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Original Article

Evaluation of Changes in Maternal Blood Sugar and Renal Function Tests during Gestational Period

Satyam Prakash[1,6], Dipendra Raj Pandeya[2,7] , Jitendra Kumar Singh[3], Khushbu Yadav[4], Basant Kumar Yadav[5]

[1]Department of Biochemistry, Janaki Medical College, Janakpurdham, Nepal
[2]Department of Biochemistry and Genetics, Medical University of the Americas, Nevis, West Indies
[3]Deparment of Community Medicine and Public Health, Janaki Medical College, Janakpurdham, Nepal
[4]Department of Health Science, Mithila Technical Academy, Janakpurdham, Nepal
[5]Department of Surgery, Janaki Medical College, Janakpurdham, Nepal
[6]Department of Biochemistry, Singhania University, Rajasthan, India
[7]Department of Biochemistry, Nepalese Army Institute of Health Sciences, Kathmandu, Nepal

Abstract

Background: The direct effects of altered maternal glucose metabolism and renal impairment from early pregnancy onwards with complications on mother and fetal growth and the risks of adverse birth outcomes. It is crucial to understand the biochemical changes to interpret standard laboratory tests for evaluating renal disease and hyperglycemia in women during pregnancy. Thus, the study was focused on estimating the variability in blood glucose and renal functions and its association with BMI during pregnancy in Southern Terai of Province No. 2, Nepal.

Methods: Fasting blood glucose was determined by enzymatic (GOD/POD) method, Serum Urea by Urease-Bertholet's Method, Serum creatinine by Jaffe's Reaction Method, and Uric acid by Uricase method. All the biochemical parameters were analyzed using a semi-automatic biochemical analyzer (Humalyzer 3500).

Results: The mean with standard deviation for fasting blood glucose (94.01±30.88; 99.71±23.97; 104.77±21.37), urea (23.22±7.89; 18.22±8.98; 20.64±9.09), creatinine (0.68±0.24; 0.65±0.20; 0.58±0.28), uric acid level with (3.14±0.93, 3.74±0.95, 3.95±0.85) was depicted in 1st, 2nd and 3rd trimester of pregnancy. Glucose and BMI were positively correlated and highly significant ($r=0.191$; $p<0.01$). On the other hand, BMI with urea was negatively correlated and was found to be highly significant ($r= -0.196$; $p<0.01$). Also, there was a negative correlation between BMI and Creatinine and was found to be significant ($r=-0.132$; $p<0.01$). However, the association of uric acid was positively correlated and statistically insignificant.

Conclusion: Blood glucose and uric acid gradually start increasing trimester-wise with the advancement of the gestational period. Nevertheless, the mean urea level decreased in the 2nd trimester compared to the 1st and 3rd trimester. Also, a slight variation in creatinine level was found in different trimesters of pregnancy. Glucose, uric acid, and BMI were positively correlated and statistically insignificant, whereas Urea and BMI were negatively correlated and highly significant. Also, there was a negative correlation between BMI and Creatinine and was found to be significant.

Keywords: Blood Sugar; Creatinine; Pregnancy; Province 2; Terai; Urea

Address for correspondence:
Satyam Prakash,
Assistant Professor, Department of Biochemistry,
Janaki Medical College, Tribhuvan University, Nepal
Email: sprakashy2424@gmail.com

Introduction

Continuous glucose monitoring provides a unique approach and understanding to daily glycemic management, glycemic patterns, and glucose variability, influencing pregnancy outcomes [1, 2]. Pregnant women belong to a high-risk population vulnerable to hyperglycemia and its consequences. Hyperglycemia in pregnancy (HIP) is explained as the most common metabolic abnormality in pregnancy confounded by various factors, including increasing population, maternal age, and obesity [3]. The World Health Organization (WHO) has defined HIP as diabetes first detected at any time during pregnancy, along with pre-existing diabetes, and is further sub-classified as diabetes in pregnancy (DIP) and gestational diabetes mellitus (GDM) [4].

