Gestational Diabetes 2

Epidemiology and management of gestational diabetes

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Gestational diabetes is defined as hyperglycaemia first detected during pregnancy at glucose concentrations that are less than those of overt diabetes. Around 14% of pregnancies globally are affected by gestational diabetes; its prevalence varies with differences in risk factors and approaches to screening and diagnosis; and it is increasing in parallel with obesity and type 2 diabetes. Gestational diabetes direct costs are US$1·6 billion in the USA alone, largely due to complications including hypertensive disorders, preterm delivery, and neonatal metabolic and respiratory consequences. Between 30% and 70% of gestational diabetes is diagnosed in early pregnancy (ie, early gestational diabetes defined by hyperglycaemia before 20 weeks of gestation). Early gestational diabetes is associated with worse pregnancy outcomes compared with women diagnosed with late gestational diabetes (hyperglycaemia from 24 weeks to 28 weeks of gestation). Randomised controlled trials show benefits of treating gestational diabetes from 24 weeks to 28 weeks of gestation. The WHO 2013 recommendations for diagnosing gestational diabetes (one-step 75 gm 2-h oral glucose tolerance test at 24–28 weeks of gestation) are largely based on the Hyperglycemia and Adverse Pregnancy Outcomes Study, which confirmed the linear association between pregnancy complications and late-pregnancy maternal glycaemia: a phenomenon that has now also been shown in early pregnancy. Recently, the Treatment of Booking Gestational Diabetes Mellitus (TOBOGM) trial showed benefit in diagnosis and treatment of early gestational diabetes for women with risk factors. Given the diabesity epidemic, evidence for gestational diabetes heterogeneity by timing and subtype, and advances in technology, a life course precision medicine approach is urgently needed, using evidence-based prevention, diagnostic, and treatment strategies.

Introduction

Gestational diabetes is generally defined as hyperglycaemia first detected at any time during pregnancy, below diagnostic thresholds for (overt) diabetes in or outside pregnancy.[1] At the first summit discussing gestational diabetes diagnosed early in pregnancy,[2] early gestational diabetes was the preferred term for gestational diabetes detected before 20 weeks of gestation, and late gestational diabetes for gestational diabetes identified at 24–28 weeks of gestation, after screening for early gestational diabetes. Increasing maternal glucose concentrations have been shown to be linearly correlated with perinatal complications in early pregnancy (<20 weeks of gestation) and late pregnancy (24–28 weeks of gestation),[3–7] but also with long-term maternal and offspring cardiometabolic risk (appendix p 1).[8–12] Furthermore, the prevalence of gestational diabetes is increasing in parallel with the increasing prevalence of type 2 diabetes and obesity across all populations.[13] Finally, there is strong evidence that management of gestational diabetes reduces the risk of pregnancy complications.[3,14,15] Up to 31% of type 2 diabetes in parous women is attributable to having previously had gestational diabetes.[16] Effective lifestyle interventions initiated postpartum to prevent women with gestational diabetes subsequently developing type 2 diabetes could therefore have a substantial impact on population health.[17] Similarly, there are lifestyle intervention opportunities to prevent future cardiovascular disease among women who have had gestational diabetes, and potentially prevent their offspring developing obesity and type 2 diabetes.[18] The trigger for these lifestyle interventions is the diagnosis of gestational diabetes, without which antenatal treatment of mild hyperglycaemia will not occur and long-term follow-up and preventive action will not be possible. However, diagnosis does not necessarily mean treatment, but might simply mean observation for future intervention, as

Search strategy and selection criteria

For this Series paper, we performed a comprehensive literature search on PubMed and MEDLINE (from database inception to Dec 31, 2023). We searched for existing reviews, large cohort studies, randomised controlled trials, and meta-analyses relating to gestational diabetes (risk factors, prevalence, obstetric and perinatal risks, screening, diagnosis, management, health economics, and early and late gestational diabetes). The key words included were: "gestational diabetes", "early gestational diabetes", "late gestational diabetes", "hyperglycaemia", "glucose", "timing", "screening", "diagnosis", "oral glucose tolerance test", "epidemiology", "risk factors", "incidence", "prevalence", "heterogeneity", "pregnancy complications", "outcomes", "obstetric risk", "perinatal risk", "mental health", "oral health", "breastfeeding", "treatment", "management", "medical nutrition therapy", "diet", "pharmacotherapy", "metformin", "sulfonylurea", "insulin", "ultrasound surveillance", "delivery", "health economics", "systematic reviews", "meta-analyses", "randomised controlled trials", and "prospective cohort studies". The search was restricted to English language studies.

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This is the second in a Series of three papers on gestational diabetes. All papers in the Series are available at www.thelancet.com/series/gestational-diabetes

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See Online for appendix

Key messages

- The 2013 WHO diagnostic criteria for gestational diabetes at 24–28 weeks of gestation, without previous screening, are based on the positive linear relationship between glucose concentrations during the oral glucose tolerance test (OGTT) in late pregnancy and perinatal complications, whereas the US Carpenter and Coustan criteria are based on the risk of postpartum type 2 diabetes
- In line with the rise in obesity, impaired glucose tolerance, and type 2 diabetes in women of reproductive age, the prevalence of gestational diabetes has also increased worldwide
- The current prevalence of gestational diabetes (standardised to WHO criteria) is 14·0% globally and ranges between 7·1% in North America and the Caribbean and 27·6% in the Middle East and north Africa region
- Of the women with gestational diabetes, 30–70% have early gestational diabetes (ie, hyperglycaemia from <20 weeks of gestation) and these women have worse pregnancy outcomes compared with women diagnosed with late gestational diabetes (ie, hyperglycaemia from 24–28 weeks of gestation)
- The Treatment of Booking Gestational Diabetes Mellitus (TOBOGM) trial showed, among women with gestational diabetes risk factors, that treatment of early gestational diabetes, compared with the historical approach of treating gestational diabetes from 24–28 weeks of gestation, reduces perinatal complications (largely driven by a reduction in neonatal respiratory distress) and reduces length of stay in the neonatal care nursery
- In addition to medical nutrition therapy, insulin therapy has long been the preferred pharmacotherapy for glucose management; metformin is widely used and increasingly considered safe and effective in treating gestational diabetes, although data are inconsistent regarding its long-term effects on offspring health
- Given recent evidence for heterogeneity in gestational diabetes, based on timing of onset and glycaemic subtype, components of the current medical and obstetric approaches to early and late gestational diabetes warrant further randomised controlled trials

discussed in the third paper in this Series.[19] A key issue then becomes when and how should this diagnosis occur and how gestational diabetes should subsequently be managed.

Diagnosis of gestational diabetes is determined through screening approaches.[20–22] Universal screening, that is, offering an oral glucose tolerance test (OGTT) to all pregnant women, is recommended by most organisations (ie, WHO, International Federation of Gynecology and Obstetrics, and the US Preventive Services Task Force). Screening that involves an immediate OGTT is known as a one-step approach. Alternative two-step screening approaches include risk factor-based approaches where one or more risk factors are used to select women who then undergo an OGTT, or using a blood test to determine who will have an OGTT.

This paper is the second of three in this Series on gestational diabetes, and reviews the different approaches to screening and diagnosis, subsequent epidemiology, perinatal complications, management, and health economics of treating gestational diabetes. Pathophysiology and long-term complications are described in the first paper.[23] The third paper focuses on transforming the current pregnancy-focused approach to a long-term, life-course perspective of gestational diabetes.[19] This second Series paper will not discuss (overt) diabetes in pregnancy, as defined by hyperglycaemia first detected in pregnancy that fulfils the criteria for type 2 diabetes (HbA_{1c} ≥6·5%, fasting glucose ≥7·0 mmol/L, 2-h glucose ≥11·1 mmol/L on an OGTT, or a combination of some or all of these).[1] The terms woman and women are used throughout this Series paper to refer to people who are pregnant or who recently gave birth.

