



Maternal and neonatal outcomes according to the timing of diagnosis of gestational diabetes: A critical appraisal

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Abstract

Gestational diabetes mellitus (GDM) is the most common metabolic abnormality of pregnancy and is associated with early and late adverse outcomes for both mothers and fetuses. Conventionally, GDM is diagnosed between 24 and 28 gestational weeks (GW) (late-onset GDM). With the increasing prevalence of prediabetes among women of reproductive age, GDM is increasingly being diagnosed before 24 GW in high-risk populations (early-onset GDM). Compared with late-onset GDM pregnancies, early-onset GDM pregnancies are at greater risk for neonatal adverse events, such as perinatal mortality, neonatal hypoglycemia, neonatal respiratory distress syndrome, and macrosomia. The TOBOGM study revealed that the initiation of treatment before 20 GW can modestly reduce composite neonatal outcomes, mainly due to a reduction in the rate of neonatal respiratory distress syndrome. The benefit was greater when treatment was initiated before 14 GW. The probable mechanisms for early-onset hyperglycemia-induced neonatal adverse events are decidual and placental defects, interference with fetal lung development, and fetal glucose steal. There is no international consensus on the GDM screening strategy in early pregnancy, and its cost-effectiveness is questioned by several professional bodies. Further prospective randomized controlled studies are strongly recommended to alleviate confusion in clinical practice regarding the management of mild hyperglycemia in early pregnancy.

Key Words: Maternal hyperglycemia; Adverse events; Gestational diabetes; Screening period; Diagnostic criteria; Prediabetes; Pregnancy outcomes; Neonatal outcomes

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Core Tip: Gestational diabetes mellitus (GDM) is the most common metabolic abnormality of pregnancy and is associated with early and late adverse outcomes for both mothers and fetuses. Hyperglycemia that satisfies the GDM diagnostic criteria is increasingly being identified in early pregnancy [early-onset GDM (E-GDM)]. Despite treatment, adverse pregnancy events are more common in E-GDM than in late-onset GDM. The TOBOGM study revealed a significant reduction in adverse neonatal events, especially neonatal respiratory distress syndrome, when GDM treatment was initiated in early pregnancy and reported the cost-effectiveness of this strategy. More prospective randomized controlled trials are needed to develop an internationally accepted criterion for E-GDM diagnosis.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is the most common metabolic disorder of pregnancy, affecting several million women worldwide[1], and its prevalence varies widely depending on the population studied and the diagnostic strategy employed. The global GDM prevalence is estimated to be 14% by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. The standardized (according to the IADPSG criteria) GDM prevalence in North America and the Caribbean, Europe, South and Central America, Africa, the Western Pacific, Southeast Asia, the Middle East and North Africa are 7.1%, 7.8%, 10.4%, 14.2%, 14.7%, 20.8% and 27.6%, respectively[2]. GDM is linked to several immediate pregnancy-related maternal and fetal adverse events, such as cesarean delivery, preterm delivery, gestational hypertension, large for gestational age (LGA) babies, macrosomia, birth trauma, neonatal hypoglycemia and polycythemia, neonatal jaundice, respiratory distress syndrome, and neonatal intensive care unit (NICU) admission[1]. Furthermore, GDM places mothers and infants at high risk for several long-term metabolic morbidities, such as obesity, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular morbidity[1,3,4].

Many aspects of GDM, such as its definition, diagnostic criteria, and timing of screening during pregnancy, remain without an international consensus. However, the oral glucose tolerance test (OGTT) is regarded as the gold standard for diagnosing GDM, despite its cumbersome nature and low reproducibility. Currently, there is no universal agreement on the timing of the OGTT, glucose load, glucose threshold values, or number of abnormal values required for GDM diagnosis. Most professional bodies recommend screening for undiagnosed “overt diabetes mellitus” at the first antenatal visit, employing the same criteria used for the nonpregnant population[5,6]. However, there is ongoing controversy on the clinical relevance of mild “hyperglycemia” (below the threshold for diabetes mellitus diagnosis) detected in early pregnancy. With the increasing prevalence of prediabetes among women of reproductive age in several countries, a significant number of pregnant women are identified as having “intermediate hyperglycemia” of undetermined significance at their first antenatal visit[7]. Conflicting recommendations from preeminent organizations have caused significant confusion in obstetric practice regarding GDM diagnosis outside the standard screening period of 24-28 gestational weeks (GW) used in many developing countries[7].

There is evidence to suggest the failure of current GDM screening and management strategies to reduce the short-term and long-term adverse events associated with GDM in women and their offspring to levels comparable to those of non-GDM pregnancies. Ye *et al*[8] conducted a meta-analysis of 156 studies involving 7506061 pregnant women from both developed and developing countries (after 1990, using different diagnostic criteria) and reported that, despite treatment, GDM pregnancy outcomes are suboptimal. In studies with no insulin use, when adjusted for confounders, pregnancies with GDM had increased odds of cesarean section [odds ratio (OR) = 1.16, 95% confidence interval (CI): 1.03-1.32], preterm delivery (OR = 1.51, 95%CI: 1.26-1.80), a low one-minute Apgar score (OR = 1.43, 95%CI: 1.01-2.03), macrosomia (OR = 1.70, 95%CI: 1.23-2.36), and infants born LGA (OR = 1.57, 95%CI: 1.25-1.97). In studies with insulin use, when adjusted for confounders, the odds of having an infant LGA (OR = 1.61, 95%CI: 1.09-2.37), respiratory distress syndrome (OR = 1.57, 95%CI: 1.19-2.08), neonatal jaundice (OR = 1.28, 95%CI: 1.02-1.62), or requiring admission to the NICU (OR = 2.29, 95%CI: 1.59-3.31) were greater in pregnancies with GDM than in those without. Another meta-analysis by García-Patterson *et al*[9] evaluated the impact of GDM treatment on medium- and long-term outcomes after pregnancy. The analysis included five studies (1140 women, 767 offspring) with follow-ups ranging from 4 to 16 years after delivery. GDM treatment did not reduce the risk of maternal diabetes [relative risk (RR) = 1.00; 95%CI: 0.82-1.23] or metabolic syndrome (RR = 0.93; 95%CI: 0.71-1.22). Additionally, treating GDM did not change the offspring's risk for impaired fasting glucose (OR = 0.79; 95%CI: 0.39-1.69) or body mass index (BMI) $\geq$ 85th centile (RR = 0.91; 95%CI: 0.74-1.12). A retrospective cohort study from a tertiary center in Sydney, Australia[10], reported that pregnancies with GDM had higher rates of several adverse outcomes. Interestingly, compared with non-GDM pregnancies, only women with GDM who attended nondedicated clinics experienced increased adverse outcomes; higher odds of hypertensive disorders of pregnancy [adjusted OR (aOR) = 1.6, 95%CI: 1.2-2.0], preterm birth (aOR = 1.7, 95%CI: 1.4-2.0), and obstetric anal sphincter injuries (aOR = 1.4, 95%CI: 1.0-2.0). These findings suggest that specialized treatment of GDM in a dedicated multidisciplinary clinic can reduce many adverse events. However, increased odds of admission to the NICU/special care nursery were observed in both the nonspecialized clinics (aOR = 1.5, 95%CI: 1.3-1.8) and the specialized GDM clinics

(aOR = 1.7, 95% CI: 1.3-2.2).

The above studies suggest the need to critically evaluate and modify our current strategies for GDM screening, diagnosis, and management with the ultimate aim of reducing adverse pregnancy outcomes to levels comparable to those of non-GDM pregnancies. The potential areas of improvement include: (1) Early identification of hyperglycemia during pregnancy and timely interventions; (2) Defining trimester- and ethnicity-specific screening and management strategies; and (3) Developing dedicated GDM care centers, especially among high-risk populations.

The main objective of this minireview is to explore the current knowledge regarding the impact of maternal hyperglycemia at different stages of pregnancy on the development of maternal and neonatal adverse events, with a special focus on hyperglycemia in early pregnancy. Additionally, the mechanisms of hyperglycemia-induced adverse pregnancy events and the benefits and cost-effectiveness of GDM treatment in early pregnancy are discussed. Furthermore, the scope of this minireview includes a brief update on the current recommendations on GDM screening strategies and the diagnostic criteria.

