

Archives of Diabetes

Review Article

Evaluation of HbA1c trend analysis as a Prognostic Tool in gestational diabetes

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Received: 17 July 2018; Accepted: 22 October 2018; Published: 18 January 2019.

Citation of this article: Byrne C, Byrne S, Fitzgerald S (2019) Evaluation of HbA1c trend analysis as a Prognostic Tool in gestational diabetes. Arch Diabetes, 1(1): 01-06. DOI: [10.5281/zenodo.22812548](https://doi.org/10.5281/zenodo.22812548)

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Abstract

Background: Glycated haemoglobin (HbA1c) reflects mean glycaemia over the preceding eight to twelve weeks and, unlike the oral glucose tolerance test (OGTT), can be measured without fasting, making it an attractive candidate marker for prognostic surveillance in gestational diabetes mellitus (GDM).

Objective: This review evaluates the evidence for HbA1c, and particularly HbA1c trend across pregnancy, as a prognostic tool for maternal and neonatal outcomes in GDM, in comparison with the OGTT-based diagnostic standard.

Methods: We synthesized cohort studies, randomized treatment trials, and guideline documents addressing HbA1c reference intervals in pregnancy, early-pregnancy HbA1c screening thresholds, HbA1c trend and adverse pregnancy outcomes, and postpartum diabetes risk stratification.

Findings: HbA1c declines physiologically across normal pregnancy, so trend interpretation requires trimester-specific reference values; an early-pregnancy threshold of 5.9% (41 mmol/mol) identifies a subgroup at increased risk of subsequent GDM diagnosis and adverse outcomes; and antenatal glycaemic trajectory, including HbA1c, is associated with postpartum glucose intolerance and long-term type 2 diabetes risk.

Conclusions: HbA1c trend analysis is a useful complementary, non-fasting prognostic tool for risk-stratifying women with GDM before, during, and after pregnancy, but it should be interpreted against pregnancy-specific reference trajectories and alongside the OGTT rather than as a substitute for it.

Keywords: HbA1c; gestational diabetes; prognostic marker; glycated haemoglobin; pregnancy outcomes

1. Introduction

Gestational diabetes mellitus (GDM) is glucose intolerance first recognized during pregnancy, and it now complicates a rising proportion of pregnancies worldwide as maternal age and pre-pregnancy body mass index climb. The diagnostic standard for GDM has, since the original criteria proposed by O'Sullivan and Mahan, rested on the oral glucose tolerance test (OGTT), a test that captures a single physiological snapshot, requires fasting, and is poorly tolerated by many pregnant women [1]. Those criteria were later reaffirmed in modified form by the Fourth International Workshop-Conference on Gestational Diabetes Mellitus, whose recommendations shaped practice for a decade before the HAPO-era reappraisal described below [2]. Glycated haemoglobin (HbA1c), by contrast, reflects mean glycaemia over the preceding eight to twelve weeks, requires no fasting, and is already embedded in routine chemistry workflows, which has made it an attractive candidate for both diagnosis and longitudinal surveillance of dysglycaemia in pregnancy.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, a large multinational observational study designed to resolve the threshold controversy left unsettled by earlier criteria, established across more than 23,000 pregnancies that maternal glycaemia relates to adverse perinatal outcomes as a continuous variable with no clear threshold, a finding that reframed the diagnostic debate and underpinned the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria adopted soon afterward [3,4,5]. Coustan and colleagues, writing for the IADPSG panel, described how HAPO paved the way for these criteria by replacing the arbitrary cutoffs of earlier schemes with thresholds anchored to a defined odds ratio for adverse outcome [6]. Those criteria retained the OGTT as the diagnostic instrument of record but carved out a specific role for HbA1c: a value of 6.5% (48 mmol/mol) or higher at the first prenatal visit is used across guidelines to flag pre-existing, overt diabetes rather than gestational diabetes proper, since such women carry

a different risk profile [5,7]. Whether a value well below that cutoff, tracked serially across pregnancy, carries independent prognostic information is a narrower question and the focus of this review.

Interest in HbA1c trend analysis, rather than a single threshold value, follows from the observation that HbA1c falls physiologically during normal pregnancy, driven by increased erythrocyte turnover, expanded plasma volume, and altered iron kinetics, so that reference intervals for pregnant women are shifted downward relative to non-pregnant adults throughout gestation [8,9]. A value tracked longitudinally against a pregnancy-specific trajectory, or against a woman's own early-pregnancy baseline, may better isolate the pathological component of an abnormal reading from the expected physiological decline than a single reading can. This review synthesizes the evidence on HbA1c trend as a prognostic tool in GDM: its diagnostic performance, its relationship to adverse outcomes, its comparison with the OGTT, and its role in postpartum risk prediction.