Epidemiology of gestational diabetes

Prevalence

The global prevalence of both early and late gestational diabetes varies greatly between countries because of the heterogeneity in approaches to screening, diagnosis, and diagnostic criteria, and differences in underlying population prevalence, social and cultural determinants of risk, and risk factors (table 1).[24–40] The global prevalence of gestational diabetes is estimated to be 14·0% by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria.[41] Whichever criteria are used, there will be women with glycaemia below the defining thresholds used whose pregnancies and long-term risks of type 2 diabetes will be affected if they have even mild hyperglycaemia.[5,9,10] The prevalence of gestational diabetes screened before 20 weeks of gestation, irrespective of the diagnostic criteria used, ranges from 0·7% to 36·8% between countries.[42] The prevalence in studies that screen for gestational diabetes before 12 weeks of gestation ranges from 0·7% to 14·2% (appendix p 2), although the gestational diabetes diagnostic methods varied between studies.[43,44]

Ethnic differences in the prevalence of gestational diabetes are particularly important, not only because of the burden of disease, but because of the associated combination of socioeconomic, cultural, and biological influences on risk, including genetic factors (eg, the Pacific-specific *CREBRF* rs373863828 allele among Polynesian women[45]) and probably polygenic factors (eg, different glycaemic profiles on the OGTT).[46,47] Asian populations are more likely to be diagnosed with elevated post-glucose load glycaemia during the OGTT, whereas European populations are more likely to be diagnosed on the fasting glucose test.[5,47] The standardised (to IADPSG criteria) prevalence of gestational diabetes is lowest in North America and the Caribbean (7·1%) and

	Study population	Duration	Number of studies (collective sample size)	Gestational age at screening	Diagnostic criteria	Gestational diabetes prevalence (%; 95% CI)	Findings of subgroup analysis
Africa							
Muche et al (2019)[24]	Africa	January, 2013, to November, 2018	23 (11 902)	Mostly 24–28 weeks of gestation except two studies that screened <14 weeks, one study that screened <20 weeks, and two studies that screened any time in pregnancy	IADPSG	Overall 13·6% (11·0–16·2); east Africa 16·8%; south Africa 14·3%; west Africa 10·7%; central Africa 20·0%; north Africa 7·6%; sub-Saharan Africa 14·3%	Subgroup analyses for prevalence were performed by subregions of Africa, publication year of studies, quality of the study, and study design
Natamba et al (2019)[25]	Sub-Saharan Africa	Searched database inception to Jan 31, 2019	28 (13 967)	Not reported	Studies used different criteria as reported in their summary of findings table	9% (7–12)	O'Sullivan and Mahan criteria prevalence was 4%; WHO 1985, 1999, and 2006 criteria prevalence was 4%; fasting blood glucose was 7%; and IADPSG or WHO 2013 criteria prevalence was 16%
Azeez et al (2021)[26]	Nigeria	2000 and 2020	36 (46 210)	Not reported	Varied	Overall 11·0% (8–13; southwest 11·0%; south-central 7·0%; southeast 12·0%; northwest 13·0%; north-central and Abuja 16·0%; northeast 11·0%	Carpenter and Coustan prevalence 5·4%; WHO 1999 criteria 5·0%; WHO 2013 criteria 9·0%; and IADPSG 20·0%
Beyene et al (2023)[27]	Ethiopia	Not reported	10 (6525)	Not reported	American Congress of Obstetricians and Gynaecologists guidelines	12·0% (8·2–15·9)	NA
Asia							
Jafari-Shobeiri et al (2015)[28]	Iran	1985 to 2012	24 (26 203)	Mostly 24–28 weeks except one study (20–28 weeks)	Not reported	3·4% (1·3–18·6)	NA
Lee et al (2018)[29]	Asia	Searched database inception to August, 2017	84 (2 314 763)	Not reported	Studies used different criteria as reported in their appendix	11·5% (10·9–12·1)	Highest prevalence was reported by IADPSG (20·9%) and one-step screening methods (14·7%)
Li et al (2018)[30]	India	1988 to 2016	46	Mostly 24–28 weeks, two studies screened at any time, two studies screened only at first visit, eight studies did not specify the gestational age	Studies used different criteria as reported in their summary of findings table	Overall 8·9% (7·1–11·1); east 1·5% (0·3–7·8); north 11·9% (8·3–16·9); south 10·8% (8·5–1·5); west 3·6% (1·7–7·6)	Urban prevalence was higher compared with rural (urban 8·1% *vs* rural 2·1%); of the diagnostic criteria used, IADPSG reported the highest prevalence (19·2%)
Gao et al (2018)[31]	China	Jan 1, 2010, to April 30, 2017	25 (79 064)	Varied from 24 weeks to 32 weeks except two studies (mean 14·4 ± 2·8 weeks and 22–40 weeks)	IADPSG (inclusion criteria)	Overall 14·8% (12·8–16·7); north 15·7%; south 20·3%	Age, weight, and family history of diabetes increased the prevalence of gestational diabetes with statistical significance
Nguyen et al (2018)[32]	East and southeast Asia	2000 to 2016	48	Not reported	Varied	10·1% (6·5–15·7)	Low-income and middle-income countries (10·8%) reported higher prevalence than high-income countries (6·7%); one-step criteria (15·7%) reported highest prevalence compared with two-step criteria (7·2%); Viet Nam (20·1%) and Singapore (18·9%) reported the highest prevalence

(Table 1 continues on next page)

	Study population	Duration	Number of studies (collective sample size)	Gestational age at screening	Diagnostic criteria	Gestational diabetes prevalence (%; 95% CI)	Findings of subgroup analysis
(Continued from previous page)							
Karaçama and Çelik (2019)[33]	Türkiye	Searched database inception to December, 2017	41 (50 767)	Mostly 24–28 weeks except one study (11–14 weeks)	Studies used different criteria as reported in their summary of findings table	7·7% (1·9–27·9)	Carpenter and Coustan criteria prevalence 5·6%; American Diabetes Association 12·5%; American Diabetes Association–American Congress of Obstetricians and Gynaecologists 5·8%; National Diabetes Data Group 3·5%; American Congress of Obstetricians and Gynaecologists 7·7%; WHO 1999 19·3%; O'Sullivan and Mahan 13·4%; and IADPSG 22·3%
Begum et al (2022)[34]	Bangladesh	Searched database inception to May, 2021	6 (6948)	Varied (reported in summary of findings table)	Studies used different criteria as reported in their summary of findings table	13% (7·0–21·0)	Older women (ie, >30 years) had a significantly higher prevalence (18·3%) than younger women (ie, <30 years; 11·6%); overweight or obese women had higher prevalence (20·5%) compared with typical weight women (13·8%)
Pokhrel et al (2022)[35]	Nepal	2000 to July, 2021	9 (20 865)	Mostly 24–28 weeks of gestation except two studies that screened after 15 weeks and 20 weeks of gestation	Studies used different criteria as reported in their summary of findings table	2·6% (1·3–5·4)	IADPSG criteria prevalence 6·6%; WHO 1999 4·8%; Diabetes in Pregnancy Study Group of India 4·7%; and Carpenter and Coustan 1·1%
Sadeghi et al (2023)[36]	Iran	Searched database inception to June, 2021	53 (56 521)	Not reported	Not reported	7·6% (6·1–9·4)	NA
Europe							
Eades et al (2017)[37]	Europe	Searched database inception to May, 2016	40 (1778 399)	Mostly 24–28 weeks of gestation except one study that tested earlier and another study that tested later	Studies used different criteria as reported in their summary of findings table	Overall 5·4% (3·8–7·8); north Europe 2·3%; west Europe 7·3%; south Europe 9·6%	National Diabetes Data Group criteria prevalence 5·3%; Carpenter and Coustan 6·9%; European Association for the Study of Diabetes (2 h only) 1·4%; IADPSG 14·1%; subgroup analyses for prevalence were performed by age, diagnostic criteria, country the study was conducted in, year of data collection started and week of gestation at testing, quality category of studies, mean BMI, ethnicity, and family history of diabetes
Badakhsh et al (2019)[38]	East Mediterranean region	Searched database inception to December 2018	33 (887166)	24–28 weeks of gestation	Studies used different criteria as reported in their summary of findings table	11·7% (10·7–12·6)	IADPSG 28·2%; Carpenter and Coustan 6·2%; WHO 15·2%; ADA 10·3%; NDDG 8·1%
Paulo (2021)[39]	Europe	2014 to 2019	133 (15 572 847)	Not reported	Studies used different criteria as reported in their summary of findings table	Overall 10·9% (10·0–11·8); north Europe 8·9% (7·9–10·0); south Europe 12·3% (10·9–13·9); west Europe 10·7% (9·5–12·0); east Europe 31·5% (19·8–44·6)	Age, gestational age at screening, overweight, and obeseity increased gestational diabetes prevalence significantly
South America							
Iser (2023)[40]	Brazil	Searched database inception to November, 2021	21 (122 635)	Mostly 24–28 weeks of gestation	Studies used different criteria as reported in their summary of findings table	18·0% (16·0–20·1) by IADPSG	Self-reported gestational diabetes 2·1%

Data are presented as percentage (95% CI) unless otherwise indicated. IADPSG=International Association of Diabetes and Pregnancy Study Groups. NA=not available.

