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Obervation Study of Association of Beta HCG, Papp A and Nuchal Tranclucency with Pre Eclampsia, Iugr and Preterm in Combination and Individually

KEYWORDS: β HCG, PAPP A and NT

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ABSTRACT *Hypertension, pre term and IUGR are major issue of concern, several predictors have been studied to know the occurrence of these conditions prior.Hence this project is undertaken to know the development of pre eclampsia, IUGR and pre term labour.*
This study is directed towards finding the inter-relationship of Beta HCG, PAPP A and NT in combination and individually in as a predictor of Pre eclampsia, IUGR and Pre term labour.This study included 100 antenatal patients who were followed till delivery.
We conclude PAPP A is sensitive with positive predictive value in predicting pre term and IUGR , where as β HCG alone is a poor predictor of pre term, IUGR and pre eclampsia but as it is well known NT is a good predictor of trisomy 21 but has no much role in the prediction of pregnancy out come in the above conditions.

INTRODUCTION
Hypertension is one of the major causes of maternal mortality in India. Preterm and IUGR are also issue of concern. Varied efforts have been taken to predict the future development of pre eclampsia, pre term and IUGR .

Predictors of abnormal pregnancy outcome especially in cases of IUGR , pre eclampsia, and pre term will not only will be able to guide us to prevention and early detection[(1)].

The recent studies regarding the pathophysiology , mechanism of hypertension in pregnancy points to early placental abnormalities[1] .Although overt illness rarely appears until third trimester, there are multiple indicators that the disease process has already begun and there are certain markers to detect outcome of the pregnancy . The root cause of pre eclampsia starts from the foundation itself that is abnormal placentation.And a small number of studies show that the raised level of β-HCG have been linked with hypertensive disorders.

Screening for these markers in the first trimester itself will help in early prediction of hypertensive disorders in pregnancy and its effective management . One such marker is serum β-HCG.Human chorionic gonadotropin is a glycopeptide hormone produced by the syncytiotrophoblasts .

Similarly Papp-A is produced by the placental trophoblasts, especially, by the extravillous cytotrophoblast. It is a 'protease' for insulin-like growth factor (IGF) binding proteins 4 and 5[2] . This means it has the ability to help release IGF from these binding proteins so that it is free to interact with its cell receptor. IGF is thought to play an important role in trophoblast invasion and hence the early development and vascularization of the placenta and the placental bed[(4)]. These early events in formation of the placenta are critical to pregnancy outcome and, when abnormal, are associated with intrauterine growth restriction (IUGR) of the baby, pregnancy-induced hypertensive disorders, fetal death in utero, premature delivery, and even cesarean section for indications of fetal or maternal compromise[3]. It has been postulated that low levels of PAPP-A, resulting in less release of IGF, could be a pathway by which placentation abnormalities occur that culminate in these poor pregnancy out come.

Nuchal tranclucency:
As a componenet of the FTS as recommended NT is an established marker when measured between 11 – 13 weeks to detect number of congenital and genetic disorders. The sensitivity of the test increases when combined with other biochemical markers like Papp-A , Beta Hcg, oestriol etc[(7).]

Taking in to account the fact that FTS is performed as a regular diagnostic procedure we have planned this study.

This study is an observational syudy to assess the association of trimester β-HCG , Papp-A and nuchal translucency[4] in prediction of pre eclampsia , pre term , and IUGR.

Materials and methods
Prospective randomised study of 100 registered antenatal patients with out any medical illnesses, were done at Department Of Obstetrics and Gynecology Bharati vidyapeeth Medical College, Pune, for 2 years where pregnant women between 11-13weeks were chosen.

NT measurement was done in radiology department according to criteria laid down by FETAL MEDICINE FOUNDATION,UK.

Beta hcg and PappA was sent to PerkinElmer labs in Chennai which is known for the genetic screening.All patients were followed till delivery and all data obtained were analysed and statistical significance was determined by Fischer exact test and value of $P < 0.001$ is considered significant.

OBSERVATION AND RESULTS:
Data of 100 patients were analysed. Patients having low PAPP A was found in 13 patients, among these 4 patients ended up in pre term labour, 2 had IUGR and 1 pre eclampsia was noted and the rest 6 had normal pregnancy out come.

No significant information was obtained from the Beta HCG or Nuchal tranclucency values in the study population.

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Table No. 1: This table is showing the number of cases according to gestational age who have under gone First trimester screening .

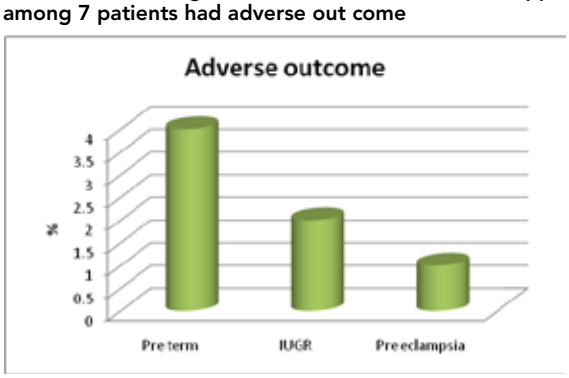
Gestational age In wks	No. of cases	%
11 weeks	41	41
12 weeks	45	45
13 – 13 weeks 6 days	14	14
Total	100	100

