DOI: JCDR/2012/3812:1987

Original Article

Biochemistry Section

Exploration of the Clinico-Biochemical Parameters to Explain the Altered Renal Mechanisms in Gestational Diabetes Mellitus

NAGALAKSHMI C.S., DEVAKI R.N., AKILA P., SUMA K.B., PRASHANT V., SUMA M.N., PARVEEN D., SUJATHA P.

ABSTRACT

Context: Gestational diabetes mellitus (GDM) is a common metabolic abnormality which affects ~2-5% of the pregnancies annually. Various risk factors such as advanced maternal age, previous infants with macrosomia, a strong family history of non-insulin dependent diabetes mellitus (NIDDM) or GDM, poor glycaemic control and a high pre-pregnancy body mass index (BMI) have been implicated for the development of GDM.

Aims: To compare the serum creatinine, uric acid and the albumin levels in patients with GDM and in normal pregnant women and to see if there existed any correlation between these biochemical markers and certain clinical parameters in the study groups.

Settings and Design: Hospital based prospective study.

Methods and Material: The study group consisted of 40 patients with gestational diabetes mellitus and 40 normal healthy pregnant women who served as the controls. We evaluated the biochemical and the metabolic alterations in these women by measuring their serum creatinine, uric acid and albumin levels. We also concentrated on the maternal complications and the perinatal outcomes.

Statistical analysis used: The independent samples *t*-test and the Pearson's correlation test.

Results: There was a significant increase in the serum creatinine and the uric acid levels and a significant decrease in the serum albumin levels in the GDM patients. The incidence of GDM in the studied groups was influenced by factors such as maternal age, gravidity, pre-pregnancy BMI and blood pressure. We observed quite a number of complications such as pre-eclampsia, polyhydramnios, hyperbilirubinaemia, RDS, etc. in the GDM women and their foetuses.

Conclusions: The estimation of serum creatinine, uric acid and albumin can help us in predicting the metabolic alterations which occur in the GDM patients and their foetuses. Further, it is quite essential to identify and manage the complications which are associated with GDM and to prevent its recurrence by considering the modifiable risk factors, since such women would in all probability be prone for GDM in their future pregnancies.

Key Words: Gestational diabetes mellitus, Serum creatinine, Uric acid, Albumin, Maternal age, Gravidity, BMI, Blood pressure, Foetal birth weight, Complications

INTRODUCTION

Gestational diabetes mellitus (GDM) affects ~2-5% of all the pregnancies annually [1]. During pregnancy, the glomerular filtration rate (GFR) increases by ~50%, thereby decreasing the serum creatinine and the uric acid levels. However, the creatinine levels towards the upper limit of the normal range is a warning sign of impending renal disease in GDM. The raised uric acid levels in GDM are a component of the metabolic syndrome that reflects insulin resistance [2]. Haemodilution and the diminished liver functions may alter the serum albumin levels in GDM. So, we aimed to see whether the changes in serum creatinine, uric acid and albumin, together with maternal age, body mass index (BMI), blood pressure and foetal birth weight could help in a better understanding of the pathophysiology and the biochemical and metabolic abnormalities in GDM, with special reference to the renal system.

METHODS

After obtaining the institutional ethical clearance and a written consent from all the subjects, pregnant women between the gestational ages of 24-28 weeks, who attended the Department of Obstetrics and Gynaecology at a tertiary care hospital, who had a negative history of a pre-pregnancy diabetic status were subjected to a 50g oral glucose challenge test (OGCT). Those who met the criteria of ≥140mg/dl of venous plasma glucose after 1 hour were then subjected to a 75g oral glucose tolerance test (OGTT) to confirm GDM by using the criteria of Carpenter and Coustan [3]. We enrolled 40 diagnosed cases of GDM and 40 age-matched, normal pregnant women and labeled them as the cases and controls respectively.

Venous blood samples were collected aseptically from both the groups of patients for estimating serum creatinine, uric acid and albumin. The data on the maternal age, the obstetric score, blood pressure, the pre-pregnancy weight, the weight gain in pregnancy, the gestational age at delivery, the foetal birth weight and maternal and foetal complications if any, were also collected. Plasma glucose was estimated by the glucose oxidase method, serum creatinine by Jaffe's method, uric acid by the uricase method and albumin by the bromo-cresol green dye binding method by using a Randox Daytona fully automated clinical chemistry analyzer (Furuno electric Co., Ltd, Japan). The exclusion criteria for the present study included a history of diabetes before pregnancy, essential hypertension, thyroid disorder, multiple pregnancy, renal disease and liver disease.