Table 1: **Prevalence of gestational diabetes reported in meta-analyses worldwide**

highest in the Middle East and north Africa (27·6%).[41] Overall, the prevalence of gestational diabetes is similar in low-income and high-income countries (14·7% and 14·4%, respectively), but is lowest in middle-income countries (9·9%).[41] Migrant communities generally have the same prevalence of gestational diabetes as their populations of origin.[48] Indigenous women have a higher prevalence of gestational diabetes compared with non-Indigenous women, with prevalence odds ratios (ORs) ranging from 1·42 (95% CI 1·24–1·63) for women in Australia to 2·04 (1·46–2·84) for women in Canada.[49] Globally, studies on the prevalence of gestational diabetes are scarce in many countries[13] and only a few studies distinguish between early and late gestational diabetes.

Pregnancy complications

Gestational diabetes is associated with an increased risk of pregnancy complications. Geographical variation of the association between gestational diabetes and adverse pregnancy complications might reflect differences in maternal characteristics in the clinical population, including ethnicity, and obstetric care (table 2).[46,59] In studies with no maternal insulin treatment, gestational diabetes is associated with an increased risk of caesarean delivery (OR 1·16, 95% CI 1·03–1·32), preterm delivery (OR 1·51, 1·26–1·80), and large-for-gestational-age offspring (OR 1·57, 1·25–1·97).[60] Neonates of women requiring insulin treatment are more likely to require neonatal intensive care unit admission (OR 2·29, 1·59–3·31).[60] Country of origin, obesity prevalence, screening approaches, and obstetric practice significantly contribute to heterogeneity between studies for pregnancy complications.[46,51–58] For example, there are ethnic differences in the impact of gestational diabetes on fetal growth, with south Asian babies being smaller and exhibiting a different growth trajectory than those of European descent.[61–63] A meta-analysis of 13 studies on pregnancy and neonatal outcomes showed increased perinatal mortality, neonatal morbidity, and insulin use in women with early gestational diabetes, compared with those diagnosed between 24–28 weeks of gestation.[64] Another systematic review of 26 studies showed a greater risk of caesarean delivery, large-for-gestational-age offspring, preterm delivery, congenital anomaly, hypertension, perinatal death, preeclampsia, shoulder dystocia, induction of labour, and insulin use in women diagnosed with early gestational diabetes compared with those diagnosed with late gestational diabetes.[42]

Mental health complications

Studies suggest a psychosocial impact of gestational diabetes in women. Depression, anxiety, and stress appear to be more pronounced in women with gestational diabetes, both at the time of diagnosis and throughout the remainder of pregnancy.[65–67] Pregnant women with gestational diabetes describe experiencing stigma in the form of overt discrimination from health-care professionals and relatives and internalised stigma with feelings of guilt, shame, and concern about the impact of gestational diabetes on their offspring.[68]

Studies focused on the quality of life of pregnant women with gestational diabetes vary in their findings.[69] Women describe adverse consequences related to gestational diabetes stigma, including avoidance of blood glucose testing, not reporting blood glucose data, disordered eating, social isolation, and not prioritising their health after delivery.[68] Furthermore, many women report concerns about insulin therapy, including feelings of fear and guilt.[65]

There is also a possible bidirectional association between mental health and gestational diabetes. Women with high depression scores in early pregnancy have an almost two-fold increased risk of gestational diabetes, even after adjusting for covariates, including pre-pregnancy BMI, age, and ethnicity.[70] Furthermore, a gestational diabetes diagnosis is associated with an adjusted 4·6-fold (95% CI 1·26–16·98) increased risk of subsequent postpartum depression.[70] Treatment of gestational diabetes diagnosed at 24–28 weeks of gestation is associated with decreased rates of depression at 3 months postpartum,[15] whereas treatment of early gestational diabetes is associated with improved quality of life at 24–28 weeks.[3] Collectively, these studies suggest that mental health is an important factor in the management of gestational diabetes and that addressing the psychosocial impact of gestational diabetes is essential to ensure individual wellbeing and treatment success.

Oral health complications

Pregnancy is associated with pregnancy gingivitis, benign oral gingival lesions, tooth erosion, tooth mobility, dental caries, and periodontitis.[71] Women with gestational diabetes are at additional increased risk of periodontitis.[72,73] In women with gestational diabetes, the oral microbiota is unique, characterised by a proinflammatory dysbiosis with an augmentation of bacteria promoting periodontitis and a depletion of bacteria promoting periodontal health maintenance.[74] A Finnish study reported a higher risk of oral care needs in women with gestational diabetes (OR 1·39 95% CI 1·14–1·69) and an even higher risk for women with recurrent gestational diabetes (OR 1·90 1·40–2·58) compared with control individuals.[75]

Breastfeeding complications

Breastfeeding is reduced in women with gestational diabetes diagnosed at 24–28 weeks' gestation.[76] Paper 3 in this Series describes some of the barriers to breastfeeding in gestational diabetes.[19]

Screening and diagnosis of gestational diabetes at 24–28 weeks of gestation

For decades, there have been two different rationales for defining gestational diabetes, leading to various sets of diagnostic criteria. The first rationale to identify woman at

