Diabetes mellitus complicates approximately 3 to 5% of all pregnancies with 90% classified as gestational and 10% as pregestational.(M. B. Landon & Gabbe, 2010) Pregestational diabetes prevalence continues to rise largely due to increases in Type 2 diabetes associated with obesity. Pregestational diabetes is a major cause of maternal and perinatal mortality and morbidity which can be directly related to hyperglycemia and vasculopathy in the mother, although meticulous glycemic control reduces risks and can lead to successful pregnancy outcomes.

Diabetes mellitus is classified by the American Diabetes Association (ADA) as Type 1, Type 2, or gestational. This classification is preferred as it reflects the underlying pathophysiology of the disease. Type 1 diabetes accounts for 5-10% of all diabetes in the general population and is a result of autoimmune destruction of pancreatic beta cells, leading to an absolute deficiency of insulin production. The vast majority of Type 1 diabetics require insulin regardless of pregnancy status. Type 2 diabetes is the result of increased peripheral insulin resistance resulting in a relative, rather than absolute, deficiency of insulin. Type 2 diabetes may eventually result in failure of the pancreatic beta cells to produce insulin. Management of the non-pregnant Type 2 diabetic is directed at improving insulin sensitivity through diet, exercise, and oral hypoglycemic medications. Some patients with Type 2 diabetes will require insulin when conservative strategies cannot achieve adequate glycemic control. However, due to the stringent control required for optimal fetal outcomes and the increased insulin resistance associated with pregnancy, Type 2 diabetes is typically managed with insulin during pregnancy, even when reasonable control has been achieved with oral agents in the non-pregnant state.

The severity of pregestational diabetes can be categorized according to the White classification system (Table 1). ACOG further utilizes a single classification based on the presence or absence of maternal vasculopathy. Patients with diabetic vasculopathy require more aggressive management.

Table 1: Classification of Diabetes Complicating Pregnancy (Cunningham et al., 2010)

Class	Onset	Fasting	2-hr Postprandial	Therapy
A1	Gestational	< 105 mg/dL	< 120 mg/dL	Diet
A2	Gestational	> 105 mg/dL	> 120 mg/dL	Oral agent or insulin
Class	**Age of onset (yr)**	**Duration (yr)**	**Vascular Disease**	**Therapy**
B*	≥ 20	< 10	None	Insulin
C*	10 to 19	10-19	None	Insulin
D*	Before 10	> 20	Benign retinopathy	Insulin
F	Any	Any	Nephropathy†	Insulin
R	Any	Any	Proliferative retinopathy	Insulin
H	Any	Any	Heart	Insulin

*Single criteria required for diagnosis: age of onset, duration, or vascular disease

†When diagnosed during pregnancy: 500mg or more proteinuria per 24 hours measured before 20 weeks' gestation.

Maternal Complications

Women with pregestational diabetes are at increased risk of preeclampsia compared to non-diabetic women (4-fold increase in risk) and at increased risk of primary cesarean delivery. Diabetic ketoacidosis (DKA) occurs in 5-10% of pregestational diabetics during pregnancy, with high rates of both maternal (2%) and fetal mortality (10%). Fetuses that survive episodes of DKA may be at risk for abnormal long-term neurodevelopment but the risk is unknown. Women with diabetic retinopathy can experience progression of retinopathy during pregnancy, ultimately leading to blindness. Women with pre-existing nephropathy (5-10% of diabetics) should anticipate worsening of proteinuria and hypertension in the third trimester, although this is rarely permanent. (ACOG, 2005) However, women with severe nephropathy (proteinuria>3g/24hours) or serum creatinine >1.5 may experience permanent progression to end stage renal disease during pregnancy.

Fetal Complications

Major congenital anomalies occur in 6-12% of diabetic pregnancies.(ACOG, 2005) The risk for anomalies increases with increasing glycosylated hemoglobin (Hgb A1c). A Hgb A1c level of approximately 5-6%, is associated with a fetal malformation rate close to that observed in normal pregnancies (2-3%), whereas a Hgb A1c concentration near 10% is associated with a fetal anomaly rate of 20-25%. (ACOG, 2005)Complex cardiac defects, renal abnormalities, CNS and skeletal abnormalities are the most common. Diabetes also increases the risk of fetal demise, preterm birth, polyhydramnios, altered fetal growth (IUGR or macrosomia) and neonatal RDS, hypoglycemia, hypocalcemia, hyperbilirubinemia, and cardiac hypertrophy.(Cunningham et al., 2010; HAPO, 2008) Glycemic control can reduce the risk for most if not all of these complications.

