Anesthesia for the Pregnant Diabetic Patient

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3.1 Introduction

3.1.1 Diabetes Mellitus Definition, Epidemiology, and Classification

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia. Type 1 DM (juvenile or insulin-dependent autoimmune disorder) is an immunologic destruction of the pancreas, causing deficiency in insulin secretion. Type 2 DM (adult-onset or noninsulin-dependent disorder) results from the combination of an inadequate insulin secretion, an increased resistance of the pancreatic cells to insulin action, and an excessive or inappropriate glucagon secretion. It accounts for 90–95% of all diabetic patients, and it has a prevalence of 6.8–8.2% in the general adult population in the USA. Its incidence has been increasing steadily, mostly because of continuing epidemic of obesity [1–5]. This has led to more Type 2 DM in women of childbearing age, with an increase in the number of parturients without previous diagnosis [6].

For a long time, gestational diabetes mellitus (GDM) was defined as any degree of carbohydrate intolerance that had first been diagnosed during pregnancy, regardless of whether the condition may have begun before the pregnancy or persisted after the pregnancy [7]. However, parturients diagnosed with DM in the first trimester should be classified as having pre-existing Type 2 DM or, rarely, Type 1 DM. Currently, parturients, who are unable to produce enough insulin to compensate insulin resistance at the receptor and postreceptor levels, are diagnosed with GDM. GDM is explained as DM that is first diagnosed in the second or third trimester of pregnancy which is not clearly either pre-existing Type 1 or Type 2 DM [1, 4].

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B. Gunaydin, S. Ismail (eds.), *Obstetric Anesthesia for Co-morbid Conditions*,
https://doi.org/10.1007/978-3-319-93163-0_3

Table 3.1 White's classification system of diabetes mellitus during pregnancy class definition [8, 9]

A_1	GDM that is diet controlled
A_2	GDM that requires insulin
B	Pre-existing DM with onset >age 20 and duration <10 years without complications
C	Pre-existing DM with onset between ages 10 and 19 or duration of ages 10–19 without complications
D	Pre-existing DM with onset age <10 or duration >20 years. Without complications
F	Pre-existing DM complicated by nephropathy
R	Pre-existing DM complicated by proliferative retinopathy
T	Pre-existing DM and status/post kidney transplant
H	Pre-existing DM complicated by ischemic heart disease

GDM gestational diabetes mellitus, *DM* diabetes mellitus

The GDM prevalence varies from 1.4% to 14% (usually between 2% and 5%) in the USA, and the amount varies in direct proportion to the prevalence of Type 2 DM [5].

A classification system was proposed for DM in pregnancy, to emphasize the relationship between the duration of DM, complications of DM, and poor fetal outcome, in 1949 (Table 3.1) [8]. In the 1950s, fetal survival rates were determined as 100% for class A, 67% for class B, 48% for class C, 32% for class D, and 3% class F [9].

3.2 Pathophysiology

The women are carbohydrate-intolerant during pregnancy. Glucose fasting levels are decreased, and serum levels following a meal or glucose load are increased compared to the nonpregnant state. In all pregnancies, circulating concentrations of insulin antagonists such as cortisol, prolactin, human placental lactogen (HPL) and leptin rise and insulin resistance increases as the pregnancy advances. This resistance results in increased insulin demand in pregnant women with pre-existing DM or predisposes some parturients to develop GDM. All these changes affect fetal placental unit growth and rapidly become reversed after delivery. This "facilitated anabolism" reveals appropriate changes in carbohydrate, amino acid, and lipid metabolism and ensures adequate nutrients for the developing fetus [1, 4].

Deficient β-cell reserve, as in any type of DM, would result in the abnormal carbohydrate, protein, and fat metabolism adaptation. Insulin is required to compensate increasing caloric needs, increasing adiposity, decreasing exercise, and increasing anti-insulin hormones in Type 1 DM. The required insulin dose to maintain normoglycemia and prevent maternal ketosis may increase up to threefold during pregnancy in Type 1 DM. Parturients with Type 2 DM may also need insulin treatment at high doses, because of physical inactivity and obesity [10, 11].

3.3 Clinical Presentation and Diagnosis of Gestational Diabetes Mellitus

Advanced maternal age; obesity (especially central obesity, dyslipidemia with high triglycerides, and/or low HDL cholesterol); glycosuria; family history of Type 2 DM, GDM, and polycystic ovarian syndrome; and/or history of fetal malformation or macrosomia, prior stillbirth, and neonatal death are the factors leading up to GDM. On the other hand, clinical presentation of DM and GDM can be associated with acute (diabetic ketoacidosis, hyperglycemic nonketotic state, and hypoglycemia) and chronic (macrovascular atherosclerosis, coronary, cerebrovascular, and peripheral vascular; microvascular, retinopathy and nephropathy; neuropathy, autonomic and somatic) complications [12].

