Improving pregnancy outcomes in women with diabetes mellitus: modern management

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Abstract | Women with pre-existing (type 1 or type 2) diabetes mellitus are at increased risk of pregnancy complications, such as congenital malformations, preeclampsia and preterm delivery, compared with women who do not have diabetes mellitus. Approximately half of pregnancies in women with pre-existing diabetes mellitus are complicated by fetal overgrowth, which results in infants who are overweight at birth and at risk of birth trauma and, later in life, the metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus. Strict glycaemic control with appropriate diet, use of insulin and, if necessary, antihypertensive treatment is the cornerstone of diabetes mellitus management to prevent pregnancy complications. New technology for managing diabetes mellitus is evolving and is changing the management of these conditions in pregnancy. For instance, in Europe, most women with pre-existing diabetes mellitus are treated with insulin analogues before and during pregnancy. Furthermore, many women are on insulin pumps during pregnancy, and the use of continuous glucose monitoring is becoming more frequent. In addition, smartphone application technology is a promising educational tool for pregnant women with diabetes mellitus and their caregivers. This Review covers how modern diabetes mellitus management with appropriate diet, insulin and antihypertensive treatment in patients with pre-existing diabetes mellitus can contribute to reducing the risk of pregnancy complications such as congenital malformations, fetal overgrowth, preeclampsia and preterm delivery.

Compared with women who do not have diabetes mellitus, those with pre-existing diabetes mellitus (either type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM)) have an increased risk of pregnancy complications[1]. Congenital malformation (for example, cardiac or musculoskeletal) is a complication that many worry about during pregnancy and that occurs more frequently in women with pre-existing diabetes mellitus than in other pregnant women[1,2]. Fetal overgrowth is also an important fetal complication. For instance, approximately half of women with pre-existing diabetes mellitus deliver infants who are large for gestational age (LGA)[3–6]. Preeclampsia with hypertension and proteinuria occurs in 9% of women, and women with diabetic kidney disease (diabetic nephropathy or microalbuminuria) are at particular risk[6]. In addition, preterm delivery before 37 weeks occurs in 17–40% of women with pre-existing diabetes mellitus, which is up to four times more frequent than in women without these conditions[3,5,6]. The high prevalence of these pregnancy complications is strongly associated with poor glycaemic control[3–6]. TABLE 1 outlines the complications in pregnancy with pre-existing diabetes mellitus covered in this Review together with predictors of their occurrence.

To reduce the risk of these complications, modern diabetes mellitus management in pregnancy includes a multi-target approach that focuses on glucose regulation, dietary advice, gestational weight gain, blood pressure control and tools for outreach patient education[7]. This Review provides an update on the modern management of pre-existing diabetes mellitus in pregnancy with a particular focus on improved glycaemic control, adequate dietary advice and the efficacy and safety of intensive antihypertensive treatment that aims to reduce the risk of severe adverse pregnancy outcomes such as fetal overgrowth, preeclampsia and preterm delivery. The use of modern diabetes mellitus management technology, such as insulin pumps, continuous glucose monitoring (CGM) and smartphone application technology, in pregnancy is also covered.

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Key points

- The cornerstones of modern diabetes mellitus management in pregnancy are appropriate diet and insulin therapy with a focus on prevention of maternal hypoglycaemia and hyperglycaemia to reduce the risk of pregnancy complications.
- Implementing an appropriate diet with a focus on the quantity and quality of carbohydrates and limiting maternal gestational weight gain are promising treatment areas to reduce the risk of fetal overgrowth.
- The use of insulin analogues, insulin pumps, continuous glucose monitoring and bolus calculators might help improve glycaemic control and reduce the risk of severe maternal hypoglycaemia in pregnancy.
- Early and intensive antihypertensive treatment with antihypertensive agents approved for use in pregnancy might reduce the risk of preeclampsia and preterm delivery, especially in women with diabetic kidney disease.
- Easily accessible patient education (that is, via smartphone application technology) is useful to reach pregnant women and provide information on modern diabetes mellitus management to improve pregnancy outcomes.

Glycaemic control

Congenital malformations. Maternal hyperglycaemia during fetal organogenesis (before 8–10 gestational weeks) has a detrimental effect, resulting in an increased prevalence of congenital malformations (for example, cardiac or musculoskeletal) in infants of women with pre-existing diabetes mellitus[8]. Accordingly, a positive association exists between peri-conception (the period from 3 months before conception to 3 months after conception) maternal hyperglycaemia and congenital malformations in women with pre-existing diabetes mellitus[2,9]. Peri-conception oxidative stress as a result of hyperglycaemia might have a role in the development of congenital malformations by exerting a teratogenic effect[10], but the exact mechanisms linking maternal hyperglycaemia to malformations are yet to be understood.

Glycaemic targets. As a result of the association with congenital malformations, it is important that diabetes mellitus is well controlled before pregnancy, with HbA_{1c} levels at least <53 mmol/mol (7.0%)[9,11]. According to the American Diabetes Association (ADA), HbA_{1c} should even be <48 mmol/mol (6.5%) before conception, as this level of HbA_{1c} is associated with the lowest risk of congenital malformations[12].

Maintaining strict glycaemic control during pregnancy is essential to prevent pregnancy-related complications. The ADA recommends that HbA_{1c} levels are maintained below 42 mmol/mol (6.0%) during pregnancy[12], if this level can be achieved without significant maternal hypoglycaemia, to minimize the risk of LGA infants. Keeping HbA_{1c} at this level also has a beneficial effect on preventing the development of preeclampsia and preterm delivery, as higher HbA_{1c} levels in the first trimester[13–19] and late (after 20 gestational weeks)[17] pregnancy are positively associated with both the risk of preeclampsia and the risk of preterm delivery[3,20].

Thus, the aim of the clinical care of women with pre-existing diabetes mellitus during pregnancy is to obtain levels of glucose that reduce the risk of adverse pregnancy outcomes while keeping episodes of mild and severe maternal hypoglycaemia to a minimum. The ADA suggests the following targets for glucose values: fasting levels of glucose <5.3 mmol/l, 1 h postprandial values of <7.8 mmol/l and 2 h postprandial values <6.7 mmol/l (REF.[12]). These levels correspond to a goal of 100% time spent in the glucose target range of 3.5–7.8 mmol/l (REF.[21]).