GDM SCREENING TIMING: CURRENT PRACTICES AND CONTROVERSIES

Several preminent professional bodies have proposed GDM screening between 24 and 28 GW (Table 1)[1,5,11-21]. The selection of this time window is guided by the assumption that placental hormones are elevated enough by 24 GW to produce adequate insulin resistance to accurately diagnose women with GDM. Furthermore, identifying GDM pregnancies before 29 GW provides adequate time for therapeutic interventions to prevent maternal and neonatal complications. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study provides strong evidence that maternal hyperglycemia between 24 and 32 GW is linked to adverse pregnancy outcomes, and controlling “mild hyperglycemia” has been shown to reduce these adverse events in various randomized controlled trials[22,23]. However, limiting the harmful effects of mild maternal hyperglycemia to only the gestational period after 24 GW raises several concerns: (1) The general concept is that the physiological decline in insulin sensitivity in the second half of pregnancy is caused by rising placental hormones, which leads to maternal hyperglycemia after 24 GW. However, pathological insulin resistance due to obesity and a prediabetic state unrelated to placental hormones can result in mild hyperglycemia in early pregnancy. With the increasing prevalence of prediabetes among women of reproductive age in many countries, a significant proportion of pregnant women have insulin resistance in the periconceptual period itself[24]; (2) Postponing GDM screening to 24 GW suggests that milder dysglycemia in early pregnancy has less clinical significance and that all maternal and fetal complications are associated with glucose intolerance occurring after 24 GW; and (3) Dysglycemia in early pregnancy is considered significant only if it persists after 24 GW; the reason cited by the IADPSG is to withdraw permission to use their criteria for GDM diagnosis before 24 GW[15].

Taking these concerns into consideration, many preminent professional organizations, such as the World Health Organization (WHO) and the Australasian Diabetes in Pregnancy (DIP) Society, permit screening for GDM in early pregnancy among high-risk populations[16,21]. However, the recommendations of professional bodies, such as IADPSG (2016 revision after initial permission in 2010), against GDM diagnosis before 24 GW raised several management issues, especially in developing countries with a high GDM prevalence[15].

GDM DIAGNOSTIC CRITERIA CHALLENGES

Several guidelines and criteria are used for GDM screening in different regions, among which the two-step criteria suggested by Carpenter and Coustan (C & C criteria) and the one-step criteria of the IADPSG have wide acceptance[12, 14] (Table 1). The first criteria for diagnosing GDM was proposed by O’Sullivan and Mahan in 1964[25]. These criteria were later validated in 1980 by ensuring their predictability for long-term glucose intolerance (22.6% at 8 years, 60% at 16 years of follow-up) and increased perinatal mortality[11]. O’Sullivan’s criteria were derived from OGTTs performed among 752 pregnant women in the obstetric department of Boston City Hospital between December 1956 and April 1957. These OGTTs represented different periods of gestation: 10-14, 15-28, and ≥ 29 GW in 30, 359, and 363 women, respectively. Therefore, glucose threshold values for GDM diagnosis were derived from the pooled blood sugar values of different trimesters (not the 24-28 GW period alone). In 1979, the National Diabetes Data Group introduced new GDM criteria by increasing O’Sullivan’s threshold values by 14% (considering the changes in laboratory standards from whole blood to plasma or serum glucose values)[13]. In 1982, Carpenter and Coustan[12] converted these threshold values for blood sugar (estimated by the Somogyi-Nelson method) to plasma glucose values (enzymatic method using glucose oxidase) to develop the popular C & C criteria. The American College of Obstetricians and Gynecologists and the American Diabetes Association support the C & C criteria for GDM diagnoses between 24 and 28 weeks, with permission for its use before 24 weeks for high-risk obstetric populations[5,17].

The IADPSG criteria (accepted by the WHO in 2013) are based on the seminal HAPO study, which included 25505 women of different races and ethnicities[14,26]. The IADPSG (2010) proposed fasting, 1-hour, and 2-hour post load plasma glucose threshold values on a 75 g OGTT on the basis of the strong association of these plasma glucose values between 24 and 32 GW and adverse pregnancy outcomes in the HAPO study. Therefore, the IADPSG criteria are the best-validated test for GDM diagnosis between 24 and 28 GW. When the criteria were introduced in 2010, a fasting plasma glucose (FPG) value ≥ 92 mg/dL was considered a diagnostic test of GDM at any stage of pregnancy. In 2016, the IADPSG retracted the recommendation to use FPG for GDM diagnoses before 24 GW[15]. This change in recommendation was based on the poor predictability of FPG in early pregnancy for GDM development after 24 GW.

Table 1 Commonly used gestational diabetes mellitus diagnostic criteria

Ref. ¹	Diagnostic approach	Standard screening period	GDM diagnosis: PG threshold values in mmol/L, at or above	GDM diagnosis: Criteria before 24 GW	Comments and controversies
O'Sullivan and Mahan [25], 1964	Two step screening, 50 g OCT, if positive, 100 g OGTT	Not specified by the authors	FPG 5, 1-hour PG 9.2, 2-hour PG 6.9, 3-hour PG 7, 2 abnormal values	Not specified by the authors	The first validated test for GDM diagnosis based mainly on future development of type 2 diabetes. No specific data of E-GDM. Controversy on sensitivity of OCT ² . 100 g glucose produces gastric discomfort
NDDG, 1979	Two step screening; 50 g OCT, if positive, 100 g OGTT	Not specified by the NDDG	FPG 5.9, 1-hour PG 10.6, 2-hour PG 9.2, 3-hour PG 8.1, 2 abnormal values	Not specified by NDDG	14% change in glucose threshold values, considering the changes in laboratory standards from whole blood to plasma or serum glucose values. Controversy on sensitivity of OCT ² . 100 g glucose produces gastric discomfort
Carpenter and Coustan [12], 1982	Two step screening, 50 g OCT, if positive, 100 g OGTT	Not specified by the authors	FPG 5.3, 1-hour 10, 2-hour 8.6, 3-hour 7.8, 2 abnormal values	Not specified by authors	Modification for plasma glucose estimation by glucose oxidase technique. Controversy on sensitivity of OCT ² . 100 g glucose produces gastric discomfort. Many organizations recommend C & C criteria for E-GDM screening
IADPSG, 2010, modified 2016	One step, 75 g OGTT	24-28 GW	FPG 5.1, 1-hour PG 10, 2-hour 8.5, one abnormal value	Recommendation of FPG ≥ 5.1 mmol/L in 2010, withdrawn in 2016	Derived from the strong pregnancy outcome data of HAPO study. Concerns about marked increase in GDM prevalence and the cost effectiveness of these criteria. Many countries use these criteria for early pregnancy
WHO, 2013	One step, 75 g OGTT	24-28 GW	FPG 5.1, 1-hour PG 10, 2-hour 8.5, one abnormal value	Recommends same criteria as of 24-28 GW for high-risk women	In 2013, the WHO changed the 1999 criteria, accepting the IADPSG criteria
ADA, 2025	One step, IADPSG, or 2 step C & C criteria	24-28 GW	Either IADPSG or C & C criteria for diagnosis	For high-risk women: FPG 6.1-6.9 mmol/L, HbA1c 41-47 mmol/mol	Approves both IADPSG and C & C criteria, causing confusion among obstetricians/diabetologists. There are major differences in GDM prevalence by these criteria. Does not recommend IADPSG or C & C criteria for use in early pregnancy
ACOG, 2018	Two step screening, 50 g OCT, if positive, 100 g OGTT	24-28 GW	Either C & C criteria or alternative NDDG: FPG 5.8, 1-hour 10.6, 2-hour 9, 2 abnormal values	For high-risk women: Same criteria as for 24-28 GW	All concerns of C & C and NDDG criteria
NICE, 2020	One step screening, screening only for high-risk women, one step 75 g OGTT	24-28 GW	FPG 5.6, 2-hour PG 7.8, one abnormal value	Recommend 75 g OGTT at booking for women with GDM history: Same diagnostic criteria as for 24-28 GW	Mainly used in United Kingdom. Concerns about racial differences in GDM diagnosis by these criteria. Permitted for use in early pregnancy for women with history of GDM only (not for other risks)
CDA, 2018	Two step screening, 50 g OCT, if positive, 75 g OGTT. Alternatively, one step IADPSG criteria	24-48 GW	If 1-hour OCT 111 or 75 g OGTT: FPG 5.3, 1-hour PG 10.6, 2-hour PG 9, one abnormal value	High risk women: Same criteria as for 24-28 GW at any stage in pregnancy	Issues related with sensitivity of screening OCT as with ACOG criteria
Govt of India Guideline, 2018	One step, non-fasting 75 g OGTT	If negative for GDM at booking, rescreen at 24-28 GW	2-hour PG 7.8	Universal screening: 75 g OGTT at booking	Only diagnostic OGTT in non-fasting state. May be of relevance in rural setting. Concerns about the validity of this test
ADIPS, 2013	One step, 75 g OGTT	24-28 GW	FPG 5.1, 1-hour PG 10, 2-hour 8.5, one abnormal value	For high-risk women 75 g OGTT at first opportunity after conception. Same criteria as for 24-28 GW	Criteria same as in IADPSG, but permits its use in early pregnancy

¹The year of last update of the criteria by the author or professional association.²Screening 50 g oral glucose challenge test can miss 20% gestational diabetes women, especially those with high fasting plasma glucose values.

