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REVIEW ARTICLE

Type 1 diabetes and pregnancy: An update on glucose monitoring and insulin treatment☆

Judit Amigó[a,*], **Rosa Corcoy**[b,c,d]

[a] *Servei d'Endocrinologia i Nutrició, Hospital Vall d'Hebron, Barcelona, Spain*
[b] *Servei d'Endocrinologia i Nutrició, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[c] *Institut de Recerca, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[d] *Centro de Investigación Biomédica en Red de Bioingeniería, Biomateriales y Nanomedicina, Instituto de Salud Carlos III, CIBER-BBN, Madrid, Spain*

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Abstract The relevance of type 1 diabetes during pregnancy stems from its impact on the health of mother and offspring and its increasing prevalence. Glycemic control during pregnancy is one of the main risk factors for adverse events. Besides, treatment becomes a major challenge not only due to the modifications in insulin requirements due to changes in hormones and cytokines but also to the stricter control targets. Given the recent appearance of new ultra-rapid and basal insulin analogues and the constant evolution of technology to treat people with diabetes, we review these aspects in relation to the treatment of women with type 1 diabetes during pregnancy.

PALABRAS CLAVE
DM1;
Gestación;
Monitorización;
Insulina;
Tecnología

Actualización en el tratamiento insulínico y la monitorización de la glucosa en gestantes con diabetes tipo 1

Resumen La relevancia de la diabetes tipo 1 durante a la gestación deriva de su impacto en la salud de madre e hijo y de una prevalencia en aumento. El mayor riesgo se debe en gran medida al grado de control glucémico durante el embarazo. Por su parte, el tratamiento

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* Corresponding author.
E-mail address: juditamigo@gmail.com (J. Amigó).

supone un reto ya que a los objetivos de control más estrictos se le suman las modificaciones en los requerimientos de insulina debido a los cambios hormonales y de citocinas. Ante la reciente aparición de nuevos análogos de insulina ultrarrápida y basal y la constante evolución de la tecnología para el tratamiento de las personas con diabetes, revisamos estos aspectos en relación al tratamiento de las mujeres con diabetes tipo 1 bajo la perspectiva de embarazo.

Introduction

In recent years, the prevalence of pregestational diabetes in Spain has been increasing.[1] According to recent articles, the prevalence of type 1 diabetes (T1DM) in particular rose from 0.14% to 0.20% between 2006 and 2015 in the Catalan population[1] and from 0.18% in 2009 to 0.24% in 2015 in the Spanish population.[2]

Diabetes fosters the development of complications in pregnant women, foetuses and newborns in relation to exposure to hyperglycaemia during pregnancy. At the same time, the disease itself and the associated complications may be seen to be affected by physiological changes in the different stages of pregnancy.[3] Against this backdrop, new maternal blood glucose monitoring devices as well as new-generation insulins appear to be allies in tackling the challenge that the management of these patients still represents.

Metabolic control and pregnancy

Most Spanish and international guidelines recommend HbA_{1c} levels <6.5% as a first-trimester target,[3,4] highlighting the importance of pregestational control. Periconception HbA_{1c} levels are directly associated with rates of congenital malformations. HbA_{1c} levels <6.5% are associated with a slightly higher risk of malformations than that seen in pregnancies not complicated by diabetes, whereas HbA_{1c} levels ≥10% are associated with a risk of malformations of 20%–25%.[3] The most common are cardiac, renal and neural tube defects. The higher risk of miscarriage in women with diabetes has been attributed to a higher risk of foetal dysmorphogenesis in relation to hyperglycaemia, as well as uteroplacental insufficiency and immunological factors.[3]

Target HbA_{1c} levels decrease during pregnancy given the lower rates of foetal adverse events in patients with HbA_{1c} levels <6% in observational studies. As such, the American Diabetes Association (ADA) recommends achieving HbA_{1c} levels <6% in the second and third trimester, since this is associated with lower prevalences of large-for-gestational-age (LGA) newborns, preterm birth and pre-eclampsia, if such levels can be achieved safely.[4] Due to the risks associated with episodes of severe hypoglycaemia, target HbA_{1c} levels can be relaxed to 6%–7% in patients who have such episodes. The British National Institute for Health and Care Excellence (NICE) guidelines, for their part, recommend maintaining the same target HbA_{1c} levels — <6.5% — throughout pregnancy, if they can be achieved without problematic episodes of hypoglycaemia (defined as ≥2 episodes per year of severe hypoglycaemia or one episode accompanied by loss of symptoms or significant lability, great fear or maladjusted behaviour).[5]

While blood glucose control that is as normal as possible during pregnancy is desired, physiological changes in pregnancy affect blood glucose control, making stable control difficult: in addition to the hyperglycaemia-inducing effects of the increase in diabetogenic hormones (cortisol and chorionic gonadotropin) and cytokines (tumour necrosis factor and leptin),[6] pregnancy can increase the frequency of episodes of hypoglycaemia and their perception.[7] These changes give rise to increased insulin requirements in the first few weeks (peaking around week nine), followed by decreased requirements (with a nadir around week 16) attributed to a decrease in progesterone and thyroid hormones along with a possible increase in C-peptide levels.[8–10] During the second half of pregnancy, requirements gradually increase, especially between weeks 28 and 32, peaking around week 37.[8] As mentioned, the increase in requirements is multifactorial, being due to changes in hormone and cytokine levels[6] and possibly other factors such as circulating exosomes.[6,11] Insulin requirements may decrease at the end of the third trimester.[3,8] This decrease has been attributed to placental insufficiency, though not by consensus in the limited references available.

