Healthcare Improvement Scotland | SIGN Makes sense of evidence

Management of diabetes in pregnancy

This guideline is dedicated to the memory of our friend and contributor Professor Fiona Denison (University of Edinburgh) who sadly died during the development of this guideline after COVID-19 devastated her mental health and wellbeing.

Peer review draft

September 2023

Key to evidence statements and recommendations

Levels of evidence

1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Recommendations

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.

R For '**strong**' recommendations on interventions that **'should'** be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more good than harm. For '**strong**' recommendations on interventions that **'should not'** be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.

R For '**conditiona**l' recommendations on interventions that should be '**considered**', the guideline development group is confident that the intervention will do more good than harm for **most** patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

Good-practice points

✓ Recommended best practice based on the clinical experience of the guideline development group.

Contents

1 Introduction

1.1 The need for a guideline

In Scotland around 1 in 175 pregnancies is complicated by pre-existing diabetes, of which around 70% are type 1 diabetes (T1DM) and 30% are type 2 diabetes (T2DM). National surveillance of pregnancy, childbirth and early care of babies in Scotland shows that maternal obesity continues to increase. In 2021–2022 the proportion of women giving birth who were overweight or obese was the highest since reporting began (56.9%).[1] Furthermore, depending on screening pathways, 4–10% of pregnancies are complicated by incident gestational diabetes (GDM).[2]

For women with pre-existing diabetes adverse outcomes, including increases in miscarriage, congenital anomaly, preeclampsia, operative deliveries, neonatal hypoglycaemia and neonatal admission and stillbirth, have been slow to improve. Major technological advances in both glucose monitoring, including development and implementation of various forms of continuous glucose monitoring, and insulin delivery, including increasingly sophisticated pump and integrated pump and sensor technology, have become available in the last five years. Consideration of the place of such technologies in supporting improvements in self management for these women is now particularly important.

For women with, or at risk of GDM there are related and additional challenges. Firstly, all services report increases in women at risk of GDM, based on increasing prevalence of risk factors including, but not confined to, adiposity and ethnicity. Further, new evidence and new recommendations have been published on criteria for detection and diagnosis of GDM since the publication of the previous version of this SIGN guideline in 2010.[3] Revisiting the optimal approach to screening and diagnosis of GDM in Scotland balances the priorities to avoid missing a diagnosis and the opportunity to improve outcomes, but also to avoid medicalising pregnancy if this can be avoided.

In all of these situations the guideline development group has sought to apply the best evidence to encourage the most appropriate level of care for women with diabetes in Scotland.

1.1.1 Patient perspective

Patients may have different perspectives on healthcare processes and outcomes from those of healthcare professionals. The involvement of patients in guideline development is therefore important to ensure that guidelines reflect their needs and concerns and address issues that matter to them.

Common concerns raised by patient groups and through research include:

- Access to diabetes technologies (for example continuous glucose monitoring) to support managing diabetes as best as possible during pregnancy.
- Being informed and listened to during discussions and decision making around pregnancy and birth. Making sure that conversations start with what matters most to the woman.
- Having timely access to support throughout pregnancy to help manage concerns particularly around sickness, increased hypos, or sudden increases in insulin requirements.

1.2 Remit of the guideline

1.2.1 Overall objectives

This guideline provides recommendations based on current evidence for best practice in the management of diabetes in pregnancy. It includes major milestones in the pregnancy journey from preconception care to follow up and surveillance in the weeks after delivery. The target

population includes:

- women with T1DM or T2DM who are planning pregnancy
- women who have previously had GDM
- pregnant women who do not have a pre-existing diagnosis of diabetes
- pregnant women with GDM
- women with moderately-raised glycated haemoglobin (HbA1c) (42–47 mmol/mol)
- women with specific risk factors for adverse pregnancy outcomes, including: current or previous intrauterine death (IUD), polycystic ovary syndrome (PCOS), age >35 years and/or Chinese or East Asian ethnicity.

1.2.2 Comorbidities to consider when managing patients with diabetes in pregnancy

Common comorbidities and coexisting health issues which have been considered when reviewing the evidence for this guideline are:

- obesity
- cardiovascular disease, in particular hypertension and dyslipidaemia
- diabetic kidney disease
- diabetic eye disease
- diabetic foot disease.

Consideration of these factors is particularly important in pregnancy planning.

1.2.3 Definitions

The term woman/women has been used throughout this document to refer to women and birthing people who are pregnant or who recently gave birth. It refers to people who share the protected characteristic of pregnancy and maternity when naming the beneficiaries of work which affects prenatal, perinatal and post-natal care. The Women's Health Plan published by Scottish Government in 2021 notes that while the majority of those who are pregnant and having a baby will identify as women, all healthcare services should be respectful and responsive to individual needs, and all individuals should be asked how they wish to be addressed throughout their care.[4] For the purpose of this document, the term woman/women includes girls. It also includes people whose gender identity does not correspond with their birth sex or who may have a non-binary identity.

1.2.4 Target users of the guideline

This guideline will be of interest to healthcare professionals in primary and secondary care involved in the care of women with diabetes and their newborn babies, including general practitioners (GPs), nurses and midwives, obstetricians, diabetes physicians, neonatal paediatricians, dietitians and community pharmacists. It will also be of interest to women with pre-existing diabetes, those who develop diabetes during pregnancy and their families.

1.2.5 Patient version

A patient version of this guideline will be developed following publication of this document.

1.3 Statement of intent

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results.

The ultimate judgement must be made by the appropriate healthcare professional(s)

responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at through a process of shared decision making with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be documented in the patient's medical records at the time the relevant decision is taken.

1.3.1 Influence of financial and other interests

It has been recognised that financial or academic interests may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from these sources, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial and academic interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies of declaration of interests forms are retained by the SIGN Executive and are available on request from the SIGN Executive.

1.3.2 Prescribing of licenced medicines outwith their marketing authorisation

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed 'off label' in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.[5]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".[5]

The General Medical Council (GMC) recommends that when prescribing a medicine 'off label', doctors should:[6]

- be satisfied that there is no suitably licensed medicine that will meet the patient's need
- be satisfied that there is sufficient evidence or experience of using the medicine to show its safety and efficacy
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine, and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so.
- make a clear, accurate and legible record of all medicines prescribed and, when not following common practice, the reasons for prescribing an unlicensed medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and Royal Pharmaceutical Society's Competency Framework for all Prescribers.

Prior to any prescribing, the licensing status of a medication should be checked in the

summary of product characteristics (www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[7]

1.3.3 Health technology assessment advice for NHSScotland

Specialist teams within Healthcare Improvement Scotland issue a range of advice that focuses on the safe and effective use of medicines and technologies in NHSScotland.

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees about the status of all newly-licensed medicines, all new formulations of existing medicines and new indications for established products. NHSScotland should take account of this advice and ensure that medicines accepted for use are made available to meet clinical need where appropriate.

SMC advice relevant to this guideline is summarised in the section on implementation.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

NOT INCLUDED IN THIS DRAFT – WORK IN PROGRESS

3 Preconception care

Optimising glycaemic control and coexisting morbidities before conception has been shown to improve pregnancy outcomes. It is important for women planning pregnancy to seek healthcare advice and support to be able to do this. This may be provided by a range of specialist services within primary or secondary care. Contraception should be used until these measures have been put in place. High-dose Folic Acid (5 mg) should be prescribed and taken for three months prior to stopping contraception to reduce the risk of congenital abnormalities. Other medications such as antihypertensives, statins, and glucose lowering treatments should be reviewed and, where required, switched to alternative medication which is more suitable for pregnancy.[8]

Blood glucose levels should be optimised when women with diabetes are planning pregnancy. To facilitate this, opportunistic conversation should be initiated during every annual review with women of childbearing age, including consideration of use of insulin pumps and continuous glucose monitoring (CGM) to optimise glycaemic control. Body mass index (BMI) should be reviewed and weight management advice offered if appropriate. Other lifestyle factors should be discussed such as healthy eating and exercise, stopping smoking and avoiding alcohol and other drugs.

3.1 Glycaemic targets when planning pregnancy

3.1.1 Blood glucose

SIGN guideline 116 (Management of diabetes) recommended that prepregnancy glycaemic control should be maintained as close to the non-diabetic range as possible, taking into account risk of maternal hypoglycaemia. In a good practice point the target for prepregnancy glycaemic control for most women was suggested, as a minimum, to be an HbA1c <53 mmol/mol although lower targets of HbA1c may be appropriate if maternal hypoglycaemia can still be minimised.[3]

No evidence was identified which compared planned or achieved blood glucose target ranges in women planning pregnancy.

The St Vincent Declaration in 1989 set a goal that pregnancy outcomes in women with pregestational diabetes should approximate those of the general population. To do this, women must achieve as near normal blood glucose levels during pregnancy as can safely be achieved without dangerous levels of hypoglycaemia. In over three decades since the Declaration, this goal has not been achieved, nor has there been clear articulation of the optimal targets required to support it.[9] 2+

With more widespread use of CGM and the advent of closed loop systems, tighter levels of glycaemic control, with higher time in range (TIR) can now be achieved without dangerous levels of hypoglycaemia.

A mixed-methods systematic review incorporated 32 studies by narrative synthesis on the impact of T2DM on women's health and wellbeing during reproductive years.[10] Several studies reported that risks associated with diabetes during pregnancy were understood by pregnant women to a different extent, including poor blood glucose control (80%), congenital malformations (48%) and fetal macrosomia (35%). Awareness of pregnancy risks for women with T2DM was reported as an incentive to attend prepregnancy care. The authors report a number of studies suggesting that while attendance at prepregnancy care was often low, those women who attended had achieve significantly improved glycaemic control before pregnancy and in the first two trimesters. 2++

The barriers to attending prepregnancy care included the pregnancy being not 'fully planned' (45%), fertility concerns (31%) and negative relationship with healthcare professionals (21%). Based on evidence from qualitative research, women reported that healthcare professionals emphasised medical aspects of diabetes management such as blood glucose levels, diet and exercise. Studies described some consultations with professionals to be like tick-box exercises as they focused on asking questions from a template that failed to include women's

reproductive needs.

From a population perspective, it may be more important to increase the proportion of women with pre-existing diabetes who actively plan for pregnancy than to focus on the ideal blood glucose target alone.

The National Pregnancy in Diabetes (NIPID) audit measures the quality of pregestational diabetes care against National Institute for Health and Care Excellence (NICE) guideline-based criteria and the outcomes of pregestational diabetic pregnancy in England and Wales. The 2021 NIPID report showed that between 2014 and 2020, 7 out of 8 women were not adequately prepared for pregnancy and this figure did not improve during that period.[11]

3.1.2 Glycated haemoglobin (Haemoglobin A1c)

Studies which provide data on the association between HbA1c and maternal and fetal outcomes are from a range of designs and are of varying quality. Evidence cited in NICE guideline NG3 on diabetes in pregnancy: management from preconception to the postnatal period includes studies published in the 1980s whose participants are less representative of contemporary Scottish women. Across all studies which were considered, the populations vary significantly and participants have a wide range of HbA1c values at baseline. This variation also includes a spectrum of ethnicities and BMI values which are less generalisable to the current Scottish population.

Evidence which includes a systematic review, prospective and retrospective cohort studies and retrospective surveys consistently suggests that lower periconceptual HbA1c is associated with lower risk of congenital anomalies,[12-14] preterm birth,[15] stillbirth,[14,16] Caesarean birth[17] and early onset pre-eclampsia[17] in women with T1DM or T2DM planning pregnancy. 2-, 2+, 3

However, studies are inconsistent in HbA1c thresholds used. Several suggest that there is no safe threshold level, but a continuous relationship between HbA1c at delivery and frequency of good perinatal outcome.[14] One systematic review reports a relative risk of 3.2 for risk of congenital anomalies in those with pregestational diabetes compared with those without.[13] A cohort study reported risk for major anomalies increasing within different ranges of HbA1c from a relative risk (RR) of 2.35 with HbA1c range 58–79 mmol/mol, RR 3.17 with HbA1c range 80–104 mmol/mol to a RR of 7.75 for those with an HbA1c of >102 mmol/mol.[12]

A retrospective cohort study conducted in France and Italy of 107 pregnancies in women with T1DM treated by insulin pumps demonstrated that lower mean HbA1c in pregnancies that were planned (prepregnancy HbA1c: 53 mmol/mol vs 64 mmol/mol), was associated with a reduced risk of preterm birth (RR 0.44, 95% CI 0.25 to 0.76).[15] There was no statistically significant difference in rates of pre-eclampsia, hypertension or delivery by Caesarean section between groups with planned and unplanned pregnancies. Compared with women in the general French population, women with T1DM in the study cohort had twice the rate of congenital anomalies, ten times the LGA rate, four times the rate of prematurity and a rate of birth by Caesarean section which was three times higher. The authors concluded that additional metrics of glucose control beside HbA1c should be considered.

A Scottish population-based study assessed the risk of stillbirth in women with T1DM or T2DM.[16] A higher rate of HbA1c prepregnancy was associated with a higher risk of stillbirth in both women with T1DM (OR 1.03) and T2DM (OR 1.02) diabetes. Overall, stillbirth rates were highest in women with T2DM (22.9/1000) compared with T1DM (16.1/1000).

A retrospective survey of 533 women with T1DM conducted in the USA reported that women who planned their pregnancies had significantly lower HbA1c at the time of conception than those who did not (mean 49 mmol/mol v 61 mmol/mol).[17] Those with higher HbA1c had higher rates of Caesarean birth, more weight gain, more hypoglycaemic episodes and earlier pre-eclampsia. 3

The NICE guideline identified five observational studies which reported associations between prepregnancy HbA1c and risk of congenital malformations or perinatal mortality.[8] There was variation in HbA1c thresholds for optimal control used across the studies (range 6.3% to 8.0%) and none of the studies set specific target values for women to achieve. The threshold

values were established by various means, including derivation from regression results of scatter plot data and arbitrary selection or inference by study authors.

In general when all studies are considered, there was inconsistency in the association between perinatal outcomes and prepregnancy HbA1c above and below the single threshold considered in each study. Some studies reported a significantly increased risk above the threshold used, while others showed no relationship. One study showed a reduced risk of congenital malformations (RR 0.30, 95% CI 0.12 to 0.74) and perinatal mortality (RR 0.28, 95% CI 0.11 to 0.68) in women with HbA1c levels of 64 mmol/mol or less compared with HbA1c >64 mmol/mol.

A further study showed no effect of HbA1c levels <52 mmol/mol on risk of congenital malformations (RR 0.74, 95% CI 0.38 to 1.44) or perinatal mortality (RR 0.55, 95% CI 0.23 to 1.23) compared with HbA1c of ≥52 mmol/mol. A retrospective cohort study found an increased risk of congenital malformations in women with HbA1c levels >45 mmol/mol compared with HbA1c of ≤45 mmol/mol (OR 5.22, 95% CI 3.15 to 8.32). 4

The NICE guideline development group noted that data from this study showed a threshold effect where the risk of congenital malformations increased in an approximately linear fashion above an HbA1c of 45 mmol/mol. Specifically, an 11 mmol/mol increase in HbA1c was associated with a 30% increase in risk. This indicates that even if women do not achieve an HbA1c below 45 mmol/mol they could still reduce their risk of having a baby with a congenital malformation. However, the NICE group felt that it was important to align the recommendations with those made in the NICE guideline on type 1 diabetes in adults[18] and therefore recommended 48 mmol/mol as the target threshold.

Based on a single study, the NICE guideline development group also noted associative data to suggest that the risk of stillbirth is particularly high for women with an HbA1c >86 mmol/mol and advised that such women should be strongly advised to avoid pregnancy.

Despite study variation, the balance of evidence is that lower HbA1c reduces the risk of pregnancy complications. The use of CGM makes these levels more attainable than in the past, however, tighter control of diabetes will increase the incidence of hypoglycaemia. The effect of this and the pressures of striving for tight glycaemic control on time and mental health should not be ignored. An individualised balance must be sought.

Although a target of <48 mmol/mol is desirable, there appears to be a linear relationship between HbA1c level and adverse perinatal outcomes suggesting that any reduction in prepregnancy HbA1c while avoiding excessive hypoglycaemia is likely to be beneficial.

R **Women with type 1 or type 2 diabetes planning a pregnancy should aim for an HbA1c as low as possible without excessive hypoglycaemia.**

✓ Advise women that an HbA1c target of <48 mmol/mol can minimise risk of perinatal mortality and morbidity, but should not be used a strict threshold for access to assisted conception services. An individualised approach should be used.