GDM: Gestational diabetes mellitus; PG: Plasma glucose; GW: Gestational weeks; NDDG: National Diabetes Data Group; IADPSG: International

Association of Diabetes in Pregnancy Study group; WHO: World Health Organization; ADA: American Diabetes Association; ACOG: American College of Obstetricians and Gynecologists; NICE: National Institute for Health and Clinical Excellence; CDA: Canadian Diabetes Association; ADIPS: Australasian Diabetes in Pregnancy Society; OCT: Oral glucose challenge test; OGTT: Oral glucose tolerance test; FPG: Fasting plasma glucose; E-GDM: Early-onset gestational diabetes; C & C criteria: Carpenter and Coustan criteria; HbA1c: Glycated hemoglobin A1c; HAPO: Hyperglycemia and Adverse Pregnancy Outcomes.

However, owing to a lack of alternative tests, many centers in both developed and developing countries continue to use the IADPSG criteria for GDM diagnosis before 24 GW[7,27,28].

Many regionally adopted criteria, such as the Australasian DIP Society, the National Institute for Health and Care Excellence (NICE) guidelines, the Ministry of Health; Government of India guidelines, and the Canadian Diabetes Association guidelines, are modifications of other internationally accepted criteria[19,20,21]. However, these modifications do not have the strength of being validated by pregnancy outcome data. Table 1 summarizes the details of various professional bodies recommendations for the GDM screening protocol (one or two steps), OGTT procedure (glucose load, timing of blood sampling, diagnostic blood/plasma glucose values), validity of the criteria for early pregnancy, and controversies. To date, there is no international consensus on the use of any of these criteria, even for GDM screening in the 24-28 GW period.

PREGNANCY OUTCOMES BY GDM DIAGNOSIS TIMING

HAPO study observations

The HAPO study data were reanalyzed in 2012 by Lowe *et al*[29] to assess the efficacy of glycated hemoglobin A1c (HbA1c) as an alternative to OGTT for GDM diagnosis. Although the study concluded that HbA1c is not a useful alternative to OGTT in this regard, the analysis yielded interesting findings. The plasma glucose levels measured during the 24-32 GW period were significantly and strongly associated with the neonate's birth weight, sum of skin folds, and a percentage of body fat > the 90th percentile. In contrast, after adjustment for the composite glucose measure, the HbA1c level during the 24-32 GW period was not significantly associated with any of the above neonatal anthropometric outcomes. However, this difference between HbA1c and plasma glucose values was not observed for primary cesarean delivery, preterm delivery, clinical neonatal hypoglycemia, or preeclampsia. This analysis is relevant, as HbA1c reflects average glycemia over the preceding three months, and the adjustment for the composite glucose measure eliminated the impact of recent maternal glycemia. Hence, it is speculated that the risks for these outcomes are influenced by glycemia earlier in pregnancy, whereas the anthropometric outcomes are more strongly associated with glycemia later in pregnancy. This observation is of clinical relevance, as the data are derived from a closely monitored multiethnic HAPO cohort with no therapeutic interventions to lower glucose at any stage of pregnancy.

Comparison of adverse pregnancy outcomes between early-onset GDM and late-onset GDM pregnancies

In 2017, a systematic review and meta-analysis on screening and treatment of early-onset GDM (E-GDM) was performed by Immanuel and Simmons[30]. Upon screening 1495 articles, only 13 cohort studies (15270 GDM women) reported long-term data on pregnancy outcomes. The authors compared the treatment response of GDM pregnancies diagnosed before 24 GW (E-GDM) with that of those diagnosed with GDM after 24 GW [late-onset GDM (L-GDM)]. All studies used OGTTs for GDM diagnosis except one, which used HbA1c. In the meta-analysis, E-GDM pregnancies had a significantly greater likelihood of perinatal mortality (RR = 3.58, 95%CI: 1.91-6.71), neonatal hypoglycemia (RR = 1.61; 95%CI: 1.02-2.55), and insulin use (RR = 1.71; 95%CI: 1.45-2.03) than L-GDM pregnancies did. In a subgroup analysis, E-GDM in developed countries was associated with a significantly greater likelihood of NICU admission (RR = 1.12; 95%CI: 1.04-1.22). There was no significant difference between E-GDM and L-GDM in terms of mean birth weight or small or LGA babies.

From this exhaustive review and meta-analysis by Immanuel and Simmons[30] in 2017 to date, we identified six studies (with proper follow-up and statistical analysis data) that compared the adverse pregnancy outcomes of GDM diagnosed in early and late pregnancy[28,31-35]. Table 2 summarizes the details of their design, diagnostic criteria, adverse outcomes, statistical methodologies, and confounding factors. Four of these studies were comparative assessments between treatment for GDM in early and late pregnancy, whereas two compared adverse outcomes with those of non-GDM pregnancies. Most of these studies were retrospective in design (except the Tirado-Aguilar *et al*'s study [35]) and were limited by their study design, GDM diagnostic criteria, and differences in the selection of GW to define E-GDM. In four studies, GDM diagnosis was based on the IADPSG criteria, and two studies used a two-step screening strategy based on the C & C criteria or National Diabetes Data Group introduced new GDM criteria. Most of these studies used risk-based E-GDM screening strategies. The GDM risk factors for the women in these studies at the time of diagnosis are shown in Table 3.

Table 4 illustrates the comparative adverse pregnancy outcomes of these cohort studies. Similar to the meta-analysis by Immanuel and Simmons[30], the present series predominantly revealed higher aORs for adverse neonatal outcomes among pregnancies with E-GDM. Four studies reported data on neonatal hypoglycemia, and three reported that the aORs for this event were greater in the E-GDM group than in the L-GDM group: RR = 18.57, 95%CI: 2.69-21.21; RR = 3.5, 95%CI: 2-6.1; and RR = 4.2, 95%CI: 2.01-9 (compared with the non-GDM group but with higher aORs in the E-GDM group than in the L-GDM group). Similarly, compared with L-GDM, E-GDM pregnancies(< 14 GW) had greater aORs for perinatal

Table 2 Design of studies comparing of adverse pregnancy outcomes between women having early gestational diabetes and late-onset gestational diabetes

