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Research Article

The Role of Glycemic Biomarkers in the Third Trimester of Pregnancy for Improving Pregnancy Outcomes

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ABSTRACT
Background: Gestational diabetes mellitus (GDM) is a common pregnancy disorder associated with adverse maternal and neonatal outcomes. During the third trimester, increased insulin resistance and rapid fetal growth require accurate glycemic monitoring. However, conventional markers like RBS and HbA1c have limitations, making short-term markers such as fructosamine, albumin-corrected fructosamine (ACF), and fructosamine–albumin ratio (FAR) useful alternatives for predicting outcomes.
Aim: To review the role of glycemic biomarkers in the third trimester of pregnancy and evaluate their usefulness in predicting adverse pregnancy outcomes in women with gestational diabetes mellitus.
Materials and Methods: A narrative review was conducted using published studies retrieved from electronic databases and relevant reference sources regarding glycemic biomarkers in gestational diabetes mellitus. Studies evaluating RBS, HbA1c, fructosamine, serum albumin, albumin-corrected fructosamine, and fructosamine-albumin ratio during the third trimester and their association with maternal and neonatal outcomes were reviewed.
Results: RBS provides only an immediate estimate of glycemia and has limited value in assessing overall glycemic control. HbA1c reflects long-term glycemic status over 8–12 weeks but may underestimate hyperglycemia during late pregnancy due to increased erythrocyte turnover, anemia, and hemodilution. Fructosamine reflects short-term glycemic control over 2–3 weeks but is influenced by serum albumin concentration. ACF and FAR minimize the effect of hypoalbuminemia and demonstrate a stronger association with adverse pregnancy outcomes, including fetal macrosomia, large-for-gestational-age infants, preterm birth, neonatal hypoglycemia, hypertensive disorders, and increased cesarean delivery.
Conclusion: Fructosamine-based biomarkers, especially ACF and FAR, appear to be superior to conventional markers for evaluating glycemic control during the third trimester. Their use may improve the prediction of adverse pregnancy outcomes and optimize the management of gestational diabetes mellitus.

Keywords: Gestational Diabetes Mellitus, Glycemic Biomarkers, Hba1c, Fructosamine, Albumin, Albumin-Corrected Fructosamine, Fructosamine-Albumin Ratio, Pregnancy Outcomes.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance first recognized during pregnancy and remains one of the most common metabolic complications of pregnancy [1]. The global prevalence of GDM is approximately 14.7%, while in India the prevalence ranges from 10–20% [2,3]. Asian and Indian women have a greater susceptibility to GDM because of genetic predisposition, sedentary lifestyle, obesity, and dietary factors [3]. GDM is associated with several adverse maternal and fetal outcomes, including fetal macrosomia, large-for-gestational-age (LGA) infants, hypertensive disorders of pregnancy, preterm birth, neonatal hypoglycemia, and increased rates of cesarean section [4]. Furthermore, women with GDM and their offspring are at greater long-term risk of developing type 2 diabetes mellitus [5]. The third trimester is the most critical period of pregnancy because insulin resistance peaks and fetal growth is at its most rapid [6]. Therefore, accurate assessment of maternal glycemic status during

this period is essential for preventing adverse pregnancy outcomes.

Physiological Basis of Glycemic Alterations in the Third Trimester

During pregnancy, placental hormones such as human placental lactogen, progesterone, cortisol, prolactin, and placental growth hormone progressively increase and induce insulin resistance [6]. These hormones reduce peripheral glucose uptake and increase hepatic glucose production. In addition, hepatic gluconeogenesis and lipolysis are enhanced in late pregnancy, leading to higher maternal glucose concentrations [7]. This metabolic adaptation ensures an adequate supply of nutrients to the fetus. However, when pancreatic β-cell compensation is insufficient, maternal hyperglycemia develops, leading to GDM [8].

Maternal hyperglycemia leads to increased transplacental transfer of glucose, causing fetal hyperglycemia and hyperinsulinemia. Fetal hyperinsulinemia stimulates excessive fetal growth and predisposes to complications such as macrosomia, birth trauma, neonatal hypoglycemia, and respiratory distress [4].