In women with T1DM, initial studies by McManus and Ryan[12] and Steel et al.[13] found no differences in perinatal outcomes. In a subsequent study by Achong et al.,[14] newborns of women who showed a ≥15% decrease in insulin requirements at the end of pregnancy more often had a low five-minute Apgar score but had less need for neonatal intensive care unit (NICU) admission. By contrast, differences were seen in two studies by Padmanabhan, one retrospective[15] and the other prospective.[16] Pregnant women with a ≥15% decrease in insulin requirements after their requirements peaked had quadruple the rate of a combination of results indicative of placental dysfunction.[16] In the prospective study, the most salient unfavourable outcome was pre-eclampsia (odds ratio [OR] 6.76), and the group with a decrease in requirements showed abnormal expression of antiangiogenic placental factors (but not of hormones or cytokines).[16] However, in these two studies, two thirds of the women had T2DM and one subgroup was treated with metformin; therefore, it would be desirable to confirm their results in women with T1DM, preferably in other geographical areas.

Immediately after birth, insulin sensitivity increased following placental expulsion,[3] although the marked change in sensitivity could not be linked to changes in weight, lipids, adipokines or cytokines.[17] As a result, insulin requirements in the immediate postpartum period decrease by up to ≃50% compared to pre-pregnancy requirements, and therefore insulin doses must be decreased to reduce the risk of hypoglycaemia.[3]

The decrease in postpartum insulin requirements in women with T1DM occurs regardless of the type of insulin therapy they receive. Their return to pre-pregnancy insulin doses occurs gradually between six and eight weeks after birth, although it may take up to four months. The reduction in insulin requirements is more marked in women with T1DM who breastfeed.[18]

Although women with T1DM face certain obstacles to breastfeeding, it has known benefits for newborns and mothers.[19] In women with T1DM, it has been shown to reduce glycaemic variability compared to mothers with diabetes who use formula feeding.[20] As their blood glucose targets are the same as in other people with T1DM, their treatment should be changed when their insulin requirements (which are up to 36% lower compared to women who do not breastfeed) decrease.[21] A group of 13 women who used Medtronic 554/754/640G, Animas or Accu-Chek Insight pumps who ingested 210 g of carbohydrates per day and breastfed required a 14% drop from their baseline rate and a 10% increase in their carbohydrate-to-insulin ratio compared to before pregnancy.[22] During the first six months of the postpartum period, 70.8% were in the target range (72–180 mg/dl), and 3.8% were below 72 mg/dl. Pump settings were barely adjusted between month one and six after birth.[22]

Ketogenesis is seen to increase in pregnancy, especially in the third trimester, as an alternative source of energy for the foetus.[23] The foetus's brain, kidneys and liver contain enzymes capable of metabolising ketones.[23] The recommendation to avoid ketogenesis during pregnancy is based on the association between elevation of the mother's ketone bodies and a lower intelligence quotient in the mother's offspring;[24] however, this association has not been consistently demonstrated. Therefore, normal levels of ketone bodies during pregnancy are not yet known, and the question of whether their gradual increase may harm the foetus, not only by harming the brain but also by increasing the risk of heart rate deceleration and oligohydramnios, also remains unanswered.[23] In addition to other questions on the importance of ketone bodies during pregnancy, their determination has recently gained more significance due to increased adherence to low-carbohydrate diets and differences between methods that use blood and urine for monitoring.[23]

Home monitoring of diabetes control

Table 1 specifies the widely-followed self-monitoring of blood glucose (SMBG) targets recommended by the ADA.[4] Continuous glucose monitoring (CGM)[25] and ketone body targets are also included.[23]

There is a consensus across associations that the recommendation of SMBG in pregnant women with T1DM should include preprandial measurements (to be able to include correct insulin doses), postprandial measurements (to assess and potentially correct glycaemic excursions) and nighttime measurements (to assess whether the figures are in the desired range).[4,18]

Table 1 Gestational metabolic control targets.

Preprandial capillary blood glucose 70–95 mg/dl
1-h postprandial capillary blood glucose 110–140 mg/dl
2-h postprandial capillary blood glucose 100–120 mg/dl
TIR 63–140 mg/dl >70%
TBR < 63 mg/dl <4%
TAR > 140 mg/dl <25%
No significant hypoglycaemia or ketone bodies

TAR:time above range; TBR: time below range; TIR: time in range.
Adapted from the American Diabetes Association.[4]

Table 2 compiles the recommendations of different guidelines on the circumstances and timing of SMBG and the determination of ketone bodies in pregnancy.