✓ Other risk factors such as BMI, smoking, hypertension and level of diabetic retinopathy control should be taken in to account when individualised HbA1c targets are being considered.

✓ Pregnancy should be avoided if HbA1c >86 mmol/mol.

Evidence from population-based studies indicates that only 34–38% of eligible women receive prepregnancy counselling.[19] As such, optimising baseline care for women of reproductive age with T2DM becomes more important, so that even without specific pregnancy planning they have a lower HbA1c.

✓ Referral of women with type 2 diabetes who are planning a pregnancy to secondary care for optimisation of their diabetes should be considered, including the possibility of the use of intermittently-scanned (flash) glucose monitoring. If not already being used, this is an opportunity to further consider medication to lower cardiovascular risk.

4 Antenatal care

4.1 Monitoring glycaemic control during pregnancy

4.1.1 Continuous glucose monitoring

Continuous glucose monitoring (CGM) provides people with diabetes with real time information on glucose levels. A sensor is worn on the skin, and measures glucose levels in the interstitial fluid. Information on glucose concentration is recorded every few minutes and is transmitted to a reader, smartphone or other device, such as a smart watch. This continuous glucose data can provide information on glucose trends throughout the day and during the overnight period. Changes in interstitial glucose and therefore sensor glucose will lag 5–10 minutes behind changes in blood glucose.

There are two main types of CGM. Intermittently-scanned CGM (isCGM, or flash CGM) requires the user wearer to actively scan the sensor (which can be worn for up to 14 days without the need for user calibration) in order to display glucose information. Real-time CGM (rtCGM) automatically measures glucose levels and displays the most recent value. Real time CGM systems have the ability to predict high and low glucose levels, and alarms can be set to alert the wearer.

In August 2023 the manufacturer of the most commonly-used isCGM system in Scotland (Freestyle Libre 2) announced a software update to the FreeStyle LibreLink app which can allow people to use the system as rtCGM under certain conditions. While this is likely to make use of CGM more consistent in Scotland, the terminology of isCGM and rtCGM are retained in this section in order to describe the evidence base and way sensors were used in these studies.

Both types of CGM display information on glucose trends in an internationally-agreed standardised format, to allow for data analysis, known as ambulatory glucose profile (AGP). Internationally-agreed target glycaemic ranges of 3.9–10.0 mmol/L have been developed for people with T1DM and T2DM. In pregnancy, the glucose target range has been adjusted to 3.5–7.8 mmol/L and it is recommended that women aim to have >70% of glucose values within this range.[20] | 4

Based on evidence that optimal glucose control before pregnancy reduces congenital malformations and miscarriage, while during pregnancy it reduces macrosomia, stillbirth, neonatal hypoglycaemia, and respiratory distress syndrome, in 2017 SIGN recommended that CGM may be considered in women with T1DM or T2DM.[21] | 4

In 2020 the Scottish Health Technology Group (SHTG) recommended that CGM should be offered to all pregnant women with T1DM in Scotland. The use of CGM during pregnancy may improve maternal glycaemic control compared with self monitoring of blood glucose (SMBG). CGM reduces neonatal hypoglycaemia and the need for and duration of neonatal intensive care. These improved clinical outcomes were reported in women who used CGM from the first trimester of pregnancy.[22] | 4

Meta-analyses and RCTs consistently demonstrate that use of CGM in women with GDM or T2DM in pregnancy leads to an improvement in glycaemic control.

One meta-analysis included ten studies of women with GDM (n=555 with 609 controls).[23] Four studies compared CGM with SMBG or blinded CGM. The type of CGM (isCGM or rtCGM) was not further described. The use of CGM was associated with significantly lower mean HbA1c in all four studies. There were no clear trends regarding preterm births, rates of Caesarean and vaginal birth or admission to higher levels of neonatal care. | 1++

A further meta-analysis included six RCTs of women with GDM (n=482).[24] The use of rtCGM was associated with lower HbA1c levels at the end of pregnancy (mean difference -0.22, 95% CI -0.42 to -0.03) compared with SMBG (units not reported but HbA1c percentage implied, this is equivalent to approximately -2.4 mmol/mol). Women using rtCGM had less gestational weight gain (mean difference -1.17, 95% CI -2.15 to -0.19), and their children had lower birth weight (mean difference -116.26, 95% CI -224.70 to -7.81) (units not reported, but interpreted | 1++

to be kilograms and grams, respectively). No differences were observed in the other outcomes evaluated.	
Despite being labelled as a prospective cohort study, a Chinese study allocated 340 pregnant women with GDM to intervention (retrospective CGM where real-time glucose levels were collected but not displayed to the participant) or routine care (SMBG) groups using a quasi-random method.[25] The allocation method did not result in complete equivalency between groups at baseline – significantly more women allocated to the CGM group received insulin compared with the SMBG group. Glucose measurements were stored in the monitor and downloaded and interpreted later to guide therapy adjustment. Use of CGM resulted in lower glycaemic variability compared with SMBG (p<0.001). Women using CGM were at lower risk of pre-eclampsia and primary Caesarean birth compared with the routine care group (p<0.05). The mean infant birth weight of women in the CGM group was lower than infants of women in the routine care group (p<0.001).	1-
A large RCT demonstrated that use of rtCGM allowed pregnant women with T1DM to achieve lower HbA1c levels, higher amounts of time in target and reduced numbers of hyperglycaemic episodes without increasing the number of episodes of hypoglycaemia.[26]	1++
A Chinese RCT randomised 124 pregnant women with T2DM at 12–14 weeks of gestation to isCGM or SMBG.[27] Glycated albumin was lower in the CGM group compared with the control group at two-week follow up (14.6 ± 2.2 v 16.8 ± 2.7, p<0.001). The women in the CGM group spent more time in the recommended glucose control target range (69 ± 10% v 62 ± 11%, p<0.001) and reduced time above target compared with those in the control group at two weeks (25 ± 7% v 31 ± 8%, p<0.001). In the second week of the study, urinary ketones in the flash monitoring group were lower than in the control group (ketonuria positive: 42 ± 5% v 54 ± 5%, p<0.001).	1-
Two meta-analyses combined studies which included women diagnosed with T1DM, T2DM or GDM. These reviews have incorporated many of the same RCTs which also overlap with some considered above.	
The first systematic review and meta-analysis included 10 RCTs (n=1,358) describing perinatal use of retrospective or rtCGM in women with diabetes. CGM significantly improved HbA1c levels (g= -0.43, 95% CI -0.63 to -0.22), lowered Caesarean section birth rate (g= -0.17, 95% CI -0.33 to -0.02) and neonatal birth weight (g= -0.16, 95% CI -0.27 to -0.04) compared with the comparator. Most studies had a low risk of bias and certainty of evidence ranged from very low to moderate.[28]	1++
A Cochrane review compared techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes across 12 RCTs (n=944).[29] The authors reported that retrospective or rtCGM may reduce hypertensive disorders of pregnancy (pre-eclampsia and pregnancy-induced hypertension) (RR 0.58, 95% CI 0.39 to 0.85; 2 studies, 384 women; low-quality evidence), although only two of the four relevant studies reported data for this composite outcome. This evidence did not translate into a clear reduction for the single outcome of pre-eclampsia (RR 0.65, 95% CI 0.39 to 1.08; 4 studies, 609 women; moderate-quality evidence). There was also no clear reduction in Caesarean birth rate (average RR 0.94, 95% CI 0.75 to 1.18; 3 studies, 427 women; moderate-quality evidence) or large-for-gestational age (average RR 0.84, 95% CI 0.57 to 1.26; 3 studies, 421 women; low-quality evidence) with CGM.	1++
A prospective single-cohort study examined the use of the most commonly currently used isCGM in 74 women with GDM, T1DM or T2DM.[30] Overall participants reported good accuracy compared with capillary blood glucose monitoring, with high levels of satisfaction with sensor wear. There were no device-related adverse events.	3
There have been several real-world studies in non-pregnant populations with T1DM that have shown that the use of isCGM leads to a significant reduction in diabetes-related distress, as well as leading to improvements in diabetes control.[31,32] Local reactions (3%) and localised bleeding (1%) were rarely reported.	
In Scotland, CGM is available for all people with T1DM, and for all women with insulin-treated T2DM in pregnancy.	

R **Consider CGM in pregnant women with type 2 diabetes.**

✓ Consider CGM in pregnant women with GDM, particularly in those using insulin.

4.1.2 Glycated haemoglobin (Haemoglobin A1c)

Evidence relating to HbA1c in early pregnancy and its importance to prepregnancy counselling is included in section 3.1.2. This will not be reiterated but is of relevance to recommendations in this section on measurement and interpretation of HbA1c in early pregnancy. Studies considered in this section have investigated the effectiveness of HbA1c monitoring in predicting adverse outcomes in women with T1DM, T2DM or GDM during pregnancy.

A retrospective cohort study investigated the association of change in HbA1c between early and late pregnancy with adverse perinatal outcomes in 347 women with pregestational T1DM or T2DM.[33] Each 6 mmol/mol absolute decrease in HbA1c was associated with a 12% reduced risk of LGA infant (adjusted relative risk/risk ratio (aRR) 0.88; 95% CI 0.81 to 0.95), and a 7% reduced risk of neonatal hypoglycaemia (aRR 0.93; 95% CI 0.87 to 0.99). Net decline in HbA1c throughout pregnancy was also associated with small reductions in preterm birth (aRR 0.93; 95% CI 0.89 to 0.98) and neonatal intensive care unit admission (aRR 0.95; 95% CI 0.91 to 0.98), but not Caesarean birth, pre-eclampsia, shoulder dystocia or respiratory distress syndrome.

A small prospective cohort study involving 27 pregnant women with T1DM reported that each 10% increase in TIR was associated with an approximate 3.3 mmol/mol reduction in HbA1c.[34] This correlation was stronger in the 2nd and 3rd trimesters than in the 1st trimester whereas correlation between TIR and glycaemic variability as measured by the Glucose Management Indicator (GMI) was equally strong in each trimester. The authors note that reasons for TIR and GMI providing a more accurate measure of glycaemic control than HbA1c in the 1st trimester may include rapid changes in blood glucose levels associated with intensive insulin treatment, natural physiological changes in early pregnancy and possible unrecognised iron deficiency. 2+

A retrospective cohort study conducted in Poland reported that lack of pregnancy planning and a high HbA1c level in the 1st trimester were independent predictors of both LGA (OR 4.99, 95% CI 1.12 to 21.0, p=0.033 and OR 3.02, 95% CI 1.19 to 7.65, p=0.019, respectively) and macrosomia (OR 8.43, 95% CI 1.36 to 51.93, p=0.021 and OR 5.47, 95% CI 1.77 to 16.87, p=0.003, respectively).[35]

The authors note that while guidelines may recommend measurement of HbA1c in early pregnancy with a single threshold of 42–48 mmol/mol to help estimate risk of congenital anomalies, recording change in HbA1c across pregnancy may also help stratify both the individual response to tightening of glycaemic control and risk of adverse perinatal outcomes at delivery.

A large population-based cohort study included 17,375 pregnancies in 15,290 women with diabetes recorded across 172 maternity clinics in England, Wales and the Isle of Man. The study reported associations between modifiable and non-modifiable risk factors and pregnancy outcomes. First trimester HbA1c ≥48mmol/mol remained significantly associated with congenital anomaly in women with T1DM (OR 1.79, 95% CI 1.2 to 2.7) and T2DM (OR 1.64, 95% CI 1.23 to 2.21).[9] 2+

No studies related to the optimum frequency and timing of HbA1c monitoring in pregnancy were identified.

Two studies were identified which explored the effectiveness of HbA1c monitoring in women with GDM or at risk of GDM.

A prospective cohort study conducted in the USA with 102 women with risk factors for GDM reported that HbA1c fell between the first and second trimester and identified only minimal discrepancy between mean glucose as estimated by HbA1c and mean oral glucose tolerance test (OGTT) between 10–15 weeks' gestation and in the postpartum phase.[36] In contrast,

during the late second trimester, HbA1c significantly underestimated mean OGTT glucose, particularly in women whose haemoglobin level fell over this time. This may be particularly important as it reflects the time of usual GDM screening. It was suggested that accounting for maternal haemoglobin levels and gestational age may help with clinical interpretation of HbA1c levels during pregnancy.

A large retrospective cohort study which included 2,275 Asian Indian women indicated that HbA1c in early pregnancy was an independent predictor of GDM but did not have sufficient sensitivity or specificity to be used as a diagnostic test. Prevalence and odds of developing GDM increased with increasing HbA1c stratified between three categories.[37]

R **For women with pre-existing diabetes** (type 1 and type 2) **HbA1c at booking should be measured as this will help to predict risk of congenital anomalies, LGA and macrosomia.**

R **Monitoring change in HbA1c between first and third trimester should be considered in those with pre-existing diabetes.**

R **Measurement of HbA1c in women with risk factors for GDM may be used to exclude pre-existing type 2 diabetes and predicts women at highest risk of GDM later in pregnancy but is not a diagnostic test for GDM.**

✓ Use continuous glucose monitoring metrics, such as TIR or GMI to assess glycaemic control during pregnancy.

4.2 Glycaemic targets during pregnancy

4.2.1 Blood glucose

SIGN 116 included a good practice point with the following glucose targets for people with T1DM or T2DM, ensuring that hypoglycaemia could be minimised:[3]

- between 4 and 6 mmol/L preprandially, and
- <8 mmol/L one hour postprandially, or
- <7 mmol/L two hours postprandially,
- >6 mmol/L before bed.

NICE guideline NG3 on diabetes in pregnancy: management from preconception to the postnatal period reviewed evidence on target ranges for blood glucose in women with T1DM, T2DM or GDM during pregnancy published up to 2014. This guideline identified six relevant studies (five studies in women with pre-existing diabetes and one in women with GDM).[8] The quality of evidence was very low for all studies.

For pregnancies in women with pre-existing diabetes, the NICE guideline noted that two studies reported reductions in LGA or macrosomia in women assigned to the tight glycaemic control groups (Landon 1987, Combs 1992) while one study showed no differences in infant size between groups (Farrag 1987).

The single study of women who largely measured the one-hour postprandial glucose values, reported a lower incidence of LGA with a target threshold of 7.8 mmol/L (Combs 1992).

4

None of the six studies showed any effect of achievement of tighter or less tight glycaemic targets on Caesarean section birth rates.

One study (Demarini 1994) showed no difference in neonatal hypoglycaemia rates in the group with tighter control compared with the standard control group. In this study no significant difference in glycaemic control between the groups was achieved.

NICE reported a secondary analysis of an RCT in which 733 women with GDM were randomised to either metformin or insulin and asked to aim for overnight fasting glucose target of <5.5 mmol/L and two-hour postprandial target of <7.0 mmol/L (Rowan 2010). A reduction in risk of LGA infants and maternal pre-eclampsia was reported both in women

who achieved fasting glucose levels ≤5.3 mmol/L compared with those achieving glucose levels >5.3 mmol/L and in those who achieved two-hour postprandial glucose levels <6.4 mmol/L compared with those achieving higher levels.

On the basis of this evidence NICE recommended that individualised targets should be agreed for self monitoring of blood glucose with women with diabetes in pregnancy, taking into account the risk of hypoglycaemia. Furthermore, NICE recommended that pregnant women with any form of diabetes should be advised to maintain their capillary plasma glucose below the following target levels, if these are achievable without causing problematic hypoglycaemia:

- fasting: 5.3 mmol/L
- one hour after meals: 7.8 mmol/L or
- two hours after meals: 6.4 mmol/L.

The current guideline has identified a further four relevant studies published since the NICE guideline of which one is a systematic review which includes only women with pre-existing diabetes and also includes the primary studies included in the NICE guideline.[38] Two studies include only women with GDM, while a further study focuses on the continuum of risk of glucose levels in women either meeting or just below the diagnostic threshold for GDM. Within this evidence base, target populations, definitions of tight and less tight control and the timing of measuring postprandial glucose levels across populations all vary. There are inconsistencies in treatment effects, with some studies showing that assigning a patient to a tight or less tight treatment strategy may have no impact on differences in glycaemia[38] while other studies show inconsistent effects on infant weight for gestational age. The majority of evidence reviewed does not include UK data. Most studies were carried out in USA, New Zealand and Australia and healthcare systems and patient demographics and ethnicity in these areas may not be fully representative of the UK.

