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**MINI-REVIEW ARTICLE**

# Glucose Treatment Targets in Pregnancy - A Review of Evidence and Guidelines

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**Abstract:** ***Background*:** Maternal diabetes mellitus during pregnancy is associated with an increased risk of pregnancy complications for both the mother and the fetus. One of the most prevalent complications is pathological fetal growth, and particularly infants are born large for gestational age (LGA), which leads to problematic deliveries, including the need for caesarean section, instrumental delivery, and further perinatal complications. Glucose monitoring during pregnancy is essential for ensuring appropriate glycaemic control and to reduce these associated risks. The current methods of glucose monitoring include measuring glycosylated haemoglobin (HbA1c), self-monitoring of capillary blood glucose (SMBG), and more recently, continuous glucose monitoring (CGM). Observational studies and randomised controlled trials (RCTs) have assessed the appropriate glycaemic targets for HbA1c, SMBG, and CGM in relation to pregnancy outcomes.

***Objective*:** In this review, we have identified current international guidelines on glycaemic targets and reviewed the supporting evidence.

***Methods*:** We performed an extensive literature search on glycaemic targets in pregnancies affected by diabetes, and we researched international guidelines from recognised societies.

***Results and Conclusion*:** The majority of studies used to define the glucose targets associated with the best pregnancy outcomes, across all modalities, were in women with type 1 diabetes. There were limited studies on women with type 2 diabetes and gestational diabetes. We, therefore, suggest that further research needs be conducted on glucose targets and clinical outcomes, specifically in these populations where CGM technology offers the greatest potential for monitoring glucose and improving pregnancy outcomes.

**Keywords:** Glucose, diabetes, pregnancy, glycaemic targets, gestational, type 1 diabetes, type 2 diabetes, pregnancy outcomes.

## 1. INTRODUCTION

Pregnancies complicated by maternal diabetes mellitus, including Type 1 (T1DM), Type 2 diabetes (T2DM), and gestational (GDM), are associated with an increased risk of complications for both the mother and the fetus. Appropriate glycaemic control is paramount in reducing the risk of these adverse obstetric and neonatal outcomes [1]. Complications that occur and that are widely studied in pregnancies complicated by diabetes include spontaneous abortions/miscarriage, congenital anomalies, and pathological fetal growth [2-5], as well as maternal outcomes, such as preeclampsia and hypoglycaemia [6]. Large for gestational age (LGA) and/or macrosomic outcomes are one of the most common complications of diabetic pregnancy, which can result in further complications during delivery, such as the requirement for a caesarean section and instrumental delivery as well as perinatal complications, including neonatal hypoglycaemia, shoulder dystocia and stillbirth [7, 8]. In addition to this, LGA infants are also at increased risk of developing obesity, cardiovascular disease, and diabetes in the future [9-13]. Interestingly, the prevalence of LGA remains high, even when pregnancies are considered well-controlled clinically, using standard methods of monitoring (SMBG and HbA1c). Therefore, it is thought that either factors other than glucose are involved and/or that these methods fail to detect the glucose variations that may result in LGA [14-16]. Glucose monitoring is the foundation of self-management in diabetes and is used to assess glycaemic control; therefore, it is important that guidelines on glycaemic targets are readily available and reviewed frequently based on the evidence. The current methods of clinical glucose monitoring include glycosylated haemoglobin (HbA1c), self-monitoring of capillary blood glucose (SMBG), and continuous glucose monitoring (CGM).

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The aim of this review is, therefore, to outline the current international guidelines on glycaemic targets for HbA1c, SMBG, and CGM in pregnancies complicated by maternal diabetes and examine the evidence for these recommendations, in relation to obstetric and neonatal outcomes.

## 2. MATERIALS AND METHODS

An initial search on PubMed was performed with the search query "glucose AND targets AND pregnancy AND diabetes" to allow for the identification of appropriate keywords, Medical Subject Headings (MeSH), and entry terms. The PubMed MeSH database was further examined to identify other relevant MeSH and entry terms. Appropriate keywords/terms were then collated, and a thorough search was conducted on PubMed, Web of Science, and Scopus. International recommendations and further evidence on glycaemic targets in diabetic pregnancies were identified in guidelines from the following societies: American College of Obstetrics and Gynaecology (ACOG), American Diabetes Association (ADA), Australian Diabetes in Pregnancy Society (AIDPS), Canadian Diabetes Association (CDA), Endocrine Society and the National Institute for Clinical Excellence (NICE).

Following abstract search and examination of full texts, final studies included randomised controlled trials (RCTs), systematic reviews, appropriate literature reviews, and observational studies published in peer-reviewed journals that focused on glucose targets in diabetic pregnancies (preexisting and GDM). A particular focus was on studies assessing the use of various methods for glucose assessment, including HbA1c, SMBG, and CGM. All studies included were publicly available or available through our university. Other relevant articles reported by the identified studies were also assessed.

## 3. HBA1C MEASUREMENTS TO ASSESS GLYCAEMIC CONTROL

Measurement of HbA1c has been used widely in the diagnosis of diabetes and for the assessment of glycaemic control. It involves a total overview of glycaemia over time, assessing the preceding 60-90 days [17, 18]. The normal reference range of HbA1c in nondiabetic individuals is 4-6% (20-42 mmol/mol), which was derived from the Diabetes Control and Complications Trial (DCCT) in 1993 [19, 20]. This trial showed that intensive glycaemic control, as close to this reference range as possible, can slow the progression of diabetic complications, such as retinopathy, nephropathy, and neuropathy [18, 20].

In pregnancy, HbA1c is primarily used preconceptionally in women with preexisting diabetes to ensure adequate control of blood glucose prior to pregnancy. During pregnancy, however, HbA1c is considered a secondary measurement for glycaemic monitoring, although it is useful in determining ongoing clinical risk. This is because HbA1c levels are lower in pregnancy as a result of haemodilution and increased red blood cell (RBC) turnover. Additionally, as HbA1c assesses glucose over a longer period of time, it does not provide information about short-term variability in maternal glucose concentrations, for example, postprandial hyperglycaemia [21].

### 3.1. Hba1c and its Association with Pregnancy Outcomes

#### *3.1.1. Peri-Conception and Early Pregnancy HbA1c*

Women of reproductive age with preexisting diabetes should be informed of the importance of glycaemic control prior to conception and in early pregnancy, as organogenesis occurs at approximately 5-8 weeks gestation [21]. However, this is not always easy to achieve, particularly when pregnancies are often unplanned or present later than 8 weeks [1, 18]. Several studies have therefore assessed the association between preconception/first trimester HbA1c and pregnancy outcomes.

##### *3.1.1.1. Type 1 Diabetes*

Miodovnik *et al.* prospectively recruited T1DM pregnant women and showed that mean first trimester HbA1 to be significantly greater for women who suffered spontaneous abortions than women whose pregnancy lasted longer than 20 gestational weeks ($p<0.05$). HbA1 of less than 12% at 8-9 weeks was associated with favourable outcomes, and greater than 12% was predictive of the incidence of spontaneous abortion ($p<0.05$). Based on this association, a HbA1 threshold of 12% (HbA1c: 10.9%, 96 mmol/mol) can be inferred from this study [4]. Comparably, Green *et al.* retrospectively assessed first trimester HbA1 in 303 T1DM pregnant women in the USA. The threshold was set as HbA1 of 9.3% (HbA1c: 8.4%, 68 mmol/mol), as derived from the mean of the study population. Risk of spontaneous abortion increased from 12.4% to 37.5% when the HbA1 was < 9.3% and > 14.4%, respectively (Relative Risk (RR): 3.0 [95% CI 1.3-7.0]). The risk of major malformation was 3.0% with HbA1 < 9.3%, compared to 40% with HbA1 > 14.4% (RR: 13.2 [95% CI 4.3-40.4]) [5]. In these early studies, HbA1 was assessed, which refers to several species of carbohydrate binding to haemoglobin, rather than glucose specifically [22].