Continuous glucose monitoring

CGM is a relatively new technology that continuously measures glucose in interstitial tissue. In recent years, its benefits for people with diabetes, especially type 1 diabetes, have been extensively demonstrated. There are two modalities: real-time continuous glucose monitoring (RT-CGM), which provides the patient with information at all times and may or may not require calibration by means of capillary blood glucose checks; and flash, or intermittent, glucose monitoring (FGM) systems, which do not require calibration and provide a reading whenever the patient brings the receiver close to the sensor. During pregnancy, both strict blood glucose control targets and constantly changing insulin requirements demand increased glucose information, thus rendering CGM a very useful tool.[5,18]

Reliability of CGM systems in pregnancy

The first RT-CGM device to appear on the market was the Guardian REAL-Time system in 2006, which led to the development of the Guardian Sensor 3 system with much more accurate results. The mean absolute relative difference (MARD) of the Guardian Sensor 3 system in the abdomen is 10.5% with calibrations twice daily and 9.5% with calibrations three to four times daily; the corresponding figures in the arms are 9.1% and 8.7%, respectively. As there are no specific data in pregnancy, the same parameters are assumed.[26] In 2020, a study on the reliability in pregnancy of the Dexcom G6® RT-CGM system and its corresponding approval for use during pregnancy was published. Thirty-two pregnant women with T1DM, type 2 diabetes (T2DM) or gestational diabetes in the second or third trimester of pregnancy were studied. Compared to the reference method, 92.5% of CGM values were ±20%/20 mg/dl. The overall MARD was 10.3%; MARDs by location used were 11.5% in the abdomen, 11.2% in the upper buttock and 8.7% in the upper arm.[27]

Table 2 Recommendations on frequency of capillary blood glucose and ketone body monitoring in pregnant women with T1DM in different clinical practice guidelines.

Monitoring	Diabetes Canada[18]	NICE[5]	GEDE[3]	ADA[4]
SMBG	Preprandial + postprandial	Baseline + preprandial + 1-h postprandial + night-time daily	3 preprandial + 3 postprandial daily +/− night-time	Baseline + preprandial + postprandial
Ketone bodies	Not mentioned	Ketonaemia if hyperglycaemia or malaise	Baseline ketonuria and if capillary blood glucose >200 mg/dl	Have test strips

ADA: American Diabetes Association; GEDE: Grupo Español de Diabetes y Embarazo [Spanish Diabetes and Pregnancy Group]; NICE: British National Institute for Health and Care Excellence; SMBG: self-monitoring of blood glucose.

Regarding the Freestyle Libre® FGM system (Abbott), its reliability in measuring glucose is reasonable for use in pregnant women with T1DM, T2DM or gestational diabetes regardless of treatment received or other parameters such as age or body mass index.[28] A study by Scott also led to its approval for use in pregnancy. In this study, published in 2018, the overall MARD was 11.8%. For values <5.6 mmol/l (100 mg/dl), the mean absolute difference was 0.53 mmol/l (9.6 mg/dl), while for values ≥5.6 mmol/l (100 mg/dl), the MARD was 11.7%.[28] There were no adverse effects resulting from use of the device.[28] It should be noted that, at present, the FreeStyle Libre 2 device has hypoglycaemia and hyperglycaemia alarms. It shares this characteristic with RT-CGM but lacks alarms that predict hypoglycaemic and hyperglycaemic events, which RT-CGM does have.

The FreeStyle Libre® and Dexcom G6® systems both have the option of non-adjuvant use (with no need for calibration), while the Medtronic system does require it. However, there is no evidence from randomised controlled trials (RCTs) on the effects of the use of these two systems compared to SMBG® on blood glucose control or perinatal outcomes. The GlucoMen Day® RT-CGM system from Menarini and the implantable Eversense® system from Senseonics have neither evidence of reliability nor an indication in pregnancy. Table 3 summarises the main sensors and associated treatments marketed in Spain and their indication for pregnancy.

Studies directly comparing different systems are limited, especially in pregnancy. Hence the noteworthiness of a recently published article[29] comparing Freestyle Libre® FGM to RT-CGM from Medtronic (Envision® Pro) for seven days in the first trimester of pregnancy. Mean glucose measured with the two devices was similar, but Freestyle Libre® FGM readings were higher in a 24-h period and lower at night-time (time below range [TBR] 6.5% versus 0%). Therefore, adjustments to prevent episodes of hypoglycaemia can clearly vary depending on the method used.

Table 3 Main CGM and CSII systems on the Spanish market and their indication in pregnancy.

CGM	Indication in pregnancy	Insulin therapy
FreeStyle Libre 2®	Yes	MDI
		CSII (not integrated)
Enlite Connect 3®	Yes	MDI
		CSII (preferably as a Medtronic MiniMed 640 G® integrated system)*
Dexcom G6®	Yes	MDI
		CSII (preferably with Tandem-t:slim x2® as a Basal-IQ integrated system)*
GlucoMen Day® Eversense®	No Off-label use can be considered in case of allergy to FreeStyle Libre®, Enlite Connect® and Dexcom®	MDI CSII (not integrated)

CGM:continuous glucose monitoring; CSII: continuous subcutaneous insulin infusion; MDI: multiple-dose insulin therapy.
* Medtronic MiniMed 670G® and 780G® hybrid closed-loop systems and the Control-IQ system that uses Dexcom G6® and Tandem-t:slim x2® have no indication for pregnancy.

Most important studies and clinical practice guidelines

The literature on this subject is limited and relatively recent. Two major clinical trials compared RT-CGM to SMBG in pregnancy (see Table 4), and a meta-analysis was performed with the data from those trials.

In 2013, Secher et al. published a study with a target population consisting of women with pregestational diabetes and a single pregnancy of less than 14 weeks. They were randomised to SMBG with or without intermittent RT-CGM (Guardian REAL-Time®).[30] No statistically significant differ-

Table 4 Benefits seen in clinical trials of RT-CGM in pregnant women with type 1 diabetes.

