

Early Detection of Chromosomal Abnormalities and Evaluation of Maternal Outcome by Biochemical Markers between 11 - 14 Weeks of Gestational Age

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ABSTRACT

BACKGROUND

Chromosomal abnormalities are important causes of perinatal death and childhood handicap. Early diagnosis of chromosomal defects is therefore essential to reduce perinatal mortality rate and to prevent the agony of the mother caring for the abnormal child. We wanted to screen for chromosomal abnormalities namely trisomy 21, 18 & 13, during the first trimester of pregnancy using biochemical tests like free β -hCG, PAPP-A and study the maternal & foetal outcome of these pregnancies.

METHODS

This is a prospective study conducted among women who were in their first trimester. After obtaining informed consent, a total of 100 pregnant women both primi & multi gravida in their first trimester were selected and properly designed proformas were filled with relevant information.

RESULTS

Prevalence of high risk after the double marker test is 7%; none of them had chromosomal anomalies. However, low PAPP-A (<0.52 MoM) was significantly associated with increased preeclampsia, preterm delivery, and miscarriage.

CONCLUSIONS

Low PAPP-A shows an association with preeclampsia, preterm labour, and miscarriage. It is a useful indicator of risk of preterm delivery and future chance of development of pregnancy-induced hypertension.

KEYWORDS

β -human Chorionic Gonadotropin (β -hCG), Pregnancy-Associated Plasma Protein-A (PAPP-A), Foetal Nuchal Translucency (NT) Thickness

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BACKGROUND

Chromosomal abnormalities are important causes of perinatal death and childhood handicap. Early diagnosis of chromosomal defects is therefore essential to reduce perinatal mortality rate and to prevent the agony of the mother caring for the abnormal child. The financial burden of caring for an abnormal child is enormous, not only for the couple and their immediate family, but also for the society and the government at large.

Maternal serum screening is a way to find out information about the developing foetus without invasive procedures. The goal of maternal serum screening is to identify those patients who have an increased risk for a foetal disorder and offer them specific diagnostic tests. Maternal serum screening has traditionally been offered in the second trimester of pregnancy, but scientific advances now allow health care providers to offer screening for Down syndrome and other abnormalities like small for gestational age, impending foetal death etc., in the first trimester of pregnancy itself. First trimester screening is also useful to predict the maternal outcome like preeclampsia, gestational hypertension, preterm delivery and intra uterine growth retardation etc.

Prenatal diagnosis by various screening methods is performed during different gestational weeks to assess the individual's risk for chromosomal anomalies of the foetus. The risk of birth defects for all patients is 2-3%. Chromosome abnormalities account for approximately 10% of birth defects. Trisomy 21, commonly known as Down syndrome is one of the commonest chromosomal anomalies occurring in approximately 1 in 500 live births.¹ Worldwide, more than 2 lakh children are born with Down syndrome every year.

In India the overall prevalence of Down syndrome is 1.17/1000 live births.² The risk of genetic burden in India according to a multi centre study by ICMR is 14% (Bangalore 12.6%, Mumbai 23%).³

In the 1970s, the main method of screening for aneuploidies was by maternal age and in the 1980s by maternal serum biochemistry and detailed ultrasonographic examination in the second trimester. In the 1990s, the emphasis shifted to the first trimester when it was realized that the great majority of foetuses with major aneuploidies can be identified by a combination of maternal age, maternal serum free β -human chorionic gonadotropin (β -hCG) and pregnancy-associated plasma protein-A (PAPP-A) and foetal nuchal translucency (NT) thickness. In the last 10 years, several additional first trimester sonographic markers have been described which improve the detection rate of aneuploidy and reduce the false-positive rate.⁴

METHODS

This is a prospective study conducted in a hospital outpatient clinic among all pregnant women who attended the

department of DDH. Those women who are in their first trimester were recruited for the study. After obtaining informed consent a total of 100 pregnant women both primi & multi gravida in their first trimester were selected and properly designed proformas are filled with relevant information.

Inclusion Criteria

Primi and multi gravidae, Period of gestation

Exclusion Criteria

Gestation age > 14 weeks and <11 weeks.

Patients attending the OPD of DDH&RC were registered and a detailed history was obtained from 100 pregnant women. Pregnant women between 11-13+6 weeks were selected for the study purpose. A specially designed proforma was filled up after obtaining written consent from the patient.

Peripheral venous blood sample was drawn for the biochemical markers (β -hCG & PAPP-A) in addition to the routine antenatal profile followed in our hospital as per protocol.