STATISTICS

The data was expressed as mean ± standard deviation (SD). SPSS for windows (version 16) was used for all the statistical calculations

by applying the independent samples *t*-test and the Pearson's correlation test. A p-value of <0.05 was considered as statistically significant.

RESULTS

The maternal age in the study groups ranged between 18–37 years. The mean maternal age was significantly higher in the cases as compared to the controls, with a p-value of 0.03. Out of 29 subjects who were aged ≥ 25 years, 19 had GDM, while only 10 had a normal pregnancy course i.e., as the age of the subjects increased above 25 years, the ratio of the incidence of GDM to normal pregnancy increased. Our findings, in association with those of other studies indicated that the risk of GDM progressively increased from the age of 25 years onwards. The incidence of GDM was higher in the primigravida as compared to the multigravida women. Significantly higher blood pressure values were recorded in the GDM patients as compared to the controls. Pregnant women with more pre-pregnancy BMI had a higher incidence of GDM than those with normal pre-pregnancy BMI. There was a significant increase in the serum creatinine and the uric acid levels and a significant decrease in the levels of serum albumin in the GDM patients as compared to the controls. The foetuses of the GDM mothers had a higher birth weight as compared to that of the foetuses of the controls [Table/Fig-1].

In addition, the complications which were encountered in the GDM group were: pre-eclampsia (n=8), polyhydramnios (n=7), hyperbilirubinaemia (n=5), respiratory distress syndrome (n=5), shoulder dystocia (n=2), birth injury (n=1), perinatal mortality (n=4), polycythaemia (n=2) and congenital anomalies (n=1). Caesarean section was performed in 24 GDM cases and 4 controls. However, 13 GDM cases and 36 controls delivered through the vaginal route. The rest of the 3 GDM cases delivered still born babies. On performing correlation analysis, we found that the serum creatinine levels correlated significantly and positively with those of serum uric acid, while the serum creatinine and serum uric acid levels correlated significantly but negatively with those of serum albumin [Table/Fig-2].

Parameter	GDM group	Controls	p value
Maternal age (years)	25.52 ± 4.74	23.47 ± 3.47	0.03*
Gravidity	P:32, M:8	P:17, M:23	---
Systolic blood pressure (mm Hg)	142.25 ± 12.23	118.00 ± 10.43	< 0.001**
Diastolic blood pressure (mm Hg)	89.90 ± 9.34	78.70 ± 8.87	< 0.001**
Body Mass Index (kg/m^2)	26.49 ± 2.26	22.65 ± 1.97	< 0.0001***
OGCT (mg/dl)	176.20 ± 28.34	102.22 ± 17.45	< 0.0001***
Serum creatinine (mg/dl)	1.75 ± 0.17	0.76 ± 0.28	< 0.001**
Serum Uric acid (mg/dl)	5.87 ± 0.61	3.13 ± 0.61	< 0.001**
Serum albumin (g/dl)	2.81 ± 0.47	3.82 ± 0.31	< 0.001**
Fetal Birth Weight (Kg)	3.78 ± 0.23	2.43 ± 0.29	< 0.0001***

[Table/Fig-1]: The distribution of clinical and biochemical parameters between GDM and normal pregnant groups

Values given are in mean ± SD; P → primi; M → multi; ***HS – very highly significant (p<0.0001) ; **HS – Highly significant (p<0.001); *S – Significant (p<0.05)

		Uric acid	Albumin
Creatinine	Pearson correlation	0.839	-0.709
	p value	<0.001	<0.001
Uric acid	Pearson correlation		-0.718
	p value		<0.001

[Table/Fig-2]: Correlation between various parameters

DISCUSSION

Like type 2 diabetes and metabolic syndrome, GDM is characterized by insulin resistance, glucose intolerance, hyperlipidaemia, impaired beta cell function and endothelial dysfunction [4]. This study was thus designed to compare the levels of serum creatinine, uric acid and albumin, as they are usually affected by GDM. Perhaps such studies add little to the complex decision making for delivery; however, the chosen biochemical parameters are simple, inexpensive and readily available tests and they should be additionally evaluated.

A maternal age of ≥ 25 years is the factor which is the most predictive for GDM and according to the American Diabetes Association (ADA) recommendations; it should replace the older cut-off value of ≥ 35 years as a risk factor for GDM [5]. Advanced maternal age is a known risk factor for the pregnancy complications including preterm delivery, low birth weight, perinatal death, GDM, gestational hypertension, placenta previa, intra-uterine growth retardation (IUGR) etc. [6].