Severe maternal hypoglycaemia. The ADA and the Endocrine Society define severe hypoglycaemia as "an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions"[22]. The risk of severe maternal hypoglycaemia is the main limiting factor for further optimization of glycaemic control in pregnant women with T1DM[23]. A glucose concentration <3.0 mmol/l is now regarded as being sufficiently low to indicate clinically important hypoglycaemia[24].

Women with T1DM are at particular risk of severe hypoglycaemia during pregnancy if they have one or more of the following clinical features: at least one event of severe hypoglycaemia the year before pregnancy, impaired hypoglycaemia awareness or hypoglycaemia unawareness[25,26]. In addition, duration of T1DM >10 years, intensive insulin treatment with HbA_{1c} ≤48 mmol/mol (6.5%) in the first trimester, fluctuating plasma levels of glucose and supplementation with insulin between main meals increase the risk[25,26]. Pregnancy-induced nausea and vomiting do not seem to be contributing factors[26].

Ten to fifteen years ago, severe maternal hypoglycaemia in T1DM occurred three to five times more frequently in the first trimester than in the year before pregnancy[25,26], whereas the risk of severe maternal hypoglycaemia was lower in the third trimester than before pregnancy[26]. On the basis of real-world data in women with T1DM from our centre in Denmark, increasing use of rapid-acting and long-acting insulin analogues, including a higher prevalence of insulin pump therapy, was associated with a statistically significantly reduced prevalence of severe maternal hypoglycaemia from 45% in 2004–2006 (REF.[26]) to 23% in 2009–2011 (REF.[27]), while maintaining good glycaemic control, and the pregnancy outcomes were the same in the two time periods[27] (FIG. 1). Various strategies are available to prevent or reduce the risk of severe maternal hypoglycaemia during pregnancy in women with pre-existing diabetes mellitus (BOX 1).

Among women with T2DM who were treated with basal-bolus or pre-mixed insulin from early pregnancy to delivery, 19% experienced at least one event with severe maternal hypoglycaemia during pregnancy, which was related to strict glycaemic control with HbA_{1c} ≤44 mmol/mol from early pregnancy onwards[28]. Diabetes mellitus caregivers and pregnant women with T2DM need to consider this potentially harmful condition when aiming for near-normoglycaemia during pregnancy.

Fetal overgrowth

The prevalence of fetal overgrowth is positively associated with HbA_{1c} levels, particularly in the second and third trimester[4,29], and is probably an important contributor to pregnancy complications such as shoulder dystocia, birth canal lacerations, operative delivery and

Table 1 | **Prevalence and risk factors for adverse pregnancy outcomes among women with T1DM**[1,19,32]

Outcome	Prevalence	Relative risk	Risk factors
Congenital malformations	5%	2.4	Increased levels of HbA_{1c}
Large-for-gestational-age infants	54%	4.5	• Increased levels of HbA_{1c} • Excessive gestational weight gain[a]
Preeclampsia	17%	5.5	• Increased levels of HbA_{1c} • Diabetic nephropathy • Microalbuminuria • Diabetic retinopathy • Hypertension
Preterm delivery	25%	4.2	• Increased levels of HbA_{1c} • Preeclampsia

T1DM, type 1 diabetes mellitus. [a]Defined as gestational weight gain above the recommendations of the Institute of Medicine: 12.5–18.0 kg for women who were underweight, 11.5–16.0 kg for those with normal weight, 7.0–11.5 kg for women who were overweight and 5.0–9.0 kg for women with obesity[31].

preterm delivery[30]. The mother's diet is also an important factor, as fetal overgrowth is also related to excessive gestational weight gain[7]. A focus on strict glycaemic control and a diet with sufficient, but not excessive, macronutrient and micronutrient intake is important in promoting appropriate fetal growth[7].

Gestational weight gain. In 2009, the Institute of Medicine (IOM) suggested the following recommendations for appropriate gestational weight gain in relation to the BMI of the pregnant women to promote appropriate fetal growth: 12.5–18.0 kg for women who were underweight, 11.5–16.0 kg for those with normal weight, 7.0–11.5 kg for women who were overweight and 5.0–9.0 kg for women with obesity[31]. For women with pre-existing diabetes mellitus, gestational weight gain at the lower end of the scale of the IOM 2009 guidelines for each pre-pregnancy weight category seems more appropriate to reduce the risk of delivering LGA infants[32].

Over half of pregnancies in women with T1DM result in excessive gestational weight gain according to the IOM 2009 guidelines[32]. Excessive gestational weight gain is a strong predictor of fetal overgrowth in the general population[31] as well as in women with T1DM[32]. Excessive weight gain and HbA_{1c} levels in early and late pregnancy are positively associated with the presence of LGA[33]. In addition, a positive association exists between gestational weight gain and offspring birthweight[32,33], which remains after adjustment for maternal glycaemic control in late pregnancy and pre-pregnancy BMI[32]. The percentage of women with pre-existing diabetes mellitus entering pregnancy with a BMI in the obese range (over 30 kg/m^2) is high and increasing, and the number of women with pre-existing diabetes mellitus and excessive gestational weight gain is also increasing over time[34]. This observation underscores that a focus on maternal BMI and recommendations on appropriate gestational weight gain according to maternal BMI category are becoming more clinically important.

Generally, the weekly weight gain is higher after 20 gestational weeks than before 20 gestational weeks[32]. However, before 20 weeks, women with T1DM who experience excessive gestational weight gain are already characterized by higher weekly gestational weight gain than women without excessive gestational weight gain[32]. A focus on appropriate weekly gestational weight gain from the beginning of pregnancy might be important to secure appropriate fetal growth.

