in 2004, a multi-speciality tertiary care centre with 240 beds facility with approximate 1,100 deliveries/ year.

### 4.2. Study design

Prospective observational cohort study

### 4.3. Inclusion criteria

Pregnant women obtaining antenatal care in the age group of 20- 40 years with Singleton, anatomically, genetically normal fetus were included.

### 4.4. Exclusion criteria

Women with multiple gestation, Previous pregnancies with gestational hypertension, preeclampsia and its sequelae, known case of autoimmune disorders, essential hypertension, kidney, cardiac and vascular disorders, Aneuploidy or anomalous babies and Women not willing to participate in the study.

### 4.5. Sample size

Details of a total of 304 antenatal women were collected between June 2017 to Jan 2019.

### 4.6. Data collection

The study was started after approval from the Institutional ethical committee (IEC).

After taking informed and valid consent, required details from the subjects were collected.

Ultrasonography for Nuchal Translucency with UA-PI and blood test for PAPP-A was done between 11–13.6 weeks.

Experienced fetal medicine experts, who had obtained The Fetal Medicine Foundation Certificate of Competence, performed 3D ultrasound and doppler scans with a

transvaginal 5-9 MHz transducer. At Lialac labs, PAPP-A levels (MoM) are evaluated by time resolved fluorometry or electrochemiluminescence. Antenatal visits were timed as per the WHO recommendation and blood pressure was noted in each visit.

As per the standard reference studies, the value of uterine artery PI in the first trimester is taken as a cut off of 2.70 (95<sup>th</sup> percentile). Any uterine artery PI value of more than or equal to 2.70 will be considered as abnormal.

As per the standard reference studies, the value of PAPP-A is taken at a cut off of 0.5 MoM (10th percentile). Any value below 0.5 MoM is more prone for development of adverse perinatal outcomes or development of gestational hypertension as per the earlier studies.

#### 4.7. Statistical analysis of the study

The collected data were analysed with IBM. SPSS statistics software 23.0 version. To find the significant difference between the bi-variate samples in independent groups, the Unpaired sample t-test was used. The Receiver Operator Characteristic (ROC) curve analysis with sensitivity, specificity, PPV and NPV was used to find the efficacy of the tools. In both the above statistical tools the probability value 0.05 is considered as significant level. P value of  $\leq 0.01$  was considered highly significant and p value of  $\geq 0.05$  was considered to be of no significance.

### 5. Review of Literature

Various predictive tests have been studied in the past and research is still heading towards the identification the best biochemical or sonological marker for GHT.

L. Velauthar et al<sup>13</sup> (2014) identified 18 studies (55 974 women) and a meta-analysis done by Cnossen and colleagues<sup>14</sup> (2008) found that first trimester UA doppler in first trimester is useful tool for predicting early onset preeclampsia as well as other adverse pregnancy outcomes.

Sangeeta G et al<sup>15</sup> (2015- India), did a prospective study of a total of 1640 antenatal women of which 140 had a low PAPP-A of less than 0.4 MoM and found the incidence of IUGR, preterm birth and low birth weight was significantly more than that of the controls.

Patil Mithil et al,<sup>16</sup> (2014 -Pune) have studied the S. Papp-A level in 560 pregnant women. 452 patients were found to have a normal Papp -A level of 0.5 MOM. 18 patients developed preterm labor and few patients developed gestational hypertension. The obstetric outcome of patients with a normal Papp-A level was fairly uneventful as compared to others with a low Papp-A level, stating that, PAPP-A has poor positive predictive value.

Neil O' Gorman, Kypros, Nicolaides (2016)<sup>17</sup> and Cai et al (2015),<sup>18</sup> China did a meta-analysis of 20 studies on 158 women by screening by a combination of maternal risk factors, UA-Doppler, mean arterial pressure, maternal

S.PAPP-A and PIGF and found that it can effectively used for screening of preeclampsia especially those requiring delivery before 34 weeks.