First trimester serum screen test includes serum free β -hCG (hCG), pregnancy associated plasma protein A (PAPP-A) combined with patient supplied maternal age. Relevant patient history (h/o previous Down syndrome pregnancy) was also noted. Complete information is necessary to interpret the test. Patient information was provided to the laboratory using the Maternal Prenatal Screening test request form.

The data was analysed with statistical methods of mean, standard deviation, chi square and P value for variable analysis of data. We have taken the support of SPSS software.

RESULTS

In the present study, data collected from 100 pregnant women between 11-14 wks. of gestational age has been analysed. Biochemical analysis was performed on maternal blood samples for serum markers (Free β -hCG, PAPP-A). Parameters that have been analysed are age, education, husband's age, parity, gestational age at screening test and consanguinity.

The mean age of pregnant women in the present study is 28 yrs. Maximum number of pregnant women in the study were in the age group of 26-30 yrs. 54% of pregnant women had degree qualification. The average age of the husbands in present study is 32.52 yrs. Maximum numbers of spouses are in the age range of 26-35 yrs. Majority of pregnant women in present study are primigravid, 64% and 36% are multigravidas.

The test was accepted by pregnant women more in 11-13 wks. and only 8 were in 14 wks. gestation age. The analysis shows 14% had a consanguineous marriage, 86% had a non-consanguineous marriage.

Variables	No. of Patients
Age	
15 - 20	3
21 - 25	27
26 - 30	51
31 - 35	14
36 - 40	4
41 - 45	1
Patient Education	
High school	21
Degree	54
PG	25
Husband Age	
20 - 25	1
26 - 30	38
31 - 35	42
36 - 40	18
41 - 45	1
Parity	
Primigravida	64
Multigravida	36
Gestational Age in Weeks	
11 wks.	31
12 wks.	35
13 wks.	26
14 wks.	8
Consanguinity	
Consanguineous	14
Non consanguineous	86
Previous History of Chromosomal or Other Anomalies	
Yes	5
No	95
Maternal Weight (kg)	
45 - 54	18
55 - 64	70
65 - 74	12
SBP mmHg	
100 - 108	64
110 - 120	36
DBP mmHg	
60 - 70	45
72 - 80	55

Table 1. Demographic Details in the Present Study

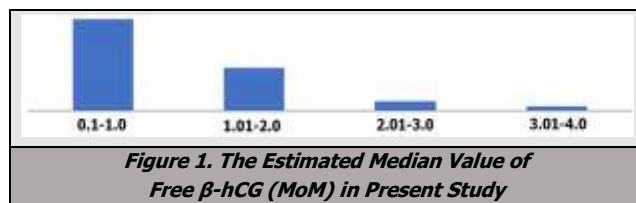


Figure 1. The Estimated Median Value of Free β -hCG (MoM) in Present Study

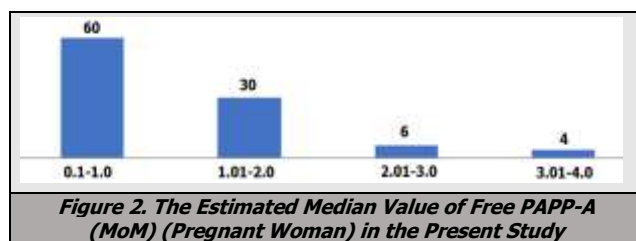


Figure 2. The Estimated Median Value of Free PAPP-A (MoM) (Pregnant Woman) in the Present Study

One woman had previous child with down syndrome, two women had family history with down syndrome, one woman had previous baby with NTD (Neural Tube Defect) & mental retardation, one woman, who had child with mental retardation, but no chromosomal abnormalities identified. Other 95 women didn't give any history of previous abnormal child or family history of abnormal child.

The average maternal weight was 58.58 Kg. Maximum weight was 74 Kg, minimum weight was 42 Kgs. The estimated median value of free β -hCG is 0.73 MoM. The

maximum value of free β -hCG is 3.14 MoM, the minimum value is 0.23 MoM. 63% of pregnant women (maximum number) had free β -hCG within the range of 0.1-1 MoM.

The estimated median value of PAPP-A found to be 0.915 MoM. The maximum value of PAPP-A is 3.46 MoM, the minimum value is 0.18 MoM. 60% of pregnant women (maximum number) had values of PAPP-A in the range of 0.1-1 MoM.

