Diabetes Updates

Review Article ISSN: 2631-5483

HbA1c in the diagnosis and management of diabetes mellitus: An update

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Abstract

Diabetes mellitus (DM) is a serious health problem worldwide. Knowledge of the diagnosis and monitoring of diabetes is essential for any practicing physician. Studies show a significant risk reduction in microvascular and macrovascular complications of DM with better glycemic control as evidenced by lower mean HbA1c. An International Expert Committee concluded that a cut-point of HbA1c ≥6.5% be used to diagnose diabetes and the goal for HbA1c in diabetic monitoring continues to be <7% in diabetic nonpregnant adults. HbA1c is a good reflection of the glucose control over the lifespan of the red blood cells (typically 120 days). HbA1c may be assessed using separation or chemical methods. International standardization and harmonization of HbA1c assays has greatly aided the management of diabetes with accurate and comparable results. The advantage of HbA1c is that it is less affected by fluctuating glucose levels after meals and other short-term changes from medical conditions. However, there are still several factors that can affect HbA1c results, including haemoglobin variants and factors that influence red blood cell longevity. HbA1c is also related to adverse pregnancy outcomes and greater risk for the development of gestational diabetes. HbA1c may emerge as a diagnostic marker for GDM.

Introduction

There has been considerable progress in the analysis and usage of glycated haemoglobin (HbA1c). In this article we provide a brief review of the progress and its current utility.

In 2017, the International Diabetes Federation (IDF) estimated that there are 451 million people aged 18-99 years with diabetes mellitus (DM) worldwide, and that this will only increase to 693 million by 2045 [1]. China and India alone have >113.9 million and >62 million diabetics respectively, making Asia a critical "hot-spot" for the diabetes epidemic [2]. Knowledge of the diagnosis and monitoring of DM is thus essential for any practicing physician. In 1993, the Diabetes Control and Complications Trial (DCCT) [3] studied 1441 patients with DM and compared intensive glucose control (≥3 insulin injections a day, or continuous insulin pump) to conventional therapies (1-2 insulin injections a day). The DCCT showed that tight glucose control delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy after 6.5 years, and reduced the development of hypercholesterolemia (LDL cholesterol >4.14 mmol/L) in diabetics. A follow-up study of the DCCT in 1995 [4] showed that lowering the HbA1c by 10% (e.g. 8% to 7.2%) in both intensive/conventional treatment groups reduced the risk of retinopathy by 43% and 45% respectively. A higher mean HbA1c was also associated with a higher risk of progression of retinopathy in each patient group. In the 1998 UK Prospective Diabetes Study (UKPDS) [5] of newly diagnosed DM2 patients (n=3867) intensive blood glucose control with sulphonylureas or insulin with diet treatment alone, reduced microvascular complications by 25%, but not macrovascular complications. However, in another arm of the UKPDS, 342 of 1704 obese patients [6] were assigned metformin as monotherapy. In this metformin subgroup there was a 39% reduction in myocardial infarction (p=0.01) and a 36% reduction in all-cause mortality (p=0.01). The UKPDS study also showed that the metformin group had greater risk reduction than sulphonylureas/insulin with regards to microvascular and macrovascular outcomes. These landmark studies clearly established the importance of maintaining well-controlled glycemia as evidenced by HbA1c to prevent diabetic complications. In a recent systemic review [7], there was an increased risk of all-cause and cardiovascular mortality when HbA1c levels are above 9.0% in diabetics and 6.0% in non-diabetics. Meta-analyses [8-10] also demonstrate a reduction in macrovascular complications with intensive glucose control, although the effect on all-cause or cardiovascular mortality was less clear. More recent studies involving newer anti-diabetic drugs such as linagliptin (DPP-4 inhibitor), albiglutide (GLP-1 receptor agonist), dapagliflozin (SGLT-2 inhibitor) [11] achieved better glycemic control and showed significant risk reduction in macrovascular complications including cardiovascular death and myocardial infarction. In a multi-ethnic Asian population [12], HbA1c of 6.5-7.0% was associated with a higher prevalence of moderate retinopathy compared with patients with HbA1c <6.5%. Variability in HbA1c control is also important [13] as a greater glycemic variability score (indicated by changes in HbA1c) was associated with a greater risk of mortality.

