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Glycated Albumin as a Novel Biomarker for Diabetes in Pregnancy: Current Status and Future Prospect

***Abstract*—**Glycemic biomarkers are important for diagnosis, monitoring, treatment, and prognostication of diabetes complications. In this rapid review, we focus on the strengths and limitation of selected glycemic biomarkers for monitoring purposes in pregnancy: Hemoglobin A1C, fructosamine, and glycated albumin (GA). We elaborated on the characteristics of each marker, the similarities, and differences. We summarize the review with important evidence on the utility and future prospect of GA beyond glycemic monitoring. In summary, GA is a good tool to address the inherent limitation of A1C as a glycemic biomarker. The elucidation provided in this review is poised to enhance the pragmatic and clinical applicability of various glycemic biomarkers in different settings in routine clinical practice.

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1 INTRODUCTION

Pregnancy is associated with glycemic aberration resulting from a series of physiological changes occurring to accommodate a growing fetus. A pregnant mother may have pre-existing diabetes before she conceives or may have developed diabetes during the pregnancy itself – known as gestational diabetes mellitus (GDM). Poor glycemic control during pregnancy poses a significant health challenge that potentially affect both maternal and fetal outcomes, including an increase in the rate of congenital malformations, especially cardiac, neurological system, musculoskeletal and limbs formation (1). Hence, accurate screening, diagnosis, and prediction of pregnancy outcomes in women with diabetes are crucial to optimize maternal and fetal health (2).

Abnormal glucose tolerance may develop in pregnant women when the compensatory effect is insufficient to accommodate the hormonal changes associated with pregnancy. During the early stage of pregnancy, once the placenta begins to replace the role of the corpus luteum, an increased in the secretion of progesterone (by 10-fold) and 17β-estrogen (by 30-fold) from the corpus luteum has been observed – such high concentrations are known to result in decreased insulin sensitivity (3). In addition, the secretion of placental lactogen and prolactin begins to increase gradually from week 12 of pregnancy (3). Placental lactogen is one of the hormones implicated for altering insulin sensitivity during pregnancy. Likewise, tumor necrosis factor-α secreted from macrophages into adipocytes and villous cells. These lead to a substantial change in glucose metabolism in pregnancy with a decreased in systemic insulin sensitivity by about 50-60% by the late stage of pregnancy (3).

Ideally, a glycemic biomarker should be both accurate and reliable for diagnosis and monitoring in pregnancy, and not affected by diverse systemic changes associated with pregnancy. Conventional method of diabetes screening in pregnancy with oral glucose tolerance test (OGTT) has its limitations. This includes the inconvenience of multiple blood sampling and the need to tolerate a high concentration of glucose load, the variability in the results, and potential misclassification (4). OGTT includes testing of fasting plasma glucose (FPG) and a 2-hour postprandial glucose test following a 75-gram glucose load. Despite being the gold standard to diagnose diabetes during pregnancy, OGTT may not capture the complete

glucose profile throughout the day, potentially missing fluctuations and inconstancy, and distant postprandial glucose abnormalities (4). Furthermore, pregnant women with gastrointestinal disorders or other conditions that limit their ability to undergo OGTT may benefit from an alternative glycemic biomarker.

Hemoglobin A1C (HbA1c) is a universally recognized biomarker used for routine monitoring purposes for glycemic status. It is used as an index of average blood glucose measurement over a period of 2-3 months and is the mainstay of general blood glucose monitoring in the clinical setting (5). This metric is easy to measure, convenient, and is relatively inexpensive, with multiple studies showing its predictive value for diabetes-related microvascular complications. However, HbA1c provides only an approximate measure of glucose control as it does not address short-term glycemic variability or history of hypoglycemic events. In pregnancy, HbA1c is not a suitable glycemic marker as the value may be underestimated due to the physiological pregnancy changes (i.e., presence of dilutional anemia due to increasing circulating blood volume and iron deficiency). Furthermore, studies have shown that the HbA1c threshold of diabetes as per current recommendation is probably too high to detect women with overt diabetes in their early pregnancy (6–8).

