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Association of First-Trimester Aneuploidy Markers with Gestational Diabetes Mellitus

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KEYWORDS

Gestational Diabetes Mellitus, Pregnancy-associated plasma protein-A, β- human chorionic gonadotropin, Nuchal translucency, Double marker test

ABSTRACT:

Introduction: The earliest identification of women who are at risk of developing GDM is becoming increasingly important to improve the prognosis, as the prevalence of gestational diabetes mellitus is rising. Our goal is to determine whether first-trimester aneuploidy markers are associated with the eventual development of gestational diabetes mellitus.

Objectives: To investigate any association of first-trimester aneuploidy markers nuchal translucency (NT), pregnancy-associated plasma protein-A (PAPP-A), human chorionic gonadotropin (β-hCG), and 'Combined risk' (ultrasound and biochemical marker) with gestational diabetes mellitus (GDM).

Material and methods: In this prospective cohort study, first-trimester aneuploidy marker tests were performed between 11-13+6 weeks of gestation and GDM screening was done at the first visit, 24-28 weeks, and 32-34 weeks of gestation. The antenatal women were divided into GDM and non-GDM as per IADPSG glycemic cut-offs. Demographic, clinical, and laboratory data of both groups were compared and predictive tests were applied to detect GDM.

Results: A total of 292 patients, 70 (23.9%) in the GDM group and 222 (76%) in the non-GDM group were included in the study. The median age, crown-rump length and nuchal translucency data were statistically similar in both groups. PAPP-A MoM (GDM:1.02 ± 0.70; non-GDM:0.95 ± 0.56; p=0.535) and β-hCG MoM (GDM: 1.04 ± 0.45; non-GDM: 1.07 ± 0.57; p=0.092) levels of the GDM group were similar to non-GDM group statistically. β-hCG >1.5 MoM (p=0.0018), predicts a lower risk of GDM development. On ROC analysis, β-hCG MoM had a higher area under the curve than PAPP-A. β-hCG at a cut-off of 1.21 MoM, the sensitivity of detecting GDM was 80% and the specificity was 37%, whereas β-hCG at 1.08 MoM, the sensitivity was 60% and the specificity was 50%.

Conclusions: Among the first-trimester aneuploidy markers, only β-hCG MoM can be utilized as a screening test to predict GDM with low predictability.

1. Introduction

An increasingly prevalent pregnancy condition that is linked to serious morbidity in both the mother and the new-born is gestational diabetes mellitus (GDM) [1,2]. GDM is defined by ACOG as any level of glucose intolerance that is first time identified during pregnancy [3]. The prevalence of gestational diabetes worldwide is 1-30% and in India is about 19-20% [4]. Maternal short-term complications from GDM include hyperglycemia crisis, which can lead to preeclampsia, preterm labour, urinary tract infections, an increased risk of caesarean delivery, operative delivery, and postpartum haemorrhage; long-term complications include a predisposition to the development of cardiovascular disorders and type 2 diabetes [5]. Intrauterine foetal demise, foetal macrosomia, birth traumas, hypoglycemia, prematurity, and pulmonary hyaline membrane disease are among the foetal and neonatal complications seen in children of GDM mothers [6] and metabolic disorders, including obesity, hypertension, dyslipidaemia, and glucose intolerance, are more common in later childhood and next-generation adulthood [2].

Between 11 and 13 weeks (plus 6 days) of gestation, first-trimester aneuploidy marker tests are usually carried out. Maternal serum indicators free beta-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) are combined with the measurement of foetal nuchal translucency (NT) by ultrasonography [7]. There is a strong correlation between high NT levels and aneuploidy and structural abnormalities. Placental indicators, such as β-hCG and PAPP-A, facilitate placental development [8]. Poor pregnancy outcomes, including spontaneous miscarriage, pre-eclampsia, preterm delivery, low birth weight, small for gestational age, and growth-restricted foetuses, are linked to

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abnormal concentrations of either PAPP-A or β-hCG [9–13]. Limited research has investigated the potential influence of first-trimester aneuploidy markers on the likelihood of gestational diabetes mellitus in the later stages of pregnancy [13–21]. The earliest identification of women who are at risk of acquiring GDM is becoming increasingly important in order to improve the prognosis, as the prevalence of GDM is rising. To determine whether first-trimester aneuploidy markers are associated with the eventual development of gestational diabetes mellitus, this is our goal.

