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ROLE OF C-PEPTIDE LEVELS AND THE RISK OF DIABETES AND PRE-DIABETES AMONG WOMEN WITH GESTATIONAL DIABETES

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ABSTRACT
Background: Women with a history of gestational diabetes mellitus GDM have a significantly increased risk for developing type 2 diabetes later in life. Connecting peptide (C-peptide), produced in equal amounts to insulin, is known to be a useful marker of beta-cell function and can be used to assess endogenous insulin secretion. **Objective:** To assess the role of C-peptide levels and the risk of diabetes and pre-diabetes among women with a history of gestational diabetes. To verify whether C-peptide can be used as a marker to screen people at a higher risk of diabetes mellitus. **Methods:** A cross sectional study in women with the history of gestational diabetes of 1-5 years after delivery was conducted in Thanjavur Medical College Hospital, Thanjavur from April 2013 to March 2018. All participants' venous blood samples were collected before fasting at least 12 hours and 2 hours after the ingestion of 75g glucose. Fasting plasma C-peptide was measured on an automatic analyser. In addition, HbA1c was also measured. **Results:** 20 out of 76 GDM patients (26.31%) showed increased levels of C-peptide levels. 12 out of these 20 patients developed type 2 diabetes after four years. 2 patients were diagnosed of prediabetes after two years. Obesity and increased BMI were also significant in these patients. **Conclusions:** Fasting plasma glucose during pregnancy and postpartum, and post-partum C-peptide levels are significant risk factors for the development of type 2 diabetes in women with GDM. Elevated C-peptide levels may be a predictor and a screening tool of postpartum diabetes and pre-diabetes among GDM women.

KEYWORDS: Gestational diabetes mellitus, C-peptide, Type 2 diabetes, Pre-diabetes.

INTRODUCTION
Gestational diabetes mellitus (GDM), defined as diabetes diagnosed in second and third trimesters of pregnancy has emerged as a global public health problem.[1] Incidence of gestational diabetes mellitus (GDM) varies globally from 2% to 14%.[2] In India alone, GDM complicates nearly 4 million pregnancies annually, representing large subset of population at high risk for adverse perinatal morbidity and mortality if left inappropriately managed.[2] Beyond perinatal implications, GDM marks beginning of a vicious cycle in which diabetes begets more diabetes, leaving a legacy for both affected mother and her offspring to face impending long-term consequences.[3],[4]

There is an increased risk of developing type 2 diabetes in females who had GDM in previous pregnancy.[5] Interestingly, data also suggest that children of mothers who had diabetes in pregnancy are at higher risk of developing diabetes later in life as compared to their siblings born to the same parents in a non-GDM pregnancy.[6] Indian women have 11 times more risk of developing GDM as compared to women in other parts of the world.[7] The prevalence of GDM in India varies in different regions with a reported prevalence of 3.8% in Kashmir, 9.5% in Western India, 6.2% in Mysore and 22% in Tamil Nadu.[8],[9],[10],[11] Differences in the prevalence rates across India could be attributed to differences in age, body mass index (BMI), socioeconomic status of females and cultural differences as well. Different screening and diagnostic criteria could also be responsible for different prevalence rates.

Connecting peptide (C-peptide), produced in equal amounts to insulin, is known to be a useful marker of beta-cell function and can be used to assess endogenous insulin secretion.[12] In clinical practice, it helps to differentiate between type 1 and type 2 diabetes 2, detect absolute insulin deficiency, and determine diabetes prognosis.[13] Recently, several studies have suggested

that C–peptide is not only an insulin secretion marker but also a biologically active peptide .[14] Very few studies have observed the risk of elevated serum C-peptide on the development of diabetes after delivery among women with GDM.[15] Our study aims to examine the association between plasma C-peptide and the risks of postpartum diabetes and pre-diabetes among women with a history of GDM in and around the delta districts of Tamilnadu, India.