Inadequate insulin therapy and infection are the most common triggering factors for both diabetic ketoacidosis (DKA) and hyperglycemic nonketotic state (HNS) [13]. DKA usually occurs in patients with Type 1 DM and may sometimes be the first clinical sign of it during pregnancy [14, 15]. The incidence of DKA is 1–2% in parturients with DM [16, 17]. DKA results from decreased uptake of glucose by tissues and greater use of free fatty acids instead and is associated with metabolic acidosis, hyperglycemia, and dehydration secondary to osmotic diuresis. Signs and symptoms such as nausea and vomiting, weakness, tachypnea, hypotension, tachycardia, stupor, and acetone on the breath frequently occur, and its diagnosis depends on the laboratory findings of hyperglycemia, ketosis, and acidosis [13, 18]. The HNS usually occurs in patients with Type 2 DM. Laboratory findings are hyperglycemia (blood glucose >600 mg/dL), hyperosmolarity (>320 mOsm/kg), and moderate azotemia (blood urea nitrogen >60 mg/dL), without ketonemia or significant acidosis.

Hypoglycemia results from an imbalance between DM medical therapy and available metabolic fuels. It is a continuing health threat for patients with both Type 1 DM and Type 2 DM [13]. The risk of hypoglycemia in parturients with Type 1 DM increases with tight glucose control [19–21]. Its rate is 3–15 times higher than the nonpregnant patients with Type 1 DM, and 80–84% of severe hypoglycemia episodes occur before 20 weeks of gestation [19, 20, 22, 23]. In contrast, it was demonstrated in a study that parturients with pre-existing Type 2 DM or GDM requiring insulin therapy experienced no episodes of severe hypoglycemia [22]. Hypoglycemia has three levels of classification, and the International Hypoglycaemia Study Group reported their related recommendations regarding severity of hypoglycemia:

Level 1: glucose level $\geq$ 70 mg/dL (3.9 mmol/L), often related to symptomatic hypoglycemia and important for dose adjustment of glucose-lowering drugs

Level 2: glucose level < 54 mg/dL (3.0 mmol/L), clinically significant

Level 3: severe, no specific glucose threshold, and may be associated with severe cognitive impairment requiring assistance [24, 25]

The prevalence of complications generally increases with the obesity, hypertension, and duration of DM [26–30]. The evidence of obesity management is strong and consistent that it can delay the progression from prediabetes to Type 2 DM and may be also beneficial in the treatment of Type 2 DM [26, 27, 31–34]. The Diabetes Control and Complications Trial including patients with Type 1 DM demonstrated a positive relationship between tight glucose control and a lowered incidence or rate of progression of diabetic chronic complications (retinopathy, nephropathy, neuropathy, coronary atherosclerosis, cardiomyopathy) [35, 36]. Another study including patients with Type 2 DM—the UK Prospective Diabetes Study (UKPDS)—showed that the tight glucose control reduced the incidence of microvascular complications but not macrovascular complications or patient mortality. In parturients with pre-existing Type 1 DM, systolic and diastolic blood pressures are higher, and these have three times more gestational hypertension risk than nondiabetic patients [37, 38]. In addition, the risk of preeclampsia is also directly proportional to the severity of DM [39]. In patients with Type 2 DM and hypertension, antihypertensive therapy lowered the incidence of both macrovascular complications and mortality [28].

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, which is a multicentral trial including more than 23,000 parturients, demonstrated that adverse maternal, fetal, and neonatal risks were continuously increased as a function of maternal glycemia at 24–28 weeks, even within ranges previously considered normal for pregnancy [40]. Although not all adverse outcomes are of equal clinical importance, these results showed that GDM carries risks for both the mother and the neonate and deserve careful reconsideration of the risk assessment, screening, and diagnostic criteria for GDM.

The American Diabetes Association recommended an approach for screening and diagnosis of GDM in 2008, which divides parturients into three GDM risk categories on the basis of history: (1) low risk, (2) very high risk, and (3) higher than low risk. As low-risk patients do not require any testing, very high-risk patients undergo standard nonpregnant testing (Table 3.2), and higher-than-low-risk category parturients undergo one of the two different screening and diagnosis approaches (one- or two-step strategies) at 24–28 weeks of gestation (Table 3.3) [1, 29, 41].

One-Step Strategy Based on a recommendation of the International Association of Diabetes and Pregnancy Study Groups (IADPSG), in the 2011 Standards of Care, the ADA recommended that all parturients not known to have prior DM undergo a 75 g oral glucose tolerance test (OGTT) at 24–28 weeks of gestation (Table 3.3) [1, 42, 43]. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to 15–20%), primarily because only one abnormal value became enough to make the diagnosis. Although the ADA recognized that the anticipated increase in the incidence of GDM would have the potential to "medicalize" pregnancies previously categorized as "normal", they still recommended these diagnostic criteria changes with the intent of optimizing gestational outcomes, because these were the only ones based on pregnancy outcomes.

