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Review Article

Continuous glucose monitoring in pregnant women with Type 1 diabetes: benefits for mothers, using pumps or pens, and their babies

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What's new?

- The CONCEPTT trial showed that real-time continuous glucose monitoring (CGM) was associated with improvements in maternal glycaemic control and in neonatal health outcomes.
- The number-needed-to-treat with CGM to prevent large-for-gestational-age infants or neonatal intensive care unit admission >24 h was six, and to prevent a case of neonatal hypoglycaemia it was eight.
- Further issues include the use of newer technologies with improved patient satisfaction, and closed-loop therapy may further improve outcomes.
- High rates of large infants despite treatment remain a challenge, and future investigations must assess the impact of dietary factors, glucose variability and information gleaned from metabolomics.

Abstract

Aims To review the current literature on the use of continuous glucose monitoring during pregnancy in women with Type 1 diabetes.

Methods We searched the literature for randomized controlled trials using continuous glucose monitoring during pregnancy in women with Type 1 diabetes.

Results Three randomized trials were found and discussed in this review. One UK study found a reduction in large-for-gestational-age infants; however, only masked continuous glucose monitoring was used in that study. A Danish study used intermittent real-time continuous glucose monitoring and found no differences. The present authors conducted the CONCEPTT trial, in which pregnant women and women planning pregnancy were

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randomized to receive continuous glucose monitoring or standard care. We found a greater drop in HbA_{1c}, more time spent in the target range, and a reduction in some adverse neonatal outcomes in women using continuous glucose monitoring. Numbers-needed-to-treat to prevent a large-for-gestational-age infant, a neonatal intensive care unit admission for >24 h, and a neonatal hypoglycaemia event were low. These findings were seen in both injection and pump users and across all countries. Possible reasons for differences in study findings are discussed. In addition, several issues need further study. Glycaemic variability and differences in dietary intake may also have played a role. Despite excellent glycaemic control, babies continue to be large. More research is needed to understand the role of glucose targets and the dynamic placental processes involved in fetal growth.

Conclusions The use of continuous glucose monitoring in women with Type 1 diabetes in pregnancy is associated with improved glycaemic control and neonatal outcomes. Further research examining the glycaemic and non-glycaemic variables involved in fetal growth and the cost–benefit of using continuous glucose monitoring in pregnancy is warranted.

Introduction

Diabetes is the commonest pre-existing medical condition in pregnancy, affecting 1.5% of pregnancies [1]. Approximately half of all pregnancies in women with pre-existing diabetes are complicated by Type 1 diabetes, and the remainder by Type 2 diabetes and other forms of monogenic diabetes [2]. The prevalence of Type 1 diabetes in young people has doubled in the past two decades, meaning that in the future even more women will enter pregnancy with potentially more complicated Type 1 diabetes and diabetes of longer duration [3]. National audit data highlight the prevalence of suboptimal control of maternal glucose levels before and during pregnancy [2,4–6]. The most recent population-based study reports that only 15%

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of pregnant women achieve target HbA_{1c} levels (≤48 mmol/mol or 6.5%) by the end of the first trimester [2]. Even after intensive multidisciplinary team input, only 40% of pregnant women with Type 1 diabetes achieve this target, which many consider to be too lenient, after 24 weeks' gestation. Furthermore, despite advances in diabetes care outside of pregnancy, with faster-acting insulin analogues and increasing use of continuous subcutaneous insulin infusions, there has been little or no progress in improving maternal glucose control in late pregnancy [2]. Whilst this may be attributable to a combination of glycaemic and non-glycaemic factors, such as higher pre-pregnancy maternal weight and/or gestational weight gain, the consequences are increased risks of complications for the mother, the developing fetus and the newborn infant. These include increased rates of preterm and early preterm delivery, and large-for-gestational-age (LGA) and extremely LGA infants [2,4–6]. Taken together, one in two babies have complications relating to maternal hyperglycaemia, with ~40% being admitted to neonatal intensive care units as a consequence of complications. Compared with appropriate-weight infants (birthweight between 10^{th} and 90^{th} percentile), LGA infants have more labour complications (birth trauma, shoulder dystocia), more emergency Caesarean sections, and more neonatal morbidity (hypoglycaemia, jaundice, respiratory distress). There is an emerging body of evidence indicating that they may also have an increased risk of cardiac and metabolic disease in later life (overweight, obesity, insulin resistance, Type 2 diabetes) [7,8]. The importance of optimal maternal glucose control for healthy mother/infant outcomes is unquestioned, but the means by which to achieve the tight recommended glycaemic control targets are unclear.