In the early 21st century, glycated albumin (GA) has been introduced as a novel biomarker and has been proposed as a potential add-on alternative to HbA1c due to its ability to reflect average glycemic control over a shorter time frame (2-3 weeks) as compared to HbA1c (2-3 months) (9). GA represents the percentage of glycated albumin in the total albumin pool and may provide a more accurate and specific reflection of recent glycemic status (9,10). GA can be measured accurately either on serum or plasma collected in tubes containing lithium heparin or ethylenediamine tetra acetic acid (EDTA) via the optimized method of new enzymatic assay that has increased the diffusion of this test. Unlike OGTT which requires multiple pricking and a prolonged testing period, GA can be measured through a single blood test. This simplicity and convenience make it more feasible for routine clinical practice, enhancing patients' compliance and reducing the burden associated with routine diagnostic process. GA may also have the potential to detect glucose abnormalities at a much earlier stage as compared to traditional markers (11,12). This will allow early detection and timely interventions with lifestyle modifications or early treatment initiation to improve both maternal and fetal outcomes (13).

Therefore, this rapid review aims to evaluate the clinical utility of GA as a biomarker for screening and monitoring glycemic status in pregnancy, comparing its characteristics and features with other conventional glycemic biomarkers, and projecting its clinical applicability beyond glycemic monitoring.

The databases used to identify the studies were Google Scholar and Medline, which includes all articles published in the year 2010 onwards to date. The search terms or keywords used were: "glycated albumin" OR "h*moglobin A1c" OR fructosamine AND "diabetes in pregnancy" OR "gestational diabetes mellitus".

2 DIABETES IN PREGNANCY: THE IMPORTANCE OF GLYCEMIC CONTROL

Recent evidence has suggested that even mild abnormal glucose tolerance increases the incidence of perinatal maternal-infant complications. This has prompted a stricter revision to the diagnostic criteria of gestational diabetes mellitus (GDM) to reduce the incidence of perinatal maternal-infant complications (14) where the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) consensus affirms that only one elevated glucose level for the OGTT is required for GDM diagnosis (Fasting ≥ 5.1 mmol/L, 1-hour ≥ 10.0 mmol/L, 2-hour ≥ 8.5 mmol/L), while the UK National Institute for Health and Care Excellence (NICE) guidelines advise a more selective screening approach, whereby women with risk factors for GDM are recommended to undergo a diagnostic OGTT at 26 to 28 weeks' gestation with a positive test indicated by the presence of one abnormal value (Fasting ≥ 7.0 mmol/L, or 2-hour ≥ 7.8 mmol/L) (15).

Maternal complications of poor glycemic control in pregnancy include pregnancy-induced hypertension syndrome, polyhydramnios, shoulder dystocia, and caesarean section. In pregnant women with pre-existing diabetes, careful attention should also be paid to the development of diabetic ketoacidosis during pregnancy, worsening of diabetic retinopathy and

diabetic nephropathy, and hypoglycemic events. For pregnancy-induced hypertension syndrome, 2% to 8% of all pregnant women are further complicated with preeclampsia, which worsens perinatal outcomes (14). The late-onset form, which accounts for 80% of all cases of pregnancy-induced hypertension syndrome, is of maternal origin and is often accompanied by old age, obesity, diabetes mellitus, and chronic hypertension (14). Next, it has been reported that 0.5% to 0.7% of normal pregnant women and 2.0% to 2.1% of patients with GDM are complicated with polyhydramnios (14). Polyhydramnios induces complications leading to premature labor, premature rupture of membranes, fetal malpresentation, umbilical cord prolapses, premature separation of placenta, and atonic postpartum hemorrhage. Shoulder dystocia is a mechanical problem occurring during a vaginal delivery characterized by failure to deliver the fetal shoulders using solely gentle downward traction and the requirement of additional delivery maneuvers and is one of the complications related to macrosomia (8,12,14). However, it has been reported that pregnant women with abnormal glucose tolerance and poor glycemic control tend to experience shoulder dystocia regardless of fetal macrosomia status (12). For these reasons and because of the fetal complications that will be mentioned in the following sequence, the percentage of caesarean section is notably higher in pregnant women with poor glycemic control; 10.7%-18.9% in normal pregnant women, compared with 19.3% to 30.9% in pregnant women with GDM and 45.2% in pregnant women with diabetes mellitus (14). Patients with GDM were also observed to carry a 7.43 times higher risk of developing type 2 diabetes mellitus after delivery than women with normal glucose tolerance during pregnancy (14).

