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HOSPITAL MANAGEMENT OF DIABETES (A WALLIA AND JJ SELEY, SECTION EDITORS)

Inpatient Glycemic Management of the Pregnant Patient

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Abstract

Purpose of Review There is a rising prevalence of type 1 diabetes (T1DM), type 2 diabetes (T2DM), and gestational diabetes (GDM) in pregnancy. Reaching and maintaining glycemic targets during and after this time are important for both the health of the mother and her baby.

Recent Findings Based on recently published guidelines from various societies, we review the diagnosis of diabetes in pregnancy, types of therapies available to maintain euglycemia, important keys to management of T1DM, T2DM, and GDM, and strategies for reaching inpatient glycemic targets during the peripartum period. Care for pregnant patients with T1DM is especially challenging, and providers should be aware of the varying insulin requirements at different stages of pregnancy and how to reduce hypoglycemia and avoid diabetic ketoacidosis. Insulin sensitivity fluctuates throughout pregnancy due to physiologic changes, especially during labor and delivery and immediately post-partum. We review recommendations regarding how to manage this dynamic time and present our own institution's inpatient management protocol. Finally, we review management of diabetes post-partum, including medications, breast-feeding, and continued monitoring and screening.

Summary With the collaborative efforts of the patient and an interdisciplinary team and in-depth knowledge of the most up-to-date management principles, it is possible to achieve euglycemia during this critical time of a mother and baby's life.

Keywords Gestational diabetes · Type 2 diabetes · Type 1 diabetes · Pregnancy · Insulin management · Euglycemic diabetic ketoacidosis

Introduction

The prevalence of diabetes continues to rise and increasingly affects individuals of all ages, including women of childbearing age. Diabetes of any type has been found to affect approximately 7% of pregnancies, and pregnancy itself profoundly affects the management of diabetes [1••]. Initial management generally involves frequent outpatient visits with endocrinology, obstetrics, and nutrition. However, despite these efforts, women who are unable to achieve glycemic targets at any point during their pregnancy may warrant hospitalization for optimization of therapy, patient education, and support.

In pregnancy, it is important to achieve glycemic targets given that these target blood glucose levels are associated with an improvement in several short and long-term adverse maternal, fetal, and neonatal complications. Maternal hyperglycemia during the first 6–8 weeks of gestation is strongly associated with increased risk of spontaneous abortions and major congenital malformations [2]. After 12-weeks gestation, hyperglycemia induces fetal hyperinsulinemia and accelerated growth. Macrosomia (birth weight > 4000–4500 g) occurs in 27–62% of infants born to mothers with diabetes compared with ~ 10% of infants born to mothers without diabetes [2]. Macrosomia is associated with increased rates of operative delivery and birth trauma, shoulder dystocia, fetal death, and neonatal complications including hypoglycemia, hypertrophic cardiomyopathy, polycythemia, and hyperbilirubinemia. In the long term, poor glycemic control during pregnancy predisposes both mothers and their children to an increased risk of obesity and cardiometabolic disorders [3, 4].

Tiffany Yeh and Michele Yeung contributed equally to the writing of this paper and are listed alphabetically

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Preconception Care of the Patient with Preexisting Type 1 or Type 2 Diabetes

All women of childbearing potential with type 1 diabetes (T1DM) or type 2 diabetes (T2DM) should be counseled on the importance of tight glycemic targets and trying to avoid pregnancy if control is suboptimal. There is no threshold for A1c values below which risk of spontaneous abortion or congenital malformations disappears entirely, but obtaining a hemoglobin A1c < 6.5% without hypoglycemia should be the goal to minimize such risks [5••].

Additionally, medication use should be reviewed ideally before conception, since many drugs commonly used to treat diabetes and its complications are contraindicated or not recommended in pregnancy, including statins, ACE inhibitors, angiotensin II receptor blockers (ARBs), and most non-insulin oral and injectable therapies.

Glycemic Goals During Pregnancy

Maternal, fetal, and neonatal complications are largely avoidable by preventing maternal hyperglycemia. Several articles have helped to define normoglycemia in pregnancy [6, 7]. Pooling data from both studies showed that the weighted average glucose values (± 1 SD) were 71 ± 8 mg/dL fasting, 109 ± 13 mg/dL at 1-h postprandial, and 99 ± 10 mg/dL at 2-h postprandial [8]. During pregnancy, increasing levels of progesterone, cortisol, prolactin, and human placental lactogen all contribute to a progressively insulin-resistant state (Fig. 1). Women with either gestational diabetes (GDM) or pregestational diabetes (type 1 or 2) lack the ability to increase insulin production sufficiently to counter this rise in insulin resistance, which results in hyperglycemia. A short period of increased insulin sensitivity during gestational weeks 10–14 has been observed in those individuals with preexisting diabetes [10]. Following this, for the remainder of the pregnancy, insulin requirements are expected to increase exponentially (Fig. 1). This fluctuating physiology poses an additional challenge in the management of diabetes in pregnancy.

Not surprisingly, glycemic targets in the pregnant patient are stricter compared to that of the non-pregnant patient. The glycemic targets pre-pregnancy and during pregnancy include: fasting and premeal glucose ≤ 95 mg/dL, 1-h postmeal glucose ≤ 140 mg/dL, and 2-h postmeal glucose ≤ 120 mg/dL (Table 1). In the first trimester, the lowest rate of adverse fetal outcomes is associated with A1c < 6–6.5%, whereas in the second and third trimester, the lowest risk of large for gestational age (LGA) infants is associated with A1c < 6%. Therefore, a target A1c of 6–6.5% is recommended, but < 6% may be optimal if able to be achieved without significant hypoglycemia.