Longitudinal studies of continuous glucose monitoring (CGM) highlight the gap between the recommended glycaemic control targets (3.5–7.8 mmmol/l) and the day-to-day glucose control achieved in real life [9]. It is a decade since we first described objectively measured day-to-day glucose control using 140 CGM profiles, each lasting 5–7 days, in 40 pregnant

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women with Type 1 diabetes [9]. Women were aged 31.1±6.1 years, with a diabetes duration of 18.5±9.3 years, booking HbA_{1c} concentration of 55 ± 4.46 mmol/mol (7.2±1.7%) and BMI 25.5 ± 4.5kg/m^2, and more than 70% of the women had planned their pregnancies. The time spent in target range was 43% (10.4 h/day) in the first trimester, 49% (11.8 h/day) in the second trimester and 56% (13.5 h/day) in the third trimester. This was accompanied by reductions in maternal HbA_{1c} from 51 mmol/mol (6.8%), 46 mmol/mol (6.4%) and 41 mmol/mol (5.9%) in each trimester, with corresponding mean glucose levels of 7.6 mmol/l, 7.1 mmol/l and 6.6 mmol/l [9]. These data opened our eyes to the complexity of glucose control and the limitations of conventional markers of glucose control. It also raised the question of whether these detailed CGM glycaemic profiles may be more helpful to pregnant women than standard self-monitoring of blood glucose (SMBG).

Studies comparing the use of SMBG with CGM readings taken in pregnant women with diabetes found that SMBG missed ~192 min or 3.2 h of hyperglycaemia per day [10]. It took 1–4 h for nocturnal hypoglycaemia to be detected by clinical symptoms or finger stick readings [10] The CGM device reads interstitial glucose continuously, producing 288 glucose readings per day. With masked CGM, glucose readings are recorded and retrospectively reviewed by the user and caregiver later, and can be used to adjust insulin dose, dietary intake and lifestyle choices, such as timing of snacks and physical activity. With real-time CGM, glucose readings are transmitted to a display (increasingly available on mobile phones or smartwatches) showing what is happening to glucose readings in real time. Alarms can be set to alert the person of high and low glucose readings that are either immediate or pending, allowing the person to respond to these readings as they occur.

Randomized trials in non-pregnant populations have shown that the use of CGM is associated with reduced HbA_{1c} and reduced exposure to hypoglycaemia [11]. There have been three randomized controlled trials of CGM in pregnant women. The first was a study from East

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Anglia, UK where 71 pregnant women (46 with Type 1 and 25 with Type 2 diabetes) were randomized to intermittent masked CGM every 4–6 weeks during the pregnancy or usual care, which involved SMBG before and after meals and bedtime (i.e. seven to 10 times per day) [12]. Women who were randomized to CGM had a lower HbA_{1c} concentration by the end of the pregnancy, and smaller babies (a reduced median customized birthweight centile, and a reduced rate of LGA infants >90th percentile) compared with women in the usual care group (Table 1). While these results were encouraging, the masked CGM device used in the study was very quickly superseded by real-time CGM; thus, by the time the study was completed and the data were published, the technology was already outdated.