Table 3.2 Risk assessment at the first prenatal visit for gestational diabetes mellitus [1, 29, 41]

Low-risk
The parturients at low-risk status must meet all of the following criteria and do not require screening
Criteria for low-risk status:
• Age < 25 years
• Weight normal before pregnancy
• Member of an ethnic group with a low prevalence of DM
• No known DM in first-degree relatives
• No history of abnormal glucose tolerance
• No history of poor obstetric outcome
Very high-risk
The parturients at very high-risk status should be screened with *standard DM diagnostic testing* as soon as pregnancy is confirmed
Criteria for very-high-risk status:
• Severe obesity
• Prior history of GDM or delivery of large-for-gestational-age infant
• Presence of glycosuria
• Diagnosis of polycystic ovarian syndrome
• Strong family history of type 2 DM
Standard DM diagnostic testing:
• Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L) Fasting is defined as no caloric intake for at least 8 h[a]
OR
• 2-h plasma glucose (PG) ≥200 mg/dL (11.1 mmol/L) during an OGTT The test should be performed by using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water[a]
OR
• HbA1c ≥ 6.5% (48 mmol/mol) (normal range is 4.1–5.9%) The test should be performed in a laboratory (using a method that is NGSP certified and standardized to the DCCT assay)[a]
OR
• A random plasma glucose ≥200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis

DM diabetes mellitus, *GDM* gestational diabetes mellitus
[a]In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing

Two-Step Strategy The National Institutes of Health (NIH) including representatives from obstetrics/gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields convened a consensus development conference to consider diagnostic criteria of GDM. The panel recommended a two-step strategy for screening that used a 1-h 50 g glucose load test (GLT) followed by a 3-h 100 g OGTT for the ones screened positive (Table 3.3) [1, 44].

Data comparing one-step versus two-step strategies have been conflicting to date [45, 46]. The American College of Obstetricians and Gynecologists (ACOG)

Table 3.3 Screening and diagnosis for gestational diabetes mellitus [1, 47–49]

One-step strategy

Plasma glucose level measurements at 24–28 weeks of gestation in women, not previously diagnosed with overt DM
Perform a 75 g OGTT in the morning after an overnight fasting of at least 8 h.
GDM is diagnosed when any of the following plasma glucose values are met or exceeded:

Fasting	92 mg/dL (5.1 mmol/L)
1-h	180 mg/dL (10.0 mmol/L)
2-h	153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Plasma glucose level measurements at 24–28 weeks of gestation in women, not previously diagnosed with overt DM.

Perform a 50 g GLT (nonfasting), with plasma glucose measurement at 1 h
If the plasma glucose level measured 1 h after the load is ≥130 mg/dL (7.2 mmol/L), 135 mg/dL (7.5 mmol/L) or 140 mg/dL[a] (7.8 mmol/L), proceed to a 100 g OGTT

Step 2: The 100 g OGTT should be performed when the patient is fasting
GDM is diagnosed if at least two of the following four plasma glucose levels are met or exceeded:

	Carpenter/Coustan (48)	**NDDG** [§] (49)
Fasting	95 mg/dL (5.3 mmol/L)	105 mg/dL (5.8 mmol/L)
1-h	180 mg/dL (10.0 mmol/L)	190 mg/dL (10.6 mmol/L)
2-h	155 mg/dL (8.6 mmol/L)	165 mg/dL (9.2 mmol/L)
3-h	140 mg/dL (7.8 mmol/L)	145 mg/dL (8.0 mmol/L)

GDM: gestational diabetes mellitus
DM: diabetes mellitus
OGTT: oral glucose tolerance test
GLT: glucose load test
*The American College of Obstetricians and Gynecologists (ACOG) (47) recommends either 135 mg/dL (7.5 mmol/L) or 140 mg/dL (7.8 mmol/L). §NDDG, National Diabetes Data Group.

updated its guidelines supporting the two-step approach in 2013 and recommended either of two sets of diagnostic thresholds for the 3-h 100 g OGTT [47–49]. GDM-diagnosed pregnancies per the IADPSG criteria, but not recognized as such, have comparable outcomes to GDM-diagnosed pregnancies by the more rigid two-step criteria [50, 51]. As the one-step strategy has been adopted internationally and pregnancy outcomes were improved with cost savings, one-step strategy seems to become the preferred approach [52].