The diagnosis of DIP is often clear-cut; there has been controversy around the diagnosis of GDM without universal consensus as to the diagnostic method to diagnose GDM best. GDM is any degree of glucose intolerance with onset or first recognition during pregnancy [5]. The International Association of Diabetes and Pregnancy Study Group (IADPSG) proposed a standardized strategy for the detection and diagnosis of GDM during the first antenatal visit with a fasting glucose level <5.1 mmol/L then following up with a 75-g oral glucose tolerance test (OGTT) at 24 to 28 weeks gestation with diagnostic criteria [4]. There is a documented global rise in the prevalence of type 2 diabetes [6].

GDM is a highly prevalent metabolic disorder in Asian, Latin-American, and Indian women [7] and complicates up to 17% of pregnancies with a significant risk factor for maternal and fetal perinatal complications [8]. The rate of incidence of GDM is constantly increasing in multiethnic populations [9]. Approximately 90% of the diabetes cases in pregnant women are considered GDM [10]. The increase in the prevalence of GDM is related to the growth of risk factors, mainly higher BMI, obesity, and lifestyle [3, 11]. The risk of developing GDM is estimated to be 2, 4, and 8 times greater in overweight, obese, and morbidly obese women, respectively, than in women of healthy weight [12]. Thus, the higher the degree of maternal obesity, the greater the risk of developing GDM, primarily because of insulin resistance [13]. Early diagnosis of GDM in pregnancy, need for insulin treatment during pregnancy, high blood glucose level at diagnosis, preterm delivery, macrosomic babies, and an abnormal oral glucose tolerance test after two months of delivery are the various factors that predict that pregnant women will develop diabetes in future [14].

Shreds of evidence support that GDM is associated with subsequent dyslipidemia, hypertension, vascular dysfunction, and other cardio-metabolic abnormalities [15-18], which are risk factors for renal impairment. Pregnancy imposes significant stress on the kidneys, resulting in an increased risk for maternal and fetal complications in subjects with established moderate-to-serious chronic kidney disease (CKD) [19-21]. Obesity is a leading cause of CKD above and beyond chronic diseases such as hypertension, diabetes, and dyslipidemia [22,23]. Traditionally, altered renal hemodynamics causing glomerular hyperfiltration and activating the renin-angiotensin system in obese patients have been associated with renal impairment [24].

Small studies on pregnancies in women with moderate to severely reduced kidney function (eGFR <60 ml/min per 1.73 m2) have demonstrated a substantially increased risk for adverse pregnancy outcomes [25-27]. Preeclampsia, hypertension (HT), cesarean delivery, and further deterioration of the kidney function are common maternal complications. More than 70% of women who become pregnant with a serum creatinine >2.5 mg/dl will experience preterm delivery, and >40% develop pre-eclampsia [28,29]. The offsprings were frequently born preterm or small for gestational age (SGA) [29]. Overall fetal loss rates were also increased compared to the general population, and stillbirths occurred in 4–8% [21,28].

Renal function can be evaluated by determining urea, creatinine, and uric acid levels in serum/plasma. The effect of renal failure on body fluids includes generalized edema, acidosis, high concentration of protein nitrogen, especially concentrations of urea, creatinine, and other nitrogenous end products of amino acid or protein metabolism; a condition known as uremia, which results from the failure of the kidneys to maintain adequate excretory, regulatory and endocrine functions [30].

The direct effects of impaired maternal glucose metabolism from early pregnancy onwards on fetal growth and the risks of adverse birth outcomes in diabetic and non-diabetic pregnant women [8]. In gestational diabetes, high sugar in the blood can lead to serious health problems, including heart disease and damage to the nerves and kidneys. Estimating renal function before and during pregnancy has clinical importance because kidney dysfunction can affect maternal and perinatal health. Therefore, it is essential to understand these changes to interpret common laboratory to evaluate renal disease and hyperglycemia in women during pregnancy [31,32]. To our knowledge, no studies so far have evaluated the biochemical variation in blood glucose and renal function profile in the Southern Terai region of Nepal. Thus, considering the severe complications for the mother and fetus and the value of predicting blood glucose and kidney function test, the study was focused on estimating the variability in blood glucose and renal functions as well as its association with BMI during pregnancy in Southern Terai of Province No. 2, Nepal.

