

Biomarkers for Assessing Glycemic Control in Pregnancy

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Abstract

Hyperglycemia accounts for one of the most common medical conditions women encounter during pregnancy. Stringent glycemic control is essential during pregnancy as present and future of two generations are at risk- the mother; and the fetus and even mild abnormality of glucose metabolism can increase the incidence of complications. Strict glycemic control cannot be attained without a reliable glycemic control marker, which is lacking till now for pregnancy. Although the determination of blood glucose is the sine qua non for both detection and treatment of hyperglycemic disorders of pregnancy, it is subject to several limitations, many of which are not widely appreciated. Acceptance of supremacy of HbA1c as glycemic control metric outside pregnancy has attracted attention for its use in pregnancy also but owing to the limitations of the HbA1c assay in pregnancy, the interest is growing towards alternative glycemic biomarkers including fructosamine, GA and 1,5-AG. Studies have postulated them as useful tools for monitoring of intermediate and short-term glycemic control in pregnancy and some have even proposed GA as superior and more reliable indicator of glycemic control on pregnancy. However, because little data from clinical studies is available, large-scale epidemiological studies among populations of different races and ethnicity are required in order to confirm any proposals.

Keywords: Pregnancy; Diabetes Mellitus; Gestational Diabetes; Glycemic Control; Haemoglobin A1c; Glycated Albumin; Fructosamine; 1,5-anhydroglucitol

Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Diabetes mellitus and less serious form of glucose intolerance are widespread in almost every population in the world and are increasing exponentially. The number of adults with diabetes in the world is estimated to increase by 122%, from 135 million in 1995 to 300 million in 2025 [2]. There will be a 42% increase, from 51 million to 72 million in the developed countries. In the developing countries, there will be a 170% increase, from 84 million to 228 million. This huge increase in diabetes is posing serious

health and social problems, afflicting all populations including women of child-bearing age. According to estimates by the International Diabetes Federation (IDF) one in six live births 16.8% are to women with some form of hyperglycemia in pregnancy [3]. Thus hyperglycemia accounts for one of the most common medical conditions women encounter during pregnancy.

Strict glycemic control is essential during pregnancy as two generations are at risk- the mother and the fetus. A meta-analysis of 20 studies have revealed that the relative risk for patients with gestational diabetes mellitus (GDM) of developing type 2 diabetes mellitus after delivery is 7.43 times higher than that of women who had normal

glucose tolerance during pregnancy [4]. Also there is increased risk of development of preeclampsia, ketoacidosis, and infections, worsening of diabetic complications, operative delivery, induced labour and hydramnios. Moreover, with the proposal of the concept of developmental origins of health and diseases [5] and the long-term effects of mothers with abnormal glucose tolerance on foetuses after birth it has become evident that glucose intolerance during pregnancy predisposes the offspring for increased risk of developing glucose intolerance in the future. This vicious is likely to influence and perpetuate the incidence and prevalence of glucose intolerance in any population. The primary prevention is likely to reverse or halt this trend, and timely action taken now in screening all pregnant women for glucose intolerance achieving Euglycemic and ensuring adequate treatment will help in not only maintaining the health of mothers and infants in the short term, but will also help to maintain the long-term health of mothers and the future generation.

Clinical chemistry plays an important role in the diagnosis and treatment of diabetes. Before 2010 virtually all diabetes societies recommended blood glucose analysis as the exclusive method to diagnose diabetes. Not with standing these guidelines, over the last few years' physicians have been using hemoglobinA1c (HbA1c) to screen for and diagnose diabetes [6]. Although considered the "gold standard" for diagnosis, measurement of glucose in the blood is quiet laborious and subject to several limitations, many of which are not widely appreciated. Therefore, it is necessary to evaluate glycemia using indicators of glycemic control both traditional and nontraditional and they have become indispensable to both routine clinical practice and experimental works. Each of these indicators of glycemic control has different characteristics as well as advantages and disadvantages [7,8]. In addition, there are both appropriate and inappropriate indicators of glycemic control during pregnancy [9]. This review will give an outline of these indicators including HbA1c, glycated albumin (GA), fructosamine, and 1,5-anhydroglucitol 1,5-AG, their utility in pregnancy and their advantages and disadvantages over each other.

