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Clinical Assortment of Preeclampsia in Women with Diabetes Mellitus Type 1 During Early Pregnancy: An Investigative Analysis

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ABSTRACT

Objective: To determine the clinical predictors of preeclampsia in T1DM women during first trimester.
Study Design: Cross-sectional study
Place and Duration of Study: Gynaecology and Obstetrics Department of Pakistan Emirates Military Hospital, Rawalpindi, Pakistan, from Dec 2022 to Oct 2023.
Methodology: A cross sectional study of 245 T1DM women was conducted in this group. Two categories of women were identified: normal (n=221) and PE (n=24). Clinical data were gathered in the first trimester, and the eGDR, (mg/kg/min) was used to quantify insulin resistance (IR) in the first trimester. Statistical analysis was done to look for variables linked to PE.
Results: Preeclampsia was diagnosed in primiparae. The greatest predictor of PE was vasculopathy (OR 28.15 95% CI 8.0-98.6, *p*=<0.0001), followed by the duration of diabetes (25 years). PE was linked to a higher gestational weight gain (GWG) of 14 kg. Blood pressure factors of PE included both diastolic and systolic readings. PE and glycated haemoglobin (HbA1c) levels (7.5; 6.2–8.6) were substantially correlated. eGDR and PE had a negative correlation (8.6(6.6–10.6)). Triglycerides (TG) (0.94(0.6–1.2)) were the lipids that showed a positive correlation with PE, and this correlation was true regardless of HbA1c levels.
Conclusion: In T1DM women, primiparity and vasculopathy were the most significant risk factors for PE. Higher GWG was also linked to PE. PE was linked to increased TG and HbA1c levels. More research is necessary to determine the relationship between IR and PE.

Keywords: Early Pregnancy, Type-1 Diabetes mellitus, Preeclampsia, Vasculopathy.

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INTRODUCTION

Preeclampsia is a fatal obstetric syndrome that occurs during pregnancy, resulting in adverse health outcomes for both the mother and the fetus.[1] It is characterized by the sudden start of high blood pressure and the presence of substantial levels of protein in the urine after the 20th week of gestation. This condition has a prevalence rate ranging from 2% to 8% among pregnant women.[2] Multiple risk factors are associated with developing Pre-eclampsia (PE), encompassing primiparity, multifetal gestation, and pregestational diabetes.[3] PE prevalence in mothers diagnosed with diabetes mellitus varies between 10% and 20%. The prevalence of diabetic nephropathy is significantly higher in women.[4]

The presence of diabetes in the environment and preexisting maternal vasculopathy can increase the likelihood of reactive oxygen species generation and impact placental function during the early stages of pregnancy.[5] Evidence indicates a correlation between hyperglycemia and the occurrence of pulmonary embolism (PE),[2] The identification of predictors of preeclampsia holds significant importance within the context of a high-risk population, specifically women diagnosed with type 1 diabetes. It is imperative to assess the impact of blood pressure and other potentially prognostic markers during early pregnancy on the occurrence of preeclampsia.[3]

Based on the existing body of literature, this research is centered on examining the clinical factors contributing to its development in women with gestational diabetes throughout the early stages of pregnancy, particularly in the healthcare setting of the Gynecology and Obstetrics Department of Pakistan Emirates Military Hospital (PEMH), Rawalpindi, Pakistan.

METHODOLOGY

This study was conducted at the Gynecology and Obstetrics Department of Pakistan Emirates Military Hospital (PEMH), Rawalpindi, Pakistan . Sample size was calculated by implementing the following statistical formula with assumption;

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$$n = \frac{z^2 \times \hat{\rho}\,(1-\hat{\rho})}{\varepsilon^2}$$

z = score of 1.96

Taking prevalence as 20% $=\hat{\rho}$ =0.2

0.2 Confidence level = 1-α = 95%

Margin of error = ε= 0.05

Using above formula:

$$n = \frac{(1.96)^2 \times 0.2(1-0.2)}{0.5^2}$$ =245

So, the study was carried out on 245 pregnant women with T1DM during a period between December 2022 and September 2023, after taking approval from Ethical Review Committee (A/28/164(2)/EC/473/2022). Potential research subjects with T1DM were be identified by the experienced doctors and recruited into the research after obtaining informed written consent. Anthropometric records, clinical information, and laboratory data was gathered.