The second randomized trial was from Denmark, where 154 women (123 women with Type 1 and 31 with Type 2 diabetes) were randomized to either intermittent real-time CGM for 6 days on five occasions (at 8, 12, 21, 27 and 33 weeks' gestation) during pregnancy or usual care [13]. The investigators found no between-group differences either in glycaemic control, or in pregnancy outcomes. As expected, maternal HbA_{1c} improved during pregnancy: 49 mmol/mol (6.6%), 42 mmol/mol (6.0%) and 43 mmol/mol (6.1%) in CGM users (with Type 1 diabetes) with similar reductions from 51 mmol/mol (6.8%) to 44 mmol/mol (6.2%) in the control group at 8, 21 and 33 weeks. One of the possible reasons could be that women started their pregnancies with good glycaemic control, as measured by maternal HbA_{1c} levels, with perhaps little room for movement. In addition, only 64% of the participants used CGM as per protocol, and very few (only five women) chose to use it continuously. They did not report CGM data either in the intervention or control group. The SMBG data provided at 8, 12 and 33 weeks were very similar to those obtained in participants using CGM in the UK study, with median (range) values of 6.9 (5.7–8.9) mmol/l, 6.5 (5.1–8.8) mmol/l and 6.3 (4.7–7.9) mmol/l. Whilst the Danish study was conducted in an international centre of excellence in Diabetes Pregnancy, women in both the CGM and intervention groups had only 58% of

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SMBG levels in the recommended target range of 4.0 to 8.0 mmol/l. Both the Danish and UK studies reported high rates of maternal hypoglycaemia (13% of SMBG users ≤3.9 in Denmark and 14.6% of CGM users in the UK). The Danish study used an older-generation real-time CGM sensor which many women found inaccurate and uncomfortable [14]. There was no run-in phase so, whilst the study included a very representative group of women attending routine clinics, many were not prepared to cope with the burdens and frustrations of CGM. There were also frequent reports of alarm fatigue, which is not surprising given that 40% of the time or ~10 h per day was spent outside the recommended target range.

The CONCEPTT trial was designed by the present authors in close collaboration with the Danish investigators to overcome many of the practical, logistical and methodological challenges they experienced. Firstly, we included a run-in phase, which is probably unnecessary with current-generation sensors, but allowed us to recruit women with some experience of CGM, who would be better able to provide informed consent and potentially be more willing to use it if randomized to the intervention group. Secondly, we excluded women with optimal glucose control, defined as booking HbA_{1c} levels ≤ 48 mmol/mol (6.5%), and/or regular CGM users who may not have equipoise between the intervention and control group. Thirdly, we developed CGM training programmes for the participants and clinical teams providing insulin dose adjustment algorithms to the insulin pump and for multiple daily injection (MDI) users allocated to CGM or SMBG. Fourthly, in addition to maternal HbA_{1c}, we collected detailed CGM data from both the intervention and control groups. Finally, we included women who were planning pregnancy as well as women in early pregnancy. Full details of the clinical study protocol have been published [15]. In brief, women with Type 1 diabetes who were pregnant or planning pregnancy, were randomized to receive either real-time CGM or usual care with SMBG seven times per day. Regarding insulin delivery, women could be using either MDI or insulin pump therapy. To be eligible for randomization, the

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women had to complete a run-in phase using masked CGM for at least 5 days. This also provided detailed baseline data for CGM measures. Randomization was stratified by type of insulin delivery and by baseline HbA_{1c}. Women in the control group were asked to perform masked CGM at 12 and 24 weeks or at conception in the planning pregnancy trial, and at 24 and 34 weeks' gestation in the pregnancy trial. Women in both groups had the same glucose (3.5–7.8 mmol/l) and HbA_{1c} targets and ≤48 mmol/mol (6.5%) if pregnant and ≤53 mmol/mol (7.0%) if planning pregnancy. As noted earlier, all women were given personalized insulin dose adjustment algorithms based on those developed for the pivotal Juvenile Diabetes Research Foundation CGM trial [16] and modified for pregnancy, and according to Dose Adjustment for Normal Eating (DAFNE) programme principles.

We chose maternal HbA_{1c} level at 34 weeks' gestation as the primary outcome measure, based on its strong clinical validity and established association with obstetric and neonatal outcomes. Only central laboratory HbA_{1c} levels were used. Prespecified secondary glycaemic outcomes were episodes of mild and severe hypoglycaemia, CGM measures of time spent above, below and in the target range, and glycaemic variability. Standard obstetric and neonatal health outcomes were used with careful definitions to avoid variations in clinical practice across the 31 study sites [17]. For example, neonatal intensive care unit admission was counted only if it was of at least 24 h duration and neonatal hypoglycaemia only if treated with intravenous dextrose.