Materials and methods

This case-control study was conducted in the Department of Biochemistry at Clinical Pathology Laboratory in association with the Department of Obstetrics and Gynecology, Janaki Medical College Teaching Hospital (JMCTH), Ramdaiya, between January 2015 to June 2017. A cluster random sampling technique was adopted. The socio-demographic information, reproductive and health history were obtained through a structured questionnaire by explaining the study's objective. The total sample size was calculated as 336 pregnant women, out of which 224 pregnant women (cases) and 112 non-pregnant healthy women (controls) were selected. A higher number of cases were decided without compromising

the power of study based on available literature and studies [33-35]. A validated pregnancy test report confirmed pregnancy status. Pregnant and non-pregnant healthy women of reproductive age were included, whereas pregnant women with gestational diabetes mellitus, hypertension, obesity, and women with other chronic diseases, drug-induced abnormal liver function test, and women over age 40 were excluded.

The blood samples were collected in a 3.5 ml vacutainer (BD Plymouth, PL6 7BP, UK, SST II Advance Tubes) to prepare serum. For biochemical parameters, fasting blood glucose was determined by the enzymatic (GOD/POD) method. Serum Urea was determined by Urease-Bertholet's Method, Serum creatinine by Jaffe's Reaction Method, Uric acid by Uricase method, respectively. All the biochemical parameters were analyzed using a semi-automatic biochemical analyzer (Humalyzer 3500) manufactured by Human Diagnostics Uganda using readymade dry chemistry kits supplied by Human Diagnostic Worldwide.

Data were entered and analyzed using SPSS for Windows package, version 20. Simple distribution of the study variables and the cross-tabulation were applied. Chi-square (x2) and one-way ANOVA were used to identify the significance of the relations, associations, and interactions among various variables. Range as the minimum and maximum values were calculated. The p-value was less than 5% ($p<0.05$) and was considered statistically significant.

The study was approved by the Research Ethical Review Board of Singhania University, Rajasthan, India. Additionally, an ethical clearance letter was also obtained from the Institutional Review Board of Janaki Medical College Teaching Hospital, Ramdaiya, Nepal.

Results

Out of the total of 336 women, 224 were pregnant, and 112 were non-pregnant. The details about the distribution of age, obstetrics history, BMI, and protein profile of study participants have been previously reported in our study [36].

Table 1: The glucose level of Participants

Para meter	Pregnant Women (Trimesters) (n=224)			Non-Pregnant Controls (n=112)	F
Fasting blood Glucose (mg/dl)	1st	2nd	3rd		
	94.01± 30.88	99.71± 23.97	104.77 ±21.37	76.58 ±14.07	28.72

*p value <0.000

Table 1 shows the glucose level of participants. This finding reflects that the glucose level was elevated in pregnant women than in healthy non-pregnant women. In addition, the difference in glucose level was found to be significant (p=0.000) among pregnant and healthy non-pregnant women.

Renal profile of participants

Table 2 reflects the kidney profile (Urea, Creatinine, Uric Acid) (mg/dl) of the study participants. This finding reveals that the mean urea level was decreased in the 2nd trimester as compared to the 1st and 3rd trimester. However, it also lowers during pregnancy as compared to non-pregnant healthy women. The F-value was 48.18, and the difference was significant (p=0.000). The slight variation in serum creatinine in different trimesters of pregnancy and found to be decreased as compared to non-pregnant healthy women. The F-value was 16.69 (p=0.000), which is statistically significant. Likewise, The mean uric acid level increased in 2nd and 3rd trimesters in pregnant women as compared to 1st as well as to healthy subjects, which were found to be statistically significant with an F-value of 50.15 (p=0.0001).

