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Serum Prolactin as an Early Biomarker for Detection of Gestational Diabetes Mellitus-An Experience at CMH Quetta

Azeema Ahmed, Saima Bashir, Hamid lqbal, Naeema Ahmed*, Muhammad Anwar, Javaria Ahsan, Fatima Sana, Khurram Haq Nawaz**

Combined Military Hospital Quetta/National University of Medical Sciences (NUMS) Pakistan, *Army Medical College/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, **Armed Forces Institute of Pathology/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To determine the association between elevated serum prolactin and the development of gestational diabetes mellitus in the first trimester.

Study Design: Prospective longitudinal study.

Place and Duration of Study: Pathology Department, Combined Military Hospital, Quetta Pakistan, from Apr 2021 to Mar 2022.

Methodology: One hundred and twenty-one patients had a measurement of serum prolactin in the first trimester, along with an oral glucose tolerance test in the second and third trimester, at the Pathology Department Combined Military Hospital Quetta Pakistan.

Results: In the study group, serum prolactin levels were raised in 51(42.1%) patients in the first trimester. A total of 44(36.3%) patients with raised serum prolactin had impaired oral glucose tolerance tests. A significant association was found between raised serum prolactin and subsequent development of gestational diabetes mellitus in pregnant females.

Conclusion: Serum prolactin can be an important biomarker for early diagnosis and monitoring of gestational diabetes mellitus.

Keywords: Gestational diabetes mellitus, Oral glucose tolerance test, Serum prolactin.

How to Cite This Article: *Ahmed A, Bashir S, lqbal H, Ahmed N, Anwar M, Ahsan J, Sana F, Nawaz KH. Serum Prolactin as an Early Biomarker for Detection of Gestational Diabetes Mellitus-An Experience at CMH Quetta. Pak Armed Forces Med J 2023; 73(1): 119-122. DOI: https://doi.org/10.51253/pafmj.v73i1.8619*

INTRODUCTION

Gestational diabetes mellitus is a grave medical issue in the developing World, with the reported prevalence of this disease in Asia reported up to 11.5% of the pregnancies.[1] Gestational diabetes mellitus is now considered one of the major causes of fetal and maternal morbidity and mortality in the World.[2]

Mothers with undiagnosed Gestational diabetes mellitus are at a higher risk of developing infections, preeclampsia, undergoing caesarean section, cardiovascular problems and post-partum type-2 diabetes mellitus.[3] Similarly, children born to mothers with untreated Gestational diabetes mellitus are at a higher risk of macrosomia, congenital defects and neonatal hypoglycemia. Early detection of gestational diabetes mellitus helps not only to prevent fetal but also maternal complications.[4,5]

Early detection of Gestational diabetes mellitus is essential to prevent maternal and child diseases. The suspicion of Gestational diabetes mellitus is usually made in the third trimester by a sonologist by estimating fetal size abnormalities.[6] The diagnosis involves an oral glucose tolerance test and glycosylated haemoglobin, which is time-consuming and may require repetitive tests.[7,8] Using chemical biomarkers, particularly maternal hormones like prolactin, progesterone and thyroid stimulating hormone, may lead to early detection of Gestational diabetes mellitus and identification of high-risk cases with the propensity to develop Gestational diabetes mellitus.[9,10] These high-risk cases can then be subsequently monitored regularly throughout the gestational period. First, serum prolactin as an early biomarker can be used as a screening test to detect potential cases of gestational diabetes mellitus and caries weightage because the currently employed oral glucose tolerance test is labour intensive, costly, and results vary with users. Secondly, fetal size abnormalities in sonology are user and machine-dependent with wide inter-user variability. This study was carried out to determine the association between elevated serum prolactin and the development of gestational diabetes mellitus in the first trimester.

METHODOLOGY

The prospective longitudinal study was carried out at the Department of Pathology at Combined Military Hospital, Quetta Pakistan, after approval of the Institutional Review Board (File No: CMH QTA-

Correspondence: Dr Azeema Ahmed, Department of Pathology, Combined Military Hospital, Quetta, Pakistan

Received: 22 Apr 2022; revision received: 24 Jun 2022; accepted: 04 Jul 2022

IRB/043) from April 2021 to March 2022. A sample size was calculated with a Raosoft sample size calculator with an 11.5% prevalence reported by Lee *et al.*[1] The patients were selected by non-probability consecutive sampling technique.

Inclusion Criteria: Pregnant female patients in the first trimester with raised serum prolactin, aged 18 to 45 years, were included in the study.

Exclusion Criteria: Known patients of diabetes mellitus, hypertension, history of fertility drugs usage and thyroid disorders were excluded from the study.

One hundred sixty-five consenting pregnant females (first trimester) were included in the study. Forty-four patients dropped out at various stages, one hundred and twenty-one patients were included in the final analysis.

On the first visit of the patient, the patient had five millilitres of venous blood drawn under aseptic conditions and serum prolactin was measured on COBAS-e 411 Immunoassay analyzer using an electrochemiluminescence methodology using Roche prolactin kit with raised levels taken as >530mili International Units/Liter (mIU/l). The range of serum prolactin was taken as 40-530mIU/l. All Patients were followed up in the second trimester for the development of gestational diabetes mellitus by performing an oral glucose tolerance test. An oral glucose tolerance test was performed according to American diabetes association guidelines, and patients were advised to stay at least 8 to ten hours overnight fast. Five millilitres of venous blood was drawn under aseptic conditions, and plasma glucose was estimated on COBAS-c 501 analyzer using the hexokinase method. After this, 75 grams of glucose was administered orally to the patients, and plasma glucose was re-estimated at one-hour and two-hour intervals. Gestational diabetes mellitus was declared if either of the three plasma glucose levels were above normal, i.e. fasting plasma glucose level >5.1 millimoles/litres, or one hour postprandial >10 millimoles/litres, or two-hour postprandial >8.5millimoles/litres. All samples were run immediately, and all patients with normal oral glucose tolerance tests in the second trimester had oral glucose tolerance tests repeated in the third trimester. All patients with gestational diabetes mellitus confirmed on oral glucose tolerance tests were managed by the medical specialist.