It is important to highlight that in pregnancy, there is a physiologic increase in red blood cell turnover; therefore, A1c levels may be monitored more frequently than usual. In addition to A1c, other markers of glycemic control include fructosamine and glycated albumin. Many proteins other than hemoglobin also undergo nonenzymatic glycation, leading to the formation of advanced glycosylation end products [13]. These glycosylated end products all contain ketoamine linkages that can be picked up by various assays. The term fructosamine refers to all ketoamine linkages that result from glycation of serum proteins [13]. Unlike A1c, fructosamine is not influenced by anemia or abnormal hemoglobin. Albumin is the most abundant serum protein, so glycated albumin (GA) is the main component of fructosamine. Fructosamine contains other components such as glycated lipoprotein and glycation globulin [13]. Since albumin has a faster turnover than hemoglobin, both fructosamine and GA serve as measurements of glycemic control during a shorter period (past 2 to 3 weeks) compared to A1c (past 3 months).

Each of these markers has their advantages and disadvantages. In disease states where protein (albumin) metabolism is

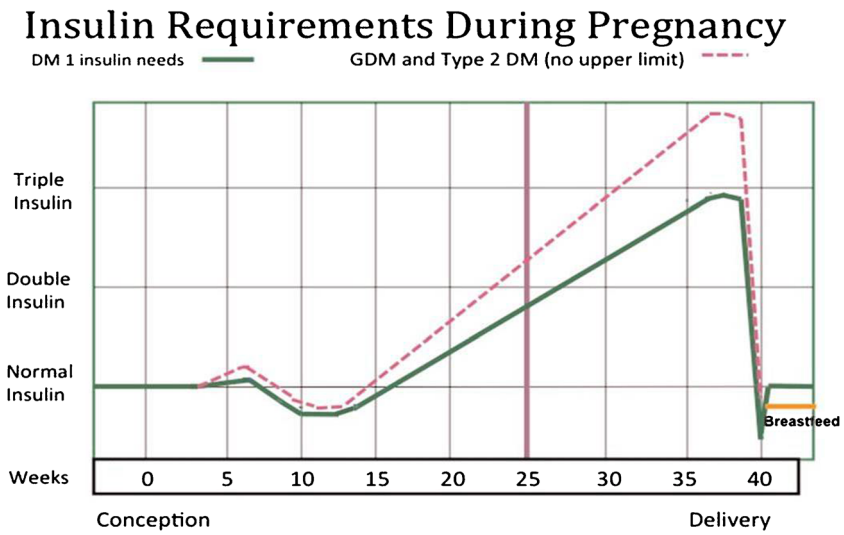

Fig. 1 Insulin requirements during pregnancy (Courtesy of: Shields, L and Tsay, GS. Editors, California Diabetes and Pregnancy Program Sweet Success Guidelines for Care. Developed with California Department of Public Health; Maternal Child and Adolescent Health Division; revised edition, Chapter 2 updated September 2015) [9]

Table 1 Glycemic goals throughout the peripartum period

Glucose goal (mg/dL)	Fasting	Pre-meals	1-h PP	2-h PP	Source
Pre-pregnancy	< 95	< 95	< 140	< 120	[5••, 11••]
Pregnancy	< 95	< 95	< 140	< 120	[5••, 11••]
Intra-partum	72–126 throughout labor and delivery 70–110 throughout labor and delivery				[5••] [1••]
Post-partum with GDM	< 100	< 100	< 140		[9]
Post-partum with pre-existing T1DM or T2DM	< 110	< 110		< 160	[9]
After C-section	< 110		< 160		[12•]
Breastfeeding	70–100	70–100	< 150	< 150	[9]
	Check glucose prior to breastfeeding and 1 h after, with goal glucose > 100 mg/dL				

PP post-prandial

increased (i.e., hyperthyroidism, nephrotic syndrome), the measured fructosamine and GA will be lower. Conversely, in disease states where protein metabolism is slowed (i.e., hypothyroidism), the measured fructosamine and GA will be higher. HbA1c reflects the percentage of hemoglobin that is glycated and GA is expressed as the ratio of glycated albumin to total albumin; therefore, HbA1c and GA are not influenced by dilution of serum which can develop during pregnancy. In contrast, fructosamine is not expressed as a ratio or percentage; therefore, it is influenced by serum protein concentration and can be affected by the dilutional anemia that occurs in pregnancy.

All these markers reflect the average glucose level, therefore may not fully capture postprandial hyperglycemia which drives macrosomia. As such, pregnant patients should also engage in frequent self-monitoring of blood glucose (SMBG). Ideally, fingerstick SMBG should be done before each meal, 1 or 2 h after each meal, and at bedtime. Recommended targets include fasting glucose ≤ 95 mg/dL, and 1-h postprandial glucose ≤ 140 mg/dL or 2-h postprandial glucose ≤ 120 mg/dL [5••]. Pregnant patients can choose to monitor either the 1-h postprandial or the 2-h postprandial glucoses as they are both equally effective in predicting fetal macrosomia or perinatal complications [14, 15]. However, one study argued that monitoring with 1-h postprandial glucose may provide stricter glycemic control as these patients had a higher rate of insulin therapy and a lower rate of LGA babies [15]. Given that hypoglycemia also comes with its own risks such as low birth weight, more or less stringent targets for A1c and SMBG may be appropriate for certain individuals particularly to minimize maternal hypoglycemia. The use of continuous glucose monitoring (CGM), currently off-label during pregnancy, may be useful for patients that are hypoglycemia-prone.