A peri-conception HbA1c above 6.9% (52 mmol/mol) was found to be associated with an increased risk of serious adverse outcomes, which continued to increase with increasing HbA1c. Perinatal mortality risk was augmented even below this identified threshold (RR: 2.8 [95% CI 1.3-6.1]) and congenital malformations significantly above HbA1c of 10.4% (90 mmol/mol) (RR: 3.9 [95% CI 1.8-7.8]) [23]. In line with this study, Vääräsmäki *et al.* showed that poor glycaemic control in the first few weeks of pregnancy in women with T1DM was the most significant risk factor for adverse fetal outcomes, including congenital malformations and neonatal death (RR: 2.91 [95% CI 1.29-6.55]) [24].

Furthermore, when peri-conception HbA1c in 2458 T1DM mothers was assessed and compared to over 1 million infants from nondiabetic mothers, the rates of major infant cardiac defects were found to be increased in mothers with T1DM. More specifically, even for those with HbA1c below the recommended target of 6.5% (48 mmol/mol), based on the ADA and other major organisation guidelines, major cardiac defects were increased over two-fold in T1DM (33/1000 *vs.* 15/1000) [25].

##### *3.1.1.2. Type 2 Diabetes*

Most studies that have looked at the relationship of HbA1c with outcomes in women with T2DM have also in-

cluded women with T1DM in their analysis without determining whether differences exist between those with T1DM and T2DM. These studies have also demonstrated that higher peri-conception/first trimester HbA1c can increase the risk of perinatal mortality and/or congenital malformations [2, 3, 26]. Lepercq *et al.* showed that odds ratios for perinatal mortality, major congenital malformations, and preterm delivery were all increased in women who had first-trimester HbA1c > 8% (64 mmol/mol) [26]. Actual HbA1c values for those recorded below 8% were not available to these authors, and therefore 8% was used as a threshold. Similarly, Bell *et al.* found that for each 1% (11 mmol/mol) increase in peri-conception HbA1c, the likelihood of the pregnancy being affected by a congenital anomaly increased by 30% (Adjusted Odds Ratio (aOR): 1.3 [95% CI 1.2-1.4]). This steadily increased for HbA1c values above 6.3% (45 mmol/mol) [2]. Women from the same cohort were also investigated by Tennant *et al.*, with the exclusion of pregnancies complicated by major congenital anomalies [3]. In these analyses, an increase in peri-conception HbA1c above 6.6% (49 mmol/mol) was independently associated with increased odds of fetal and infant death (aOR: 1.02 [95% CI 1.0-1.04], $p$=0.01).

Although the above studies report adverse outcomes associated with HbA1c in the early stages of pregnancy, a very recent German study by Hauffe *et al.* showed that a first trimester HbA1c above 6.5% (48 mmol/mol) in women with T1DM and T2DM only results in significantly increased adverse outcomes, such as admission to neonatal intensive care unit (NICU) and preterm delivery, if the HbA1c is also above 6% (42 mmol/mol) in the third trimester [27]. This suggests that, for outcomes other than congenital malformations, poor glucose control in the first trimester may be compensated for by good control later in pregnancy. Interestingly, in this study, high HbA1c in the first trimester was not associated with congenital malformations, although the numbers of congenital malformations were low ($n$=9). Similarly, the study by Vääräsmäki *et al.* in T1DM pregnancy showed that the association of poor glycaemic control with LGA only occurred when this poor glycaemic control persisted throughout the pregnancy (OR: 2.73 [95% CI 1.11-6.75]), but not when glycaemic control was improved up to 28 weeks' gestation (OR: 0.53 [95% CI 0.10-2.69]) [24].

### *3.1.2. HbA1c During Pregnancy*

While HbA1c is not often recommended alone for monitoring glycaemic control during pregnancy and should be used in combination with SMBG [28], several studies have been identified that assess appropriate HbA1c levels during preexisting diabetic pregnancies.

#### *3.1.2.1. Type 1 Diabetes*

In T1DM pregnancy, several studies have shown that high HbA1c later in gestation increases the risk of preterm delivery and other poor pregnancy outcomes [29-31]. Ekbom *et al.* showed that the strongest predictor of preterm birth was HbA1c levels at 28 weeks' gestation, compared to levels at 10 and 20 weeks ($p$<0.001). A threshold of 6.5% was determined based on the normal range for nonpregnant individuals in the study (4.1-6.4%); however, even in women with HbA1c below 6.5% (48 mmol/mol) at 28 weeks, the incidence of preterm delivery was increased compared to those with HbA1c below 5.7% (39 mmol/mol; 24% *vs.* 7%), suggesting that 5.7% may be a more appropriate target [29]. A secondary analysis of a previous RCT on vitamin treatments in T1DM pregnancies showed that HbA1c between 6.5% (48 mmol/mol) and 6.9% (52 mmol/mol) at 26 weeks was associated with an increased risk of preterm delivery (OR: 2.5 [95% CI 1.3-4.8]), preeclampsia (OR: 4.3 [95% CI 1.7-10.8]), neonatal hypoglycaemia with a need for glucose infusion (OR: 2.9 [95% CI 1.5-5.6]) and a composite adverse outcome (OR: 3.2 [95% CI 1.3-8.0]) [32]. HbA1c between 6% (42 mmol/mol) and 6.4% (46 mmol/mol) at 26 weeks was also associated with LGA (OR: 1.7 [95% CI 1.0-3.0]). A post-hoc analysis of a previous RCT comparing insulin treatment showed that elevated HbA1c in the third trimester was a significant predictor of poor outcomes in late pregnancy [33]. A poor outcome was defined as either a composite endpoint including preeclampsia, delivery before 37 weeks, and perinatal death; or delivery before 37 weeks alone or excessive fetal growth (LGA > 80$^{th}$ centile or macrosomia > 4000g) alone. In terms of excessive fetal growth, when categorically analysing HbA1c in the third trimester as < 5.5%, 5.5-5.9%, 6-6.4% and >6.4%, the incidence of LGA/macrosomia was increased at 19%, 26%, 35% and 54%, respectively [31]. Additionally, an earlier study by Evers *et al.* also demonstrated third trimester HbA1c as the strongest predictor of birth weight above the 90$^{th}$ centile in T1DM pregnancies; however, its predictive capacity was reported to be low [14].

In addition to the values discussed above, Lepercq *et al.* found that HbA1c was 6.3% and 5.9% in the first and second trimesters of those with good perinatal outcomes, compared to 7.0% and 6.6% in the first and second trimesters of those with poor perinatal outcomes in women with T1DM. In univariate analyses, HbA1c was significantly associated with good perinatal outcomes in the first and second trimesters, as well as in peri-conception. Good perinatal outcomes were defined as the uncomplicated delivery of a normally formed, non-LGA infant after spontaneous labour ≥ 37 weeks or induction of labour ≥ 38 weeks, with no perinatal complications [34].

#### *3.1.2.2. Type 2 Diabetes*

In T2DM pregnancies, one study showed HbA1c ≥ 6% (42 mmol/mol) during pregnancy to be associated with preterm birth, special care nursery, neonatal hypoglycaemia and jaundice, when compared with those with HbA1c below 6% (42 mmol/mol; $p$<0.05) [35]. Furthermore, in a very recent audit of 17,375 pregnancies in 15,290 women with T1DM (8,690 pregnancies) and T2DM (8,685 pregnancies) conducted across clinics in England, Wales and the Isle of Man, third trimester HbA1c ≥ 6.5% (48 mmol/mol) was shown to be an independent risk factor for perinatal death (OR: 3.06 [95% CI 2.16-4.33]) in the entire cohort. Similarly, first trimester HbA1c ≥ 6.5% (48 mmol/mol) was shown to be an independent risk factor for congenital anomalies in the entire cohort (OR: 1.70 [95% CI 1.35-2.14]). Both associations between HbA1c and perinatal death/congenital anomalies remained significant when T1DM and T2DM were assessed individually. Furthermore, women with T2DM in pregnancy had higher rates of perinatal death across all third trimester

HbA1c categories (below 43 mmol/mol, 42-52 mmol/mol, 53-63 mmol/mol, 64-74 mmol/mol and 75-85 mmol/mol) compared to pregnant women with T1DM. This suggests that while HbA1c may not necessarily be the best way of monitoring glucose control in the short-term during pregnancy, it has value as a marker of risk for poor pregnancy outcomes [36].