	Secher 2013[30]	Feig 2017[31]
Type of study	RCT	RCT
Control group	SMBG	SMBG
Intervention group	Intermittent RT-CGM (Guardian REAL-Time®)	RT-CGM (Guardian REAL-Time®)
Maternal outcomes	NS	TIR (%): mean difference 7 (2.57—11.43)*
		HbA_{1c} (%): mean difference −0.18 (−0.36—0.00)*
		HbA_{1c} <6.5% (n): RR 1.27 (1—1.62)*
Foetal outcomes	NS	Neonatal hypoglycaemia: RR 0.54 (0.31—0.94)*
		>24-h NICU admission: RR 0.63 (0.42—0.93)*
		LGA: RR 0.77 (0.61—0.96)*

The text describes the meta-analysis of the results.
FGM:flash glucose monitoring; LGA: large for gestational age; NICU: neonatal intensive care unit; NS: not significant; RCT: randomised clinical trial; RT-CGM: real-time continuous glucose monitoring; SMBG: self-monitoring of blood glucose; TIR: time in range.
* 95% CI.

ences were seen in terms of blood glucose control either in mothers or in neonates.[30]

In 2017, Feig et al. published the Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy (CONCEPTT) study,31 consisting of two randomised clinical trials. Only women with T1DM (215 pregnant women and 110 women planning to have a baby) were included and randomised to SMBG (capillary blood glucose monitoring) with or without associated RT-CGM. In the RCT conducted in pregnant women, this study found a slight improvement in HbA_{1c} levels (−0.19%); an improvement in metrics at 34–35 weeks (an increase in time in range (TIR) [68% versus 61%] and a decrease in time above range (TAR) [27% versus 32%]); similar numbers of episodes of severe hypoglycaemia; and an improvement in neonatal outcomes, with fewer LGA neonates (53% versus 69%; OR 0.51; 95% CI, 0.28–0.90), fewer NICU admissions, fewer neonatal episodes of hypoglycaemia requiring intravenous glucose treatment and shorter neonatal hospital stays.[31] No differences were seen in the RCT aimed at patients with pregestational follow-up. This multicentre study concluded by recommending CGM in all pregnant women with T1DM.[31] In late 2020, the NICE prepared an evidence document including a meta-analysis of the results of the two above-mentioned RCTs.[32] This meta-analysis noted that, although there is little evidence of variable quality, the evidence that exists significantly favours RT-CGM versus SMBG in terms of TIR (mean difference 7% [95% CI, 2.57—11.43]); HbA_{1c} levels (mean difference −0.18% [−0.36—0.00]); HbA_{1c} levels <6.5% (RR 1.27 [1—1.62]), Caesarean birth (RR 0.82 [0.69—0.99]), neonatal hypoglycaemia (RR 0.54 [0.31—0.94]) and >24-h NICU admission (RR 0.63 [0.42—0.93]).[32]

Regarding clinical practice guidelines, these update their positions over time as evidence on the subject is generated.

Diabetes Canada noted that CGM can help to identify periods of hypoglycaemia and hyperglycaemia and to observe blood glucose variability, especially in women with T1DM.[18] These guidelines set out the most important studies on CGM in pregnancy. They refer to a study by Murphy et al.[33] in which intermittent and blinded CGM demonstrated, in pregnant women with T1DM and T2DM, an improvement in blood glucose control with a decrease in HbA_{1c} levels (5.8% ± 0.6 versus 6.4% ± 0.7 at 32–36 weeks) as well as a reduction in the rate of newborns with a birth weight above the 90th percentile (odds ratio [OR] 0.36; 95% CI, 0.13—0.98).[33] However, they note that similar benefits were not seen with the use of intermittent RT-CGM in pregnant women with T1DM and T2DM in a study by Secher et al.[30] This difference can be explained in part by the fact that the blood glucose control and perinatal outcomes in the control group were better than in the study by Murphy. They conclude by referring to the above-mentioned CONCEPTT[31] study. They list the favourable outcomes achieved for CGM in detail, highlighting TIR and neonatal outcomes.[18]

The Grupo Español de Diabetes y Embarazo [Spanish Diabetes and Pregnancy Group] (GEDE) agreed in specifying that RT-CGM or FGM must be offered to women with T1DM and recommending the targets indicated above.[3]

The 2015 NICE guidelines did not recommend the systematic use of CGM.[34] They considered only patients with episodes of severe hypoglycaemia and/or a great deal of glycaemic variability to be potential beneficiaries.[34] In 2019, NICE announced that the guidelines had been revised to include CGM in pregnancy, considering the observational study with RT-CGM and FGM[35] and the clinical benefits for the mother and newborn reported in the two RCTs with RT-CGM conducted with the Medtronic® system.[30,31] The 2020 update advocated for universal RT-CGM in pregnant women with T1DM.[5] The recommendations specified that RT-CGM must be offered when the pregnant woman is allergic to flash devices, was a prior user of RT-CGM or requires predictive alerts that her FGM does not offer.[5] They also specify that it must be offered if the pregnant woman chooses RT-CGM and it is financially feasible.

On the effects of CGM on blood glucose control, the ADA very briefly mentions the CONCEPTT study, which found a reduction in HbA_{1c} levels with no increase in rates of episodes of hypoglycaemia and improvement in neonatal outcomes.[4] It rates it as grade B evidence and notes that the benefits have been seen when CGM has been used in association with SMBG.