Diagnosing Gestational Diabetes Mellitus

The Endocrine Society, International Association of Diabetes and Pregnancy Study Group (IADPSG) and World Health Organization (WHO) all recommend screening for diabetes starting at the very first prenatal visit, by checking either fasting plasma glucose, HbA1c, or an untimed random plasma glucose. Diabetes is diagnosed if a woman has a fasting glucose ≥ 126 mg/dL, a random glucose ≥ 200 mg/dL, or HbA1c ≥ 6.5% [5••, 16]. In the absence of unequivocal hyperglycemia (i.e., patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥ 200 mg/dL), repeat testing should be done to confirm the results [17]. It is recommended that either the same test be repeated or a different test can be performed for confirmation [17]. Women who pass the initial screen should also undergo a 2-h, 75-g oral glucose tolerance test (OGTT) at 24–28 weeks gestation. This test is performed after an overnight fast of at least 8 h and uses a one-step screening approach where gestational diabetes can be diagnosed if a woman meets any one of the following parameters: fasting glucose ≥ 92 mg/dL, glucose at 1-h ≥ 180 mg/dL, or glucose at 2-h ≥ 153 mg/dL [5••].

It is important to note that these recommendations differ from that of the American College of Obstetricians and Gynecologists (ACOG). ACOG recommends that all pregnant women should be first screened for GDM at 24–28 weeks of gestation, with the caveat that earlier screening for undiagnosed type 2 diabetes should be considered in those women who are overweight or obese and have one or more risk factors [1••]. These risk factors include a first-degree relative with diabetes, high-risk race, or ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander), previously giving birth to an infant weighing 4000 g or more, previous GDM, impaired fasting glucose on previous testing, cardiometabolic derangements including high-density lipoprotein cholesterol less than 35 mg/dL, triglyceride level

Table 2 ACOG, Endocrine Society, and WHO Guidelines for Diagnosing GDM

	ACOG		Endocrine Society/ WHO
	Two-step screening: 50-g, 1-h OGTT followed by a 100-g, 3-h OGTT (if necessary)		One-step Screening: 75-g, 2-h OGTT
	Carpenter and Coustan	National Diabetes Data Group	
Fasting	95 mg/dL	105 mg/dL	92 mg/dL
1 h	180 mg/dL	190 mg/dL	180 mg/dL
2 h	155 mg/dL	165 mg/dL	153 mg/dL
3 h	140 mg/dL	145 mg/dL	N/A

greater than 250 mg/dL, or history of cardiovascular disease [1••]. If early screening results are negative, screening should be repeated at 24- to 28-weeks gestation. Different from the other organizations, ACOG recommends a two-step screening approach. Step 1 involves administering a 50-g oral glucose solution followed by measuring the 1-h plasma glucose. The thresholds for the 1-h glucose challenge vary from 130 to 140 mg/dL, with a range of sensitivities and specificities reported. Providers should select a cutoff and use it consistently for their practice. Women whose glucose levels at the 1-h mark meet or exceed the screening threshold then undergo step 2, which is a 100-g, 3-h diagnostic OGTT. ACOG recommends interpreting the 3-h OGTT using one of the two threshold sets listed below (Carpenter and Coustan or National Diabetes Data Group) (Table 2).

There is still much debate over which strategy for screening and diagnosing GDM is better, the two-step approach or the one-step approach. Lee et al. recently conducted a retrospective cohort study comparing the two screening strategies [18]. They initially found that the one-step group had a higher incidence of GDM (21.6 versus 5.0%). Initial results also suggested higher rates of neonatal hypoglycemia, phototherapy for hyperbilirubinemia, and a lower rate of gestational HTN. However, after adjustment for demographics, parity, and prior history of GDM, these differences disappeared, but a lower rate of LGA infants was discovered [18]. Further studies are still needed to show which screening approach is ideal. Given that currently there does not seem to be conclusive evidence favoring one strategy over another, providers can select the approach they or their institution prefers.

Management of GDM and Pre-existing Type 2 Diabetes

An interdisciplinary approach should be utilized to manage hyperglycemia in pregnancy. This includes medical nutrition therapy, weight management, and pharmacologic therapy. Meal plans should be individualized to the mother taking into account food preferences and culture, and ideally developed with the help of a registered dietitian and/or diabetes educator familiar with pregnancy nutrition. As a general guideline, women with GDM or overt diabetes should consume a balanced diet that is divided into three meals and two to three snacks [19]. In pregnancy, women are more susceptible to ketosis; therefore, it is important to emphasize a balanced diet rather than restricting calories, to avoid inciting starvation ketoacidosis. Additionally, for the individuals who spend large parts of their day away from home, it is important to discuss with the registered dietitian and/or diabetes educator healthy snack options to carry when they are out of the house. In the inpatient setting, a dietitian can provide education specific to diabetes and pregnancy. The dietitian can offer an individualized dietary prescription that provides adequate nutrition to support fetal and maternal well-being, maintain euglycemia with absence of ketones, and achieve appropriate weight gain in pregnancy.

Physical activity programs including aerobic activity and resistance training should be encouraged [20]. Unless a woman has medical reasons to avoid physical activity during pregnancy, such as premature labor, significant cardiopulmonary disease, or preeclampsia, she can engage in moderate-intensity aerobic physical activity throughout her pregnancy. It is recommended for pregnant women to engage in 30 min of moderate intensity physical activity on most days of the week, with goal of a minimum total of 150 min per week [20]. Modes of activity can include walking, stationary cycling, swimming, prenatal exercise classes, or resistance training. Moderate intensity activity is defined as reaching 40–59% of target heart rate [20]. Women who are more deconditioned may start at a lower intensity and progress to moderate levels. Women who are already highly active can continue their exercise activities during pregnancy.