A large stepped wedge, cluster randomised trial conducted in New Zealand showed no reduction in LGA in women with GDM (diagnosed with fasting glucose ≥5.5 mmol/L or two-hour glucose ≥9.0 mmol/L) assigned to tight glycaemic control of fasting level ≤5.0 mmol/L, one-hour level ≤7.4 mmol/L and two-hour level ≤6.7 mmol/L compared with women assigned to less tight glycaemic targets of fasting level <5.5 mmol/L, one-hour level <8.0 mmol/L and two-hour level <7.0 mmol/L (14.7% v 15.1%, aRR 0.96, 95% CI 0.66 to 1.40).[39] However, the composite secondary outcome measures of serious health outcome for the infant (perinatal death, birth trauma, or shoulder dystocia) was significantly reduced (1.3% v 2.6%, aRR 0.23, 95% CI 0.06 to 0.88). There was an unexpected significant increase in adverse maternal health outcomes such as major haemorrhage, coagulopathy, embolism, and obstetric complications in women assigned to the tighter glycaemic control group (5.9% v 3.0%, aRR 2.29, 95% CI 1.14 to 4.59). 1++

Similar targets were used in a regression discontinuity study which estimated treatment effects by comparing outcomes between a treated group of women diagnosed with GDM using International Association of the Diabetes and Pregnancy Study Group (IADPSG) criteria (see section 5) to an untreated (counterfactual) group just below the diagnostic threshold.[40] Women with GDM delivered earlier and had 57% higher rates of induced deliveries compared with the untreated group below the diagnostic threshold. Treated women with GDM had lower rates of LGA (4.6% v 12.6%, RR 0.37, 95% CI 0.16 to 0.85) while neonates of women treated for GDM had lower mean birth weight and lower neonatal mean BMI. Women with GDM and BMI ≥30 had reduced absolute Caesarean section birth rates (32.9% v 55.9%, RR 0.59, 95% CI 0.4 to 0.87); and primary Caesarean section birth rates (26.4% v 45.8%, RR 0.58, 95% CI 0.35 to 0.94) compared with untreated women in the counterfactual group with BMI ≥30.

A small RCT carried out in the USA randomised 60 overweight or obese women with GDM diagnosed between 12 and 32 weeks' gestation to either intensive (fasting <5 mmol/L, one-hour postprandial <6.7 mmol/L) or standard (fasting <5.3 mmol/L, one-hour postprandial <7.8 mmol/L) glycaemic targets. Mean birthweight (3431 ± 623 *v* 3351 ± 518 g; p=0.59) and percentage of body fat (12.10 ± 4.81 *v* 11.48 ± 5.47; p=0.67) were similar between women treated with intensive compared with standard glycaemic targets. There were no differences 1+

in rates of SGA and LGA birthweight.[41]

Associations between tighter glycaemic control achieved and reduced risk of LGA / macrosomic babies were seen in some[40] but not all studies.[41] Similar inconsistency was seen in studies cited in the NICE guideline.[8] This may impact on future health and reduce emergency Caesarean birth rates[40] although some studies show no difference in Caesarean birth rates.[38] Better glycaemic control may reduce neonatal hypoglycaemia and serious neonatal health outcomes.[8, 39]

Some studies have suggested that tighter glycaemic control may result in an increase in obstetric complications.[39,40] Maternal hypoglycaemia may be increased.[8,40] Achieving improved glycaemic control is associated with more intensive use of glucose-lowering medications. One study reported that up to 61% of the GDM population who were assigned to tight glycaemic control required insulin to achieve the targets.[40] Achieving tight targets may require more intensive follow up from healthcare professionals with weekly interventions.[42]

R **In pregnant women with pre-existing diabetes, tight glycaemic control should be encouraged as this may improve LGA, and reduce the need for emergency Caesarean sections but levels should be individualised and balanced with risk of hypoglycaemia. The main assessment of glycaemia in these women is by CGM.**

R **In pregnant women with GDM tight glycaemic control should be encouraged to help reduce Caesarean birth rates, LGA, neonatal hypoglycaemia and pre-eclampsia. This may result in the increased use of medication and requires more intensive follow up.**

Summary and conclusions

The guideline development group noted that the strongest evidence on the relative effects of different glucose targets was available from the stepped wedge cluster randomised trial of women with GDM which showed women who achieved fasting glucose targets of <5.5 mmol/L, one hour postprandial targets of <8 mmol/L and two hour postprandial targets of <7 mmol/L experienced similar rates of LGA infants (primary outcome) to those achieving tighter glucose targets.[39] The group noted that subgroup analyses suggested fewer harms for infants however greater obstetric harms (secondary outcomes) for women who achieved lower targets. A further RCT supported these primary outcome results[41] while an observational study which analysed clinical outcomes in women around the IADPSG diagnostic criteria for GDM to estimate treatment effects suggested treatment of women to tighter glucose targets may reduce LGA infants.[40]

The guideline development group acknowledged that while there is inconsistency in the evidence, the strength and volume of the evidence base was stronger than the older, observational studies used to support the target recommendation in the NICE guideline, while the absolute values of the less tight targets in the stepped wedge cluster randomised trial are broadly comparable with this.[8] The group also noted that while most studies only include women with GDM, a Cochrane review published in 2016 which investigated different intensities of glycaemic control for pregnant women with pre-existing diabetes included three trials of women with T1DM. The authors note that the evidence was very limited and quality of evidence was rated as low or very low, but reported few differences in outcomes between very tight and tight-moderate glycaemic control targets in pregnant women with pre-existing T1DM, including actual glycaemic control achieved. They report evidence of harm (increased pre-eclampsia, Caesarean section births and birthweights greater than 90th centile) for women achieving 'loose' control (fasting blood glucose above 7 mmol/L).[38] For women with T1DM and many women with T2DM use of CGM renders these older assessment methods outdated.

Based on the balance of evidence and clinical experience, the guideline development group concludes that recommending a single treatment target for all women with diabetes in pregnancy based on the strongest available current evidence will help to promote concordance in optimisation of glycaemic control. Treatment should be offered to all women to support achievement of these targets.

R **The following glucose targets are recommended for women with type 1, type 2 and gestational diabetes:**

- **fasting glucose level <5.5 mmol/L**
- **one-hour postprandial glucose level <8 mmol/L, and**
- **two-hour postprandial glucose level <7 mmol/L.**

✓ Self monitoring glucose targets pertain most clearly to women with GDM but may be helpful in considering diurnal patterns in CGM in women with pre-existing diabetes.

Emerging evidence from the use of newer technologies such as CGM and hybrid closed loop insulin pumps may adjust how glycaemic control is monitored.

Women with diabetes in pregnancy should aim to spend at least 70% time in range (3.5–7.8 mmol/L) (see section 4.1.1).

4.2.2 Glycated haemoglobin (Haemoglobin A1c) and later pregnancy risk prediction

In the non-pregnant population HbA1c is widely used to provide an estimation of a person's glycaemic control over a two to three month period but this measurement can be less robust in situations where there is reduced red cell survival and this may result in falsely lowered results. It is well recognised that red cell turnover is increased and iron deficiency is common during pregnancy and so the role of HbA1c monitoring may be less helpful in this setting.

A number of studies were identified which investigated the association between HbA1c targets and adverse perinatal outcomes. With the exception of one RCT, most were prospective or retrospective cohort studies of poor to moderate quality. No studies allocated participants to different targets and compared outcomes.

The Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT) recruited women 18–40 years old, who were receiving intensive insulin therapy for T1DM. The women could use either continuous subcutaneous insulin infusion or multiple daily injections and were randomised to receive either CGM in addition to intermittent capillary glucose monitoring or intermittent glucose monitoring alone. Separate analyses were carried out for women planning pregnancy and those already pregnant.[26]

For pregnant women the trial reported a small but statistically significant reduction in HbA1c favouring CGM over intermittent glucose monitoring (−0.19%, 95% CI −0.34 to −0.03, p=0.02; equivalent to approximately -2.0 mmol/mol). Women planning a pregnancy demonstrated a similar between-group difference in change in HbA1c, but because of the smaller sample size (compared with the pregnancy group) and consequent lack of power, the confidence intervals were wider and included the null value (−0.17%, 95% CI −0.43 to 0.09, p=0.20).

In a follow up subanalysis, the authors investigated the extent to which trial participants achieved HbA1c and CGM targets during each trimester of pregnancy and compared these data to pregnancy outcomes.[43] HbA1c targets were <48 mmol/mol and <42 mmol/mol during the second and third trimesters as recommended by NICE and the American Diabetes Association (ADA) respectively. CGM targets included Time in Range (TIR) >70%, Time Above Range (TAR) <25% and Time Below Range (TBR) <4%. 1++

CGM target attainment during each trimester (first/second/third) was TIR: 7.7/10.2/35.5%, TAR: 14.5/14.2/37.2% and TBR: 30.3/52.8/52.9%. The proportion of women achieving the stricter ADA HbA1c target was low and did not increase significantly during pregnancy (23.5/27.9/23.8%). HbA1c target attainment was associated with a lower risk of preterm birth, large-for-gestational age and neonatal hypoglycaemia. The study reported some associations between achievement of CGM and HbA1c targets and clinical outcomes. Achieving the TIR target in the third trimester was associated with a lower risk of preterm birth, achieving the TAR target in the second trimester was associated with a lower risk of an LGA infant and achieving the TAR target in the third trimester was associated with lower risks of both preterm birth and LGA. For HbA1c targets, women who achieved the NICE target of <48 mmol/mol in the first trimester had a lower risk of LGA, while those who achieved the stricter ADA target of <42 mmol/mol had a lower risk of preterm birth, LGA, neonatal hypoglycaemia and NICU admission in the second trimester and a lower risk of preterm birth,

LGA and neonatal hypoglycaemia in the third trimester.

The authors also noted that all targets (HbA1c and CGM) were more likely to be achieved by women using rtCGM than using capillary blood glucose monitoring at 34 weeks' gestation.

In a large population-based cohort study conducted in England, Wales and the Isle of Man women with T2DM had higher rates of perinatal death than women with T1DM across all third trimester HbA1c categories below 86 mmol/mol (see Table 1).[9] When examined according to type of diabetes, third trimester HbA1c ≥48 mmol/mol was significantly associated with perinatal death in both T1DM (OR 2.47, 95% CI 1.49 to 4.08) and T2DM (OR 3.93, 95% CI 2.51 to 6.16). 2+

Table 1: Third trimester perinatal death rates stratified by HbA1c and type of diabetes

HbA1c (mmol/mol)	**Third trimester perinatal death rate** (%)	
	Type 1 diabetes	Type 2 diabetes
<43	0.6	0.9
44–52	1.2	2.7
53–63	1.7	4.0
64–74	1.7	4.9
75–85	8.3	10.0

A population-based cohort study in Canada collected preconception, early and mid-pregnancy HbA1c results from women with prepregnancy diabetes.[44] Across the cohort, HbA1c decreased from 55.2 mmol/mol preconception to 46.4 mmol/mol in early/mid pregnancy. 497 of 3,459 pregnancies were associated with a congenital anomaly (14.4%). Reduction in HbA1c was associated with lower risk of congenital anomaly (RR 0.94, 95% CI 0.89 to 0.98), lower risk of preterm birth (RR 0.89, 95% CI 0.86 to 0.91) and lower risk of severe maternal morbidity or death (RR 0.90, 95% CI 0.84 to 0.96) per 6 mmol/mol net decrease in HbA1c.

A US retrospective cohort study of 347 women with pre-existing diabetes investigated the association between net change in HbA1c during pregnancy and adverse perinatal outcomes.[33] HbA1c was recorded at median of 9 weeks' gestation (early pregnancy) and median of 31 weeks' gestation (late pregnancy). Mean HbA1c decreased from early (59 mmol/mol) to late (47 mmol/mol) pregnancy. Each 6 mmol/mol absolute decrease in HbA1c was associated with a 12% reduced risk of LGA infant (RR 0.88, 95% CI 0.81 to 0.95), a 7% reduced risk of neonatal hypoglycaemia (RR 0.93, 95% CI 0.87 to 0.99), a 7% reduced risk of preterm birth (RR 0.93, 95% CI 0.89 to 0.98) and a 5% reduced risk of neonatal intensive care unit admission (RR 0.95, 95% CI 0.91 to 0.98) There was no association between decreased HbA1c and Caesarean delivery, pre-eclampsia, shoulder dystocia and respiratory distress syndrome.

A French retrospective cohort study included 678 births in women with T1DM and investigated the association between HbA1c and adverse perinatal outcomes.[45] While mean prepregnancy HbA1c was 55 mmol/mol, mean levels fell to 50 mmol/mol in the first trimester, 45 mmol/mol in the second trimester and rose to 46 mmol/mol in the third trimester. A composite outcome which consisted of preterm delivery, pre-eclampsia, LGA, SGA, and Caesarean section was defined as reached if at least one component was present.

Higher HbA1c during the first trimester was associated with the composite outcome (OR 1.04, 95% CI 1.02 to 1.06 per 1.1 mmol/mol increase). Higher HbA1c during the third trimester was also associated with the composite outcome (OR 1.07, 95% CI 1.03 to 1.10 per 1.1 mmol/mol increase). The authors note that early HbA1c also independently predicted several adverse

outcomes including LGA, SGA, pre-eclampsia, and preterm delivery.

These results suggest that when all complications are combined, the composite outcome was associated with HbA1c in the first trimester and the third trimester, with a greater risk of onset when the HbA1c level was high. The authors confirm that the tighter the glycaemic control achieved, the lower the risk of maternal-fetal complications.

A national registry-linked retrospective cohort study in Sweden investigated the association between periconceptual HbA1c values in women with T1DM and risk for preterm birth and further secondary outcomes.[46] The overall rate of preterm delivery among 2,474 births of 2,038 mothers with T1DM was 22.3%. The incidence of preterm birth was 13.2% for women with a periconceptual HbA1c level below 47.5 mmol/mol, 20.6% for those with a level of 47.5 to 61.7 mmol/mol, 28.3% for those with a level of 61.7 to 76 mmol/mol, and 37.5% for those with a level of ≥76 mmol/mol. The association between progressively higher HbA1c levels and risk for preterm birth was independent of the timing of the periconceptual HbA1c measurement.

Risks for the secondary outcomes of LGA infants, macrosomia, hypoglycaemia, respiratory distress, and low Apgar score all increased with rising HbA1c levels. The excess risk for stillbirth and neonatal death was substantially and statistically significantly increased, but in only the upper HbA1c categories (≥61.7 mmol/mol).

A national records-linked observational study carried out in Scotland investigated the association between stillbirth and maternal and fetal characteristics in mothers with diabetes.[16] Mean pre-pregnancy HbA1c was 11 mmol/mol higher in pregnancies of women with T1DM ending in stillbirth (p=0.0002) and 12 mmol/mol higher in the pregnancies of women with T2DM ending in stillbirth (p=0.01). In mothers with T1DM, higher birthweight was related to higher HbA1c.

The authors note that "women with T1DM who suffer a stillbirth have higher mean HbA1c levels at all stages of pregnancy, although blood glucose level improves in both groups over the course of pregnancy… Pre-pregnancy HbA1c appears a more important predictor in T2DM, and unexpectedly there was no independent association in later pregnancy."

The National Pregnancy in Diabetes audit (see section 3.1.1) reported congenital anomalies and perinatal death are lowest in women who achieved early pregnancy HbA1c targets ≤48 mmol/mol but noted that this is achieved only in a minority of women with diabetes.[11]

After 24 weeks' gestation, perinatal deaths, preterm births, LGA, birthweight and neonatal care admissions are all lower in women with HbA1c <43 mmol/mol suggesting that achieving lower HbA1c targets is associated with optimal neonatal outcomes.

In women with T1DM LGA infants were reported in up to 50% of pregnancies where HbA1c levels of 43–48 mmol/mol were achieved, but were close to 30% in those achieving HbA1c levels <43 mmol/mol. Women with T2DM achieving an HbA1c level <43 mmol/mol had rates of LGA infants approximating the background maternity population.

The NICE guideline identified four studies on target values for HbA1c during pregnancy but noted that these all had significant limitations and variable findings.[8] NICE also acknowledged that obtaining an HbA1c level incurs an opportunity cost, both in terms of laboratory analysis and staff time. There is uncertainty about what would be a normal range of HbA1c in pregnancy and how it may vary across different trimesters and the group were unable to develop any recommendations.