Other studies have also assessed cohorts of women with T1DM and T2DM without determining whether differences exist between the types of preexisting diabetes (Table **1**). Joshi *et al.* showed HbA1c to be associated with a risk of neonatal hypoglycaemia in a logistic regression model (OR: 1.42, $p$=0.02); however this was only significant with second trimester and not third trimester HbA1c levels [44]. Nonetheless, maternal HbA1c levels were significantly higher in women who had infants with neonatal hypoglycaemia in the second trimester (6.8% [50 mmol/mol] *vs.* 6.5% [46 mmol/mol]) and in the third trimester (6.7% [50 mmol/mol] and 6.3% [46 mmol/mol]). Furthermore, in the study discussed earlier by Tennant *et al.*, in later pregnancy, third trimester HbA1c above 43 mmol/mol (6.1%) was significantly associated with the odds of infant death or late still birth (aOR: 1.06 [95% CI 1.03-1.09], $p$<0.001) [3]. In contrast, one study demonstrated a limited ability of HbA1c in predicting adverse pregnancy outcomes. Yong *et al.* retrospectively assessed HbA1c in the third trimester at 29-30 weeks' gestation in 11 pregnant women with T1DM and 261 pregnant women with T2DM in Malaysia. In this cohort, HbA1c ≥ 6.1%, a target utilised in their hospital as suggested by Nielsen *et al.* [45], was associated with preterm delivery, caesarean section, LGA, respiratory distress, neonatal hypoglycaemia, and composite adverse neonatal outcomes ($p$<0.05) [46]. Preeclampsia, however, was increased at a lower cut-off threshold of 5.6% ($p$=0.039). However, both thresholds of ≥ 6.1 and > 5.6% HbA1c were not ideal for predicting adverse pregnancy outcomes due to the low sensitivity and specificity of the 6.1% threshold and low specificity of the 5.6% threshold, thus suggesting the need for careful interpretation of HbA1c during pregnancy.

Other studies which have assessed HbA1c in T2DM pregnancies include a recent placebo-controlled trial investigating the impact of metformin, a treatment increasingly being used to treat T2DM in pregnant women. Feig *et al.* found that in women treated with metformin, HbA1c levels were reduced (41 mmol/mol [5.9%] *vs.* 43.2 mmol/mol [6.1%] with placebo treatment, $p$=0.015), in addition to less insulin required, fewer caesarean sections and less weight gain. Infants of women treated with metformin also weighed less, and 9% of infants weighed above the 97$^{th}$ percentile in the metformin group, compared to 15% in the placebo group (RR: 0.58 [95% CI 0.34-0.97], $p$=0.041). Moreover, 12% of infants weighed greater than or equal to 4000 g at birth in the metformin group, compared to 19% in the placebo group (RR: 0.65 [95% CI 0.43-0.99], $p$=0.046). This study suggests that metformin treatment can improve glycaemic control, as measured by HbA1c, in turn improving pregnancy outcomes, including LGA infants [47].

#### *3.1.2.3. Gestational Diabetes*

A limited number of studies have been identified specifically focusing on HbA1c in women with GDM. One retrospective cohort study by Barnes *et al.* investigated HbA1c at GDM diagnosis in 1695 women with singleton pregnancies [48]. A threshold of 5.5% was set based on findings by Mosca *et al.,* who identified this as the upper limit of HbA1c in the third trimester of normal pregnancies [49]. In their analyses, when modelled as a categorical variable (≤ 5.5% or > 5.5% [37 mmol/mol]), HbA1c as a predictor of LGA was marginally significant (OR: 1.382 [95% CI 1.008-1.895], $p$=0.044), although this was not seen when modelled as a continuous variable. Similarly, HbA1c was not a significant independent predictor of LGA or small for gestational age (SGA). In a contrasting study, higher HbA1c at the time of GDM diagnosis was shown to be associated with gestational hypertension/preeclampsia, preterm birth, NICU admission, low birth weight, and macrosomia (> 4,000g), compared to those with HbA1c between 4.5-4.9% (26-30 mmol/mol) in multiple regression analyses, suggesting that HbA1c above 4.9% (30 mmol/mol) increases this risk [50].

Based on the limited number of studies identified, in addition to many studies with low sample sizes of GDM patients, the impact of HbA1c in GDM needs to be further studied to improve targets during pregnancy. As HbA1c is primarily used prepregnancy and is not often recommended routinely in GDM during pregnancy [28, 38, 39], this may explain the lack of studies identified investigating this.

The above studies have aided in the determination of appropriate HbA1c targets in the peri-conception period and throughout pregnancy, as proposed by major societies. The guidelines on the currently recommended HbA1c targets have been outlined in Table **1**.

## 4. SELF-MONITORING OF CAPILLARY BLOOD GLUCOSE TO ASSESS GLYCAEMIC CONTROL

Women with diabetes in pregnancy are advised to self-monitor their blood glucose throughout gestation. These measurements are usually collected at fasting, prior to meals (preprandial), or 1-2 hours following a meal (postprandial). Self-monitoring includes the use of a memory-based glucose meter, which can be used to record capillary glucose measurements throughout the day [51]. This is important, as therapies, such as insulin and other pharmacological agents, can then be adapted to control fluctuations in blood glucose throughout the day and improve perinatal outcomes [18, 52].

### 4.1. Self-monitoring of Blood Glucose and its Association with Pregnancy Outcomes

The use of SMBG is integral in standard diabetes care, and throughout pregnancy, it is a widely accepted method of monitoring glucose levels on a daily basis in women with diabetes [53]. In several studies, it has been shown to improve glycaemic control, pregnancy outcomes, and economic parameters, such as the number of hospital stays and patient expenses, when compared to not using SMBG [54-56].

#### *4.1.1. Type 1 Diabetes*

Three RCTs in women with T1DM have assessed appropriate targets for blood glucose monitoring [51, 57, 58]. In the study by Demarini *et al.*, 137 women with insulin-dependent diabetes were randomly assigned to either a strict control group with a 1.5-hour postprandial target of < 6.7

**Table 1. HbA1c targets in pregnancy and preconception, as recommended by various professional societies.**

| Professional Society | Pre-Pregnancy | During Pregnancy | Refs. |
|---|---|---|---|
| American College of Obstetrics and Gynaecology (ACOG) | < 6% | - | [37, 38] |
| American Diabetes Association (ADA) | < 6.5% | < 7% or < 6%* | [21] |
| Australian Diabetes in Pregnancy Society (AIDPS)[#] | < 7% or < 6%* | < 7% or < 6%* | [39-41] |
| Canadian Diabetes Association (CDA) | ≤ 7% or ≤ 6.5%* | ≤ 6.5% or ≤ 6.1%* | [42] |
| Endocrine Society | ≤ 7% or ≤ 6.5%* | ≤ 7% or ≤ 6.5%* | [43] |
| National Institute for Clinical Excellence (NICE) | < 6.5% * | - | [28] |

**Note:** [*]If possible, without causing hypoglycaemia; [#]preexisting diabetes, not detailed in GDM guidelines.

mmol/L to represent euglycaemia or a customary management group with a 1.5-hour postprandial target of < 7.8 mmol/L (140 mg/dL) to represent standard community care, in addition to fasting targets of < 4.4 mmol/L (79 mg/dL) and < 5.6 mmol/L (100 mg/dL) for the strict group and customary management group, respectively. The control group was admitted to the hospital immediately upon entry into the study to achieve tight control, whereas those in the customary management group were only admitted if they did not meet their targets after 1 week of outpatient management. Their main findings were that neonatal hypocalcaemia was significantly lower in neonates from the strict control compared to the customary control group (17.6% *vs.* 31.9%, $p<0.05$). Other outcomes, such as birth weight, gestational age at delivery, Apgar score, fetal distress, and pregnancy-induced hypertension, were not significantly different [58].