Preconception Counseling

Maternal hyperglycemia during the first trimester is a risk factor for abnormal fetal organogenesis; thus, diabetic women should be encouraged to have preconception counseling. The visit should include discussions regarding fetal and maternal effects of diabetes, importance of maintaining euglycemic control before pregnancy, review of medications, and conversion of women on oral agents to insulin prior to conception. Glycemic control goals during the preconception period include:

- Pre-prandial blood sugar levels <95, 1-hr post-prandial levels <140, and 2-hr post-prandial levels <120.

- HgbA1c <6.4%
- If glycemic control is inadequate:
    - recommend contraception use until Hgb A1c goal is reached
    - refer to endocrinology or internal medicine for insulin therapy

In addition, examinations for underlying vasculopathy should be conducted on selected women including retinal exam by an ophthalmologist, a 24-hour urine for protein and creatinine clearance, and an ECG. Since up to 40% of type 1 diabetic women have thyroid dysfunction, thyroid studies should be obtained. Diabetic women are at high risk for neural tube defects, thus they should be instructed to begin taking a multivitamin with at least 400 µg of folic acid before conception. (ACOG, 2005)

Pregnancy Management

At the initial prenatal visit all diabetics should have nutritional counseling with a diabetic educator, HgbA1c to assess prepregnancy control, assessment of renal function using serum creatinine and urine protein/creatinine ratio or 24 hour urine, EKG for patients with diabetes for > 5 years or with co-morbid conditions, referral for comprehensive eye exam by an ophthalmologist if not performed in the last 6 months, and Type 1 DM patients should have thyroid function tests: TSH and free T4.

Subsequent visits should occur every 2 weeks in the first and second trimester to evaluate blood sugars with more frequent evaluation in those women with poor control or requiring multiple insulin adjustments. Weekly visits should occur after 28-30 weeks. The patient should be referred to a MFM for a targeted ultrasound and fetal echocardiogram at 18-24 weeks. Ultrasounds for fluid and growth should be conducted approximately every 4 weeks commencing at 24-28 weeks and a Hgb A1c collected each trimester. Antenatal fetal testing should be conducted every week beginning at 32 weeks with NST, BPP, modified BPP or CST. Patients with IUGR, hypertension, diabetic vasculopathy or history of IUFD may warrant earlier and more frequent testing. While the evidence is clear that antenatal testing results in a decrease in perinatal morbidity and mortality, it is unclear that any one form of antenatal testing offers a distinct improvement in outcome versus any other. Therefore, the method of antenatal testing can be individualized to the practice setting, resource availability, and individual patient as needed.

Diet modification, exercise, frequent blood sugar assessments, and insulin are the key management tools for glucose control. Patients should be encouraged to keep a log of food intake to correlate with insulin dosages, exercise, and glucose values.

Diet Modification

Dietary therapy is essential for the management of diabetes. All diabetic OB patients require nutrition counseling. Caloric recommendations are based on the patient's pre-pregnancy weight: 35-40 kcal/kg for the underweight patient, 30-35 kcal/kg for the average weight patient, and 25 kcal/kg for the overweight patient.(ACOG, 2005) The diet should consist of 40-50% complex carbohydrates, 20-30% unsaturated fats, and 20-30% protein. Calories may be distributed as follows: 10-20% at breakfast; 20-30% at lunch; 30-40% at dinner; and up to 30% for snacks, especially a bedtime snack to reduce nocturnal hypoglycemia. (ACOG, 2005) Artificial sweeteners, saccharin, aspartame (Equal), and sucralose (Splenda), may be safely used in moderate amounts. Concentrated sweets should be excluded. Total weight gain recommendations for pregnancy are BMI specific and are not altered by diabetes.

Exercise

All women should follow a program of moderate exercise (30 minutes of walking at least 5 times per week) as part of the treatment plan, barring any medical or obstetrical contraindication to this level of physical activity.