Ref.	Study time	Country	Study design	GDM diagnostic criteria	Adverse outcomes assessed in the study, statistical methodology, confounding factors
Feghali <i>et al</i> [31]	January 2009 to October 2012	United States	Retrospective study; PGDM excluded; E-GDM < 24 GW, <i>n</i> = 167; L-GDM ≥ 24 GW, <i>n</i> = 1202; routine GDM care to all	Two step screening using; C & C criteria for both E-GDM and L-GDM; risk-based E-GDM screening	Macrosomia, preterm delivery, gestational hypertension, neonatal morbidity, conditional logistic regression analysis, reference L-GDM, confounding factors; maternal age, maternal race, education, private insurance, nulliparity, prepregnancy BMI, tobacco use, GDM history, 50 g glucose challenge test value, reference L-GDM
Shub <i>et al</i> [32]	January 2005 to January 2016	Australia	Retrospective study; PGDM exclusion: Not mentioned; E-GDM < 20 GW, <i>n</i> = 170; L-GDM ≥ 20 GW, <i>n</i> = 171; no GDM, <i>n</i> = 547; routine GDM care to all	One step screening; same criteria for E-GDM and L-GDM; till 2013: FPG ≥ 5.5 mmol/L, or 2-hour PG ≥ 8 mmol/L. From 2014: IADPSG criteria, risk-based E-GDM screening	Composite obstetric outcome (caesarian, macrosomia, LGA, perineal tear, shoulder dystocia), composite neonatal outcomes (Apgar < 7 at 5 minutes, NICU admission, neonatal hypoglycemia, major birth defect). Multivariate logistic regression, reference “no GDM”. Confounding factors; maternal age, BMI, parity and region of birth
Punnose <i>et al</i> [33]	January 2011 to September 2017	India	Retrospective study; PGDM excluded; E-GDM < 24 GW, <i>n</i> = 255 (< 14 GW, <i>n</i> = 125, 14-23 GW, <i>n</i> = 130); L-GDM ≥ 24 GW, <i>n</i> = 467; routine GDM care to all	One step screening by IADPSG criteria for both E-GDM and L-GDM; risk-based E-GDM screening	Premature birth, caesarian delivery, LGA babies, NICU admission, gestational hypertension, induction of labor, macrosomia, Apgar < 7 at 1 or 5 minutes. Multivariate regression analysis, reference “no-GDM”. Confounding factors; age, gravida, gestational age at delivery (except for premature delivery and LGA babies), hemoglobin, socioeconomic level, education, hypertension in pregnancy (except for gestational hypertension), BMI
Yefet <i>et al</i> [34]	August 2005 to January 2018	Israel	Retrospective study; PGDM excluded; study groups, GDM < 14 GW (T1), <i>n</i> = 117, GDM 14-23 GW (T2), <i>n</i> = 116, GDM ≥ 24 GW (T3), <i>n</i> = 2334. Also grouped as E-GDM < 24 GW, <i>n</i> = 233, L-GDM ≥ 24 GW, <i>n</i> = 2334; routine GDM care to all	Two step screening; C & C criteria or NDDG criteria for E-GDM and L-GDM. Risk based E-GDM screening	Composite neonatal outcomes (LGA babies, neonatal hypoglycemia, neonatal hyperbilirubinaemia. Other outcomes: Preterm birth, shoulder dystocia, birth trauma, foetal malformations. Multivariable logistic regression analysis, reference L-GDM. Confounding factors: Type of GDM control (A1 with diet alone, A2 with medications, age, BMI, parity, delivery week
Tirado-Aguilar <i>et al</i> [35]	January 2022 to May 2023	Mexico	Prospective study; PGDM excluded; E-GDM < 24 GW, <i>n</i> = 173; L-GDM 24-28 GW, <i>n</i> = 196; routine GDM care	One step screening, IADPSG for both E-GDM and L-GDM groups. Universal OGTT at first prenatal visit, if negative repeat screening 24-28 GW	Gestational hypertension, neonatal hypoglycemia, respiratory distress syndrome, neonatal asphyxia, neonatal hyperbilirubinaemia, mechanical ventilation, neonatal death. Logistic regression model analysis, reference L-GDM. Confounding factors; maternal age, pregestational BMI
Regnault <i>et al</i> [28]	2018 French National Health Data	France	Retrospective study; PGDM excluded from GDM; 84705 women with hyperglycemia in pregnancy. GDM < 22 GW, <i>n</i> = 31134; GDM 22-30 GW, <i>n</i> = 44412; GDM > 30 GW, <i>n</i> = 8789; no GDM treatment details	Before 24 GW: FPG ≥ 5.1 mmol/L. > 24 GW: IADPSG criteria	Maternal outcomes: Caesarian, pre-eclampsia, ante and post-partum hemorrhage. Neonatal outcomes: Perinatal death, congenital malformations, LGA, Erb's palsy and calvarial fracture, foetal distress, NICU admission, neonatal hypoglycemia preterm delivery. Multilevel Poisson regression analysis, reference L-GDM. Confounding factors; maternal age, socioeconomic status, and gestational age of delivery except for preterm delivery

PGDM: Pregestational diabetes mellitus; E-GDM: Early-onset gestational diabetes; L-GDM: Late-onset gestational diabetes; GDM: Gestational diabetes mellitus; GW: Gestational weeks; BMI: Body mass index; FPG: Fasting plasma glucose; PG: Plasma glucose; IADPSG: International Association of Diabetes in Pregnancy Study Group; LGA: Large for gestational age babies; NICU: Neonatal intensive care unit; BMI: Body mass index; C & C criteria: Carpenter and Coustan criteria; T1: First trimester; T2: Second trimester; T3: Third trimester; NDDG: National Diabetes Data Group; OGTT: Oral glucose tolerance test.

mortality (Regnault *et al*[28]: RR = 1.51, 95%CI: 1.19-1.91), shoulder dystocia (Yefet *et al*[34]: RR = 10.3, 95%CI: 2.4-44.6), respiratory distress (Shub *et al*[32]: RR = 4.6, 95%CI: 1.91-15.16), Erb's palsy (Regnault *et al*[28]: RR = 1.55, 95%CI: 1.22-1.99), and preterm labor (Punnose *et al*[33]: RR = 2.3, 95%CI: 1.45-3.64). An interesting observation in the study by Punnose *et al*[33] was a 19% increase in aOR for premature delivery for every 4 weeks decrease of gestational age from 28 GW[33]. An increase in aOR for LGA babies/macrosomia was observed in three studies. Regnault *et al*[28]: RR = 1.10, 95%CI: 1.08-1.175, Feghali *et al*[31]: RR = 2.00, 95%CI: 1.4-4.1, and Punnose *et al*[33]: RR = 1.61, 95%CI: 1.10-2.67 in the < 14 GW group but not in the 14-23 GW group. The Renault study has limitations due to its failure to include maternal prepregnancy BMI as a confounding factor in the analysis of LGA babies[28]. Immanuel and Simmons[30] did not attempt to assess the impact of GDM diagnostic criteria on adverse pregnancy outcomes. The GDM diagnoses in four studies included in the present analysis were based on the IADPSG criteria, whereas two studies used tighter C & C

Table 3 Comparative assessment of gestational diabetes mellitus risk factors and maternal glycemia at diagnosis, among early gestational diabetes and late gestational diabetes women, mean $\pm$ SD/mean (interquartile range)/n (%)

Ref.	Number of GDM women (n)	Age, years	BMI, kg/m ²	Nulliparity	History of GDM	Family history of diabetes	Race	FPG, mmol/L	1-hour PG, mmol/L	2-hour PG, mmol/L
Feghali <i>et al</i> [31]	E-GDM, 160; L-GDM, 1202	32.4 $\pm$ 5.2, 31.2 $\pm$ 5.5, $P = 0.007$	35.4 $\pm$ 8.5, 29.4 $\pm$ 7.5, $P = 0.001$	62 (37.1), 619 (51.5), $P = 0.001$	54 (32.9), 113 (9.5), $P < 0.001$		White 725%, White 76%, $P = 0.1$	5.51 $\pm$ 0.96, 5.06 $\pm$ 0.83, $P < 0.0001$	11.17 $\pm$ 1.71, 10.84 $\pm$ 1.46, $P = 0.04$	9.99 $\pm$ 2.23, 9.84 $\pm$ 1.47, $P = 0.5$
Shub <i>et al</i> [32]	E-GDM, 170; L-GDM, 171	33 (30-36), 32 (30-35), $P < 0.001$	29 (25-35), 27 (23-35), $P = 0.15$	39 (22.9), 43 (25.1), $P = 0.01$				5.01 $\pm$ 5.02, 4.63 $\pm$ 0.37, $P < 0.001$	9.82 $\pm$ 1.82, 8.18 $\pm$ 1.48, $P < 0.001$	8.41 $\pm$ 1.36, 6.41 $\pm$ 1.02, $P < 0.001$
Punnose <i>et al</i> [33]	E-GDM, 255; L-GDM, 467	29.42 $\pm$ 4.01, 28.35 $\pm$ 3.62, $P < 0.001$	26.4 $\pm$ 4.45, 25.37 $\pm$ 4.19, $P = 0.021$	111 (43.53), 234 (50.11), $P = 0.273$	107 (41.96), 178 (38.12), $P = 0.111$	103 (40.39), 110 (23.55), $P < 0.001$	255 (100), 461 (100), all Asian Indians	5.26 $\pm$ 0.46, 5.19 $\pm$ 0.43, $P = 0.089$	9.08 $\pm$ 1.72, 9.36 $\pm$ 1.60, $P = 0.023$	7.55 $\pm$ 1.43, 7.47 $\pm$ 1.37, $P = 0.675$
Yefet <i>et al</i> [34]	E-GDM, 243; L-GDM, 2334	33.3 $\pm$ 5.3, 32.1 $\pm$ 5.5, $P = 0.002$	30.5 $\pm$ 6.2, 27.5 $\pm$ 8.7, $P < 0.001$	30 (12), 642 (28), $P = 0.001$						
Tirado-Aguilar <i>et al</i> [35]	E-GDM, 173; L-GDM, 196	32 (28-37), 32 (27-37), $P = 0.657$	8.5 (25.1-32.4), 27.6 (24.2-31.6), $P = 0.067$					5.17 (4.8-5.4), 4.97 (4.6-5.3), $P = 0.010$	8.94 (7.8-9.8), 9.27 (7.8-10), $P = 0.173$	7.06 (6-8.1), 7.39 (6.3-8.6), $P = 0.016$
Regnault <i>et al</i> [28]	E-GDM, 31134; L-GDM, 44412	32.3 $\pm$ 5.3, 32.3 $\pm$ 5.3								

GDM: Gestational diabetes mellitus; BMI: Body mass index; FPG: Fasting plasma glucose; PG: Plasma glucose; E-GDM: Early-onset gestational diabetes; L-GDM: Late-onset gestational diabetes.

criteria. The heterogeneity of the study design and lack of uniformity in the assessment of adverse events in studies using different criteria are major limitations to making a comparative assessment of the impact of different diagnostic criteria on adverse events.