Similarly, Farrag randomised 60 T1DM patients into one of the three groups based on the following glycaemic targets: below 5.6 mmol/L (100 mg/dL; group A), between 5.6-6.7 mmol/L (100-120 mg/dL; group B) and between 6.7-8.9 mmol/L (120-160 mg/dL; group C). Insulin adjustment was used to achieve the targets. Maternal hypoglycaemia occurred in 7 patients in group A, but not in group B ($p=0.00025$) or group C ($p=0.00435$). Birth weights were significantly higher in group C (4250 g) compared to groups A (3200 g) and B (3280 g; both $p<0.01$). Respiratory distress was also significantly higher in group C (6 cases) compared to group A (1 case) and group B (2 cases; $p<0.01$). As maternal hypoglycaemia occurred in group A, and adverse neonatal outcomes were increased in group C, it appears the range in group B, 5.6-6.5 mmol/L, is optimal in this study [57]. However, while it was detailed that fasting, 2 hour postprandial and midnight blood sugar profiles were checked early in the study, it is unclear whether the defined targets were used for all these measurements. Furthermore, Sacks *et al.* randomised 22 women with T1DM into rigid and less rigid groups for SMBG. Glucose targets for fasting and preprandial were 60-90 mg/dL (3.3-5 mmol/L) and 95-115 mg/dL (5.3-6.4 mmol/L) for the rigid and less rigid groups, respectively. For 1 hour postprandial, the targets were 120-140 mg/dL (6.7-7.8 mmol/L) for the rigid group and 155-175 mg/dL (8.6-9.7 mmol/L) for the less rigid group [51]. These targets were based on thresholds for spontaneous abortion, malformations, and perinatal mortality in previous studies [59, 60]. Mean maternal glucose concentrations were greater in the first trimester (147 mg/dL *vs.* 125 mg/dL, $p=0.03$) and second trimester (145 mg/dL *vs.* 127 mg/dL, $p=0.01$) of the less rigid groups; however, hypoglycaemia was reported more frequently in the rigid group. No differences were seen in birth weights, neonatal glucose requirements, and caesarean section. This suggests that higher glucose targets may reduce maternal hypoglycaemia without impacting perinatal morbidity. However, a systematic review that identified these three studies reported that these trials were at high risk of bias due to unclear methods of randomisation, selective reporting of outcomes and absence of blinding [18].

Other studies have also considered the appropriate timing of blood glucose monitoring and SMBG in T1DM, particularly in relation to LGA/macrosomic outcomes [61, 62]. Herranz *et al.* showed mean glucose and the percentage of glucose readings above the target to be higher in women with LGA neonates, where preprandial targets were 3.9-5.6 mmol/L (70-100 mg/dL) and postprandial targets were 5.6-7.8 mmol/L (100-140 mg/dL) [62]. Furthermore, third-trimester variables were indicators of LGA, including mean glucose (OR: 3.45 [95% CI 1.52-7.80]), mean preprandial glucose (OR: 2.97 [95% CI 1.34-6.60]), mean postprandial glucose (OR: 2.09 [95% CI 1.19-3.67]) and the percentage of glucose readings above target (OR: 2.97 [95% CI 1.34-6.60]). Similarly, Combs *et al.* found that in women with T1DM studied between 13-36 weeks, where the targets were < 5.9 mmol/L (105 mg/dL) for fasting and < 7.8 mmol/L (140 mg/dL) for postprandial, macrosomia was associated with higher postprandial glucose levels up to 32 weeks [61]. Their findings also showed that if glucose was kept below 7.3 mmol/L, the risk of macrosomia was reduced or eliminated if kept below 6.7 mmol/L; however, glucose values below 7.3 mmol/L were associated with higher rates of SGA. In contrast, Herranz *et al.* did not assess rates of SGA and excluded any pregnancy with evidence of intrauterine growth restriction (IUGR) [62]. However, both studies assessed birth weights >90$^{th}$ centile for gestational age, and both studies indicated late pregnancy control of glucose as the strongest predictor of fetal overgrowth. In addition to these studies, both also refer to the earlier study by Jovanovic-Peterson *et al.,* who also demonstrated that macrosomia is

associated with postprandial glucose levels in the third trimester and not fasting [63]. Combs and Jovanovic-Peterson both identified that when multiple regression analyses were used to control third-trimester glucose, hyperglycaemia during early pregnancy and macrosomia were no longer significant.

An RCT has also been conducted in women with T1DM who were randomised to SMBG at fasting with either preprandial monitoring or 1 hour postprandial monitoring [64]. Targets for insulin therapy were 3.3-5 mmol/L (60-90 mg/dL), 3.3-5.9 mmol/L (60-106 mg/dL) and < 7.8 mmol/L (140 mg/dL) for fasting, preprandial and postprandial, respectively. The glucose values recorded in the last 4 weeks of pregnancy were analysed, and while compliance was similar between the groups, those in the postprandial monitoring group had a greater percentage for achieving these glycaemic targets (51.6% *vs.* 29.4% and 55.5% *vs.* 30.3% for trimester 2 and 3, respectively; $p<0.001$). In terms of maternal adverse outcomes, the incidence of preeclampsia was reduced in the postprandial group (3% *vs.* 21%, $p<0.048$). Neonatal triceps skinfold thickness was also reduced ($4.5 \pm 0.9$ *vs.* $5.1 \pm 1.3$, $p=0.05$), although other neonatal outcomes, such as LGA, birth trauma, NICU admission, respiratory distress, and neonatal hypoglycaemia were not significantly different. However, this was a small trial conducted on 61 women.

Overall, the majority of these studies highlight that postprandial glucose levels appear to be the most effective in determining macrosomia and other adverse pregnancy outcomes.

### *4.1.2. Type 2 Diabetes*

Only one study was identified that assessed glycaemic targets for SMBG specifically in T2DM pregnancies. Sacks *et al.* retrospectively compared SMBG levels and outcomes between T1DM and T2DM pregnant women in the USA treated with diet and insulin therapy. Insulin treatment was adjusted to maintain fasting glucose between 60-90 mg/dL (3.3-5 mmol/L) and all other glucose levels between 60-105 mg/dL (3.3-5.8 mmol/L) for both groups. Although no differences were observed between T1DM and T2DM women in terms of macrosomia (≥90$^{th}$ centile), caesarean section, shoulder dystocia, and neonatal hypoglycaemia, pregnant women with T2DM had a higher percentage of values in the targets (57% *vs.* 35%, $p<0.001$) and lower average daily glucose (97 mg/dL *vs.* 112 mg/dL, $p<0.001$) compared to those with T1DM. Maternal hypoglycaemia was also more common in those with T1DM as at least one daily glucose value below 50 mg/dL (2.8 mmol/L) occurred in 19% of observation days for T1DM, but only 2% of observation days for T2DM ($p<0.001$) [59]. This suggests that different targets should be utilised in T1DM and T2DM, particularly due to the incidence of hypoglycaemia in T1DM pregnancies.