In the offspring of women with T1DM, the birthweight adjusted for sex and gestational age is only similar to the minority of offspring in the general population who have an inappropriate gestational weight gain[32]. Meanwhile, the offspring of women with T1DM and appropriate weight gain are slightly heavier at delivery than offspring born to women in the general population[32].

Dietary advice. During pregnancy, dietary adjustments are needed to cover the extra energy expenditure while also focusing on achieving appropriate gestational weight gain. The main dilemma is that it is primarily carbohydrates that induce postprandial hyperglycaemia, but sufficient carbohydrate intake is also mandatory during pregnancy. Both the maternal brain and the developing fetal brain mainly use glucose as a fuel, thus the IOM recommends 35 g extra carbohydrate intake during pregnancy to promote normal fetal growth and brain development[35]. Furthermore, insufficient carbohydrate intake might lead to lipolysis and ketone production, and pregnant women are more prone to ketosis than non-pregnant women[36,37]. Elevated maternal levels of ketone bodies might have a negative effect on the developing fetal central nervous system[38,39].

To secure sufficient carbohydrate intake, the IOM recommends that healthy pregnant women have a minimum total daily carbohydrate intake of 175 g (REF.[31]). In women with diabetes mellitus, this target can be met by recommending a daily carbohydrate intake of 150 g from the main carbohydrate sources (bread, whole grain, dairy products, fruits, rice, potatoes and pasta) and 25 g from other carbohydrate sources (such as vegetables), whereas consumption of sweets should be limited[40] (BOX 2). Carbohydrate intake is generally recommended to constitute 45–65% of the total daily calorie intake[35], and this recommendation can be followed in pregnant women with pre-existing diabetes mellitus. A positive association between HbA_{1c} levels and the quantity of carbohydrates consumed in early pregnancy

has been observed[41] on diets in which carbohydrates constitute 40% of the total daily calorie intake, and this diet seems to be safe[40]. A moderate restriction of carbohydrate intake while securing an intake of at least 175 g daily can therefore be recommended[40].

To avoid single large meals and hyperglycaemia after breakfast, the daily carbohydrate intake can be distributed as 20 g, 40 g and 40 g for breakfast, lunch and dinner, respectively, and 10–20 g at 2–4 snacks[40]. Regular meals are probably important to avoid hypoglycaemic and hyperglycaemic excursions during pregnancy in womn with pre-existing diabetes mellitus[40] (BOX 2).

In early pregnancy, women with diabetes mellitus should be referred to a registered dietician familiar with the management of pre-existing diabetes mellitus in pregnancy for medical nutrition therapy, including an individualized nutrition plan[40] (BOX 2). To reduce the incidence of glycaemic excursions, a typical diet for pregnant women with T1DM contains carbohydrates with a low glycaemic index[40]. Carbohydrate counting is essential for matching the amount of rapid-acting insulin needed to keep a stable glucose level after a meal or snack[42]. In a cohort study, pregnant women with T1DM using carbohydrate counting obtained better glycaemic control (estimated by HbA_{1c}) early in pregnancy than women who did not count carbohydrates[41]. In addition, a positive association between HbA_{1c} levels and the quantity of carbohydrates consumed in early pregnancy was observed[41].

Smartphone applications are available in many languages to ease carbohydrate counting and to calculate a flexible meal insulin dose on the basis of the carbohydrate intake and carbohydrate-to-insulin ratio, as well as on the pre-meal glucose level and insulin sensitivity factor (which indicates how much, in millimoles per litre, the level of glucose drops for each unit of insulin taken for correction of a high glucose value).

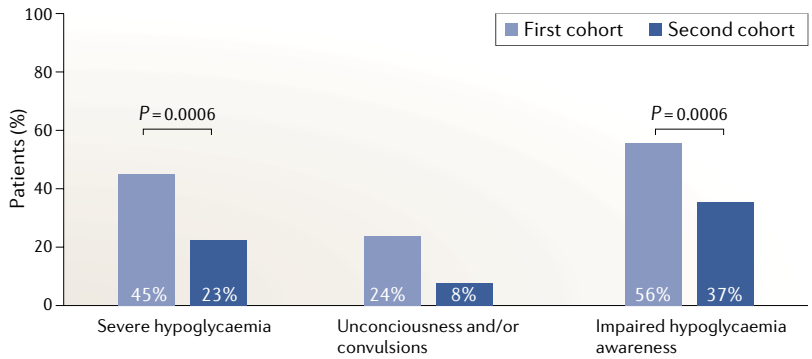

Fig. 1 | **The prevalence of severe maternal hypoglycaemia in pregnancy can be reduced.** The prevalence of severe maternal hypoglycaemia during pregnancy in women with type 1 diabetes mellitus was lower in a second cohort (2009–2011) than in the first cohort (2004–2006). In the second cohort, women were more frequently using insulin analogues and were educated on how to prevent hypoglycaemia (as described in BOX 1). Levels of HbA_{1c} were similar in both cohorts. Data are from REF.[27]. Impaired hypoglycaemia awareness was derived from the question "Do you recognize symptoms, when you have a hypoglycaemic event?". If women in a questionnaire answered anything but 'always' or 'almost always', they were categorized as having impaired hypoglycaemia awareness[26].

Modern glycaemic management

Modern insulin treatment is based on insulin analogues in combination with a diet designed for those with diabetes mellitus. These strategies are the most important tools to obtain good glycaemic control with near-normal glucose levels in pregnant women with pre-existing diabetes mellitus and might include the use of diabetes mellitus technologies such as insulin pumps and CGM. Randomized controlled trials (RCTs) have investigated the use of insulin analogues[43–46] and the use of CGM in pregnancy[47–50], which will be discussed in more detail here.

Rapid-acting and long-acting insulin analogues. The rapid-acting insulin analogues aspart, glulisine and lispro control postprandial glucose levels by offering a fast-onset, short duration of action and reduced risk of late hypoglycaemia[51–53]. The long-acting insulin analogues detemir, glargine and degludec are active for up to 24–42 h and have an almost peakless profile with a low risk of hypoglycaemia, particularly at night[54]. Rapid-acting insulin for meal-time dosing and long-acting insulin to cover 24 h needs might be used in a multiple daily injection regimen in pregnant women with pre-existing diabetes mellitus[12]. In women with T1DM, insulin pump therapy with rapid-acting insulin constitutes an alternative insulin regimen[55].

