REVIEW ARTICLE

Insulin therapy for the treatment of type 1 diabetes during pregnancy

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Abstract

Pregnancies affected by type 1 diabetes (T1D) carry a major risk for poor fetal, neonatal and maternal outcomes. Achieving normoglycemia while minimizing the risk of hypoglycemia is a major goal in the management of T1D as this can greatly reduce the risk of complications. However, maintaining optimal glucose levels is challenging because insulin requirements are not uniform throughout the course of the pregnancy. Over the past decade, there has been significant improvement in the methods for glucose monitoring and insulin administration, accompanied by an increase in the number of treatment options available to pregnant patients with T1D. Through study of the scientific literature and accumulated evidence, we review advances in the management of T1D in pregnancy and offer advice on how to achieve optimal care for the patient.

Introduction

Diabetes is one of the most common chronic diseases among women of reproductive age, observed in about 10% of pregnancies in the US and approximately 0.2–0.5% of these are in women with type 1 diabetes (T1D).

T1D pregnancies are associated with an increased rate of complications, including late intrauterine death or major congenital malformations, which can lead to increased fetal morbidity and mortality compared to non-diabetic pregnancies. Maternal complications are also more frequent, with increased rates of preeclampsia, cesarean section and maternal mortality. Poor glycemic control at the time of conception and organogenesis during the first trimester is a major cause for an increased risk of birth defects and pregnancy complications. It has been recognized that a positive correlation exists between hemoglobin A1c (HbA1c) levels during early pregnancy and the incidence of fetal malformations. Therefore, good glycemic control could lead to a reduction of congenital abnormality rates to almost non-diabetic levels [1].

Preconception counseling and strict glycemic control have improved pregnancy outcomes in women with T1D, as evident from reduced rates of congenital malformations, preterm delivery and decreased neonatal morbidity, manifested by reduced macrosomia and admissions to neonatal care units. This is further exemplified by a case study from our clinic (Table 1). Patients receiving prenatal care have been shown to maintain better HbA1c levels, resulting in a reduction of infant mortality from 20% in the 1950s to less than 3% in the 1980s. This would not have been possible without the significant evolution in glucose monitoring methods, the introduction of insulin pumps and the development of insulin analogs.

Challenges in the treatment of T1D during pregnancy

One of the main challenges in the care for pregnant women with diabetes is the proper control of blood glucose. Metabolic changes occurring as a result of the pregnancy complicate this task. During the first trimester, increased insulin sensitivity combined with the constant attempts to achieve normoglycemia through insulin therapy, raise the risk of hypoglycemia. The second and third trimesters of pregnancy are characterized by an enhanced secretion of placental hormones, growth factors and cytokines, leading to an increased insulin resistance and hyperglycemia. Hyperglycemia results in the transport of increased amounts of glucose across the placenta, causing fetal hyperinsulinemia and macrosomia. Macrosomia can cause maternal and fetal complications and is observed in about 27–62% of infants of mothers with diabetes. Careful monitoring of glucose levels and constant adjustment of insulin therapy are needed to prevent hyperglycemia during pregnancy.

T1D women face an increased risk of pregnancy complications. Diabetic ketoacidosis (DKA), common in T1D

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Table 1. Prenatal care for a pregnant T1D patient – a case study.

Patient	A 31-year-old female with T1D presented to the office for evaluation. She had just relocated and found out that she was pregnant and expressed a wish for ''things [to] go better this time''.
History	She developed diabetes at age 14 and always had poor glycemic control. Her most recent HbA1c was 14.2%. Her diabetes was complicated by retinopathy with laser surgery, peripheral neuropathy, autonomic neuropathy in the form of hypoglycemic unawareness and diabetic cystopathy with frequent urinary tract infections and incontinence. She had been pregnant two other times. Her first pregnancy ended with a spontaneous abortion at 21 weeks. An analysis showed an unspecified developmental defect. With her second pregnancy she developed preeclampsia at 31 weeks of gestation, requiring antihypertensive medications. She developed preterm labor at 33 weeks and delivered shortly after that. Her neonate developed septicemia and died in the ICU. This patient had never seen an endocrinologist or maternal fetal medicine specialist, as these specialists were not available where she lived. Her diabetes had always been treated with two injections per day of NPH and regular insulin.
Treatment	After meeting with a certified diabetes educator her insulin regimen was intensified to four injections per day, with a variable amount of aspart at meals, as determined by carbohydrate counting. NPH was used at bedtime. The insulin regimen was adjusted multiple times, and her HbA1c declined to 6.9%. Following a dilated retinal exam, an ophthalmologist treated her with panretinal photocoagulation laser therapy.
Outcome	The patient developed preeclampsia at 36 weeks of gestation, and was treated with antihypertensives. She gave birth at 39 weeks and had a healthy baby. Both the mother and her neonate were discharged to home.