There are no specific RCTs for the breastfeeding period, although observational data are satisfactory. For example, in a study by Ringholm that used FGM for six months in the postpartum period, the percentage of time in hypoglycaemia during the night was low in women who breastfed

with sufficient carbohydrate intake and suitable insulin dose reduction.[36]

Insulin therapy

Drug

Regarding the type of insulin to be used, it is recommended that human insulin/insulin analogues be used with a preference for the latter.

Concerning rapid-acting analogues, there is RCT evidence on insulin aspart[37] and evidence from use in clinical practice and safety notices for insulin lispro and insulin glulisine (in the case of the latter, in a small number of women).[38] In the RCT on aspart versus regular insulin, blood glucose control based on HbA_{1c} levels was similar, with lesser postprandial excursion at breakfast and a tendency towards fewer serious and night-time episodes of hypoglycaemia with aspart.[37] The use of lispro has been associated in observational studies with lower rates of jaundice and higher rates of LGA newborns compared to regular insulin, with no differences in blood glucose control.[38,39] The drug's summary of product characteristics notes that the evidence on exposure in large numbers of pregnancies does not point to any adverse effects of lispro during pregnancy or on the health of the foetus/newborn.[40]

The use of fast-acting aspart and lispro U-200 is accepted in pregnancy as they consist of the same compound as aspart and lispro, respectively. An RCT comparing fast-acting insulin aspart to aspart in 220 women with T1DM and T2DM to evaluate its effectiveness and safety in pregnancy and breastfeeding (NCT03770767) is currently ongoing (it should be noted that the primary objective is not maternal blood glucose control but a neonatal outcome: the standard deviation for birth weight).

Regarding basal insulins, in the RCT on insulin detemir versus neutral protamine Hagedorn (NPH) insulin, blood glucose control based on HbA_{1c} levels was similar in the two groups, and baseline blood glucose was lower with insulin detemir.[41] Although no clinical trials have been conducted with insulin glargine during pregnancy, the results of several meta-analyses have backed its safety.[18] The use of glargine U-300 is also accepted as it consists of the same compound. In the case of insulin degludec, an observational study has been published comparing insulin degludec to glargine in a small number of patients and finding some differences (e.g. higher baseline HbA_{1c} levels and longer pregnancies in the group treated with insulin degludec, which might be attributed to the study design).[42] A recently completed RCT, currently pending publication, in 225 women with T1DM compared the effectiveness and safety of insulin degludec versus insulin detemir, in both cases in combination with aspart (NCT03377699).

Overall, the data point to the safety of analogues, with the limitation that some data are only observational and/or collected in limited numbers of pregnancies. With regard to benefits, rapid-acting analogues require less waiting time before intake, and both rapid-acting and long-acting analogues reduce or tend to reduce numbers of maternal episodes of hypoglycaemia (data from RCTs/observational studies).[38,41]

The different clinical practice guidelines[18,34] recommend using rapid-acting insulin analogues (aspart/lispro) over regular insulin during pregnancy. The ADA makes no special mention of insulin type. Insulin is present in breast milk[43] where it is actively transported[44] and is considered to play a physiological role in infant gut maturation.[45] As a result, exogenous insulin and analogues are also excreted in breast milk but their use is not considered a contraindication for breastfeeding.

Multiple-dose insulin therapy versus an insulin pump

Concerning the main systems of insulin therapy available, multiple-dose insulin (MDI) therapy or a continuous subcutaneous insulin infusion (CSII) pump, publications on the subject have not shown CSII to have benefits during pregnancy. However, it is important to note that the RCTs included were conducted decades ago, and both the pumps and the insulins used are of little relevance to current treatment.[46] A 2016 systematic review by Farrar analysed five Italian single-centre clinical trials (154 pregnancies) published between 1984 and 2005 and found no differences in primary outcomes (Caesarean birth, LGA or perinatal mortality) or secondary outcomes apart from a higher birth weight in children of mothers treated with CSII. It is difficult to extrapolate conclusions considering the limited numbers of studies, the sample size and the characteristics of the population included.[46] However, several routine clinical practice studies have documented a satisfactory course in pregnant women treated with CSII versus MDI, bearing in mind that diabetes follows a longer course in the former. A study by Chico et al. included women who had been pregnant between 1984 and 2006 treated with MDI or CSII.[47] Women treated with CSII had longer durations of diabetes and differences in other aspects of medical history such as serious malformation. Perinatal outcomes did not differ in the bivariate analysis. In the multivariate analysis, the use of CSII was associated with higher mean glucose in the third trimester and higher rates of LGA newborns (OR 2.22 [1.066—0.619]).[47] In a retrospective study by Kallas-Koeman, women with CSII had lower HbA_{1c} levels throughout pregnancy; the difference between these women and MDI users was 0.3%–0.7%.[48] Pump users had longer durations of diabetes as well as higher rates of retinopathy and pregestational follow-up. There were no differences in terms of rates of adverse events in mothers or neonates with the exception of more LGA neonates born to patients with CSII; this difference was not confirmed in the multivariate analysis.[48]

The new indications for CSII in pregestational follow-up will be, in line with the NICE guidelines,5 in women being treated with MDI who do not achieve satisfactory blood glucose control without episodes of significant hypoglycaemia.