4

The SIGN guideline development group noted that due to increased red blood cell turnover and the higher risk of iron deficiency, HbA1c is less useful for monitoring glycaemic control than in women who are not pregnant. Also, as it does not reflect the variances in blood glucose equally throughout pregnancy, the group felt that setting a universal target which all women should achieve may be unhelpful.

The group expressed concern about setting low or near normal targets for women with diabetes in pregnancy which are difficult to achieve as this may increase risks associated with failing to achieve these targets, such as losing confidence in their ability to self manage their diabetes. It also may increase perceptions that pregnancy can seem overmedicalised.

This could potentially result in less engagement, increased stigma or guilt and worse control, which may result in poorer outcomes.

The group noted that, while not providing evidence for a single universal target, a number of studies have reported significantly poorer outcomes, including perinatal death, in women with third trimester HbA1c ≥48 mmol/mol.

The group reflected that optimal clinical practice in Scotland involves individualised, person-centred care and shared decision making to discuss, set and review blood glucose and HbA1c targets, with support from diabetes and obstetric teams.

R **For women with type 1 or type 2 diabetes, individualised pre-pregnancy HbA1c targets should be maintained during pregnancy while avoiding excessive hypoglycaemia.**

There is insufficient evidence to support an HbA1c target in women with GDM.

✓ HbA1c levels ≥48 mmol/mol during the third trimester should be considered a marker of clinical risk.

4.3 Ketone monitoring

No appropriate evidence was identified to determine the effectiveness of blood ketone monitoring compared with urine ketone monitoring for women with type 1, type 2 or gestational diabetes during pregnancy.

✓ Advise pregnant women with T1DM to check blood ketones if blood glucose level is ≥10 mmol/L or during illness.

✓ Ensure that Board protocols for ketone monitoring and management of diabetic ketoacidosis are followed.

4.4 Timing of birth

NICE guideline NG3 identified six studies which provided evidence on the gestational age-specific risk of intrauterine death in pregnancies with T1DM, T2DM or GDM, and the optimal timing of birth.[8] The quality of evidence was rated as low or very low. Four studies involved women with GDM, one study involved women with T1DM and one study included women with T1DM or T2DM. Only one study included data from the UK. A literature search carried out for the current guideline identified one further systematic review published since the NICE guideline.[47]

The NICE guideline reported data from a large UK analysis of retrospective audit data from pregnancies involving women with pre-existing diabetes in England which included data on over 3.5 million pregnancies. This study showed that rates of stillbirth per 1,000 live births were similar in women with and without diabetes until 39 weeks' gestation and later, when rates were significantly higher in women with T1DM or T2DM compared with Office for National Statistics data for all women in England and Wales (RR 7.2, 95% CI 1.31 to 39.63). The lowest rate of stillbirth was during 37 to 38^{+6} weeks' gestation in women with T1DM or T2DM.

The NICE guideline also reported data from a large retrospective cohort study from Norway (n=1,162,399) which used record linkage to examine perinatal mortality rates in babies of women with pregestational T1DM compared with those without T1DM. There was a U-shaped trend in perinatal mortality reported in both women who did and did not have T1DM with the highest risk reported at 32–34 weeks' gestation and falling thereafter. In women with T1DM but not in those without diabetes, perinatal mortality risk rose at week 39 and again in weeks 41-45 of gestation leading to a significantly increased relative risk of mortality at weeks 39 (RR 4.25, 95% CI 1.38 to 13.11) and weeks 41–45 (RR 12.42, 95% CI 4.06 to 37.93). 4

Based on these studies and RCT data suggesting that delivery at or around 38 weeks reduced the numbers of babies with macrosomia, the NICE guideline recommended that

pregnant women with T1DM or T2DM and no other complications should be advised to have an elective birth by induction of labour, or by elective Caesarean section if indicated, between 37^{+0} weeks and 38^{+6} weeks of pregnancy.

For women with GDM, the NICE guideline reported data from a large retrospective cohort study conducted in the USA (n=4,190,953 deliveries) which reported a trend of falling stillbirth rates from 36 to 40 weeks of gestation and higher rates thereafter in all women, irrespective of GDM status. The incidence of stillbirth was higher in babies of women with GDM compared with those without throughout weeks 36 to 41, but only rose to statistical significance during weeks 37 (RR 1.13, 95% CI 1.06 to 1.70) and 39 (RR 1.30, 95% CI 1.01 to 1.66). In week 42, the incidence of stillbirth was higher in women without gestational diabetes compared with those with gestational diabetes. Approximately one third of women included in this study were from Latina ethnicity which may limit the generalisability of findings to the Scottish context.

The guideline noted that the absolute stillbirth rate in the women with GDM was lowest at 40 weeks before rising again thereafter. There were U-shaped trends for the incidence of neonatal and infant death in the babies of women with and without GDM, which were highest for babies delivered at 36 weeks and which fell to the lowest rates at 39–40 weeks before rising again at 41 weeks. Based on these findings, NICE recommended that in women with GDM without any maternal or fetal complications, delivery could be delayed until 40 weeks.

One Cochrane systematic review on optimal mode of delivery was identified which was published after the NICE guideline.[47] This review included a single RCT involving 425 women with GDM. The authors note that there were no clear differences between women randomised to induction of labour and women randomised to expectant management for maternal mortality or serious maternal morbidity (RR 1.48, 95% CI 0.25 to 8.76); Caesarean section (RR 1.06, 95% CI 0.64 to 1.77); or instrumental vaginal birth (RR 0.81, 95% CI 0.45 to 1.46). There were no maternal or perinatal deaths reported in either group and no differences were found for serious maternal morbidity, defined as admissions to intensive care unit. 1++

A retrospective cohort study which included deliveries to mothers with T1DM (n=3,778) or T2DM (n=1,614) between 1998 and 2016 in Scotland reported that a third of stillbirths were recorded in women delivering at term with highest rates in the 38th week (7.0, 95% CI 3.7 to 12.9 per 1,000 ongoing pregnancies) among mothers with T1DM and in the 39th week (9.3, 95% CI 2.4 to 29.2) for T2DM.[16]

National audit data in Scotland indicate that delivery in women with diabetes is generally expedited within 40 weeks' gestation.

The guideline development group endorses the following recommendations published in the NICE guideline on diabetes in pregnancy: management from preconception to the postnatal period.[8]

R **Discuss the timing and mode of birth with pregnant women with diabetes during antenatal appointments, especially during the third trimester.**

R **Advise pregnant women with type 1 or type 2 diabetes and no other complications to have an elective birth by induction of labour, or by elective Caesarean section if indicated, between 37^{+0} weeks and 38^{+6} weeks of pregnancy.**

R **Advise women with gestational diabetes to give birth no later than 40^{+6} weeks, and offer elective birth (by induction of labour, or by Caesarean section if indicated) to women who have not given birth by this time.**

R **Consider elective birth before 40^{+6} weeks for women with gestational diabetes if there are maternal or fetal complications.**

5 Gestational diabetes

Gestational diabetes mellitus (GDM) is diabetes with first onset or recognition during pregnancy. The optimal approach to testing for glucose intolerance in pregnancy, including GDM, has been controversial.[48] In 2010 SIGN recommended use of the diagnostic criteria for GDM of the consensus panel of the International Association of the Diabetes and Pregnancy Study Group (IADPSG)[49] which were later adopted by the World Health Organization (WHO) in 2013.[50] This approach involves use of 75 g oral glucose tolerance test (OGTT) in either all pregnant women or those with risk factors for development of diabetes in pregnancy (which were not specified by IADPSG) at 24–28 weeks' gestation. A diagnosis of GDM is indicated if one or more values of fasting, one-hour or two-hour plasma glucose are above specified thresholds.

In 2008 NICE recommended screening for GDM using risk factors assessed at the booking appointment. Women with any of the specified risk factors were recommended to be offered an OGTT at 24–28 weeks' gestation and diagnosed based on criteria established by WHO in 1999. In 2015 NICE published recommendations which included revised diagnostic criteria and risk factors (see Table 2).

The UK National Screening committee in 2021 did not endorse population screening for diabetes during pregnancy but did recommend adherence to NICE guidelines for women at high risk (https://view-health-screening-recommendations.service.gov.uk/gestational-diabetes/). In this guideline the advantages and disadvantages of NICE and WHO/IADPSG criteria are considered for the Scottish context and taking into account estimated prevalence and clinical and patient outcomes.

The evidence for testing for GDM in the first trimester is also considered. With increasing obesity and mean age at pregnancy, the rate of undiagnosed pre-existing diabetes at the onset of pregnancy is likely to be increasing and its detection is of clinical importance. The effects of identifying and treating milder forms of glucose intolerance where HbA1c results are above normal for the non-pregnant state but below diagnostic criteria for diabetes are uncertain and are considered in this section.

5.1 Risk factors

Uncertainty about the optimal methods for identifying women most likely to benefit from treatment of GDM has led to a range of different approaches being recommended worldwide. In addition to the question of the appropriate screening test and thresholds for diagnostic criteria, any such approaches can be offered either to higher-risk women (selective screening) or to all eligible women within a population (universal screening). Limiting diagnostic testing only to women at high risk of diabetes may be cost saving compared with universal testing, and more convenient, as completion of an OGTT requires pregnant women to fast overnight and attend clinic for at least two hours. On the other hand, testing all pregnant women may result in more women with GDM being identified and treated to reduce hyperglycaemia, in turn reducing adverse outcomes.

While large observational studies have reported a continuous association between levels of maternal hyperglycaemia and perinatal complications (see section 5.2.1) it remains unclear whether screening women without risk factors and treating milder cases of GDM also leads to improved maternal and fetal outcomes to the same extent.

Some organisations, for example NICE, recommend selective screening of women with known risk factors for hyperglycaemia during early pregnancy using OGTT and repeat testing later in pregnancy (usually at 24–28 weeks gestation) for those with risk factors who were not screened positive at first testing.[8] Other organisations, for example the ADA[51] and the Australian Diabetes in Pregnancy Society (ADIPS)[52] recommend that after similar screening of women with risk factors during early pregnancy, all pregnant women should be offered an OGTT in mid-pregnancy irrespective of risk factors.

In 2008 NICE clinical guideline 63 included advice that the following independent risk factors for GDM should be recognised by healthcare professionals. These were endorsed by SIGN in 2010[3] and retained in the 2015 version of the NICE guideline:[8]

- BMI more than 30 kg/m²
- previous macrosomic baby weighing 4.5 kg or more
- previous gestational diabetes
- family history of diabetes (first-degree relative with diabetes)
- family minority ethnic origin with a high prevalence of diabetes.

It is acknowledged that universal screening approaches with lower diagnostic thresholds will identify women with levels of hyperglycaemia that may be considered 'milder' than those identified with higher thresholds. A retrospective observational study compared GDM diagnoses in Switzerland after transition from a selective, two-step approach using a glucose challenge test (GCT) to a universal approach with less strict diagnostic criteria (IADPSG).[53] The authors noted that including and treating more mild cases of hypoglycaemia in Switzerland with the IADPSG criteria slightly reduced GDM-related events only in women with risk factors. They speculated that the relationship between adverse perinatal outcomes, glycaemia during pregnancy and the IADPSG diagnostic thresholds might differ with the risk factors observed in the screened population.

A systematic review and meta-analysis assessed the predictive accuracy of different combinations of risk factors to identify women at high risk of GDM. In addition to noting that risk factors for GDM differ with the diagnostic criteria used, the authors reported that no evidence was identified that screening strategies using several risk factors or risk prediction models offered significant benefit over the simpler strategy of identifying one or two risk factors. Individual patient data analyses suggest that the risk factor combination of maternal age and BMI (≥25 years and BMI ≥25 kg/m^2) would identify the majority of women with GDM, but would mean inviting most women for an OGTT. Although this is as effective as more complex strategies (risk prediction models for example) it may not vary greatly from offering all women an OGTT. As sensitivity increases (and more women are identified), the number needed to receive a diagnostic test also increases. To achieve a sensitivity of over 90%, nearly all women would need to undergo an OGTT.[54] 2+

There are a number of risk factors recommended for inclusion in the diagnostic pathway by various organisations which have not been previously recommended by NICE or SIGN and these are explored below.

5.1.1 Polycystic ovary syndrome

A systematic review and meta-analysis of 63 observational studies compared outcomes in pregnant women with and without polycystic ovary syndrome (PCOS). Women with PCOS had an increased risk of several perinatal outcomes, including GDM (OR 2.89, 95% CI 2.37 to 3.54, 39 studies (n=188,861).[55] Different diagnostic criteria for GDM in the included studies made the interpretation of results more challenging. The authors note that age was associated with increased rate of miscarriage on meta-regression, particularly above age 35 years,(see section 5.1.3) however the independent influence of PCOS was difficult to determine as other factors may also be involved with miscarriage. 2++

An overview of systematic reviews conducted a narrative synthesis of 23 systematic reviews which evaluated complications and comorbidities associated with PCOS. The authors reported that PCOS was associated with a wide range of adverse pregnancy outcomes compared with women who did not have PCOS, including GDM (one systematic review) and risk of type 2 diabetes (one systematic review).[56] 2++

A further systematic review, meta-analysis and meta-regression of 48 studies (43 observational studies and five RCTs) investigated the impact of metformin treatment on GDM in women with PCOS.[57] Regardless of metformin therapy, the prevalence of GDM diagnosed in the second trimester among women with PCOS was significantly higher than healthy controls that was independent of obesity. The authors note that the increased risk of GDM 2++

among women with PCOS, compared to healthy controls, disappeared after the adjustment of metformin therapy.

A large population-based study compared risk of GDM and hypertensive disorders of pregnancy (HTN) in 9.1 million pregnancies in Canada over ten years.[58] In all pregnancies, women with PCOS were more likely to develop GDM (adjusted OR 2.19, 95% CI 2.02 to 2.37).

5.1.2 East Asian ethnicity

No studies were identified which estimated the contribution of East Asian ethnicity as an independent risk factor for development of GDM.

An NHS health technology assessment carried out a systematic review to determine the prevalence of GDM in the UK and Irish obstetric population, using published reports citing diagnostic rates and comparing estimates from three individual participant data (IPD) cohorts.[59] The HTA identified two published studies reporting prevalence of GDM by ethnicity. Both of these studies were undertaken in the 1990s when recommended diagnostic criteria thresholds were higher than those now suggested by IADPSG or NICE and consequently report lower GDM prevalence than would be expected today. The studies report differing GDM prevalence by ethnicity, with women of Asian and South Asian origin having the highest rates. Among the IPD cohorts, GDM prevalence varied widely, but was always higher in South Asian populations than White British populations (at a ratio which ranged from 1.33 to 4.54:1). 2++

Two systematic reviews and meta-analyses provided estimated pooled prevalence statistics of GDM in Asia.

A systematic review and meta-analysis of 84 studies which included pregnancy data from 2,314,763 women across 20 countries estimated the pooled prevalence of GDM in Asia to be 11.5% (95% CI 10.9–12.1).[60] Significant variation was noted between countries which is partly accounted for by use of different diagnostic criteria and screening methods, with the highest prevalences in countries using IADPSG criteria compared with original WHO or ADA criteria and in countries using one-step compared with two-step screening methods. The review reported prevalence of GDM in the following East Asian regions as: Taiwan 38.6%, Hong Kong 32.5%, China 12.6%, South Korea 10.5%, Japan 2.8%. 2++

A further systematic review and meta-analysis calculated pooled prevalence of GDM in studies conducted in mainland China using IADPSG diagnostic criteria to be 14.8% (95% CI 12.8 to 16.7%).[61] 2+

5.1.3 Age

Maternal age over 35 years has been associated with a range of adverse complications of pregnancy.

A systematic review and meta-analysis of 75 observational studies investigated the association between maternal age and adverse pregnancy outcomes.[62] Risk of GDM was significantly increased among all women aged 35 years or over compared with those aged under 35 years (OR 2.85, 95% CI 2.46 to 3.32, 28 studies). Risk of GDM increased approximately linearly with maternal age. 2++

A further systematic review and meta-analysis investigated the association between maternal age and GDM in 127,275,067 pregnant women, including 3,432,209 pregnant women with GDM and 123,842,858 pregnant women without GDM.[63] Authors report similar linear increase in GDM with increasing maternal age with an almost five-fold increase in GDM risk in pregnant women aged over 40 years compared with those aged under 20 years. For each one-year increase in maternal age from 18 years of age, GDM risk for the overall population, Asian, and Caucasian increased by 7.90% (95% CI 7.15 to 8.65), 12.74% (95% CI 10.91 to 14.56), and 6.52% (95% CI 5.58 to 7.45), respectively. From the age of 25, Asian women had a significantly higher risk of developing GDM than Caucasian women. 2++

A further systematic review and meta-analysis investigated risk factors associated with GDM and included 103 studies involving 1,826,454 pregnant women. The authors reported that a 2++

wide range of factors were independent risk factors for GDM, including maternal age of 25 years or over (OR 2.47, 95% CI 2.12 to 2.87).[64]

R **Pregnant women with a history of PCOS should be considered for screening for GDM** (odds ratio for GDM diagnosis 2–3).