HbA1c

In 2009, an International Expert Committee appointed by the American Diabetes Association (ADA), the European Association for the Study of Diabetes, and the International Diabetes Federation,

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Key words: *diabetes, Hba1c, harmonization, analytics, pregnancy*

Received: December 13, 2019; **Accepted:** December 25, 2019; **Published:** January 06, 2020

concluded that a cut-point of HbA1c ≥6.5% can be used to diagnose diabetes [14]. In 2011, the World Health Organization (WHO) supported the use of HbA1c >6.5% for diagnosing diabetes. The goal for HbA1c in diabetic monitoring continues to be <7% in diabetic nonpregnant adults [15], with flexible goals dependent on the clinical scenario.

The standardization and harmonization of HbA1c analysis has greatly aided the management of diabetes with internationally accurate and comparable results. This has allowed guidelines to use uniform reference values and decision cut-points in the assessment of HbA1c across laboratories. In harmonization, efforts are made such that results are comparable among different measurement procedures for the same analyte, whereas standardization refers to the use of a reference measurement procedure and a defined analyte as a reference material. Before international standardization and harmonization, the inter-laboratory variation of HbA1c was large and thus results were not comparable between assays. This changed when the DCCT and UKPDS harmonize HbA1c measurements early in the 1990s [16], with standardization introduced by the NGSP and IFCC shortly after [17] using pure A1c/A0 standard reference materials. Today, many manufacturers can boast that their laboratory automated analysers align with IFCC reference materials and methods are NGSP certified.. The NGSP network consists of a central primary reference laboratory that runs the reference high performance liquid chromatography method, supported by two other primary reference laboratories and several other secondary reference laboratories that utilize a variety of highly precise commercial methods. The NGSP certification and monitoring processes are also updated regularly. The latest certification criteria in 2019 are: manufacturer and level II lab need 36 of 40 results within ± 5%; level I lab needs 37 of 40 results within ± 5%) [18]. The goal of having all glycated haemoglobin reported as HbA1c has been largely achieved, and from 2000 to 2014, the CVs of all-method HbA1c had improved from 5-6% to 3.5%, with CVs being <3.5% over the past 8 years [18]. Although not all POC devices follow the international standards, more than 30 POC methods have been certified by the NGSP, and it is imperative to check with manufacturers to ascertain whether their device is NGSP certified. Independent harmonization schemes were developed by Japan and Sweden for HbA1c [19,20], although Japan has begun reporting NGSP values of HbA1c since 2010.

Analytical methods

The glycation of haemoglobin occurs by a non-enzymatic reaction between glucose and the N-terminal end of the beta-chain. This forms a Schiff base (pre-A1c) that is converted into Amadori products which includes HbA1c. As the average plasma glucose increases, so does the amount of glycated haemoglobin (and thereby HbA1c) in the plasma. HbA1c is a good reflection of the glucose control over the period of the red blood cell's lifespan (typically 120 days). There are two main methods for the assessment of HbA1c, separation (including ion exchange chromatography, capillary electrophoresis and affinity chromatography) and chemical methods (Immunoassays and enzymatic assays) [21]. These methods have been incorporated into main laboratory automated analysers, and increasingly into point of care devices that can use finger-prick capillary blood samples for the rapid assessment of HbA1c.

In between the IFCC and NGSP results, there is a difference in HbA1c units with a master equation of NGSP%=(0.915 x IFCC%) + 2.15 (22). It is recommended that HbA1c methods have intra-laboratory %CV <2 and inter-laboratory %CV of <3.5 [22] a total error of no more than 0.5% (5mmol/mol) at 6.7% (50 mmol/mol) is recommended [23]. These international standards ensure that HbA1c results are transferrable in between centres, which is a great boon for patient treatment.