Whilst the groups were well balanced in terms of maternal demographic and clinical characteristics, there were some minor differences [17]. The CGM group had a 1-year longer duration of diabetes and higher BMI (~0.5 kg/m^2), while the control group had more cigarette smokers (21 vs 12%) and fewer women with college level education (72 vs 81%). Adherence to the clinical study protocol was good, with high rates of women completing the study visits and frequent between-visit telephone and email contacts. Whilst CGM sensor compliance

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was generally good (median 6.1 days/week), pregnant women required additional support and training with additional contacts for CGM and for CGM-related diabetes management issues.

The between-group difference in maternal HbA_{1c} levels was small, –0.2%, with an absolute reduction of –0.54% in the CGM group compared with –0.35% in the control group (*P*=0.04). Sixty-six percent of women in the CGM group and fifty-two percent of women in the control group achieved target HbA_{1c} levels. The most striking difference between the CGM and SMBG groups was in the directly observed CGM measures, with women in the CGM group spending an additional 1.7 h or ~100 min/day in target range at 34–35 weeks' gestation. This was mainly attributed to reduced time spent in hyperglycaemia (~1.2 h or 70 min/day) in CGM users. There were no differences in rates of hypoglycaemia, which were notably low in both groups (3% CGM and 4% SMBG).

The rates of severe hypoglycaemia were notably lower than in earlier CGM studies (18 CGM users, 21 controls) between randomization and 36 weeks' gestation. The trial was not powered to detect differences in time spent below target (3% vs 4%), with a non-significant 15 min less time spent in hypoglycaemia for pregnant women randomized to CGM. Interestingly, the CGM treatment effect was comparable in insulin pump and MDI users, with both achieving mean CGM glucose levels of 6.7 mmol/l and 66–69% time in target range [17], although MDI users had lower HbA_{1c} levels.

Although the magnitude of the average CGM treatment effect was similar in women planning pregnancy (a –0.2% lower HbA_{1c} concentration) the intra-individual variability was greater, and the between-group difference was not statistically significant [17]. Interestingly, there was a positive association between CGM compliance and treatment response in women planning pregnancy, which was not apparent in pregnant women.

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There was a trend towards 0.8 kg more gestational weight gain in control group mothers (9.7 kg vs 8.9 kg from 16 to 34 weeks; *P* =0.09), consistent with the finding that improvements in glucose control in CGM users was not accompanied by higher rates of hypoglycaemia or higher total daily insulin doses. Gestational age at delivery was very similar (median (interquartile range) 37.4 (36–38) weeks' gestation), with no differences in rates of maternal hypertensive disorders or preterm deliveries (~40% <37 weeks' gestation). the median birthweight centile was significantly lower in infants of mothers using CGM (92^{nd} vs 96^{th} percentile; *P*=0.05) calculated using Gestation Related Optimal Weight (GROW) customized percentiles, adjusted for maternal ethnicity, height, weight and neonatal sex and gestational age.

While mean birthweight was similar between the groups (3.5 kg), of more clinical relevance is the spread of birthweight centiles, indicating that more CGM babies were closer to the normal weight range and they had a lower rate of LGA neonates (53% vs 69%; *P*=0.02). As in other Type 1 diabetes populations, there were fewer than expected small-for-gestational-age infants (only 2% in both groups). The between-group differences in birthweight centiles, with a halving of the odds ratio for LGA infants, were seen across the UK, Canada, Italy and Spain. The precise mechanism for this clinically relevant reduction, is unclear but is probably related to mothers using CGM spending, on average, 100 min less time in hyperglycaemia and/or reductions in glycaemic variability measures. The finding that only six mothers using CGM were required to prevent one LGA infant, across a range of clinical settings suggests that CGM is of benefit in settings with higher and lower baseline LGA rates.

An earlier analysis of the combined UK and Danish CGM datasets, reported no differences between maternal glucose control (measured either by HbA_{1c} or CGM time in target) in mothers of infants that were and were not LGA [18]. During the third trimester, the mean CGM glucose levels were slightly lower in mothers of appropriate birthweight infants (6.4 vs

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6.5 mmol/l), as was the lability index, one of the many markers of glycaemic variability [18]. They also suggested that having an LGA infant may be associated with maternal hypoglycaemia during the first trimester. It is difficult to understand all the dynamic placental processes throughout pregnancy, with some suggesting that 'fetal glucose steal' may be relevant in early gestation [19]. Another possible explanation is that better glucose control early on is associated with remodelling of the spiral arteries to ensure adequate blood flow, with a larger (and presumed healthier) placenta supporting growth of a baby, which becomes larger later in pregnancy because glucose levels and other metabolites, while improved, are still too elevated.