MATERIALS AND METHODS

This narrative review was conducted to evaluate the role of glycemic biomarkers in gestational diabetes mellitus (GDM) and their association with pregnancy outcomes. A comprehensive literature search was performed using electronic databases including PubMed, Google Scholar, and Scopus. Relevant published articles were such as "gestational diabetes mellitus," "glycated hemoglobin," "fructosamine," "albumin-corrected fructosamine," "fructosamine-albumin ratio," and "pregnancy outcomes."

Studies including observational studies, clinical trials, systematic reviews, and meta-analyses focusing on glycemic biomarkers in GDM were included. Articles evaluating the association of these biomarkers with maternal and fetal outcomes were also considered. Studies not available in full text, and those not directly related to glycemic assessment in pregnancy, were excluded. In this review, glycemic biomarkers evaluated during the third trimester of pregnancy included random blood sugar (RBS), glycated hemoglobin (HbA1c), fructosamine, albumin-corrected fructosamine (ACF), and fructosamine–albumin ratio (FAR). These biomarkers were selected based on their clinical relevance in assessing short-term and long-term glycemic control in gestational diabetes mellitus (GDM).

RBS was considered a measure of immediate glycemic status, while HbA1c was included as a standard long-term marker reflecting average glucose levels over the preceding 8–12 weeks. Short-term glycemic markers, including fructosamine, were evaluated due to their ability to reflect glycemic control over a shorter duration (2–3 weeks), which is particularly relevant in late pregnancy.

To address the influence of altered serum albumin levels during pregnancy, especially in the third trimester, corrected indices such as albumin-corrected fructosamine (ACF) and fructosamine–albumin ratio (FAR) were also included. ACF was calculated using the formula:

ACF = (Fructosamine [μmol/L] ÷ Albumin [g/L]) × 30

FAR was calculated as:

FAR = Fructosamine (μmol/L) ÷ Albumin (g/L)

Studies included in this review were analyzed for the methodology used to measure these biomarkers and their association with maternal and neonatal outcomes. Particular emphasis was placed on studies comparing conventional markers (RBS, HbA1c) with short-term markers (fructosamine, ACF, FAR), especially in the context of physiological changes such as altered erythrocyte lifespan and hypoalbuminemia during the third trimester.

Data from selected studies were reviewed and synthesized to summarize the role of different glycemic markers and their clinical relevance in predicting pregnancy outcomes. Emphasis was placed on studies evaluating short-term and long-term glycemic markers and their diagnostic and prognostic significance.

RESULTS

In the present review, multiple glycemic biomarkers, including random blood sugar (RBS), glycated hemoglobin (HbA1c), fructosamine, albumin-corrected fructosamine (ACF), and fructosamine–albumin ratio (FAR), were evaluated for their utility in the third trimester of gestational diabetes mellitus (GDM). Each of these markers reflects different durations of glycemic exposure and has distinct advantages and limitations in late pregnancy.

Biomarkers in the Third Trimester

Random Blood Sugar (RBS): Random blood sugar is a single capillary or venous glucose measurement obtained at any time of the day without regard to meals [9]. It is simple, inexpensive, and useful for detecting acute hyperglycemia or hypoglycemia. However, RBS is highly influenced by recent food intake, emotional stress, physical activity, and the timing of sample collection. Therefore, it provides only immediate information regarding glycemic status and has limited value in assessing overall glycemic control during pregnancy [9].

Glycated Hemoglobin (HbA1c): HbA1c is formed by non-enzymatic glycation of hemoglobin at the N-terminal valine of the β-chain and reflects average blood glucose levels over the preceding 8–12 weeks [10]. Approximately half of the HbA1c value reflects glycemia during the preceding month [10]. In pregnancy, HbA1c may be affected by increased red blood cell turnover, shortened erythrocyte lifespan, iron deficiency anemia, and hemodilution [11,12]. These changes are particularly pronounced in the third trimester and may lead to falsely low HbA1c values despite the presence of hyperglycemia [11]. Moreover, because HbA1c changes slowly, it may not accurately reflect rapid changes in glycemic status occurring during late pregnancy [12].