Maternal Weight (Kgs)	Free β -hCG (Median in MoM)	PAPP-A (Median in MoM)
45 - 54	0.65	0.975
55 - 64	0.74	0.905
65 - 74	0.735	0.902
Gestational Age (in Weeks)		
11	0.66	0.98
12	0.84	0.94
13	0.625	0.75
14	0.89	0.66

Table 2. Mean Weight and Gestational Age in Association with vs. Free β -hCG, PAPP-A

The median values of free β -hCG was low in the lower weight categories and PAPP-A and NT values were higher in the lower weight groups. Low free β -hCG and high PAPP-A in the lower gestational age when compared to higher gestational age in the first trimester screening analysis.

Free β -hCG vs Gest. HTN			Gest. HTN		Total
			No	Yes	
Free β -hCG	<0.539	Count	27	1	28
		% within free β -hCG	96.4%	3.6%	100.0%
	>=0.54	Count	63	9	72
		% within free β -hCG	87.5%	12.5%	100.0%
Total		Count	90	10	100
		% within free β -hCG	90.0%	10.0%	100.0%
Free β -hCG vs Preeclampsia			No	Yes	
Free β -hCG	<0.539	Count	25	3	28
		% within free β -hCG	89.3%	10.7%	100.0%
	>=0.54	Count	64	8	72
		% within free β -hCG	88.9%	11.1%	100.0%
Total		Count	89	11	100
		% within free β -hCG	89.0%	11.0%	100.0%
Free β -hCG vs Miscarriage			No	Yes	
Free β -hCG	<0.5	Count	23	1	24
		% within free β -hCG	95.8%	4.2%	100.0%
	>=0.5	Count	72	4	76
		% within free β -hCG	94.7%	5.3%	100.0%
Total		Count	95	5	100
		% within free β -hCG	95.0%	5.0%	100.0%
PAPP-A and Maternal Outcome			No	Yes	
PAPP-A	<0.52	Count	9	3	12
		% within PAPP-A	75.0%	25.0%	100.0%
	>=0.52	Count	81	7	88
		% within PAPP-A	92.0%	8.0%	100.0%
Total		Count	90	10	100
		% within PAPP-A	90.0%	10.0%	100.0%
PAPP-A with Preeclampsia			No	Yes	
PAPP-A	<0.52	Count	8	4	12
		% within PAPP-A	66.7%	33.3%	100.0%
	>=0.52	Count	81	7	88
		% within PAPP-A	92.0%	8.0%	100.0%
Total		Count	89	11	100
		% within PAPP-A	89.0%	11.0%	100.0%
PAPP-A vs. Preterm Delivery			No	Yes	
PAPP-A	<0.52	Count	9	3	12
		% within PAPP-A	75.0%	25.0%	100.0%
	>=0.52	Count	85	3	88
		% within PAPP-A	96.6%	3.4%	100.0%
Total		Count	94	6	100
		% within PAPP-A	94.0%	6.0%	100.0%
PAPP-A vs. Miscarriage			No	Yes	
PAPP-A	<0.4	Count	5	3	8
		% within PAPP-A	62.5%	37.5%	100.0%
	>=0.4	Count	90	2	92
		% within PAPP-A	97.8%	2.2%	100.0%
Total		Count	95	5	100
		% within PAPP-A	95.0%	5.0%	100.0%
Table 3. Free β -hCG and PAPP-A in Association with Maternal Outcome					

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In women with free β -hCG less than 0.54 MoM, 3.6% developed gestational hypertension and in those with free β -hCG equal $\geq$ 0.54 MoM, 12.5% had gestational hypertension. The correlation is not statistically significant (P value 0.181).

In women with free β -hCG less than 0.54 MoM, 10.7% developed preeclampsia. In those with free β -hCG equal or above 0.54 MoM, 11.1% had preeclampsia. The correlation is not statistically significant (P value 0.955).

The analysis shows 4.2% of pregnant women who had free β -hCG $<$ 0.5 MoM had miscarriage. 5.3% of women with equal or above 0.5 MoM value of free β hCG had miscarriage. The correlation is not statistically significant (P value 0.830).

PAPP-A estimation have been analysed based on the levels to see the effect on gest. HTN, preeclampsia, preterm delivery, miscarriage.

The analysis shows 25% of pregnant women had gestational hypertension in whom PAPP-A is less than 0.52 MoM. 8% of women with PAPP-A equal or above 0.52 MoM had Gest. HTN. The correlation is not statistically significant value (P value 0.065).