Congenital anomaly is one of the fetal complications of poor glycemic control in pregnancy. According to a report in Japan, the incidence of congenital anomaly is as high as 24.1% when the HbA1c is 8.4% and above (16). Macrosomia is a fetal developmental anomaly unique to pregnancy in women with diabetes mellitus. The hyperglycemia-hyperinsulinemia hypothesis as proposed by Pedersen suggests that maternal hyperglycemia induces fetal hyperglycemia that results in the fetal pancreatic β-cells hyperplasia and hypersecretion of insulin, leading to excessive growth of the fetuses (14). It has also been reported that serotonin that is present downstream of the prolactin signal promotes pancreatic β-cell growth and contributes to an increase in the cell volume (17). Infants of diabetic mothers are also at risk of hypoglycemia, polycythemia, hyperbilirubinemia (related to polycythemia), neonatal respiratory distress syndrome, hypocalcemia, and myocardial hypertrophy (14).

Apart from the perinatal complications described above, a recent review also showed a possible tendency of hyperglycemia by itself to impair the protective antibacterial function of the neutrophils, while insulin was shown to restore the inflammatory response (18).

3 GLYCEMIC BIOMARKERS IN PREGNANCY: PAVING WAY FOR GLYCATED ALBUMIN

Efficient diagnostic modality and accurate glycemic monitoring of diabetic patients are cornerstones to reduce the risk of myriad of diabetic complications. Generally, the conventional diagnostic, monitoring, and prognostic strategies in the management of diabetes are mainly plasma based (or capillary) glucose and glycated hemoglobin (HbA1c) monitoring. Nevertheless, these measures may be biased by several clinical, pre-analytical and analytical factors.

HbA1c has limited use in pregnancy as the physiological changes during pregnancy renders underestimation of HbA1c due to the dilutional anemia effect from the increased blood volume. HbA1c also exhibits biphasic changes, decreasing between the first and second trimester and increasing in the third due to the decreased in systemic glucose concentration in the first trimester, which is followed by a relative iron deficiency (19). Therefore, the introduction of other indices of glycemic homeostasis in clinical practice such as the fructosamine and GA are regarded as an attractive alternative, especially in patients in whom the measurement of HbA1c may be inaccurate or unreliable (such as in pregnancy, patients with rapid and larger glycemic excursions, and presence of hemoglobinopathies) (20).

Fructosamine (1-amino-1-deoxy fructose) is a stable ketoamine that is formed by the reaction between glucose and the amino group of protein

(predominantly albumin, but also includes globulins and lipoprotein) (21). A study among 849 pregnant women concluded that serum fructosamine is a poor test to screen for GDM as a fasting serum fructosamine (cFruc) threshold of 237 µmol/l achieved only acceptable sensitivity of 85.8% (95% CI 78.0–91.0%) with a poor specificity at 23.4% (95% CI 20.0–27.0%) and a positive predictive value of just 14.7% (22). Furthermore, fructosamine levels are not generally corrected for albumin or total protein concentration. Thus, physiological or pathologic conditions linked to hypoproteinemia (i.e., pregnancy or malnutrition) are likely to result in biased fructosamine measurement (19). Serum fructosamine levels were found to correlate with maternal and gestational age, hence specific reference range needs to be established throughout pregnancy to improve its diagnostic accuracy and efficiency.

GA on the other hand, reflects the systemic glucose level, and unlike HbA1c, is not influenced by iron deficiency of pregnancy. Its newly improvised enzymatic assay is not only rapid and sensitive but is adaptable on any routine clinical chemistry analyzers. GA allows evaluation of the glycemic status over a period of approximately three weeks and is a promising biomarker in pregnancy.

Table 1 delineates the characteristic features of selected glycemic biomarkers in pregnancy.

Despite HbA1c being the gold standard indicator of glycemic control in patients with diabetes mellitus in general, it does not accurately reflect glycemic control during pregnancy due to the presence of dilutional anemia and iron deficiency.