Confounding factors

The major advantage of HbA1c is that it is less affected by fluctuating glucose levels after meals and other short-term changes from medical conditions. However, there are still several factors that can affect HbA1c results. Haemoglobin (Hb) variants (including elevated levels of HbF) and thalassemia can affect HbA1c results, with the interference from Hb variants more pronounced in ion exchange methods. This can cause falsely high/low HbA1c levels, depending on the manufacturer. In a recent study [24] 49 different rare Hb variants were assessed by 4 HPLC methods, 1 enzymatic method, 1 capillary-electrophoresis method, and a reference HPLC and IFCC method. For most variants, interference was seen with 1 or more of the ion-exchange methods, proving the larger effect of Hb variants on separation methods. Thankfully, patients with full homozygosity for Hb variants are rare, and this interference is not commonly seen. A list of the effects of various Hb variants and interferents on different assays has been listed by the NGSP [25] and most modern immunoassay methods are not affected by the common Hb variants.

Conditions that affect the longevity of erythrocytes can also affect HbA1c values. In diseases with a shortened RBC lifespan (e.g. anaemia in chronic kidney disease with erythropoietin use, hemolytic anemias, post-transfusion, recovery from acute blood loss), HbA1c can be spuriously low [21]. The converse is true in conditions with prolonged RBC lifespans. Altered glycation rates and abnormal RBC turnover, found in iron deficiency anaemia, can also cause falsely raised HbA1c [26,27]. In a large population study, significant differences were found in the classification of diabetes and prediabetes using HbA1c across categories of iron-deficiency and/or anaemia status [28].

Another factor is the effect of age on HbA1c values. Published data shows age-related increases in HbA1c value of approximately 0.1% per decade in non-diabetics [29,30]. In another study [31], the diagnostic efficiency of HbA1c was lower in patients >75 years old, with ROC analysis showing an AUC of 0.755 vs 0.878 in groups of patients >75 years old compared to 45-54 years old, likely due to a reduced RBC count with advanced age. Some have proposed the use of age specific reference intervals for HbA1c [32], although the upper limit for HbA1c in patients >60 years old was still close to the diagnostic cut-point for diabetes (URL of 6.6% in males and 6.5% in females). Whether age-related reference intervals for HbA1c will improve diagnostic classification still requires further study.

The effects of ethnicity on HbA1c are still being debated. In a recent meta-analysis [33], in individuals free of diabetes HbA1c was higher in Blacks, Asians, and Latinos compared to Caucasians, although ethnicity did not modify the association between HbA1c and the risk of cardiovascular or end-stage renal disease. This has also been established in other studies where significantly higher hbA1c was found in Black, Hispanic and Asian patients than Caucasian patients with impaired glucose tolerance [34]. In a study of an Asian population [12], although HbA1c levels were higher in Indians and Malays, the prevalence of moderate retinopathy below HbA1c <6.5% was <1% in all ethnic groups. The Atherosclerosis Risk in Communities study [35] also did not find any significant difference between race, HbA1c and cardiovascular disease or stroke despite higher HbA1c values in nondiabetic Blacks. Thus, even though there may be some differences

between HbA1c among races, whether this exerts a difference in diabetic complications is still not well established.

HbA1c in pregnancy

HbA1c levels decrease during early pregnancy due to increased erythrocyte synthesis and decreased fasting blood glucose levels due to insulin-independent glucose uptake by the fetus and placenta. However, later in pregnancy, postprandial hyperglycemia, insulin resistance and increased carbohydrate intolerance develop due to diabetogenic placental hormones [36,37]. Iron deficiency anaemia also occurs in pregnancy, with the complications in HbA1c interpretation as discussed above. HbA1c falls to a nadir by the early second trimester, but a review of recent literature [38] suggests that in Caucasian and Japanese women, an HbA1c >5.7% in the first and second trimester can be considered elevated.

If GDM is treated intensively during the entire period of pregnancy, HbA1c may not be able to accurately diagnose diabetes at follow up shortly after giving birth [39], and it is agreed that the assessment for diabetes ideally should be made during preconception visits or in the first trimester where a HbA1c diagnostic cut point of >6.5% can still be used to diagnose diabetes [37,40]. Nevertheless, HbA1c is usually used during pregnancy to monitor glycaemic control in women with known diabetes. Known diabetics have increased risks of perinatal loss with increasing HbA1c at conception [41] and are also at greater risk of pre-eclampsia and preterm birth with higher HbA1c during the second and third trimesters [42].