Glycated Haemoglobin(HbA1c)

HbA1c is glycated hemoglobin, formed by glycation of NH₂-terminal valine residue of the β -chain of globin and can be used as an indicator of a patient's glycemic status over the preceding 12 weeks [10]. Currently, HbA1c is widely accepted as an index of mean glycemia, a measure of risk for the development of diabetes complications, and

a measure of the quality of diabetes care. So, enthusiasm is growing for greater use of HbA1c for both screening and diagnosis of diabetes as it is less cumbersome than OGTT, provides an integrated measure of glycemia that is less susceptible to short-term modulation than blood glucose and is useful for tracking therapy within individuals with diabetes. Thus, supplementation with HbA1c, as is common outside pregnancy, seems appropriate. Before pregnancy, the target for metabolic control in women with diabetes is HbA1c values near the normal range [11]. Although the HbA1c reference intervals for the general population are well established, reference intervals for healthy pregnant women are not clearly defined and are generally established from the non pregnant state [12]. Studies have shown that HbA1c concentrations in healthy pregnant women are lower than the non pregnant women [13-16]. The changes that result in these decreased levels of HbA1c in healthy pregnant women could be because of the fact that the concentration of HbA1c is influenced not only by the glucose levels but also by the formation rate and lifespan of erythrocytes. In pregnancy, there is higher turnover and shortened lifespan of erythrocytes which may be due to emergency hematopoietic [17,18]. Also the glucose levels in the fasting state are reduced [19, 20] in pregnancy.

Few studies have shown that there is a small fall of HbA1c levels in pregnancy from first to second trimester followed by slight increase in third trimester [13,14] but others have shown a further decline in HbA1c levels in third trimester of pregnancy [15,21]. The low level of HbA1c in the first trimester of pregnancy is caused by the low mean pre-prandial and postprandial blood glucose values and by the increase in young erythrocytes which diminishes the percentage of glycosylated hemoglobin. Further decline in HbA1c levels in third trimester of pregnancy may be probably due to sustained decrease in fasting blood sugar levels throughout the pregnancy. The increase in HbA1c in the third trimester of pregnancy is partially because of the HbA1c enhancing effect of iron deficiency which is frequently present in pregnant women [22,23]. Moreover, recent evidence has shown that despite effective preconception care and planned pregnancies providing good glycemic control in early pregnancy with optimal HbA1c concentrations, the development of diabetes-associated complications cannot always be prevented [24,25]. These considerations highlight the need to carefully revise the target for glycemic control during an uncomplicated pregnancy. Besides there are number of factors, that can either falsely lower HbA1c test results or raise HbA1c test results independent of glycemia and pregnancy. These includes

structural hemoglobinopathies, thalassemia syndromes, and chemical alterations of hemoglobin moreover any condition that decreases mean erythrocyte age will falsely lower HbA1c test results regardless of the assay method used [26]. Iron deficiency, which effects up to 20% of menstruating women [27] and many pregnant women, has been reported to increase HbA1c test results by altering the structure of the hemoglobin molecule and making it easier to glycosylated [28]. Racial and ethnic differences in HbA1c have also been described in non diabetes populations that do not appear to be explained by differences in glycemia [29-31]. Thus although measurement of HbA1c for diagnosis is appealing in pregnancy as with one number, a total, integrated view of glycemia over time is derived but it has some inherent limitations and the non glycaemic factors that affect assays be more clearly defined and laboratories and clinicians should be aware of them.