Both fructosamine and GA levels increase in states of high glucose concentrations such as diabetes, and hence, can be used for monitoring glycemic control over an intermediate time frame. With respect to hemoglobin whose life span in erythrocytes spans over approximately 90-120 days, non-immunoglobulin serum proteins have a lower half-life of approximately 14-21 days. Therefore, HbA1c provides a longer overview of glycemic control of 2-3 months, while the measurement of fructosamine or GA provides information on glycemic control limited to the recent 2-4 weeks. The rate of nonenzymatic glycation of albumin is approximately 9- to 10-fold higher than hemoglobin, enabling precise determination of glycemic excursions, if present (19,23).

Serum fructosamine is inversely associated with markers of glucose homeostasis and inflammation, partially influenced by albumin concentrations. The gradual decrease in circulating fructosamine and increase in the concentration of albumin-corrected fructosamine are in tandem with physiological decrease in albumin (due to dilutional effect) and inflammation settling observed during pregnancy (24). The intermediate picture of glycemic pattern observed with fructosamine that is coupled with HbA1c measurement may give a dynamic advantage to improve the predictive value of glucose intolerance, though second trimester fructosamine has been found to be a poor predictor of gestational glucose tolerance due to trimester-specific changes with fructosamine levels (25,26).

Based on the aforementioned evidence, the general efficiency of GA as a diagnostic modality surpasses that of fructosamine across various clinical scenarios. The present technique for GA measurement is also more consistently standardized and is less susceptible to pre-analytical factors as compared to the methods employed for fructosamine measurement. Furthermore, GA offers added benefits compared to HbA1c, including reduced reagent expenses and the potential to automate GA analysis using standard laboratory equipment (19).

Despite so, some physiological or pathological conditions that affect protein metabolism can potentially influence the measurements of both fructosamine and GA, such that observed in protein-losing states: nephrotic syndrome, diminished protein production in severe hepatic cirrhosis, and overt thyroid disease. However, GA levels can be presented as a ratio (i.e., percentage) of total albumin, while fructosamine levels are not generally corrected for albumin or total protein concentration. Another disadvantage of fructosamine is that its concentration is significantly affected by the levels of immunoglobulins), especially IgA, which may be present in suprathreshold concentration in a broad range of clinical conditions. Despite fructosamine and GA were found to be highly correlated, given the higher specificity and accuracy, GA testing in the clinical setting is currently preferred over fructosamine (19).

Table 1: Characteristics of selected glycaemic biomarkers in pregnancy

	Hemoglobin A1c	Fructosamine	Glycated albumin
Type	Stable adduct of glucose to the N-terminal valine of the β-chain of hemoglobin	Glycated serum protein of 1-amino-1-deoxy-D-fructose group (including glycated lipoproteins and globulins)	Albumin-containing lysine residues bound to glucose
No. of glycation site	One	Multiple	Multiple
Glycation speed	1:1	Relatively similar to GA	1:4.5 (1% increase of A1c corresponded to 2.84% increase of GA[12])
Localization	Erythrocytes	Systemic	Systemic
Laboratory methods	• Immunoassay • Ion-exchange high-performance liquid chromatography • Boronate affinity HPLC • Enzymatic assays	• Colorimetric-based assays	• Automated enzymatic assay • Boronate affinity chromatography • Ion exchange chromatography • High performance liquid chromatography • Immunoassays (i.e., enzyme-linked immunosorbent assays or radioimmunoassays) • Raman spectroscopy • Refractive index measurements • Capillary electrophoresis
Methods limitation/strengths	• The presence of hemoglobin variants (i.e., HbC, HbF >30.6%, HbE, HbD, etc.) may interfere with results.	• Samples require no pretreatment. • Assay is less expensive than HbA1c. • Method is affected by changes in ambient temperature and remains poorly standardized. • Molecules with reducing activity (such as bilirubin and vitamins) may interfere in the measurement.	• Enzymatic assay is better standardized and more precise, is not influenced by the concentration of molecules with reducing activity.
Monitoring timeline	3 months	2-3 weeks	2-3 weeks
Test limitations	• Dependent on glucose level in erythrocytes and lifespan of erythrocytes	• Depends on concentration, half-life, and number of glycation sites in each serum protein (i.e., albumin, glycated lipoproteins, and glycated globulins) • Poor reproducibility	• Depends on half-life of albumin (hence, reading is inaccurate for severe liver disease, acute or chronic kidney disease, overt clinical hypo/hyperthyroidism)

Apart from the biomarkers discussed, the 1,5-anhydroglucitol (1,5AG) has also been gaining popularity as a potential glycemic biomarker in pregnancy. Previous research has shown that fluctuations in 1,5AG levels in the bloodstream during pregnancy might indicate a slight shift in carbohydrate metabolism.