Inclusion Criteria: Women in 1st trimester i.e., early pregnancy (10-12 weeks of gestation) and pregnant women suffering from gestational diabetes.

Exclusion Criteria: Pregnant women in mid- or end-of pregnancy and women suffering from pre-gestational diabetes, pre-gestational hypertension and the women who had history of pre-eclampsia, pre-term delivery, miscarriage, delivery at another care center, or lost to follow-up.

As per outcome of the pregnancy metrics, women were divided into two groups; normal or control women (diabetic pregnant women with no PE) and women developing Preeclampsia. Age, weight, height, Waist-to-Hip (WHR) ratio was also assessed. Moreover, maternal age, body temperature, time since diabetes diagnosis, Blood pressure, BMI, pulse, parity, and vasculopathy was also investigated.

For clinical examination, 3-5 mL of blood was drawn from the patients after fasting overnight at the stipulated time of gestation. Certain blood tests were performed, inclusive of a serum test for HbA1c level in whole blood (The normal range for this test is 4.8–6.0% (29–42 mmol/mol) for a nonpregnant population), RFTs, Total serum cholesterol, High-Density Lipoprotein (HDL) cholesterol, as well as Triglyceride (TG) levels. Low-density lipoprotein (LDL) cholesterol was calculated by applying the following formula.[1]

$$LDL\ Cholesterol = Total\ Cholesterol - HDL\ Cholesterol - \frac{TG}{5}$$

Insulin Resistance (IR) was quantified via eGDR with the following equation:

$eGDR = 24.31 - (12.22 \times WHR) - (3.29 \times HTN) - (0.57 \times HbA1)$

where,

eGDR is estimated glucose disposal rate expressed in mg/kg/min [1]

WHR is waist-to-hip ratio,

HTN is hypertensive status

(0 = no; 1 = yes), and

HbA1c as a percentage.

The data was analyzed through SPSS version 22.0. Quantitative variables such as maternal age, gestational age, age at time of diagnosis of diabetes, duration of diabetes, body mass index (BMI), waist-to-hip ratio, GWG, systolic and diastolic blood pressure were presented as mean and standard deviation. Qualitative variables such as parity, Vasculopathy, SGA neonates, LGA neonates were presented as frequency and percentages. However, gestational age at delivery, and birth weight were mentioned in the interquartile range and median. To search for the most significant preeclampsia-associated factor, the odds ratio was calculated using MedCalc Software.[6]

RESULTS

A total of 245 pregnant females were included in the study. Of the women included in the final analysis, 221 (90.2%) patients were normal or control (didn't develop preeclampsia), and 24(9.7%) patients developed preeclampsia.

Tables 1 and 2 present the details of the study subgroups. There were no discernible variations in the average gestational age at the point of study enrollment, maternal age, body mass index (BMI), or waist-to-hip ratio (WHR) across the two study subgroups. No significant disparities were seen in the distribution of women across various BMI values. The prevalence of overweight was found to be greater among women who had preeclampsia (PE) compared to the control group. A statistically insignificant pattern was seen, indicating a tendency towards increased weight gain in pregnant females who had preeclampsia. Women who were presented with preeclampsia (PE) had an earlier onset of diabetes diagnosis and a prolonged duration of the disease

compared to females who had no PE. A notable disparity existed in the percentage of primipara and multipara within the two groups. All incidences of PE were diagnosed in primiparous women. Women who experienced the development of preeclampsia exhibited elevated levels of blood pressure in comparison to the control group. The average birth weight of neonates of mothers with preeclampsia (PE) was shown to be lower compared to control groups. However, the proportions of neonates classified as small for gestational age and sex, as well as those classified as large for gestation age and sex, were similar across both groups.