Fructosamine

Fructosamine is a ketoamine, derived from the nonenzymatic glycation reaction between glucose and aldimine. As the side chain binding of ketoamine has the fructose structure, ketoamine is generically named fructosamine. The term fructosamine includes all glycosylated proteins. Although the main component of fructosamine is GA, but fructosamine contains other components such as glycosylated lipoprotein and glycation globulin. Glycemic control is measured by fructosamine owing to its reducing ability under alkaline conditions [9]. Serum fructosamine values can be used clinically as markers of recent changes in glycemic control as they reflect mean blood glucose concentrations over the previous two to three weeks [32]. As assay for fructosamine is not affected by the food eaten during the day so it can be measured at any time during the day, an aspect very useful in pregnancy. Studies have shown that a good correlation between HbA1c values and serum fructosamine [33, 34] and fructosamine assays are cheaper and easier to perform than HbA1c assays. Also fructosamine is not influenced by abnormal haemoglobin and iron deficiency anaemia which is quite prevalent in pregnancy especially in developing countries. The clinical data thus supports that fructosamine assay can provide a good index of glycemic control especially in diabetic pregnant patients due to their reliability, technical simplicity, low cost, and reduced analytical time [35,36] but there are also some limitations to the use of serum fructosamine measurements including higher within-subject variation and non reliability in conditions leading to altered protein metabolism like nephrotic syndrome, severe liver disease, or protein-losing enteropathy and thyroid disorders[9,32,34]. Moreover as fructosamine

assays measure all glycosylated proteins therefore, lacks specificity. Also because of measurement of fructosamine by colorimetric determination produced by reduction colour reaction, it is influenced by substances with reducing ability such as bilirubin. In addition as fructosamine is expressed as reducing ability per 1ml of serum so is influenced by serum protein concentration, and in dilution anaemia, which may develop during pregnancy; fructosamine measured by this method may give falsely low results [9].

GA

GA is a ketoamine formed by non enzymatic oxidation reaction between four lysine residues of albumin and glucose [9]. GA is similar to serum fructosamine in many aspects including its formation and utility as an index of glycemic control which is not affected by disorders of hemoglobin metabolism unlike HbA1c but overall GA is superior to fructosamine assays as it is expressed as the ratio of albumin; therefore like HbA1c, GA is not influenced by dilution of serum[9,37]. Since the half-life of albumin is about 14 days, GA reflects the short-term status of glycemic control (during the past 2 to 3 weeks) compared with HbA1C. GA is strongly associated with HbA1c and fasting glucose but the level of GA is approximately three times higher than that of HbA1c [32,38,39]. In relation to reference and time course during normal pregnancy although much data is not available but according to a report by the Japanese Society of Diabetes and Pregnancy [40], the reference range for GA in Japanese normal pregnant women was considered to be 11.5% to 15.7% and regarding trimester specific values of GA it was inferred from the same report that GA tends to decrease gradually toward the end stage of pregnancy.

GA has several advantages for monitoring of glucose control in management of hyperglycemic disorders of pregnancy. Firstly, GA provides a more accurate assessment of recent glycemia. Secondly, unlike fructosamine, GA is not influenced by dilution anemia during pregnancy [9]. Thirdly, as compared to HbA1c, GA reflects postprandial plasma glucose and glucose excursions more accurately [41,42]. In pregnancy, for the management of hyperglycemia, evaluation of mean plasma glucose level at a time point nearer to the time of consultation with a doctor and evaluation of postprandial plasma glucose level are vital, and GA proves really useful in this respect. Lastly, as opposed to HbA1c, GA is not influenced by abnormal RBC lifespan and iron deficiency anemia or iron deficiency state [43]. As iron deficiency is very common in pregnancy especially by the third trimester, so the factitious interpretation of glycemic

control by HbA1c can be avoided with the use of GA as an index of glycemic control.

Although as an indicator of glycemic control GA has several advantages but as it is influenced by albumin metabolism, so has anomalous values in diseases that result in abnormal albumin metabolism and so is of limited value in conditions such as nephrotic syndrome[44]and abnormal thyroid function[45]. Because of its several advantages, GA has been found to be a particularly useful indicator of glycemic control in pregnancy and few authors have recommended it to be the most reliable indicator in pregnancy [9]. Although interesting and lucrative, these proposals are based on scarce clinical data. Moreover the normal range of GA and its time course during pregnancy has not been established in populations of different races and ethnicity; hence there is need of large scale population based epidemiological before confirming any proposals.