This suggests that 1,5AG could serve as an additional indicator alongside HbA1c for pregnant women dealing with diabetes (27). However, further investigation is warranted to substantiate this assertion.

4 BEYOND GLYCEMIC MONITORING IN PREGNANCY: FUTURE PROSPECT OF GLYCATED ALBUMIN

According to Ninomiya in his review paper collating a total of 18 studies published in 2014, poor glycemic status is associated with a greater risk of dementia by l.5- to 2.5-fold among community-dwelling elderly people (28), Alzheimer's disease, and vascular dementia (29). Since GA reflects postprandial plasma glucose better than A1C, GA is hypothesized as a potential surrogate marker for dementia. The associations between GA and the incidence of dementia have also been established in a community-based Atherosclerosis Risk in Communities (ARIC) study involving a cohort of 5,099 patients (30).

Apart from the relation to glycemic status, the community based Hisayama study also reported that an increased in GA/A1C ratio is significantly associated with the risk of Alzheimer's disease in subjects with or without glucose intolerance, and a higher serum GA and a higher GA/HbA1c ratio are significantly associated with brain and hippocampal atrophy (31) and an increased in white matter hyperintensity, resulting in a potential decrease in cognitive function and the ability to perform essential everyday tasks (32). Further exploration is necessary to validate these hypotheses and clarify the underlying mechanisms. Therefore, GA might serve as a notable risk indicator for dementia, applicable not only to individuals with diabetes but also to those exhibiting a normal glycemic control status.

Impaired fasting and random glucose tolerance were also known risk factors for cancer mortality. In a Japanese case cohort study conducted within the framework of the Japan Public Health Center–based Prospective Study (JPHC Study), encompassing 3,036 cancer cases and 3,667 control subjects found that the hazard ratios of the development of colon and liver cancers, between the highest and lowest levels of GA stood at 1.43 (95% CI: 1.02–2.00) and 2.02 (95% CI: 1.15–3.55), respectively (33). Furthermore, a sera-epidemiological nested case-control investigation under the Japan Collaborative Cohort Study (JACC Study) spotlighted the potential elevation in colorectal cancer risk among men with elevated GA levels (34). Similarly, findings from the ARIC cohort study suggested a connection between GA and the susceptibility to fatal prostate cancer (35). Despite the ongoing research endeavor aimed at unraveling the intricate pathophysiological relationship connecting poor glycemic control and cancer, the present understanding offers a multifaceted portrayal of the prevailing scenario. Notably, it is pertinent to recognize that not only does poor glycemic status potentially contribute to the development of cancer, but latent cancer might also precipitate the emergence of diabetes mellitus. Consequently, the concept of reverse causality in a vicious cycle emerges, exacerbating prognostic outcomes and accentuating the morbidity and mortality burden.

5 CONCLUSION

This mini review addressed the clinical utility of selected glycemic biomarkers in pregnancy. We presented our findings in a streamlined approach and synthesizing evidence for the purpose of informing emergent knowledge and identify the gaps in literature related to glycemic indicator in pregnancy. Accordingly, fructosamine and GA measurements hold a clinical value not only as a substitute gauge of glycemic regulation in instances where HbA1c lacks reliability, but also for the detection of glycemic aberrations prior to discernible change in HbA1c measurement.

In conclusion, GA is a good tool to complement A1C when the A1C has its limitations. To further elucidate this notion, clinicians need to be aware of the distinct attributes of each glycemic biomarker and make their selection judiciously based on the specific clinical context to enhance the therapeutic outcomes. It is anticipated that the insights presented in this review will furnish the practical and clinical utility of glycemic biomarkers in routine practice.

DECLARATION OF INTEREST

The authors declare no relevant financial or non-financial interests related to this publication.

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