RCTs in pregnancy involving insulin aspart[43,45] and insulin detemir[44,46] have shown benefits in terms of improved glucose profiles and pregnancy outcomes compared with human insulin. Insulin aspart reduces postprandial plasma levels of glucose with similar rates of maternal hypoglycaemia compared with human insulin[45] and a trend towards fewer fetal losses and preterm deliveries[43]. To accelerate glucose disposal and potentially improve postprandial glucose control, fast-acting insulin can be injected 15–30 min before meals to overcome delayed insulin absorption, especially in late pregnancy[56]. Insulin detemir reduces fasting plasma levels of glucose with similar rates of maternal hypoglycaemia[46] and results in higher gestational age at delivery than human insulin[44].

No RCTs have been undertaken on the use of insulin glargine in pregnancy. The main concerns are glargine's increased affinity for the insulin-like growth factor receptor and increased mitogenic potential in vitro as these features could theoretically promote fetal tissue growth and accelerate maternal retinopathy[54]. As such, some clinicians might prefer neutral protamine Hagedorn insulin (an intermediate-acting insulin) and insulin detemir over insulin glargine, as the mitogenic potential is reported as being lower[54]. However, insulin glargine U100 and U300 are now widely used in pregnancy, and data on a large number of exposed pregnancies do not indicate any adverse effect on pregnancy or on the health of the infant[57–59].

The faster-acting insulin aspart (Fiasp) is insulin aspart in a new formulation in which the addition of nicotinamide (vitamin B_3) for accelerated initial absorption and of the formulation-stabilizing amino acid L-arginine results in a faster initial insulin absorption than is seen with insulin aspart[60,61]. The duration of action is shorter for Fiasp than for insulin aspart[60]; therefore, according to our clinical experience, a higher Fiasp dose overall might

be necessary, particularly in insulin pumps. However, no severe adverse events have been observed during insulin pump therapy with Fiasp or insulin aspart in non-pregnant patients with T1DM[62]. As the formulation of Fiasp differs from that of insulin aspart only by the addition of the inactive ingredients vitamin B_3 and L-arginine[61], Fiasp is approved by the European Medicines Agency for use in pregnancy[60]. To date, no clinical studies have evaluated the effect of Fiasp on glycaemic control and pregnancy outcomes in pregnant women with pre-existing diabetes mellitus[54]. Insulin lispro is widely used in pregnancy, and data on a large number of exposed pregnancies do not indicate any adverse effect on pregnancy or on the health of the infant[53]. By contrast, insulin glulisine has not been approved for use in pregnancy, and caution should be exercised if prescribing it to pregnant women owing to the lack of data on the use of insulin glulisine in pregnancy[52].

In 2013, the long-acting insulin analogue degludec was launched. Insulin degludec has a half-life of >25 h and a duration of action exceeding 42 h (REF.[63]). In case reports of women with pre-existing diabetes mellitus treated with insulin degludec in early pregnancy, no pregnancy complications or congenital malformations have been observed[64,65]. An ongoing multi-centre RCT (the EXPECT study) in pregnant women with T1DM is comparing the efficacy and safety in women on insulin degludec or insulin detemir, both combined with insulin aspart[66]. Results are expected in 2021.

Insulin pump therapy. An alternative method of insulin administration is continuous subcutaneous insulin infusion by insulin pump therapy, which can lead to improved glycaemic control in non-pregnant patients with T1DM, with a reduced prevalence of severe hypoglycaemia[67]. However, cohort studies[55,68,69] and a meta-analysis[70] involving pregnant women could not demonstrate that insulin pump therapy is superior to multiple daily injection therapy with regard to glycaemic outcomes, gestational weight gain, fetal overgrowth, preeclampsia, preterm delivery and other pregnancy outcomes in women with T1DM[55,68–70].

In an observational report from a large multi-centre study including pregnant women with pre-existing diabetes mellitus, women on multiple daily injection therapy were more likely to have better glycaemic outcomes and less likely to have neonates with neonatal hypoglycaemia or be admitted to the neonatal intensive care unit than women who used insulin pumps[71]. Approximately half of the women were on insulin pump therapy and half of the women used CGM in both groups. The data were adjusted for several important baseline characteristics, such as maternal age, diabetes mellitus duration, parity, levels of HbA_{1c}, smoking status and pregnancy planning[71]. Nonetheless, insulin pump therapy during pregnancy is becoming more prevalent. At our centre, approximately one-third of women with T1DM use insulin pump therapy.

A newly developed automated system that suspends basal insulin administration when low glucose is predicted has shown a reduction in hypoglycaemic events in children[72,73] and non-pregnant adult[74,75] patients with T1DM, but it might be at the expense of increased time in hyperglycaemia[72,73]. Its use in pregnancy needs to be explored in future studies.

A hybrid closed-loop insulin pump that automatically adjusts basal insulin delivery every 5 min on the basis of CGM values, and suspends delivery of insulin when hypoglycaemia is predicted, has been available since 2017 (REF.[76]) but is not approved for used in pregnancy. The target glucose level with this pump is 6.7 mmol/l, which is considerably higher than the target glucose level of 4.8 mmol/l that is used in pregnancy[55].

Oral hypoglycaemic agents for T2DM in pregnancy. The incidence of T2DM in pregnancy is rising and rates of serious adverse maternal and fetal outcomes remain high[5,6,34,77–79]. Outside of pregnancy, metformin and other oral hypoglycaemic agents are widely used for the treatment of T2DM[12]. Meanwhile, according to the ADA and many local guidelines, insulin treatment is the preferred method for managing pre-existing diabetes mellitus in pregnancy because it does not cross the placenta[12]. Treatment with oral hypoglycaemic agents, including metformin, sulfonylureas, dipeptidyl peptidase 4 inhibitors, sodium–glucose cotransporter 2 inhibitors, meglitinides, thiazolidinediones and injectable glucagon-like peptide 1 agonists, might cross the placenta and thereby have an effect on fetal development[12]. Women with T2DM who are being treated with these agents are recommended to switch to insulin before conception or at the latest when pregnancy is confirmed[12].