Table 2. Selected ADA and ACOG recommendations [6,7].

	ADA	ACOG
Glycemic goals	• Pre-meal values of 3.3–5.5 mmol/L (60–99 mg/dL). • Peak postprandial glucose of 5.5–7.2 mmol/L (100–129 mg/dL). • Bedtime and overnight glucose of 3.3–5.5 mmol/L (60–99 mg/dL). • Mean daily glucose of <6.1 mmol/L (<110 mg/dL) and HbA1c <6.0%.	• Fasting glucose level of <5.3 mmol/L (<95 mg/dL). • Pre-meal values of <5.5 mmol/L (<100 mg/dL). • 1-h postprandial levels <7.8 mmol/L (<140 mg/dL), and 2-h postprandial values of <6.7 mmol/L (<120 mg/dL). • During the night, glucose levels should not decrease to <3.3 mmol/L (<60 mg/dL). • Mean capillary glucose levels should be maintained at an average of 5.5 mmol/L (100 mg/dL); HbA1c ≤6.0%.
Glucose monitoring	• Daily self-monitoring both before and after meals, at bedtime and occasionally at 2:00 AM–4:00 AM. • HbA1c test at the initial visit during pregnancy, monthly tests until target levels <6.0% are achieved, followed by testing every 2–3 months thereafter.	• Daily self-monitoring in the fasting state, before and 1 or 2 h after each meal and before bed. In selected patients, especially those on insulin pumps, glucose determinations at 2:00 AM–3:00 AM may help detect nocturnal hypoglycemia. • HbA1c measurement provides an indication of glycemic control over the past 2–3 months and should be performed during each trimester.
Prevention of severe hypoglycemia	• Assess the presence of clinically diminished counter-regulatory responses to hypoglycemia and educate patients to minimize its occurrences. • CGM may be a supplemental tool to self-monitoring for selected patients with T1D, especially those with hypoglycemia unawareness.	• Patients should be questioned to determine if they can recognize when their glucose levels decrease to <3.3 mmol/L (<60 mg/dL). • Patients and their families should be taught how to respond quickly and appropriately to hypoglycemia.

patients, develops faster during pregnancy due to decreased insulin sensitivity in the second and third trimesters. DKA remains a major cause of fetal loss, affecting 1–3% of patients with pregestational diabetes [2,3]. T1D pregnancies are also characterized by an increased frequency of vascular complications. Gestational hypertension is a common complication and a major risk factor for cardiovascular events, retinopathy and nephropathy. Furthermore, rates of preeclampsia are 2- to 4-times higher in pregnant women with T1D, leading to infant complications, including poor growth and premature birth [4]. Preeclampsia can also be associated with serious maternal problems such as eclampsia and ''hemolysis, elevated liver enzymes, low platelet count'' (HELLP) syndrome. HELLP syndrome, a life-threatening complication, has been linked to severe hypoglycemia attacks during pregnancy [5]. Optimal glycemic control reduces the risk of preeclampsia and related complications. T1D women who develop preeclampsia tend to have significantly higher HbA1c values before and during pregnancy. This highlights the importance of monitoring HbA1c during pregnancy in women with T1D.