Fructosamine: Fructosamine measures glycated serum proteins, primarily albumin, formed by non-enzymatic glycation [13]. Since albumin has a half-life of approximately 17–21 days, fructosamine reflects average blood glucose levels over the preceding 2–3 weeks [13]. Fructosamine is particularly useful in the third trimester because it reflects recent glycemic changes more rapidly than HbA1c. In addition, fructosamine is not affected by hemoglobinopathies or altered erythrocyte lifespan. However, fructosamine depends largely on serum protein concentration. Pregnancy is associated with physiological hypoalbuminemia due to plasma volume expansion and hemodilution, which may result in falsely low fructosamine values independent of glycemic status [14].

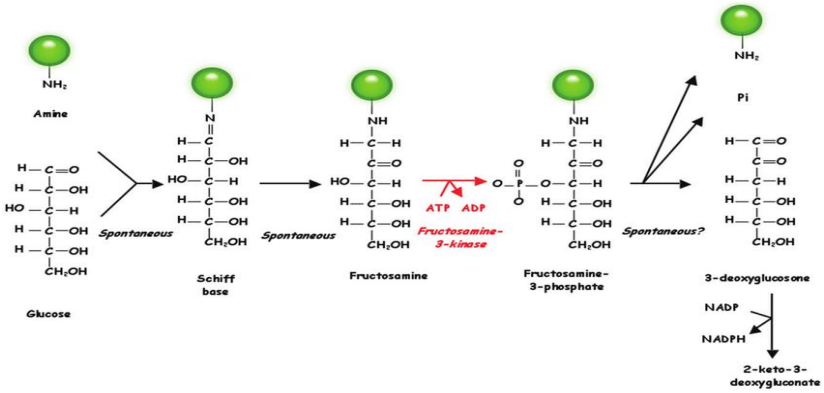

Fig 1: Formation of Fructosamine by Non-Enzymatic Glycation of Serum Proteins

Serum Albumin: Albumin is the major serum protein and contributes approximately 60–70% of total glycated serum proteins [14]. During the third trimester, serum albumin concentration decreases because of plasma volume expansion and dilutional hypoalbuminemia. Therefore, serum albumin plays an important role in the interpretation of fructosamine values [15].

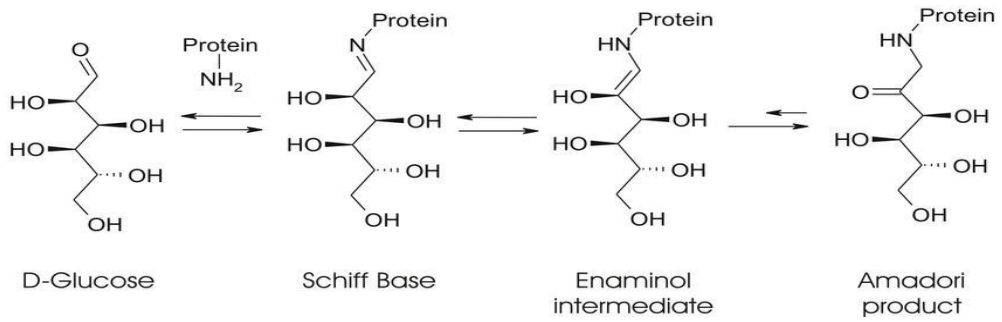

Fig 2: Formation of Glycated Albumin (Fructosamine) Through Non-Enzymatic Glycation (Maillard Reaction)

Albumin-Corrected Fructosamine (ACF): To overcome the influence of altered albumin levels, albumin-corrected fructosamine has been proposed. ACF is calculated as: ACF = (Fructosamine [µmol/L] ÷ Albumin [g/L]) × 30**.** The constant value 30 represents the average serum albumin concentration used for standardization [15].

ACF provides a more accurate estimate of short-term glycemic control during pregnancy. Studies have demonstrated that ACF correlates better with mean blood glucose than uncorrected fructosamine and HbA1c [15, 16].