The relative effect and the absolute risk difference for E-GDM treatment compared with L-GDM treatment for different adverse events are shown in Table 5. Immanuel and Simmons[30] reported absolute risk differences of 8.2% and 0.6% for neonatal hypoglycemia and perinatal mortality, respectively. Significant absolute risk differences were observed for neonatal hypoglycemia in two studies (Tirado-Aguilar *et al*[35] 10.6% and Yefet *et al*[34] 6.8%), respiratory distress in one study (Tirado-Aguilar *et al*[35] 9.8%), shoulder dystocia in one study (Yefet *et al*[34] 2.8%), and macrosomia in one study (Feghali *et al*[31], 7.9%). However, the risk difference for perinatal mortality in the present analysis was not significant.

Maternal glycemia before 24 GW and adverse events

A large retrospective cohort study among 12918 high-risk women in Hong Kong, China, reported a continuous increase in adverse pregnancy outcomes with increasing FPG and 2-hour plasma glucose (PG) levels before 24 GW[27]. The increased risk of developing any pregnancy complications started with an FPG of 4.5-4.7 mmol/L and a 2-hour PG of 6.2-6.9 mmol/L. Every increase of 1 mmol/L in FPG or 2-hour PG level increased the risk of developing any complications (aOR 1.614 for FPG and 1.131 for 2-hour PG), preeclampsia (aOR 1.472 for FPG and 1.143 for 2-hour PG), maternal insulin use (aOR 12.821 for FPG and 2.366 for 2-hour PG), primary cesarean section (aOR 1.274 for FPG and 1.099 for 2-hour PG), shoulder dystocia (aOR 1.941 for FPG and 1.282 for 2-hour PG), macrosomia (aOR 2.203 for FPG and 1.072 for 2-hour PG), and LGA babies (aOR 2.157 for FPG and 1.074 for 2-hour PG). The results of this study suggest that glycemic levels during early pregnancy (< 24 GW) among high-risk women are positively associated with adverse pregnancy events, even at levels below the current recommended diagnostic criteria for GDM.

Maternal glycemia in the first trimester (< 14 GW) and adverse pregnancy outcomes

Evaluating the importance of mild maternal hyperglycemia, which does not satisfy an overt diabetes diagnosis in early pregnancy, is vital for many population groups where prediabetes is common. This is often unmasked during the routine screening for overt diabetes by FPG and HbA1c estimation at booking. Several studies have investigated the association of mild hyperglycemia in the first trimester with adverse pregnancy outcomes.

Riskin-Mashiah *et al*[36] undertook a study of FPG in the first trimester in 6129 women at a median of 9.5 GW. FPG levels were analyzed in seven categories, as in the HAPO study. The frequency of LGA neonates/macrosomia increased from 7.9% in the lowest (< 4.17 mmol/L) to 19.4% in the highest (5.56-5.83 mmol/L) FPG category (aOR = 2.82; 95%CI: 1.67-4.76). Primary cesarean delivery increased from 12.7 to 20.0% in these categories; the aOR was 1.94, 95%CI: 1.11-3.41. There was no significant association between the fasting glucose category and either preterm delivery (< 37 GW) or NICU

Table 4 Adverse pregnancy outcomes among treated early gestational diabetes women in comparison with late-onset gestational diabetes or non-gestational diabetes mellitus women

Outcome	Immanuel and Simmons [30], Ref: L-GDM, E-GDM, RR (95%CI)	Feghali et al [31], Ref: L-GDM, E-GDM, aOR (95%CI)	Tirado-Aguilar et al [35], Ref: L-GDM, E-GDM, aOR (95%CI)	Regnault et al [28], Ref: L-GDM, E-GDM, aPR (95%CI)	Yefet et al [34], Ref: L-GDM, E-GDM, aOR (95%CI)	Punnose et al [33]		Shub et al [32]	
						Ref: No GDM, L-GDM, aOR (95%CI)	Ref: No GDM, E-GDM, aOR (95%CI)	Ref: No GDM, L-GDM, aOR (95%CI)	Ref: No GDM, E-GDM, aOR (95%CI)
LGA babies	1.07 (0.86-1.35)			1.10 ¹ (1.06-1.14)	NS	1.37 ¹ (1.08-1.75)	2.02 ¹ (1.51-2.71)	0.6 (0.40-1.02)	0.8 (0.49-1.23)
Perinatal mortality	3.58 ¹ (1.91-6.7)		0.29 (0.18-2.78)	1.51 ¹ (1.19-1.91)					
Neonatal hypoglycemia	1.61 ¹ (1.02-2.55)		18.57 ¹ (2.69-21.2)	1.08 (0.96-1.22)	3.5 ¹ (2-6.1)			3.3 ¹ (1.5-7.06)	4.2 ¹ (2.01-9.00)
NICU admission	1.16 (0.9-1.49)			1.04 (0.98-1.12)		1.59 ¹ (1.22-2.07)	1.89 ¹ (1.37-2.62)	1.4 (0.85-2.29)	1.6 (0.95-2.63)
Small for gestational age	1.27 (0.92-1.75)								
Macrosomia	1.05 (0.77-1.41)	2 ¹ (1-4.2)							
Gestational hypertension or preeclampsia	1.34 (0.98-1.82)	1 (0.5-1.8)	0.71 (0.18-2.78)	0.96 (0.88-1.05)		0.74 (0.43-1.27)	0.82 (0.43-1.56)	0.52 (0.22-1.25)	0.48 (0.2-1.31)
Preterm	1.16 (0.84-1.61)	1.6 (0.9-2.9)		1.01 (0.95-1.07)	NS	2.04 ¹ (1.54-2.69)	3.14 ¹ (2.28-4.33)		
Caesarian	1.09 (0.94-1.26)			1.03 (1-1.05)		1.02 (0.83-1.26)	1.38 ¹ (1.05-1.81)		
Shoulder dystocia	1.76 (0.96-3.24)				10.3 ¹ (2.4-44.6)				
Hyperbilirubinemia	1.16 (0.91-1.48)		1.14 (0.68-2.24)		1.3 (0.9-1.8)				
Respiratory distress	1 (0.76-1.32)		4.76 ¹ (1.91-15.16)						
Erb's palsy and clavicular fracture				1.55 ¹ (1.22-1.99)					
Apgar at 5-minute < 7/neonatal asphyxia			3.29 (0.61-17.9)			1.54 (0.59-2.51)	1.59 (0.86-1.08)	0.6 (0.17-2.30)	0.37 (0.08-1.80)
Induction of labor						1.45 ¹ (1.17-1.8)	1.25 (0.94-1.65)	2.48 ¹ (1.61-3.84)	2.46 ¹ (1.55-3.93)
Neonatal composite		1 (0.6-1.7)						1.4 (0.9-2.23)	1.8 ¹ (1.15-2.92)
Obstetric composite								0.78 (0.53-1.12)	1.16 (0.79-1.71)
Others			NS. For still birth, enterocolitis, mechanical ventilation, ventricular hemorrhage	NS. For ante or post-partum hemorrhage, congenital malformations	NS. For birth trauma, fetal malformations			Comparable perineal tear, major birth defects	Comparable perineal tear, major birth defects

¹Statistically significant.