Severe hypoglycemia, a major challenge in the management of T1D, has been reported in 19–44% of pregnant diabetes patients treated with intensive insulin therapy, especially in the first trimester. Severe hypoglycemia is dangerous for the mother and can lead to loss of consciousness, seizures and death. Repeated hypoglycemic episodes can lead to hypoglycemia unawareness, causing further loss of symptoms associated with the autonomic response to hypoglycemia. Additionally, symptoms of hypoglycemia (nausea, anxiety, etc.) might be mistaken for normal pregnancy symptoms, increasing the danger of severe hypoglycemia. A major goal in the management of T1D during pregnancy is the prevention of hypoglycemic episodes. Table 2 summarizes recommendations from the American Diabetes Association (ADA) and the American Congress of Obstetricians and Gynecologists (ACOG) for glycemic goals, glucose monitoring and prevention of severe hypoglycemia [6,7]. One of the ways to prevent hypoglycemia is through individualized insulin dosing. The patient might, in fact, need to reduce the insulin dose during the first trimester in order to prevent

Table 3. Characteristics of insulin and insulin analogs [17].

Insulin or insulin analog	Onset of action (minutes)	Time to peak concentration (minutes)	Maximum duration of action (hours)
Insulin			
Regular insulin	30–60	90–120	5–12
NPH insulin	60–120	240–480	10–20
Bolus insulin analogs			
Insulin lispro	10–15	30–60	3–4
Insulin aspart	10–15	40–50	3–5
Insulin glulisine	10–15	55	3–5
Basal insulin analogs			
Insulin glargine	60–120	None	24
Insulin detemir	60–120	None	20–24

Adapted from Trujillo AI. Diabetes Spectr. 2007.

hypoglycemic episodes [8]. Several studies suggest that the use of insulin analogs instead of human insulin may lower the risk of severe hypoglycemia in women with diabetes [9–11]. In addition, real-time continuous glucose monitoring (CGM) with set alarms for low glucose values, might be useful for pregnant women with hypoglycemia unawareness.

Targets for glycemic control

For patients with T1D, the therapeutic insulin dose is adjusted to the patient's glucose profile. Daily monitoring is essential for proper insulin dosing, as insulin requirements vary during pregnancy. ADA and ACOG recommend self-monitoring several times throughout the day and occasionally at night in order to detect nocturnal hypoglycemia (Table 2) [6,7].

ADA and ACOG also recommend maintaining mean daily glucose levels between 5.2 and 6.1 mmol/L (95–110 mg/dL) and HbA1c <6.0%, with specific goals for preprandial, postprandial and bedtime glucose [6,7]. The goal during labor is to avoid maternal hyperglycemia in order to prevent subsequent neonatal hypoglycemia (by maintaining blood glucose levels <6.1 mmol/L [<110 mg/dL], as assessed by hourly blood glucose readings) [7]. Insulin requirements generally fall after delivery.

Progress in the management of T1D in pregnant women

The use of insulin analogs

Currently, the treatment of pregnant women with T1D is influenced by the fact that patients are better informed about the disease. A higher percentage of pregnancies are planned, providing an opportunity for adequate preparation of the patient in anticipation of potential complications from T1D.

Glucose levels are controlled through the administration of long-acting (basal) insulin analogs and rapid-acting (bolus) insulin analogs. Patients follow a multiple daily injection regimen (MDI) that involves four, and even up to seven, insulin injections administered before meals and pre-bedtime. The goal of rapid-acting insulin administration is to achieve postprandial glucose control. Compared with regular human insulin, bolus insulin analogs have a more rapid onset and a shorter duration of action (Table 3), resulting in a more effective reduction of postprandial hyperglycemia and avoidance of hypoglycemic events between meals [12].

Two rapid-acting insulin analogs, lispro and aspart, are currently classified as pregnancy risk category B, based on reports demonstrating fetal, perinatal and maternal outcomes similar to regular human insulin [13–15]. Lispro and aspart are at least as effective as regular human insulin in achieving glucose control, as evident from HbA1c levels. The main benefit of insulin analogs is the reduction of severe hypoglycemic events in pregnant T1D patients. Glulisine is another rapid-acting insulin analog available for use in the general diabetic population. However, there are no controlled studies addressing its safety in pregnancy [12], and glulisine is not recommended for pregnant women with T1D.