Furthermore, a systematic review by Middleton *et al.,* which searched the Cochrane Pregnancy and Childbirth Group's Trials Register for RCTs comparing different glycaemic targets in pregnant women with preexisting diabetes, did not identify any studies on T2DM, being in line with our findings [18]. This suggests that further trials in pregnant women with T2DM should be conducted. This is particularly important as the National Diabetes in Pregnancy audit in 2016 revealed that the proportion of pregnant women with T2DM has increased to 50%, compared to 27% in 2002-2003 [1].

### *4.1.3. Gestational Diabetes*

Studies on GDM include that by Rowan *et al.* [65], who analysed a previous RCT comparing metformin and insulin treatment in women with GDM [66]. During the treatment period, self-monitored fasting glucose was predictive of composite neonatal complications ($p<0.001$), which included one or more of the following: recurrent neonatal hypoglycaemia, respiratory distress, need for phototherapy, birth trauma, preterm birth, and a 5-minute Apgar score less than 7. Moreover, postprandial glucose (2 hours) was predictive of preeclampsia ($p=0.016$) and, similar to the studies in T1DM above, LGA outcomes ($p=0.001$). In terms of appropriate glucose targets, the lowest risk of complications was seen at fasting and postprandial glucose < 4.9 and ≤ 6.4 mmol/L, respectively. Bonomo *et al.* used similar targets to those outlined in the above study, including 90 mg/dL (5 mmol/L) for fasting and 120 mg/dL (6.7 mmol/L) for postprandial. A total of 229 women with GDM were randomised to either a conventional group utilising these targets for SMBG or a modified management group. Targets were based on ultrasound measurements of abdominal circumference. For example, if the abdominal circumference (AC) was ≥ 75$^{th}$ centile or < 75$^{th}$ centile, then 80/100 mg/dL (4.4/5.6 mmol/L) or 100/140 mg/dL (5.6/7.8 mmol/L) targets were used, respectively. Significantly lower rates of LGA (>90$^{th}$ centile; 7.9% *vs.* 17.9%, $p<0.05$), and macrosomia (≥4,000g; 3.3% *vs.* 11.5%, $p<0.05$) were observed in the modified management group compared to the conventional group [67]. This suggests that ultrasound measurements of insulin-sensitive tissues may allow more appropriate targets to be determined throughout pregnancy. However, in those with AC ≥ 75$^{th}$ centile, more insulin was required in the modified group in comparison to the conventional group (59.7% *vs.* 15.4%, $p<0.01$), which is likely due to the lower glucose targets in this group. This suggests that insulin was also required more frequently in a high percentage of women with accelerated fetal growth.

In one systematic review, clinical trial registers were searched to assess the impact of glycaemic control in GDM pregnancies on pregnancy outcomes [68]. Here, one Canadian trial of 180 women with GDM, in abstract form only, was identified, which compared strict and liberal glycaemic target groups. For the strict group, the preprandial target was 5.0 mmol/L (90 mg/dL) and the 1 hour postprandial target was 6.7 mmol/L (120 mg/dL). For the liberal group, the preprandial target was 5.8 mmol/L (104 mg/dL) and the 1 hour postprandial target was 7.8 mmol/L (140 mg/dL). However, no significant differences were observed in any outcomes, including macrosomia, SGA, birth weight, and gestational age, making it unclear what targets should be recommended in GDM pregnancies [69]. As only one study was identified, further studies are needed to assess the appropriate blood glucose targets for GDM [70].

In studies investigating appropriate timing of blood glucose monitoring in GDM, de Veciana *et al.* randomly assigned women to either preprandial measurements or 1 hour

postprandial measurements, in addition to fasting measurements [71]. Women with GDM were included who required diet treatment and insulin treatment at or prior to 30 weeks pregnancy. The targets were 3.3-5 mmol/L (60-90 mg/dL), 3.3-5.9 mmol/L (60-106 mg/dL) and < 7.8 mmol/L (140 mg/dL) for fasting, preprandial and postprandial, respectively. The achievement of these targets was similar for preprandial and postprandial groups (86% *vs.* 88%). The mean change in HbA1c was greater in the postprandial group in comparison to the preprandial group, demonstrating that the decrease in HbA1c during treatment was significantly greater in this group. In terms of neonatal outcomes, infant birth weight was lower (3469 g *vs.* 3848 g, $p$=0.01), as well as a lower rate of neonatal hypoglycaemia (3% *vs.* 21%, $p$=0.05), LGA (12% *vs.* 42%, $p$=0.01) and caesarean section due to cephalopelvic disproportion (12% *vs.* 36%, $p$=0.04) in the postprandial group was observed. A similar study by Manderson *et al.* in women with T1DM proposed that some participants in this study may have had undiagnosed T2DM as GDM was diagnosed at initial antenatal visits, and then at 24-28 weeks gestation but only if the antenatal visit screening results were normal [64]. Nonetheless, both studies suggest that monitoring postprandial glucose appears to be associated with improved pregnancy outcomes in women with T1DM in pregnancy and GDM.

In line with these studies, Weisz *et al.* compared the use of 1-hour postprandial SMBG and 2-hour postprandial SMBG in 112 pregnant women with GDM [72]. However, this trial was not randomly allocated and was determined based on the treatment centre. The targets were < 140 mg/dL (7.8 mmol/L) for 1 hour postprandial or < 120 mg/dL (6.7 mmol/L) for 2 hours postprandial, based on ADA and ACOG guidelines. All participants were also required to measure fasting glucose. Diet was used as a treatment and insulin was administered when glucose levels exceeded 95 mg/dL (5.3 mmol/L) at fasting or exceeded the postprandial targets. Although the rates of LGA, macrosomia, and caesarean section were increased in the 2 hour group, they did not reach significance. Birth weight, gestational age, and birth weight percentiles were also similar between the groups. While the results were not significant, there is a potential for 1 hour postprandial targets to be superior to 2 hours for improving pregnancy outcomes. It is also thought that the longer period following meals may cause women to forget, reducing their compliance with monitoring. Insulin therapy was also initiated in the 2 hour group more frequently compared to the 1 hour group (40% *vs.* 28%, $p$<0.05), which could suggest that 1 hour measurements provide more effective information for adjusting diet, reducing the need for insulin therapy. However, this could be due to the tighter target at 2 hours postprandial.

Overall, SMBG is an established and widely used method to assess glycaemic control in diabetic pregnancies. The numerous studies reviewed demonstrate the ability of SMBG to prevent/predict adverse pregnancy outcomes. Based on these, the guidelines on the currently recommended SMBG targets, including the frequency of measurements, have been summarised in Table **2**. Several societies recommend that SMBG glucose levels should be below these targets if achievable without causing problematic hypoglycaemia. The NICE guideline also advises pregnant women with diabetes on insulin therapy to maintain glucose levels above 4 mmol/L [28].

## 5. CONTINUOUS GLUCOSE MONITORING TO ASSESS GLYCAEMIC CONTROL

Recent data show that CGM use significantly improves pregnancy outcomes, and guidelines are currently in the process of being updated to accommodate this new evidence and enable more widespread uptake [73, 74]. Numerous metrics can be calculated from the extensive data collected from CGM devices. The most frequently analysed metrics include mean glucose over time, time in range (TIR), time above range (TAR) and time below range (TBR), and measures of glycaemic variability (such as standard deviation [SD] and coefficient of variation [CV]) [73, 74].