R **Pregnant women over 40 years should be screened for GDM** (odds ratio for GDM diagnosis 4.86).

R **Pregnant women aged 35–40 years should be considered for screening for GDM** (odds ratio for GDM diagnosis 2.85).

5.2 Diagnosis

The OGTT has traditionally been the diagnostic test of choice for all forms of diabetes in the general population, including GDM. A range of OGTT diagnostic criteria have been proposed and adopted, to different extents, worldwide and some controversy remains about which of these may be optimal. While HbA1c has been used for monitoring patients with diabetes since the early 1980s it was only formally accepted by the World Health Organization (WHO) as a diagnostic tool in 2010.

While the evidence base for the usefulness of CGM as a tool to monitor glycaemic control during pregnancy continues to accumulate, in future, criteria may be derived for diagnosis of GDM using metrics delivered by continuous monitoring tools. Large studies are investigating CGM in women at risk of developing GDM, however the evidence base has not matured to support recommendations as yet.[65,66]

5.2.1 Existing diagnostic and screening criteria for gestational diabetes

In 1965, the WHO recommended that GDM be diagnosed by either a 50 g or 100 g OGTT using the two-hour postload glucose value, using the identical threshold as for diagnosing diabetes in the non-pregnant population. This criterion remained current until WHO endorsed the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) revised diagnostic criteria in 2013.

Since 1970s, screening for GDM frequently involves either a one-step method involving a single OGTT measured either at one hour or two hours after glucose loading, or a two-step procedure with a 50 g one-hour glucose challenge test (GCT) followed by a later OGTT if the GCT is positive. Diagnostic and screening criteria have been revised over time based on emerging epidemiological evidence of an association between perinatal glucose levels and risks of obstetric and neonatal complications, however there remains a lack of agreement on the optimal thresholds. This has resulted in greater and smaller populations of women being diagnosed, and hence managed, with GDM.

A large, international, prospective, observational study (The Hyperglycemia and Adverse Pregnancy Outcomes, (HAPO)) investigated the relationship between glucose levels from a 75 g two-hour OGTT performed at 24 to 32 weeks' gestation in over 25,000 pregnant women with a wide range of adverse perinatal outcomes.[67] The study reported a continuous positive linear relationship between maternal fasting glucose levels; one- and two-hour glucose levels obtained on the OGTT, below those that were diagnostic of diabetes outside pregnancy; and risk of primary outcomes. The authors note that there were no specific glucose thresholds at which obstetric and neonatal complications significantly increased.

In 2010, based on the HAPO results, the IADPSG revised its diagnostic criteria for GDM. Using a consensus method and despite the lack of a clear diagnostic glucose threshold, IADPSG set diagnostic thresholds for the fasting, one- and two-hour glucose values for the 75 g two-hour OGTT based on the average glucose values at which the odds of the primary outcomes were 1.75 times the odds of these outcomes occurring at the mean glucose levels for the HAPO cohort.[49]

Shortly after this publication, WHO and a number of other international organisations (including the American Diabetes Association, Endocrine Society, International Federation of

Gynecology and Obstetrics, Australasian Diabetes in Pregnancy Association, Japan Diabetes Society and European Board of Gynecology and Obstetrics) endorsed the IADPSG approach for universal testing of all pregnant women and GDM diagnosis at the thresholds specified.

The IADPSG screening strategy was noted to result in a rise in incidence of GDM and increased burden on healthcare systems compared with previous approaches.[68] Some studies have reported cost savings and improved pregnancy outcomes associated with adopting the IADPSG screening criteria,[69,70] while others did not find similar benefits.[71,72] Using a universal GDM screening strategy may be perceived as medicalising previously healthy pregnancies, with potential implications on women's quality of life. Consequently, some European countries, including Scotland, have adopted the IADPSG criteria only in women with specific risk factors for GDM. This selective screening approach may help to focus diagnostic efforts on women most at risk of developing GDM but has been shown to miss 5–45% of GDM cases.[73]

A number of organisations did not follow IADPSG criteria, including the National Institutes of Health[74] in the USA and NICE[8] in the UK. NICE recommends a selective testing approach, by which women with risk factors for GDM undergo a diagnostic 75 g two-hour OGTT at 26–28 weeks' gestation, with a higher fasting glucose diagnostic threshold and lower two-hour glucose diagnostic threshold than the IADPSG diagnostic criteria for GDM (see Table 2).

5.2.2 Optimal diagnostic criteria

Given the continuous relationship between glucose and some maternal and neonatal outcomes demonstrated by the HAPO study, it is unsurprising that the diagnostic level may be set at different levels. There is an argument that the precise level should reflect underlying risk in the population and may therefore be different in different populations.[75]

In Scotland, standard practice for diagnosis of GDM involves offering a 75 g OGTT at 24–28 weeks' gestation and reviewing postload glucose levels against IADPSG thresholds in those with any of the following risk factors:

- BMI ≥30 kg/m^2 (restricted to ≥35 kg/m^2 in some areas)
- Previous macrosomia (baby with birth weight ≥4,500 g)
- Previous GDM
- Family history of diabetes (T1DM or T2DM in first degree relative, ie child, parent, brother, sister)
- Family origin with a high prevalence of diabetes (South Asia, Middle Eastern, or Black African/Caribbean).

While IADPSG approaches have generally been favoured due to increased identification of women potentially at risk of GDM, the publication of a revised approach by NICE based on increased cost effectiveness challenges healthcare professionals in Scotland to compare and evaluate the strengths and weaknesses of these standards.

Several systematic reviews and RCTs were identified which offer information relating to the impact of different diagnostic criteria for GDM. The evidence base is difficult to synthesise as outcomes vary by population, by screening strategy used (risk-factor-based or universal) and application of screening in the first trimester. A number of RCTs investigate screening approaches which do not align with methods used in Scotland, for example with oral GCT prior to OGTT. Nevertheless, these trials potentially inform approaches to criteria with lower (diagnosing larger part of population as GDM) and higher glucose thresholds. In general, due to the nature of managing women differently according to the diagnostic strategy groups to which they were allocated in trials, it is difficult to maintain blinding across all participants, clinicians and researchers and the evidence is therefore susceptible to provider bias.

In addition, a large volume of observational studies conducted in a wide range of countries and settings was identified which provide information on the prevalence of GDM according to diagnostic criteria used, and some information on sensitivity and positive predictive value of different diagnostic thresholds. The applicability and quality of these studies varied.

Table 2: Selected diagnostic and screening criteria for GDM

UNIVERSAL TESTING APPROACHES

Organisation	Screening test and threshold	Diagnostic test and threshold
IADPSG, WHO, ADIPS, FIGO, JDS, EBCOG, ADIPS, Endocrine Society, China Ministry of Health	One-step diagnostic test	75 g two-hour OGTT Fasting glucose ≥5.1 mmol/L One-hour glucose ≥10 mmol/L Two-hour glucose ≥8.5 mmol/L *One abnormal value required for diagnosis*
ADA[51]	Either one-step diagnostic test, or two-step: 50 g GCT with screen positive threshold at ≥7.2–7.8 mmol/L	75 g two-hour OGTT, Fasting glucose ≥5.1 mmol/L One-hour glucose ≥10 mmol/L Two-hour glucose ≥8.5 mmol/L *One abnormal value required for diagnosis* or 100 g three-hour OGTT Fasting glucose: ≥5.3 mmol/L One-hour glucose: ≥10 mmol/L Two-hour glucose: ≥8.6 mmol/L Three-hour glucose: ≥7.8 mmol/L *Two abnormal values required for diagnosis*

SELECTIVE TESTING APPROACHES

Organisation	Screening criteria (risk factors)	Diagnostic criteria
NICE	BMI >30 kg/m^2, previous macrosomia (≥4,500 g), previous GDM, family history of diabetes, and family origin with a high prevalence of diabetes (South Asian, Black Caribbean, Middle Eastern)	75 g two-hour OGTT Fasting glucose ≥5.6 mmol/L Two-hour glucose ≥7.8 mmol/L *One abnormal value needed for diagnosis*

NICE v IADPSG criteria

A number of studies compared prevalence of GDM or clinical outcomes for women when applying IADPSG or NICE diagnostic criteria for GDM. Eight studies reported that use of the NICE diagnostic criteria led to a smaller proportion of women being diagnosed with GDM based on the same glucose levels compared with the IADPSG criteria.[76-83] One study showed that NICE criteria identified a larger proportion of women with GDM.[84] In populations of pregnant women who underwent universal screening IADPSG criteria resulted in a 1.07 to 2.4-fold increase in prevalence, and a 4.2-fold increase in risk factor based screening.

A number of observational studies looked at how outcomes of women who would not have been diagnosed with either criterion differed from outcomes in women diagnosed with one criterion but not the other, or both (ie negative in both criteria 'IADPSG- NICE-'; compared with those diagnosed with IADPSG criteria but not NICE criteria 'IADPSG+ NICE-'; and those diagnosed with NICE criteria but not IADPSG criteria 'IADPSG- NICE+'; and those diagnosed by both criteria IADPSG+ NICE+'). Notably all of these types of analysis are often difficult to interpret as they are generally carried out in treated populations.

One study reported similar outcomes in treated women using either criterion.[85] Several studies noted increased risk in women with fasting glucose levels of 5.1–5.5 mmol/L (IADPSG+ NICE-) compared with women without GDM by either criterion.[78,80-83,86] By contrast there were no significant adverse maternal and perinatal outcomes observed in women diagnosed as GDM by NICE criteria but not IADPSG criteria (IADPSG- NICE+) compared to women without GDM.[83]

Other screening strategies

A high-quality RCT randomised women to assessment for possible GDM using two criteria. The lower diagnostic thresholds matched with IADPSG criteria based on a 1.75 odds ratio of the mean values for adverse perinatal outcomes in the HAPO study (see section 5.2.1), while the higher thresholds were a fasting glucose level of ≥5.5 mmol/L or a two-hour level of ≥9.0 mmol/L. GDM was diagnosed in 15.3% of women in the lower threshold group (IADPSG) and 6.1% of women in the higher threshold group.[87]

Large-for-gestational-age infants were born to 178 of 2,019 women (8.8%) in the lower-glycaemic-criteria (IADPSG) group and to 181 of 2,031 women (8.9%) in the higher-glycaemic-criteria group (unadjusted RR 0.99, 95% CI 0.81 to 1.21; p=0.91). The risk of a large-for-gestational-age infant was similar in the adjusted analyses (aRR, 0.98, 95% CI 0.80 to 1.19; p=0.82).

In a subgroup analysis which included women in both groups whose OGTT results fell between lower and higher diagnostic thresholds it was possible to compare outcomes of those receiving treatment and those who did not. The characteristics of these women were similar.

Among the women included in the subgroup analysis (those women in both groups whose OGTT results fell between the lower and higher glycaemic criteria), those in the lower-threshold group gave birth to fewer LGA infants than those in the higher-threshold group (6.2% vs 18.0%; adjusted RR, 0.33, 95% CI 0.18 to 0.62). The number of women needed to diagnose and treat GDM in order to prevent one LGA infant in this subgroup was 4 (95% CI 2 to 17). Results of a number of other outcomes favoured the lower-threshold group, including lower maternal weight gain during gestation, lower incidence of pre-eclampsia, a lower proportion of infants with macrosomia, and higher pharmacological treatment for GDM and use of health services. Neonatal hypoglycaemia was detected and treated more often in the lower-threshold group, perhaps reflecting the fact that mothers in this group were diagnosed with GDM which led to infants being screened for possible hypoglycaemia. 1++

Interpretation of the trial results is not straightforward. The authors note that results of the subgroup analysis suggest clinically important, short-term maternal and infant health benefits for the women who received a diagnosis of a milder degree of GDM and also received treatment, compared with those who did not. However, based on results on the primary outcome they also note that “Overall, the risks of giving birth to a large-for-gestational-age infant and of other infant or maternal complications were not lower with the lower glycaemic criteria than with the higher glycaemic criteria”

A meta-analysis of 55 observational studies evaluated the impact of several diagnostic criteria for GDM on the risk of adverse neonatal outcomes.[88] Regardless of GDM diagnostic criteria used, the risk of adverse neonatal outcomes including LGA infants, neonatal intensive care unit admission, preterm birth, neonatal hypoglycaemia, birth trauma, macrosomia, hyperbilirubinaemia and respiratory distress syndrome significantly increased in women with GDM compared with the non-GDM group. Similar results were seen across all diagnostic criteria analysed. Notably, meta-regression revealed that the magnitude of the risk of these adverse neonatal outcomes in the subgroup of women diagnosed using IADPSG criteria was not significantly different to those identified by other less strict diagnostic criteria. 2++

A large cluster randomised non-inferiority trial which included 35,528 pregnant women in Iran compared outcomes in women diagnosed with GDM using a fasting glucose threshold >5.1 mmol/L (IADPSG) with less strict criteria (fasting glucose threshold >5.6 mmol/L).[89] While prevalence of GDM was higher when the IADPSG criterion was used, the less strict criteria were non-inferior to IADPSG for macrosomia and Caesarean section births and not significantly different for all other maternal and neonatal outcomes analysed. The authors 1++

suggest that the consequences of labelling women with fasting plasma glucose levels of 5.2–5.6 mmol/L may increase the prevalence of GDM without any positive effect of adverse pregnancy outcomes.

A further RCT compared 1-step universal screening by 75 g OGTT (using IADPSG thresholds) with 2-step universal screening with non-fasting glucose challenge test followed by OGTT if positive in 23,472 pregnant women.[90] GDM incidence was 16.5% in women randomised to the 1-step approach, compared with 8.5% with the 2-step approach (RR=1.94, 95% CI 1.79 to 2.11). There were no significant differences in maternal or perinatal outcomes between pregnancies randomised to receive 1-step or 2-step screening as part of their clinical care, despite twice as many women having been diagnosed with GDM by the 1-step, versus 2-step approach.

While GDM is traditionally assessed at 24–28 weeks' gestation and individuals receiving a diagnosis are subsequently managed, a further large multinational RCT recruited a population of pregnant women before 20 weeks' gestation with at least one risk factor for GDM.[91] Based on results of an OGTT completed during this early pregnancy period, women who met IADPSG criteria for GDM were randomised to immediate treatment (intervention arm) or to control groups. A follow up OGTT was carried out in those allocated to the control group at 24 to 28 weeks' gestation and individuals were further allocated to deferred treatment (for those whose results met the IADSPG criteria at this time point) or no treatment for those who did not meet the diagnostic criteria.

Women were stratified according to glycaemic range based on the 1.75 and 2.0 odds ratios for adverse pregnancy outcomes at 24 to 28 weeks' gestation as identified in the HAPO study. Women in the higher glycaemic range had a fasting glucose level of 5.3 to 6.0 mmol/L, a one-hour glucose level of ≥10.6 mmol/L, or a two-hour glucose level of 9.0 to 11.0 mmol/L (ie HAPO 2.0). Women in the lower glycaemic range had a fasting glucose level of 5.1 to 5.2 mmol/L, a one-hour glucose level of 10.0 to 10.5 mmo/L, or a two-hour glucose level of 8.5 to 8.9 mmol/L (ie HAPO 1.75, which is equivalent to IADPSG criteria) and did not meet any criteria for the higher range. 1++

Significantly fewer women in the early treatment group experienced an adverse neonatal outcome event (24.9%) compared with the control group (24.9% v 30.5%; adjusted risk difference, −5.6%; 95% CI −10.1 to −1.2). There was no significant between group differences in pregnancy-related hypertension or neonatal lean body mass.

Exploratory subgroup analyses reported a significant effect of early treatment for GDM on the primary composite outcome of adverse neonatal outcomes in the (HAPO 2.0) higher glycaemic range group (RR 0.77, 95% CI 0.67 to 0.89) but not the (HAPO 1.75/IADPSG) lower glycaemic range group (RR 0.91, 95% CI 0.60 to 1.38). The results also suggest a possibility of an increased risk of small-for-gestational-age infants among mothers who had OGTT results that were in the lower glycaemic range.