Table 2: Kidney Function Profile of Participants

Kidney Function Profile	Pregnant Women (Trimesters) (n=224)			Non pregnant Controls (n=112)	F-value
	1st	2nd	3rd		
Urea	23.2±7.9	18.22±9	20.64±9.1	31.62±7.9	48.2*
Creatinine	0.68±0.2	0.65±0.2	0.58±0.3	0.84±0.3	16.7*
Uric acid	3.14±0.9	3.74±1	3.95±0.9	4.93±1.1	50.2*

*p value <0.000

Correlation between BMI and Glucose level

Table 3 highlights that there was a positive correlation between Glucose and BMI. It was found highly significant ($r=0.191$; $p<0.01$).

Table 3: Correlation between BMI and Glucose level (N=336)

Statistical test		BMI	Glucose
BMI	Pearson Correlation	1	-
	Sig. (2-tailed)	-	-
Glucose	Pearson Correlation	.191**	1
	Sig. (2-tailed)	.000	-

(BMI-Body Mass Index)

Correlation between BMI and Renal function profile

Table 4 shows that the relationship between BMI with urea was negatively correlated and was found to be highly significant ($r= -0.196$; $p<0.01$). Also, there was a negative correlation between BMI and Creatinine and was found to be significant ($r= -0.132$; $p<0.01$). However, the relationship between BMI and uric acid was positively correlated and statistically insignificant.

Table 4: Correlation between BMI and Renal function profile

Statistical test		BMI	Urea	Creatinine	Uric Acid
BMI	Pearson Correlation	1	-	-	-
	Sig. (2-tailed)	-	-	-	-
Urea	Pearson Correlation	-.196**	1	-	-
	Sig. (2-tailed)	.000	-	-	-
Creatinine	Pearson Correlation	-.132*	.440**	1	-
	Sig. (2-tailed)	.016	.000	-	-
Uric acid	Pearson Correlation	.004	.238**	.157**	1
	Sig. (2-tailed)	.937	.000	.004	-
**. Correlation is significant at the 0.01 level (2-tailed).					
*. Correlation is significant at the 0.05 level (2-tailed).					

Discussion

Pregnancy involves noteworthy orchestration of physiologic changes [37]. Glucose homeostasis depends on its production by liver and insulin secretion from pancreatic beta cells [38]. The gestational periods in which maternal blood glucose has a more significant influence on the appearance of complications were the second and third quarters, indicating the need for care further enhanced in these vulnerable periods since they are related to the intensive development and fetal growth [39,40]. The present study reveals the mean fasting blood glucose level (mg/dl) among pregnant women in 1st, 2nd, and 3rd trimester was 94.01±30.88, 99.71±23.97, and 104.77±21.37 with a standard deviation of 30.88, 23.97, and 21.37 respectively and in non-pregnant healthy women it was 76.58±14.07 with SD of 14.07. There was a positive correlation between Glucose and BMI. It was found highly significant (r=0.191; p<0.01).

A similar type of study was carried out by Akinloye et al., [41] in 2013 at the Department of Chemical Pathology, Faculty of Basic Medical Sciences, College of Health Sciences, Nigeria found the glucose level in 1st trimester 70.04±0.46, 2nd trimester 73.88±0.86, 3rd trimester 77.04±1.15 and in non-pregnant control as 88.20±2.28. This finding is consistent with the results of the present study. Agbecha and Anwana [42] also demonstrated similar types of results. In another cross-sectional study on a total of 300 women with ages ranging from 18 to 35 years in the Department of Physiology of Mymensingh Medical College, Mymensingh depicted that the serum glucose levels increased in the third trimester significantly, almost parallel to this study [43].

