Original Research

Assessing the need for adjustment of first trimester screening markers in Diabetic Women

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ABSTRACT:

Introduction & Objective: *First trimester screening is done to detect aneuploidy pregnancies; the tests include serum Pregnancy Associated Plasma Protein A (PAPP A), free β subunit of human Chorionic Gonadotropin (β hCG) and Nuchal Translucency (NT) thickness. This study was done to compare serum PAPP A and free β hCG levels in diabetic and non-diabetic women with normal NT thickness, during first trimester aneuploidy screening and to assess the need for adjustment of screening markers in diabetic women.*

Materials and Methods: *The study design is cross-sectional involving 632 non diabetic and 55 diabetic women who underwent first trimester (11 to 13 weeks 6days) aneuploidy screening from January 2014 to June 2015 at Sri Ramachandra Medical Centre. Serum PAPP A and free β human chorionic gonadotropin were measured by solid phase, two site fluoroimmunometric assay.*

Results: *Results were analysed using SPSS software version 18. Serum PAPP A concentration in diabetic women were found to be significantly low compared to non-diabetic women (p < 0.000). There was no significant difference in free β hCG between two groups.*

Conclusion: *Significantly low MoM PAPP A in diabetic pregnant women may necessitate to consider for adjustment of PAPP A values while calculating individual aneuploidy risk.*

Keywords: *PAPP A, free beta hCG, anueploidy screening, Diabetes Mellitus.*

INTRODUCTION

First trimester Aneuploidy screening is a non-invasive test done for early detection of aneuploidy pregnancies (like Downs, Patau and Edward syndromes). It is a combined test which includes 1) Nuchal Translucency (NT) thickness, 2) Pregnancy associated Plasma Protein A (PAPP A), 3) free β subunit of human Chorionic Gonadotropin (free β hCG). The test is done from 11weeks to 13weeks, 6days of gestation. Measurement of these serum biochemical markers are affected by pregnancy and maternal characteristics like Race/Ethnicity, age of mother, maternal weight, parity, method of conception, smoking status of mother, multifetal gestation and Diabetes Mellitus[12]. This combined test has detection rate of approximately 80 to 87% and false positive rate of 5% for Downs's syndrome[4]. Diabetes Mellitus being a metabolic disorder affects maternal serum PAPP A and hCG levels[3.]

Maternal serum PAPP A is a glycoprotein, Zinc binding metalloproteinase belonging to the metzincin superfamily of metalloproteinases[1]. PAPP A is produced by placental syncytiotrophoblast and deciduas[1]. In circulation it exists either as free form or as heterotetrameric complex, complexed with eosinophil major basic protein (pro MBP). Pro MBP is an endogenous inhibitor of proteolytic activity of PAPP A[5]. During pregnancy, 99% of PAPP A is bound to pro MBP. In normal pregnancy, PAPP A in maternal circulation increases exponentially with

doubling time of 3-4 days during first trimester, and raises constantly till delivery and returns to normal by 2-3 days after delivery[5]. PAPP A concentration is 100 fold low in fetal blood and 1000 fold lower in amniotic fluid on comparision with maternal blood.[5] IGFBPs (insulin like growth factor binding proteins) 4 and 5 inhibit IGF 1 and 2 by binding to them. PAPP A acts as a protease on IGFBPs and release IGF (insulin like growth factor). IGF has role in trophoblast invasion which helps in early development and vascularisation of placenta. Low PAPP A levels are found in trisomy pregnancies.

Maternal serum free β hCG is a glycoprotein. It consists of two non-covalently linked α and β subunits produced by syncytiotrophoblast cells. Subunit β is unique for this hormone. Free β subunit comprises of 0.3 to 4% of total hCG in maternal circulation. Other circulatory forms are intact hormone, free α subunit, nicked subunits and hyperglycosylated forms. hCG has role in growth and differentiation of endometrium, localised suppression of immune response, modulation of uterine morphology and coordination of signals between uterus and endometrium.

Nuchal translucency(NT) thickness is a subcutaneous collection of fluid between skin and cervical spine in the fetus[1]. NT test measures nuchal fold thickness. NT thickness is maternal age dependent and has to be matched to gestational age and CRL .Increased NT is observed in aneuploidy pregnancies (about 2.0 MoM), major heart and great

artery defects in fetus, skeletal dysplasias, genetic syndromes and delayed development of lymphatic system in fetus[19].

The objective of this study is to compare serum free β hCG and PAPP A in diabetic and non-diabetic women during first trimester screening program, and to evaluate whether correction factors are needed in calculating individual risk for aneuploidy in diabetic women.

MATERIALS AND METHODS
Study design:

This cross sectional study includes women with singleton pregnancy with gestational age between 11weeks and 13weeks & 6days, who enrolled for routine first trimester screening. The study was conducted at Sri Ramachandra Medical Centre for a period of one and half year from January 2014 to June 2015. It includes 632 non diabetic women and 55 diabetic women (known cases of DM before pregnancy). Women with multiple pregnancy, previous h/o aneuploidy, increased risk of aneuploidy in present pregnancy and women conceived by assisted reproductive techniques were excluded from the study.

Biochemical parameters like free β subunit of hCG and PAPP A are analysed in maternal serum sample by solid phase Fluoroimmunometric assay on Auto Delfia Automatic Immunoassay System manufactured by Perkin Elmer. Nuchal translucency thickness is measured by ultrasound.