At 24–28 weeks' gestation, GDM was diagnosed in 78.0% of the women in the subgroup with a higher glycaemic range and in 51.4% of those in the subgroup with a lower glycaemic range. The authors note that the results suggest the possibility that treatment may be more likely to benefit women with higher glucose levels at early screening and may be more likely to confer harm among those with lower values.

Health economics

An economic analysis in the UK has reported that use of the universal IADPSG/WHO testing approach is less cost effective than NICE's selective screening approach, although will identify more women potentially at risk of adverse perinatal outcomes.[92] Despite using similar methods to those used in the economic modelling in the NICE guideline this analysis yields quite different results.

A large NHS health technology assessment included a cost utility analysis to assess the cost-effectiveness of a wide range of screening, testing and diagnostic threshold strategies for GDM.[59] The analysis indicated that while generating improved health outcomes, all of the included strategies are not cost effective compared with no testing or treatment, when the willingness to pay for health sat in the conventional ranges (£20,000 to £30,000 per quality adjusted life year (QALY)). This included the diagnostic strategies recommended by NICE

and IADPSG. There are generalisability issues with the modelled population which simulated women in Bradford, who may differ from women in Scotland. In particular, over 50% women included in the Bradford cohort are of South Asian ethnicity.

The authors report having tested several scenarios in sensitivity analyses. One of the most significant was the inclusion of additional benefits from the early detection of T2DM in mothers. Inclusive of those benefits, intervention became cost effective when the willingness to pay was £24,000 per QALY or greater. It was unclear which screening, testing and diagnostic thresholds strategies that applied to. Further, those results appeared to be highly linked to the underlying risk of T2DM, which may be higher in the modelled population than in Scotland due to ethnic differences. Similarly, the data used to estimate the treatment effect were from Bradford and Ireland leading to external validity problems.

These results support the view that although intervention at lower glucose thresholds does improve health outcomes, the resources required result in the displacement of greater health outcomes elsewhere in the NHS. The authors note that if clinicians use a lower diagnostic glucose threshold than that suggested by the model then the result will be a greater volume of women being treated, and hence an increase in the absolute volume of resources required and, correspondingly, an increase in the absolute amount of health displaced elsewhere in the NHS.

The evidence reviewed in the health technology assessment of identification and treatment of women for GDM is not sufficient to justify the cost of treatment at a cost-effectiveness threshold of £20,000 per QALY. However, if longer-term outcomes are included in the model (although evidence is limited) and costs of providing GDM treatment are reduced by more efficiently deploying existing resources then it may be cost effective to intervene in populations with a high prevalence of glucose intolerance.

Summary and interpretation

The guideline development group notes:

- the existence of observational evidence suggesting that women with fasting glucose levels which lead to diagnosis using IADPSG criteria but not using NICE criteria are at increased obstetric risk, however acknowledges the absence of high-quality RCT evidence comparing these approaches.
- that recent large RCTs comparing lower and higher diagnostic criteria did not display improved outcomes associated with lower criteria at population- or whole study level, although a subgroup analysis was supportive of lower criteria. Furthermore, an RCT of early treatment suggested benefit predominately in women with diagnostic fasting glucose levels ≥5.3 mmol/L or two-hour glucose levels ≥9.0 mmol/L (HAPO 2.0 criteria) but not in those with fasting glucose levels 5.1–5.2 mmol/L or two-hour glucose levels 8.5–8.9 mmol/L (IADPSG / HAPO 1.75 criteria) who were also at increased risk of SGA infants.[91]
- that while the majority of OGTT in Scotland are currently performed at 24–28 weeks' gestation, women with previous GDM routinely have an OGTT at 14–16 weeks and are diagnosed using current (IADPSG) criteria.

In forming a draft recommendation, the guideline development group considered a number of practical issues, including that:

- as implemented, very few or no centres in Scotland were measuring a one-hour glucose value, but were relying on fasting and two-hour glucose values
- due to the large numbers of women with risk factors requiring OGTT, not all centres in Scotland had managed to implement OGTT testing in all women eligible for testing.

Therefore, the guideline development group sought to set a minimal reasonable standard where evidence of benefit appears clear. In doing so they considered diagnostic levels early and later in pregnancy and whether there was sufficient evidence to recommend early testing in all women with risk factors. They also considered whether adoption of different diagnostic criteria in early and late pregnancy might potentially lead to confusion – with a preference to

a single set of criteria unless strong evidence that two criteria were appropriate existed.

It was concluded that:

- when an OGTT is performed at less than 20 weeks gestation, there is sufficient evidence to diagnose GDM in women with glucose levels which exceed HAPO 2.0 thresholds.
- there is developing, but not yet definitive, evidence examining higher and lower diagnostic thresholds at 24–28 weeks' gestation. However, at this time, the guideline development group considered there to be a significant potential for confusion if more than one set of diagnostic criteria is used between early and later pregnancy and therefore supports using the same criteria (HAPO 2.0) for later pregnancy.
- OGTT in early and late (if first test negative) pregnancy is offered to women with previous GDM at present. There would be a considerable resource implication if this were extended to all women and it was considered that further, high-quality studies are required to ascertain in which groups these extra tests might be most effectively targeted.

R **The diagnosis of GDM is made using a single-step 75 g OGTT when one or more of the following results are recorded in those with risk factors during routine testing:**

- **fasting plasma glucose ≥5.3 mmol/L**
- **(one-hour post 75 g oral glucose load ≥10.0 mmol/L, where used)**
- **two-hour post 75 g oral glucose load ≥9.0 mmol/L.**

✓ In light of developing evidence that earlier treatment of GDM may be beneficial, while the current testing windows of 14–16 weeks (for women with prior GDM) and 24–28 weeks should be maintained, where possible women should be tested at the beginning of those windows (ie at 24–26 weeks).

Evidence for use of OGTT is predominantly in women up to gestation 32 weeks and units have used strategies other than OGTT to exclude significant hyperglycaemia at later gestations in women deemed at risk.

5.3 Detecting glucose intolerance

5.3.1 First trimester

An evidence review was conducted to investigate whether pregnant women with moderately raised HbA1c (but below the diagnostic threshold for diabetes) in the first trimester of pregnancy are at risk of adverse pregnancy outcomes. Three systematic reviews of observational studies[93-95] and 12 cohort studies[45,96-106] were included for appraisal, however most studies were designed to assess HbA1c as an indicator for the development of GDM in the third trimester rather than to predict risks of adverse pregnancy outcomes.

One systematic review included data from seven cohort studies and one non-systematic review on the use of HbA1c as a screening tool in the first trimester.[93] There was wide variation in the populations, methods and quality of included studies with poor follow up reported. The authors note that there is no evidence to support use of HbA1c as a screening tool in early pregnancy. The validity of HbA1c as a marker for future adverse pregnancy outcomes may vary throughout pregnancy and between population subgroups. Studies have concluded that HbA1c in healthy pregnant women is generally lower than in non-pregnant women due to a combination of increased haemoglobin turnover in pregnancy and younger mean age than the general (non-pregnant) population. There are also natural variations in HbA1c between trimesters of pregnancy which make it harder to establish thresholds of a 'normal' range. 2+

Another systematic review evaluated the overall accuracy of HbA1c in the diagnosis of GDM and included data from eight studies of 6,406 women of whom 1,044 had GDM.[95] There was 2++

a high heterogeneity among the studies due to variations in ethnicities, different criteria for OGTT interpretation and the individual performance of HbA1c methods. The diagnostic accuracy of HbA1c was reported at different thresholds ranging from 36 mmol/mol (5.4%) to 42 mmol/mol (6.0%), and the area under the curve (AUC) was 0.825 (95% CI 0.75 to 0.90), indicating a good level of overall accuracy. The pooled sensitivities and specificities were 50.3% (95% CI 24.8% to 75.7%) and 83.7% (67.5% to 92.7%); 24.7% (10.3% to 48.5%) and 95.5% (85.7% to 98.7%); 10.8% (5.7% to 19.41%) and 98.7% (96.2% to 99.5%); 12.9% (5.5% to 27.5%) and 98.7% (97.6% to 99.3%), for the cut-offs of 36 mmol/mol (5.4%), 39 mmol/mol (5.7%), 40 mmol/mol (5.8%) and 42 mmol/ mol (6.0%), respectively. Thus HbA1c presents high specificity but low sensitivity regardless of the threshold used to diagnose GDM.

A further systematic review, which included 11 high-quality studies, examined the use of HbA1c levels in early pregnancy as a predictor of GDM.[94] HbA1c levels between 39 mmol/mol (5.7%) and 46 mmol/mol (6.4%) in early pregnancy consistently identified patients who went on to develop GDM. The evidence that particular levels are associated with adverse outcomes was less robust. Adverse pregnancy outcomes were associated with elevated HbA1c levels in four of six studies and included pre-eclampsia, induced labour, shoulder dystocia, Caesarean section birth, large-for-gestational-age birth weight, macrosomia, congenital anomalies, and perinatal death. Two studies found no association with adverse events. 2+

In a post-hoc analysis of data from the vitamin D And Lifestyle Intervention for GDM prevention (DALI) trial, 900 women with singleton pregnancies, aged >18 years, with a BMI of ≥29 kg/m^2 who were attending a participating antenatal clinic before 20 weeks of gestation participated.[107] A 2-hour, 75 g OGTT was carried out at baseline, at 24–28 weeks, and at 35–37 weeks' gestation. Women fulfilling the criteria for GDM by IADPSG criteria or for overt diabetes were excluded from the DALI trial interventions and received treatment. The main outcome measure for this observational study was the development of GDM.

At a mean gestation of 15 weeks, the mean baseline HbA1c was 33 mmol/mol (5.2%) (range 23–45 mmol/mol (4.3–6.3%)), while 12.8% (N=111) had an HbA1c ≥39 mmol/mol (5.7%) and 4.3% (N=37) had an HbA1c >41 mmol/mol (5.9%).

The baseline HbA1c showed a poor area under the curve (AUC) for identifying women with GDM. An HbA1c threshold of 39 mmol/mol (5.7%) showed low sensitivity (15.9%) but high specificity (89.4%) for GDM at any time during pregnancy. Overall, 51.4% of the women in the HbA1c ≥39 mmol/mol (5.7%) group developed GDM, and 72% of these cases were detected before 20 weeks. Women with a higher (≥39 mmol/mol (5.7%)) HbA1c in early pregnancy had a 1.7 times higher risk for GDM sometime in pregnancy compared with women with an HbA1c of <39 mmol/mol (5.7%) (adjusted odds ratio (aOR) of 1.72 (1.02–2.89)). 2+

There was no significant association between a higher HbA1c (≥39 mmol/mol (5.7%)) and the risk of adverse pregnancy outcomes.

The authors note that their results clearly show the poor sensitivity of HbA1c measured in early pregnancy for detecting GDM. While the 39 mmol/mol (5.7%) cutoff was highly specific for GDM, this threshold did not correctly identify most of the cases of GDM with a false negative rate of 81.8% before 20 weeks and 84.1% for GDM at any time. In this study, women with an HbA1c of ≥39 mmol/mol (5.7%) were not at increased risk of adverse pregnancy outcomes. Among those with negative OGTT results using IADPSG criteria, there was no relationship between higher HbA1c and adverse pregnancy outcomes.

R **HbA1c in early pregnancy** (first trimester) **should be considered to detect overt diabetes in pregnancy** (HbA1c ≥48 mmol/mol) **and to identify a cohort at risk of GDM who may benefit from earlier intervention.**

R **HbA1c is not a sufficiently sensitive test to detect GDM. While higher levels in early pregnancy are associated with increasing risk of GDM, as women will be offered testing later in pregnancy glucose monitoring is recommended in those with HbA1c ≥42 mmol/mol.**

✓ Where women are monitoring glucose levels and these appear normal, consider OGTT later in pregnancy.

5.4 Managing women with gestational diabetes

THIS SECTION REMAINS IN DEVELOPMENT - WORK IN PROGRESS

5.4.1 Non-pharmacological interventions

Women with diabetes in pregnancy should be referred to a dietitian for advice about healthy diet in pregnancy.

5.4.2 Pharmacological interventions

Women with GDM should be offered blood glucose monitoring and advised on target ranges for blood glucose in pregnancy. Women with post-prandial glucose levels that are above target after 1–2 weeks should be offered treatment with metformin. Use of glibenclamide is restricted due to lack of availability.

If fasting glucose is elevated or if post-prandial glucose remains above target despite use of metformin, or if metformin is not tolerated, then women should be offered insulin therapy.

6 Intrapartum and postnatal care

6.1 Detecting glucose intolerance after pregnancy

Gestational diabetes is associated with an increased risk of T2DM and cardiovascular disease. Early detection of T2DM or pre-diabetes may allow earlier interventions to reverse diabetes or reduce the risk of complications.

6.1.1 Choosing appropriate tests

Gestational diabetes is associated with a range of adverse outcomes in pregnancy and may also indicate the risk of long-term adverse metabolic outcomes for the mother with rates of up to 70% of women diagnosed with GDM being diagnosed with T2DM at 10 years.[108] Earlier detection of abnormalities in glucose metabolism, including T2DM, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), after delivery may allow the implementation of lifestyle interventions to reverse onset of T2DM or delay and avoid progression of IFG and IGT to frank T2DM.

A small cohort study of women with previous GDM in Ireland showed rates of abnormal glucose tolerance of 20% four years after delivery if WHO criteria were applied, increasing to 56% if ADA criteria (which includes the use of HbA1c as a test for pre-diabetes) were applied.[109] Finding a quicker more convenient and acceptable test may have benefits in improving uptake of screening. Outwith screening women with a past history of GDM, fasting plasma glucose and HbA1c are commonly used tests for diagnosing diabetes.

NICE guideline NG3 identified 13 studies investigating postnatal classification of glucose tolerance in women who have had GDM.[8] All studies focussed on use of fasting plasma glucose to diagnose diabetes postnatally, with four studies also investigating use of fasting plasma glucose to detect IFG and IGT postnatally. One study investigated the diagnostic accuracy of HbA1c to detect diabetes postnatally. These studies were very low quality with very serious limitations. Searches completed for the current guideline identified a further four studies comprising one systematic review and three cohort studies. 4

Evidence reported by NICE showed that a fasting plasma glucose cut-off of 6.0 mmol/L appeared to provide the best balance between ruling in and ruling out diabetes, with fasting plasma glucose at or above this level is a very useful test for ruling in diabetes, and fasting plasma glucose below this level moderately useful for ruling out diabetes. There was no evidence from four cohort studies of a strongly predictive fasting plasma glucose threshold for detecting IGT, but a level less than 7.0 mmol/L was moderately useful for ruling out IGT. A single retrospective cohort study investigating HbA1c to detect postnatal glucose intolerance reported HbA1c cut-offs ranging from 34 to 47 mmol/mol. A value greater than or equal to 39 mmol/mol was very useful for ruling in diabetes. HbA1c was not useful for ruling out diabetes.

Uptake of postnatal screening after a diagnosis of GDM is universally low. Rates of uptake in the UK of 28.2% of eligible women having undergone screening at 12 months postpartum and only 18.5% before six months.[108] The authors of this systematic review suggested that strategies such as reminder services, screening co-ordinators and education of women and HCP to avoid underplaying risks of GDM after delivery may be helpful strategies in improving uptake. 2++

Changes in the haemoglobin levels and red cell turnover during pregnancy may make HbA1c unreliable in the weeks immediately after pregnancy. A cohort study investigated whether fasting glucose measured 24–72 hours after delivery may be helpful to rule out glucose intolerance.[110] The study found that fasting levels at this point were lower than those at six weeks postpartum and therefore could not be used to exclude persisting glucose abnormalities in women with previous GDM. This was thought to reflect reduction in food intake during labour and ongoing effects of the lifestyle changes encouraged following a diagnosis of GDM. A small cohort study of 74 women in Ireland suggested that a combination of HbA1c and fasting glucose for later screening of women at four years postpartum would identify 75% of women diagnosed with abnormal glucose tolerance on a GTT.[109]

R **Fasting plasma glucose and HbA1c should not be used to determine glucose status before six weeks after delivery as levels may not be representative.**

R **OGTT is most likely to diagnose all individuals with abnormal glycaemic states in the postnatal period, but resource issues and patient acceptability may limit the utility of this as a diagnostic test and so should not be routinely offered.**

R **Between 6 and 13 weeks after delivery fasting plasma glucose levels may be helpful in categorising glycaemia in the postnatal period. This could be done at six-week postnatal check or timed to co-ordinate with baby vaccination schedule.**

R **After 13 weeks a combination of HbA1c and fasting glucose could increase diagnostic certainty but further research may be needed.**

✓ Introduction of screening co-ordinators may improve the uptake and acceptability of screening.