Metformin crosses the placenta and might interact with fetal environmental factors to influence offspring outcomes[80–82]. In utero exposure to metformin might be associated with adverse long-term consequences in the children born to women with gestational diabetes mellitus in the form of higher weight and larger arm and waist circumferences, increased triceps skinfold and increased fat mass as well as increased lean mass at the age of 9 years[82]. In two RCTs involving women with polycystic ovary syndrome treated with metformin in pregnancy, metformin-exposed children had a higher BMI and increased prevalence of overweight or obesity at 4 years of age than children not exposed to metformin[83]. An ongoing multi-centre RCT aims to

Box 1 | **Strategies to reduce the risk of severe maternal hypoglycaemia**

- Reduction of insulin dose by approximately 10–20% at 8–16 gestational weeks.
- Use of supplementary insulin between meals requires caution.
- Carrying oral glucose tablets or other oral carbohydrate sources.
- Use of rapid-acting and long-acting insulin analogues.
- Avoidance of pre-bedtime plasma glucose values <5.0 mmol/l.
- Early identification of women with pre-existing diabetes mellitus at high risk, which includes those with self-estimated impaired hypoglycaemia awareness[a] and/or a history of severe hypoglycaemia during the year preceding pregnancy.
- Use of insulin pump therapy and/or real-time continuous glucose monitoring with an alarm in women at high risk of severe hypoglycaemia.

[a]Assessment of hypoglycaemia awareness status was derived from the question "Do you recognize symptoms, when you have a hypoglycaemic event?". If women in a questionnaire answered anything but 'always' or 'almost always', they were categorized as having impaired hypoglycaemia awareness[26]. Adapted with permission from REF.[125], Wiley-VCH.

Box 2 | **Dietary advice for pregnant women with pre-existing diabetes mellitus**

- An individualized nutrition plan should be developed in early pregnancy by a registered dietician with a focus on minimizing glycaemic excursions and aiming for appropriate gestational weight gain.
- Carbohydrate counting at each meal and snack is recommended.
- Low-glycaemic-index carbohydrates should be the main type of carbohydrate in the diet.
- A minimum total daily carbohydrate intake of 175 g is recommended, which consists of 150 g from the main sources (that is, bread, whole grain, dairy products, fruits, rice, potatoes, pasta and sweets) and 25 g from vegetables or other carbohydrate sources. Consumption of sweets should be limited.
- Three main meals containing 20 g, 40 g and 40 g of carbohydrates for breakfast, lunch and dinner, respectively, and 10–20 g of carbohydrates at 2–4 snacks.

Reprinted by permission of Taylor & Francis, Roskjaer, A. B. et al. Dietary advices on carbohydrate intake for pregnant women with type 1 diabetes. *J. Matern. Fetal Neonatal Med.* (2015), (REF.[40]).

compare the effectiveness of adding metformin to insulin with standard care (insulin plus placebo) in women with T2DM in pregnancy[84].

Glyburide crosses the placenta only to a minor extent but is associated with higher birthweight and more neonatal hypoglycaemia than insulin in offspring of women with gestational diabetes mellitus. Information on long-term effects on the exposed offspring is not available for women with T2DM treated with glyburide during pregnancy[78]. In summary, treatment with diet and insulin is recommended as the first-line treatment of pre-existing diabetes mellitus during pregnancy, but metformin and glyburide might be used in selected cases.

Continuous glucose monitoring. Technology to aid the management of diabetes mellitus is constantly improving and its cost is reducing. CGM is a tool to monitor glucose levels over 24 h for several days. As such, it can be used to identify specific times of day and night with maternal glucose excursions and uncover asymptomatic hypoglycaemia, especially at night-time, and postprandial hyperglycaemia, which might not be identified with regular finger-stick measurements of plasma levels of glucose and HbA_{1c} (REFS[21,47–49,85]).

The use of CGM in addition to finger-stick glucose measurements during pregnancy in women with T1DM has been investigated in four RCTs with conflicting results. Three of these studies applied intermittent use of CGM during pregnancy[48–50]. The first study demonstrated improvement in glycaemic control and a reduced risk of LGA infants with retrospective CGM (where the glucose results were not available immediately, but only after uploading at the regular visits with the diabetes caregiver)[48]. The second study with a real-time CGM device, where the obtained levels of glycaemic control were closer to near-normal levels, could not detect a positive effect of CGM[49]. Similarly, retrospective CGM did not reduce the risk of LGA infants in a third study[50].

The fourth study, a well-performed multi-centre RCT, found that continuous use of CGM during pregnancy was associated with a reduced risk of LGA infants, neonatal hypoglycaemia, neonatal intensive care unit admissions and a 1-day shorter length of hospital stay than the use of finger-stick glucose measurements alone[47]. The effect of CGM was similar in all countries, and the reductions in LGA infants between women using CGM and controls were of the same magnitude in all centres. The pregnancy outcomes in the CGM group were, however, far from excellent in all centres, which might be attributable to factors such as diet, maternal BMI and gestational weight gain[47]. Data on CGM in women with pre-existing diabetes mellitus who deliver infants without fetal overgrowth have revealed that time spent in the glucose target range of 3.5–7.8 mmol/l increased during pregnancy from 64% in the first trimester to 71% in the second trimester and 73% in the third trimester[21].

In a single-centre real-world cohort study, use of real-time CGM with alarms did not reduce the risk of severe maternal hypoglycaemia in women with T1DM at high risk of this condition. In fact, patient education and frequent clinical visits were equally effective at improving outcomes as the use of CGM[86].

During delivery, glucose control or neonatal outcome was not improved in women using a CGM device[87,88]. Obtaining good glycaemic control during pregnancy and frequent glucose monitoring, whether by CGM or self-monitoring of plasma glucose, during delivery might help achieve maternal near-normoglycaemia and reduce the risk of fetal overgrowth and neonatal hypoglycaemia[87].