Whilst the longer-term consequences of LGA offspring in Type 1 diabetes are unknown, there is no doubting the impact of neonatal hypoglycaemia, which separates mothers and babies and negatively affects rates of breastfeeding. The infants of CGM mothers had almost half as many episodes of neonatal hypoglycaemia requiring treatment with intravenous dextrose (15% vs 28%; *P*=0.02). In addition, and most likely related to the lower rates of LGA infants and neonatal hypoglycaemia, fewer infants of CGM group mothers were in the neonatal intensive care unit for >24 h (27 vs 43%; *P*=0.02). Overall, infants stayed 1 day less in hospital (3.1 vs 4.0 days; *P*=0.02). Notably, one needs to treat only six women with CGM to prevent one LGA infant and one neonatal intensive care unit admission >24 h, and eight women to prevent one neonatal hypoglycemic event.

We conducted CONCEPTT, the largest study examining CGM in pregnant women with Type 1 diabetes, and the only study examining the use of CGM in pregnancy from the first trimester to delivery. Our study was multicentre and multinational, with consistent findings across countries, making the results applicable to all pregnant women on intensive insulin therapy, including both pump and MDI users. It is the only Type 1 diabetes pregnancy trial to date with detailed CGM measures in the intervention and control groups. Furthermore, in

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addition to routine clinical assessments of maternal HbA_{1c}, we used a single laboratory for central HbA_{1c} measurement. For a variety of reasons, pregnancy losses, missed appointments, lost samples and antenatal admissions, we were missing HbA_{1c} levels in 20% of women. More women in the CGM group had unscheduled contacts (which included face-to-face visits, telephone and email communications), primarily for CGM-related reasons, although given the high rates of skin reactions and the stringent reporting of adverse events required from a randomized trial, this is hardly surprising. Unfortunately, we do not have data regarding the additional healthcare time required to support women learning to integrate CGM into their diabetes self-care. The time required is likely to be both device- and person-specific and is also dependent on the resources provided by device manufacturers (YouTube training videos, 24-h telephone support lines etc.).

Several questions remain for further discussion. Approximately 80% of women reported frustrations with the older-generation CGM used. Many of the CGM burdens will be alleviated by more modern sensor technology, such as the Guardian Sensor 3, FreeStyle Libre or Dexcom G4/G5. Unfortunately, no device other than the FreeStyle Libre is specifically indicated for use in pregnancy. The FreeStyle Libre does not incorporate all the features of real-time CGM so results from CONCEPTT cannot be extrapolated to that device. We anticipate similar, if not better, results from the latest-generation Dexcom and Medtronic devices. Can the small difference in HbA_{1c} account for the large reductions in neonatal outcomes? Although high HbA_{1c} concentration is likely to be a good overall indicator of risk during pregnancy, it may not accurately reflect dynamic changes in glycaemic changes during pregnancy. The CGM measure of time in target may be a more sensitive indicator of glycaemic control, although it could be argued that the target range is still too lenient. Can 70 min per day less hyperglycaemia and 100 min per day more time in target range lead to the observed improvements in neonatal outcomes? Whilst the role of maternal hyperglycaemia

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is well established in the development of neonatal complications, there may have been other glycaemic and non-glycaemic effects from CGM. We found that women using CGM had less glucose variability. Glucose variability, independent of hyperglycaemia, is increasingly implicated in the development of diabetes complications and may play a role in spiral artery remodelling, placentation and fetal growth. In addition, women using CGM may have changed their diet in response to seeing their glycaemic profiles. Earlier data using stable-label isotope tracers indicated the appearance of evening meal-related glucose for up to 6 h postprandially [20,21]. A prespecified analyses of maternal dietary intake in UK study participants will help to understand the impact of CGM on eating behaviour during pregnancy.