The screening for GDM later in pregnancy is performed between 24-28 weeks gestation, and many guidelines still recommend either one-step or two-step glucose challenge tests to screen for GDM, with diagnostic criteria based on OGTT results (36). However, glucose testing is poorly reproducible, and the multiple levels of testing are prone to accumulative uncertainty. A higher HbA1c has already been shown to be related to adverse pregnancy outcomes. In a recent study on 1989 pregnant women [43], higher mid-pregnancy HbA1c at 23-32 weeks >4.9% were significantly associated with increased risks of pre-eclampsia, gestational hypertension, preterm delivery, low birth weight and macrosomia. This is also reflected in other studies [44] where a HbA1c of >6.0% in women with type 1 diabetes at 26 weeks gestation was associated with increased risk of macrosomia and pre-eclampsia. The ADA has stated [37] that HbA1c can be used as a useful secondary measure of glycemic control in pregnancy along with self-monitoring of blood sugar levels, and that monthly targets of HbA1c <6% is optimal during pregnancy if it can be achieved without significant hypoglycaemia. There is also existing evidence that a higher HbA1c is a risk factor for GDM, with some studies [45] showing that before 20 weeks of gestation, women with HbA1c 5.7-6.4% have a higher rate of GDM, with HbA1c ≥5.9% having a specificity of 98.4% for GDM. Other studies [46] have shown that women with early HbA1c of 5.7-6.4% have a higher chance of developing GDM compared with women with HbA1c <5.7%. Another study [47] comparing 107 GDM cases and 214 controls showed that women who later developed GDM had significantly higher HbA1c (mean 5.3%) than women without GDM (mean 5.1%), with a significant linear association between HbA1c and GDM risk (0.1% increase in HbA1c at 8-13 weeks was associated with an adjusted 22% increased risk of GDM), and inclusion of HbA1c significantly improved GDM prediction when included with other risk factors. The sensitivity of HbA1c at 8-13 weeks gestation and GDM ranged from 96% at HbA1c 3.5% to 12% at HbA1c 6.0%, and the specificity ranged from 10% at HbA1c of 3.5% to 98% at HbA1c 6.0%, which was fairly similar to another study [48] that found that a HbA1c of 5.7-6.4% in the first trimester had a 13% sensitivity and 94% specificity for GDM in the second trimester. The current evidence provides a strong foundation for the use of HbA1c as a possible diagnostic marker for GDM in the future, although further studies are required.

Conclusion

While some minor interferences remain in the analysis of HbA1c, its measurement has come a long way over the past decade. With the international harmonization and standardization of HbA1c assessment, as well as established HbA1c targets and guidelines, HbA1c has become one of the strongest tests we have in the assessment, diagnosis and management of diabetes. It is an extremely convenient result to interpret. With the advent of more point of care devices being certified by regulating bodies, the use of rapid HbA1c assessment to treat diabetes will become even more widespread.

References

1. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, et al (2018) IDF Diabetes atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* 138: 271-281. [Crossref]
2. Zheng Y, Ley SH, Hu FB (2018) Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* 14: 88-98. [Crossref]
3. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, et al. (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329: 977-986. [Crossref]
4. [No authors listed] (1995) The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes* 44: 968-983. [Crossref]
5. [No authors listed] (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352: 837-853. [Crossref]
6. [No authors listed] (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352: 854-865. [Crossref]
7. Cavero-Redondo I, Peleteiro B, Alvarez-Bueno C, Rodriguez-Artalejo F, Martinez-Vizcaino V (2017) Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis. *BMJ Open* 7: e015949.
8. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, et al. (2009) Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 373: 1765-1772. [Crossref]
9. Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, et al. (2009) Systematic review: glucose control and cardiovascular disease in type 2 diabetes. *Ann Intern Med* 151: 394-403. [Crossref]
10. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, et al. (2011) Effect of intensive glucose lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ* 343: d4169.
11. Schnell O, Standl E, Catrinoiu D, Itzhak B, Lalic N, et al. (2019) Report from the 4th Cardiovascular outcome trial (CVOT) summit of the diabetes & cardiovascular disease (D&CVD) EASD study group. *Cardiovasc Diabetol* 18: 30.
12. Sabanayagam C, Khoo EY, Lye WK, Ikram MK, Lamoureux EL, et al. (2015) Diagnosis of diabetes mellitus using HbA1c in Asians: relationship between HbA1c and retinopathy in a multi-ethnic Asian population. *J Clin Endocrinol Metab* 100: 689-696.
13. Forbes A, Murrells T, Mulnier H, Sinclair AJ (2018) Mean HbA1c, HbA1c variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. *Lancet Diabetes Endocrinol* 6: 476-486.
14. International Expert Committee (2009) International expert committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 32: 1327-1334. [Crossref]