	USA[50] 2014–20	China[51] 2015	France[52] 2012	Israel[53] 2015–17	Australia[54] 2018–20	Brazil[55] 2010–14	Ethiopia[56] 2018–19	South Korea[57] 2001–13	Qatar[58] 2011
Screening; diagnostic approach	75 g 2-h OGTT; IADPSG criteria	75 g 2-h OGTT; IADPSG criteria	75 g 2-h OGTT; IADPSG criteria	Not specified	75 g 2-h OGTT; IADPSG criteria	75 g 2-h OGTT; IADPSG criteria	75 g 2-h OGTT; IADPSG criteria	50 g glucose challenge test 140mg/L then 100 g 3-h OGTT; Carpenter and Coustan criteria	50 g glucose challenge test 140mg/L then 75 g 2-h OGTT; Carpenter and Coustan criteria
Maternal outcomes									
Caesarean delivery	40·6% (40·5-40·7)	51·4% (46·1–56·7)	27·8% (27·4–28·2)	47·6% (43·3–51·9)	42·5% (40·6–44·4)	52·1% (48·4–55·8)	NA	59·0% (53·5–64·5)	26·7% (21·3–32·1)
Preterm delivery	11·3% (11·2–11·3)	4·3% (2·2–6·4)	8·4% (8·2–8·6)	11·3% (8·6–14·0)	12·0% (10·7–13·3)	7·1% (5·2–9·0)	22·0% (14·5–29·5)	5·2% (2·7–7·7)	12·6% (8·6–16·6)
Pre-eclampsia or gestational hypertension	12·4% (12·4–12·5)	NA	2·6% (2·5–2·7)	4·6% (2·8–6·4)	5·4% (4·5–6·3)	10·2% (8·0–12·4)	NA	NA	7·3% (4·2–10·4)
Infant outcomes									
Neonatal intensive care unit admission	11·3% (11·2–11·3)	14·3% (10·6–18·0)	NA	NA	16·7% (15·2–18·2)	5·1% (3·5–6·7)	NA	23·5% (18·8–28·2)	NA
Large for gestational age	18·0% (18–18·1)	9·5% (6·4–12·6)	NA	10·4% (7·8–13·0)	8·4% (7·3–9·5)	16·2% (13·5–18·9)	26·3% (18·4–34·2)	21·8% (17·2–26·4)	NA
Macrosomia	10·5% (10·5–10·6)	6·2% (3·7–8·7)	15·7% (15·4–16·0)	NA	NA	1·9% (0·9–2·9)	21·2% (13·8–28·6)	11·7% (8·1–15·3)	10·3% (6·6–14)
Small for gestational age	8·0% (8–8·1)	9·1% (6·1–12·1)	NA	4·6% (2·8–6·4)	8·7% (7·6–9·8)	2·1% (1·0–3·2)	5·9% (1·6–10·2)	NA	4·6% (2·1–7·1)
Birth trauma	40·6% (40·5–40·7)	NA	0·7% (0·6–0·8)	2·2% (1·0–3·5)	NA	NA	NA	NA	8·0% (4·7–11·3)
Hypoglycaemia	11·3% (11·2–11·3)	NA	NA	7·1% (4·9–9·3)	8·0% (6·9–9·1)	NA	NA	12·1% (8·5–15·7)	NA
Polycythaemia	12·4% (12·4–12·5)	NA	NA	37·7% (33·6–41·8)	NA	NA	NA	NA	NA
Jaundice	NA	NA	NA	59·1% (54·9–63·3)	NA	NA	NA	NA	12·6% (8·6–16·6)
Respiratory distress syndrome	NA	NA	3·6% (3·4–3·8)	NA	9·6% (8·4–10·8)	NA	NA	NA	NA

Data are presented as percentage followed by 95% CI. IADPSG=International Association of the Diabetes and Pregnancy Study Groups. NA=not available. OGTT=oral glucose tolerance test.

Table 2: **Incidence of complications among pregnancies complicated by gestational diabetes in specific countries**

future risk of type 2 diabetes was built on the work of Miller, who in 1946 described the characteristics of babies of women who developed diabetes later in life.[77] The other rationale, which centred around protecting the fetus, built on the work of Pedersen, who in 1952 postulated that maternal hyperglycaemia was transmitted to the fetus, resulting in fetal hyperinsulinaemia and diabetic fetopathy, including increased deposition of body fat.[78] From the 1960s, a range of diagnostic approaches were subsequently developed to identify gestational diabetes, which included overt diabetes in pregnancy.

In 2008, the results of the international prospective Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study,[5] which involved 25 505 women, were published, showing a positive linear relationship between maternal fasting, 1-h and 2-h blood glucose concentrations on the 75 gm 2-h OGTT at 24–32 weeks of gestation, and perinatal complications, including birthweight greater than the 90th percentile for gestational age, primary caesarean section delivery, neonatal hypoglycaemia, and cord blood serum C-peptide greater than the 90th percentile.[5] Not only were the fasting, 1-h, and 2-h glucose concentrations of women with gestational diabetes lower than those of individuals diagnosed with diabetes or impaired glucose outside pregnancy, there was also no inflection point at which pregnancy complications significantly increased.[5] In 2010, the IADPSG, representing diabetes in pregnancy societies around the world, produced consensus guidelines for the diagnosis of both gestational diabetes and overt diabetes in pregnancy.[1] Overt diabetes in pregnancy was defined by the criteria for diabetes in non-pregnant adults.[1] These guidelines were adopted by WHO in 2013[20] and include universal testing with the 75 gm 2-h OGTT at 24–28 weeks of gestation; the diagnostic glucose thresholds are based on an OR of 1·75 for the HAPO primary outcomes compared with the mean glucose concentration for the overall cohort.[5] Given their linear association, only one elevated glucose concentration was required for diagnosis.[1] Although the IADPSG diagnostic criteria for gestational diabetes were adopted by the major international diabetes and obstetric organisations (appendix p 4),[1,20,21,79–84] others, such as the National Institutes of Health, did not adopt the IADPSG criteria, generally because of the predicted increased diagnoses

and workload for health-care systems with no randomised controlled trial evidence of substantial clinical benefit of using the one-step (IADPSG) versus the two-step (Carpenter and Coustan) approach.[85–89]

Some health services in low-income and-middle income countries would have difficulty in implementing the WHO 2013 gestational diabetes guidelines due to insufficient resources for both the OGTT and caring for an increased number of individuals with gestational diabetes, resulting from the lower diagnostic thresholds.[90,91] A simple approach to reduce diagnostic burden has been to use selected risk factors to limit the number of women attending for an OGTT and therefore being diagnosed with gestational diabetes. These risk factors are similar to those for type 2 diabetes, although their effect magnitudes might differ within and between populations.[92,93] Risk factors for gestational diabetes can generally be classified as modifiable and non-modifiable, and the ORs for each risk factor are shown in the figure. Excess adiposity and bodyweight are the strongest and most consistent risk factors for gestational diabetes,[24,26,28,34,105–109] and are associated with greater risk of macrosomia and large-for-gestational-age offspring.[110] However, for many populations, the majority of women have at least one risk factor and the added complexity of risk factor-based screening increases the chance of women with risk factors not being invited for screening (eg, due to inaccurate identification of risk factors).[111]

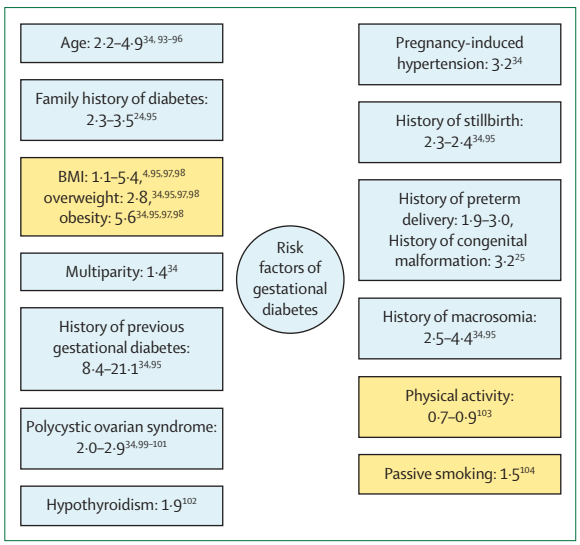

***Figure*: Risk factors of gestational diabetes and their odds ratios from meta-analyses**
Yellow boxes are modifiable risk factors, blue boxes are non-modifiable risk factors. Risk factors are generally consistent across countries except that some effect magnitudes differ, probably attributable to measurement heterogeneity rather than true differences.

Recognising heterogeneity of gestational diabetes based on timing of onset: early gestational diabetes

The IADPSG criteria for gestational diabetes were originally to be applied both in early and late pregnancy (appendix p 4). However, studies that repeated testing in early and late pregnancy showed low reproducibility of a gestational diabetes diagnosis.[3,112] This finding is partly due to the known physiological decrease in maternal fasting glucose from 6 weeks of gestation in typical pregnancy,[113] reducing the correlation between early and later glucose concentrations during pregnancy.[112] The IADPSG subsequently advised against the use of a fasting glucose threshold of 5·1 mmol/L in early pregnancy,[1] instead proposing the use of an early pregnancy HbA_{1c} with a threshold of at least 5·9% to detect overt diabetes and perinatal complications.[114] However, HbA_{1c} is insufficiently sensitive and cannot be used to identify early or late gestational diabetes, and some pregnancy complications in any health-care setting, including low-resource settings.[115] Recent research suggests that early HbA_{1c} might be able to be used to rule out gestational diabetes at 24–28 weeks of gestation but more research is needed.[116,117]

Women with early gestational diabetes, compared with late gestational diabetes, have worse pregnancy outcomes.[42,64,118] Recent evidence suggests treatment of early gestational diabetes reduces some perinatal and maternal complications beyond the historical approach of treating late gestational diabetes from 24 weeks to 28 weeks of gestation.[3] Panel 1 summarises why early gestational diabetes should now be screened for based on Wilson and Jungner's principles.[126,127]

There are currently a range of screening and diagnostic approaches for gestational diabetes in early pregnancy under review in several countries (appendix p 4).