3.4 Interaction of Diabetes Mellitus with Pregnancy

3.4.1 The Effect of Pregnancy on Diabetes Mellitus [4, 12]

1. Insulin antagonist hormones such as HPL, placental growth hormone (GH), cortisol, and progesterone rise and cause progressive resistance to insulin.
2. Pancreatic islet cell mass and glucose sensitivity increase secondary to progesterone and lactogenic hormone stimuli in the endocrine pancreas [53, 54].

3. Maternal adipokines play a role in insulin resistance and facilitate the supply of maternal fuels for the fetus.
4. In parturients with GDM, peripheral insulin resistance cannot be sufficiently compensated. GDM can be seen as a preclinical state of glucose intolerance in some patients, which is not detectable before pregnancy.
5. In parturients with pre-existing DM, insulin requirements generally increase progressively during pregnancy [55]. However, maternal overnight insulin requirements decrease near term, because the growing fetus gets maternal fuels [56].
6. In parturients without DM, endogenous insulin secretion can be affected by several factors, and only one of them is plasma glucose concentration. During painful labor of these patients, glucose production and utilization are higher; however, plasma insulin concentrations increase briefly during the third stage of labor and immediately postpartum. This finding shows that glucose use during labor is largely independent of insulin whether the patient is with or without analgesia [57, 58].
7. In parturients with Type 1 DM, insulin requirements decrease with the onset of the first stage and increase during the second stage of labor. The use of epidural analgesia or oxytocin does not affect exogenous insulin requirements during the first two stages of labor [59, 60]. Insulin requirements decrease markedly after delivery for at least several days and then gradually return to prepregnancy levels within several weeks of delivery [56, 61, 62].

Several complications including both the mother and the fetus occur in these patients during pregnancy and delivery, and even after delivery. This should be kept in mind that both Type 1 and Type 2 DM confer significantly greater maternal and fetal risk than GDM [4, 63].

3.4.2 The Effect of Diabetes Mellitus on Parturient [4, 12]

1. The parturients with GDM are at increased risk for Type 2 DM later in life.
2. The parturients with pre-existing DM require more insulin during pregnancy.
3. The parturients with Type 1 DM are at significant risk for hypoglycemia development, especially during early pregnancy, despite increased insulin requirements.
4. The relative insulin resistance in parturients with Type 1 DM is associated with enhanced lipolysis and ketogenesis; and DKA can occur at significantly lower glucose levels (200–250 mg/dL) than is typically associated with DKA in nonpregnant patients. It most commonly occurs in the second and third trimesters and may be triggered by the infection and the administration of β-adrenergic drugs for tocolysis and glucocorticoids for fetal lung maturation.
5. The incidence of preeclampsia is increased in parturients with any type of DM.
6. Polyhydramnios is more common in parturients with DM.

3.4.3 The Effect of Diabetes Mellitus on Fetus [4, 12]

1. DM in pregnancy may increase the risk of obesity and Type 2 DM in offspring later in life.
2. Non-reassuring fetal heart rate patterns may also be associated with the presence of DKA. Fortunately, these patterns usually resolve once the maternal metabolic abnormalities have been corrected. Therefore, fetal intervention and/or preterm delivery should be avoided, unless the heart rate abnormalities persist after DKA treatment.
3. An increased incidence of abnormal fetal heart rate patterns may lead to the reduction in uteroplacental perfusion.
4. Uteroplacental perfusion is decreased by 35–45% in patients with DM compared to patients without DM. Blood flow may also decrease in women with well-controlled GDM.
5. The intrauterine fetal death/spontaneous abortion incidence is increased in parturients with DM. Reduced uteroplacental perfusion is thought to be a significant contributing factor. Nevertheless, aggressive antenatal fetal surveillance in parturients with DM has been successful in decreasing the number of intrauterine fetal deaths.
6. The risk of congenital anomalies is increased in parturients with pre-existing DM and is now the leading cause of perinatal mortality in diabetic pregnancies [64]. The incidence of major malformations is 8.5–10%, which is a two- to sixfold increase compared to patients without DM. The most common complications are cardiovascular (transposition of great vessels, ventricular septal defect, situs inversus, single ventricle, hypoplastic left ventricle) and central nervous system (anencephaly, encephalocele, meningomyelocele, spina bifida, holoprosencephaly) malformations. Skeletal (caudal regression), renal (agenesis, multicystic dysplasia), gastrointestinal (anal or rectal atresia, small left colon), and pulmonary (hypoplasia) complications can also be seen. Although the etiology is usually multifactorial, the most important factor seems to be the poor glucose control during organogenesis. Therefore, initiation of tight glycemic control during the preconception period decreases the incidence of congenital anomalies.
7. Fetal macrosomia, large for gestational age, is also common in parturients with any type of DM. Pre-existing DM results in fetal macrosomia in 9–25% of parturients—a four- to sixfold higher rate than patients without DM. The risks of shoulder dystocia and birth injury are increased in these macrosomic fetuses during vaginal delivery. Therefore, Cesarean delivery is more likely performed.
8. Neonatal hypoglycemia occurs in 5–12% of parturients with pre-existing DM and GDM [65]. This is a 6- to 16-fold increase compared to infants of nondiabetic mothers. The fetal hyperinsulinemia that arises in response to maternal hyperglycemia is believed to be the reason.
9. DM was thought to be as one of the independent risk factors for fetal lung immaturity and infant respiratory distress syndrome (RDS), especially in