✓ There may be benefit in trying to co-ordinate testing with other important milestones post-partum such as vaccinations.

6.1.2 Timing of tests

For women diagnosed with GDM it is important to identify any persisting abnormalities of glucose metabolism following the birth such as impaired glucose tolerance or progression to T2DM to allow appropriate preventative measures or treatment strategies to be introduced. Early confirmation of dysglycaemia may be helpful to improve outcomes in future pregnancies. There are some theoretical disadvantages to testing too early after delivery with some studies suggesting false negative readings when women were tested using glucose values up to 72 hours after delivery[110] and this may result in false reassurance and failure to intervene. NICE guideline NG3 highlighted that if HbA1c was used up to 13 weeks after delivery an incorrect positive diagnosis could be made as the HbA1c during this period could reflect pregnancy related hyperglycaemia.[8]

The NICE guideline identified 51 studies investigating when testing should be undertaken postnatally to identify glucose intolerance in women who have had GDM but are euglycaemic when they are transferred to community care.[8] All evidence was rated as very low quality. For practical implementation, studies were categorised according to testing being performed: 4

- 0–13 weeks after birth
- more than 13 weeks and up to one year after birth
- more than one year after birth.

Testing from 0–13 weeks after birth

For this time interval, NICE reported that using a 75 g OGTT and WHO 1999 diagnostic criteria, diabetes was detected in a median percentage of 8.5% of women (range 1.3% to 50%). IGT was detected in a median percentage of 12.9% of women (range 2.5% to 15.3%). IFG was detected in a median percentage of 6.9% of women (range 1.1% to 15.6%). During this time interval, the median percentage of women taking up the offer of 75 g OGTT was 49.8% (range 13% to 87%).

For this time interval, NICE reported that using a fasting plasma glucose measurement of at least 7.0 mmol/L (the threshold based on the 75 g OGTT applied using the WHO 1999 diagnostic criteria), diabetes was detected in a median percentage of 7.0% of women (range 1.6% to 11.5%). IFG was detected in a median percentage of 9.3% of women (based on a single non-UK study). During this time interval, the median percentage of women taking up the offer of a fasting plasma glucose test was 53% (range 16% to 86%).

No evidence was identified for inclusion relating to testing for diabetes, IGT or IFG using an HbA1c measurement at up to 13 weeks after the birth.

Testing from more than 13 weeks and up to one year after birth

For this time interval, NICE reported that using a 75 g OGTT and WHO 1999 diagnostic criteria, diabetes was detected in a median percentage of 22.5% of women (range 9.2% to 48.1%). No evidence was identified relating to testing for IGT or IFG at more than 13 weeks and up to one year. During this time interval, the median percentage of women taking up an offer of a 75 g OGTT was 61.5% (range 52% to 73%).

For this time interval, no evidence was identified relating to testing for diabetes or IFG using a fasting plasma glucose measurement or for testing for diabetes, IFG or IGT using HbA1c.

Testing performed at more than one year after birth

For this time interval, NICE reported that using a 75 g OGTT and WHO 1999 diagnostic criteria, diabetes was detected in a median percentage of 12.5% of women (range 7.7% to 43.1%). IGT was detected in a median percentage of 23.8% of women (range 13.4% to 24.1%). IFG was detected in a median percentage of 3.6% of women (in one cohort study). During this time interval, the median percentage of women taking up the offer of 75 g OGTT was 54% (range 45% to 85%).

For this time interval, NICE reported that using a fasting plasma glucose measurement of at least 7.0 mmol/L (the threshold based on the 75 g OGTT applied using the WHO 1999 diagnostic criteria), diabetes was detected in a median percentage of 12.4% of women (range 6.8% to 18%). No evidence was identified relating to testing for IFG. During this time interval, the median percentage of women taking up the offer of a fasting plasma glucose test was 68.5% (range 63% to 74%).

For this time interval, no evidence was identified relating to testing for diabetes, IGT or IFG using an HbA1c measurement at more than one year after the birth.

The NICE guideline development group concluded, based on the evidence reviewed, that fasting glucose appears to be the most reliable test for identifying women with dysglycaemia or who may progress to T2DM after delivery in women diagnosed with GDM in pregnancy. They recommended that this should take place ideally between 6 and 13 weeks postnatally which allows early recognition and treatment. The group recognised that a fasting glucose test may not be practical for a women with a new baby who may be breastfeeding and may also be challenging to provide and so pragmatically suggested that a (non-fasting) HbA1c could be offered. As this would need to be delayed until at least 13 weeks after delivery to avoid false positive results which reflect hyperglycaemia during pregnancy, the longer the gap before this test was performed, the greater risk of delaying diagnosis of glucose intolerance. NICE highlighted that whilst OGTT may increase the diagnosis rates significantly after 13 weeks, the practical considerations meant that uptake of screening may be further reduced. NICE highlighted the lack of uptake of screening and suggested that uptake rates and barriers to uptake of screening should be monitored and explored.

From evidence reviewed after the publication of the NICE guideline, a single-cohort study conducted in South Africa investigated the utility of postpartum in-hospital glucose evaluation to identify women at risk of developing diabetes.[110] Fasting plasma glucose levels measured 24–72 hours after delivery were significantly lower compared with both antenatal diagnostic measures (after 24 weeks' gestation) and postnatal OGTT 4–12 weeks postpartum. None of the women identified with hyperglycaemia using OGTT 4–12 weeks postpartum had abnormal fasting glucose levels at 24–72 hours after delivery. The authors note that early postnatal glucose testing failed to identify high-risk individuals and did not demonstrate that in-hospital fasting glucose measurement could help to direct resources to those most in need of surveillance.

A systematic review of barriers and facilitators of attending postnatal screening for T2DM identified 11 primary studies and three systematic reviews of qualitative and quantitative design which provided evidence categorised into seven themes by the review authors.[108] Barriers were noted to be:

- the OGTT test
- competing demands on maternal time

- a lack of education and information.
- risk perception and fear
- knowledge amongst healthcare professionals
- problems with continuity and co-ordination of care, eg, poor communication between professionals, including from secondary to primary care.

The authors also noted several interventions which may improve uptake, including:

- the use of reminders
- increasing awareness of GDM and the risk of subsequent T2DM, by education
- introduction of a more user-friendly and convenient blood glucose test than the OGTT.

The SIGN guideline development group endorse the following recommendations from the NICE guideline:

R **Test blood glucose in women who were diagnosed with gestational diabetes to exclude persisting hyperglycaemia before they are transferred to community care.**

R **Explain to women who were diagnosed with gestational diabetes about the risks of gestational diabetes in future pregnancies, and offer them testing for diabetes when planning future pregnancies.**

R **For women who were diagnosed with gestational diabetes and whose blood glucose levels returned to normal after the birth:**

- **Offer lifestyle advice (including weight control, diet and exercise).**
- **Offer a fasting plasma glucose test 6–13 weeks after the birth to exclude diabetes (for practical reasons this might take place at the 6-week postnatal check).**
- **If a fasting plasma glucose test has not been performed by 13 weeks, offer a fasting plasma glucose test, or an HbA1c test if a fasting plasma glucose test is not possible, after 13 weeks.**
- **Do not routinely offer a 75 g 2-hour OGTT.**

R **For women having a fasting plasma glucose test as the postnatal test:**

- **Advise women with a fasting plasma glucose level below 6.0 mmol/L that:**
  - **they have a low probability of having diabetes at present**
  - **they should continue to follow the lifestyle advice (including weight control, diet and exercise) given after the birth**
  - **they will need an annual test to check that their blood glucose levels are normal**
  - **they have a moderate risk of developing type 2 diabetes, and offer them advice and guidance in line with the forthcoming guideline on preventing type 2 diabetes.**
- **Advise women with a fasting plasma glucose level between 6.0 and 6.9 mmol/L that they are at high risk of developing type 2 diabetes, and offer them advice, guidance and interventions in line with the forthcoming SIGN recommendations on prevention, early recognition and treatment, and remission of type 2 diabetes.**
- **Advise women with a fasting plasma glucose level of 7.0 mmol/L or above that they are likely to have type 2 diabetes, and offer them a diagnostic test to confirm diabetes.**

The SIGN guideline development group has developed the following additional recommendations.

R **Rates of uptake of screening should be monitored and the effects of strategies, such as education of women and healthcare professionals, and introduction of screening co-ordinators, should be tested to evaluate improvement in uptake.**

R **Strategies to improve uptake of screening are vital to allow early interventions and improve metabolic outcomes, for example trying to co-ordinate with other milestones such as vaccinations.**

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7 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing diabetes in pregnancy with patients and carers and in guiding the development of locally produced information materials.

7.1 Publications from SIGN

SIGN patient versions of guidelines are documents that 'translate' guideline recommendations and their rationales, originally developed for healthcare professionals, into a form that is more easily understood and used by patients and the public. They are intended to:

- help patients and carers understand what the latest evidence supports around diagnosis, treatment and self care
- empower patients to participate fully in decisions around management of their condition in discussion with healthcare professionals
- highlight for patients where there are areas of uncertainty.

A patient version of this guideline will be developed following publication of this document.

7.2 Sources of further information

7.2.1 Diabetes-specific sources

Diabetes Scotland / Diabetes UK
Helpline: 0141 212 8710, Monday to Friday, 9am–6pm
www.diabetes.org.uk/in_your_area/scotland
Twitter: @DiabetesScot

Diabetes Scotland provides a wide range of information on diabetes including leaflets, fact sheets, details of support groups and advice on all aspects of diabetes. The Diabetes UK Learning Zone offers videos, quizzes and interactive tools for managing diabetes day-to-day which are tailored for each individual.

Juvenile Diabetes Research Foundation (JDRF)
Tel: 01224 248677 (Scotland), 07442 332872 (Central Scotland)
https://jdrf.org.uk/
Email: scotland@jdrf.org.uk
Facebook: http://www.facebook.com/jdrf.scotland

JDRF drives research to cure, treat and prevent type 1 diabetes, accelerates access to type 1 diabetes treatment technologies and medicines and supports people living with type 1 diabetes.
Through its international JDRF network, funding of UK researchers, advocacy work with the NHS and the support it provides to people with type 1 diabetes, JDRF pushes new boundaries and generates unprecedented progress to prevent, treat and ultimately find cures for type 1 diabetes.

Insulin Dependent Diabetes Trust
Tel: 01604 622 837
www.iddt.org
Twitter: @UK_diabetes

The Insulin Dependent Diabetes Trust is run by people living with diabetes to raise awareness of important issues for people with diabetes. It provides information in non-medical language.

Insulin Pump Awareness Group
www.ipag.co.uk
Twitter: @iPAG_Scot

The Insulin Pump Awareness Group was formed and run by a group of people who are either pump users, likely to use pumps in the future, or parents of children with Type 1 diabetes.

My Diabetes My Way
www.mydiabetesmyway.scot.nhs.uk
Twitter: @MyDiabetesMyWay

My Diabetes My Way is NHSScotland's interactive diabetes website which helps to support people who have diabetes and their family and friends.

7.2.2 Other national sources

NHS 24
Tel: 111
www.nhs24.scot

NHS 24 is an online and out-of-hours phone service providing the Scottish people with access to health advice and information 24 hours a day, 365 days a year.

NHS Inform
Tel: 0800 224 488
www.nhsinform.scot

This is the national health and care information service for Scotland. It includes information and links to resources and to support people with diabetes and health conditions that can develop during pregnancy.

Breathing Space
Tel: 0800 83 85 87 (Monday to Thursday, 6pm to 2am, Friday to Monday, 6pm to 6am)
www.breathingspace.scot

Breathing Space is a free and confidential phone and webchat service for anyone in Scotland over the age of 16 who may be feeling down or experiencing depression and need someone to talk to.

British Heart Foundation
Tel: 0300 330 3311
www.bhf.org.uk
Twitter: @TheBHF

The British Heart Foundation provides a telephone information service for people looking for information on health issues to do with the heart, as well as providing a range of information on its website.

Chest, Heart and Stroke Scotland (CHSS)
Tel: 0131 225 6963
www.chss.org.uk
Twitter: @CHSScotland

Chest, Heart and Stroke Scotland aims to improve the quality of life of people affected by chest, heart and stroke illnesses by offering information, advice and support in the community. It produces leaflets on the links between diabetes, heart disease and stroke.

Citizens Advice Scotland
www.cas.org.uk
Twitter: @CitAdviceScot

Citizens advice bureaux are local independent charities that provide free, confidential and impartial advice to people who need it.

Driver and Vehicle Licensing Agency (DVLA)
www.gov.uk/diabetes-driving
Twitter: @DVLAgovuk

The DVLA is an executive agency of the UK Government Department for Transport. It is responsible for issuing driving licenses and vehicle registration certificates, and also recording driver endorsements, disqualifications and medical conditions. People who use insulin for >3 months to control their diabetes are required to inform DVLA.

7.3 Checklist for provision of information

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Women who already have diabetes before pregnancy
• Discuss pregnancy planning with women with diabetes of childbearing age at their annual review. Discussion of care during pregnancy with women of childbearing age should include before pregnancy, while pregnant and after pregnancy. This should be discussed at the annual review but also when it is timely and appropriate for women. • Advise women with diabetes who are preparing for pregnancy that information around preconception planning is available and that they will be offered access to a prepregnancy multidisciplinary clinic and outline the benefits of multidisciplinary management. • Explain that HbA1c will be measured at the booking appointment and may be monitored regularly during pregnancy. • Suggest that women should aim for an HbA1c as low as possible, and/or time in range >70% without hypoglycaemia prior to pregnancy. Provide information on the risks of diabetes to both mother and fetus. Explain why a review of glycaemic control is necessary. • Advise that folic acid 5 mg (available on prescription only) should be taken for three months prior to conception, or as soon as possible after pregnancy is confirmed, and until the end of week 12 of pregnancy. • Offer lifestyle advice, for example, on stopping smoking, alcohol and drug use, weight management and exercise, in line with all pregnancies. Explain about the need for a review with the dietitian. • Discuss increased frequency of appointments also add who will be involved and who to contact? • Explain that a review of all medication will be necessary when planning a pregnancy and offer advice on which medications may need to be stopped, the reasons behind stopping and what the alternatives are. Provide contact telephone numbers. • Ensure process of care/complications screening are up to date and address relevant issues period to pregnancy including wellbeing and psychology.

- Review use of diabetes technologies and consider insulin pump therapy and CGM appropriate to the individual.
- Offer advice about sick day rules and planning for periods of illness (including minor ailments) which may cause hyperglycaemia. This may include:
    - appropriate use of insulin or glucose-lowering medication
    - appropriate dietary alterations to maintain normal glucose levels
    - how often to measure blood glucose levels and when to check for ketones
    - when and how to contact the diabetes team.

Women who are being tested for or are diagnosed with diabetes in pregnancy or gestational diabetes

- Explain that a review of all medication will be necessary when pregnant and offer advice on which medications may need to be stopped, the reasons behind stopping and the alternatives available.
- Advise women about the risks of hypoglycaemia, how to recognise the warning signs and symptoms and what treatment they may require. Ensure they have a glucagon kit and know how and when to use it.
- Advise that during pregnancy tight glycaemic control is important and they will need to monitor their blood glucose more often. Be clear about the glucose targets that need to be achieved.
- Discuss use of CGM in women diagnosed with GDM who need to use insulin.
- Offer advice about sick day rules and planning for periods of illness (including minor ailments) which may cause hyperglycaemia. This may include:
    - appropriate use of insulin or glucose-lowering medication
    - appropriate dietary alterations to maintain normal glucose levels
    - how often to measure blood glucose levels and when to check for ketones
    - when and how to contact the diabetes team.
- Explain about the need for a review with the dietitian.
- Offer lifestyle advice, for example, on stopping smoking, alcohol consumption and exercise.
- Offer advice on safe driving and ensure that women inform the DVLA and their insurance company if they are starting on insulin.
- Discuss with women about the risk of retinopathy and advise that they will have retinal screening during each trimester. Explain what screening involves and what treatment to expect if retinopathy is found.
- Emphasise importance of postpartum testing for glucose intolerance and discuss future risk of T2DM and GDM in future pregnancies.
- Provide contact telephone numbers.