Fructosamine-Albumin Ratio (FAR): The fructosamine-albumin ratio is another corrected biomarker that reduces the confounding effect of low albumin levels. FAR is calculated as: FAR = Fructosamine (µmol/L) ÷ Albumin (g/L)**.**

FAR provides a more reliable estimate of protein glycation relative to albumin concentration and appears to be a better predictor of adverse pregnancy outcomes than fructosamine alone [17]. Studies suggest that FAR demonstrates a stronger association with poor glycemic control, fetal macrosomia, neonatal hypoglycemia, and cesarean delivery [18]

Table 1: Summary of Key Studies on Glycemic Biomarkers in GDM

Author	Population	Biomarker	Key Findings	Conclusion
Bhavadharini et al.	Indian pregnant women	OGTT	Improved detection of GDM	Supports universal screening
Parrinello et al.	Diabetic patients	ACF	Better correlation with glucose	Improved accuracy
Selvin et al.	General population	Glycemic markers	Better prediction than HbA1c	Useful alternative
Chen et al.	Diabetic patients	FAR	Strong correlation with outcomes	Better diagnostic marker
Roberts et al.	GDM patients	Fructosamine	Reduced macrosomia risk	Predictive marker
Mendes et al.	Pregnant women	Fructosamine	Higher AUC vs HbA1c	Better predictor
Goyal et al.	Diabetic patients	HbA1c & Fructosamine	Strong correlation	Alternative marker
Toyoshima et al.	Diabetic subjects	Fructosamine	Reflects rapid changes	Short-term marker
Patel et al.	Diabetic patients	Fructosamine	Strong correlation	Monitoring tool
Mahmoud et al.	β-thalassemia	Fructosamine	Higher sensitivity	Useful in special conditions

Table 2 summarizes the comparative characteristics of glycemic biomarkers used in the third trimester, emphasizing their clinical utility, strengths, and limitations in assessing glycemic control during pregnancy.

Table 2: Comparative Evaluation of Biomarkers in Third Trimester

Biomarker	Time Frame	Advantages	Limitations	Clinical utility

RBS (mg/dL)	Immediate	Simple, rapid, easily available	High variability; influenced by meals and stress	Acute glycemic assessment
HbA1c (%)	8-12 weeks	Reflects long-term glycemic control; standardized	Affected by altered RBC lifespan, hemodilution, and anemia	Long-term glycemic monitoring
Fructosamine (µmol/L)	2-3 weeks	Reflects short-term glycemic control; not affected by Hb variants	Dependent on serum albumin levels	Monitoring recent glycemic changes
Albumin (g/dL or g/L)	2-3 weeks	Major serum protein; essential for interpretation and correction of fructosamine; reflects nutritional and physiological status	Decreased in pregnancy due to hemodilution; influenced by liver and renal conditions	Supportive marker for ACF and FAR; improves the accuracy of glycemic assessment
Albumin-corrected fructosamine (µmol/gm)	2-3 weeks	Corrected for albumin variation; improved accuracy in pregnancy	Limited availability; lack of standard reference ranges	Reliable short-term assessment in pregnancy
Fructosamine-albumin ratio (µmol/gm)	2-3 weeks	High precision; minimizes albumin effect; better correlation with outcomes	Limited validation and clinical standardization	Emerging biomarker for predicting adverse outcomes

Association of Glycemic Biomarkers with Pregnancy Outcomes:

Fetal Macrosomia and Large-for-Gestational-Age Infants: Maternal hyperglycemia is the major determinant of fetal overgrowth. Elevated HbA1c values have been associated with increased risk of macrosomia and LGA infants [19]. A meta-analysis reported that women with HbA1c ≥5.5% had approximately 1.7 times greater risk of delivering an LGA infant [20].

Short-term biomarkers such as fructosamine, ACF, and FAR may predict fetal overgrowth more accurately because they reflect glycemic control during the period of rapid fetal weight gain. Fructosamine values below 2.5 mmol/L have been associated with reduced incidence of macrosomia [21].

Hypertensive Disorders of Pregnancy: Maternal hyperglycemia contributes to oxidative stress, endothelial dysfunction, and vascular abnormalities, thereby increasing the risk of preeclampsia and pregnancy-induced hypertension [22]. Elevated HbA1c and fructosamine-based biomarkers have been associated with increased risk of these disorders [22].

Preterm Birth: Poor glycemic control during the third trimester is associated with increased risk of preterm delivery. HbA1c values ≥6.5% have been shown to significantly increase the risk of preterm birth [23]. Similarly, increased fructosamine and ACF levels indicate poor glycemic control and may predict greater risk of preterm delivery.