infants whose mothers had poor glycemic control during pregnancy. Then, it was understood that RDS is more common among newborns, who are delivered preterm or are surgically delivered. Later studies have not demonstrated a significant difference in the incidence of neonatal RSD between diabetic and non-diabetic pregnancies [65–67].

10. Intrauterine or neonatal death during pregnancy, neonatal hyperbilirubinemia, glucose intolerance, and cognitive impairment are also DM-related complications.
11. Offsprings of mothers with DM are at increased risk for development of DM because of a combination of genetic and intrauterine environmental factors. Studies of monozygotic human twins have demonstrated that genetic factors have a greater role in Type 2 DM than in Type 1 DM (100% vs 20–50% concordance, respectively) [68]. Moreover, fathers with Type 1 DM are five times more likely than mothers to have a child with Type 1 DM.

3.5 Obstetric Management

Optimal glycemic control is the major focus at each phase of obstetric care of parturients with DM, as it minimizes fetal structural malformations. In the preconception period, the women of childbearing age with DM should be counseled about the importance of tight glycemic control and prevention of complications and given appropriate treatment to avoid hyperglycemia. They should be informed that the elevations in HbA1c during the first 10 weeks of pregnancy are directly proportional to increased risk of diabetic embryopathy, anencephaly, microcephaly, congenital heart disease, and caudal regression. The optimal glycemic control prior to conception and during pregnancy (HbA1c < 6–6.5% (42–48 mmol/mol)) is associated with the lowest risk of congenital anomalies [69–74].

During early pregnancy, parturients with Type 1 DM are sensitive to insulin, and their glucose levels and insulin requirements are lower. Later on, during the second and third trimesters, this situation rapidly reverses as insulin resistance increases and insulin requirement progressively increases. In parturients with normal pancreatic function, insulin production is sufficient to meet the challenge of this insulin resistance and to maintain normal glucose levels. Nevertheless, in women with pre-existing DM and GDM, hyperglycemia occurs if treatment with diet, exercise, and insulin therapy is not appropriate [1]. Self-monitoring of glucose measurements with a reflectance meter and transdermal or subcutaneous glucose monitoring systems is performed several times each day during pregnancy. In order to maintain adequate glycemic control, insulin therapy is frequently changed with progressively increasing requirements throughout pregnancy. The treatment regimen may include three to four insulin injections per day or continuous subcutaneous insulin pump [4].

Fasting, preprandial and postprandial monitoring of blood glucose are recommended to achieve metabolic control in parturients with DM. Preprandial monitoring is recommended for patients with pre-existing DM using insulin pumps or basal bolus therapy, and postprandial monitoring is associated with better glycemic control and lower risk of preeclampsia [75–77].

The American College of Obstetricians and Gynecologists [47] and the ADA (1) recommended the similar following blood glucose target values for women with Type 1 DM, Type 2 DM, or GDM:

- Fasting ≤95 mg/dL (5.3 mmol/L)
- 1-h postprandial ≤140 mg/dL (7.8 mmol/L) or 2-h postprandial ≤120 mg/dL (6.7 mmol/L)

These are optimal control values if they can be achieved safely. If patients cannot achieve these targets without significant hypoglycemia, the ADA suggests less strict targets based on clinical experience and individualization of care [1].

Treatment of GDM begins with medical nutrition therapy, physical activity, and weight control. Studies recommend that 70–85% of women diagnosed with GDM can control their GDM with lifestyle modification alone, depending on the population [1]. Early initiation of pharmacologic treatment may be needed for the women with greater initial degrees of hyperglycemia, and it has been demonstrated to improve perinatal outcomes [78]. Insulin is the first-line agent recommended for treatment of GDM in the USA and is the preferred agent for management of both Type 1 and Type 2 DM in pregnancy. Previously, oral antidiabetic agents were not used extensively in pregnancy, because of concerns about potential teratogenicity and fetal hyperinsulinemia. In current practice, many women with GDM are treated with glyburide, glipizide, or metformin [79, 80]. The short-term safety and efficacy of metformin (lowers the risk of neonatal hypoglycemia and maternal weight gain and however may increase the risk of prematurity) and glyburide (associated with a higher rate of neonatal hypoglycemia and macrosomia) have also been shown. However, long-term safety data are not available [1, 81–84].