The newly developed Flash glucose monitoring system (a sensor worn on the skin that can be scanned to obtain a glucose level reading) is designed to replace the potentially painful finger-stick blood glucose measurements required each day for the self-management of pre-existing diabetes mellitus[89]. This system can be a useful aid because up to ten finger-stick measurements of plasma levels of glucose are required each day to achieve good glycaemic control during pregnancy[90]. The Flash glucose monitoring system might be clinically useful during all stages of pregnancy in women with diabetes mellitus regardless of diabetes mellitus type, age or BMI[91]. In addition, high levels of patient satisfaction are seen[91]. In non-pregnant patients, the device is associated with a reduction in hypoglycaemia and improvements in HbA_{1c} levels[89]. However, the accuracy for levels of glucose ≤4.0 mmol/l might be low[89]. According to the manufacturer's website (FreeStyle Libre System), the Flash glucose monitoring system might inaccurately indicate hypoglycaemia when plasma leves of glucose are actually over 4.5 mmol/l, and patients should adhere to their finger-stick measurement routine while using the system. Owing to the inaccuracy of the Flash glucose monitoring system in the near-normal plasma glucose range[89], women with pre-existing diabetes mellitus using the Flash glucose monitoring system might be recommended to adhere to pre-prandial finger-stick measurements of plasma levels of glucose for insulin dosing and when the system indicates hypoglycaemia.

In summary, the presented data on Flash glucose monitoring and CGM are promising and support the increasing use of this diabetes mellitus technology in women with pre-existing diabetes mellitus during pregnancy.

Bolus calculators. Automated bolus calculators are advanced blood glucose metres that help users of multiple daily injections who are carrying out carbohydrate counting to determine the size of their insulin bolus. In non-pregnant people with poorly controlled T1DM, improved glycaemic control and patient satisfaction have been documented in RCTs[92–95] and in real-world conditions[96]. Bolus calculators might also be useful when calculating appropriate meal-time insulin dosing during pregnancy and are integrated parts of many insulin pumps.

Hypertension in pregnancy

Hypertensive disorders in pregnancy, such as chronic hypertension and pregnancy-induced hypertension (including preeclampsia), occur in up to 40% of women with pre-existing diabetes mellitus[97]. The prevalence is highest among women with diabetic kidney disease[98]; however, women with pre-existing diabetes mellitus and normal kidney function are more frequently affected by hypertensive disorders than healthy pregnant women[99,100].

Preeclampsia and preterm delivery. Preeclampsia is defined as hypertension and proteinuria presenting after 20 gestational weeks[6]. Preeclampsia develops most commonly in women with pre-existing diabetes mellitus who have high levels of HbA_{1c} in early[13–19] and late[17] pregnancy, diabetic kidney disease (which includes microalbuminuria[19,79,100–102] and nephrotic proteinuria[103,104]) and/or elevated blood pressure[13,14,18,19,104]. In 2018, high blood pressure and the presence of diabetes mellitus complications in early pregnancy were shown to be main predictors of preeclampsia in women with pre-existing diabetes mellitus[6]. Almost one in five women with pre-existing diabetes mellitus develop preeclampsia during pregnancy[19]. According to unpublished data from our centre, a high proportion of cases of preeclampsia in women with pre-existing diabetes mellitus develop before 37 weeks and often lead to preterm delivery (L.R., P.D. and E.R.M., unpublished work).

Diabetic kidney disease in pregnancy. In pregnant women with T1DM, urinary albumin excretion and blood pressure have been demonstrated to gradually increase before onset of preeclampsia compared with women who remain normotensive. Moreover, early in pregnancy, blood pressure is slightly raised in women who develop preeclampsia[14]. The prevalence of preeclampsia is substantially higher in women with pre-existing diabetes mellitus when microalbuminuria is present in early pregnancy than in women with pre-existing diabetes mellitus and normal kidney function[79,105,106]. The incidence of early preterm delivery (before 34 weeks) is considerably increased in women with T1DM and microalbuminuria, which is mostly attributable to early development of preeclampsia[105,107]. Similarly, preterm delivery before 37 weeks is prevalent in these women and is often related to onset of preeclampsia[79,100,105].

A strong association exists between suboptimal blood pressure control in early pregnancy and risk of preterm delivery in women with diabetic kidney disease[19,79,100–102]. In a study including 43 pregnancies complicated by diabetic kidney disease, women with suboptimal blood pressure control in early pregnancy were more likely to deliver before 32 gestational weeks than women with normal blood pressure (38% versus 5%)[108].

Strategy for hypertension management. In an international multi-centre study published in 2018, 981 women with nonproteinuric chronic hypertension or gestational hypertension were randomly assigned to tight (target diastolic blood pressure below 85 mmHg) or less tight (target <100 mmHg) blood pressure control using antihypertensive treatment. Tight blood pressure control was associated with less severe hypertension at all stages of pregnancy, but particularly so when initiated before 28 weeks. No adverse events related to tight blood pressure control were reported. By contrast, less tight blood pressure control was associated with an increased incidence of preterm delivery[109]. With the application of early and intensive antihypertensive treatment to women with pre-existing diabetes mellitus, the prevalence of preeclampsia in pregnant women with diabetic kidney disease can be reduced[6,79,100,102].

At our centre, antihypertensive treatment is initiated when blood pressure ≥135/85 mmHg and/or urinary levels of albumin excretion ≥300 mg per 24 h are documented. Use of this strategy in a cohort of women with T1DM and microalbuminuria meant that none of the women developed preeclampsia, and the prevalence of preterm delivery was 20%[100]. A similar effect on the prevalence of preeclampsia and preterm delivery has been observed in women with T2DM and diabetic kidney disease who were treated according to the same strategy[79]. Among women with pre-existing diabetes mellitus who were followed up during pregnancy at our centre, chronic hypertension is present in 6%, while 8% develop gestational hypertension and 8% develop preeclampsia[6]. In total, approximately 25% of the women with pre-existing diabetes mellitus at our centre require antihypertensive treatment during pregnancy to maintain blood pressure below 135/85 mmHg and/or urinary albumin excretion below 300 mg per 24 h (REF.[6]).