METHODS

A cross sectional study was conducted in women with the history of gestational diabetes of 1-5 years after delivery in Thanjavur Medical College Hospital, Thanjavur from April 2013 to March 2018. Seventy-six women with the diagnosis of GDM in their first pregnancy were recruited for this study. Institutional Ethics Committee approval was obtained. Written informed consent was obtained from each patient in regional language. Women with pre-existing diabetes were excluded from the study.

The diagnosis of GDM was made by an oral glucose tolerance test (OGTT) at 24-28 weeks gestation, by either a fasting venous plasma concentration of ≥5.5 mmol/L glucose and/or ≥8.0 mmol/L glucose 2 h after a 75 g oral glucose load. The women who participated in this study had an OGTT performed at 12 weeks postnatally, and only those women that had a normal glucose tolerance were further evaluated for this study.

All participants completed a self-administered questionnaire at the survey. The questionnaire included the women's history of GDM (fasting and 2-h glucose in the OGTT and the treatment of GDM during the pregnancy), socio-demographics (age, marital status, education , income and occupation), family history (diabetes, hypertension, coronary heart disease, stroke, cancer), dietary habits, physical activity including sedentary activities, frequency and duration of leisure time, other habits such as alcohol intake, smoking habits and passive smoking status. The physical examination mainly included the measurement of height, body weight, and blood pressure. BMI for all participants was calculated by dividing their weight in kilograms by the square of height in meters. All participants' venous blood samples were collected before fasting at least 12 hours and 2 hours after the ingestion of 75g glucose. Fasting plasma C-peptide was measured on an automatic analyser. In addition, HbA1c was also measured. The participants were followed up once in a year for 5 years.

RESULTS

Gestational diabetes was prevalent in 26-30 age group of patients in our study (Figure 1). Family history of diabetes was present in 14 patients (18%). Six patients had hypothyroidism and eleven patients had treatment for hypertension (Table 1).

Twenty out of 76 GDM patients (26.31%) showed increased levels of C-peptide levels. Twelve of these 20 patients developed type 2 diabetes after four years. Two patients were diagnosed of prediabetes after two years. As per American Diabetes Association (ADA)'s criteria, type 2 diabetes was defined as fasting glucose ≥7.0 mmol/L and/or 2-h glucose ≥11.1 mmol/L 24 and pre-diabetes was defined as either impaired fasting glucose (IFG, fasting glucose ≥5.6 mmol/L and <7.0 mmol/L), or IGT (2-h glucose ≥7.8 mmol/L and <11.1 mmol/L).Thirty of these 76 women required insulin during the third trimester of their pregnancy.

A positive associations of plasma C-peptide with the risks of postpartum type 2 diabetes and pre-diabetes was found among women with a history of GDM independent of major diabetes risk factors including BMI. There were statistically significant interactions of age (minimum 19.33±1.15, maximum 33±1.41) and BMI (minimum 21.66±0.77, maximum 30.9±2.23) on the risks of pre-diabetes ($p<0.05$) (Table 2). In this current study HbA1c values were elevated in women with GDM. SPSS software was used for different biochemical parameters and the p value was evaluated by the regression ($p<0.05$). Logistic regression models were performed to assess the association between C-peptide concentrations and the risks of type 2 diabetes and pre-diabetes.