The complications of DM can also occur in parturients, and their management is usually similar to those for nonpregnant patients [4]:

1. DKA: Frequent arterial blood gas assessments, serum glucose, and electrolyte measurements are essential. Intensive intravenous hydration with normal saline is required because of volume depletion. Intravenous insulin treatment is administered to control glucose levels. An intravenous potassium infusion (10–20 mEq/h) should be initiated, if the serum potassium level is reduced. Bicarbonate is administered when the patients have severe acidosis (pH < 7.1).
2. Fetal heart rate abnormalities: Maneuvers to optimize the fetal status include left uterine displacement and supplemental oxygen. Fetal condition usually improves with suitable medical therapy of the mother without any intervention.
3. Intrauterine fetal death: Routine antenatal fetal surveillance is important during the third trimester. At 28–32 weeks of gestation, most obstetricians begin nonstress tests twice weekly [55, 85, 86]. A nonreactive test will lead to performance of a contraction stress test or a fetal biophysical profile to evaluate fetal status. If fetal testing is reassuring, delivery can be delayed until after 38 weeks of gestation [55, 85]. If fetal testing is abnormal and amniotic fluid analysis shows fetal pulmonary maturity, the fetus should be delivered as soon as possible. In the

abnormal fetal testing and immature fetal lungs confirmed by amniotic fluid analysis, timing of delivery decisions is more difficult. Both the timing and the route of delivery are of great importance in parturients with DM, because the goal of obstetricians is to deliver an infant with mature lungs while avoiding an intrauterine fetal death in pregnancy.

4. Fetal macrosomia: The decision of delivery method requires consideration of estimated fetal weight and condition, cervical dilation and effacement, and previous obstetric history. Some obstetricians choose elective induction of labor at 38–40 weeks of gestation for not only avoiding complication of late stillbirth but also the associated risks with fetal macrosomia including shoulder dystocia and birth injury. The others often prefer elective Cesarean delivery in diabetic parturients for similar reasons.

3.6 Anesthetic Management

There have been few studies regarding anesthetic management of parturients with DM. Clinical decisions of these patients are usually guided by logical extensions of the studies of nonpregnant patients with DM and parturients without DM.

The anesthesiologist should focus on the glycemic control in parturients with DM in addition to the usual preanesthetic evaluation including history and physical examination. In women with pre-existing disease, DM-related acute and chronic complications should be determined. Possible complications include cardiac, vascular, and renal involvements as well as autonomic neuropathy and dysfunction. Parturients with DM have additional risks associated with autonomic neuropathy such as hypertension, orthostatic hypotension, painless myocardial infarction, decreased heart rate variability, decreased response to some medications (atropine and propranolol), resting tachycardia, neurogenic atonic bladder, decreased cough reflex threshold, and increased incidence of obstructive sleep apnea and gastroparesis. In patients with long-standing DM, ischemic heart disease or autonomic dysfunction can be identified by an electrocardiogram (ECG). In the anesthetic management of these patients, major concerns include hypotension requiring aggressive hydration and vasopressors, and aspiration [4, 87, 88].

On the other hand, the women with Type 1 DM should be screened for evidence of the "stiff joint" syndrome by looking for the "prayer sign," despite its rarity. This syndrome may be associated with the limited movement of atlanto-occipital joint, which may lead to difficult direct laryngoscopy and intubation [4, 12].

3.6.1 Management and Analgesia for Labor and Vaginal Delivery

Epidural analgesia is beneficial for labor pain management in patients with DM. It provides excellent analgesia for labor itself, instrumentally assists delivery and episiotomy, attenuates the physiologic response to pain, and results in decreased maternal plasma catecholamine concentrations.

As uteroplacental blood flow is reduced in parturients with DM, the decrease in catecholamine levels associated with neuraxial analgesia would also lead to improved uteroplacental perfusion. Additionally, as catecholamines are insulin antagonist hormones that oppose insulin activity, the theory is that epidural labor analgesia improves glucose control during labor and delivery. This improvement indirectly increases placental blood flow and reduces the maternal lactic acid production and hence fetal acidosis.

Certain precautions should be taken into consideration when administering epidural analgesia to parturients with DM. Patients with pre-existing DM and autonomic neuropathy are especially prone to hypotension during the initiation of sympathetic blockade. Therefore, aggressive volume expansion with a non-dextrose-containing solution and slow dosing of the epidural catheter to accomplish a slower onset of sympathetic blockade during epidural analgesia should be emphasized. Otherwise, hypotension related to epidural analgesia may lead to fetal compromise because of the reduction in uteroplacental perfusion associated with DM. If hypotension occurs, it should be treated promptly and aggressively with ephedrine. Uteroplacental blood flow reduction by 35–45% in parturients with DM increases the risk for fetal distress during labor and necessitates an urgent Cesarean delivery. Hence, epidural analgesia is usually preferable to combined spinal-epidural (CSE) analgesia in many parturients with DM, especially in the ones with non-reassuring fetal heart rate tracings [4, 88].