15. American Diabetes Association (2019) 6. Glycemic Targets: Standards of medical care in diabetes - 2019. *Diabetes Care* 42: 61-70.

16. Little RR, Rohlfing CL, Wiedmeyer HM, Myers GL, Sacks DB, et al. (2001) The national glycohemoglobin standardization program: a five-year progress report. *Clin Chem* 47: 1985-1992. [Crossref]

17. Jeppsson JO, Kobold U, Barr J, Finke A, Hoelzel W, et al. (2002) Approved IFCC reference method for the measurement of HbA1c in human blood. *Clin Chem Lab Med* 40: 78-89. [Crossref]

18. Little RR, Rohlfing C, Sacks DB (2019) The national glycohemoglobin standardization program: Over 20 years of improving haemoglobin A1c measurement. *Clin Chem* 65: 839-848.

19. Shima K, Endo J, Oimomi M, Omori Y, Katayama Y, et al. (1998) Interlaboratory difference in GHb measurement in Japan. The fifth report of the GHb standardization committee, the Japan diabetes society. *J Japan Diab Soc* 41: 317-323.

20. Jeppsson JO, Jerntorp P, Sundkvist G, Englund H, Nylund V (1986) Measurement of haemoglobin A1c by a new liquid-chromatographic assay: methodology, clinical utility, and relation to glucose tolerance evaluated. *Clin Chem* 32: 1867-1872. [Crossref]

21. Weykamp C (2013) HbA1c: a review of analytical and clinical aspects. *Ann Lab Med* 33: 393-400. [Crossref]

22. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, et al. (2011) Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Diabetes Care* 34: 61-99.

23. English E, Lenters-Westra E (2018) HbA1c method performance: The great success story of global standardization. *Crit Rev Clin Lab Sci* 55: 408-419.

24. Little RR, La'ulu SL, Hanson SE, Rohlfing CL, Schmidt RL (2015) Effects of 49 different rare Hb variants on HbA1c measurement in eight methods. *J Diabetes Sci Technol* 9: 849-856. [Crossref]

25. NGSP (2019) HbA1c Assay Interferences. HbA1c methods: effects of hemoglobin variants (HbC, HbS, HbE and HbD traits) and elevated fetal hemoglobin (HbF) Available from: http://www.ngsp.org/interf.asp

26. Kim C, Bullard KM, Herman WH, Beckles GL (2010) Association between iron deficiency and A1C Levels among adults without diabetes in the National Health and Nutrition Examination Survey, 1999-2006. *Diabetes Care* 33: 780-785. [Crossref]

27. Ahmad J, Rafat D (2013) HbA1c and iron deficiency: a review. *Diabetes Metab Syndr* 7: 118-122. [Crossref]

28. Attard SM, Herring AH, Wang H, Howard AG, Thompson AL, et al. (2015) Implications of iron deficiency/anemia on the classification of diabetes using HbA1c. *Nutr Diabetes* 5: e166. [Crossref]

29. Ziemer DC, Kolm P, Weintraub WS, Vaccarino V, Rhee MK, et al. (2010) Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. *Ann Intern Med* 152: 770-777. [Crossref]