Kyung UK Sung<sup>19</sup> (2017) in Korea in 2014 did a prospective study on 155 women where in the multiples of the median (MoM) of PIGF and PAPP-A were determined in first trimester. It was found that PAPP-A is a potentially useful marker for SGA and PE.

Mariya Angelova et al<sup>20</sup> (2016) in Bulgaria did a prospective study of 106 singleton pregnancies, to determine the prognostic value of the low PAPP-A levels in the first trimester of pregnancy independently and in combination with UA doppler during the second half of pregnancy (22–23 weeks GA). Thirty-six pregnant women had PAPP-A level below 0.4 MoM, whereas 20 of them developed preeclampsia and 7–early preeclampsia. The combination of the low PAPP-A values and the abnormal Doppler test of the uterine arteries is with a considerably better prognostic value in regards to the risk of developing preeclampsia.

Anthony O Odibo et al<sup>21</sup> (2011) in Washington between 2009-2011 did a prospective study of 452 women for the efficacy of PAPP-A, PP-13 and UA-PI (between 11-13 weeks) in the prediction of PE. 42 women were diagnosed with preeclampsia. It was found that first-trimester PP13, PAPP-A and UA-PI are reasonable, individual predictors of women at risk to develop preeclampsia.

Burak Yucel et al<sup>22</sup> (2016) in Turkey in 2016 prospectively recruited 602 women. The combination of increased PI of uterine artery with low placental volume and low PAPP-A levels in the first trimester achieved better results than either test alone in the prediction of PE.

### 6. Results

In my study, data was collected from 304 antenatal women. Of which 287 could be studied throughout the antenatal period. 17 patients were dropped out of the study. The reasons being lost to follow up, medical termination of pregnancy due to anomalies detected at 18-20 weeks of gestation, cervical incompetence or chorioamnionitis.

In our study, out of 304 women, total 287 pregnancies were included, out of which 254 (88.5%) were spontaneous conceptions, 4 (1.4%) were by IUI, 29 (10.1%) were by IVF. In the study, 165 (57.5%) were primigravida and 122 (42.5%) were multigravida. In our study, the age group of women was 23-39 years (Mean–31.8), gestational fetal age at delivery was 31-40.4 weeks (38.3 weeks) and fetal weight at delivery was 1.26-4.2 kg (2.99 kg).

Of the 287 pregnancies, 145 (50.5%) women did not have or develop any maternal or fetal complications in pregnancy, 16 (5.6%) women developed Fetal growth restriction, 6 (2.1%) women had developed SGA fetus. 111 (38.7%) had other incidental complications like polyhydramnios, cervical incompetence, oligohydramnios,

preterm premature rupture of membranes, cholestasis of pregnancy, gestational diabetes mellitus etc.

Of the 287 pregnancies studied, 28 (9.8%) women had a UA-PI of more than 2.70 which is considered to be high resistance (abnormal).

Of the total 287 pregnancies studied, 11 (3.8%) women had PAPP-A of less than 0.5 MoM which is considered to be abnormal.

Of the total 287 women, 219 (76.3%) were normotensive and rest of the 68(23.7%) developed gestational hypertension

In my study of 287 women, 9.8% (28 women) had an abnormal UA-PI and 90.2% (259 women) had a normal UA-PI. Of the abnormal UA-PI group, 24 women developed GHT and 4 remained normotensive.

By computing these data in the Receiver Operator Characteristics curve (ROC) the p-value is found to be 0.0005 which is found to be statistically significant. This study showed that UA-PI value in first trimester is a statistically significant predictor of development of GHT. But, the Papp-A was found to be statistically insignificant predictor for GHT.

In my study of 287 women, 31 women developed adverse fetal outcomes. The p value of the association of the development of all the adverse fetal outcomes with abnormal UA- PI and PAPP-A was found to be statistically insignificant.