3.6.2 Anesthesia for Cesarean Delivery

Cesarean delivery is more likely in patients with DM compared to the healthy ones, and regional anesthesia is generally preferred over general anesthesia throughout all parturients. Previously, an association was found between spinal-epidural anesthesia for Cesarean delivery and umbilical cord-neonatal acidosis in parturients with DM. However, later on, the reasons for the acidosis were determined to be the dextrose-containing fluids (5% dextrose), maternal hyperglycemia, and hypotension [4, 89, 90]. When providing epidural or spinal anesthesia in a parturient with DM, adequate hydration with a non-dextrose-containing solution should be accomplished, maternal glycemic control should be satisfactory, and hypotension should be treated promptly and aggressively with vasopressors to avoid neonatal acidosis [91, 92]. To date, the comparison of spinal and epidural anesthesia techniques for Cesarean delivery in parturients with DM has not been made in terms of the maternal or neonatal effects. However, when the Cesarean delivery is elective and there is adequate time to initiate epidural anesthesia, it may be preferable. Epidural anesthesia is also of choice when a parturient with DM has a chronic uteroplacental insufficiency. Its slower onset of sympathetic blockade could decrease the risk of anesthesia-induced hypotension/hemodynamic alterations, and the avoidance of hypotension is important to ensure fetal well-being in patients with DM. When the

Cesarean delivery is urgent and does not allow time for epidural block, spinal anesthesia is usually preferred over general anesthesia because of its safety profile, despite its hypotension risk. If hypotension occurs, it can quickly be treated with a vasopressor to avoid fetal compromise [4].

Although spinal and epidural anesthesia techniques are more commonly used, we should keep in mind that patients with DM are more vulnerable to neurologic injury for the reasons including susceptibility to infection, having vascular diseases and peripheral neuropathy. These patients are at increased risk for spontaneous or catheter-associated epidural abscess, anterior spinal artery syndrome, and worsening of neuropathy [93–97]. On the other hand, after epidural anesthesia for Cesarean delivery, an increased incidence of neonatal hypoglycemia was observed in patients with pre-existing DM. In this study, maternal glycemic control was fair (mean fasting plasma glucose (FPG) was 127 mg/dL), a non-dextrose-containing solution was used for hydration, and intravenous insulin therapy was adjusted on the basis of frequent blood glucose determinations. This illustrates the neonate's vulnerability to hypoglycemia despite meticulous anesthesia care at the time of delivery [92].

Parturients with DM undergo general anesthesia either because of urgent Cesarean delivery (especially if an epidural catheter has not been placed for labor analgesia) or contraindications that preclude neuraxial anesthesia. The same principles are valid to provide general anesthesia for any parturient when caring for women with DM. General anesthesia can sometimes be problematic because of limited atlanto-occipital joint extension, increased hemodynamic response to intubation, and impaired insulin antagonist hormone responses to hypoglycemia and gastroparesis [98, 99]. No published data has been published indicating the effects of DM on the pharmacokinetics and pharmacodynamics of anesthetic agents in parturients. However, in nonpregnant women, DM was found to be associated with delayed onset of muscle relaxation with tubocurarine and prolonged blockade with vecuronium [100, 101].

Some special considerations exist in patients with pre-existing DM, because these are at risk for autonomic neuropathy. The anesthesiologist should be prepared for more frequent and severe hypotension attacks in these parturients. Left uterine displacement and intravenous hydration are the methods used preoperatively and intraoperatively to prevent hypotension. If prompt hypotension occurs, aggressive therapy is necessary. It was shown that autonomic dysfunction was associated with increased vasopressor requirements during general anesthesia in nonpregnant patients with DM [87]. In addition, the increased risk of aspiration secondary to gastroparesis can also be minimized by the administration of metoclopramide.

Finally, the "prayer sign" occurs in patients with long-standing, pre-existing DM and is associated with nonfamilial short stature, joint contractures, tight skin, limited atlanto-occipital joint movement, and noncompliant epidural space [12, 93, 102]. Therefore, the anesthesiologist should carefully evaluate the parturients with DM for the risk of difficulty in direct laryngoscopy, intubation, and requirement for awake intubation [4, 12].