Management of gestational diabetes

Randomised controlled trials comparing pregnancy outcomes with and without gestational diabetes treatment in late and early pregnancy

The first two major randomised controlled trials that studied treating late gestational diabetes showed that treatment reduced the risk of numerous health complications.[14,15] The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial showed that treating late gestational diabetes reduced the risk of a composite of major perinatal complications (eg, death, shoulder dystocia, bone fracture, and nerve palsy), with an adjusted relative risk (aRR) of 0·33 (95% CI 0·14–0·75).[15] The Maternal-Fetal Medicine Units Network (MFMU) trial showed that treating gestational diabetes reduced the risk of several prespecified secondary perinatal complications, including macrosomia (relative risk [RR] 0·41, 97% CI 0·26–0·66), large-for-gestational-age offspring (RR 0·49, 0·32–0·76), caesarean section (RR 0·79, 0·64–0·99), and preeclampsia (RR 0·46, 0·22–0·97).[14]

By 2021, there were nine randomised controlled treatment trials of late gestational diabetes (none of which systematically tested for early gestational diabetes) within a US Preventive Services Task Force meta-analysis,

***Panel 1*: Rationale and evidence for early screening to detect early gestational diabetes**

- The condition sought should be an important health problem
  - Early gestational diabetes complicates up to 37% of pregnancies and is associated with major pregnancy complications[42,43,119]
  - Early gestational diabetes comprises 30–70% of all women with gestational diabetes[120]
- The natural history of the condition, including development from latent to declared disease, should be adequately understood
  - Early gestational diabetes includes those entering pregnancy with either impaired glucose tolerance, impaired fasting glucose, or both, and those with lesser degrees of hyperglycaemia; early gestational diabetes is not always still present at 24–28 weeks of gestation, as regression can occur
  - In the overall Treatment of Booking Gestational Diabetes Mellitus (TOBOGM) trial cohort, a positive linear relationship between early pregnancy oral glucose tolerance test (OGTT) glucose, later gestational diabetes, and perinatal complications was observed, and was strongest for 1-h glucose;[4] similar correlations were found in two cohort studies[6,112]
- There should be a recognisable latent or early symptomatic stage
  - Early gestational diabetes is associated with a detectable increased abdominal circumference before 24–28 weeks of gestation[121–123]
- There should be a suitable test or examination
  - An OGTT is the traditional test for gestational diabetes and glucose concentrations correlate linearly with pregnancy complications
- The test should be acceptable to the population
  - The OGTT is the gold standard for late gestational diabetes and for diabetes diagnosis outside of pregnancy
  - The proportion of women declining OGTT early in pregnancy is low[124]
- There should be an agreed policy on whom to treat as patients
  - Those with a positive OGTT are treated as patients
- There should be an accepted treatment for patients with recognised disease
  - Early gestational diabetes has effective treatment;[3] treatment options include lifestyle change and pharmacotherapy
- Facilities for diagnosis and treatment should be available
  - Women with early gestational diabetes can be managed within the various gestational diabetes models of care
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
  - Diagnosing and treating gestational diabetes is cost saving if the TOBOGM upper band (HAPO Study odds ratio 2·0: fasting glucose concentration ≥5·3 mmol/L, 1-h post-load glucose ≥10·6 mmol/L, or 2-h post-load glucose ≥9·0 mmol/L, or a combination of these) is used[123]
- Case-finding should be a continuing process and not a once-and-for-all project
  - Women with glycosuria, symptoms of hyperglycaemia, polyhydramnios, macrosomia, or a combination of these, can be retested; retesting also occurs at 24–28 weeks of gestation

with treatment associated with lower risk of primary caesarean delivery (adjusted risk difference [ARD] –5·3%, 95% CI –10·3 to –0·24), shoulder dystocia (ARD –1·3%, –4·3 to –1·6), macrosomia (ARD –8·9%, –12·0 to –5·9), large-for-gestational-age offspring (ARD –8·4%, –10·8 to –6·1), neonatal intensive care unit admission (ARD –2·0%, –4·5 to 0·5), and reduced risk of birth injury (OR 0·33, 95% CI 0·11 to 0·99).[128]

More recently, there has been growing interest in whether treatment of early gestational diabetes is of benefit. Table 3 summarises the randomised controlled trials of diagnosis and treatment of early gestational diabetes, including the Treatment of Booking Gestational Diabetes Mellitus (TOBOGM) trial.[3] The TOBOGM international randomised controlled trial showed that in 802 women with gestational diabetes risk factors, immediate treatment of gestational diabetes (diagnosed using the WHO 2013 criteria) before 20 weeks of gestation reduced the risk of the perinatal composite (ie, preterm birth <37 weeks of gestation, birth trauma, birthweight ≥4500 g, respiratory distress, phototherapy, stillbirth or neonatal death, or shoulder dystocia) from 30·5% in the control group to 24·9% in the immediate-treatment group (ARD –5·6%, 95% CI –10·1 to –1·2; number needed to treat [NNT] 18). Prespecified subgroup analyses suggested a potentially greater effect of early intervention among women with higher glycaemic values on the OGTT, based on the 2·0 OR for adverse pregnancy outcomes shown in the HAPO Study (fasting glucose 5·3–6·0 mmol/L, 1 h glucose ≥10·6 mmol/L, 2-h glucose concentration 9·0–11·0 mmol/L, or a combination of one or more of these glucose concentrations; NNT 12) versus women in the lower glycaemic band (NNT 44), based on the 1·75 OR for adverse pregnancy outcomes in the HAPO Study (fasting glucose 5·1–5·2 mmol/L, 1-h glucose 10·0–10·5 mmol/L, 2-h glucose 8·5–8·9 mmol/L, or a combination of one or more of these glucose concentrations), and among women who underwent an OGTT earlier than 14 weeks of gestation (NNT 10; NNT at 14–19^{+6} weeks gestation 21). A potential for harm was also shown in the lower glycaemic band with

more small-for-gestational-age offspring (ARD 5·5%, 95% CI 1·4–9·7).[3] Further secondary outcomes reported included reductions in third and fourth degree perineal tears (ARD –2·8%, 95% CI –1·5 to 4·1). Delayed treatment (compared with immediate treatment) was associated with significantly lower breastfeeding initiation (OR 0·64,