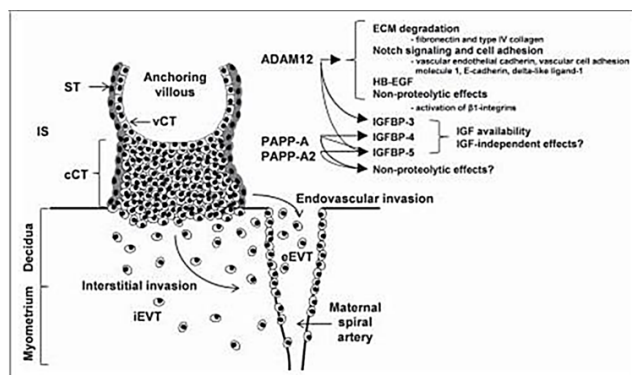
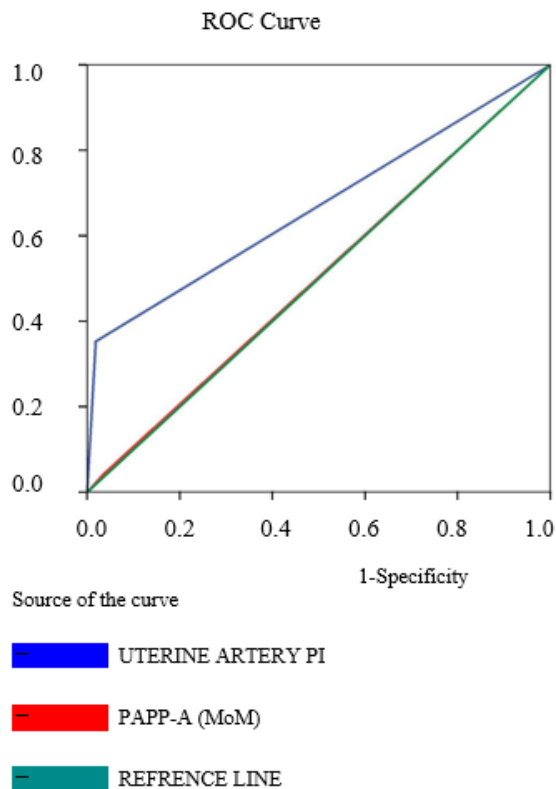


Fig. 1: Abnormal placental implantation

7. Discussion

In my study of 287 women, 57.5% were primigravida and 42.55% were multigravida and 254 (88.5%) were spontaneous conceptions. Gomez et al (2008) showed similar conception rates, maternal age and parity to our study.

In my study of 287 women, (145)50.5% did not have any obstetric complications, (16)5.65% developed FGR, (9) 3.1% developed preterm labour, (6)2.1% had SGA babies. Sangeeta et al (2015) did a study that had a higher incidence



Graph 1: Receiver operator characteristicS (ROC) curve for GHT and PAPP-A

of mentioned complications than our study.

In my study of 287 women, showed that UA-PI in first trimester is a statistically significant predictor of GHT.

L Velauthar et al (2014) did a meta analysis which showed that UA- PI in the first trimester is a useful tool for the prediction of PE which is consistent with that of our study

However, study by R Goetzing et al (2013) who did a study on 578 patients found that UA-PI either alone or in combination with biochemical markers was not found to have efficacy in PE prediction. This is inconsistent with that of our study.

Ozkar Ozdaman et al (2014) study found the association of PAPP-A with development of PE. The incidence of PE in the study group was 25% making this study comparable to that of our study.

Kyung UK Sung et al (2017) study found that PAPP-A was a not a good predictor for development of GHT. This is comparable to that of our study.

Sangeeta et al (2015) study found that PAPP-A to be good predictor of PE.. This study was in contrary to that of our study.

L Velauthar et al (2014) and Cnossen and colleagues<sup>17</sup> (2008) did a meta analysis, found that the specificity of UA-

**Table 1:** Uterine artery- pulsatility index (UA-PI) and PAAP- A levels in the study group

	<b>Total- 287 women</b>	<b>Percent</b>
Normal UA –PI (<2.70)	259	90.2
Abnormal UA-PI (>2.70)	28	9.8
Normal PAAP-A (>= 0.5 MoM)	276	96.2
Abnormal PAAP-A (<= 0.5 MoM)	11	3.8