GDM: Gestational diabetes mellitus; E-GDM: Early-onset gestational diabetes; L-GDM: Late-onset gestational diabetes; RR: Risk ratio; aOR: Adjusted odds ratio; aPR: Adjusted prevalence ratio; CI: Confidence interval; LGA: Large for gestational age; NICU: Neonatal intensive care unit; NS: No difference in univariate analysis, no further multivariate analysis.

admission. Even after women who developed GDM later in pregnancy were excluded, the association between FPG in the first trimester and adverse pregnancy outcomes remained almost unchanged (aOR = 1.5, 95%CI: 1.18-1.95). The fact that FPG in the first trimester *per se* can be associated with adverse events (even without the development of L-GDM) signifies the importance of screening for maternal hyperglycemia in the first trimester. We reported a similar association of HbA1c in the first trimester with adverse pregnancy events among non-GDM women. In a survey of 1618 Asian Indian pregnant women who did not develop GDM later, having an HbA1c level between 37 and 46 mmol/mol (5.5%-6.4%) in the first trimester was linked to a greater chance of preterm birth (aOR = 2.10, 95%CI: 1.11-3.98)[37]. Additionally, for every five mmol/mol (0.5%) increase in HbA1c during the first trimester, there was a greater risk of primary cesarean delivery (aOR = 1.27; 95%CI: 1.06-1.52).

Even for those women who develop GDM in late pregnancy, a prediabetic state in the first trimester can be an additional risk factor for adverse events. Wilkie *et al*[38] retrospectively assessed 956 women with a GDM diagnosis after 24 GW. In this cohort, 696 women had prediabetes (by FPG, HbA1c, or OGTT) in the first trimester, whereas 260 women screened negative for prediabetes. Compared with women who screened negative for prediabetes, infants born to GDM mothers who screened positive for prediabetes in the first trimester were more likely to have NICU admission compared to those women who screened negative for prediabetes (aOR = 8.5; 95%CI: 1.5-49.9). Similarly, in a study among 686 GDM women in our center, an HbA1c of 37-46 mmol/mol (5.5%-6.4%) in the first trimester was associated with higher odds of preterm birth (OR = 1.86; 95%CI: 1.10-3.14) than an HbA1c < 37 mmol/mol[39]. These studies further reinforce the relevance of mild maternal hyperglycemia in the first trimester, regardless of subsequent GDM development.

In a Spanish multiethnic cohort of 1228 women in their first trimester, Mañé *et al*[40] (2019) reported that women with an HbA1c $\geq$ 5.8% (39.9 mmol/mol) had an increased risk of macrosomia (aOR = 2.69; 95%CI: 1.16-6.24). An HbA1c $\geq$ 5.9% (41 mmol/mol) was independently associated with a threefold increased risk of preeclampsia (95%CI: 1.03-9.9), and an HbA1c $\geq$ 6% (42.1 mmol/L) was associated with a fourfold increased risk of LGA babies (95%CI: 1.49-11.07)[36]. There was no association between preterm birth and HbA1c[40]. Hence, in many retrospective cohort studies, there is a suggestion for greater adverse neonatal outcomes among women with isolated mild hyperglycemia in the first trimester. This finding is relevant to many countries with a high prevalence of prediabetes among women of reproductive age[24]. These women might have developed the risk for adverse pregnancy events even before the pregnancy was diagnosed.

GDM diagnosis during different gestational periods within 24-32 weeks of gestation and adverse pregnancy outcomes

The HAPO study revealed a continuous association between maternal glycemia between 24 and 32 GW and adverse pregnancy outcomes[26]. However, the IADPSG and other organizations recommend GDM screening in pregnancy between 24-28 GW[14,17]. Will the delay in the initiation of GDM treatment until 32 GW affect adverse pregnancy outcomes? In a secondary analysis of the Maternal-Fetal Medicine Units Network randomized GDM treatment trial, Palatnik *et al*[41] examined the associations between gestational age at the start of GDM treatment and adverse pregnancy outcomes. The GDM diagnosis in this study was based on the two-stage modified C & C criteria (only women with FPG < 95 mg were included). The pregnancy outcomes of interest were compared between treated and untreated women in each GW category (stratified as 24-26, 27, 28, 29, and 30-31 GW). Within the above GW categories, earlier initiation of treatment was not associated with any differences in the following perinatal outcomes: Perinatal mortality, hypoglycemia, hyperbilirubinemia, neonatal hyperinsulinemia, birth trauma, LGA, cesarean delivery, or NICU admission. The findings of this study justify a few weeks of delay in the initiation of GDM treatment after the diagnostic OGTT results, a common practical difficulty in obstetric practice. However, this study has the limitation of excluding many GDM women with high FPG values (between 95-125 mg/dL). These findings need to be confirmed by a study including all GDM pregnancies satisfying the C & C criteria, as well as GDM diagnoses according to the more liberal IADPSG criteria.

THERAPEUTIC INTERVENTIONS IN EARLY PREGNANCY AND ADVERSE PREGNANCY OUTCOMES

Hillier *et al*[42] retrospectively assessed the impact of GDM screening in the first trimester among 40206 pregnant women (without pregestational diabetes; 9156 were obese) and GDM management on maternal and perinatal outcomes from 2009-2013 in Oregon and Southwest Washington, United States. The results were compared with the pregnancy outcomes in the same region during the three years of the preintervention period (2006-2009). After the intervention, the adjusted risk for LGA (aOR = 0.89, 95%CI: 0.82-0.96) and cesarean delivery (aOR = 0.78, 95%CI: 0.65-0.94) was lower than that before the intervention. These findings support the clinical recommendation of GDM screening in early pregnancy for patients with obesity.

The Booking GDM (TOBOGM) trial (2023) was a multicenter randomized controlled trial performed in 17 hospitals in Australia, Austria, Sweden, and India[43]. A total of 793 women who were diagnosed with GDM (IADPSG criteria) before 20 GW (at a mean gestational age of 15.6 ± 2.5 years) were assigned to either the immediate treatment group ($n = 406$) or the control group ($n = 396$) (who received no GDM treatment during pregnancy). Composite adverse neonatal outcomes occurred in 24.9% of the immediate treatment group, whereas they occurred in 30.5% of the control group. Adjusted risk difference, -5.6 percentage points; 95%CI: -10.1 to -1.2, $P = 0.02$. The RR reduction was 0.82 (95%CI: 0.68-

Table 5 The relative effect and anticipate absolute effects on adverse events: Comparison between treated early gestational diabetes and late-onset gestational diabetes women

Outcome	Immanuel and Simmons[30]			Feghali et al[31]			Tirado-Aguilar et al[35]			Regnault et al[28]			Yefet et al[34]		
	Relative effect, relative risk (95%CI)	Anticipated absolute effect, risk with L-GDM treated per 1000 women	Anticipated absolute effect, risk difference with E-GDM treated per 1000 women	Relative effect, aOR (95%CI)	Anticipated absolute effect, risk with L-GDM treated per 1000	Anticipated absolute effect, risk difference with E-GDM treated per 1000	Relative effect, aOR (95%CI)	Anticipated absolute effect, risk with L-GDM treated per 1000	Anticipated absolute effect, risk difference with E-GDM treated per 1000	Relative effect; adjusted prevalence ratio (95%CI)	Anticipated absolute effect, risk with L-GDM treated per 1000	Anticipated absolute effect, risk difference with E-GDM treated per 1000	Relative effect, aOR (95%CI)	Anticipated absolute effect, risk with L-GDM treated per 1000	Anticipated absolute effect, risk difference with E-GDM treated per 1000
Large for gestational age babies	1.07 (0.86-1.35)	187	13 more (26 fewer to 66 more)							1.10 (1.06-1.14)	170	17 more (11 more to 24 more)			
Perinatal mortality	3.58 (1.91-6.71)	2	6 more (2 more to 14 more)				0.29 (0.18-2.78)	10	8 fewer (9 fewer to 18 more)	1.51 (1.19-1.91)	2	1, 0 fewer to 2 more			
Neonatal hypoglycemia	1.61 (1.02-2.55)	134	82 more (3 more to 207 more)				18.57 (2.69-21.2)	6	106 (11 more to 122 more)	1.08 (0.96-1.22)	20	2 (2 fewer to 5 more)	3.5 (2-6.1)	27	68 more (27 more to 138 more)
Caesarian delivery	1.09 (0.94-1.26)	313	28 more (19 fewer to 81 more)							1.03 (1-1.05)	250	8 more (0 fewer to 13 more)			
Shoulder dystocia	1.76 (0.96-3.24)	16	12 more (19 fewer to 36 more)										10.3 (2.4-44.6)	3	28 more (5 more to 131 more)
Respiratory distress	1 (0.76-1.32)	38	0 fewer to 12 more				4.76 (1.91-15.16)	26	98 (24 more to 369 more)						
Macrosomia	1.05 (0.77-1.41)	108	5 more (25 fewer to 55 more)	2 (1-4.2)	79	79 more, 0 fewer to 253 more									
Erb's palsy										1.55 (1.22-1.99)	2	1 more, 0 fewer to 2 more			

E-GDM: Early-onset gestational diabetes; L-GDM: Late-onset gestational diabetes; aOR: Adjusted odds ratio; CI: Confidence interval.