The analysis detected preeclampsia in 33.3% of women with PAPP-A less than 0.52 MoM and 8% of women with PAPP-A with equal or above 0.52 MoM had preeclampsia. The correlation is statistically significant (P value 0.008).

The analysis shows 25% of pregnant women had preterm delivery in whom PAPP-A is less than 0.52 MoM whereas 3.4% of women with values equal or above 0.52 MoM had preterm labour. The correlation is statistically significant (P value 0.003).

The analysis shows miscarriage occurred in 37.5% of pregnant women with PAPP-A less than 0.4 MoM and in 2.2% of women with PAPP-A equal or above 0.4 MoM. The correlation is statistically significant (P value 0.0001).

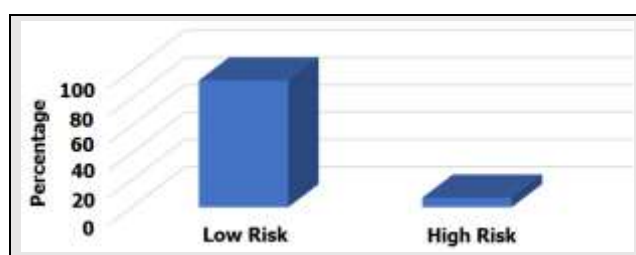


Figure 3. Double Marker Risk (Free β -hCG, PAPP-A) Assessment and Maternal Outcome

The screening test results shows High risk category for chromosomal abnormalities 7%. Low risk pregnant women are 93%. On follow up of delivery, among these high risk women, 1% had abortion. The analysis of the abortus showed normal karyotype.

Parameter	Maternal Outcome	Statistical Significant
PAPP-A ($<$ 0.52 MoM)	Preeclampsia	0.008
PAPP-A ($<$ 0.52 MoM)	Preterm delivery	0.003
PAPP-A ($<$ 0.4 MoM)	Miscarriage	0.0001
Double marker test assessment (high risk)	Preeclampsia	0.0001

Table 4. PAPP-A vs. Gestational Hypertension

DISCUSSION

Chromosomal abnormalities are one of the most important causes of perinatal mortality, childhood handicap, lifelong difficulties & enormous socioeconomic burden. The risk of birth defects for all pregnancies is 2-3% and chromosome abnormalities account for approximately 10% of them. Trisomy 21, commonly known as Down syndrome is one of the commonest chromosomal anomalies occurring in approximately 1 in 500 live births.¹

As there is no cure available yet for chromosomal abnormalities, medical termination is the only available option for major congenital anomalies. The earlier the detection of these anomalies, the safer it is for the mother to take a decision either to undergo the procedure of termination or to continue for a natural course.

The mean age of pregnant women was 28 yrs. According to Ronald Wapner et al,⁵ in their study, mean maternal age was 42 yrs. They found the prevalence of chromosomal anomalies (trisomy 21) was 1: 321. But in the present study we did not have trisomy 21, probably because of low mean age i.e. 28 yrs. in the study group and low sample size. According to Valerie J Rappaport et al,⁶ the risk of down syndrome 1: 1031 and risk of other chromosomal abnormality 1: 435 at 28 years of maternal age.

In present study all women are educated, 54% of them are graduates. 64% were primigravida, the pregnancies were followed up to term and postpartum period. They developed the following complications; preeclampsia (8 %), gestational hypertension (4%), preterm delivery (4%) and miscarriage (2%). 36% were multiparous, in whom preeclampsia was found in 3% of women, gestational hypertension in 6%, preterm labour in 2% and miscarriage in 3%.

The analysis shows 14% with consanguineous marriages. On follow up, no chromosomal abnormality was detected. One miscarriage occurred at 14 wks. of GA because of hydrops foetalis. Karyotyping of the abortus was found to be normal.

There was one woman who had previous child with Down syndrome, two women had family history of down syndrome, and one woman had previous baby with NTD (neural tube defect) & mental retardation, one woman who had child with mental retardation but no chromosomal abnormalities. Other 95 women didn't give any history of previous abnormal child or family history of abnormal child.

It is known that drugs which are embryo toxic are categorized by US FDA into A, B, C, D and X based on their severity of its toxicity based on evidence. Anticonvulsants, anticoagulants, psychoactive drugs, retinoids and few analgesics etc., will cause teratogenicity. In this study none of the pregnant women took these drugs. All of them have taken folic acid and a few of them have taken pantoprazole, doxylamine and pyridoxine during the first trimester.