For those who are unable to achieve glycemic targets with medical nutrition therapy and physical activity, the recommendation is to initiate pharmacotherapy. Insulin is recommended as the first-line agent. Regular insulin (U-100 and U-500), insulin aspart, insulin lispro (U-100 and U-200), NPH, and insulin detemir all carry a pregnancy category B, indicating that there is sufficient human data to deem them low risk in pregnancy. Insulin glulisine, insulin degludec, and

insulin glargine are category C agents, as there is no human data during pregnancy [21•]. In 2015, the FDA removed the pregnancy letter categories replacing it with the "Requirements for *Pregnancy* and Lactation *Labeling*" [22]. For example, although glargine lacks human safety data, it has been widely used in pregnancy with evidence of safety in this setting [23].

Compared with NPH insulin, use of the long-acting insulin analogs insulin detemir or insulin glargine is associated with lower rates of nocturnal hypoglycemia [24]. Typically, a long-acting basal insulin such as glargine or detemir is initiated in conjunction with a rapid-acting bolus insulin analog taken with meals. Women with T2DM who have had prior pregnancies may already have an insulin regimen that was used in a previous pregnancy that could serve as a starting point. In women who are insulin naive, insulin can be initiated based on a woman's body weight and gestational week. In the first trimester, the total daily insulin requirement is 0.7 units/kg/day, in the second trimester, it is 0.8 units/kg/day, and in the third trimester, it is 0.9–1.0 units/kg/day [21•]. The calculated total daily dose of insulin should be divided into 2 halves: one half given as basal insulin at bedtime and the other half divided between 3 meals and given as a rapid-acting insulin analog before meals. Insulin analogs such as lispro and aspart have a more rapid onset and a shorter duration of action, and thus cause less hypoglycemia compared to regular human insulin. Insulin doses should be adjusted frequently in order to achieve euglycemia as soon as possible. Given such close monitoring of blood glucose in the inpatient setting, insulin doses can be safely adjusted as frequently as every 1–2 days. Caution should be taken during the end of the first trimester, when there may be a period of temporary increased insulin sensitivity. Insulin doses may need to be decreased during weeks 10–14 to avoid severe hypoglycemia.

Some women can exhibit such severe insulin resistance during pregnancy that the volume of insulin needed becomes problematic. The concentrated U-500 regular insulin (U-500) has been well studied in the non-pregnant population. Although there are several case reports demonstrating improved glycemic control using U-500 insulin in pregnancy, to date, there are no randomized controlled studies evaluating the specific safety and efficacy of U-500 insulin in pregnant women [25, 26]. U-500 insulin has different pharmacokinetic and pharmacodynamic profiles compared to U-100 insulin, so caution should be taken if initiating U-500 insulin during pregnancy.

While oral antidiabetic medications are often used as first-line treatment in the management of T2DM, the options in pregnancy are limited. In fact, no oral antidiabetic medication is approved by the US Food and Drug Administration to be used in pregnancy [27•]. Metformin and glyburide are the two oral agents that have efficacy and short-term safety data which has resulted in their increased use in pregnancy.

In general, metformin can be started at 500 mg once daily for 1 week, then increased to 500 mg twice daily. The maximum dose is 2000 mg per day in divided doses. The side effects of abdominal pain and diarrhea can be minimized by increasing the dosage slowly and recommending to take metformin with meals. One of the earliest studies was conducted by Rowan et al. in 2008 in which 751 women with GDM were randomized to either metformin or usual treatment with insulin therapy. The primary outcome included a composite of neonatal hypoglycemia, respiratory distress, need for phototherapy, 5-min Apgar score < 7 or premature birth (before 37 weeks), and there was no difference seen between the two treatment groups [28]. More recently, findings from meta-analyses support the safety of using metformin in pregnancy [29, 30••]. However, it is important to note that up to 46% of women on metformin only eventually need to be supplemented with insulin for adequate glycemic control [28].

Glyburide can be administered as 2.5–20 mg per day as a daily dose or divided into twice daily for doses greater than 5 mg. It has been demonstrated that glyburide is effective for glycemic control in pregnancy [31]. The main concern surrounding using glyburide in pregnancy is the rate of neonatal hypoglycemia, though the data is conflicting. In a prior study, Langer et al. showed that there were no significant differences in neonatal hypoglycemia between the glyburide and insulin groups [32]; however, more recent data including a meta-analysis demonstrated that glyburide significantly increased the risk of neonatal hypoglycemia [risk ratio (RR) 1.89] [33]. Additionally, evidence shows that glyburide is associated with higher birth weights and a more than twofold higher rate of macrosomia when compared to insulin [34••]. In light of this evidence, if an alternative to insulin is required, metformin would be a preferable option given its more favorable short-term profile [34••].

It is reasonable to continue metformin for women with pre-gestational T2DM already taking metformin prior to pregnancy. Metformin can also be used as an adjunct treatment for GDM to help reduce insulin requirements. In general, taking into account the limited long-term neonatal safety data for oral hypoglycemics, insulin is considered the preferred treatment for diabetes in pregnancy [1••]. In women who decline or cannot use insulin, metformin (preferred) and glyburide are reasonable treatment alternatives.

Case 1: A 25-year-old woman G3P2002 at 10 weeks of gestation with history of obesity and T2DM is admitted from clinic with elevated blood glucose levels. She was diagnosed with diabetes 2 years ago and has been treated with metformin 1000 mg twice daily only. Her hemoglobin A1c was 8.9 prior to pregnancy and 9.1 about 8 weeks ago. In the last 8 weeks, she has met with a dietitian several times and is

following a well-balanced meal plan. She now also engages in 60 min of aerobic activity and resistance training 3–4 times per week. On arrival to the obstetrics unit, her vital signs are stable, she weighs 142 kg and her fingerstick blood glucose is 289 mg/dL. Her repeat hemoglobin A1c today is 9.3%.

What is the next step in the management of this patient's hyperglycemia during pregnancy?