Statistical analysis was carried out on Statistical Package for the social sciences (SPSS) version 23.00. Quantitative variables were summarized as Mean±SD and qualitative variables were summarized as frequency and percentages. The chi-square test was used to test the significance of raised serum prolactin in the first trimester of pregnancy and the subsequent development of gestational diabetes mellitus. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

A total of one hundred and twenty-one pregnant females volunteered for the study with a mean age of 28.3±4.3 years (Range: 19 to 39 years).

Serum prolactin levels were raised in 51(97%) patients, with mean levels of 515.2±24.7(mIU/l) in the study population of 121 patients. Among these 51 (42.1%) patients, 44(36.3%) had deranged oral glucose tolerance. While one patient with a deranged oral glucose tolerance test had normal serum prolactin levels. A significant association was found between raised serum prolactin and subsequent development of gestational diabetes mellitus in pregnant females as shown in Table.

Table: Association of Serum Prolactin with Oral Glucose Tolerance Test (n=121)

Oral Glucose Tolerance Test	Serum Prolactin			*p*-value
	Raised	Normal	Total	
Deranged	44(36.3%)	1(0.8%)	45(37.1%)	<0.05
Normal	7(5.7%)	69(57.2%)	76(62.9%)	

DISCUSSION

In our study, serum prolactin has a statistically significant chance of predicting gestational diabetes mellitus in pregnant females as determined by an oral glucose tolerance test conducted in the second or third trimester.

In a cohort study conducted by Retnakaran *et al.* three hundred and sixty-seven pregnant women underwent Serum Prolactin estimation with confirmation with a follow-up oral glucose tolerance test. They concluded that serum prolactin is an emerging predictor of pancreatic Beta-cell function. Raised serum prolactin within the first trimester indicates the deregulation of pancreatic Beta-cells with an increased risk of developing gestational diabetes mellitus confirmed on the oral glucose tolerance test. Therefore, the authors concluded that serum prolactin is a significant independent predictor of gestational diabetes mellitus in the first trimester of pregnancy.[10] In a nested case-control study, Li *et al.* studied one hundred and seven incident cases of gestational diabetes mellitus and matched them with two hundred and fourteen. They found that an early diagnosis of gestational diabetes mellitus carries a better prognosis for the fetus. Early

diagnosis of gestational diabetes mellitus is possible with monitoring biomarkers like serum prolactin.[11]

Augustine *et al.* concluded that in pregnant females, prolactin-related inhibition of oxytocin neurons dampens oxytocin release. This prolactin-mediated oxytocin homeostasis dis-regulation leads to increased glucose production and the subsequent development of gestational diabetes mellitus.[12] A prospective longitudinal study by Ekcini *et al.* of 154 pregnant females found that serum prolactin was an independent biomarker in pregnant females for deranged glucose tolerance as correlated with the results of the oral glucose tolerance test. The authors concluded that high serum prolactin levels have an adverse metabolic impact that might lead to a pregnancy-induced hyperglycemia state. In addition, raised serum prolactin affects glucose metabolism by hypertrophy of pancreatic B cells.[13] Rassie *et al.* in a meta-analysis of more than 100 articles on gestational diabetes mellitus, found that serum prolactin levels gradually increase as the pregnancy advances. However, higher first-trimester serum prolactin levels indicate increased insulin resistance in pregnant women and a higher chance of developing gestational diabetes mellitus.[14] Kampmann *et al.* in a review study, elaborated on serum prolactin's role as a possible mediator of the change in insulin sensitivity in pregnancy. This change is essential to maintain adequate serum glucose levels in the maternal-fetal compartment. Raised serum glucose levels in the maternal-fetal compartment will increase morbidity and mortality in both mother and fetus.[15]

Auriemma *et al.* found that glucose-insulin metabolism was negatively affected by high circulating serum prolactin levels. This negative feedback caused a decrease in the insulin section from pancreatic Beta cells. This, in turn, increases serum glucose levels.[16] Eschler *et al.* in a cross-sectional study conducted in two centres, non-diabetic and gestational diabetic age, race, body mass index and gestational age-matched patients had serum biomarkers compared. The authors found that although serum prolactin causes up-regulation of pancreatic B-cells and increases serum glucose levels, the difference in serum prolactin of both groups was not significant.[17]

A significant number of untreated gestational diabetes mellitus after delivery progress to type-2 diabetes mellitus with a significant risk of developing other health problems like cardiovascular accidents, hypertension and renal compromise. Therefore, early detection of impaired glucose metabolism in pregnant females may prevent this disease.[18]

ACKNOWLEDGEMENT

The authors would like to acknowledge Mr. Muhammad Shahid for his invaluable services in clinical chemistry.

CONCLUSION

Serum prolactin can be used as an early biomarker for diagnosing and monitoring gestational diabetes mellitus in pregnant females.

Conflict of Interest: None.

Author's Contribution

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

AA & SB: Study design, data interpretation, critical review, approval of the final version to be published.

HI & NA: Conception, study, drafting the manuscript, approval of the final version to be published.

MA & JA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

FS & KHN: Critical review, 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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