Antihypertensive agents used in pregnancy. In women with pre-existing diabetes mellitus and diabetic kidney disease, early and intensive antihypertensive treatment might ameliorate the symptoms of preeclampsia[79,100,110]. Women using angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers before pregnancy should be changed to antihypertensive agents approved for use in pregnancy (that is, methyldopa, labetalol, nifedipine or diltiazem). Methyldopa is often the first choice, but a combination of more antihypertensive agents might be indicated to control hypertension and urinary albumin excretion[102,110,111] (FIG. 2). In women treated with furosemide or thiazide before pregnancy, this treatment can be continued during pregnancy in stable doses[98]. Discontinuation of diuretics in pregnant women should be discouraged owing to the risk of rebound fluid retention with increasing hypertension and proteinuria[102,110]. As in healthy women during pregnancy, new treatment with diuretics should not be initiated in pregnant women with pre-existing diabetes

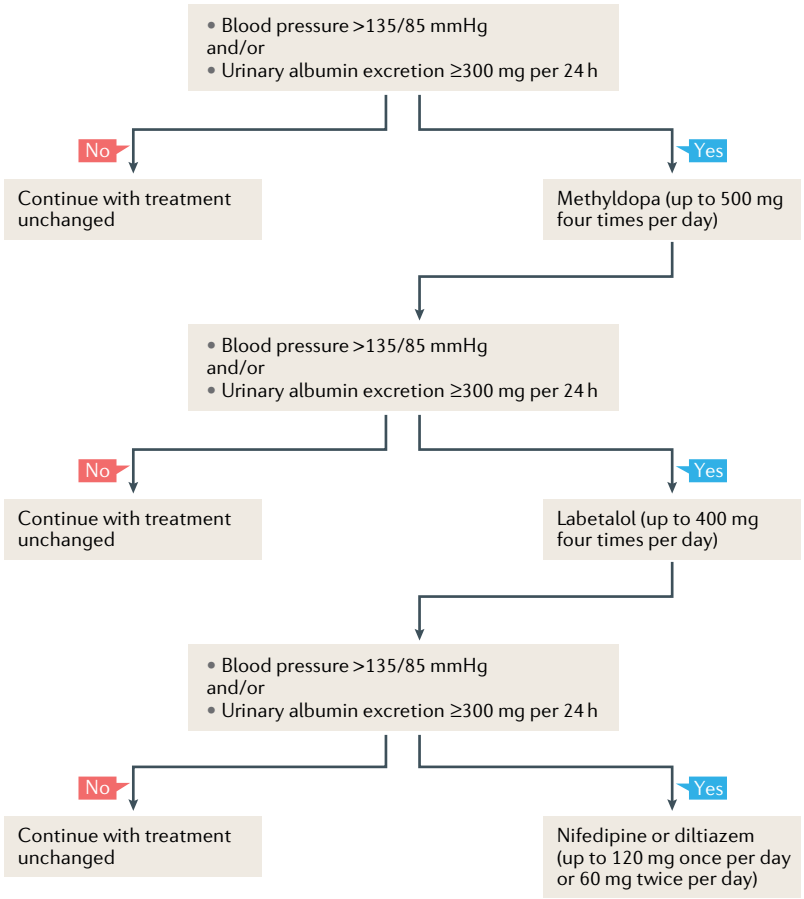

Fig. 2 | **Treatment algorithm for antihypertensive treatment in pregnancy.** Methyldopa is used as the first choice. If necessary, labetalol and/or nifedipine or diltiazem can be added as the second and third choice, respectively. If given before pregnancy, furosemide or thiazide can be continued during pregnancy.

mellitus[98]. Up to four classes of antihypertensive agents might be required to control blood pressure[100,102,110]. Antihypertensive agents do not seem to increase the risk of intrauterine growth restriction in offspring of women with pre-existing diabetes mellitus[79,100,112].

The largest study to date concerning pregnancies in women with T1DM and diabetic nephropathy demonstrated suboptimal hypertension management. In this study, only one-third of women were on renin angiotensin receptor inhibitors before pregnancy, and only one-quarter of the women used antihypertensive agents in the first trimester[18]. Target blood pressure in the first trimester (<130/80 mmHg) was reached in only 39% of women. Furthermore, severe hypertension and nephrotic proteinuria became prevalent in late pregnancy, and three-quarters of women delivered before 37 gestational weeks, mostly as a result of preeclampsia. Blood pressure ≥130/80 mmHg and protein excretion ≥1 g per 24 h in the first trimester were associated with preterm delivery before 37 gestational weeks[18]. This study[18] and studies from Denmark[79,100,102], Germany[107] and the USA[108] support the idea that women with diabetic kidney disease might benefit from early and intensive antihypertensive treatment.

In non-pregnant individuals with diabetic kidney disease, the reno-protective effect of antihypertensive treatment is well documented[113]. Antihypertensive treatment reduces blood pressure and urinary albumin excretion and might improve endothelial function by stabilizing the albumin leakage from the microcirculation. Therefore, antihypertensive treatment might alleviate the clinical features of preeclampsia that are related to maternal endothelial dysfunction. In pregnancy, antihypertensive treatment might also increase the vasodilatory capacity, which has a beneficial effect on placental development[98].

Fetal blood flow during antihypertensive treatment. In a small prospective study including nine women with pre-existing diabetes mellitus, antihypertensive treatment with methyldopa was initiated at 35 gestational weeks on the indication of new-onset pregnancy-induced hypertensive disorders[114]. One week after initiation of methyldopa treatment, all fetal ultrasound flow evaluations demonstrated normal and stable values compared with before treatment initiation. None of the routine non-stress tests led to obstetrical intervention and all infants had normal Apgar scores (a measure of the physical condition of a neonate 1 min and 5 min after delivery)[114]. These findings are in agreement with previous observations of stable fetal haemodynamics in women without diabetes mellitus who developed hypertensive disorder during pregnancy and who initiated methyldopa treatment in late pregnancy[115–117].