All women with diabetes during pregnancy

Discuss the following issues with women during pregnancy:

- retinal screening during each trimester
- frequency and nature of appointments
- changes in symptoms of hypoglycaemia or hyperglycaemia
- planning of delivery, including timings, methods, pain relief, and management of diabetes during labour.

Women should be made aware of who will be involved in their care at different appointments/stages – include when mentioning MDT.

Post-natal care

Discuss the following issues with women after delivery:

- changes in insulin requirements – note preconception rates
- target range changes – increased chance of hypos
- support for breastfeeding
- gestational diabetes and increased risk of type 2 diabetes

- changes in the frequency of appointments, including what service will you move to and who to contact.

7.4 Useful resources

The following resources are available for free from Diabetes UK

Your guide to type 1 diabetes (PDF)

Your guide to type 2 diabetes (PDF)

Planning for a pregnancy when you have diabetes (website)

Managing your diabetes during pregnancy (website)

Gestational diabetes (website)

Your guide to gestational diabetes (PDF)

What diabetes care to expect if you have gestational diabetes (PDF)

After the birth (website)

The following resources are available for free from Juvenile Diabetes Research Foundation (JDRF)

Pregnancy and type 1 diabetes (website)

8 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

8.1 Implementation strategy

Implementation of national clinical guidelines is the responsibility of each NHS board, including health and social care partnerships, and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities.

8.2 Resource implications of key recommendations

No recommendations are considered likely to reach the £5 million threshold which warrants resource impact analysis.

8.3 Auditing current practice

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- analysis of 75g OGTT and clinical outcomes in women without risk factors compared with those receiving diagnosis of GDM under the criteria recommended in this guideline
- analysis of outcomes in women with fasting glucose levels 5.1–5.2 mmol/L and non-diagnostic two-hour glucose values
- analysis of outcomes in women with two-hour glucose values 7.8–9 mmol/L and non-diagnostic fasting values. (Collectively, these two points identify values which include women diagnosed using NICE and IADPSG criteria).

9 The evidence base

9.1 Systematic literature review

The evidence base for this guideline was synthesised in accordance with SIGN methodology. Evidence was drawn from NICE clinical guideline NG3 and from a systematic review conducted by SIGN. Evidence identified by NICE for guideline NG3 on diabetes in pregnancy: management from preconception to the postnatal period covering the search range 1946–2014 was extracted and used by the guideline development group, where appropriate.

A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2015–2022. Internet searches were carried out on various websites for relevant evidence-based resources (NICE, GIN, TRIP, CADTH, INAHTA). The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two Evidence and Information Scientists using standard SIGN methodological checklists before conclusions were considered as evidence by the guideline development group.

When this guideline is published, the search strategies will be available on the SIGN website, www.sign.ac.uk

9.1.1 Literature search for patient issues

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to early management of patients with a head injury. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Advisor and presented to the guideline development group.

9.1.2 Literature search for cost-effectiveness evidence

The guideline development group identified key questions with potential cost-effectiveness implications, based on the following criteria, where it was judged particularly important to gain an understanding of the additional costs and benefits of different treatment strategies:

- treatments which may have a significant resource impact
- opportunities for significant disinvestment or resource release
- the potential need for significant service redesign
- cost-effectiveness evidence could aid implementation of a recommendation.

A systematic literature search for economic evidence for these questions was carried out by a SIGN Evidence and Information Scientist covering the years 2010–2022. Databases searched include Medline, Embase and NHS Economic Evaluation Database (NHS EED). Each of the selected papers was evaluated by a Health Economist, and considered for clinical relevance by guideline group members.

Interventions are considered to be cost effective if they fall below the commonly-accepted UK threshold of £20,000 per Quality-Adjusted Life Year (QALY).

9.2 Recommendations for research

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (see Annex 1). The following areas for further research have been identified:

- randomised controlled trials comparing the effectiveness of blood ketone monitoring with urine ketone monitoring for women with T1DM or T2DM during pregnancy or GDM.

- observational and/or mixed methods studies to investigate the optimal balance between achieving tighter blood glucose targets and avoiding hypoglycaemia to prevent adverse perinatal outcomes in women with pre-existing diabetes who are planning pregnancy.
- further randomised controlled trials investigating whether improvements in glycaemic control linked to CGM use during pregnancy compared with SMBG is associated with reductions in adverse perinatal outcomes in women with GDM, and separately in women with T2DM.
- randomised controlled trials comparing perinatal outcomes in pregnant women with diabetes who achieve pre-established HbA1c targets compared with pre-established glucose variability metrics (as assessed by CGM).
- observational studies to determine the reference intervals of HbA1c in each trimester of pregnancy in healthy pregnant women in Scotland.
- observational and/or mixed methods studies to investigate the optimal balance between achieving tighter blood glucose targets and avoiding hypoglycaemia to prevent adverse perinatal outcomes in women with pre-existing diabetes during pregnancy.
- randomised controlled trials with economic evaluations comparing outcomes in women diagnosed and treated using IADPSG 1.75 and IADPSG 2.0 criteria.

10 Development of the guideline

10.1 Introduction

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at **www.sign.ac.uk**

This guideline was developed according to the 2019 edition of SIGN 50.

10.2 The Guideline Development Group

Dr Robert Lindsay *(Chair)*	Reader in Diabetes and Endocrinology University of Glasgow/ NHS Greater Glasgow and Clyde
Ms Juliet Brown	Evidence and Information Scientist, Healthcare Improvement Scotland
Dr David Carty	Consultant Diabetologist, Glasgow Royal Infirmary, NHS Greater Glasgow and Clyde
Dr Carolyn Chiswick	Consultant Obstetrician, University of Edinburgh, NHS Lothian
Ms Emma Doble	Patient Representative, Stirling
Ms Iona Duckett	Senior Midwife, Ninewells Hosptial, NHS Tayside
Ms Noreen Dunnachie	Lead Midwife for Diabetes, Crosshouse Hospital, NHS Ayrshire & Arran
Dr Fiona Green	Consultant Physician, Dumfries Royal Infirmary, NHS Dumfries & Galloway
Ms Leanne Jenkins	National Care Advisor, Diabetes UK and Diabetes UK Cymru
Ms Susan Johnston	Diabetes Specialist Nurse, Royal Infirmary of Edinburgh, NHS Lothian
Ms Alice McInnes	Consultant Midwife, University of Dundee, NHS Tayside
Ms Lesley Macher	Senior Pharmacist, Western General Hospital, NHS Lothian
Dr Rahat Maitland	Consultant Diabetologist, Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde
Dr Nicola Miller	Consultant in Obstetrics & Gynaecology, Forth Valley Royal Hospital, NHS Forth Valley
Dr Moray Nairn	Programme Manager, SIGN
Professor Rebecca Reynolds	Professor of Metabolic Medicine, University of Edinburgh/ NHS Lothian
Dr Katrina Shearer	Consultant Obstetrician, Aberdeen Maternity Hospital, NHS Grampian
Dr Lydia Simpson	Consultant Obstetrician, Royal Infirmary of Edinburgh, NHS Lothian
Dr Wendy Watson	Consultant Diabetologist, Aberdeen Royal Infirmary, NHS Grampian

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available on request from the SIGN Executive.

Guideline development and literature review expertise, support and facilitation were provided by SIGN Executive and Healthcare Improvement Scotland staff. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on request from the SIGN Executive.

Kirsty Allan	Distribution Co-ordinator, SIGN
Karen Graham	Patient and Public Involvement Advisor, SIGN
Jenni Hislop	Senior Health Economist, Healthcare Improvement Scotland
Scott Mahony	Senior Health Economist, Healthcare Improvement Scotland
Domenico Romano	Publications Designer, Healthcare Improvement Scotland
Gaynor Rattray	Guideline Co-ordinator, SIGN
Carolyn Sleith	Evidence and Information Scientist, Healthcare Improvement Scotland

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Professor Fiona Denison *(deceased)*	Professor of Translational Obstetrics, University of Edinburgh
Ailsa Halliday	Project Officer, SIGN
Dr Marie Anne Ledingham	Consultant, Queen Elizabeth Hospital, NHS Greater Glasgow and Clyde
Ms Wendy Legge	Patient Representative, Aberdeenshire
Ms Jill Little	Lead Diabetes Specialist Nurse, Borders General Hospital, NHS Borders
Ms Maureen McSherry	Consultant Midwife, NHS Lanarkshire

10.3 Consultation and peer review

A report of the consultation and peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees and other contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

10.3.2 Specialist reviewers invited to comment on this draft

Ms Amy Brown	*Advanced Pharmacist Diabetes and Endocrinology, Glasgow Royal Infirmary, NHS Greater Glasgow & Clyde*
Ms Sarah Bruce	*Diabetes Specialist Nurse & Independent Nurse Prescriber, Aberdeen Royal Infirmary, NHS Grampian*
Dr Sinead Currie	*Lecturer in Health Psychology and Health Psychologist, University of Stirling*
Dr Anna Rachel Dover	*Consultant in Diabetes and Endocrinology, Edinburgh Centre for Endocrinology and Diabetes. Royal Infirmary of Edinburgh*
Dr Maria Flynn	*General Practitioner, Edinburgh*
Dr Shridevi Gopi-Firth	*Specialty Doctor, Eating Disorder Service, NHS Forth Valley*
Miss Una Hendry	*Senior Charge Midwife/Diabetes Specialist Midwife, Aberdeen Maternity Hospital, NHS Grampian*
Ms Denise Hoxley	*Nurse Therapist, Eating Disorder Service, NHS Forth Valley*
Ms Alison Irvine	*Lead Diabetes Specialist Nurse, Gilbert Bain Hospital, Lerwick, Shetland*
Dr Jan Islei	*General Practitioner, Aviemore*
Dr Mohammad Sadiq Jeeyavudeen	*Consultant in Diabetes and Endocrinology, Western General Hospital, Edinburgh*
Dr Kirsty MacLennan	*Consultant Clinical Psychologist, Aberdeen Royal Infirmary, NHS Grampian*
Mrs Siobhan McGuinness	*Lived experience representative, Glasgow*

Ms Nicola McPherson	*Clinical Associate in Applied Psychology and Clinical Health Psychology, Ayrshire Central Hospital, NHS Ayrshire and Arran*
Dr Kenneth Muir	*Consultant in Diabetes and Endocrinology, Raigmore Hospital, Inverness, NHS Highland*
Ms Fiona O'Malley	*Diabetes Specialist Nurse, Gartnavel General Hospital, NHS Greater Glasgow & Clyde*
Mrs Caroline Page	*Diabetes Specialist Nurse, Balfour Hospital, Kirkwall, Orkney*
Dr Christine Park	*Consultant in Diabetes and Endocrinology, Dr Gray's Hospital, Elgin, NHS Grampian*
Professor Sam Philip	*Consultant Physician, Diabetes and Endocrinology and Clinical lead SCI-Diabetes, Grampian Diabetes Research Unit, Aberdeen*
Mrs Linda Reevell	*Lived experience representative, Glasgow*
Dr Hannah Robertson	*Consultant in Diabetes and General Medicine, Aberdeen Royal Infirmary, NHS Grampian*
Dr Anna Smart	*Specialty Doctor in Diabetes, NHS Grampian*
Dr Fiona Strachan	*Consultant in Diabetes and Endocrinology, Dr Gray's Hospital, Elgin, NHS Grampian*
Dr Pauline Strachan	*Consultant Physician with special interest in Diabetes, Gilbert Bain Hospital, Lerwick, Shetland*

10.3.2 Public consultation

The draft guideline was also available on the SIGN website for a month to allow all interested parties to comment.

Abbreviations

ADA	American Diabetes Association
ADIPS	Australian Diabetes in Pregnancy Society
AGP	ambulatory glucose profile
aOR	adjusted odds ratio
aRR	adjusted risk ratio or relative risk
AUC	area under the curve
BMI	body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CGM	continuous glucose monitoring
CHSS	Chest, Heart and Stroke Scotland
CI	confidence interval
CONCEPTT	Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial
DALI	Vitamin D And Lifestyle Intervention for GDM prevention trial
DVLA	Driver and Vehicle Licensing Agency
GCT	glucose challenge test
GDM	gestational diabetes
GIN	Guidelines International Network
GMI	glucose management indicator
GP	general practitioner
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes study
HbA1c	glycated haemoglobin
HTA	health technology assessment
HTN	hypertensive disorders of pregnancy
IADPSG	International Association of the Diabetes and Pregnancy Study Groups
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
INAHTA	The International Network of Agencies for Health Technology Assessment
IPD	individual participant data
isCGM	intermittently-scanned continuous glucose monitoring
JDRF	Juvenile Diabetes Research Foundation
LGA	large for gestational age
MA	marketing authorisation
NICE	National Institute for Health and Care Excellence
NPID	National Pregnancy in Diabetes
OGTT	oral glucose tolerance test

OR	odds ratio
PCOS	polycystic ovary syndrome
QALY	quality adjusted life year
RR	risk ratio or relative risk
rtCGM	real-time continuous glucose monitoring
SGA	small for gestational age
SHTG	Scottish Health Technologies Group
SIGN	Scottish Intercollegiate Guidelines Network
SMBG	self monitoring of blood glucose
SMC	Scottish Medicines Consortium
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TAR	time above range
TBR	time below range
TIR	time in range
TRIP	Turning Research into Practice
USA	United States of America
WHO	World Health Organization

Annex 1
Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Guideline section	Key question	
4.2.2, 5.3	S1	Are pregnant women with moderately-raised HbA1c in the first trimester (but below the diagnostic threshold for diabetes) at increased risk of adverse pregnancy outcomes?
5.1	S2	Are the following factors associated with development of gestational diabetes? • previous intra uterine death (IUD) • polycystic ovary syndrome (PCOS) • older age • Chinese/East Asian ethnicity
5.2	S3	Which criteria should be used to diagnose gestational diabetes using the 75 g OGTT?
3.1.1	N4	What are the target ranges for blood glucose in women with type 1 or type 2 diabetes who are planning pregnancy?
3.1.2	N5	What is the target value for haemoglobin A1c (HbA1c) in women with type 1 or type 2 diabetes who are planning pregnancy?
4.1.2	N6	What is the effectiveness of the following procedures in detecting glucose intolerance in the first trimester diagnosed using a 75g OGTT: • risk factor based screening • urine test for glycosuria • random blood glucose test • 50 g oral glucose challenge test • fasting blood glucose test • HbA1c test.
4.1.2	N7	What is the effectiveness of the following procedures in detecting glucose intolerance in the second trimester diagnosed using a 75g OGTT: • risk factor based screening • urine test for glycosuria • random blood glucose test • 50 g oral glucose challenge test • fasting blood glucose test • HbA1c test
5.4	N9	What is the effectiveness of the following interventions (alone or in combination) in women with gestational diabetes: • non-pharmacological interventions (diet and/or exercise) • pharmacological interventions (metformin, glibenclamide and insulin)?
4.3	N11	What is the effectiveness of blood ketone monitoring compared with urine ketone monitoring for women with type 1, type 2 or gestational diabetes during pregnancy?
4.2.1	N12	What are the target ranges for blood glucose in women with type 1, type 2 or gestational diabetes during pregnancy?

4.1.2	N13	What is the effectiveness of HbA1c monitoring in predicting adverse outcomes in women with type 1, type 2 or gestational diabetes during pregnancy?
4.2.2	N14	What is the target value for HbA1c in women with type 1, type 2 or gestational diabetes during pregnancy?
4.1.1	N15	What is the effectiveness of continuous glucose monitoring in pregnant women with diabetes compared with intermittent capillary blood glucose monitoring?
4.4	N17	What is the gestational age-specific risk of intrauterine death in pregnancies with type 1, type 2 or gestational diabetes, and the optimal timing of birth?
6.1.1	N18	What is the effectiveness of the following tests in detecting glucose intolerance after pregnancy in women who have had gestational diabetes (but are not hyperglycaemic before they are transferred to community care): • fasting plasma glucose test • HbA1c test • 75 g OGTT?
6.1.2	N19	What is the optimal timing of postnatal testing for the detection of glucose intolerance after pregnancy in women who have had gestational diabetes (but are not hyperglycaemic before they are transferred to community care)?

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