0.98). The number of women who needed to be treated to prevent one such event was 18.

The median number of bed days in the NICU was also lower in the intervention group; the RR was 0.60 (95%CI: 0.41-0.89). A component analysis of the composite neonatal outcome group revealed that the risk reduction was due to a

reduction in neonatal respiratory distress; the RR was 0.57 (95% CI: 0.41-0.79). The maximum benefit in terms of composite neonatal outcome reduction was obtained when the treatment was initiated before 14 GW (RR = -8.9, 95% CI: -15.1 to 2.6). There were no benefits of treatment associated with other adverse pregnancy outcomes, such as pregnancy-related hypertension, cesarean delivery, induction of labor, neonatal lean body mass, or large or small for gestational age babies.

The TOBOGM study is the first randomized controlled study to reveal a benefit in terms of major complications such as neonatal respiratory distress by early initiation of treatment among GDM (IADPSG criteria) pregnancies diagnosed before 20 weeks of gestation. The observation of greater benefit among the subgroup of women who initiated treatment before 14 GW is of paramount importance for many high-risk ethnic groups. The post-hoc analysis of the TOBOGM study data revealed several interesting findings, suggesting that we are “one step closer to a definition of E-GDM”[44]. Furthermore, the reduction in adverse neonatal outcomes observed in the TOBOGM trial makes E-GDM treatment more cost-effective than conventional care[45].

LIMITATIONS OF THE COMPARATIVE ASSESSMENT OF STUDIES ASSESSING THE IMPACT OF GDM TIMING ON ADVERSE PREGNANCY OUTCOMES

The main limitation of the comparative assessment of L-GDM and E-GDM in this minireview is the marked heterogeneity of the design of the various studies, a difficulty noted by Immanuel and Simmons[30] as well in their meta-analysis. The mix of studies used for this minireview lacked uniformity in the definition of E-GDM (< 20, < 22, < 24 GW) and in the GDM diagnostic criteria (IADPSG 4 studies, C & C criteria 2 studies). Even for comparisons between the E-GDM and L-GDM groups in a given study, different diagnostic criteria were used in different study periods (Shub *et al*[32], Regnault *et al*[28]). Most of these studies were retrospective, and GDM screening was mostly risk-based, except in one study (Tirado-Aguilar *et al*[35]). Although multivariate regression analysis was available for all studies, there are inadequacies in the use of confounding factors across different studies. The methodology was strikingly defective in the Regnault *et al*'s study[28], where GDM screening was risk-based (BMI > 25 kg/m², family history of diabetes, history of macrosomic infants, and age > 35 years); only maternal age was used as a confounding factor[28]. Except for the TOBOGM study, none of these studies assessed the cost benefit of early treatment. The details regarding the mode of care, including dedicated clinics and standard care, are not available in any of these studies. For treated women with GDM, the details of glycemic control and gestational weight gain are not uniformly available. The lack of uniformity of the available data and missing essential data in the present study series are major limitations for assessing the impact of various diagnostic criteria, glucose load, confounding factors, and modes of care on adverse pregnancy outcomes. This analysis is not available in the meta-analysis by Immanuel and Simmons[30] either. TOBOGM is the only study in early pregnancy where the cost-effectiveness of early therapeutic intervention was assessed, and the results are favorable[45].

A literature search failed to yield any studies comparing the impact of different diagnostic criteria used selectively for E-GDM diagnosis on adverse pregnancy outcomes. A recent meta-analysis involving 30 studies (642355 participants; GDM and non-GDM controls, with no distinction of E-GDM or L-GDM) comparing the different criteria for GDM diagnosis suggested “no significant difference in risk between lower and higher blood glucose cut-offs used in GDM diagnosis”[46]. There was no difference between the IADPSG and non-IADPSG criteria for the effect of GDM on adverse maternal and fetal outcomes.

MECHANISMS OF MATERNAL HYPERGLYCEMIA-INDUCED ADVERSE PREGNANCY EVENTS

Two recent reviews on GDM by Hivert *et al*[3] and Wicklow and Retnakaran[47] provide a detailed analysis of probable pathogenic mechanisms for adverse pregnancy events in GDM from preconception, during pregnancy, and beyond. The physiology of fetal development and the mechanisms of hyperglycemia-induced derangements in different stages of development are summarized in Table 6. The widely held concept is that GDM affects the fetus only in late pregnancy, influencing several metabolic and anthropometric developments, fetal adiposity, macrosomia, LGA, and neonatal hypoglycemia. However, fetal development is more complex in early pregnancy and can be significantly influenced by the in utero metabolic milieu of that period. The strongest evidence in this regard is the effect of maternal hyperglycemia in uncontrolled pregestational diabetes on organogenesis[48]. Although it is much less common than pregestational diabetes is, E-GDM might also influence organ development, an effect that can be ameliorated by early initiation of GDM treatment (TOBOGM study)[43].

The main benefit of early intervention in the E-GDM group in the TOBOGM study was on the neonatal composite outcome, especially neonatal respiratory distress. Our analysis and Immanuel and Simmons's meta-analysis also revealed that pregnancies in the E-GDM group were more prone to adverse neonatal outcomes[30]. The exact mechanisms linking hyperglycemia in early pregnancy with adverse neonatal outcomes are not clearly defined. The widely accepted reason for neonatal respiratory distress in GDM is fetal hyperglycemia/hyperinsulinemia-induced lung surfactant deficiency and atelectasis, which are more prevalent in preterm delivery[49]. Decidual and placentation defects in early pregnancy, as occur in E-GDM (Table 6), can trigger preterm delivery and neonatal respiratory distress[50]. GDM might affect fetal lung development and maturation because of: (1) The potential impact of early hyperglycemia on the canalicular phase of lung development; (2) Trophoblast-derived exosomes obstructing the fetal lung terminal airway branching process; and (3) Delaying the switching of fetal lung fluid physiology from chloride-driven fluid secretion to sodium-driven fluid

Table 6 Hyperglycemia in early pregnancy and fetal damage: Proposed mechanisms

Gestational period in weeks	Foetal physiology	Maternal hyperglycemia effects
0-14 GW	Implantation; early embryo organogenesis; decidual histotropic function; early placental development; spiral artery plugging. Low oxygen environment and anaerobic metabolism of glucose (glycolysis) and protection of embryo from oxygen-free radical-mediated damage	Mothers with pregestational prediabetes. Have several metabolic abnormalities: Mild dysglycemia and hyperinsulinemia, changes in HDL-C and triglycerides, C-reactive protein, tissue plasminogen activator antigen, adipokines, and insulin-like growth factor binding protein 2. Needs to explore the influence of these parameters on fetal physiology in the perinatal period and the benefits of preventive strategies GDM diagnosed in the first trimester. Probable hyperglycemia-induced organogenesis, implantation and decidual dysfunctions, and placentation defects. Greater pro-oxidant and pro-inflammatory intrauterine milieu induced by hyperglycemia disturb the anaerobic environment, leading to fetal changes and miscarriage
14 GW onwards	Extravillous cytotrophoblast cells invade and remodel decidual cells to enable the entry of fully oxygenated maternal blood to reach the intervillous space and fetoplacental unit. Hematotropic nutrition and fetal growth and development. Placental-derived signals like hormones and extracellular vesicles induce adaptive responses in maternal physiology to support the fetoplacental unit. The mother-placenta interplay persists throughout pregnancy	Hyperglycemia and hyperinsulinemia-induced changes in spiral artery remodeling can interfere with oxygen and nutrient supply to the fetus. This will alter fetal growth dynamics throughout gestation. Hyperglycemia can induce epigenetic alterations affecting the signaling pathway. Insulin is detected in fetal circulation by 12 weeks, and maternal hyperglycemia can trigger a “fetal glucose steal phenomenon” to produce LGA babies. Fetal hyperinsulinemia at 17 GW is associated with insulin resistance and high free fatty acids in the offspring at age 5. This observation suggests that maternal hyperglycemia prior to 24 GW may trigger fetal programming for metabolic outcomes in the offspring. This is presumed to be due to epigenetic factors like DNA methylation, histone post-translational modifications, and non-coding RNAs

GDM: Gestational diabetes mellitus; GW: Gestational weeks; LGA: Large for gestational age; HDL-C: High density lipoprotein cholesterol.

absorption[3].