Seabra et al., [44] estimated women who had a cesarean delivery had higher fasting glucose levels in the second (80.4 mg/dL vs. 78 mg/dL, post hoc = 0.034) and third (80.4 mg/dL and 77.1 mg/dL; post hoc = 0.005) trimesters than women who had a normal delivery. Also, higher fasting glucose levels were found in the second semester for women whose infants had macrosomia than for women whose newborns were normal weight (86.2 mg/dL and 78.8 mg/dL; post hoc = 0.003) The random blood glucose levels increased significantly in the third trimester, and the value was low among nulliparous women in the study carried by Bako et al., [45]. The increasing frequency of blood glucose levels in the third trimester may predispose the women to hyperglycemia or gestational diabetes. Random blood glucose level tends to increase during parity and at advanced reproductive age.

However, in contrast to our study Romero and Spinedi [46] demonstrated that blood glucose and insulin levels measured at 2 hours after a 75 g oral glucose use in pregnant women; results showed that people with high blood insulin levels have a higher risk for pre-eclampsia. Also, studies show that women with pre-eclampsia have an increased risk for developing diabetes later in life [47].

The possible reasons may be that glucose tolerance is standard or slightly improved during the first and early second trimesters of pregnancy, and peripheral (muscle) sensitivity to insulin and hepatic basal glucose production is expected [48]. In addition, the increased maternal estrogen and progesterone could cause these in early pregnancy, which increases and promotes pancreatic ß-cell hyperplasia causing an increased insulin release [49]. This explains the rapid increase in insulin level in early pregnancy in response to insulin resistance. However, in the second and third trimester, the steady increase in the fetoplacental factors will decrease maternal insulin sensitivity, and this will stimulate mother cells to use sources of fuels (energy) other than glucose, such as free fatty acids, and this will increase the supply of glucose to the fetus [50].

Although, pregnancy is associated with an increase in beta-cell mass and an increase in insulin level throughout pregnancy. Certain pregnant women cannot up-regulate insulin production relative to the degree of insulin resistance that develops in the second and third trimesters and consequently becomes hyperglycemic, developing gestational diabetes [51]. In pregnancy, the decreased insulin sensitivity is best characterized as a post-receptor defect resulting in the decreased ability of insulin to bring about glucose transporter (GLUT4) mobilization from the interior of the cell to the cell surface [48]. In conclusion, the increasing frequency of blood glucose levels to the borderline in the third trimester of pregnancy may predispose women to hyperglycemia or gestational diabetes and other adverse pregnancy outcomes.

The kidneys are central players in the evolving hormonal

milieu of pregnancy, responding and contributing to the changes in the environment for the pregnant woman and fetus. Urea is the primary waste product of protein breakdown. It is synthesized in the liver from ammonia which is toxic to the body but formed due to deamination of amino acids [52]. The present study reveals the mean urea level with standard deviation in the study participants in their 1st, 2nd, and 3rd trimesters were 23.22±7.89, 18.22±8.98, 20.64±9.09, respectively, and the urea level in healthy subjects was 31.62±7.89. The urea level was found to be decreased gradually in the gestational period. The relationship between BMI with urea was negatively correlated and was found to be highly significant($r= -0.196$; $p<0.01$). A similar study carried by Patriciain, 2013 measured Serum Urea was 3.60±0.72; 3.49 ±0.80; 3.29±0.78 in first, second and third trimesters and in control as 4.11±0.71. Our analytical results agreed with other authors, namely Dunlop et al., Macdonald et al., Korda et al., [53-55].

The decrease in serum urea of pregnant women in all trimesters, even though not significant, might be due to hydration, a rise in glomerular filtration rate (GFR), increased anabolic rate, and demand of the developing fetus on the protein of pregnant mothers. A rise in the GFR was thought to account for the increased excretion of urea. As GFR increases without substantial alteration in urea production due to limited protein intake, the concentration of this molecule decreases in plasma [56]. It is a well-known fact that the level of urea in urine acutely decreases when dietary protein is restricted, which indicates reduced plasma urea. It appears, therefore, that as GFR increases in normal pregnancy, in addition to increased anabolic rate, the serum concentration of urea decreases [56]. The alteration in protein metabolism in late pregnancy suggests that amino acids are conserved for tissue synthesis.