Gestational hypertension which accompanies GDM is associated with a higher frequency of complications, since it aggravates the course [7]. The rate of pre-eclampsia and even its severity may be influenced by the severity of GDM and pre-pregnancy BMI. Hyperglycaemia associated insulin resistance, together with an activated sympathetic nervous system, changes in lipids and lipoproteins, circulating cytokines and other metabolic processes such as hyperinsulinaemia and hyperuricaemia, can contribute to the pathogenesis of preeclampsia in GDM [8].

Higher pre-pregnancy BMI is a risk factor for developing GDM, since maternal obesity is an independent risk factor for pregnancy induced hypertension, GDM, post-partum haemorrhage, foetal macrosomia, congenital malformations and operative delivery [4]. Thus, maintaining the optimal weight before and during the pregnancy is very much essential. Further, the independent association of BMI with gestational hypertension addresses the topic of the correlation between insulin resistance, obesity and hypertension [7].

Higher creatinine levels or even those towards the upper limit of the normal range can act as a warning sign of the impending renal disease in the GDM pregnancies, since chronic renal disease is often clinically silent until at an advanced stage and as serum creatinine may change only slightly until its clearance falls below 50ml/min [2]. As reported by the current study, Tarim et al., reported that the patients with GDM had higher levels of creatinine, but they reported that this association did not reach statistical significance [9, 10].

The hyperuricaemia in GDM has been explained to be a component of the metabolic syndrome which reflects insulin resistance and it has been shown to have a positive correlation with the creatinine levels. Further, hyperuricaemia has been correlated with obesity, dyslipidaemia and diabetes mellitus [2]. In a univariate analysis, gestational hyperuricaemia was found to be significantly associated with a high rate of maternal and foetal complications, along with proteinuria and hypertension [11]. Hyperinsulinaemia may activate the sympathetic nervous system and both of them may be independently associated with a reduced urinary excretion of

uric acid. Thus, the raised serum uric acid levels may reflect both these mechanisms [12]. There are very few studies which have measured the uric acid levels in GDM women, which have shown higher serum uric acid levels [2].

The protein metabolism is altered to a great extent in GDM and since albumin signifies the synthetic function of the liver, it has been reported to have shown decreased levels in GDM. Micro-albuminuria in GDM may well be a sign of early renal disease and a long-term follow-up of all the GDM patients for the markers of renal disease have been strongly indicated [13]. We found a very significant correlation among all the three biochemical parameters, which was in accordance with the findings of few other studies.

Foetal macrosomia, a well known problem which has been associated with GDM, leads to many complications like respiratory distress syndrome (RDS), shoulder dystocia, birth injuries, etc. and it can be prevented by maintaining a strict glycaemic control [14].

We observed quite a few maternal and neonatal complications in the GDM cases such as pre-eclampsia, polyhydramnios, hyper-bilirubinaemia, RDS, shoulder dystocia, birth injuries, perinatal mortality, polycythaemia, caesarean delivery and congenital anomalies. Many of these were associated with an increased risk of perinatal morbidity and mortality [15]. A likely explanation for polyhydramnios was foetal polyuria which resulted from foetal hyperglycaemia [16]. If polyhydramnios is encountered during an ultrasound evaluation, consideration should be given to the possibility of latent or uncontrolled diabetes mellitus or foetal macrosomia or anomalies. Foetal surveillance and a genetic evaluation should also be considered [17]. Hyperbilirubinaemia in the GDM foetuses may be due to prematurity and polycythaemia with haemolysis. Renal vein thrombosis has also been reported to result from polycythaemia. The foetal lung maturation will be delayed in diabetic pregnancies. The gestational age, rather than overt diabetes, is likely to be the most significant factor which governs the development of RDS [16]. Further, RDS, shoulder dystocia and birth injuries can be explained on the basis of the foetal macrosomia, as has been already mentioned [14].

The limitation of our study could be the relatively small sample size. Further studies with a larger sample size and those which incorporate newer biochemical markers such as cystatin C, urinary NGAL (neutrophil gelatinase-associated lipocalin), etc., can be interesting.

CONCLUSION

Biochemical parameters such as serum creatinine, uric acid and albumin, can help in predicting the early onset and progression of GDM. Further, such an early diagnosis will help the clinicians in the proper treatment of GDM and its attendant complications, both maternal and neonatal, and will thus improve the quality of life of the GDM patients and their offsprings. Further studies with additional biochemical and clinical markers can be interesting.

REFERENCES

[1] Koivunen RM, Juutinen J, Vauhkonen I, Morin-Papunen LC, Ruokonen A, Tapanainen JS. Metabolic and steroidogenic alterations which are related to an increased frequency of polycystic ovaries in women with a history of gestational diabetes. *J Clin Endocrinol Metab* 2001; 86:2591-99.