The role of the fetus in determining pregnancy outcomes is increasingly recognized. One such mechanism for increased fetal adiposity (macrosomia) before 24 GW is fetal glucose steal, which is established early in pregnancy[3,51]. Maternal hyperglycemia triggers the development of fetal hyperinsulinemia. Once fetal hyperinsulinism is established, it drives fetal glucose disposal, increasing the downward glucose gradient from the mother to the fetus and creating fetal glucose steal. Fetal hyperinsulinism favors persistently high glucose flux even at times when maternal glucose is normal. An exaggerated glucose steal by a hyperinsulinemic fetus could attenuate maternal glucose levels during OGTT, providing some mothers with fetuses with characteristics of diabetic fetopathy and “normal” maternal glucose tolerance. Fetal glucose steal can lead to the development of fetal obesity before 24 GW, which can be ameliorated by proper glycemic control in early pregnancy[51].

Several protein markers (adipokines and placental-derived biomarkers), nucleic acids (cell-free DNA and RNA), and metabolic biomarkers are under evaluation as predictive biomarkers for GDM diagnosis, management, and pregnancy outcomes. A detailed discussion of these biomarkers is available in a recent scoping review by Rathnayake *et al*[52]. Similarly, several epigenetic changes, such as DNA methylation, histone modifications, and microRNA gene silencing, have been identified in GDM patients, and they are increasingly being found to be associated with GDM pathophysiology and nutrigenetics[53]. Additionally, the intergenerational risk of increased excess adiposity and dysglycemia in the products of GDM pregnancies may be attributed to shared genetics, a shared family environment, and fetal programming as a result of the intrauterine metabolic environment[3].

RELATIONSHIP BETWEEN EARLY GDM AND PRE-EXISTING DIABETES MELLITUS

Apart from being a predisposing factor for adverse pregnancy events, maternal “hyperglycemia” in early pregnancy is being evaluated as a marker of preexisting maternal dysglycemia. In earlier sections of this minireview, the possibility of early GDM as a continuum of a preexisting pregestational prediabetic state was discussed. There is emerging evidence to link early GDM with a preexisting diabetic state as well[54,55]. Furthermore, those women who have hyperglycemia earlier in pregnancy are at higher risk of adverse perinatal outcomes compared to those who develop GDM later in pregnancy. In a retrospective analysis, Sweeting *et al*[56] observed that the adverse pregnancy events among women having GDM in the first trimester (after exclusion of preexisting diabetes) were comparable to those observed among pregnant women with preexisting diabetes. Another large population-based cohort study in Ontario, Canada, observed increased perinatal mortality among women having undiagnosed type 2 diabetes in pregnancy[57].

Currently, several professional bodies recommend screening at the first antenatal visit for undiagnosed preexisting diabetes or diabetes in pregnancy (DIP)[5,14,16,19,20]. The proposed diagnostic criteria for DIP include FPG ≥ 126 mg/dL, 2-hour PG ≥ 200 mg/dL, or HbA1c $\geq 6.5\%$ (any one of the three). In a large prospective cohort study from New Zealand, Hughes *et al*[55] reported that HbA1c $\geq 5.9\%$ (41 mmol/mol) before 20 GW could identify all cases of DIP and a group of women at 2-4-fold risk of adverse pregnancy events. In a retrospective analysis of 69417 pregnancies in Israel, Yefet *et al*[54] suggested HbA1c $\geq 5.8\%$ in early pregnancy (before 24 GW) as an accurate independent marker for undiagnosed type 2 diabetes [area under curve 91% (95%CI: 81%-100%), 89% sensitivity, 86% specificity][54]. In this

study, no independent association for FPG and 2-hour PG values with DIP, nor diagnostic threshold values, could be identified. These studies suggest that even at HbA1c values lower than the threshold value of 6.5% for DIP diagnosis, women having GDM in early pregnancy are at higher risk for adverse pregnancy events.

It is challenging to distinguish undiagnosed preexisting diabetes from GDM in early pregnancy. There are practical limitations to conducting pre-conception testing for assessing the glycemic status of all women planning for pregnancy. A definite distinction between preexisting diabetes and GDM can be made only in the postpartum period. Furthermore, no validated risk prediction models exist for pre-existing diabetes in early pregnancy. The current diagnostic criteria for DIP are derived from the PG and HbA1c threshold values for diagnosing diabetes among the non-obstetric population. However, the metabolic, hormonal, and hematological changes in pregnancy can induce physiological fluctuations in fasting PG, 2-hour PG, and HbA1c levels in different stages of pregnancy: Decline of PG levels in the first trimester[58] and decline of HbA1c values in the second trimester[59]. Hence, there is a strong need for further research to identify reliable markers for preexisting diabetes among early GDM women.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

There are major knowledge gaps in our understanding of E-GDM, especially in the context of increasing obesity and prediabetes prevalences among women of reproductive age. The global prevalence of prediabetes among women of reproductive age is 12%, suggesting that a significant number of pregnant women have E-GDM at the time of conception itself[60]. Hyperglycemia at this stage can impact implantation, decidualization, placental development, and organogenesis. There is a strong need for further basic science research to delineate the biochemical, cytological, immunological, and epigenetic effects of hyperglycemia on early fetal development. The results of the TOBOGM study suggest greater benefits for preventing neonatal respiratory distress syndrome with the initiation of treatment before 14 weeks. Similar randomized controlled trials to assess the benefits of treating mild hyperglycemia in the periconceptual period itself are relevant for improving pregnancy outcomes in high-risk populations. This concept was further strengthened by a United States study linking preconception glycemia to preterm birth[61].

The lack of international consensus to define GDM before 24 GW causes major confusion in clinical practice. As shown in Table 1, many professional bodies, such as American College of Obstetricians and Gynecologists, the WHO, and Canadian Diabetes Association, permit screening for E-GDM with the same criteria used for GDM diagnosis > 24 GW. Currently, the IADPSG has no recommendation for E-GDM diagnosis, whereas the NICE permits E-GDM diagnosis only for women with a GDM history. This NICE recommendation ignores the fact that many primigravida women in high-risk ethnic groups are at high risk of developing E-GDM. The United States Preventive Services Task Force statement that “current evidence is insufficient to assess the balance of benefits and harms of GDM screening before 24 GW” adds to the already existing clinical confusion on E-GDM screening among these high-risk women[62]. More research and an international consensus are urgently needed to develop pregnancy outcome-based E-GDM diagnostic criteria. Following the TOBOGM study, the first IADPSG summit was held in November 2022 in Sydney, Australia[63]. Most delegates agreed on the use of a one-step 75 g OGTT test for E-GDM, preferring the Canadian Diabetes Association criteria over the IADPSG criteria. The TOBOGM Summit highlighted the need to consider resources, costs, and consumer views when applying TOBOGM findings to E-GDM treatment. The relevance of health economic analysis in different populations was stressed at this summit. There is an urgent need for prospective randomized controlled studies to assess the benefits and risks of E-GDM screening and management. A HAPO-like study (without any therapeutic interventions) in different stages of early pregnancy (considering the first and early second trimesters separately) may be valuable for resolving the ongoing controversy. Furthermore, an international consensus on GDM diagnosis will ensure uniformity in clinical care and future research.

There is little guidance from any professional organization regarding a specific gestation period for defining E-GDM. Researchers use different gestational periods ranging from < 20 to < 24 GW as the criteria for categorization into E-GDM and L-GDM groups (Table 2). As the TOBOGM study defined E-GDM as < 20 GW, this time is used in discussions on the benefits of early intervention use. To maintain uniformity in research, it is valuable to have an international consensus on the definition of E-GDM. There are many gaps in our knowledge regarding the pathophysiology of GDM. GDM is considered a heterogeneous condition and may be triggered by factors before pregnancy, can have deleterious effects in all stages of pregnancy, and can impart metabolic and cardiovascular risks to both mothers and offspring throughout their lives. Most of the suggested mechanisms of fetal damage in early pregnancy are speculative and need to be confirmed by further research.

CONCLUSION

This minireview explored the current knowledge of adverse pregnancy outcomes in relation to hyperglycemia at different stages of pregnancy. Many studies (mostly retrospective) have revealed that despite treatment, GDM diagnosed in early pregnancy is associated with a greater risk of adverse neonatal events than GDM diagnosed after 24 GW. The recently published TOBOGM study revealed a modest but significant reduction in neonatal respiratory distress among E-GDM pregnancies having treatment before 20 GW. We strongly recommend further prospective studies to unravel several mysteries related to mild hyperglycemia in different stages of pregnancy. The results will help in designing trimester-specific screening and preventive strategies for GDM.

FOOTNOTES

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