	Trial name, number, and location	Participants (N)	Study population	Timeframe testing (weeks)	Gestational diabetes criteria	Comparison	Primary outcome
Randomised controlled trials for early treatment for gestational diabetes							
Osmundson et al (2016)[129]	USA	83	Women with singleton pregnancy and without overt diabetes in pregnancy	<14·0 weeks of gestation	HbA_{1c} between 39·0–46·0 mmol/mol (5·7–6·4%) before 14 weeks; 2-h 75 g OGTT IADPSG criteria	Usual care versus early treatment for gestational diabetes with diet, blood glucose monitoring, and insulin as needed	Result of the 75 g OGTT at 26 weeks to 28 weeks of gestation
Hughes et al (2018)[130]	PINTO feasibility study; New Zealand	47	Women with singleton pregnancy and without overt diabetes in pregnancy	<14·0 weeks of gestation	HbA_{1c} between ≥41·0–46·0 mmol/mol (5·9–6·4%) before 14 weeks of gestation; 2-h 75 g OGTT New Zealand criteria	Standard of care versus early intervention in pregnancies complicated by prediabetes	Recruitment rate, adherence to protocol, and validation of potential primary outcomes
Simmons et al (2018)[131]	TOBOGM pilot study; Australia	79	High-risk women with singleton pregnancy	<20·0 weeks of gestation (4·0–19·6 weeks)	2-h 75 g OGTT; IADPSG criteria	Women with early gestational diabetes receiving immediate care (clinical referral or ongoing treatment) versus deferred (no) treatment versus women without early gestational diabetes	To test the protocol for a larger-scale randomised controlled trial comparing pregnancy outcomes among women with early gestational diabetes receiving immediate or deferred treatment
Vinter et al (2018)[132]	Lifestyle in Pregnancy study; Denmark	90	Obese pregnant women (BMI 30–45 kg/m²) with singleton pregnancy	12–15 weeks of gestation	2-h 75 g OGTT; IADPSG Criteria	Lifestyle intervention versus standard of care	To study effects of lifestyle intervention on metabolic and clinical outcomes in obese women
Roeder (2019)[133]	USA	157	Women with hyperglycaemia and singleton pregnancy without overt diabetes in pregnancy	≤15·0 weeks of gestation	HbA_{1c} or fasting plasma glucose, or both, in early pregnancy; specifically 39·0–46·0 mmol/mol (5·7–6·4%) for HbA_{1c}; and 5·1–6·9 mmol/L (92–124 mg/dL) for fasting plasma glucose; 2-h 75 g OGTT; IADPSG criteria	Early pregnancy versus third trimester treatment of hyperglycaemia	The proportion of infants with neonatal umbilical cord C-peptide >1·77 nmoL (90th percentile)
Vambergue (2020)	NCT04451915; France	2010	Singleton pregnancy	<20·0 weeks of gestation	Fasting plasma glucose 5·1–6·1 mmol/L (92–110 mg/dL) with at least one risk factor in early pregnancy; at 24–28 weeks of gestation: 2-h 75 g OGTT; IADPSG criteria	Early management of gestational diabetes versus late management of gestational diabetes	The occurrence of materno–fetal complications at delivery (large-for-gestational age, neonatal hypoglycaemia, or shoulder dystocia, birth traumatisms, or a combination of these)
Simmons et al (2023)[3]	TOBOGM; international	802	High-risk women with singleton pregnancy	<20·0 weeks of gestation (4·0–19·6 weeks)	2-h 75 g OGTT; IADPSG criteria	Immediate treatment for early gestational diabetes (intervention group) versus deferred or no treatment for early gestational diabetes (control group)	Three primary outcomes: a composite of adverse neonatal outcomes (birth at <37 weeks of gestation, birth trauma, birthweight of ≥4500 g, respiratory distress, phototherapy, stillbirth or neonatal death, or shoulder dystocia), pregnancy-related hypertension (pre-eclampsia, eclampsia, or gestational hypertension), and neonatal lean body mass
Randomised controlled trials for early screening for gestational diabetes							
Harper et al (2020)[134]	EGGO study; USA	922	Obese women (BMI ≥30 kg/m²) without overt diabetes in pregnancy and history of bariatric surgery	14–20 weeks of gestation	Two-step method: 1-h 50 g glucose challenge test followed by a 3-h 100 g OGTT; Carpenter and Coustan criteria	Early gestational diabetes screening (14–20 weeks of gestation) versus routine screening (24–28 weeks of gestation)†	A composite of macrosomia (>4000 g), primary caesarean section, hypertensive disease of pregnancy, shoulder dystocia, neonatal hyperbilirubinemia, and neonatal hypoglycaemia (assessed within 48 h of birth)

(Table 3 continues on next page)

	Trial name, number, and location	Participants (N)	Study population	Timeframe testing (weeks)	Gestational diabetes criteria	Comparison	Primary outcome
(Continued from previous page)							
Hung-Yuan Li	TESGO study; NCT03523143; Taiwan	967	Singleton pregnancy without overt diabetes in pregnancy	18–20 weeks	75 g 2-h OGTT; IADPSG criteria	Early screening group (18–20 weeks of gestation) versus standard screening group (24–28 weeks of gestation)†	The occurrence rate of any of the following adverse outcomes, including caesarean section, birthweight >90th percentile, cord serum C-peptide ≥90th percentile, neonatal hypoglycaemia, pregnancy-induced hypertension, pre-eclampsia, birth trauma, hypoglycaemia, and cord serum C-peptide greater than the 90th percentile
Wilkie (2023)	NCT05388643; USA	80	High risk for developing gestational diabetes by American Congress of Obstetricians and Gynaecologists clinical risk factors guidelines with singleton pregnancy	<12 weeks of gestation	3-h 100 g OGTT; American Congress of Obstetricians and Gynaecologists criteria	Enhanced first trimester gestational diabetes screening versus standard of care gestational diabetes screening	Confirmed diagnosis of gestational diabetes based on 3-h 100g OGTT between 24 weeks and 28 weeks of pregnancy

This table provides an overview of randomised controlled trials focusing on the impact of early treatment for gestational diabetes on maternal and neonatal outcomes when compared with routine treatment, and of randomised controlled trials focusing on the impact of early screening for gestational diabetes on maternal and neonatal outcomes when compared with routine screening. EGGO=Early Gestational Diabetes Screening in the Gravid Obese Woman. HbA_{1c}=haemoglobin A1c. IADPSG=International Association of the Diabetes and Pregnancy Study Groups. OGTT=oral glucose tolerance test. PINTO=Prediabetes in pregnancy, can early intervention improve outcomes. RR=relative risk. TESGO=The Effect of Early Screening and Intervention for Gestational Diabetes Mellitus on Pregnancy Outcomes. TOBOGM=Treatment of Booking Gestational diabetes Mellitus. *Principal investigator was contacted and has confirmed these data. †After diagnosis with gestational diabetes, women received treatment. ‡Principal investigator was contacted, but no confirmation received.

Table 3: **Randomised controlled trials for early treatment and early screening for gestational diabetes**

95% CI 0·42–0·98) after adjusting for maternal characteristics) with no effect of birth and neonatal characteristics. The proportion initiating breastfeeding within 1 h was similar between the two groups.[135]

Medical and obstetric management

Outcomes of pregnancies complicated by gestational diabetes are substantially influenced by the medical and obstetric management approach. A discussion about barriers to gestational diabetes care is found in Series paper 3.[19] Trials have generally used variations of the medical and obstetric management approaches described here.

There is a single pathway for the medical management of gestational diabetes regardless of the timing of diagnosis. Panel 2 summarises the components of the medical management of gestational diabetes, and various gestational diabetes medical management guidelines are summarised in the appendix (p 8). The use of oral agents varies internationally, with scarce data regarding their long-term safety for the offspring (panel 3; appendix p 8). Other than lifestyle interventions, the optimal medical treatment strategy for early gestational diabetes, including glucose treatment thresholds, has not yet been identified. Metformin use in early pregnancy is not associated with an increased risk of birth defects,[176] and can be combined with insulin; however, metformin crosses the placenta and therefore raises uncertainty over possible long-term sequelae in the offspring.[176] In women at risk for or who have hypertension, preeclampsia, or fetal growth restriction, metformin should be used cautiously given the potential greater risk of small-for-gestational-age offspring and fetal acidosis with placental insufficiency,[176] as suggested in trials evaluating metformin in type 2 diabetes in pregnancy.[167,177]

Peripartum glycaemic management aims to prevent maternal hypoglycaemia and hyperglycaemia.[178] Pregnancy-associated insulin resistance falls rapidly postpartum, and insulin therapy often requires careful management around operative delivery.[179] Glucose-lowering therapies are usually discontinued postpartum.[178] Follow-up glucose testing is essential. Women should also receive advice on reducing the risk of type 2 diabetes and cardiovascular disease postnatally and the benefits of breastfeeding and planning of future pregnancies.[19,178]

The evidence for different obstetric and surveillance strategies for pregnancies complicated by gestational diabetes remains scarce, with no studies of whether approaches should differ between early and late gestational diabetes. Panel 4 summarises key aspects of the obstetric management of gestational diabetes, and in the appendix (p 12) various gestational diabetes obstetric management guidelines are summarised.