This patient has hyperglycemia in the setting of pregestational T2DM. Her HgbA1c of 9.3% is well above the goal of < 6–6.5% in pregnancy. At this time, the patient should be started on a basal/bolus insulin regimen. She is in her first trimester and weighs 142 kg so her total daily dose (TDD) calculates to be approximately 100 units of insulin (142 kg × 0.7 units/kg). Half of the TDD, 50 units, should be given as basal insulin and the remaining 50 units should be given divided between her 3 main meals each day. The recommendation is to start the patient on insulin glargine 50 units at bedtime and insulin aspart 16 units with each meal. Since metformin is safe in pregnancy and may lessen insulin requirements, she can continue taking metformin 1000 mg twice daily. A gestational diabetes meal plan should be ordered and fingerstick blood glucose levels should be checked fasting and 1 h after each meal. In the inpatient setting, insulin doses can be adjusted every 1 to 2 days.

Management of Type 1 Diabetes

Management of pregnant women with type 1 diabetes can be particularly challenging. Pregnancy creates a relative insulin-deficient state due to the increased production of counter-regulatory hormones, including glucagon, cortisol, and human placental lactogen [35]. These hormones lead to an increase in insulin resistance, resulting in a ketosis-prone state. Although this is true for all pregnant women with GDM, T1DM, and T2DM, it is important to note that those with T1DM are already ketosis prone due to their absolute lack of insulin production. This leads to women with T1DM being at even higher risk for developing diabetic ketoacidosis (DKA). The presentation of DKA can also be atypical, as it may develop faster and present with lower blood glucose levels than in non-pregnant states. Although maternal death due to DKA is rare, fetal demise has been reported in up to 35% of cases [35].

Criteria for diagnosis of DKA includes: calculated anion gap > 10 mEq/L, acidosis (serum bicarbonate < 18 mEq/L or arterial pH < 7.3), and positive urine or serum ketones. In classic DKA, hyperglycemia (serum glucose > 250 mg/dL) is a key part of the presentation. However, DKA in pregnancy can present with variable serum glucose levels. In fact, it has been reported in the literature that pregnancy can be one of the rare causes of euglycemic DKA, when serum glucose levels are < 250 mg/dL [36•, 37]. Treatment of both classic or euglycemic DKA at our institution involves starting an intravenous insulin infusion, in which a regular insulin 0.15 U/kg intravenous bolus is given, followed by a 0.1 U/kg/h continuous intravenous infusion [38]. Insulin infusion rates should be adjusted based on hourly fingerstick blood glucose levels. The insulin infusion is continued until the anion gap closes (≤ 10 mEq/L). Isotonic saline should be given aggressively as long as there are no contraindications. Dextrose should be added to the fluids when serum glucose falls below 250 mg/dL. Lastly, electrolytes should be monitored every 2–4 h and potassium repleted as needed [36•].

Severe hypoglycemia is another major challenge in the management of T1DM in pregnancy [35]. This risk is highest early in pregnancy, especially during the first trimester, not only because of the increased insulin sensitivity during gestational weeks 10–14, but it is also the timeframe where women will typically experience nausea and vomiting associated with pregnancy. In some women, these symptoms can be mild. However, others can have persistent and excessive vomiting, leading to metabolic disturbances such as carbohydrate depletion, dehydration, and electrolyte imbalance (hyperemesis gravidarum) [39]. Hyperemesis gravidarum is prevalent in approximately 0.3–3% of all pregnancies [40]. For the women with preexisting gastroparesis, symptoms may worsen and/or occur more frequently, causing severe hyperemesis gravidarum that can last the entire pregnancy [41]. To add another layer of complexity, vomiting and decreased nutritional intake even for a short period of time can precipitate ketoacidosis. This exaggerated response to fasting, with increased ketone formation in pregnancy, has been well described [42]. We now know that pregnant women with T1DM carry a number of risk factors that predispose them to metabolic acidosis. These risk factors are often difficult to manage, but treatments include antiemetics for nausea, dietary modifications, promotility agents for gastroparesis, and diabetes education for nutrition as well as early detection and prevention of DKA.

Case 2: A 24-year-old woman G3P0020 at 9 weeks of gestation with history of type 1 diabetes and gastroparesis is admitted with abdominal pain, nausea, and vomiting. In the past 3 days, she was unable to tolerate solid foods due to nausea and vomiting. The last hemoglobin A1c done 1 month prior was 8.6%. The patient weighs 58 kg. Upon arrival to the medicine unit, patient has a fingerstick blood glucose level of 156 mg/dL. Admission labs show an anion gap of 9 mEq/L, serum bicarbonate 20 mEq/L, and venous pH 7.4. She is continued on her home dose of glargine 15 units at bedtime, a low dose aspart scale every 4 h, and normal saline hydration. Overnight, patient continues to have several episodes of nausea with vomiting. The next morning, her fingerstick blood glucose level is 147 mg/dL, but labs show an anion gap of 15 mEq/L, serum bicarbonate 13 mEq/L, venous pH 7.24, and small serum ketones.

What is the diagnosis and what should be the treatment?

We are concerned for euglycemic DKA in this patient. She has an elevated anion gap, low serum bicarbonate, acidic pH, and elevated serum ketones with a fingerstick blood glucose level that is < 250 mg/dL. Subcutaneous basal and bolus insulin injections should be discontinued, and she should be started on an intravenous insulin infusion at 0.1 units/kg/h with D5½NS. Fingerstick blood glucose levels should be checked every hour, and serum basic metabolic panel checked every 4 h. Although this patient has several reasons to develop DKA (pregnancy, poor oral intake for several days, T1DM), other triggers such as infection should be considered.

Diabetes Technology: Insulin Pumps and Continuous Glucose Monitoring Systems

Diabetes technology continues to evolve over time and is becoming more prevalent in the general population. The two most common devices are: continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring systems (CGMS).