2. Materials and methods:

2.1 Study population-

The research was carried out after the Institute Ethics Committee (IEC) clearance from July 2022 to December 2023. It was a prospective observational cohort study which included 343 antenatal women. The inclusion criteria were Maternal age 18-40 years, regular cycles and known LMP and singleton pregnancy. The exclusion criteria were k/c/o Diabetes Mellitus, impaired glucose tolerance in the first trimester of current pregnancy as indicated by 75 gm Oral Glucose Tolerance Test (OGTT) or lab reports of FBS ≥ 125 mg/dl, RBS >200 mg/dl, or HBA1C ≥6.5%, multifetal pregnancy, positive aneuploidy soft tissue markers or the presence of a fetal congenital anomaly in present pregnancy, chronic medical disorders, taking steroids, substance abuse. 41 women were excluded due to non-availability of double marker test and 10 women were lost to follow up. Among the remaining 292 participants, 70 were diagnosed as GDM and 222 were non- GDM.

2.2 Brief methodology-

After an informed and written consent, antenatal women in the first trimester were enrolled in the study. The study duration was 18 months, but the study population was recruited in the first 6 months. The participants' comprehensive medical history, including demographic information, past obstetrics history, history of gestational diabetes mellitus (GDM), history of macrosomia (child with birth weight >4 kg) in previous pregnancy, family history of diabetes in first degree relatives, pre-existing PCOS (polycystic ovary syndrome), pre-pregnancy weight, and body mass index, were reviewed in order to determine the risk factors for developing GDM in the current pregnancy.

Between 11 weeks and 13 weeks and 6 days of gestation, the first-trimester aneuploidy marker (ultrasound + biochemical) test was conducted. Radiologists with experience conducted the ultrasound examination. According to the established procedure of the Foetal Medicine Foundation (FMF) criteria, NT was measured at crown-rump length (CRL) ranging from 45 to 84 mm(22). Once the amnion and foetal skin were distinguished, the nuchal translucency was measured in the largest region between the soft tissue overlay of the cervical spine and the fetus's skin in the mid-sagittal plane and neutral posture. The foetal nasal bone was also measured and recorded as missing, hypoplastic, or present. There were three categories for NT readings in our study: <1.5 mm, 1.5-2 mm, and >2 mm.

Double marker test was done from a standardized laboratory as per our institutional protocol. Utilising standardised software such as PRISCA version 5.0.2.37 (Siemens Healthineers India), DELPHIA, ROSH with adjustment for gestational age, the absolute levels of β-hCG and PAPP-A were converted to a multiple of the expected normal median (MoM). This included the mother's age, her pre-pregnancy weight, the number of foetuses, any structural or chromosomal anomalies in her previous child, her smoking status, and the mode of conception in their risk algorithm of aneuploidy prediction. In this study, we classified free β-hCG readings as low, normal, or high based on whether they were less than 0.5 MoM, between 0.5 and 1.5 MoM, or greater than 1.5 MoM. Low and high PAPP-A levels were defined as PAPP-A readings falling below 0.5 MoM and beyond 0.5 MoM, respectively.

During the first trimester, each patient underwent a 75gm oral glucose tolerance test (OGTT) and deranged OGTT patients were excluded. The participants with normal OGTT were subjected to OGTT between 24-28 weeks of gestation. Patients with normal OGTT at 24-28 weeks of gestation, repeat OGTT was done at 32-34 weeks of gestation. Using the glycaemic cut-off values of Fasting ≥92, 1ST hour ≥180, and 2nd hour PP ≥153 mg/dl (any abnormal value), GDM was diagnosed in accordance with IADPSG criteria[23].

Patients were followed up till 36 weeks and divided into two groups- GDM and Non-GDM. Statistical analysis was done comparing the demographic and clinical parameters and the first-trimester aneuploidy markers- NT, β-hCG (MoM), PAPP-A (MoM), and the combined risk (Ultrasound+ Biochemical) data between the GDM and Non-GDM group.