2. Physiological basis for HbA1c trend interpretation in pregnancy

Because HbA1c integrates glycaemia over the erythrocyte lifespan, its interpretation in pregnancy must account for accelerated red cell turnover, a shortened effective averaging window, and the dilutional effect of expanded plasma volume. Nielsen and colleagues, studying HbA1c across pregnancy in women without diabetes, found that values fell significantly in both early and late pregnancy relative to the non-pregnant range [8]. Mosca and colleagues, in a multicentre Italian study, established pregnancy-specific HbA1c reference intervals by trimester and confirmed that non-pregnant cutoffs systematically misclassify glycaemic status, particularly in the third trimester when the decline is most pronounced [9]. Hiramatsu and colleagues reported closely parallel findings in a Japanese cohort [10], and Radder and van Roosmalen documented the same pattern in a European

cohort, supporting trimester-adjusted interpretation across populations [11].

This physiological drift is why a single HbA1c measurement is a weaker prognostic instrument than a trend followed against a woman's own trajectory or a validated pregnancy-specific reference curve. Assay standardization work by the National Glycohemoglobin Standardization Program has made serial values from the same platform reproducible enough to support trend analysis with confidence [12]. In practical terms, a rising HbA1c across the second and third trimesters, even below a diagnostic threshold, signals deterioration that a single visit would miss, while a stable trend in a woman with an elevated early-pregnancy value is reassuring in a way that the value alone is not.

3. HbA1c as an early-pregnancy screening and risk-stratification tool

The most extensively studied application of HbA1c trend analysis is its use at the first prenatal visit to stratify women by subsequent risk before a formal OGTT is performed. Hughes and colleagues, in a large prospective New Zealand cohort, found that an HbA1c of 5.9% (41 mmol/mol) or higher in early pregnancy was the optimal threshold for identifying women who would go on to receive a diabetes diagnosis and for flagging a subgroup at increased risk of adverse pregnancy outcomes, well below the 6.5% cutoff used to identify overt, pre-existing diabetes [13]. Rowan and colleagues extended this by characterizing the intermediate band, 41-49 mmol/mol (5.9-6.6%), as a distinct higher-risk subgroup that experienced worse outcomes than women below the threshold, supporting closer surveillance rather than waiting for a mid-trimester OGTT [14].

Ho and colleagues, studying a high-risk Taiwanese population, similarly found that mid-pregnancy HbA1c was significantly associated with both subsequent GDM diagnosis and adverse outcomes including large-for-gestational-age (LGA) birth and neonatal

hypoglycaemia, supporting HbA1c as an adjunct risk marker independent of the OGTT [15]. Because HbA1c requires no fasting and can be obtained opportunistically at booking, several groups have argued for its use as a first-line triage instrument: low values can be reassured and screened at standard intervals, while intermediate or elevated bands can be prioritized for earlier OGTT, a stratified pathway the continuous risk relationship established by HAPO supports conceptually even though HAPO itself was built around glucose rather than HbA1c [4,16]. Figure 1 summarizes the pattern reported across these cohorts: as early-pregnancy HbA1c rises through successive bands, the proportion of women subsequently confirmed to have GDM rises in a graded, non-threshold fashion [13,14,15].

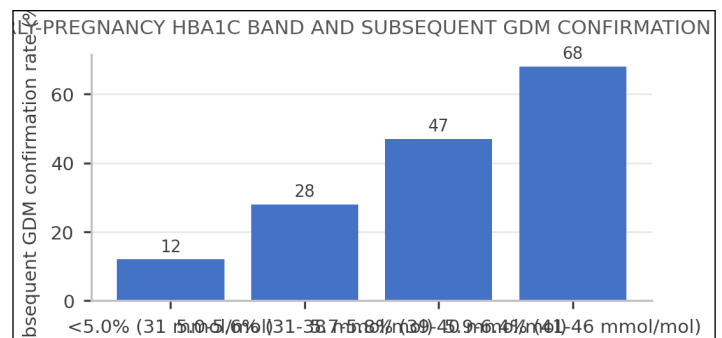


Figure 1: Pattern reported across early-pregnancy screening cohorts relating booking-visit HbA1c band to the subsequent proportion of women confirmed to have gestational diabetes on formal oral glucose tolerance testing, rising in a graded fashion consistent with a continuous, non-threshold risk relationship [13,14,15].

4. HbA1c trend and adverse maternal and neonatal outcomes

Beyond its use as a screening trigger, HbA1c trend across pregnancy carries independent prognostic information about the outcomes guideline bodies use to justify intervention: macrosomia and LGA birth weight, neonatal hypoglycaemia, shoulder dystocia, and caesarean delivery. The HAPO Study Cooperative Research Group's original report established that maternal glycaemia related continuously to birth weight above the 90th percentile, cord-blood C-peptide, and neonatal adiposity with no clear inflection point, and Catalano and

colleagues' companion analysis showed the relationship persisted after adjustment for maternal obesity, indicating glycaemia and adiposity contribute independently [4,16]. Because HbA1c correlates with the same chronic glycaemic exposure, a rising trajectory across pregnancy is biologically plausible as a marker of increasing risk for the same outcome cluster, and the HAPO Follow-Up Study confirmed lasting associations between maternal glycaemia and childhood glucose metabolism [17].