3.7 Postpartum Management

In the postpartum period, insulin requirements usually decrease significantly, and after labor and delivery, glycemic control does not need to be as tight as before. If an insulin infusion is utilized during labor, it should not be continued after delivery to avoid maternal hypoglycemia [4].

Most patients with GDM return to normal glucose tolerance after delivery but remain at increased risk for Type 2 DM and the recurrence of GDM later in life [103]. The prevalence of postpartum DM has been reported as 2.4% in the UK, and the recurrence rate for GDM is 35–70% [104, 105].

As GDM may represent pre-existing undiagnosed Type 1 or Type 2 DM, women with GDM should be tested for persistent DM or prediabetes at 4–12 weeks of postpartum with a 75 g OGTT using nonpregnancy criteria. The OGTT is recommended over HbA1c at that time point, because HbA1c may be persistently lowered by the increased red blood cell turnover related to pregnancy or blood loss at delivery. The OGTT is also more sensitive at detecting glucose intolerance, including both prediabetes and DM [1].

Women at reproductive age with prediabetes may develop Type 2 DM during their next pregnancy and will need evaluation. As GDM is associated with increased maternal risk for DM, although the 4–12 weeks of 75 g OGTT is normal, women should be tested every 1–3 years thereafter. The frequency of testing depends on other risk factors including family history, prepregnancy body mass index, and insulin- or oral glucose-lowering medication requirement during pregnancy. The evaluation may be continued with any recommended glycemic test including HbA1c, FPG, or 75 g OGTT using nonpregnant thresholds [1].

Key Learning Points

- Gestational DM (GDM) is described as DM that is first diagnosed in the second or third trimester of pregnancy, which is not clearly either pre-existing Type 1 or Type 2 DM.
- Clinical presentation of DM and GDM can be associated with acute (diabetic ketoacidosis, hyperglycemic nonketotic state, and hypoglycemia) and chronic (macrovascular atherosclerosis, coronary, cerebrovascular, and peripheral vascular; microvascular, retinopathy and nephropathy; neuropathy, autonomic and somatic) complications.
- Optimal glycemic control is the major focus at each phase of obstetric care of parturients with DM, as it minimizes fetal structural malformations. Treatment of GDM begins with medical nutrition therapy, physical activity, and weight control. Insulin, glyburide, glipizide, and metformin are the other possible medical therapy options.
- During preanesthetic evaluation, anesthesiologist should focus on the glycemic control in parturients with DM in addition to routine history and physical examination. In women with pre-existing disease, DM-related

acute and chronic complications including cardiac, vascular, and renal involvements as well as autonomic neuropathy and dysfunction should be determined. These patients may have additional risks associated with autonomic neuropathy such as hypertension, orthostatic hypotension, painless myocardial infarction, decreased heart rate variability, decreased response to some medications (atropine and propranolol), resting tachycardia, neurogenic atonic bladder, decreased cough reflex threshold, and increased incidence of obstructive sleep apnea and gastroparesis. The women with Type 1 DM may present with "stiff joint" syndrome, and this syndrome is associated with the limited movement of atlanto-occipital joint, which may lead to difficult direct laryngoscopy and intubation.

- For labor pain management, epidural technique provides excellent analgesia in parturients with DM, especially if instrumentally assisted delivery and episiotomy are required. Additionally, the decrease in catecholamine levels associated with neuraxial analgesia leads to improved uteroplacental perfusion.
- Certain precautions should be taken into consideration when administering epidural analgesia to parturients with DM. Patients with pre-existing DM and autonomic neuropathy are especially prone to hypotension during the initiation of sympathetic blockade. Therefore, aggressive volume expansion with a non-dextrose-containing solution and slow dosing of the epidural catheter to accomplish a slower onset of sympathetic blockade should be emphasized.
- Cesarean delivery is more likely in patients with DM compared to the healthy ones, and regional anesthesia is generally preferred over general anesthesia throughout all parturients. During epidural or spinal anesthesia performance in a parturient with DM, adequate hydration with a non-dextrose-containing solution should be accomplished, maternal glycemic control should be satisfactory, and hypotension should be treated promptly and aggressively with vasopressors to avoid neonatal acidosis.
- When the Cesarean delivery is elective and there is adequate time, epidural anesthesia is a preferable option with its slower onset of sympathetic blockade. However, if the Cesarean delivery is urgent and does not allow time for epidural block, spinal anesthesia would usually be preferred over general anesthesia because of its safety profile, despite its hypotension risk.
- Parturients with DM undergo general anesthesia either because of urgent Cesarean delivery (especially if an epidural catheter has not been placed for labor analgesia) or contraindications that preclude neuraxial anesthesia. General anesthesia can sometimes be problematic because of limited atlanto-occipital joint extension, increased hemodynamic response to intubation, and impaired insulin antagonist hormone responses to hypoglycemia and gastroparesis.

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