3. Statistical analysis-

The statistical analysis was conducted using SPSS 20 for Windows statistical software (SPSS Inc., Chicago, IL, USA). The data was given as mean ± SD for categorical variables and percentages for continuous variables. To compare the two groups, the student t-test was utilised. To identify the categorical variables connected to GDM, a logistic regression analysis was performed. To evaluate a continuous variable's ability to discriminate in predicting GDM, receiver-operating-characteristic (ROC) analysis was used. At $p<0.05$, two-sided p values were regarded as statistically significant.

4. Results:

Table 1: Comparative analysis of various clinical factors and first trimester aneuploidy markers between GDM and non-GDM groups.

Characteristics	GDM (N=70)	Non-GDM (N=222)	p value
Age (years)	28 (25.7-32)	28 (25-31)	0.846
Pre-pregnancy BMI[1] (kg/m2)	22.3 (21-24)	22.2 (21-23)	0.187

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Family history of Diabetes, N	14 (20)	16 (7.2)	**0.002#**
PCOS^, N	10 (14.2)	13 (5.58)	**0.022#**
Gravidity, N	1 (47.1)	1 (62.1)	0.26
Time of First trimester aneuploidy screening test (weeks)	12.3 (12-12.6)	12.3 (12-12.6)	0.73
CRL* (mm)	61.4 (57.4-67.2)	62.5 (56.4-67.5)	0.837
NT⁎ (mm)	1.3 (1.1-1.5)	1.3 (1.1-1.5)	0.532
NT MoM°	0.88 (0.76-1.06)	0.86 (0.75-0.98)	0.96
β-hCG² MoM	1.04 (0.74-1.19)	1.07 (0.82-1.39)	0.092
PAPP-A³ MoM	1.02 (0.67-1.37)	0.95 (0.69-1.25)	0.535
Combined risk <1:10000, N	51 (72.8)	154 (69.3)	0.53

#P<0.05 significant, ¹BMI- Body mass index, ²β-hCG- beta-human chorionic gonadotrophin, ³PAPP-A- Pregnancy associated plasma protein-A, ^PCOS- polycystic ovarian syndrome, *CRL- crown rump length, ⁎NT- nuchal translucency, °MoM- multiple of meridian

4.1 Characteristics of the study population-

A total of 292 patients with 70 (23.9%) in the GDM cohort group and 222 (76%) in the non- GDM cohort group were included in the study. Comparative analysis of various clinical factors and first trimester aneuploidy markers between the groups are shown in table 1. The median age of GDM group: 28 (25.7-32) years and non-GDM group: 28 (25-31) years, p= 0.846 and the median crown-rump length of GDM group:61.4 (57.4-67.2) mm and non-GDM group:62.5 (56.4-67.5) mm, p= 0.837 were statistically similar. There was shown to be a substantial correlation between GDM and the known risk factors, such as a family history of diabetes (p value = 0.002) and polycystic ovarian syndrome (p value = 0.02). Compared to the non-GDM group, both variables were linked to the onset of gestational diabetes mellitus (GDM).

4.2 First trimester aneuploidy markers as a predictor of GDM-

The β-hCG MoM levels in the GDM group were found to be lower than those in the non-GDM group, however the difference between the two groups did not reach statistical significance (P > 0.05). Between the two groups, there was no statistically significant difference in NT or PAPP-A MoM (Table-1).

Study population distribution according to different cut-off of β-hCG MoM (Table 2) showed the association between GDM and β-hCG MoM is statistically significant at cut-off values of 0.5 to 1.5 MoM and >1.5 MoM (p value- 0.0002 and 0.0018 respectively), which suggests β-hCG >1.5 MoM predicts lower risk of GDM development.

To determine the individual role of each marker as a predictor of GDM, logistic regression analysis was performed (Table 3). Applying the Wald test, it was observed that, adding NT, β-hCG MoM, PAPP-A MoM, Trisomy 21 risk did not significantly enhance the predictability of GDM.