Statistics:

Statistical analysis was done using SPSS software version 18. Multiples of Median (MoM) was calculated by dividing individual analyte value with median value corresponding to their gestational age[1]. Calculated MoM values are then adjusted for age and weight of the mother[13]. Adjusted MoM values are then compared between diabetic and nondiabetic group using an independent student's t test where p value <0.05 is considered as significant.

RESULTS

Distribution of women according to gestational age is given in figure 1. Most of the women undergo first trimester screening during 12 weeks of pregnancy.
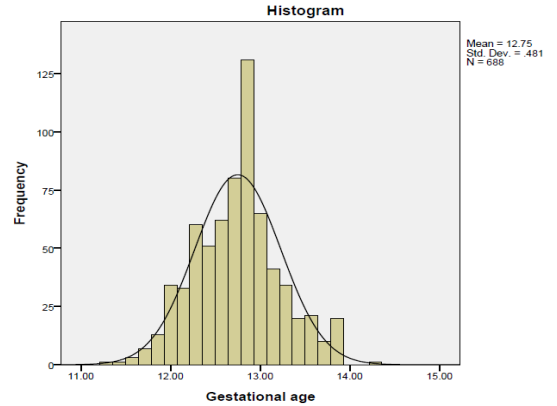

Fig. 1: Population histogram

In the present study, 687 pregnant women were included and their distribution according to age, maternal weight, gestational age and maternal blood glucose levels are given in table 1.

Table 1: Descriptive statistics

Variable	Diabetic women (n=55)	Non diabetic women (n=632)
Maternal age (mean±SD) in yrs	29.1±4.8	26.53±0.895
Gestational age in weeks(at time of screening) (mean±SD)	12.7±0.48	12.69±0.96
Maternal weight (mean±SD) in kg	65±12.8	61.25±22.60
Fasting blood glucose (mg/dl)	106.8	82.9
Post prandial blood glucose (mg/dl)	169.8	107
Glycated haemoglobin (%)	6.48	**-**

Considering Maternal age and weight there is no significant difference in serum PAPP A and free β hCG in diabetic individuals. HbA1c was measured only in 31 non diabetic individuals with a mean value of 5.2%.

Table 2: comparison of aneuploidy markers in diabetic and nondiabetic individuals

variable	Diabetic (n=55)	Nondiabetic (n=632)	Sig.(2 tailed)
PAPP A (MoM)	0.834	1.186	**0.000**
free β subunit of hCG (MoM)	1.142	1.179	0.759

In our study, MoM for serum PAPP A was found to be 1.186 for non-diabetics as compared to 0.834 in diabetics (table 1). In diabetics the reduction in serum PAPP A (~ 29%) is statistically significant (p value < 0.000). MoM of serum β hCG in diabetic women is 1.142 and non-diabetic is 1.179. The reduction in serum β hCG was not statistically significant.

Negative correlation was observed between serum PAPP A and HbA1C, but not statistically significant.

DISCUSSION

The findings of the present study showed maternal serum PAPP A level (of first trimester aneuploidy screening) MoM to be significantly decreased by 29% in diabetic pregnant women. This might lead to increase false positive rates of first trimester aneuploidy risk calculation. This finding is consistent with studies done by Padmalatha Gurram, George Wells, Kevin Spencer, Fialova.L and Jaideep Malhotra.

In our study, slight reduction (4%) of maternal serum free β hCG levels is observed in diabetic pregnant women, which is not statistically significant when compared with normal counterparts (non diabetic women). Spencer and collegues, Geralvn Lambert in their studies found no change in free β hCG levels between diabetic and non-diabetic pregnant women. In contrast, reduction in free β hCG in the diabetic group is reported in studies done by Padmalatha Gurram and Jaideep Malhotra.

According to the published Literature, there is no significant difference in NT thickness in diabetic and non-diabetic women[9]. In previously done studies, by Kevin Spencer, Geralvn Lambert show no significant difference in these biochemical parameters. One study conducted by Spencer and colleagues show low PAPP A and no difference in free β hCG in known IDDM pregnant women. In previously done studies, by George Wells, Kerin Bleicher, PAPP A was reduced by 41.3% in type 2 DM individuals; by Padmalatha Gurram, Kevin Spencer shows that PAPP A is reduced by 12% and total hCG is reduced by 18% (they included both T1DM and T2DM women); by Kevin Spencer and Nicholas J Cowans show reduction in both PAPP A and hCG in GDM; a meta-analysis done by Fialova L ,Malbohan IM show low PAPP A; by Jaideep Malhotra show low PAPP A and free β hCG.

Our study population included south Indian population, non-smokers, women with singleton pregnancy and women with natural conception and the cases were pregnant women with either T1DM or T2DM diagnosed earlier. In pregnancies with Downs syndrome, maternal serum PAPP A is reduced (median=0.4-0.5 MoM) and free β hCG is increased (median=1.7-2.2 MoM), and pregnancies affected by trisomy 13 or 18, both the serum parameters are decreased. In diabetic women, who had low serum PAPP A values, if not corrected while calculating individual risk for Downs syndrome, there is a high possibility that it could result in increased false positive rate for aneuploidy screening and that these individuals will be subjected to further testing – second trimester screening or invasive procedures.

LIMITATIONS

Limitations of our study are small sample size and the diabetes mellitus cases included not being categorized into type 1 and type 2.

CONCLUSION

In women with Diabetes Mellitus during pregnancy, PAPP A is significantly low (29%) and there is no change in β hCG when compared with non-diabetic women. This may necessitate to consider adjustment of PAPP A levels in diabetic women for calculating individual aneuploidy risk.

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