1,5-AG

1,5-AG is a naturally occurring monosaccharide with a structure in which hydroxyl at the first position of glucose is reduced [46]. It is a major polyol in human serum [47] and is found in all organs and tissues. 1,5-AG is derived mainly from dietary sources with its dietary intake estimated to be 4.0-5.5mg/day, although there is a small amount (0,5mg/day) of de novo synthesis also [48,49]. All intake of this non metabolizable glucose analogue is balanced by urinary excretion and nearly 99.9% is reabsorbed by the kidneys at a specific sodium glucose active co transporter (SGLT4) [48,49]. This is the reason why during Euglycemic, serum 1,5-AG concentrations are maintained at a constant steady state and when serum glucose level exceeds the renal threshold for glucosuria (typically >180mg/dl), urinary glucose suppresses reabsorption of 1,5-AG via SGLT4 at proximal tubules of kidney, leading to a loss of 1,5-AG in the urine and a rapid reduction of this polyol in serum levels [49-51]. Owing to this mechanism, serum 1,5-AG indirectly reflects episodes of hyperglycemia during the past 24 h and so can be used as an indicator of very short-term glycemic control [49,52].The half-life of 1,5-AG is 1-2 weeks and its reference plasma levels in healthy human subjects range from 12 to 40µg/ml [53]. Utilizations of 1,5-AG as an index of glycemic control in pregnancy and otherwise; has several advantages, including retained metabolic inertness, steady-state levels in all tissues, and negligible influence of sampling conditions such as collection time, body weight, age, sex, and food intake of the subjects[49,54]. However, serum 1,5-AG levels may be influenced by several physiologic factors or diseases

associated with altered or impaired renal function [55-57].

Based on the fact that renal function during pregnancy is characterized by considerable changes in filtration and tubular reabsorption, dependent on gestational age and the time of a day [58], various authors have concluded that differences in renal glucose threshold between patients limit the usefulness of 1,5-AG as a reliable marker of glycemic control in pregnant women [49,58,59]. However, Dworacka et al. [58] suggested that the deviation in renal threshold for glucose is an important constraint for the use of 1,5-AG for diabetes screening, but not for diabetes monitoring; and this marker may serve as a useful tool of daily glucose excursion in pregnant women with diabetes, as an adjunct to HbA1C monitoring and can provide valuable information regarding effectiveness of treatment. As majority of interpretations for utility of 1,5-AG in pregnancy are based on scant clinical data so there is scope of potential possibilities for its use in pregnancy and continuous and rigorous research may allow its new applications in pregnancy in the future.

Conclusion

Stringent glycemic control is essential during pregnancy as present and future of two generations are at risk- the mother; and the fetus and even mild abnormality of glucose metabolism can increase the incidence of complications. Strict glycemic control cannot be attained without a reliable glycemic control marker, which is lacking till now for pregnancy. Although the determination of blood glucose is the sine qua non for both detection and treatment of hyperglycemic disorders of pregnancy, it is subject to several limitations, many of which are not widely appreciated. Acceptance of supremacy of HbA1c as glycemic control metric outside pregnancy has attracted attention for its use in pregnancy also but owing to the limitations of the HbA1c assay in pregnancy, the interest is growing towards alternative glycemic biomarkers including fructosamine, GA and 1,5-AG. Studies have postulated them as useful tools for monitoring of intermediate and short-term glycemic control in pregnancy and some have even proposed GA as superior and more reliable indicator of glycemic control on pregnancy. However, because little data from clinical studies is available, large-scale epidemiological studies among populations of different races and ethnicity are required in order to confirm any proposals. Moreover, if diabetic patients are to have their control assessed during pregnancy through determination of any of the traditional or non-traditional indicator of glycemic control; the

physician and obstetrician should interpret the results in the knowledge of above demonstrable physiological changes that are pertinent to pregnancy and should not merely extend the results established from the non-pregnant state.

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