[2] Güngör ES, Danisman N, Mollamahmutoglu L. Relationship between serum uric acid, creatinine, albumin and gestational diabetes mellitus. *Clin Chem Lab Med* 2006;44:974-77.

[3] Gokcel A, Bagis T, Killicadag EB, Tarim E, Guvener N. Comparison of the criteria for gestational diabetes mellitus by NDDG and Carpenter and Coustan, and the outcomes of pregnancy. *J Endocrinol Invest* 2002;25:357-61.

[4] Innes KE, Byers TE, Marshall JA, Barón A, Orleans M, Hamman RF. Association of a woman's own birth weight with the subsequent risk for gestational diabetes. *JAMA* 2002;287:2534-41.

[5] Lao TT, Ho LF, Chan BC, Leung WC. Maternal age and the prevalence of gestational diabetes mellitus. *Diabetes care* 2006;29:948-49.

[6] Khatun N, Latif SA, Uddin MM. Risk factors for the development of gestational diabetes mellitus. *Mymensingh Med J* 2009;18:S20-23.

[7] Kvetny J, Poulsen HF. Incidence of gestational hypertension in gestational diabetes mellitus. *Arch Gynaecol Obstet* 2003;267:153-57.

[8] Yogev Y, Xenakis EM, Langer O. The association between pre-eclampsia and the severity of gestational diabetes: the impact of glycaemic control. *Am J Obstet Gynaecol* 2004;191:1655-60.

[9] Kale SD, Kulkarni SR, Lubree HG, Meenakumari K, Deshpande VU, Rege SS, et al., Characteristics of the gestational diabetic mothers and their babies in an Indian diabetic clinic. *J Assoc Physicians India*. 2005; 53: 857-63.

[10] Megahed MA, Taher IM. Folate and homocysteine levels in pregnancy. *Br J Biomed Sci*. 2004; 61(2): 84-87.

[11] Brown MA, Buddle ML. Hypertension in pregnancy: maternal and fetal outcomes according to the laboratory and clinical features. *Med J Aust* 1996;165:360-65.

[12] Verdecchia P, Schillaci G, Reboldi G, Santeusanio F, Porcellati C, Brunetti P. The correlation between serum uric acid and the risk of cardiovascular disease in essential hypertension – The PIUMA study. *Hypertension* 2000; 36(6): 1072-78.

[13] Friedman S, Rabinerson D, Bar J, Erman A, Hod M, Kaplan B, et al., Microalbuminuria following gestational diabetes. *Acta Obstet Gynaecol Scand* 1995;74:356-60.

[14] Baxi L, Barad D, Reece EA, Farber R. Use of glycosylated hemoglobin as a screen for macrosomia in gestational diabetes. *Obstet Gynaecol* 1984;64:347-50.

[15] Horvath K, Koch K, Jeitler K, Matyas E, Bender R, Bastian H, et al. Effects of the treatment in women with gestational diabetes mellitus: A systematic review and meta-analysis. *BMJ* 2010;340:c1395

[16] Diabetes. In: Cunningham FG, Lenovo KJ, Bloom SL, Hauth JC, Gilstrap III L, Wenstrom KD, editors. Williams Obstetrics. 22nd edition: McGraw-Hill companies; 2005; 1169-88.

[17] Cheema S, Ahmad A, Tarique N. Polyhydramnios; study of the causes and the fetal outcome. *Professional Med J* 2010; 17(4): 660-64.

AUTHOR(S):

1. Dr. Nagalakshmi C.S.
2. Dr. Devaki R.N.
3. Dr. Akila P.
4. Dr. Suma K.B.
5. Dr. Prashant V.
6. Dr. Suma M.N.
7. Dr. Parveen D.
8. Mrs. Sujatha P.

NAME OF DEPARTMENT(S)/INSTITUTION(S) TO WHICH THE WORK IS ATTRIBUTED:

Department of Biochemistry and Department of Obstetrics and Gynaecology, JSS Medical College and Hospital, JSS University, Mysore-570015, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Nagalakshmi C.S.
PG in Biochemistry, JSS Medical College
S S Nagar, Bannimantap, Mysore – 570015
Karnataka, India.
E-mail: nagu.smile@gmail.com; nagu_kolar@yahoo.co.in

FINANCIAL OR OTHER COMPETING INTERESTS:

None.

Date of Submission: **Dec 12, 2011**
Date of peer review: **Jan 19, 2012**
Date of acceptance: **Feb 09, 2012**
Date of Publishing: **May 01, 2012**