### 5.1. CGM and its Association with Pregnancy Outcomes

#### *5.1.1. Type 1 Diabetes*

One of the recent clinical trials which aided in defining the limits for TIR during pregnancy was the large, multicentre CGM RCT in pregnant women with T1DM on intensive insulin therapy, known as CONCEPTT [75]. In this study, 215 pregnant women were randomised to either CGM (in addition to SMBG) or SMBG alone, stratified by mode of insulin delivery and baseline HbA1c levels. The CGM sensors were real-time and unmasked in the CGM group, and a masked sensor was worn in the control group. The results of this study showed that CGM use in pregnancy was associated with lower rates of LGA infants (> 90$^{th}$ centile; OR: 0.51 [95% CI 0.28-0.90], $p$=0.0210). At 34 weeks' gestation, women in the CGM group spent more TIR (3.5-7.8 mmol/L; 68% *vs.* 61%, $p$=0.0034), which equates to an additional 1.7 hours/day in the target and had a lower TAR (27% *vs.* 32%, $p$=0.027), which equates to around 1 hour less per day hyperglycaemic than those using SMBG alone. The increase in TIR was achieved without increasing the rate of hypoglycaemia, gestational weight gain, or insulin dose. This suggests that the additional information on glucose levels provided by CGM assisted the women with insulin dosing and self-management of their diabetes [1]. Women in the CGM group also had improved glycaemic variability measures at 34 weeks, including SD of mean glucose and mean amplitude of glucose excursions.

Similarly, an observational study by Kristensen *et al.* in women utilising either real-time or intermittent CGM showed that LGA neonates, defined as two standard deviations above the mean for gestational age and sex, were associated with elevated mean CGM glucose levels in the second and third trimesters (OR: 1.53 [95% CI 1.12-2.08] and OR: 1.57 [95% CI 1.12 and 2.19], respectively). In addition to this, LGA was also associated with TIR (3.5-7.8 mmol/L), TBR, TAR, and HbA1c levels in all trimesters [76]. A high percentage of TIR in the second and third trimesters was associated with a reduced risk of LGA (OR: 0.96 [95% CI 0.94-0.99], $p$<0.01 and OR: 0.97 [95 % CI 0.95-1.00], $p$<0.04, respectively), however, the incidence of LGA in neonates was still high, even with CGM. More specifically, in mothers of women with non-LGA infants, the average TIR was 57.9% in trimester 2 and 62.2% in trimester 3, whereas in mothers with LGA infants, the average TIR was 51.8% in trimester 2 and 57.6% in trimester 3. This suggests that around a 5-6% increase in TIR in trimesters 2 and 3 can improve outcomes in terms of LGA neonates.

**Table 2. SMBG targets during pregnancy and their required frequency as recommended by various professional societies.**

| Professional Society | Fasting (mmol/L) | 1 Hour Postprandial (mmol/L) | 2 Hours Postprandial (mmol/L) | Frequency of Glucose Measurements | Refs. |
|---|---|---|---|---|---|
| American College of Obstetrics and Gynaecology (ACOG) | < 5.3 | < 7.8 | < 6.7 | In GDM, four times a day at fasting and once after each meal. In preexisting diabetes at fasting, postprandially, and before bed. Preprandially is recommended if insulin dose is based on these values. Also, consider overnight measurements to avoid hypoglycaemia in selected patients, especially those on insulin pumps. | [38] |
| American Diabetes Association (ADA) | < 5.3 | < 7.8 | < 6.7 | Fasting and postprandial measurements recommended in preexisting and GDM. Preprandially is recommended if using insulin pumps or basal-bolus therapy. | [21] |
| Australian Diabetes in Pregnancy Society (AIDPS) | ≤ 5 (GDM)<br>4.0-5.5 (T1DM, T2DM) | ≤ 7.4 (GDM)<br>< 8.0 (T1DM, T2DM) | ≤ 6.7 (GDM)<br>< 7 (T1DM, T2DM) | In preexisting diabetes, it is recommended that tests be performed at fasting and 1-2 hours after meals. Additionally, testing before meals or overnight may be useful, particularly in people with T1DM. | [39, 41] |
| Canadian Diabetes Association (CDA) | < 5.3 | < 7.8 | < 6.7 | In preexisting diabetes, frequent monitoring, including pre- and post-prandially. Also, consider overnight measurements to avoid hypoglycaemia in T1DM patients. In GDM, measure fasting and postprandially. | [42] |
| Endocrine Society | ≤ 5.3 or ≤ 5.0* | ≤ 7.8 | ≤ 6.7 | In women with GDM or preexisting diabetes it is recommended monitoring preprandially and either 1 or 2 hours postprandially and as indicated at bedtime and during the night. | [43] |
| National Institute for Clinical Excellence (NICE) | < 5.3 * | < 7.8 * | < 6.4 * | In T1DM patients and those with T2DM or GDM on multiple daily insulin injections monitoring is recommended at fasting, preprandially, 1 hour postprandially and at bedtime. In those with T1DM or GDM on diet/exercise therapy, oral therapy, single-dose or intermediate-acting/long-acting insulin it is recommended at fasting and 1 hour postprandially. | [28, 70] |

**Note:** *If possible, without causing problematic hypoglycaemia.

Furthermore, Kristensen *et al.* found the following CGM metrics as the most important predictors of neonatal composite outcome (NCO): mean glucose, TIR, TBR, and TAR in all trimesters and SD of mean glucose in the third trimester. NCO was defined as one or more of the following: macrosomia (> 4500 g), shoulder dystocia, neonatal hypoglycaemia, or NICU admission for over 24 hours. Correspondingly, in the CONCEPTT study, the rates of neonatal hypoglycaemia and NICU admission (>24 hours) were reduced in those with CGM, as well as 1 day shorter hospital stay. Although, other outcomes usually associated with LGA infants, such as preterm birth, birth weight ≥ 4000 g, caesarean section, and shoulder dystocia were not significantly altered. In a secondary analysis of CONCEPTT, neonatal hypoglycaemia was also associated with suboptimal control of glucose, as mothers who had hypoglycaemic neonates had a lower TIR and a higher TAR. Based on this, a 5-7% increase in TIR in the second and third trimesters of pregnancy is considered to be associated with a reduced risk of neonatal hypoglycaemia [77].

Although there are many differences between the Kristensen study and CONCEPTT, such as patient population, study design, CGM systems, and duration of sensor use (near-daily use for Kristensen *et al.* and minimum 6 days for CONCEPTT), the CGM profiles of the patients are very similar; both reported TIR around 50% and 60% and TAR

around 40% and 30% in the first and the third trimester, respectively. The target range in both studies was 3.5-7.8 mmol/L [78].

A recent secondary analysis of the study by Kristensen *et al*. compared CGM results from women administering insulin with pumps (continuous subcutaneous insulin infusion; CSII) and with multiple daily injections (MDI) [79]. In terms of outcomes, no significant differences were observed between groups, and LGA was high in both the MDI group (49%) and the pump group (63%). Glycaemic indices, including mean glucose, mean amplitude of glucose excursion, and TIR significantly improved in both groups each trimester, but these were not different between women with insulin pumps and women with MDI. In contrast, HbA1c did not improve after the second trimester, which further emphasizes the importance of using CGM as a marker for glycaemic control rather than monitoring HbA1c alone. However, mean glucose and TAR were high in both groups, and the recommended TIR (70% between 3.5-7.8 mmol/L) was not achieved in either group, suggesting poor metabolic control within this cohort. Overall, this study highlights the importance of CGM for monitoring glycaemic control compared to standard methods of monitoring and demonstrates how CGM can generate large amounts of data on maternal glucose profiles in a clinical setting.

Previous studies have also assessed different modes of insulin administration, including insulin pumps and MDI during pregnancy in T1DM, and have shown that insulin pump administration can improve HbA1c throughout pregnancy [80, 81]. However, these studies do not utilise current CGM technology, and it is therefore difficult to assess the differences between modes of administration with respect to the range of glucose metrics that can be assessed with CGM.

Overall, the CGM studies in women with T1DM in pregnancy have provided further insights on CGM use for these cohorts, specifically in improving LGA outcomes, the main outcome of concern in diabetic pregnancy.