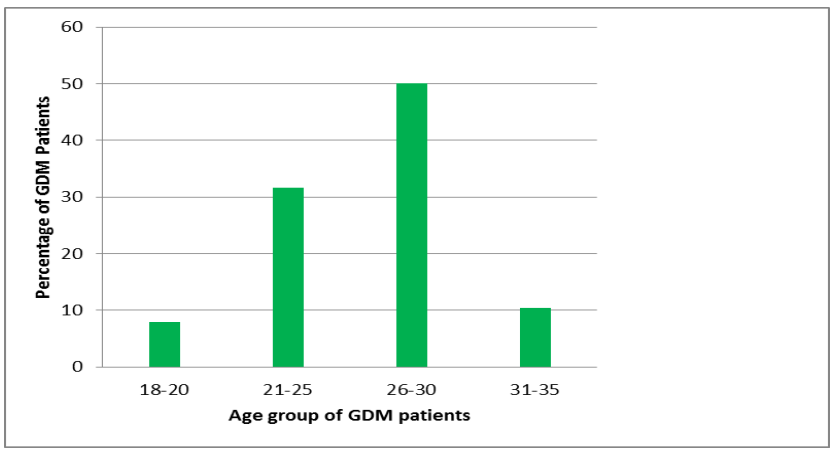

Figure 1: Gestational diabetes with different age groups.

Table 1: Characteristics of GDM Patients.

Patients (N=76)	n(%)
Socio-demographic	
Educational Status	
5th standard	7 (9%)
8th Standard	12 (15%)
SSLC	29 (38%)
HSC	12 (15%)
Diploma	5 (6%)
UG	6 (7%)
PG	5 (6%)
Family Economic	
Labour	27 (35%)
Former	20 (26%)
Driver	16 (21%)
Clerk	7 (9%)
Business	6 (7%)
History of Clinical complications	
Hypertension	11 (14%)
Hypothyroidism	6 (7%)
Family History of Diabetes	14 (18%)
Other chronic conditions	5 (6%)
No previous history	40 (52%)

Table.2: Clinical investigations.

Parameter	Age Group				P Value
	18-20 years	21-25 years	26-30 years	31-35 years	
Age	19.33±1.15	23.33±1.15	28.05±1.35	33±1.41	0.00589*
BMI	21.66±0.77	26.19±5.25	26.43±4.95	30.9±2.23	0.00589*
Clinical Diagnosis					
Fasting Glucose	81±13	79.43±11.55	86±14.82	90±19.04	0.149872
P. Glucose	117±16.37	124.08±21.22	140.21±24.35	128.75±15.52	0.10901
GCT	167.66±4.50	139.5±27.54	129.94±27.00	135.75±53.69	0.43440
Cholesterol	182.66±21.22	192.75±45.45	193.15±38.42	195.75±36.16	0.82248
TGL	207±35.76	242.58±56.46	248.52±101.38	211.5±42.72	0.37723
HDL	36.66±4.16	38.66±8.89	38.94±6.73	39.25±7.13	0.99223
LDL	104.33±24.68	105.41±30.09	109.05±35.35	115±22.77	0.69407
C peptide	0.037±0.03	0.306±0.28	0.265±0.31	0.242±0.23	0.89485
Hba1c	2.25±0.39	2.426±0.56	3.095±1.01	4.187±1.47	0. 95374

DISCUSSION

Women with GDM have a substantially increased risk of developing type 2 diabetes later in life. Given the epidemic increase in the prevalence of type 2 diabetes, the identification or early detection of those at increased risk provides an opportunity for early treatment to prevent onset or progression of the disease. In this study, we show that, in addition pregnant fasting glucose and postpartum fasting glucose, postpartum plasma C-peptide concentrations are significant predictors for subsequent development of type 2 diabetes.

The present study demonstrated that the C-peptide level progressively increased from women with normal glucose through those with pre-diabetes and diabetes. The higher concentrations of C-peptide were associated with an increased risk of pre-diabetes and diabetes. While the clinical role of C-peptide has not been routinely recommended as a measure of risk for type 2 diabetes, C-peptide has been advocated as a tool to screen people at a high risk of diabetes.

CONCLUSION

Our study shows that there is a strong association between raised C- peptide level and the development of type 2 diabetes in women with GDM. Hence continuous monitoring of C-peptide level may be an early diagnostic tool of postpartum diabetes and pre-diabetes among GDM women. Further study with larger sample size and continuous follow up of these patients for another 5 years are needed.

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DECLARATIONS

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Ethical approval: The study was approved by the Institutional Ethics Committee.

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