The most significant predictor of PE was the existence of vasculopathy (Figure), which was followed by a long-term history of diabetes (Table-I). After taking vasculopathy into account, diabetes duration was not found to be predictive of PE. There was a significant connection between increased gestational weight gain and the occurrence of preeclampsia (PE), even after controlling for body mass index (BMI) in the first trimester. The study found that the diastolic, as well as systolic measurements taken during the first trimester, were found to be important factors in predicting the occurrence of preeclampsia. There was a substantial association observed between levels of HbA1c in the 1st trimester and the occurrence of preeclampsia (PE). A negative correlation was observed between eGDR and Preeclampsia. In the case of lipids, it was observed that the triglyceride (TG) level exhibited a positive correlation with preeclampsia (PE). Notably, this link remained significant regardless of the levels of glycated haemoglobin (HbA1c). No significant correlation was observed between mother age, body mass index (BMI), waist-to-hip ratio (WHR), preconception care, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) with the occurrence of preeclampsia (PE).

Table-I: Mean and Standard Deviation of Quantitative Variables

	Group A Normal (N=221)	Group B Preeclampsia (N=24)
Gestational age at onset of study, weeks (Mean±SD)	8±2	9±1
Maternal age at onset of study, years (Mean±SD)	29±2	29±2
Preconception care (n [%])	198(89.6%)	23 (95.80%)
Age at the time of diagnosis of diabetes (Mean±SD)	19±3	7±1
Duration of diabetes, years (Mean±SD)	23±4	25±2
BMI at study onset, (kg/m^2 (Median (IQR)	24 (20±29.8)	25 (23.2±27.7)
Waist-to-hip ratio at onset of study (Mean±SD)	0.86±0.09	0.90±0.08
Gestational weight gain, kg (Mean±SD)	10.8±0.5	14±0.6
Primipara/multipara	132/89	24/0
Vasculopathy (cases/group, %)	44/221(20%)	21/24, (87.5%)
Systolic blood pressure at onset of the study, mmHg (Mean±SD)	114±2	132±7
Diastolic blood pressure at onset of the study, mmHg (Mean±SD)	70±1	77±1
Gestational age at delivery, weeks (median [IQR])	37(36±38)	36 (35±37)
Birth weight, g (median [IQR])	3471 (3019±3970)	3970 (3495±4226)
SGA newborns (cases/group,%)	11/208, 5.2%	0/24, 0%
LGA newborns (cases/group,%)	72/208, 34.6%	9/24, 37.5%

Table-II: Tested Laboratory Parameters in the Subgroups of Type-I Diabetic Pregnant Women

	Group A Normal (N=221)	Group B Preeclampsia (N=24)
HbA1c; %	5.9(5.2±6.9)	7.5(6.2±8.6)
mmol/mol	50(40±59)	63(51±74)
eGDR; mg/kg/min	10.5(9.0±11.7)	8.6(6.6±10.6)
Triglycerides; mmol/L	0.68(0.49±0.86)	0.94(0.6±1.2)

Figure: Odds Ratio of Vasculopathy as the Most Significant PE Predictor in Pregnant Women with T1DM

DISCUSSIONS

Our study's objective was to categorise the clinical predictors of PE in first-trimester pregnant

women with T1DM. Every woman in this prospective observational trial was treated at a single diabetes-specific obstetric centre. We demonstrated that a wide range of factors may have a role in the pathophysiology of PE in females with type 1 diabetes; nevertheless, the relative poor predictive value of any factor alone. A study,[7] provided evidence that T1DM was a substantial risk factor for PE in their extensive epidemiological investigation. The findings appear to be supported by our investigation, which found that elevated blood sugar levels were associated with a higher risk of PE.[7]

Diabetes has been demonstrated to cause placental dysfunction, which is comparable to that seen in PE and is characterised by abnormalities in both angiogenic indicators and reduced foetal growth.[8] This is especially true when the diabetes is long-standing and worsened by vascular disease. Longer-term diabetes and mellitus vascular disease were linked to PE in the current investigation. However, when accounting for the existence of vasculopathy, the duration of diabetes was no longer linked to PE. This suggests that women might avoid acquiring PE and its related problems by maintaining optimal glycemic control, which is the primary strategy for preventing diabetic vascular disease.[9]