### *5.1.2. Type 2 Diabetes*

In this review, no studies were identified that assessed the use of CGM specifically in T2DM pregnancies. Although, earlier RCTs have assessed CGM in cohorts including women with T1DM and T2DM. Murphy *et al.* observed a lower number of macrosomic neonates ($\geq 90^{th}$ centile) in women using CGM compared to SMBG alone (35% *vs.* 60%). Those in the CGM group also had a reduced risk of macrosomia (OR: 0.36 [95% CI 0.13-0.98], $p$=0.05) [16]. Additionally, median birth weight centiles were 69% in the CGM group and 93% in the control SMBG group ($p$=0.02). This study did not report the CGM metrics/glycaemic levels that were associated with this reduced risk of macrosomia, or improvements in birth weight centiles, and therefore, does not provide evidence to determine appropriate CGM targets in diabetic pregnancies. Nonetheless, women with CGM had improved HbA1c levels between 32-36 weeks' gestation, suggesting that CGM can improve glycaemic control and LGA outcomes. In contrast, intermittent use of CGM in the RCTs by Secher *et al.* did not improve the prevalence of LGA neonates in those with T1DM and T2DM. Additionally, HbA1c levels and experience of severe hypoglycaemia were comparable between the groups [82]. Subgroup analyses were also performed based on the type of diabetes, despite low numbers of women with T2DM (16 and 15 women in the CGM and the control group, respectively). Here, maternal and perinatal outcomes, including preeclampsia, LGA, neonatal hypoglycaemia, and preterm delivery, were similar between the groups. While Secher *et al.* stratified the randomisation of measurement strategy by type of diabetes, and performed subgroup analyses based on the type of diabetes, Murphy *et al.* did not; therefore, an unequal distribution of women with T1DM and T2DM between groups may have influenced the results, nor did they perform subgroup analyses based on diabetes type. Furthermore, while participants in the Secher *et al.* study were encouraged to use CGM continuously, only a few women in the study were willing to use CGM more frequently than the designated study periods (6 days at gestational weeks 8, 12, 21, 27 and 33), suggesting that its use for longer periods maybe more beneficial.

This limited amount of evidence has hindered the ability to determine appropriate CGM targets in T2DM pregnancies, and therefore research into CGM use in this population needs to be investigated further.

### *5.1.3. Gestational Diabetes*

In several RCTs in women with GDM, CGM did not affect the incidence of LGA or macrosomia [83-86]. Similarly, no differences in other neonatal or maternal outcomes were observed within these studies, such as neonatal hypoglycaemia, preeclampsia, and caesarean section, or were not assessed by the authors, except for an improvement in gestational weight gain observed with CGM in one study [85]. However, CGM influenced the use of pharmacotherapy treatment throughout the pregnancy. For example, insulin therapy was used more often (31.3% *vs.* 12.7%, $p$=0.02), and insulin/metformin therapy was introduced more often in those with CGM (31% *vs.* 8%, $p$=0.0419) compared to those with SMBG alone, in the studies by Wei *et al.* [85] and Kestilä *et al.* [84], respectively. In the study by Kestilä *et al.,* the treatment mode was based on CGM or SMBG, depending on the allocated group. Insulin treatment was offered if postprandial measurements were above 8 mmol/L. In contrast, Wei *et al.* reported that treatments were based on SMBG data alone. In the trial by Alfadhli *et al.*, participants were able to view their CGM data in real-time; 52.3% of women in the CGM group reported some response thereafter to correct for hyperglycaemia or hypoglycaemia [86]. Although no differences were observed in insulin therapy or insulin dose between those with CGM and SMBG, 48% had alterations to their management plan based on downloaded CGM glucose profiles. However, the specific CGM metrics and glucose levels that were determined after treatment adjustments were not reported. Additionally, by the last day of CGM sensor wear, there was a significant improvement in glycaemic variability parameters, including mean sensor glucose and SD. In addition to these studies, an RCT conducted in Malaysia in women with GDM found improved HbA1c in women with CGM compared to controls, however, maternal and neonatal outcomes, including birth weight, mode of delivery, preterm birth and neonatal hypoglycaemia, were comparable [87].

Overall, these studies on CGM in GDM patients provide some evidence on the benefits of CGM in terms of treatment modifications and in one study on gestational weight gain. However, as very few maternal and neonatal outcomes were altered with CGM use, it is difficult to determine appropriate glucose targets for CGM which would improve adverse outcomes. Generally, these studies utilise targets between 3.5 and 7.8 mmol/L, similar to recent studies in pregnant women with T1DM, however, the appropriate time to be spent within this range for GDM pregnancy needs to be further studied.

Finally, in addition to those studies discussed, Voormolen *et al.* conducted an RCT in a cohort of women with either T1DM, T2DM, and insulin-treated GDM. The primary outcome was LGA neonates (> 90$^{th}$ centile), which was not significantly different between those with CGM and those with standard care [88]. One significant finding was a lower incidence of preeclampsia in those with CGM (3.5% *vs.* 28.4%; RR: 1.06 [95% CI 0.83-1.37]); however, when subgroup analyses for the type of diabetes were performed, this was restricted to women with T1DM. Another study also showed that mean CGM sensor values gave significantly lower estimates than mean SMBG values in a cohort of women with T1DM, T2DM, and GDM. This was thought to affect the treatment of hypoglycaemia and adjustment of insulin regimens. Other maternal and neonatal outcomes were not assessed [89]. In this cohort of 33 participants, only 4 had T2DM and only 4 had GDM, limiting the findings for these groups of women. Moreover, the heterogenous cohort used is a caveat of these studies as pregnancy outcomes and glycaemic control in women with T1DM, T2DM, and GDM are very different, which makes it difficult to determine whether CGM is beneficial in women with GDM [1, 73, 90].

### 5.2. Additional Information Obtained from Analysing CGM Temporal Glucose Profiles

The extensive volume of data produced by CGM devices can be difficult to analyse and interpret, which has contributed to the reliance on summary statistics, such as TIR, TAR, TBR, and averages. However, the advantage of CGM is that it provides visual information about glucose variations across the 24-hour day, and summary statistical analysis removes much of this useful temporal information. Functional data analysis (FDA) is a technique that allows differences in temporal glucose profiles to be assessed in relation to clinical outcomes, and has been employed by several studies to give additional information about glucose levels in pregnancy using CGM [15, 90, 91]

The previous studies by Murphy *et al.* [16] and Secher *et al.* [82] were re-analysed by Law *et al.* [15] comparing mothers with LGA infants and those without by FDA and standard CGM metrics. Mean HbA1c was 45 mmol/mol, and no differences were observed between mothers of LGA infants and non-LGA infants, indicating both had 'well-controlled' glycaemia. However, in standard CGM metrics, LGA was associated with a lower mean glucose in the first trimester (7 mmol/L *vs.* 7.1 mmol/L, $p<0.01$) and higher mean glucose in the second and third trimesters (7 mmol/L *vs.* 6.7 mmol/L, $p<0.001$ and 6.5 mmol/L *vs.* 6.4 mmol/L, $p<0.01$, respectively). FDA determined the specific times of the day where these differences were apparent, *i.e.*, in the first trimester, glucose values were significantly lower mid-morning (09:00-11:00) and early evening (19:00-21:30). In line with this, these authors also performed FDA on 153 women with GDM who wore masked CGM for 7 days at 30-32 weeks gestation. Mean glucose was significantly higher in mothers of LGA infants compared to those that had appropriate for gestational age (AGA) infants (6.2 mmol/L *vs.* 5.8 mmol/L, $p=0.025$); however, no differences were observed in TIR (3.9-7.8 mmol/L), TAR, TBR or glucose variability measures. FDA demonstrated that women with LGA infants had higher nocturnal glucose for a 6-hour period overnight (00:30-06:30) [90]. Finally, in a recent study, Scott *et al.* [91] performed a secondary analysis of the CONCEPTT study, including pregnant women which had complete birth weight data and over 96 hours of continuous CGM data. The CGM measurements at baseline, 24, and 34 weeks' gestation were assessed. Various comparisons were made, including LGA outcomes *vs.* non-LGA. In mothers of LGA infants, a significantly higher glucose level of 0.4-0.7 mmol/L for 4.5 hours per day (21:00-01:30) was seen at baseline. A significantly higher glucose by 0.4-0.9 mmol/L for 16 hours per day was seen at 24 weeks' gestation, and significantly higher glucose by 0.4-0.7 mmol/L for 14 hours per day was seen at 34 weeks' gestation, predominantly during daytime hours. In all the above studies, LGA was defined as ≥ 90$^{th}$ centile.