Integrated systems

The implementation of continuous monitoring together with CSII, called sensor-augmented pump therapy (SAPT), is considered a useful tool for blood glucose management in pregnant women, especially those at high risk of hypoglycaemia. In 2017, a prospective observational study was

published on women treated with SAPT during pregnancy (Paradigm 722® or Paradigm VEO® with suspension due to low glucose).[49] It included 34 women, 18 of whom started therapy during pregnancy and 16 of whom were prior users. Both subgroups showed improvement in HbA_{1c} levels throughout pregnancy, and 66% achieved HbA_{1c} levels <6.5% in the third trimester.[49] There were no differences in blood glucose control in relation to insulin suspension. In patients with a prior history of severe or undetected hypoglycaemia, it proved a safe option as there were no cases of severe hypoglycaemia. There were no differences in pre-eclampsia, prematurity, hypoglycaemia or NICU admission.[49]

There are no specific data for the postpartum period.

Closed-loop systems

Recent technological advances such as hybrid closed-loop systems have demonstrated benefits in adults and children with T1DM. In 2016, the Cambridge group evaluated the functioning of an algorithm for automatic night-time insulin infusion with a blood glucose target of 104—131 mg/dl.[50] Thirteen patients in the first or second trimester of pregnancy participated in a crossover study comparing closed-loop systems to SAPT at night-time. The devices used were the DANA Diabecare R Insulin Pump (SOOIL)® and the FreeStyle Navigator II® (Abbott). The percentage of TIR during the night increased by + 15.2% (74.7% versus 59.5%), and mean night-time glucose decreased (119 versus 133 mg/dl).[50] Three years later, the same group published safety and efficacy data on closed-loop systems used throughout the day in a crossover study with SAPT.[51] Similar TIR was seen with the two systems, but the closed-loop system was associated with less time in hypoglycaemia (1.6% versus 2.7%) as well as fewer episodes of hypoglycaemia (median 8 versus 12.5 in a 28-day period).[51]

Commercial systems are very promising, but to date only case reports using the MiniMed 670G® system are available. Polsky et al. recently published a series of three cases using the MiniMed 670G® system in pregnant women, one starting during pregnancy, which showed an improvement in blood glucose control up to the end of pregnancy. All three women had pre-eclampsia and LGA newborns.[52] In Spain, there was a recent report of a pregnant woman who started treatment with the MiniMed 670G® system; her pregnancy followed a good course, and she achieved TBR < 4% at the end of gestation.[53] All studies have agreed that longer, multicentre, randomised clinical trials must be conducted to determine the efficacy of this system in pregnant women with T1DM and its effects on perinatal outcomes. Several RCTs to test the MiniMed 670G® (PICLS, NCT03774186), MiniMed 780G® (CRISTAL, NCT04520971), CamAPS (AiDAPT, NCT04938557) and Control-IQ (CIRCUIT, NCT04902378) systems and compare their safety and efficacy in pregnancy to SAPT or standard treatment (a pump or MDI) are registered on https://clinicaltrials.gov. There is also a registered RCT to test the MiniMed 670G® system versus SAPT during breastfeeding (CLIMB, NCT04420728).

In conclusion, treatment of pregnant women with T1DM is complex due to both the metabolic changes that occur and the strict targets required during pregnancy; constituting a paradigmatic situation to leverage technological advances in insulin monitoring and administration. The use of rapid-acting insulin analogues versus regular insulin is preferred by most scientific associations as good outcomes have been achieved in pregnancy. The literature features high-quality evidence on the benefits of RT-CGM represents for perinatal outcomes, but there is a lack of RCTs on automatic insulin supply systems and new analogues (glargine U-300, insulin degludec and fast-aspart), although some RCTs are ongoing. The coming years will bring significant advances in T1DM treatment, and we hope that they will extend to T1DM treatment in pregnancy.

Conflicts of interest

JA declares that she has no conflicts of interest.

RC has worked with Abbott, Ascensia, Medtronic, Menarini, Novo Nordisk, Lilly and Sanofi in the form of consulting, conferences, etc.

References

1. Gortazar L, Goday A, Flores-Le Roux JA, Sarsanedas E, Payà A, Mañé L, et al. Trends in prevalence of pre-existing diabetes and perinatal outcomes: a large, population-based study in Catalonia, Spain, 2006–2015. BMJ Open Diabetes Res Care. 2020;8(1).
2. López-de-Andrés A, Perez-Farinos N, Hernández-Barrera V, Palomar-Gallego MA, Carabantes-Alarcón D, Zamorano-León JJ, et al. A population-based study of diabetes during pregnancy in Spain (2009–2015): trends in incidence, obstetric interventions, and pregnancy outcomes. J Clin Med. 2020;9(2).
3. Grupo Español de Diabetes y Embarazo (GEDE), Available from: https://d2q8uh6bd0ohj9.cloudfront.net/wp-content/uploads/2020/11/26174715/Guia-Diabetes-Mellitus-Embarazo-y-Covid19.Nov-2020_final.pdf, 2020.
4. American Diabetes Association. 14. Management of diabetes in pregnancy: standards of medical care in diabetes—2021. Diabetes Care. 2021;44 Supplement 1:S200–10.
5. National Institute for Health and Care Excellence Guideline Diabetes in pregnancy: management from preconception to the postnatal period Draft for consultation, September 2020 [Internet]. [Accessed 9 May 2021]. Available from: https://www.nice.org.uk/guidance/ng3/update/ng3-update-1/documents/draft-guideline.
6. Kirwan JP, Hauguel-De Mouzon S, Lepercq J, Challier J-C, Huston-Presley L, Friedman JE, et al. TNF-alpha is a predictor of insulin resistance in human pregnancy. Diabetes. 2002;51(7):2207–13.
7. Ringholm L, Pedersen-Bjergaard U, Thorsteinsson B, Boomsma F, Rehfeld JF, Damm P, et al. Impaired hormonal counterregulation to biochemical hypoglycaemia does not explain the high incidence of severe hypoglycaemia during pregnancy in women with type 1 diabetes. Scand J Clin Lab Invest. 2013;73(1):67–74.
8. García-Patterson A, Gich I, Amini SB, Catalano PM, de Leiva A, Corcoy R. Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction. Diabetologia. 2010;53(3):446–51.
9. Ilic S, Jovanovic L, Wollitzer AO. Is the paradoxical first trimester drop in insulin requirement due to an increase in C-peptide concentration in pregnant Type I diabetic women? Diabetologia. 2000;43(10):1329–30.
10. Jovanovic L, Knopp RH, Brown Z, Conley MR, Park E, Mills JL, et al. Declining insulin requirement in the late first trimester of diabetic pregnancy. Diabetes Care. 2001;24(7):1130–6.