ROC analysis was done for NT, β-hCG MoM, PAPP-A, and Trisomy 21 Risk or combined risk parameters (Table 4). No statistical significance was obtained by ROC analysis of the markers. ROC analysis for β-hCG MoM (Figure 1) showed AUC to be 0.567 with p-value of 0.092. β-hCG at a cut-off of 1.21 MoM, the sensitivity of detecting GDM was found to be 80% and the specificity 37%, whereas β-hCG at a cut-off of 1.08 MoM, the sensitivity was 60% and the specificity was 50%.

Table 2: Distribution of study population according to different cut-offs of β-hCG MoM

β-hCG^ MoM°	GDM N (%)	Non GDM N (%)	Total N (%)	p value
<0.5	2 (2.8)	18 (8.1)	20 (6.8)	0.129
0.5-1.5	63 (90)	150 (67.5)	213 (72.9)	**0.0002***
>1.5	5 (7.1)	54 (24.3)	59 (20.2)	**0.0018***
Total	70 (100)	222 (100)	292 (100)	

Chi square test, *p<0.05 significant

^β-hCG- beta-human chorionic gonadotrophin, °MoM- multiple of meridian

Table 3: Logistic regression analysis to identify any association of first trimester aneuploidy markers with GDM

Variable	OR[a] (95% CI⁎)	p value	Standard error
NT¹ (mm)	0.663 (0.038-11.467)	0.777	1.454

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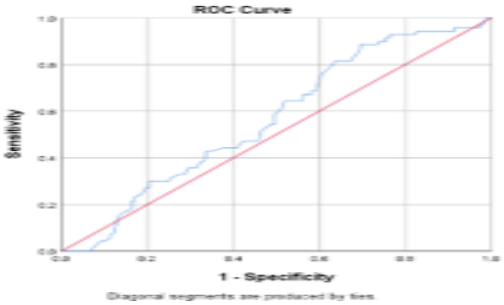
β-hCG[2] MoM*	2.343 (0.045-122.506)	0.673	2.019
PAPP-A[3] MoM*	1.561 (0.165-14.803)	0.698	1.148
Combined risk (USG+ Biochemical)	1.000 (1.000-1.000)	0.824	0.000

[a]OR- Odds ratio, ⁎CI- Confidence interval, [1]NT- Nuchal translucency, [2]β-hCG- Beta-human chorionic gonadotrophin, [3]PAPP-A- Pregnancy associated plasma protein-A, *MoM- Multiple of median

Table 4: ROC analysis of first trimester aneuploidy markers

	Area under Curve	Standard error	95% Confidence Interval	p value	Sensitivity (Sn) and Specificity (Sp) at specific cut-off
β-hCG MoM	0.567	0.037	0.495-0.639	0.092	Sn-80% and Sp-37% at 1.21 MoM Sn-60% and sp-50% at 1.08 MoM
PAPP-A MoM	0.475	0.040	0.396-0.554	0.535	Sn-50% and Sp-40% at 1.03 MoM Sn-70% and Sp-21% at 1.34 MoM
NT (mm)	0.525	0.041	0.445-0.604	0.534	Sn-54% and Sp-48% at 1.2mm Sn-88% and Sp-13% at 0.99mm
Combined risk (USG+ Biochemical)	0.572	0.095	0.387-0.758	0.439	Sn-60% and Sp-27% at 1:10699 Sn-70% and Sp-15% at 1:30113

Figure 1: ROC curve of sensitivity/specificity balance for beta-human chorionic gonadotrophin (β-hCG) multiple of median (MoM) value



5. Discussion:

A significant association between GDM and the established risk factors like family history of diabetes (p value- 0.002) and history of polycystic ovarian syndrome (p value- 0.02) was observed. We observed that the first trimester aneuploidy markers have a very low predictability of GDM. GDM correlated negatively with β-hCG concentrations >1.5 MoM. Our data is in line with comparable studies by Visconti et al. [15] in an Italian population and Sirikunalai P et al. [19] in a large Thai population, suggesting that high free β-hCG levels (β-hCG > 2.0 MoM) in the first trimester may reduce the probability of GDM. Reduced first trimester levels of β-hCG are linked to an increased risk of developing GDM, according to a few studies [13,14], as well as a systematic review and meta-analysis [24]. showed that reduced first trimester level of β-hCG is associated with the risk of GDM development. While in several studies β-hCG did not have any prognostic value for GDM [20,21,25].