Overall, our infants were quite large despite the excellent time in glucose target range. Further studies need to elucidate whether our glucose targets are too lax given normal glucose values in pregnancy are lower, or whether we need to improve on other non-glycaemic targets, such as overall energy or specific macronutrient intake and gestational weight gain. Contributions of other variables such as maternal obesity need to be further examined. Studies assessing metabolomics in women who did and did not have LGA babies may help elucidate other important factors contributing to fetal growth acceleration.

Previous reviews have suggested that using CGM in conjunction with insulin pump therapy may improve pregnancy outcomes [21]. The data from CONCEPTT show that CGM is of equal benefit to pump and MDI users and to women with higher and lower HbA_{1c}, although we cannot comment on use among women with near-optimal peri-conception glucose control. Authors of future studies should be aware of the limitations of HbA_{1c} and consider CGM time-in-target as a primary outcome measure [22]. We hope that subsequent analyses of data from CONCEPTT will further our understanding of the complex relationships between conventional and novel markers of glycaemic control and pregnancy outcomes. Another

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important area of investigation will be to identify which women benefit most from CGM and which women are potential candidates for closed-loop insulin delivery [23].

There will be some who say that advances in CGM and insulin pump technology have not yet lived up to the expectations of people with diabetes or healthcare practitioners. There will be no single 'magic bullet' or revolutionary cure, but anything that helps the majority of pregnant women spend more time with glucose levels in the target range and has beneficial healthcare outcomes for the newborn should be adopted, especially when the numbers-needed-to-treat suggest the potential for cost-effectiveness. Sensor-integrated or automated insulin delivery is definitely an exciting frontier for Type 1 diabetes pregnancy [24], but in the meantime women using injections or pumps with CGM can achieve close to 70% time-in-target-range. Faster-acting insulins, newer-generation CGM devices and/or closed-loop systems might be needed to prevent postprandial highs which may help reduce neonatal adverse outcomes even further.

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Competing interests

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Table 1 Comparison of outcomes in randomized trials using continuous glucose monitoring

Variable	**Murphy *et al.* [12]**	**Secher *et al.* [13]**	**Feig *et al.* [17]**
HbA_{1c} reduction in intervention group: intervention vs controls	Mean difference 0.6% (*P*=0.007) 39.3 vs 46.4 mmol/mol (5.8% vs 6.4%)	HbA_{1c} 43 (32–62) vs 43 (29–66) mmol/mol (6.1% vs 6.1%); *P* = 0.39	Mean difference −0.19%, 95% CI −0.34 to −0.03 (*P*=0.0207)
CGM: time spent in target range (3.5 mmol/l to 7.8 mmol/l)	Not done	SMBG time in target (4.0 to 8.0 mmol/l) 58% vs 58%	68% vs 61% (*P*=0.0034)
CGM: time spent above target range (3.5 to 7.8 mmol/l)	Not done	Not done	27% vs 32% (*P*=0.0279)

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LGA reduction in intervention group; intervention vs controls	Odds ratio 0.36, 95% CI 0.13 to 0.98 (*P*=0.05); 13% vs 18% (*P*=0.05)	45% vs 34% (*P* = 0.19)	Odds ratio 0.51, 95% CI 0.28 to 0.90 (*P*=0.021); 53% vs 69% (*P*=0.021)
Birthweight centile: intervention vs controls	Median birthweight centile 69 vs 93 (*P*= 0.02)	Birthweight z-score 1.07 (–2.32 to 3.78) vs 0.66 (–1.13 to 3.45) *P*=0.20	Median customized centile 92 vs 96 (*P*=0.0489)
Neonatal hypoglycaemia: intervention vs controls	3% vs 5% (*P*=0.5)	36% vs 40% (*P*=0.62) Severe neonatal hypoglycaemia requiring intravenous glucose 13% vs 14% (*P*=0.88)	Severe neonatal hypoglycaemia requiring intravenous glucose 15% vs 28% (*P*=0.025)
NICU admissions >24 h: intervention vs controls	Any admission to NICU: 9% vs 6% (*P*=0.8)	Not done.	27% vs 43% (*P*=0.0157)

NICU, neonatal intensive care unit; SMBG, self-monitoring of blood glucose.

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