If the cut off of the Papp A levels are < 0.5 MoM then we found 3 patients doing into pre term out of 13 abnormally low levels.And specificity and sensitivity being the following

Sensitivity =(True +ve) / (Total +ve) = 3 / 4 = 75.0 %
Specificity =(True -ve) / (Total -ve) = 86 / 96 = 89.6 %
Positive Predictive =(True +ve) / (Test +ve) = 3 / 13 = 23.1 %
Negative Predictive =(True -ve) / (Test -ve) = 86 / 87 = 98.80

Papp A	Total Adverse outcome		Total	Fisher Exact test P
	YES	NO		
<0.5	6	7	13	<0.001 HS
0.5 +	1	86	87	
Total	7	93	100	

GRAPH 1: Showing Out of decreased levels of Papp A among 7 patients had adverse out come



Comment : Maximum patients out of low Papp A population went into pre term labour

DISCUSSION:

The First Trimester Screen is a new, optional noninvasive evaluation that combines a maternal blood screening test with an ultrasound evaluation of the fetus to identify risk for specific chromosomal abnormalities, including Down Syndrome Trisomy-21 and Trisomy-18[3].

In addition to screening for these abnormalities, a portion of the test (known as the nuchal translucency) can assist in identifying other significant fetal abnormalities, such as cardiac disorders[8].

Also it has been found in the recent studies that first trimester screening is also helpful in screening of the conditions like pre eclampsia,IUGR and preterm births[9]._ PAPP-A in promoting growth and development by breaking down IGF binding proteins and causing the release of free IGF for uptake into cells to promote growth. In those cases that eventually result in poor fetal growth, levels of PAPP-A at 11-14 weeks are significantly lower than normal-in this instance, lowered PAPP-A would result in less free IGF being available for cell uptake and growth stimulation. Further studies may elucidate if screening using such modalities can lead to new potential treatments for poorly growing fetuses.

Pregnancy-associated plasma protein A (PAPP-A); a low level of the first trimester marker PAPP-A is a major risk factor for delivery of an SGA neonate.

In a study conducted in Cathey General hospital ,Taiwan[6] ,

There was a statistically significant difference in PAPP-A values in the examined groups in all gestational ages ($p < 0.01$). The value of the PAPP-A concentration in different gestational ages with equal statistical significance indicated the possibility of complications, which was examined during pregnancy in relation to the control group of pregnant women with physiological pregnancies. This study confirmed that there was a statistically significant difference in fetal body weight at birth (p

< 0.05), Apgar score in 5 min after birth ($p < 0.05$), and gestational age at birth ($p < 0.05$), as parameters of the outcome of pregnancy course, between the examined groups of pregnant women in relation to the value of PAPP-A concentration.

Similarly production of hCG by the placenta in early pregnancy is critical for implantation and maintanance of the blastocyst. Since it is postulated that preeclampsia is likely a trophoblastic disorder, it may be essential for understanding of this disease, to investigate the pathologic and secretory reaction of the placenta. Twin pregnancies and molar pregnancies produce higher levels of hCG and they are associated with a higher incidence of preeclampsia than uncomplicated singleton pregnacies. An association was reported between preeclampsia and elevated third trimester hCG levels , whereas early experience with first trimester levels suggests a link between increased hCG and other adverse pregnancy outcomes .

Considerable evidence suggests an association between serum hCG levels and preclampsia . We therefore investigated whether the level of serum Beta-hCG does correlate with development of preeclampsia.

In our study all these levels of PAPP A ,β HCG and nuchal tranclucency has been taken in to consideration in relation to adverse out of the pregnancy such as pre eclampsia , pre term and IUGR .

As per table No. 2. 13% of patients had PAPP A levels less than 0.5 MoM which were abnormal and statistically significant. Out of the 13 % patients,7 patients had adverse pregnancy out come suggesting 4 patients having pre term delivery followed by 2 patients having IUGR and 1 having pre eclampsia.

Pre term labour complicates approximately 10 % of pregnancies. It contributes to significant neonatal mortality and morbidity.

Very often ,the diagnosis of pre term is made at too advanced stage in labour to effectively stop it or act upon it . This appears to be true both in developed and in developing countries. How ever ,in recent years neonatal out come appears to have improved and this is mainly due to improvement in neonatal intensive care unit .

In our study total No. of patients having per term were 4 in number and rest levels of PAPP A in 96% of patients were statistically not significant.

Sensitivity of the patients having pre term accounts to about 75%, and specificity being 89% hence low levels of PAPP A is

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not that significant in estimation of pre term births.

Only 2% of patients with low PAPP A had IUGR which was statistically significant with a sensitivity of 100% and specificity of 88.8% .

In our study only 1 patient developed pre eclampsia with low levels of PAPP A with a sensitivity of 85.7% and specificity of 92.5% .

The FTS is a screening modality with a integration of maternal characteristics and first trimester maternal serum biomarkers (free β-hCG and PAPP A) provided a possible screening for early-onset Pre eclampsia, pre term in IUGR[5].

According to our study PAPP A is sensitive with positive predictive value in predicting pre term that is 4 patients, 2 patients had IUGR and 1 patient having pre eclampsia.

In our study β HCG alone is a poor predictor of pre term, IUGR and pre eclampsia but as it is well known NT is a good predictor of trisomy 21 but has no much role in the prediction of pregnancy out come.

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