Randomised controlled trials comparing whole obstetric population pregnancy outcomes with different screening and testing approaches for late and early gestational diabetes

A meta-analysis on gestational diabetes treatment included a number of randomised controlled trials that used either

***Panel 2*: Medical management of gestational diabetes**

- Medical nutrition therapy is the first-line treatment for gestational diabetes internationally,[136] and is associated with benefits for some pregnancy complications;[137-139] there is insufficient evidence to support one dietary approach over another,[139] in part because of the challenges of performing randomised controlled trials of dietary interventions and the high risk of bias in many published studies[136]
- Preventing excessive gestational weight gain might decrease the need for pharmacotherapy and reduce risk of pregnancy complications;[140-142] although reducing gestational weight gain is recommended by international clinical guidelines, there is scarce evidence on gestational weight gain targets in gestational diabetes
- Physical activity is widely recommended but clinical benefits and optimum type or timing of exercise in gestational diabetes remains unclear;[143-145] two meta-analyses showed that exercise did not improve maternal glycaemia or neonatal outcomes in gestational diabetes pregnancies[144,145]
- Sleep duration and quality might influence glycaemia in women with gestational diabetes,[146-148] but measuring sleep accurately in pregnancy is challenging; how modifiable sleep duration or quality are during pregnancy is also unclear, but educational interventions appear feasible[149]
- Self-monitoring of blood glucose is an integral part of gestational diabetes management and guides the introduction of pharmacotherapy,[150] but can contribute to anxiety following the diagnosis
  - Glucose targets for self-monitoring of blood glucose have a limited evidence base and vary internationally (appendix p 8); the TARGET trial showed that tighter glucose targets (ie, fasting ≤5·0 mmol/L, 1-h post-prandial ≤7·4 mmol/L, 2-h post-prandial ≤6·7 mmol/L) were associated with less serious infant morbidity but more maternal morbidity[151]
  - Evidence (including cost-effectiveness data) does not currently support the use of continuous glucose monitoring for all women with gestational diabetes; however, continuous glucose monitoring might improve glycaemia, reduce gestational weight gain, and optimise birthweight compared with self-monitoring of blood glucose[152,153]
- HbA_{1c} monitoring is influenced by haemoglobin turnover and is of limited clinical use in gestational diabetes with no specific targets, despite a linear association with increased risk of pregnancy complications[114,154,155]
- Other glycaemic markers, such as glycated albumin and fructosamine, have limited value as they are influenced by gestational age, BMI, pregnancy-induced haemodilution, altered renal function, and serum protein concentrations[156-158]
- Pharmacotherapy is tailored according to disease severity and complications. The proportion of women requiring pharmacotherapy for gestational diabetes varies internationally (approximately 25–50%, almost 66% in early gestational diabetes[3]), and differs according to the timing of diagnosis;[64,159] women with high BMI, family history of diabetes, previous gestational diabetes, higher HbA_{1c} at the time of gestational diabetes diagnosis, or a diagnosis of gestational diabetes in early pregnancy are more likely to need pharmacotherapy[160]

the one-step IADPSG or the two-step Carpenter and Coustan approach in the USA.[128] This meta-analysis evaluated the impact of screening on the total obstetric population, as opposed to randomised controlled treatment trials evaluating the impact of intervention specifically for women affected by gestational diabetes (eg, ACHOIS[15] and MFMU[14]). The meta-analysis showed no significant difference in pregnancy complications (besides significantly more neonatal hypoglycaemia detected and able to be treated with one-step testing) alongside an approximate 6·6% difference in women diagnosed with gestational diabetes between the two approaches; specifically, 11·5% of women were diagnosed per IADPSG criteria, whereas 4·9% were diagnosed per Carpenter and Coustan criteria.[128] Of the 6·6% of women who met the diagnostic criteria of the IADPSG, but not the Carpenter and Coustan approach, the large-for-gestational-age offspring rate was 20%, which after treatment could be approximately halved (to ~10%), as per findings of the MFMU randomised controlled trial.[7,14] Such a small total obstetric population impact (10% reduction in large-for-gestational age offspring among the ~6·6% of affected women) would be unlikely to influence the choice of gestational diabetes diagnostic approach. Therefore, in addition to considering the pregnancy complications of the obstetric population, and the corresponding burden on health-care systems, it is important to consider those women whose gestational diabetes status is altered by choice of screening approach, and how their outcomes change. This question is reflected in the Gestational Diabetes Mellitus Study of Detection Thresholds (GEMS) trial, which evaluated lower (IADPSG) versus higher New Zealand glucose criteria (fasting glucose ≥5·5 mmol/L or a 2-h glucose ≥9·0 mmol/L, or both) for the one-step 75 gm 2-h OGTT among over 4000 New Zealand women.[193] Results of the trial suggested that, at the population level, the prevalence of gestational diabetes as assessed by the IADPSG criteria was 15·3%, more than double the prevalence of the New Zealand criteria (6·1%), with no difference in pregnancy complications in the overall population. However, a prespecified secondary analysis among the 9·2% of women with gestational diabetes using the IADPSG criteria, but classified as normoglycaemic using the New Zealand criteria, compared pregnancy outcomes between treated and untreated women. Treatment was associated with clinically meaningful

Panel 3: Pharmacotherapy used in the management of gestational diabetes

- The use of oral diabetes agents has been increasing in many regions of the world due to their low cost, safety, availability, and convenience
- Insulin has long been used as the drug of choice in gestational diabetes, including regular human insulin, neutral protamine Hagedorn, and some short-acting and long-acting insulin analogues
  - The data are scarce about the risks and effectiveness of insulin glulisine and second-generation basal insulin analogues, such as insulin degludec and glargine U-300, in women with gestational diabetes[161]
  - Recent work has showed that a patient-led insulin dose-titration regimen is safe and beneficial[162]
  - Continuous subcutaneous insulin infusion and U500 insulin have been used when insulin needs are high[21,163]
- Metformin is widely used and generally considered safe and effective in treating gestational diabetes, with reduced adverse maternal and neonatal outcomes compared with insulin and minimal risk of hypoglycaemia[164-166]
  - Metformin has been associated with reduced rates of large-for-gestational-age offspring and lower birthweight
  - Some organisations recommend avoiding metformin in conditions where an increased risk of growth restriction exists (eg, women with hypertensive disorders)[167]
  - Data on metformin use in pregnancy are inconsistent regarding an association with offspring obesity in childhood[168-170]
- Glyburide improves glycaemia,[162,169] but is associated with more neonatal morbidity compared with using insulin and is not widely used internationally[164,171,172]
- Other pharmacological agents, such as acarbose,[173] dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists,[174] have rarely been used during pregnancy due to an absence of safety data; thiazolidinediones are considered unsafe during pregnancy[175]

Panel 4: Obstetric management of gestational diabetes

- Early visits in the first trimester enable accurate dating of pregnancy,[180–184] identification of risk factors, early gestational diabetes diagnosis, and individual planning of surveillance, management, and possible interventions during pregnancy[185]
- Monitoring fetal growth in women with gestational diabetes (particularly those with a high BMI) guides possible interventions, such as induction of labour
  - A detailed scan at 18–20 weeks of gestation (for identification of structural malformations) is recommended by most professional bodies for all pregnancies
  - Ultrasound-assessed abdominal circumference and estimated fetal weight have been shown to be useful in guiding therapy and improving birthweight distribution,[183] but is associated with increased insulin treatment[184,186]
  - Fetuses from pregnancies complicated by gestational diabetes, even when appropriate for gestational age, can still have increased subcutaneous fat deposition[186]
- Fetal surveillance is mentioned in most international guidelines, including cardiotocography and biophysical profile from 38 weeks of gestation
  - However, there is scarce evidence that the use of such tests prevent fetal compromise and stillbirth
  - One observational study reported that cardiotocography could show changes suggestive of fetal hypoxia in births complicated by gestational diabetes, supporting the use of continuous cardiotocography during delivery[187]
  - Whether earlier treatment of gestational diabetes reduces hypoxia-related cardiotocography changes during labour is unknown
- Timing and mode of delivery is largely individualised;[188–191] currently there is an absence of strong evidence regarding the appropriate use of induction of labour at different gestational weeks in gestational diabetes[192]
- In low-resource settings, where the burden of gestational diabetes can be high, it might be impractical to offer weekly surveillance, routine early inductions, or provide continuous monitoring, especially when there is no strong evidence of benefit

reductions in large-for-gestational-age offspring (adjusted OR 0·49, 95% CI 0·29–0·83, adjusted NNT 4) and pre-eclampsia (adjusted OR 0·08, 0·002–0·60) compared with women who were not treated.[193] Because of the inherent pitfalls of subgroup analyses, these findings require cautious interpretation until more data are available from other randomised controlled trials.