Blood Sugar Monitoring

Table 2. Self-monitored Capillary Blood Glucose Goals (ACOG, 2005)

Specimen	Level (mg/dl)
Fasting	≤ 95
Premeal	≤ 100
1-hr postprandial	≤ 140
2-hr postprandial	≤ 120
0200-0600	≥ 60
Mean (average)	100
Hb A1c	≤ 6%

Women should be advised to monitor their blood sugars at least 4 times/day: fasting (AM) and post-prandial (breakfast, lunch, dinner). Post-prandial blood sugars may be monitored 1- or 2-hours after a meal and may be individualized for patient ease and convenience. The goal for fasting blood sugars is <95, for 1-hour post-prandial <140, and for 2-hour post-prandial <120. Women with Type 1 diabetes or with difficult management (i.e. hyperglycemic and hypoglycemic episodes) may require more frequent monitoring with the addition of pre-prandial, bedtime, and 3-AM blood sugars. Women using continuous subcutaneous insulin (i.e. an insulin pump) should be monitored with 7 times/day blood sugars (fasting both pre-prandial, and post-prandial for all 3 meals).

Oral Hypoglycemic Agents

The use of oral agents for treatment of pregestational diabetes has not been well studied in pregnancy. The physiologic increasing insulin resistance of pregnancy and the desire for strict glycemic control during pregnancy necessitate the use of insulin during pregnancy. The use of oral agents in

women with pregestational diabetes is not recommended except in rare circumstances when used as an adjunct to improve insulin sensitivity or in patients who refuse insulin treatment despite counseling.

Insulin Therapy

The goal of insulin therapy is to mimic the physiology of the pancreas: a basal rate of insulin release to allow glucose uptake into cells, a bolus of insulin with meals to inhibit gluconeogenesis and lipolysis and avoid hyperglycemia. This may be achieved with either multiple daily insulin injections or with continuous subcutaneous infusion of insulin.

In the last 10-15 years, advances have been made in the field of insulin analogues, although the obstetric field has been slow to change to their use due to concerns for safety. Outside of pregnancy, the most physiologic insulin replacement therapy is considered to be a basal-bolus regimen, where a long-acting insulin with no peak (i.e. insulin glargine, aka Lantus) is used to provide control of fasting and pre-prandial blood sugars with a fast-acting insulin at meals (i.e. Lispro or Aspart) to provide control of post-prandial blood sugars. Compared to pre-mixed insulins, NPH and regular, the basal-bolus approach has similar control of hyperglycemic episodes with decreased hypoglycemia. Retrospective studies, pharmacokinetic studies and meta-analyses all suggest that insulin analogues do not cross the placenta, are not associated with increased risks of anomalies, and are associated with pregnancy outcomes similar to traditional insulin regimens. Although this approach may require more injections, they give the patient the most flexibility in terms of timing of eating and choice of meals while minimizing the risk of hypoglycemia. Given these findings, a basal-bolus approach using insulin glargine or detemir with rapid-acting insulin at each meal is preferred. However, those well-controlled on their pre-pregnancy insulin regimen may continue their current insulin.

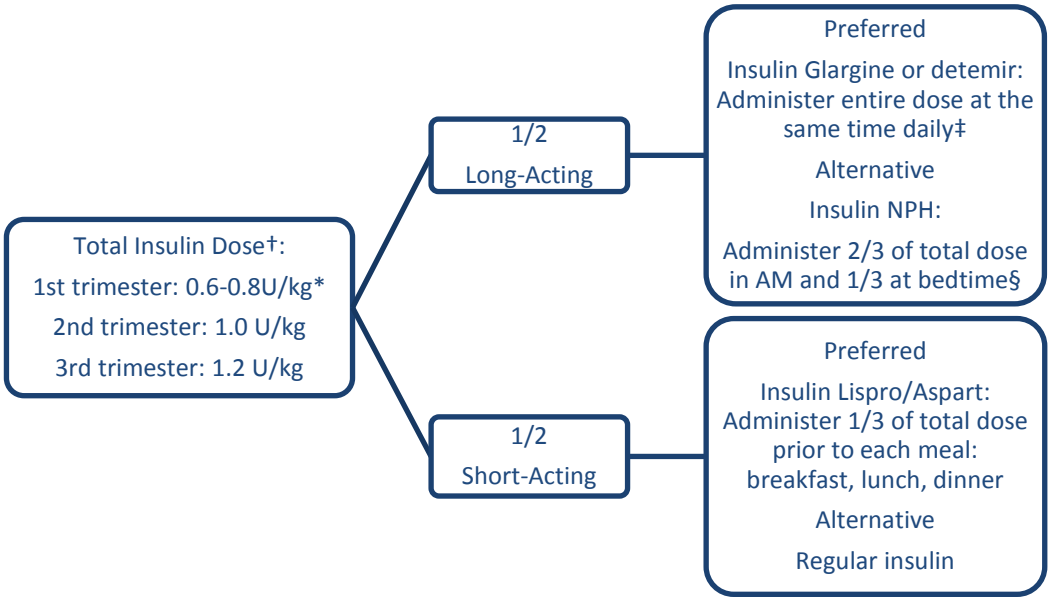
Table 3. Action profile of commonly used insulin (Gabbe & Graves, 2003)