**Table 2:** Area under the curve

Test Result Variable(s)	Area	Std. Errora	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Uterine Artery PI	.667	.042	0.0005 Statistically significant	.584	.750
PAPP-A (MoM)	.504	.040	0.925 Statistically insignificant	.425	.583

**Table 3:** Comparison of UA-PI and incidence of GHT

	<b>Normal BP</b>	<b>GHT</b>	<b>Total</b>
Normal UA-PI <2.7	215	44	259(90.2%)
Abnormal UA-PI>2.7	4	26	28(9.8%)
Total	219	68	287
	Sensitivity- 35.29%	PPV- 85.71%	P value- 0.0005-
	Specificity- 98.17%	NPV- 83.01%	significant
		Accuray-66.73%	

**Table 4:** Comparison between PAAP- A values and incidence of GHT

	<b>Normal BP</b>	<b>GHT</b>	<b>Total</b>
Normal PAAP-A >0.5	211	65	276 (96.2%)
Abnormal PAAP-A <0.5	8	3	11 (3.8%)
Total	219	68	287
	Sensitivity- 4.41%	PPV- 27.27%	P value- 0.925
	Specificity- 96.35%	NPV- 76.45%	statistically not significant
		Accuray-50.38%	

**Table 5:** Comparison between UA-PI values and development of adverse fetal outcomes

Complication	FGR	Count	UA-PI		Total	P Value
			Abnormal	Normal		
Obstetric	PRETERM	Count	6	10	16	Not significant
		% within UA-PI	66.7%	45.5%	51.6%	
Obstetric	SGA	Count	3	6	9	
		% within UA-PI	33.3%	27.3%	29.0%	
Total		Count	0	6	6	
		% within UA PI	0.0%	27.3%	19.4%	
Total		Count	9	22	31	0.213
		% within UA PI	100.0%	100.0%	100.0%	

**Table 6:** Comparison of PAAP-A with the development of adverse fetal outcomes

			PAPP-A		Total	P Value
			Abnormal	Normal		
Obstetric complication	FGR	Count	2	14	16	
		% within PAPP-A	50.0%	51.9%	51.6%	
	PRETERM	Count	1	8	9	
		% within PAPP-A	25.0%	29.6%	29.0%	
	SGA	Count	1	5	6	
		% within PAPP-A	25.0%	18.5%	19.4%	
Total	Count	4	27	31		
	% within PAPP-A	100.0%	100.0%	100.0%	0.949	

PI for FGR is high (93.3%) but the sensitivity is low (15.4%) making it a moderate predictor.

Patil Mithil et al (2014) did a study that stated PAPP-A an important predictor for adverse fetal outcomes but it has a poor positive predictive value. This was consistent with that of our study.

Sangeeta et al (2015) and Kyung Uk Sung et al (2017) did a study and found PAPP-A as a valuable predictor of adverse fetal outcomes. This study is not consistent with that of our study.

## 8. Conclusion

This was a prospective observational cohort study on antenatal women, whose 1<sup>st</sup> trimester UA-PI and PAPP-A MoM values were obtained and were studied for the development of GHT and adverse fetal outcomes.

The sensitivity of UA-PI for prediction of GHT was 35.29%, specificity was 98.17%, accuracy was 66.73% and p-value was 0.0005 which is statistically significant. This shows that UA-PI is a good predictor of GHT. The sensitivity of PAPP-A for the prediction of GHT was 4.41%, specificity was 96.35%, accuracy was 50.38% and p-value was 0.925 which is statistically insignificant. This shows that PAPP-A is not a good predictor of GHT.

Both UA-PI and PAPP-A value were not found to be useful markers in the prediction of adverse fetal outcomes in my study.

## 9. Recommendations

1. From my study, I would recommend the use of UA-PI in the first trimester as a predictor test for GHT.
2. Our relatively small sample size probably limited our statistical power to detect the significance of UA-PI and serum PAPP-A to predict GHT. Future studies in a larger cohort and multi-centric studies would be needed to give better predictive markers for GHT.

## 10. Source of funding

None.

## 11. Conflict of interest

None.

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