11. Kampmann U, Knorr S, Fuglsang J, Ovesen P. Determinants of maternal insulin resistance during pregnancy: an updated overview. J Diabetes Res. 2019;2019:5320156.
12. McManus RM, Ryan EA. Insulin requirements in insulin-dependent and insulin-requiring GDM women during final month of pregnancy. Diabetes Care. 1992;15(10):1323–7.
13. Steel JM, Johnstone FD, Hume R, Mao JH. Insulin requirements during pregnancy in women with type I diabetes. Obstet Gynecol. 1994;83(2):253–8.
14. Achong N, Callaway L, d'Emden M, McIntyre HD, Lust K, Barrett HL. Insulin requirements in late pregnancy in women with type 1 diabetes mellitus: a retrospective review. Diabetes Res Clin Pract. 2012;98(3):414–21.
15. Padmanabhan S, McLean M, Cheung NW. Falling insulin requirements are associated with adverse obstetric outcomes in women with preexisting diabetes. Diabetes Care. 2014;37(10):2685–92.
16. Padmanabhan S, Lee VW, Mclean M, Athayde N, Lanzarone V, Khoshnow Q, et al. The association of falling insulin requirements with maternal biomarkers and placental dysfunction: a prospective study of women with preexisting diabetes in pregnancy. Diabetes Care. 2017;40(10):1323–30.
17. Waters TP, Kim SY, Sharma AJ, Schnellinger P, Bobo JK, Woodruff RT, et al. Longitudinal changes in glucose metabolism in women with gestational diabetes, from late pregnancy to the postpartum period. Diabetologia. 2020;63(2):385–94.
18. Diabetes Canada Clinical Practice Guidelines Expert Committee, Feig DS, Berger H, Donovan L, Godbout A, Kader T, et al. Diabetes and pregnancy. Can J Diabetes. 2018;42 Suppl 1:S255–82.
19. Sparud-Lundin C, Wennergren M, Elfvin A, Berg M. Breastfeeding in women with Type 1 diabetes: exploration of predictive factors. Diabetes Care. 2011;34(2):296–301.
20. Achong N, McIntyre HD, Callaway L, Duncan EL. Glycaemic behaviour during breastfeeding in women with Type 1 diabetes. Diabet Med. 2016;33(7):947–55.
21. Ringholm L, Stougaard EB, Nørgaard SK, Damm P, Mathiesen ER. Diabetes management during breastfeeding in women with Type 1 diabetes. Curr Diab Rep. 2020;20(8):34.
22. Nørgaard SK, Nørgaard K, Roskjær AB, Mathiesen ER, Ringholm L. Insulin pump settings during breastfeeding in women with Type 1 diabetes. Diabetes Technol Ther. 2020;22(4):314–20.
23. Tanner HL, Dekker Nitert M, Callaway LK, Barrett HL. Ketones in pregnancy: why is it considered necessary to avoid them and what is the evidence behind their perceived risk? Diabetes Care. 2021;44(1):280–9.
24. Rizzo T, Metzger BE, Burns WJ, Burns K. Correlations between antepartum maternal metabolism and intelligence of offspring. N Engl J Med. 1991;325(13):911–6.
25. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42(8):1593–603.
26. GuardianTM Sensor (3) Performance [Internet]. [Accessed 5 May 2021]. Available from: https://www.medtronicdiabetes.com/sites/default/files/library/download-library/user-guides/MP6026113-2AF1DOC_A_FINAL.pdf.
27. Castorino K, Polsky S, O'Malley G, Levister C, Nelson K, Farfan C, et al. Performance of the Dexcom G6 continuous glucose monitoring system in pregnant women with diabetes. Diabetes Technol Ther. 2020;22(12):943–7.
28. Scott EM, Bilous RW, Kautzky-Willer A. Accuracy, user acceptability, and safety evaluation for the freestyle libre flash glucose monitoring system when used by pregnant women with diabetes. Diabetes Technol Ther. 2018;20(3):180–8.
29. Nørgaard SK, Mathiesen ER, Nørgaard K, Ringholm L. Comparison of glycemic metrics measured simultaneously by intermittently scanned continuous glucose monitoring and real-time continuous glucose monitoring in pregnant women with Type 1 diabetes. Diabetes Technol Ther. 2021.
30. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. Diabetes Care. 2013;36(7):1877–83.
31. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet. 2017;390(10110):2347–59.
32. NICE, Available from: https://www.nice.org.uk/guidance/ng3/evidence/a-evidence-reviews-for-continuous-glucose-monitoring-pdf-8955770797, 2020.
33. Murphy HR, Rayman G, Lewis K, Kelly S, Johal B, Duffield K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ. 2008;337:a1680.
34. NICE. National Institution for Care and Excelence (NICE) guideline. Diabetes in pregnancy: managment from preconception to the postnatal period. Draft for consultation; 2015.
35. Kristensen K, Ögge LE, Sengpiel V, Kjölhede K, Dotevall A, Elfvin A, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. Diabetologia. 2019;62(7):1143–53.
36. Ringholm L, Roskjær AB, Engberg S, Andersen HU, Secher AL, Damm P, et al. Breastfeeding at night is rarely followed by hypoglycaemia in women with type 1 diabetes using carbohydrate counting and flexible insulin therapy. Diabetologia. 2019;62(3):387–98.
37. Mathiesen ER, Kinsley B, Amiel SA, Heller S, McCance D, Duran S, et al. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. Diabetes Care. 2007;30(4):771–6.
38. Lv S, Wang J, Xu Y. Safety of insulin analogs during pregnancy: a meta-analysis. Arch Gynecol Obstet. 2015;292(4):749–56.
39. González Blanco C, Chico Ballesteros A, Gich Saladich I, Corcoy Pla R. Glycemic control and pregnancy outcomes in women with type 1 diabetes mellitus using lispro versus regular insulin: a systematic review and meta-analysis. Diabetes Technol Ther. 2011;13(9):907–11.
40. Ficha técnica o resumen de las características del producto [Internet]. [Accessed 16 April 2021]. Available from: https://www.ema.europa.eu/en/documents/product-information/humalog-epar-product-information_es.pdf.
41. Mathiesen ER, Hod M, Ivanisevic M, Duran Garcia S, Brøndsted L, Jovanovic L, et al. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. Diabetes Care. 2012;35(10):2012–7.
42. Keller MF, Vestgaard M, Damm P, Mathiesen ER, Ringholm L. Treatment with the long-acting insulin analog degludec during pregnancy in women with type 1 diabetes: an observational study of 22 cases. Diabetes Res Clin Pract. 2019;152:58–64.
43. Koldovský O. Hormones in milk. Vitam Horm. 1995;50:77–149.
44. Whitmore TJ, Trengove NJ, Graham DF, Hartmann PE. Analysis of insulin in human breast milk in mothers with type 1 and type 2 diabetes mellitus. Int J Endocrinol. 2012;2012:296368.
45. Shehadeh N, Gelertner L, Blazer S, Perlman R, Solovachik L, Etzioni A. Importance of insulin content in infant diet: suggestion for a new infant formula. Acta Paediatr. 2001;90(1):93–5.
46. Farrar D, Tuffnell DJ, West J, West HM. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. Cochrane Database Syst Rev [Internet]. 2016, http://dx.doi.org/10.1002/14651858.CD005542.pub3/full [Accessed 11 December 2020];(6). Disponible en:.