Insulin	Onset of action	Peak of action (hrs)	Duration (hrs)
Lispro/Aspart (Humalog, Novolog)	Rapid-1-15 min	1-2	4-5
Regular	Short 30-60 min	2-4	6-8
Neutral Protamine Hagedorn (NPH)	Intermediate 1-3 hrs	5-7	13-18
Glargine (Lantus)	60	Mild at 6-8	24
rDNA insulin detemir (Levemir)	120-240	Mild at 3-9	dose dependent

*Levemir dose of 0.2 U/kg last 5-12 hrs, 0.4 U/kg last 19 hrs, 0.8 U/kg last 24 hrs. Levemir may be dosed once or twice a day.

Calculation of insulin dosages:

Insulin requirements will increase throughout pregnancy, especially during the weeks between 28-32 weeks. Insulin needs increase from a range of 0.7-0.8 U/Kg/d in the first trimester, 0.8-1.0 U/Kg/d in the second, and 0.9-1.2 U/kg/d in the third. (ACOG, 2005)



*Type 1 diabetics generally need a lower insulin dose (0.6 units/kg) than Type 2 diabetics (0.8-1.0 units/kg). The majority of Type 1 diabetics will be on insulin prior to pregnancy; their insulin dosing should be determined by prior requirements and current control.

† For insulin naïve subjects, consideration may be given to reducing the starting dose by 25% with aggressive titration up after 3-7 days of blood glucose monitoring.

‡ The maximum dose of insulin glargine that should be administered in one injection is 70 units. If a patient requires more than 70 units of insulin glargine, administer as BID dosing.

§ The evening dose of NPH may be administered at dinner to reduce the number of injections; however this strategy is associated with an increased frequency of night-time hypoglycemia.

Patients who are on insulin prior to pregnancy may be familiar with carbohydrate counting. These patients may elect to continue carbohydrate counting with sliding scale insulin for their pre-meal insulin dosages as this strategy gives patients maximum flexibility. Highly motivated patients who have not done carbohydrate counting before but desire more flexibility in their schedule and diet may wish to adopt this approach.

A. Adjustments to Insulin Therapy
   - Adjustments to long-acting insulin glargine should not be made more frequently than every 48 hours as its long half-life prevents more frequent adjustments.

- Adjustments to insulin regimen should be made when >50% of blood sugars are greater than target (>95 fasting, >140 1-hour post-prandial, >120 2-hours post-prandial).
- Adjustments to long-acting insulin will correct fasting blood sugars.
- Adjustments to pre-meal short acting insulin will correct the post-prandial blood sugar for that meal.
- Increases to insulin can be made in increments of 10%. For patients in the inpatient setting, more aggressive dose-adjustment can be performed in the face of marked hyperglycemia.

B. Safety & Counseling

- Fast-acting insulin should not be injected unless the patient is planning to eat immediately.
- Any patient on insulin should receive a prescription for a glucagon kit. If possible, the patient should have two glucagon kits – one to keep with her at all times and one in an accessible & reliable location in her house. At least one family member or housemate should be instructed on how and when to administer glucagon.