CSII, referred to as insulin pumps, are continuous insulin infusion devices that deliver rapid acting insulin subcutaneously. There are tethered pumps (with tubing) and non-tethered (patch) pumps, with variations of the two on the market and in development. A tethered pump consists of the control unit (pump) itself that contains a reservoir of insulin, tubing that delivers the insulin, and an insertion site that consists of an adhesive overlying a small subcutaneous cannula. The cannula is typically inserted on the abdomen, thigh, lower back, or posterior arms. The patch pump is a type of CSII that does not have tubing and consists of a pod of insulin attached to the body and a control device. The pump can be controlled remotely to make dosing changes, although there are a few patch pumps with bolus buttons available or in development.

The insulin pump works by providing a continuous infusion of insulin at variable rates throughout the day and night to mimic "basal insulin" delivery. Basal insulin is the amount of insulin the patient requires to maintain euglycemia when not eating. The basal rates are pre-set in the pump and should change based on settings programmed by the patient and/or health care provider. There is also a "bolus" setting, which is programmed to calculate a bolus insulin dose based on preset insulin-to-carbohydrate ratios and insulin sensitivity factors. This provides insulin needed to cover food intake and correct hyperglycemia. The benefit of an insulin pump is that it avoids multiple subcutaneous injections throughout the day, has been shown to decrease hemoglobin A1c, and increases time in target glycemic range. Of note, it is not an automated system, and the patient needs to be educated and comfortable with accessing basic and advanced pump features such as extended boluses and temporary basal settings.

Continuous glucose monitors (CGMs) are devices that constantly measure the glucose level of subcutaneous interstitial fluid. They communicate wirelessly to a receiver that displays the most recent sensor glucose (SG) level. Some devices have predictive alarms to alert patients of impending hypoglycemia based on glycemic trend, which can allow them to prevent hypoglycemia, rather than react to an event. In non-pregnant patients, CGMs have been shown to reduce hemoglobin A1c and reduce time in hypo- and hyperglycemia ranges. Given that the recommendation for pregnant women with diabetes is to check blood glucose levels 4–8 times per day, and that there is a significant risk for hypo- and hyperglycemia due to changing insulin resistance, CGMs are helpful to attain glycemic goals in this population. Based on a recent study by Scott et al., a specific type of CGM, the FreeStyle Libre (Abbott Diabetes Care), was shown to have clinical accuracy comparable to SMBG in pregnant women. It was used in women with T1DM, T2DM, and GDM and was demonstrated to be safe, accurate, and acceptable by users. Accuracy was not affected by the type of diabetes, age, body mass index (BMI), or the stage of pregnancy [43]. Though CGMs are not FDA approved for use in pregnancy, they are approved for non-pregnant women with pre-existing T1DM and T2DM. Studies are on-going to assess improvement in glycemic control and pregnancy outcomes with CGMs. Per the Endocrine Society guidelines, CGMs should be used when self-monitored blood glucose levels are not sufficient to assess glycemic control and prevent hypoglycemia [5••].

At our institution, we allow patients to either continue wearing their CSII while inpatient or they can switch to subcutaneous insulin injections. For those who choose to remain on their own insulin pump, close monitoring and coordination are necessary between the patient, nursing staff, obstetrics team, and endocrine consult service. Patients are recommended to have extra pump supplies with them, and pharmacy is notified so that a vial of formulary rapid acting insulin is available for refills. They can continue wearing a CGM, but as per our hospital policy, they must have fingerstick blood glucose levels checked at regular intervals by the nurse using a hospital point-of-care blood glucose meter. The hospital meter must be used for insulin dosing and treatment of hypoglycemia. Patients are notified that if at any point they are unable to operate the pump safely (either due to impaired cognition or mechanical difficulties), they should be switched to subcutaneous insulin injections or an intravenous insulin infusion for glycemic control [44].

Intra-Partum Glycemic Management

The main goals during the intra-partum period are to minimize maternal hyper- and hypoglycemia, maximize fetal tolerance

Table 3 New York Presbyterian Insulin Infusion Protocol during the peripartum period

Regular insulin 100 units/100 mL (1 unit/mL)
Adjust insulin infusion as required to maintain maternal blood glucose between 80 and 120 mg/dL

Blood glucose (mg/dL)	Insulin rate (units/h)	mL/h	IV fluids
< 80	0	0	D5½NS or D5LR at 125 mL/hand notify MD
81–100	0.5	0.5	D5½NS or D5LR at 125 mL/h
101–120	1	1	D5½NS or D5LR at 125 mL/h
121–140	1	1	NS or LR at 125 mL/h
141–180	1.5	1.5	NS or LR at 125 mL/h
181–200	2	2	NS or LR at 125 mL/h
> 200	2.5	2.5	NS or LR at 125 mL/h

of labor, and reduce the likelihood of newborn hypoglycemia (which is correlated to maternal glycemic control during labor) [12•, 45]. There is not yet a nationwide consensus on the best way to achieve these goals. Management will vary based on if the woman has T1DM, T2DM, or GDM. Oral intake is typically limited, and labor itself imposes a significant glucose requirement, especially during the active phase and maternal pushing. Of note, neonatal hypoglycemia may still occur due to poor glycemic control throughout the pregnancy, leading to fetal pancreatic islet cell hyperplasia and excessive endogenous insulin production [12•].

Insulin requirements will vary throughout the stages of labor and delivery. Overall, requirements decrease in active labor, along with an increase in glucose requirements. This is due to increased glucose utilization during a metabolically active time. Then, insulin requirements drop even more so after delivery of the placenta, due to an abrupt reduction of placental hormones mediating insulin resistance. This results in increased insulin sensitivity, decreased insulin requirements, and increased risk for hypoglycemia [45, 46]. As per the American College of Obstetricians and Gynecologists (ACOG), a target glucose range of 70–110 mg/dL in labor is ideal. The Endocrine Society recommends a target of 72–126 mg/dL (Table 1). Multiple other studies have shown that glucose levels up to 140 mg/dL were not significantly associated with increased neonatal risk [5••, 12•].