Collectively, this research demonstrates the ability of CGM to identify short-term glucose excursions across the 24-hour day, which would go undetected by standard metrics or other methods of glucose monitoring. These studies also show how these excursions can contribute to adverse pregnancy outcomes, such as LGA infants. The ability to observe these subtle glucose fluctuations with CGM in pregnancies complicated by maternal diabetes provides further insight into glucose profiles, which may be useful when determining appropriate targets in these pregnancies.

### 5.3. Continuous Glucose Monitoring Targets and Guidelines

The international consensus for TIR targets was outlined in Battelino *et al.* [74]. Based on this, the glucose target range of 3.5-7.8 mmol/L was outlined for both preexisting diabetes in pregnancy and GDM. The upper limit of 7.8 mmol/L is in line with most SMBG postprandial targets (Table **2**). The lower limit is based on the most recent clinical trials and observational studies in T1DM pregnancies discussed above [75, 76]. For T1DM pregnancies, the percentage of readings within this range should be above 70% or 16 hours and 48 minutes. TBR should be less than 4% or 1 hour below 3.5 mmol/L and less than 1% or 15 minutes below 3 mmol/L, and TAR should be less than 25% or 6 hours above 7.8 mmol/L. These targets were achieved in the Kristensen *et al.* and CONCEPTT studies towards the end of the third trimester. Furthermore, in the CONCEPTT study, twice as many participants managed to achieve HbA1c target of 6.5%, compared to the TIR targets, which suggests that the TIR is a more challenging but appropriate goal [78].

The studies reviewed particularly highlight the benefits of CGM in women with T1DM in pregnancy, which has allowed these TIR targets to be determined; however, for

**Table 3. Use of CGM during pregnancy as recommended by various professional societies.**

| Professional Society | CGM Recommendations | References |
|---|---|---|
| American College of Obstetrics and Gynaecology (ACOG) | - | [37, 38] |
| American Diabetes Association (ADA) | CGM can be used in addition to SMBG to help achieve HbA1c targets but should not be used as a substitute to SMBG to achieve pre- and postprandial targets. | [21] |
| Australian Diabetes in Pregnancy Society (AIDPS) | - | [39, 41] |
| Canadian Diabetes Association (CDA) | Women with T1DM should be offered CGM to improve glycaemic control and to reduce neonatal complications. | [42] |
| Endocrine Society | Use in women with GDM if SMBG levels or in women with preexisting diabetes if HbA1c levels are not sufficient to assess glycaemic control. | [43] |
| National Institute for Clinical Excellence (NICE) | Offered to all pregnant women with T1DM to help them meet their blood glucose targets and improve neonatal outcomes. Flash/intermittently scanned (isCGM) can be offered to pregnant women with T1DM who are unable to use CGM or have a preference.<br>Can be considered for those on insulin therapy, who do not have T1DM, and have severe hypoglycaemia or unstable blood glucose levels. | [28, 93] |

T2DM and GDM, there is limited evidence, and more research is needed to determine the appropriate timings for TIR, TBR and TAR. Nonetheless, CGM use is increasing; therefore, guidelines on the use of CGM from major societies have been summarised in Table **3**. A recent review of the international guidelines for diagnosis and management of GDM also found that most medical societies recommend the use of SMBG and set similar targets for fasting and postprandial glucose. Furthermore, comparable to our findings, CGM was reported to only be used in specific cases, where a stricter control of glucose is required, and no clear CGM targets were defined for those with GDM [92].

## SUMMARY

Based on the studies discussed throughout, all methods of monitoring have shown the potential to predict pregnancy outcomes and demonstrate the importance of controlling glycaemia within defined targets. Although HbA1c is cost-effective and easy to monitor, this method is an average measure of glycaemia over a period of 2-3 months and is therefore widely recommended to be used in combination with SMBG to consider glycaemia daily. Several studies have provided evidence for appropriate targets for SMBG use and have shown that while optimal control is needed to prevent adverse pregnancy outcomes, too 'tight' restrictions may result in maternal hypoglycaemia, particularly in those with T1DM. This is evident in many of the guidelines, which recommend either higher glucose targets to avoid hypoglycaemia or additional evening and overnight measurements to monitor hypoglycaemic episodes. Furthermore, the timing of SMBG is essential in the control of maternal glucose, and several studies have shown that postprandial is the most effective, particularly later in pregnancy and in the prevention of LGA/macrosomic neonates.

In addition to these widely used methods, CGM has been shown to improve pregnancy outcomes and can further provide detailed information on glucose profiles over time, including glycaemic excursions and subtle glucose fluctuations. It also has the important advantage over SMBG of being able to prevent hypoglycaemia, through predictive trend arrows and alerts, allowing women to achieve tighter glucose targets more safely. When used unmasked, CGM can immediately inform the patients of their glycaemic control, allowing self-management of therapy and lifestyle. Clear targets for CGM metrics, such as TIR, have also been defined for pregnant women with T1DM; however, these are less well defined in T2DM and GDM pregnancies due to the lack of evidence, which therefore needs to be studied further. Among all glycaemic monitoring methods assessed, very few studies focus on T2DM pregnancy, which has increased in prevalence in recent years, and which has poor pregnancy outcomes, especially in stillbirth, further supporting the need for further research.

## CONCLUSION

Overall, glucose monitoring in pregnancies complicated by maternal diabetes is essential for appropriate glycaemic control and in preventing adverse pregnancy outcomes. Here, we outline the current evidence that supports the international recommendations and propose that future studies should be directed to T2DM and GDM, and CGM should be implemented further into routine clinical use.

## AUTHORS' CONTRIBUTION

EMS and KF contributed to conceptualization, writing, review and editing of the manuscript, as well as funding acquisition. Literature review, literature curation and writing were done by ARB. KF and ES supervised the study. All authors read and approved the final manuscript.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| (a)OR | = | (Adjusted) Odds Ratio |
| AC | = | Abdominal Circumference |
| ACOG | = | American College of Obstetrics and Gynaecology |
| ADA | = | American Diabetes Association |
| ADIPS | = | Australian Diabetes in Pregnancy Society |
| AGA | = | Appropriate for Gestational Age |
| CDA | = | Canadian Diabetes Association |
| CGM | = | Continuous Glucose Monitoring |
| CSII | = | Continuous Subcutaneous Insulin Infusion |
| CV | = | Coefficient of Variation |
| FDA | = | Functional Data Analysis |
| GDM | = | Gestational Diabetes Mellitus |
| HbA1c | = | Glycosylated Haemoglobin |
| IUGR | = | Intrauterine Growth Restriction |
| LGA | = | Large for Gestational Age |
| MDI | = | Multiple Daily Injections |
| MeSH | = | Medical Subject Headings |
| NCO | = | Neonatal Composite Outcome |
| NICE | = | National Institute for Clinical Excellence |
| NICU | = | Neonatal Intensive Care Unit |
| RCT | = | Randomised Controlled Trial |
| SD | = | Standard Deviation |
| SGA | = | Small for Gestational Age |
| SMBG | = | Self Monitoring of Blood Glucose |
| T1DM | = | Type 1 Diabetes |
| T2DM | = | Type 2 Diabetes |
| TAR | = | Time Above Range |
| TBR | = | Time Below Range |
| TIR | = | Time In Range |

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## CONFLICT OF INTEREST

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