C. In-Patient Management

- For most patients, blood sugar management is an outpatient issue. Insulin can be initiated as an outpatient and titrated for control with frequent visits.
- Patients for whom in-patient management should be considered include:
  - Patients with recurrent or severe hypoglycemia, particularly those who are unable to sense hypoglycemic symptoms, may require hospitalization while insulin dosages are titrated.
  - Patients with significant hyperglycemia with the majority of blood sugar measurements > 250mg/dl.
  - Type 1 diabetics and poorly controlled type 2 diabetics who are unable to obtain diabetic supplies (glucometer, lancets, syringes, and insulin) on the day of their clinic visit.
  - Suspicion of diabetic ketoacidosis, as evidenced by ketonuria and blood sugar > 180 mg/dl.
  - Inability to tolerate oral intake.

Continuous Subcutaneous Insulin Infusion

Continuous subcutaneous insulin infusions, commonly known as insulin pumps, may be used in motivated, Type 1 diabetic patients. CSII provides similar control to the basal-bolus technique but is associated with an increased risk of diabetic ketoacidosis. **Patients on an insulin pump should be managed in conjunction with an endocrinologist and/or MFM; in these cases it is important to designate which physician will be making alterations to the insulin regimen.**

The basic principle of the CSII is to provide a basal, low-dose of insulin infused continuously. Generally, approximately 3-4 different basal doses are required throughout the day to avoid hypo- and

hyperglycemia (different basal rates for waking-lunch, lunch-dinner, dinner-bedtime, overnight). The pump may then provide a bolus of insulin with meals, depending on the number of carbohydrates consumed and the insulin sensitivity (i.e. the drop in blood sugar anticipated for each unit of insulin). The insulin pump may be adjusted by adjusting basal rates, carbohydrate: insulin ratio, and insulin sensitivity.

Hypoglycemia

Symptomatic hypoglycemia can be life threatening and must be prevented. Patients should be instructed on the use of emergency glucose. If hypoglycemia is complicated by stupor, inability to tolerate oral treatment or the patient is unconscious, glucagon 1mg IM should be administered. Type 2 patients who are prone to hypoglycemia and all Type 1 diabetics should have glucagon available for home use and family members instructed on its use.

Hyperglycemia, Urinary Ketones and Diabetic Ketoacidosis

Pregestational diabetic patients are at risk for diabetic ketoacidosis when ill and should be instructed on the use of urine ketone strips when blood glucose is elevated. Urine ketones should be assessed when blood sugar is greater than 180 mg/dL or when Type 1 diabetics are ill. Women with moderate to large ketones should be instructed to contact their physician immediately and additional insulin should be administered promptly. Ketoacidosis can occur rapidly in pregnancy due to the ketogenic state of pregnancy and can develop even with blood glucose levels as low as 200-250 mg/dL. It is usually due to non-compliance or stressors including infection. Each episode of DKA is associated with a 5-10% risk of fetal mortality, therefore prompt treatment is imperative. In general, these patients should be admitted to an ICU environment and assistance from a critical care or MFM specialist sought. In the setting of significant maternal

Management of Diabetic Ketoacidosis During Pregnancy (M. B. Landon, Catalano P.M., and Gabbe S.G., 2007)

1. Lab Assessment:
   - Obtain arterial blood gases to document degree of acidosis
   - measure glucose, ketones, and electrolyte levels at 1 to 2 hour intervals
2. Insulin:
   - Low-dose, intravenous
   - Loading dose: 0.2-0.4 U/kg
   - Maintenance: 2-10 U/h
3. Fluids:
   - Isotonic sodium chloride
   - Total replacement in first 12 hours equals 4-6 L
   - 1 L in first hour
   - 500-1,000 ml/h for 2-4 hours
   - 250 ml/h until 80% replaced
4. Glucose:
   - Begin 5% dextrose in normal saline when plasma level reaches 250 mg/dl (14 mmol/L)
5. Potassium:
   - If initially normal or reduced, an infusion rate up to 15-20 mEq/h may be required; if elevated, wait until levels decrease into the normal range, then add to intravenous solution in a concentration of 20-30 mEq/L
6. Bicarbonate
   - Add one ampule (44 mEq) to 1 L of 0.45 normal saline if Ph is <7.1

acidemia, the fetus will be acidemic and the fetal tracing non-reassuring. Fetal resuscitation via maternal resuscitation is the best treatment and delivery should not be undertaken for a non-reassuring tracing until the mother has been stabilized and the maternal acidemia corrected. Consideration should be given to transferring these patients to a tertiary center for management once initial resuscitative efforts have been begun.