30. Dubowitz N, Xue W, Long Q, Ownby JG, Olson DE, et al. (2014) Aging is associated with increased HbA1c levels, independently of glucose levels and insulin resistance, and also with decreased HbA1c diagnostic specificity. *Diabet Med* 31: 927-935. [Crossref]

31. Wu L, Lin H, Gao J, Li X, Xia M, et al. (2017) Effect of age on the diagnostic efficiency of HbA1c for diabetes in a Chinese middle-aged and elderly population: The Shanghai Changfeng Study. *PLoS One* 12: e0184607. [Crossref]

32. Masuch A, Friedrich N, Roth J, Nauck M, Muller UA, et al. (2019) Preventing misdiagnosis of diabetes in the elderly: age-dependent HbA1c reference intervals derived from two population-based study cohorts. *BMC Endocr Disord* 19: 20.

33. Cavagnolli G, Pimentel AL, Correa Freitas PA, Gross JL, Camargo JL (2017) Effect of ethnicity on HbA1c levels in individuals without diabetes: Systematic review and meta-analysis. *PLoS One* 12: e0171315.

34. Herman WH, Cohen RM (2012) Racial and ethnic differences in the relationship between HbA1c and blood glucose: Implications for the diagnosis of diabetes. *J Clin Endocrinol Metab* 97: 1067-1072.

35. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, et al. (2010) Glycated haemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 362: 800-811. [Crossref]

36. Johns EC, Denison FC, Norman JE, Reynolds RM (2018) Gestational diabetes mellitus: Mechanisms, treatment, and complications. *Trends Endocrinol Metab* 29: 743-754.

37. American Diabetes Association (2019) 14 Management of diabetes in pregnancy: Standards of medical care in diabetes-2019. *Diabetes Care* 42: 165-172. [Crossref]

38. Hughes RC, Rowan J, Florkowski CM (2016) Is there a role for HbA1c in pregnancy? *Curr Diab Rep* 16: 5. [Crossref]

39. American Diabetes Association (2019) Classification and diagnosis of diabetes: Standards of medical care in diabetes - 2019. *Diabetes Care* 42: 13-28.

40. International association of diabetes and pregnancy study groups consensus panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, et al. (2010) International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 33: 676-682. [Crossref]

41. Tennant PW, Glinianaia SV, Bilous RW, Rankin J, Bell R (2014) Pre-existing diabetes, maternal glycated haemoglobin, and the risks of fetal and infant death: a population-based study. *Diabetologia* 57: 285-294. [Crossref]

42. Damm P, Mersebach H, Rastam J, Kaaja R, Hod M, et al. (2014) Poor pregnancy outcome in women with type 1 diabetes is predicted by elevated HbA1c and spikes of high glucose values in the third trimester. *J Matern Fetal Neonatal Med* 27: 149-154. [Crossref]

43. Ho YR, Wang P, Lu MC, Tseng ST, Yang CP, Yan YH (2017) Associations of mid-pregnancy HbA1c with gestational diabetes and risk of adverse pregnancy outcomes in high-risk Taiwanese women. *PLoS One* 12: e0177563.

44. Maresh MJ, Holmes VA, Patterson CC, Young IS, Pearson DW, et al. (2015) Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes. *Diabetes Care* 38: 34-42. [Crossref]

45. Hughes RC, Moore MP, Gullam JE, Mohamed K, Rowan J (2014) An early pregnancy HbA1c ≥5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. *Diabetes Care* 37: 2953-2959. [Crossref]

46. Fong A, Serra AE, Gabby L, Wing DA, Berkowitz KM (2014) Use of haemoglobin A1c as an early predictor of gestational diabetes mellitus. *Am J Obstet Gynecol* 211: 641.

47. Hinkle SN, Tsai MY, Rawal S, Albert PS, Zhang C (2018) HbA1c Measured in the first trimester of pregnancy and the association with gestational diabetes. *Sci Rep* 8: 12249.

48. Osmundson SS, Zhao BS, Kunz L, Wang E, Popat R, et al. (2016) First trimester hemoglobin a1c prediction of gestational diabetes. *Am J Perinatol* 33: 977-982. [Crossref]