It is recommended that women are switched from subcutaneous insulin to continuous intravenous insulin infusion during the peripartum period, with dextrose fluids available if necessary [9, 45, 47]. Our institution has an inpatient protocol for insulin infusion during the peripartum period [48]. If glucose rises above 80 mg/dL, an insulin infusion should be started per our institution protocol (Table 3) [48]. Women with T2DM or GDM not on insulin prior to labor/delivery may have sufficient insulin production and glycogen storage to maintain euglycemia without insulin and dextrose fluids. Women with T2DM or GDM on insulin should be started on an intravenous insulin infusion and/or intravenous glucose as needed. Women with T1DM often require both insulin and glucose during labor to prevent ketosis [12•, 45]. Urine ketones should be checked with each void; if ketones are greater than trace, the rate of dextrose fluid should be increased, along with the insulin infusion rate as needed. Serum glucose levels should be monitored hourly to titrate the insulin infusion; dextrose fluids should be started if serum glucose falls below 120 mg/dL.

For women wearing their own insulin pump, they can either continue wearing the pump or discontinue it and switch to intravenous insulin. Studies have shown that women who continue on insulin pumps may actually have better glucose control during delivery [47]. For those remaining on the pump, close monitoring and coordination between the obstetrics team, nursing staff, and inpatient endocrine consult service are necessary. Serum glucose levels should be monitored hourly. Pre-labor basal rates should be reduced by 50% during the second/active stage of labor. Bolus doses of insulin can be given in order to correct for hyperglycemia > 110 mg/dL. Attention should be paid to location of the insertion site, in the situation that the patient may need to undergo a cesarean section. Women who have impaired cognition from anesthesia or pain medication and cannot operate the pump safely should be recommended to switch to subcutaneous insulin injections or intravenous insulin infusion temporarily [9, 12•].

Cesarean Section Glycemic Management

For a planned cesarean section, similar to vaginal deliveries, insulin requirements fluctuate during delivery, and generally decrease overall. Women on basal insulin should take 50–80% of their long-acting insulin the night before surgery. For women on an insulin pump, the basal rate should be reduced by 50% at the start of the cesarean section. If they are treated with metformin, they can continue the same regimen the day before surgery, but discontinue the medication the day of surgery. If they take glyburide, they should be instructed to either discontinue the evening dose, particularly if they are scheduled for an early morning surgery, or to take a lower dose the night prior to C-section. Glyburide should be held the day of the

surgery [9, 12•]. During the cesarean section itself, serum glucose levels should be checked hourly. Intravenous fluids should depend on serum glucose levels: if < 70 mg/dL, start dextrose containing fluid; if 70–110 mg/dL, give non-dextrose containing fluid; if > 110 mg/dL persistently, start both insulin and dextrose infusion [12•]. Insulin and dextrose fluids should be titrated to maintain euglycemia throughout the surgery (Table 3).

Post-Partum Glycemic Management

Increased insulin resistance from placental hormones ends abruptly after delivery of the placenta, and insulin sensitivity increases before returning to pre-pregnancy levels 1–2 weeks after delivery (Fig. 1). Women may need only one-half or even one-third of their third trimester insulin requirements and should be continued on reduced basal/bolus insulin amounts.

Immediately post-partum, for those on an insulin infusion, the infusion rate should be decreased by 50%. For women on an insulin pump, they should continue on a 50% reduced basal rate. Serum glucose levels should be monitored every 1 to 2 h, as there is a risk for hypoglycemia, especially if the patient is not eating. Women with T2DM or GDM may not need an insulin infusion if their blood glucose levels are within the normal range. It is important to remember that for women with T1DM, even if blood glucose levels fall to the normal range or below, they will always need some continuous insulin infusion (minimum total daily dose of 0.1 units/kg/day) to prevent diabetic ketoacidosis. This may require starting dextrose fluids to maintain euglycemia in women with T1DM [45, 47].

In the first 1 to 2 days post-partum, in addition to increased insulin sensitivity, oral intake may vary, especially after a cesarean section. It is recommended to use short or rapid-acting insulin based on fingerstick blood glucose measurements until the woman is able to reliably tolerate solid food consistently [12•]. In patients who are not on insulin pumps, it is important to remember to continue long-acting basal insulin at approximately one-half the pre-delivery dose in women with T1DM to prevent the risk of DKA. Carbohydrate ratios should be decreased by up to one-third to one-half to prevent hypoglycemia. Insulin pump settings should be reduced accordingly, often returning to pre-pregnancy settings. Women with T2DM on insulin should be given one-half their pre-delivery basal insulin dose and continue to have blood glucose levels monitored closely [45]. Women on oral agents, or with lifestyle-controlled T2DM or GDM, can be monitored with routine glucose monitoring to assess any insulin requirements post-partum. Metformin and glyburide can be used while breastfeeding; however, they should only be continued if hyperglycemia persists. Within 1–2 weeks post-partum, insulin sensitivity should return to pre-pregnancy levels [11••, 12•].