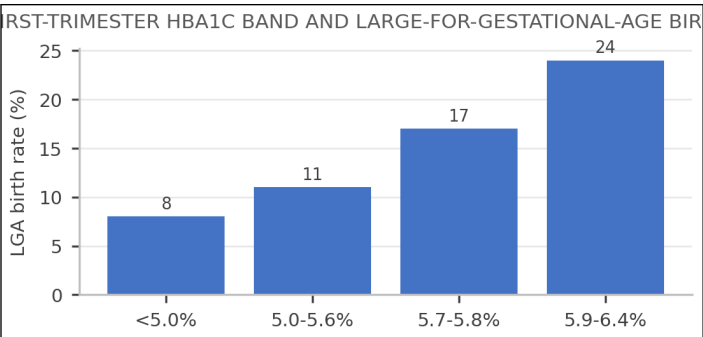


Figure 2: Pattern reported across cohorts relating first-trimester HbA1c band to subsequent large-for-gestational-age birth rate, broadly consistent with the continuous glycaemia-outcome relationship established by the HAPO study and its follow-up analyses [4,17,16].

Randomized trial evidence on treating mild gestational hyperglycaemia reinforces why a marker capable of flagging deterioration matters clinically. The ACHOIS trial found that treatment of mild GDM significantly reduced serious perinatal complications compared with routine care [18], and the subsequent trial led by Landon and colleagues confirmed reductions in macrosomia, LGA birth, shoulder dystocia, and caesarean delivery with treatment [19]. Because both trials showed that treating glycaemic control changes outcomes, HbA1c trend that flags deterioration between scheduled OGTT assessments has direct clinical utility, an argument reinforced by earlier work from Langer and colleagues on the consequences of leaving mild gestational hyperglycaemia untreated [20]. A recent systematic review and meta-analysis by Ye and colleagues reaffirmed that this outcome cluster tracks maternal glycaemic burden closely enough that any marker flagging deterioration earlier

retains practical value [21]. Figure 2 illustrates the pattern reported across cohorts relating first-trimester HbA1c band to subsequent LGA birth rate, broadly consistent with the continuous glycaemia-outcome relationship established by HAPO and its follow-up [4,17,16].

5. Comparison with the oral glucose tolerance test

HbA1c and the OGTT capture different physiological information, and their imperfect concordance is itself informative. Because HbA1c reflects an integrated average over two to three months while the OGTT captures a single provoked response, women with predominantly postprandial excursions, a common pattern in GDM, can have a near-normal HbA1c despite an abnormal OGTT, while women with sustained mild fasting hyperglycaemia may show the reverse [22]. Zhu and colleagues, evaluating fasting plasma glucose at the first prenatal visit in a large Chinese cohort, found imperfect concordance with later OGTT-based diagnosis, a pattern that generalizes to HbA1c as another early marker imperfectly capturing a diagnosis the OGTT defines by convention [22,23].

This imperfect concordance argues against HbA1c as a stand-alone replacement for the OGTT, but strengthens the case for HbA1c trend as a complementary, longitudinal signal layered on top of scheduled OGTT screening. The WHO criteria for hyperglycaemia first detected in pregnancy retain the OGTT as the diagnostic anchor while reserving HbA1c of 6.5% or higher for overt diabetes, an approach mirrored by the IADPSG and national society guidance [24,5,25]. Table 1 summarizes how HbA1c thresholds are positioned across major frameworks alongside the empirically derived early-pregnancy risk threshold identified by Hughes and colleagues [5,24,7,13].

Table 1: HbA1c thresholds for hyperglycaemia in pregnancy as positioned across major diagnostic frameworks, alongside the empirically derived early-pregnancy risk threshold reported by Hughes and colleagues [5,24,7,13].

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Source / framework	HbA1c threshold	Clinical use in pregnancy
IADPSG consensus criteria	>=6.5% (48 mmol/mol)	Identifies overt, pre-existing diabetes at first prenatal visit
WHO criteria for hyperglycaemia in pregnancy	>=6.5% (48 mmol/mol)	Diagnoses diabetes in pregnancy; OGTT remains anchor for GDM
ADA Standards of Medical Care in Diabetes	>=6.5% (48 mmol/mol)	Consistent with non-pregnant diabetes diagnostic cutoff
Hughes et al. empirical cohort threshold	>=5.9% (41 mmol/mol)	Optimal cutoff for flagging increased risk before OGTT

6. Postpartum and longer-term prognostic value

HbA1c trend analysis extends usefully beyond the antenatal period into postpartum risk stratification, where women with GDM face a substantially elevated lifetime risk of type 2 diabetes. Bellamy and colleagues, in a systematic review and meta-analysis, found that women with a history of GDM had a more than sevenfold increased risk of subsequently developing type 2 diabetes, establishing GDM as one of the strongest identifiable risk factors for future diabetes in women of reproductive age [26]. Kim and colleagues' earlier review reported a similarly striking cumulative incidence, with risk continuing to accrue for years after the index pregnancy [27].