Neonatal Hypoglycemia: Maternal hyperglycemia causes fetal hyperinsulinemia, which persists after birth and predisposes the neonate to hypoglycemia [24]. Lower maternal fructosamine and ACF levels have been associated with reduced fetal insulin secretion and lower risk of neonatal hypoglycemia [21].

Cesarean Delivery: Women with poorly controlled GDM have an increased risk of cesarean section due to fetal macrosomia, cephalopelvic disproportion, and fetal distress

[22]. Elevated HbA1c, fructosamine, ACF, and FAR have all been associated with increased rates of operative delivery.

DISCUSSION

The third trimester is the most critical period for monitoring glycemic status because insulin resistance peaks and fetal growth accelerates rapidly. Although HbA1c is widely accepted for long-term glycemic monitoring, its utility during pregnancy is limited by physiological changes, including increased erythrocyte turnover, hemodilution, and anemia [11,12]. Fructosamine offers an important advantage because it reflects glycemic status over the preceding 1–3 weeks and therefore captures recent changes more accurately than HbA1c [13]. However, interpretation of fructosamine may be misleading in pregnancy because of physiological hypoalbuminemia [14]. Corrected biomarkers such as ACF and FAR overcome this limitation and provide a more accurate assessment of glycemic control during late pregnancy [15,17]. Several studies have demonstrated that these biomarkers correlate more strongly with adverse pregnancy outcomes than HbA1c or fructosamine alone [16-18]. Among all biomarkers, ACF and FAR appear to be superior predictors of fetal macrosomia, neonatal hypoglycemia, and operative delivery. Their use may therefore facilitate early identification of women at high risk and permit timely intervention. However, despite their potential, the clinical use of ACF and FAR remains limited because standardized pregnancy-specific reference intervals are lacking, and only a few studies have evaluated these biomarkers in large populations.

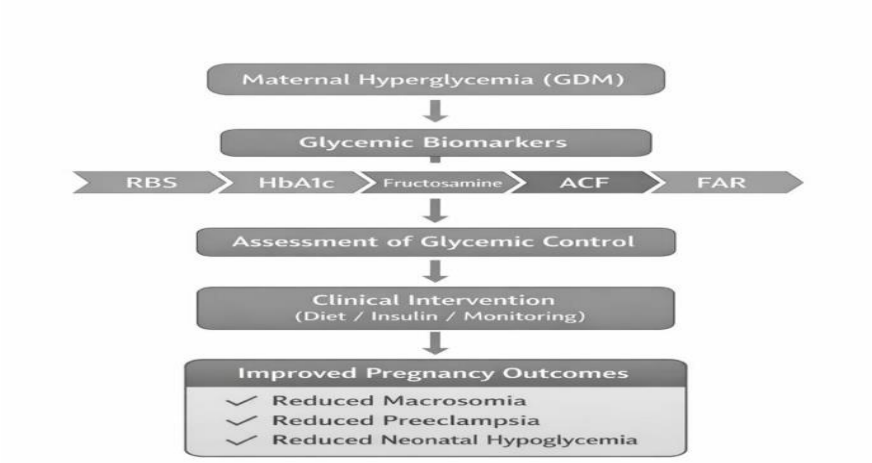

Fig 3: Schematic Representation of the Role of Glycemic Biomarkers in the Third Trimester for Improving Pregnancy Outcomes.

Limitations of the Review

Most studies evaluating albumin-corrected fructosamine and fructosamine-albumin ratio have relatively small sample sizes and heterogeneous methodologies. There is a lack of standardized reference ranges for these biomarkers during pregnancy, particularly in the Indian population. In addition, only limited studies have directly compared these biomarkers throughout the third trimester.

CONCLUSION

Conventional biomarkers such as RBS and HbA1c have limited utility in the third trimester because they either reflect only immediate glycemia or are influenced by physiological changes of pregnancy. Fructosamine-based biomarkers, particularly ACF and FAR, provide a more accurate estimate of short-term glycemic control and show a stronger association with adverse pregnancy outcomes. Therefore, incorporation of ACF and FAR into routine antenatal monitoring may improve the prediction of adverse maternal

and neonatal outcomes and enhance management of gestational diabetes mellitus.

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