Basal insulin is required for the maintenance of glycemic control between meals. Until recently, neutral protamine Hagedorn (NPH), an intermediate-acting insulin, was the only insulin approved for use as basal therapy in pregnant T1D patients and was considered as the standard of care for diabetes in pregnancy. However, NPH use can be associated with a peak in concentration 4–8 h post-injection (Table 3) and high intrasubject variability that may lead to an increased risk of hypoglycemic events between meals and at night [16,17].

In recent years, glargine and detemir have become the basal insulin analogs of choice in the general T1D population. Glargine shows a relatively flat action profile with a near 24-h duration (Table 3) [18]. Glargine also shows lower intrasubject variability compared to NPH, as measured by the coefficient of variation for the 24-h glucose infusion rate – 48% for glargine versus 68% for NPH [19]. As a result, glargine used in the general population leads to glycemic control that is at least comparable to that of NPH, but with significantly lower risk for hypoglycemia [20]. While there are numerous reports on the off-label use of glargine in pregnant women, there are no randomized clinical trials assessing its safety during pregnancy [17]. Therefore, insulin glargine is currently classified as pregnancy risk category C and is not approved for use in pregnant women.

Detemir also shows a flatter action profile with a longer duration of action than NPH, approaching 24 h at clinically relevant doses [21,22]. Detemir has the lowest intrasubject variability among the basal insulins (27%) [19]. These characteristics suggest that detemir has the potential to be an improvement over NPH for the control of T1D.

A significant advance in the care for pregnant women with T1D was marked in 2012 with the reclassification of

detemir as pregnancy risk category B, based on results from a randomized, active-controlled study by Mathiesen et al. [23]. This study evaluated the efficacy and safety of detemir in 310 pregnant T1D patients, randomized 1:1 to receive either detemir or NPH in a basal-bolus regimen with aspart. Treatment was initiated up to 1 year before pregnancy (48%) or at 8 to 12 weeks during pregnancy (52%). The primary endpoint of the study was HbA1c at 36 gestational weeks. Additional endpoints included maternal safety.

In terms of efficacy, detemir demonstrated non-inferiority to NPH with respect to the primary endpoint of the study [23]. A significant number of women in both groups (41% in the detemir group; 32% in the NPH group) reached the target of HbA1c ≤6.0% at 24 and 36 weeks of gestation. Interestingly, fasting plasma glucose was significantly lower in the detemir group at 24 and 36 weeks of gestation, especially in patients initiating treatment with detemir before pregnancy. No difference in the rate of hypoglycemia was observed between the two study arms. The incidence of preeclampsia was slightly higher in the detemir group, but within expected rates for pregnancies complicated by diabetes [24]. No significant differences in early fetal death or the health of the fetus and newborn were seen with detemir [24].

Insulin premixes have proven somewhat useful for the treatment of the general population with diabetes, especially patients who need simplified dosing regimens. However, premixes are not useful for the treatment of pregnant T1D patients, as premixed formulations cannot provide the required dosing flexibility during the different periods of pregnancy [25].

Methods for glucose monitoring and insulin administration

Accurate determination of blood glucose levels is important for the proper control of diabetes. Until recently, this was achieved solely by the self-monitoring of capillary blood glucose using glucose meters. The development of continuous glucose monitoring (CGM) devices represents an advance that can provide real-time measurements and warnings when patients face hypoglycemia. Several studies have examined the benefits of CGM for the general population, but only a few studies have been performed in pregnant women with T1D. A study by Yogev et al. showed that CGM use during pregnancy can detect hyperglycemic and nocturnal hypoglycemic events that might have gone unnoticed with intermittent blood glucose monitoring [26]. A small, randomized trial performed by Murphy et al. showed that CGM improved glycemic control in women with T1D and T2D, led to lower birth weight and reduced risk of macrosomia [27]. Based on these results, the American Association of Clinical Endocrinologists (AACE) recommended the use of CGM for all pregnant patients with T1D. A recent randomized trial investigated the intermittent use of real-time CGM during pregnancy (study arm) in addition to self-monitored plasma glucose levels seven times daily (control arm) [28]. HbA1c, self-monitored plasma glucose, severe hypoglycemia events and prevalence of large-for-gestational-age infants for women using CGM were comparable to controls. These results suggest that the intermittent use of CGM in pregnant patients with well-controlled diabetes does not further improve disease management and pregnancy outcomes. Additional large controlled studies examining maternal and neonatal outcomes with CGM use are still needed to confirm its benefit [29].