Katon and colleagues found that antenatal glycaemic markers, including HbA1c, were associated with abnormal glucose tolerance persisting after delivery, supporting HbA1c trend as an early signal for which women warrant closer postpartum surveillance [28]. Retnakaran and colleagues similarly demonstrated that the degree of antenatal glucose intolerance predicted future pre-diabetes or diabetes risk in a graded fashion [29]. This evidence supports incorporating antenatal HbA1c trend, alongside the OGTT-based GDM diagnosis, into postpartum screening intensity, since women whose HbA1c rose most across pregnancy, or reached the intermediate band described by Rowan and colleagues, appear to warrant earlier and more frequent postpartum

testing [14,26].

Table 2: Antenatal glycaemic markers and their reported association with postpartum and longer-term diabetes risk following a gestational diabetes pregnancy [28,27,26,29].		
Study	Antenatal marker examined	Reported long-term association
[28]	Antenatal glycaemic markers including HbA1c	Associated with persistence of abnormal glucose tolerance postpartum
[27]	GDM diagnosis (systematic review)	Cumulative incidence of type 2 diabetes rises for years after delivery
[26]	GDM diagnosis (meta-analysis)	More than sevenfold increased risk of future type 2 diabetes
[29]	Degree of antenatal glucose intolerance	Graded prediction of future pre-diabetes or diabetes risk

7. Limitations and confounders

HbA1c trend analysis carries limitations that temper its clinical application in pregnancy. Haemoglobinopathies, iron deficiency anaemia, and the physiological anaemia of normal pregnancy alter erythrocyte turnover and can shift measured HbA1c independent of true glycaemic status, a confounding pathway more prevalent across a pregnant population than in the general adults used to derive most reference standards [12,9]. Because the physiological decline itself varies between individuals, a modest rise in HbA1c between two visits can reflect either genuine deterioration or a smaller-than-average physiological fall, and distinguishing the two requires a validated trimester-specific reference trajectory rather than a fixed change threshold [8,10].

Population variation in HbA1c-glycaemia relationships means that thresholds derived in one population, such as the 5.9% cutoff from a predominantly New Zealand cohort, may need local validation elsewhere [13,30]. This is conceptually related to the observation that tight early glycaemic control specifically matters for women with pre-existing diabetes, where Suhonen and colleagues showed periconceptional control predicted congenital malformation risk in a graded fashion, underscoring that an elevated early marker carries different weight in

pre-existing versus gestational-onset dysglycaemia [31]. Weight gain and pre-pregnancy body mass index further modulate the glycaemia-outcome relationship, and studies of gestational weight gain caution that HbA1c trend should be interpreted alongside, not instead of, standard risk factors such as maternal weight trajectory [32,33]. Finally, because most of this literature is observational rather than trial-based, the added value of routinely incorporating HbA1c trend into antenatal care has not been established with the same rigour as the treatment trials that justify intervening on GDM once diagnosed [18,19].

8. Conclusion

HbA1c, interpreted as a trend across pregnancy rather than as a single cross-sectional value, offers real but circumscribed prognostic value in gestational diabetes. It cannot substitute for the OGTT as the diagnostic anchor that the IADPSG, WHO, and national guideline bodies have adopted, but the evidence reviewed here supports at least three complementary roles: an early-pregnancy triage tool that stratifies women into risk bands well before a scheduled OGTT, drawing on thresholds such as the 5.9% cutoff validated by Hughes and colleagues [13,14]; a longitudinal signal, properly adjusted for the physiological decline documented across normal gestation, that can flag glycaemic deterioration between scheduled visits and support earlier escalation of care in the window where randomized trial evidence shows treatment reduces serious perinatal complications [8,18,19]; and a postpartum risk-stratification marker that, combined with the antenatal GDM diagnosis itself, helps identify which women warrant the most intensive and earliest follow-up for progression to overt type 2 diabetes [28,26]. Realizing this value in routine practice will require pregnancy- and trimester-specific reference trajectories validated across diverse populations, alongside prospective trials directly comparing HbA1c-augmented care pathways with standard OGTT-based screening, before HbA1c trend analysis can be recommended as a

standard component of antenatal surveillance rather than the useful adjunct the current evidence supports.

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