Low-dose aspirin. In a multi-centre, double-blind, placebo-controlled RCT, treatment with early-onset (at 11–14 gestational weeks) low-dose (150 mg) aspirin at night-time in a mixed group of women at high risk of early onset of preeclampsia (before 37 gestational weeks), including some women with diabetes mellitus, resulted in a lower incidence of preeclampsia than in women receiving placebo[118]. Low-dose aspirin should be prescribed to all pregnant women with pre-existing diabetes mellitus to reduce the risk of preeclampsia[12,118–120]. The treatment should begin before 16 weeks but is often first initiated around 10 gestational weeks after the organogenesis has taken place[98].

Smartphone application technology

Today, smartphones are widely used among women of childbearing age in many countries, and nearly all pregnant women in our centre have a smartphone[121]. Several smartphone applications (apps) for patients with diabetes mellitus are available[122]. In 2014, we launched the app 'Pregnant with Diabetes', which uses evidence-based clinical recommendations from our centre[121]. The target group includes women with pre-existing diabetes mellitus who are pregnant or planning pregnancy. The aim is to provide easily accessible patient education by communicating clinically important antenatal health information and thereby improve pregnancy outcomes. Danish, English and Swedish versions of the app are available, and a version tailored for Australia was added in 2016. All versions are available free of charge at Google Play and the App Store. The app is frequently used, with half of the users at our centre obtaining information from the app when planning pregnancy and the majority use it

Table 2 | **The effect of intensified treatment on pregnancy outcomes**

Outcome	Before (1993–1999[a])[123,124]	After (2012–2016[b])[6]
Birthweight standard deviation score	1.83 ± 2.1	1.04 ± 1.4
Large-for-gestational-age infants	62.5%	42%
Preeclampsia	18.1%	9%
Preterm delivery	42%	17%

[a]Population-based cohort study including all of Denmark (5.5 million inhabitants) before an intensified multi-target treatment including diet, use of insulin analogues and antihypertensive treatment was initiated. [b]Population-based cohort study from a single centre covering the eastern part of Denmark (2.6 million inhabitants) on an intensified multi-target treatment including diet, use of insulin analogues and antihypertensive treatment.

repeatedly during pregnancy[121]. Internationally, the app has been downloaded by >35,000 individuals covering most countries around the world. In our experience, it is possible to combine the use of the app 'Pregnant with Diabetes' with other apps, such as an app for carbohydrate counting and apps for calculating meal-time insulin dose using the individual's carbohydrate-to-insulin ratio.

Future directions

Nationwide data from Denmark in 1993–1999 (REFS[123,124]) and data from the eastern part of Denmark (including Greater Copenhagen) in 1996–2000 (REF.[105]) documented poor pregnancy outcomes in women with T1DM. The majority of children born to women with T1DM were LGA with a birthweight standard deviation score of almost 2.0, preeclampsia occurred in almost one in five pregnancies and 40% of children were born preterm[105,123,124].

In the era of modern diabetes mellitus management during pregnancy, women with pre-existing diabetes mellitus in our region (Copenhagen, Denmark) are treated with insulin analogues, they are recommended to follow a diet that focuses on the quantity and quality of carbohydrates to achieve appropriate gestational weight gain and selected women are advised to use CGM[7,86]. With this approach, we have obtained improved pregnancy outcomes with healthier infants, who more often are born with birthweights that are appropriate for gestational age and at term, as documented in a population-based cohort study covering the eastern part of Denmark (including Greater Copenhagen) that included pregnancy outcomes in 494 women with pre-existing diabetes mellitus in 2012–2016 (REF.[6]) (TABLE 2). However, the prevalence of fetal overgrowth, preeclampsia and preterm delivery is still markedly higher than in the general population[6].

Interventions to improve pregnancy outcomes in women with pre-existing diabetes mellitus include a structured pre-pregnancy care programme and combined clinics delivered by experienced diabetologists and obstetricians with support from nurses, midwives and dieticians offering diabetes mellitus visits on a bi-weekly basis, and more often if indicated[34]. With this approach, a reduction in congenital malformations over a 10-year period has been achieved[34]. Future studies should investigate the use of newer insulin analogues, such as Fiasp, with regard to effects on glycaemic control and pregnancy outcomes. Refinement of antihypertensive treatment with home monitoring of blood pressure before initiation of and adjustment of antihypertensive treatment should also be addressed. In addition, treatment tools to improve women's motivation to adhere to dietary advice and self-adjustment of insulin dose as it changes during pregnancy are urgently needed. The indications for diabetes mellitus technology, including glucose monitoring systems and closed-loop therapy (CGM with an algorithm to determine the optimal amount of insulin delivered through an insulin pump), need to be carefully explored in well-designed studies.

Conclusions

Modern diabetes mellitus management in pregnancy includes a multi-target focus on glucose regulation, dietary advice, appropriate gestational weight gain, blood pressure control and tools for outreach patient education. The use of insulin analogues and CGM might improve pregnancy outcomes and reduce the risk of severe maternal hypoglycaemia. Furthermore, appropriate carbohydrate intake and restricted maternal gestational weight gain are promising treatment modalities to optimize fetal growth. In addition, antihypertensive treatment might contribute to reducing the risk of preeclampsia and preterm delivery. Smartphone application technology is a new tool that can be used to share the latest evidence-based clinical recommendations in diabetes mellitus and pregnancy with patients and diabetes mellitus caregivers.

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Author contributions

L.R. researched data for the article, contributed to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission. P.D. and E.R.M. contributed to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission.

Competing interests

L.R., P.D. and E.R.M. are participating in multi-centre and multi-national clinical studies on the use of insulin in pregnant women with pre-existing diabetes mellitus in collaboration with Novo Nordisk; no personal honorarium is involved. E.R.M. is in the speaker's bureau of Novo Nordisk.

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