Additionally, patients requiring insulin therapy need to consider the method of administration. Patients can choose between MDI using a syringe or insulin pen and continuous subcutaneous insulin infusion (CSII) via an insulin pump. Several observational studies have attempted to evaluate the effectiveness of insulin pumps versus MDI in pregnant women with T1D. In 2012, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review summarizing the results of these studies [30]. The AHRQ found that HbA1c values improved with either MDI or CSII and there was no statistically significant difference in outcomes between the two delivery methods. Because no randomized controlled trials had been performed, the strength of evidence was insufficient to show statistically significant differences in any other maternal or fetal outcomes; therefore, the risk of bias was high. A newer, retrospective, observational study by Wender-Ozegowska et al., confirmed a reduction in HbA1c to similar levels with both CSII and MDI use during pregnancy [31], although there were fewer hypoglycemic and hyperglycemic episodes in the CSII group. No differences in maternal, fetal and perinatal outcomes were detected. The use of CSII in pregnant women with diabetes is an established practice. Insulin pump utilization is high (about 40%) in the general T1D US population due to improvement in the quality of life and observed decrease in HbA1c. Further studies focused on pregnant women with T1D are necessary to confirm any superiority of CSII use.

CSII insulin delivery has drawbacks, such as higher cost of the pump and pump supplies, difficulty of use requiring the patient to be motivated and compliant and willingness to test glucose multiple times daily, that might limit its usefulness in pregnant T1D patients. In addition, there is a risk of hypoglycemia or even DKA in case of a pump malfunction or infection at the infusion site.

Sensor-augmented pump (SAP) therapy (combinations of CGM and CSII) might improve the treatment of T1D patients even further. Use of open-loop SAP (patient reads the CGM values and manually adjusts the pump) in non-pregnant patients with inadequately controlled T1D results in a significant improvement of HbA1c levels [32]. The use of SAP in pregnant women has been tested only on a small scale and did not show a significant benefit, except during the first trimester [33]. However, the study was too small to be adequately powered.

Closed-loop SAP therapy uses a control algorithm to guide insulin delivery based on real-time CGM measurements. Closed-loop systems could be of great benefit to pregnant women with T1D as the algorithm should, in theory, be capable of maintaining optimal glucose levels. The development of such systems is still ongoing.

Conclusions

T1D in pregnancy is a high-risk clinical situation associated with significant chances of complications for the mother

and the fetus. However, clinical practice and research have shown that pregnancy planning, preconception counseling and maintaining optimal glucose levels have a positive effect on pregnancy outcomes.

The main goal in caring for the pregnant patient with T1D should be achieving near-normal blood glucose levels while minimizing the risk of hypoglycemia. The development of insulin analogs with improved safety and efficacy profiles has facilitated the achievement of normoglycemia. Evidence supports the use of the bolus insulins, lispro and aspart, as the mealtime component of MDI or as used in CSII. The recent reclassification of detemir to pregnancy risk category B provides pregnant T1D women with a basal insulin analog, further expanding treatment options for this patient population. Evidence supports the use of insulin detemir, or NPH, as the basal component of an MDI regimen.

Women with T1D should attend pre-pregnancy services and antenatal clinics led by professionals with endocrine and obstetrical expertise, in order to maximize the likelihood of positive pregnancy outcomes. The objective is to optimize glycemic control prior to pregnancy (HbA1c < 6.5%), to start folic acid supplementation (recommended 4 mg daily), to alter medications unsuitable for pregnancy and to ensure that medical issues are addressed before conception and during pregnancy.

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Declaration of interest

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