However, our research shows no correlation between PAPP-A MoM and GDM. Our findings are consistent with three other studies that found no significant change in first trimester serum PAPP-A levels and no prognostic significance in pregnant women who progressed to develop GDM [20,21,25]. Our findings conflict with several research' findings that GDM was predicted by a low PAPP-A (PAPP-A MoM <1) [13,14,16–18,25]. GDM was not linked to foetal nuchal translucency (NT) [13–15].

There could be a correlation between the severity of GDM in the study population and the variations in the outcomes of the many research (Table-5). According to the severity of GDM, PAPP-A levels were shown to have decreased in certain studies; the GDM on insulin group experienced a greater reduction in PAPP-A levels than the GDM on diet control group [14,18,26]. We did not stratify GDM in our analysis based on whether glycaemic control was achieved with insulin, metformin, or medical nutrition therapy. The variations in the diagnostic standards applied in the aforementioned investigations could provide additional support for the disparate results.

ROC analysis for the first trimester aneuploidy markers (Nuchal translucency, β-hCG MoM, PAPP-A MoM, and combined risk) as a predictor of GDM were statistically not

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significant. β-hCG at a cut-off of 1.21 MoM, the sensitivity was 80% and the specificity was 37%, whereas β-hCG at a cut-off of 1.08 MoM, the sensitivity was 60% and the specificity was 50% to predict GDM. Similarly, Visconti et al. [15] in their study found that nuchal translucency, β-hCG MoM, and PAPP-A MoM were statistically not significant but the combined risk (FTCT value) was significant.

The study's shortcomings included its single-centre design, which limited its capacity to generalise its findings to a wider range of ethnic groups and populations. The double marker test report (biochemical part of the first trimester aneuploidy marker) was obtained from different centers as per the institutional protocol, as the test is not being done in our institute. Though standardized software was being used in the calculation of the test report, bias due to inter-laboratory analytical variations could not be avoided. The study's statistical power and capacity to identify significant differences may be diminished by the limited sample size.

6. Conclusion:

Our study findings do not provide strong evidence regarding the association of first trimester aneuploidy markers with the risk of developing Gestational Diabetes Mellitus. The predictive significance of the tests is very low for predicting GDM. The first trimester aneuploidy markers are being used routinely in every pregnant woman as a screening tool for fetal aneuploidy, some of its components (β-hCG) may be utilized as a screening test to predict GDM with low predictability. These results of our study mandate further investigation with a standardized protocol along with a large sample size from both low and high-risk pregnant women with different ethnicities.

Table 5: The published data from multiple research studies on the first trimester biochemical marker MoM levels in pregnancies that were later diagnosed with GDM.

Study	Year	Number		β-hCG MoM		PAPP-A MoM	
		Non-GDM	GDM	Non-GDM	GDM	Non-GDM	GDM
Our study	2023	222	70	1.07	1.04	0.95	1.02
Visconti et al.[15]	2019	1828	596	0.91	1.02	1.19	1.02
Sweeting et al.[16]	2017	732	248	0.99	0.98	1	0.81 *
Xiao et al.[17]	2017	986	599	1.06	1.01	0.97	0.88 *
Spencer K et al.[14]	2013	6559	870	1	0.93 *	1	0.91 *
Savvidou et al.[21]	2012	41,007	779	1	0.95	1	0.94
Benevenuti et al.[18]	2011	228	228	1	0.9	1.2	0.70 *
Tul et al.[20]	2003	1109	27	0.99	0.86	1.01	0.98
Ong et al.[13]	2000	4297	49	1.01	0.78 *	1.05	0.85 *
Weighted average		6329	385	1	0.94	1.04	0.9

*P<0.05 (two-sample t-test or Mann-Whitney U-test). Data are median or mean log10 presented in the original scale.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The study was conducted after the Institute Ethics Committee (IEC) clearance in the Department of Obstetrics and Gynaecology at All India Institute of Medical Sciences (AIIMS), Raipur (IEC Proposal No.-AIIMSRPR/IEC/2022/1157).

Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Contributorship

Chandrashekhar Shrivastava and Priyanka Mondal wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Guarantor

Chandrashekhar Shrivastava is the guarantor of the study.

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