Delivery and Postpartum Management

Early delivery may be indicated in some patients with vasculopathy, nephropathy, poor glucose control, or a prior stillbirth. It is recommended that these patients have an amniocentesis to assess for fetal lung maturity for deliveries before 39 weeks. For patients with poor control or multiple co-morbidities, amniocentesis for fetal lung maturity at 36-38 weeks can be considered. For patients with well-controlled diabetes and reassuring antenatal testing, pregnancy can be allowed to continue until 39-40 weeks. Expectant management beyond the patient's EDC is not recommended. To prevent traumatic birth injury, cesarean delivery may be considered if the EFW is ≥ 4200-4500 grams. (ACOG, 2005)

Insulin Management During Labor and Delivery (ACOG, 2005)

- Usual dose of intermediate-acting or long-acting insulin is given at bedtime.
- Morning dose of intermediate-acting insulin is withheld. (If the patient takes long-acting insulin in the A.M., it may be given)
- Intravenous infusion of normal saline is begun.
- Once active labor begins or glucose levels decrease to less than 70 mg/dL, the infusion is changed from saline to 5% dextrose and delivered at a rate of 100-150 cc/h (2.5 mg/kg/min) to achieve a glucose level of approximately 100 mg/dL.
- Glucose levels are checked hourly using a bedside meter allowing for adjustment in the insulin or glucose infusion rate.
- Regular (short-acting) insulin is administered at a rate of 1.25 U/h if glucose levels exceed 100 mg/dL.

During induction of labor, maternal glycemia can be controlled with an IV infusion of regular insulin titrated to maintain hourly readings of blood glucose levels < 110 mg/dL. Patients using an insulin pump may continue their basal infusion during delivery. Intrapartum glycemic control is critical as it is a major determinant of neonatal glucose. Intrapartum maternal hyperglycemia increases the risk of neonatal hypoglycemia markedly. (ACOG, 2005)

Insulin requirements decrease rapidly after delivery. One half of the pre-delivery dose may be reinstituted after starting regular food intake. Breastfeeding should be encouraged and will require an additional 500 kcal/d more than the prepregnancy caloric intake. (ACOG, 2005)

Quality Indicators/Benchmarks

- Hgb A1c at initial visit
- Targeted ultrasound and fetal echocardiogram referral
- Antepartum fetal testing by 34 weeks

- Diabetic education before 20 weeks

Obstetric Management

In addition to routine prenatal labs and care the following is recommended for the monitoring of, and intervention for, fetal and obstetric complications of diabetes.

First OB Visit:

- Nutrition counseling
- Schedule visits with diabetic educator
- Hgb A1c to assess prepregnancy control and assist in counseling
- Renal function assessment- serum creatinine and urine protein/creatinine ratio (or 24-hour urine for protein)
- Comprehensive eye examination by an ophthalmologist if not completed in the last 6 months
- EKG—for those with diabetes >5 years or co-morbid conditions
- Prescribe insulin therapy
- Pattern blood sugars (PBS)
- Type 1 DM:
  - TSH and free T4

Subsequent OB visits:

- Visits every 2 weeks in the first and second trimester to evaluate blood sugars. More frequent evaluation is necessary in those with poor control or requiring multiple insulin adjustments.
- Weekly visits after 28-30 weeks
- Targeted ultrasound at 18-20 weeks
- Fetal echocardiogram at 22-24 weeks
- Ultrasound for fluid and growth approximately every 4 weeks from 24-28
- Hgb A1c each trimester
- Antenatal fetal testing q week beginning at 32 weeks with NST, BPP, modified BPP or CST. Patients with IUGR, hypertension, diabetic vasculopathy or history of IUFD may warrant earlier and more frequent testing.

Delivery:

- Schedule for delivery between 39-40 weeks with reassuring testing
- Ultrasound for fetal growth within 3 weeks of delivery
- Recommend elective cesarean for estimated fetal weight ≥ 4500 grams
- Assess glycemic control. If there is evidence of poor glucose control, maternal vasculopathy or nephropathy (White's ≥ D), consider delivery between 38-38^{6} weeks. If evidence of fetal growth restriction, HTN, or other complications develops, earlier delivery should be considered.

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