Remarkably, in our cohort, there was no correlation found between elevated BMI during the first trimester and PE. Previous research has shown this connection.[10] The subjects in our sample who were overweight or obese may account for the absence of correlation between BMI and PE. Persson *et al*. recently showed that the incidence of PE was unaffected by BMI in a population-based cohort research involving diabetic women; however, among women with type 1 diabetes, the odds of PE rose in tandem with parental overweight and obesity.[9] However, among T1DM women, the relationship between maternal weight and PE risk was not very strong. The authors speculate that this could be due to the fact that T1DM is a far more potent risk factor for PE than BMI.

Furthermore, it has been discovered that, in the general population, GWG up to 12 weeks of pregnancy increases the risk of PE during pregnancy, regardless of prepregnancy weight.[11] Although we only examined GWG in the first trimester of our investigation, the outcomes were comparable. This implies that maintaining a healthy weight throughout pregnancy may help reduce the risk of PE in women with type 1 diabetes.[12]

One of the main risk factors for PE is primiparity. Every PE case in our investigation was identified in primiparae. This implies that among women with T1DM, primiparity may also be a risk factor for PE; however, several studies did not find this connection.[13,14]

During pregnancy, optimal glycemic management is essential for healthy foetal development. Consistent with the findings of earlier research, we demonstrated a favourable correlation between HbA1c levels and the development of PE.[15] Attending preconception care had no effect on the incidence of PE in our population, which is consistent with the findings of the Temple *et al*. study.[16] Nonetheless, we discovered a relationship between first trimester HbA1c and PE risk, which is consistent with most research' findings.[17] but not with Temple *et al*.'s findings, which did not reveal this relationship. Given that the pathophysiology of PE is thought to begin early in pregnancy, hyperglycemia during that time can have a deleterious effect on placental shape and function.[18] Therefore, we recommend stringent glycemic management from the start of pregnancy for primary PE prevention in women with T1DM.

It has been demonstrated that women without diabetes and those with gestational diabetes are more susceptible to PE due to elevated IR, another oxidative stress parameter.[19] In early pregnancy, IR was assessed in T1DM women as well. IR and eGDR readings have an inverse relationship. We proved that there was a negative correlation between eGDR and PE. Our study also reveals a fresh finding: there is a positive correlation between TG levels and PE. Previous research has demonstrated a similar link, but it was primarily conducted on non-diabetics.[20] Metabolic syndrome is commonly characterised by elevated IR and hypertriglyceridemia. Therefore, interventional trials are necessary to ascertain if dietary intervention and prepregnancy weight loss can reduce the risk of PE in women with T1DM.

Intrauterine growth limitation has been demonstrated to be predisposed to by PE. It's interesting to note that the PE group contained no babies with SGA. The birth weight distribution of children T1 diabetic mother is pushed to the right of the usual reference, as shown by Pearson *et al*.[9] Some growth-restricted foetuses of diabetic women may be mistakenly "normalised" by maternal hyperglycemia, according to a theory.[20] Given that our subjects with

PE had worse metabolic regulation than controls, this may have happened.

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LIMITATIONS OF STUDY

Similar to previous prospective investigations, few women experienced PE. Furthermore, we excluded information about anti-diabetic medicines use from the analysis. Nevertheless, pregnant women in Rawalpindi, Pakistan, very seldom utilised this prophylactic because there were no guidelines for it in the

CONCLUSIONS

This study found that there is still a high frequency of PE in women with T1DM and that a variety of factors may contribute to its pathophysiology. However, more study is required in this field, particularly to look for practical approaches to PE prevention, like dietary changes and controlling weight before pregnancy to lower insulin resistance in the first trimester of pregnancy. Case of pregestational diabetes.

Conflict of interest: None

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AK & BA: Data acquisition, data analysis, critical review, approval of the final version to be published.

TY SZ: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SFC: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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