Infections like toxoplasmosis, rubella, cytomegalovirus, herpes (TORCH), parvo virus and syphilis etc., will cause teratogenicity but none of the pregnant women had these infections & tested negative for TORCH screen.

The mean gestational age of pregnant women was 12 wks. The analysis shows at 11 wk., 12 wk., 13 wks. and at 14 wks. of GA the median PAPP-A levels were 0.98 MoM; 0.94 MoM; 0.75 MoM; 0.66 MoM respectively and median free β -hCG were 0.66 MoM, 0.84 MoM; 0.625 MoM and 0.89 MoM respectively. The women with weight ranges of 45-54 Kg, 55 – 64 Kg and 65 – 74 Kg had median PAPP-A and free β -hCG of 0.975 MoM, 0.65 MoM; 0.905 MoM, 0.74 MoM; 0.902 MoM, 735 MoM respectively.

According to K. Spencer et al⁷, <11 wks. mean GA the median PAPP-A was 0.396 MoM, free β -hCG was 1.82 MoM. According to K. Spencer et al⁷ at >/11 wks. mean GA the median PAPP-A was 0.437 MoM, free β -hCG was 1.95 MoM. In the same study they found women with weights in the ranges of 45-54 kg, 55 – 64 Kg and 65 – 74 Kg had median PAPP-A and free β -hCG values of 1.21 MoM, 1.21 MoM; 1.09 MoM, 1.01 MoM; 0.90 MoM, 0.96 MoM respectively. Therefore it may be inferred that PAPP-A levels are decreasing with increasing maternal weight.

The data showed 63% of women had free β - hCG in the range of 0.1-1.0 MoM. Women with free β -hCG <0.54 MoM, 10.7% developed preeclampsia and 3.6% had gestational hypertension. According to Audibert et al, free β -hCG for diagnosis of preeclampsia is 0.548 (0.453-0.643).⁸ In the same study they found that gestational HTN developed at 1.16 (0.76-1.56) MoM values of free β -hCG.

The women with free β - hCG of <0.5 MoM, miscarriage occurred in 4.2%, and 10.7% had preterm delivery. According to Gagnon A et al,⁹ in the first trimester, low free β - hCG <0.5 MoM was associated with an increased frequency of adverse obstetrical outcomes.

The data showed 60% of women had PAPP-A in the range of 0.1-1.0 MoM. Women with PAPP-A <0.52 MoM, 33.3% developed preeclampsia and 25% had gestational hypertension.

According to Uccella S et al¹⁰, in <0.52 MoM PAPP-A values, the risk of gestational hypertension or preeclampsia was 11.2% and risk of severe preeclampsia was 3.9%. According to Audibert et al⁸, PAPP-A for diagnosis of preeclampsia is 0.570 (0.482-0.657).

The analysis shows 25% of pregnant women with PAPP-A <0.52 MoM developed preterm delivery. According to Uccella S et al¹⁰ the risk of preterm delivery <37 wks. of gestation developed in 11.8% of pregnant women with PAPP-A values <0.52 MoM.

Miscarriage occurred in 37.5% in those with PAPP-A <0.4 MoM. According to Gagnon A et al⁹ in the first trimester unexplained low PAPP-A values of <0.4 MoM are associated with an increased frequency of adverse obstetrical outcomes.

According to Markku Ryyne et al¹¹ maternal serum low PAPP-A values in the first trimester is an independent risk factor for adverse pregnancy outcome like miscarriage, SGA (Small for Gestational Age), preeclampsia and aneuploidy.

The double marker test was offered to approximately 150 pregnant women in my study. Thorough counseling about the test was done in the woman's native language.

100 women accepted to undergo the test i.e. 2/3rd of women choose to accept this test. Present study had women belonging to all socioeconomic strata. Out of the 50 women who declined the test, the socioeconomic status was also mixed. So this suggests that if proper counseling is done, most women choose to undergo this test irrespective of their socioeconomic status. Hence double marker test is recommended as a screening test, in first trimester even though the cost is a limiting factor.

CONCLUSIONS

Acceptability of screening test in our population is high because of its non-invasive nature and possibility of early detection of chromosomal abnormalities. Low PAPP-A shows an association with preeclampsia, preterm labour and miscarriage.

As the sample size of this study is small, there is a need for larger population studies for further analysis of prevalence of chromosomal abnormalities.

Financial or Other Competing Interests: None.

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