In addition to decreased insulin requirements, glycemic goals are relaxed post-partum (Table 1). Per the American Diabetes Association (ADA), for a non-critically ill, hospitalized patient, glucose levels should be between 140 and 180 mg/dL. Some women may benefit from a glucose goal 110–140 mg/dL, such as those post-Cesarean section, as long as their glucose levels can be monitored to avoid hypoglycemia [49]. According to the California Diabetes and Pregnancy Program, target blood glucose levels in post-partum women with GDM in the fasting state are < 100 and < 140 mg/dL 1 h post-prandial. Women with pre-existing diabetes should aim for fasting and pre-meal glucose levels of 100–110 mg/dL and 2-h post-meal glucose levels of 100–160 mg/dL [9]. In order to optimize cesarean section wound healing, Garrison et al. recommend a fasting glucose of < 110 mg/dL and 1-h post-meal glucose of < 160 mg/dL [12•]. Women on insulin therapy should continue blood glucose monitoring pre- and post-meals until follow-up with their outpatient health care provider. Women with GDM or pre-existing T2DM not on insulin therapy should continue monitoring blood glucose levels pre-meals and at bedtime while in the hospital, and at least fasting blood glucose levels after discharge until follow-up with an outpatient clinician. Some women with T2DM may not need any medication for a few days to 1 week after delivery, so monitoring is warranted to assess when to resume medications [9, 11••, 12•]. After discharge, the fasting blood glucose target is 70–100 mg/dL and 1–2 h post-meal is < 150 mg/dL [9].

Unfortunately, about 50–70% of women with gestational diabetes go on to develop T2DM over the next 25 years. At 5 years post-partum, 15% of women with GDM will have impaired glucose tolerance or T2DM. Those most at risk include women with morbid obesity, failure to lose weight gained in pregnancy, first or second trimester diagnosis of GDM, significant daily insulin requirements in pregnancy (100–150 units/day), and history of GDM in a prior pregnancy [9, 11••]. Per the ADA and Endocrine Society guidelines, women should be tested for persistent diabetes or impaired glucose tolerance at 4–12 weeks post-partum with a 2-h 75-g OGTT using non-pregnancy diagnostic criteria. This is preferred over hemoglobin A1c due to increased red blood cell turnover during pregnancy which may still be impacting the A1c level [5••, 11••, 45]. Even if normal, women should still be screened every 1–3 years, depending on other risk factors, such as family history, need for insulin during pregnancy, and BMI. They are also three times more likely to develop metabolic syndrome and abnormal lipid profiles. All women should receive counseling on lifestyle modifications and planning for future pregnancies [5••, 9, 11••].

Case 3: A 33-year-old woman G1P1 with a history of type 1 diabetes wearing her own insulin pump underwent a planned cesarean section. Her total basal insulin dose prior to the surgery was 29.7 units/day, with an insulin to carbohydrate ratio of 1:12 for all meals, and an insulin sensitivity factor of 1:40. She continued on the same insulin pump settings when going to the operating room (OR). The cesarean

section was then complicated by an episode of hypoglycemia in the OR, which responded to dextrose fluid. She is now post-partum in the recovery room.

What could have been done prior to surgery to prevent the hypoglycemia, and how should her type 1 diabetes be managed post-partum?

Her intra-operative hypoglycemia was most likely due to continuing on the same basal insulin rate that she was on prior to the surgery. She should have been instructed to decrease her basal rate by 50% prior to the OR. Blood glucose levels were checked hourly, and intravenous dextrose fluids were started appropriately. Post-partum, she is less insulin resistant, and should continue on the insulin pump with a decreased basal rate of about 15 units/day (or 50% of the prior basal rate), along with a decreased insulin to carbohydrate ratio and insulin sensitivity factor. Fingerstick blood glucose levels should be checked before eating, at bedtime, and prior to breastfeeding.

Breastfeeding

In addition to nutritional, immunologic, and psychosocial benefits, breastfeeding is associated with a decreased risk of developing T2DM in childhood for the baby and further lowers insulin requirements for the mother [9, 46]. For women who still need pharmacologic therapy for diabetes management, insulin, metformin, and glyburide can all be used for breastfeeding mothers. Of note, studies have shown that metformin crosses into breastmilk at very low levels, but with no negative impact on infants' blood glucose levels. Glyburide has not been detected in breastmilk in small studies, and infant hypoglycemia has not been seen [9, 27•]. It is recommended to check blood glucose levels fasting, just before and 1 h after breastfeeding, at bedtime, and at 3 AM to monitor for hypoglycemia in the mother, especially in the first 3 days post-partum. If blood glucose is < 100 mg/dL prior to breastfeeding, women should eat a protein-rich snack along with 15 g of carbohydrates, such as a small apple with peanut butter (Table 1) [9]. In addition to breastfeeding, lifestyle modifications such as meal planning and physical activity that promote weight loss can further improve insulin sensitivity and reduce the necessity or the amount of diabetes medications post-partum [11••, 12•].

Conclusion

With the rising prevalence of T1DM, T2DM, and GDM in pregnancy, it is important for clinicians to know how to best maintain euglycemia for the health of the mother and baby. Insulin sensitivity changes throughout pregnancy, and tight glycemic goals are recommended to optimize health of the developing fetus. Metformin, glyburide, and insulin (via subcutaneous injection or patient's own insulin pump) are safe to use during pregnancy, with close fingerstick blood glucose monitoring and guidance from a health care provider. At the time of delivery, insulin requirements are dynamic, and close inpatient monitoring and management with an insulin protocol is recommended. Finally, after delivery, insulin requirements decrease significantly, and it is important to counsel women on the risk for hypoglycemia during breastfeeding, changing or stopping medications as indicated, and ongoing screening for persistent diabetes. An interdisciplinary team consisting of obstetrics, maternal fetal medicine, endocrinology, nutrition, nursing, and pharmacy is key to achieve best outcomes during this time throughout and after pregnancy.

Compliance with Ethical Standards

Conflict of Interest Tiffany Yeh, Michele Yeung, and Felicia A. Mendelsohn Curanaj declare that they have no conflicts of interest.

Human and Animal Rights This study does not contain any studies with human or animal subjects performed by any of the authors.

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