Similar issues are reflected in table 3, which summarises the randomised controlled trials of early screening (as opposed to diagnosis) for gestational diabetes across the general obstetric population including the Early Gestational Diabetes Screening in Gravid Obese Woman (EGGO) trial.[134] This trial showed no difference in a perinatal composite outcome with early screening for gestational diabetes in 922 women with BMI of equal to or greater than 30 kg/m² (two-step Carpenter and Coustan criteria). The trial included only a small number of women ultimately diagnosed and treated for gestational diabetes—69 (15·0%) of 459 women in the early screening group compared with 56 (12·1%) of 463 women in the routine screening group—and these women had a late average gestational age at the time of diagnosis (24·3 weeks, SD 5·2 in the early screening group and 27·1 weeks, SD 1·7 in the routine screening group).[134]

Cost-effectiveness of screening and treatment for gestational diabetes

The cost-effectiveness of screening and treatment for gestational diabetes depends on whether the increased costs of screening and treatment are offset by savings arising from delaying or preventing adverse infant and maternal outcomes. Striking this balance in turn depends on available resources, competing health demands, the prevalence of gestational diabetes, the yield of screening, and the effectiveness of treatment. In general, a treatment is considered cost-effective when it produces 1 additional year of healthy life at a cost less than three-times a country's per capita gross domestic product.[194] In 2022, the per capita gross domestic product ranged from US$741 in low-income countries to $49 430 in high-income countries.[195]

Cost-effectiveness analyses have assessed the costs of screening for gestational diabetes to include the costs of screening at the booking visit, during the first trimester, and at 24 to 28 weeks of gestation and as either a one-step procedure or two-step procedure. Analyses have also varied as to which costs were included in treating gestational diabetes, including lifestyle management, medications, self-monitoring of blood glucose, fetal monitoring, treatment of preeclampsia, induction of labour, and treatment in hospital.[196] Further variation has occurred in which short-term infant outcomes (eg, macrosomia, large-for-gestational-age offspring, shoulder dystocia, hyperbilirubinaemia, hypoglycaemia, respiratory distress, neonatal intensive care unit admission, and death) and short-term maternal outcomes (eg, gestational diabetes, hypertensive disorders, treatment in hospital, induction of labour, caesarean delivery, laceration, haemorrhage, and death) were included. Fewer cost-effectiveness analyses have assessed the costs of long-term infant outcomes (eg, obesity, type 2 diabetes, cardiovascular disease, and premature mortality) and maternal outcomes (eg, type 2 diabetes, cardiovascular disease, and premature mortality).

A systematic review in 2019 assessed the cost-effectiveness of screening and treatment for gestational diabetes based on six studies (four randomised control trial-based and two model-based analyses).[197] They compared the interventions with standard of care, used empirically observed rates of retention and compliance, and performed intention-to-treat analyses. Only one trial-based analysis and one model-based analysis found screening and treatment to be cost-effective. Three factors appeared to impact cost-effectiveness. The first was the prevailing standard of care in the community. When screening and treatment for gestational diabetes were already well established, the health benefits of screening the whole population for gestational diabetes and treating those not previously diagnosed did not outweigh the additional investment needed to screen. A second factor was adherence to treatment: when adherence to treatment was low, health outcomes were little improved, and the costs of screening were not offset by improved outcomes. The third factor was the time horizon used for the analysis: using a shorter time horizon that considered only perinatal outcomes provided a less favourable cost-effectiveness picture than when longer term maternal and offspring outcomes were also considered.

A meta-analysis and systematic review in 2021 summarised the results of ten economic evaluations of different gestational diabetes screening strategies in diverse settings.[196] However, all of the selected studies were observational, hence open to wider influences compared with randomised controlled trials and should be interpreted with caution. Most compared screening to no screening (eight of ten), assumed 100% uptake of screening (eight of ten), and included the costs of gestational diabetes screening, gestational diabetes treatment, delivery, and neonatal care (eight of ten). Two studies also considered the costs of treating preeclampsia and permanent brachial plexus injury and two considered the costs of mothers' lost productivity. In general, screening was cost-effective or even cost-saving over no screening, and one-step screening was more likely to be cost-effective than two-step screening. Universal screening was more likely to be cost-effective than targeted screening in high-risk populations. Notably, none of the six studies included in the earlier systematic review[196] were included in the more recent meta-analysis.[197]

The only health economic analysis of diagnosing and treating early gestational diabetes was based on the results of the TOBOGM randomised controlled trial.[198] Compared with the control group (table 3), immediate treatment was associated with a 10% reduction in total health-care costs due to a large reduction in costs related to complicated deliveries and neonatal intensive care unit or special care nursey admissions.

In general, screening and treatment for gestational diabetes is more likely to be cost-effective when the prevalence of gestational diabetes is high, there is little screening and treatment in the community, diagnosis and treatment is commenced earlier in pregnancy, adverse infant and maternal outcomes are common and expensive, and when screening and treatment have high uptake and are inexpensive, safe, and effective.[134,193]

What are the gaps?

Although approaches differ, there is global agreement that screening for gestational diabetes and subsequent treatment should occur routinely at 24–28 weeks of gestation. The emergence of early gestational diabetes as a clinical entity provides an opportunity to review and ideally resolve the current diagnostic discord for screening at 24–28 weeks of gestation. Findings from epidemiological studies and randomised controlled trials that have not differentiated early and late gestational diabetes are not redundant, but have become harder to interpret in the setting of this heterogeneity. Although the OGTT is a problematic test, it remains the gold standard diagnostic tool for gestational diabetes. Other glycaemic measures, such as fasting glucose or HbA1c,

have major limitations, and no randomised controlled trials of these measures, glucose sensors, or other novel biomarkers and approaches have yet taken place in early pregnancy, or in low-resource settings.

New approaches should therefore consider gestational diabetes a heterogenous condition where different phenotypes (and genotypes) might require distinct diagnostic and management approaches. Emerging evidence suggests that subtyping gestational diabetes based on pathophysiologic markers (eg, insulin resistance and insulin secretion defects) could identify gestational diabetes pregnancies at increased risk of complications, as highlighted in Series paper 1.[23] Other precision medicine biomarkers might also become useful to risk stratify within gestational diabetes.[132] Consistent screening, diagnostic, and treatment approaches for both early and late gestational diabetes might be pragmatic, but in view of the heterogeneity identified, validation studies are needed, with consideration of different resource settings and the life-course nature of gestational diabetes.

Recognising gestational diabetes heterogeneity should ignite research to support clinical and policy changes to improve the intergenerational wellbeing of women with both early and late gestational diabetes and their offspring.

Contributors

DS was responsible for conceptualisation of all papers in this Series. All authors contributed to the original draft of different sections of this paper. AS, WH, and KB contributed to conceptualisation of figures. All authors reviewed and edited the final manuscript before submission.

Declaration of interests

KB reports research funding and receipt of study devices from Medtronic for the investigator-initiated CRISTAL study; receipt of study devices from Dexcom for the investigator-initiated GLORIA study; receipt of study medication from Novo Nordisk for the investigator-initiated SERENA study; and consulting fees from AstraZeneca and Lilly; and served on the speakers bureau for Novo Nordisk, AstraZeneca, and Mundipharma. DS reports receipt of study devices on loan from Tandem for the CIRCUIT study; and speaker fees from Ascensia and Sanofi. All the other authors declare no competing interests.

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