47. Chico A, Saigi I, García-Patterson A, Santos MD, Adelantado JM, Ginovart G, et al. Glycemic control and perinatal outcomes of pregnancies complicated by type 1 diabetes: influence of continuous subcutaneous insulin infusion and lispro insulin. Diabetes Technol Ther. 2010;12(12):937–45.
48. Kallas-Koeman M, Khandwala F, Donovan L. Rate of preconception care in women with Type 2 diabetes still lags behind that of women with Type 1 diabetes. Can J Diabetes. 2012;36:170–4.
49. Gómez AM, Marín Carrillo LF, Arévalo Correa CM, Muñoz Velandia OM, Rondón Sepúlveda MA, Silva Herrera JL, et al. Maternal-fetal outcomes in 34 pregnant women with Type 1 diabetes in sensor-augmented insulin pump therapy. Diabetes Technol Ther. 2017;19(7):417–22.
50. Stewart ZA, Wilinska ME, Hartnell S, Temple RC, Rayman G, Stanley KP, et al. Closed-loop insulin delivery during pregnancy in women with Type 1 diabetes. New Engl J Med. 2016;375(7):644–54.
51. Stewart ZA, Wilinska ME, Hartnell S, O'Neil LK, Rayman G, Scott EM, et al. Day-and-night closed-loop insulin delivery in a broad population of pregnant women with type 1 diabetes: a randomized controlled crossover trial. Diabetes Care. 2018;41(7):1391–9.
52. Polsky S, Akturk HK. Case series of a hybrid closed-loop system used in pregnancies in clinical practice. Diabetes Metab Res Rev. 2020;36(3):e3248.
53. Moreno-Fernández J, García-Seco JA. Commercialized hybrid closed-loop system (minimed medtronic 670 g) results during pregnancy. AACE Clinical Case Reports [Internet]. 6 de enero de 2021 [Accessed 16 April 2021]. Available from: https://www.sciencedirect.com/science/article/pii/S2376060521000080.