Creatinine is a muscle metabolite excreted by the kidney in the urine. Serum creatinine is probably the most widely used indirect measure of GFR and one way of assessing kidney function [57]. This study reports the mean creatinine levels with standard deviation were 0.68±0.24, 0.65±0.20, and 0.58±0.28 in their 1st, 2nd and 3rd trimesters, respectively, and 0.84±0.30 in healthy controls. Also, there was a negative correlation between BMI and Creatinine and was found to be significant ($r= -0.132$; $p<0.01$). This finding reveals that the mean urea level decreased in the 2nd trimester compared to the 1st and 3rd trimester. This observation is in agreement with the studies by Patricia et al. [58]. The creatinine level was found to be decreased with an augmentation in the gestational period. The significant progressive decrease in serum creatinine levels from the 1st to the 3rd trimester of pregnancy may be due to an increase in glomerular filtration rate during pregnancy. The increase in glomerular filtration rate (GFR) results in an increase in the clearance rate of urea and creatinine but a decrease in urea and creatinine levels in the serum [59,60].

Likewise, our study reports mean uric acid level with standard deviation in healthy non-pregnant women was 4.93±1.07, and these figures in the pregnant women were 3.14±0.93, 3.74±0.95, and 3.95±0.85 in their 1st, 2nd, and 3rd trimester of pregnancy. The association of uric acid was positively correlated and statistically insignificant. Likely, a study carried by Patricia et al., [58] estimated serum Uric acid (µmol/l) were found as 122.0±23; 199.0±32; 360.0±27 in first, second, and third trimesters and in control 308.0 ±26 which was found to be increased and following our study. The considerable increase in serum uric acid level seen in the third trimester of pregnancy may be due to increased tubular reabsorption of uric acid and decreased urate clearance by the proximal convoluted tubules. It was reported that in late pregnancy, tubular renal function decreases, leading to a decrease in glomerular filtration rate, while reported that pre-eclamptic hyperuricemia is a result of decreased urate clearance by the proximal convoluted tubules of the kidney. Hyperuricaemia is an increase in the concentration of plasma uric acid and has been associated with increasing symptoms of pre-eclampsia [61,62].

However, in contrast, a study conducted in an Islamic university in Gaza noted uric acid concentrations were lowered in pregnant women in the 1st, 2nd, and 3rd trimesters than non-pregnant women [63]. Similar results were also obtained by Williams and Davison [64] following the present study. Thus, the significant decrease in serum uric acid level during gestational trimesters may be due to decreased renal tubular threshold, with an increase in cardiac output, renal blood flow, and glomerular filtration rate. This is in agreement with the report that the renal tubular threshold is lowered in pregnancy, which results in increased excretion of uric acid while cardiac output and renal blood flow are increased. These lead to an increased GFR, with the resultant decrease in serum urea, creatinine, and uric acid [65-67].

Conclusion

The study concludes with novel data in Southern Terai region, Province 2, Nepal that with the advancement in gestational age, blood glucose and uric acid level gradually starts increasing. Glucose and BMI were positively correlated and highly significant. However, the mean urea level decreased in the 2nd trimester compared to the 1st and 3rd trimester and was negatively correlated but highly significant. The creatinine level depicted a slight variation in different trimesters of pregnancy and was statistically significant. The association with BMI with uric acid was positively correlated and statistically insignificant. The findings can be helpful to avoid periods of hypoglycemia and hyperglycemia, the most adverse maternal and fetal outcomes, increased rates of spontaneous abortion, congenital malformations, intrauterine fetal death, macrosomia, prematurity, chronic kidney disease, neonatal metabolic and respiratory disorders by monitoring blood

glucose and renal profile during the antenatal check-ups. Therefore, the need for diet therapy and a planned diet for pregnant women becomes very relevant, and periodic screening is recommended for pregnant mothers.

Limitations of study: Due to the small sample size, it cannot be related to the whole population of Province 2, Nepal. Therefore, follow-up researches with a large sample size are recommended in the future in this region of Nepal.

Declarations: None Declared

Conflict of interest: None Declared

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