Northwest Perinatal Center

Perinatal Progress

Diabetes Mellitus

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Both pregestational and gestational diabetes mellitus (DM) have potential maternal and fetal implications during pregnancy. The prevalence of these conditions is increasing worldwide, concomitant with rising obesity rates. It is inevitable that providers will care for women either at risk for, or already affected by, diabetes, and will need to consider the role of additional screening and monitoring during pregnancy. In this *Perinatal Progress*, diagnosis, management, and post-delivery recommendations for women at risk for, or already affected by, diabetes are provided.

Pregestational Diabetes

Type 1 DM (T1DM) is due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency. Patients with T1DM are insulin-dependent for life. This disorder has many potential antepartum, intrapartum, and postpartum complications, and maternal-fetal medicine primary management (or consultation if endocrinology is managing the diabetes primarily) is recommended. For this reason, further discussion of T1DM during pregnancy is not included here.

Type 2 diabetes mellitus (T2DM), known previously as "non-insulin-dependent diabetes" or "adult-onset diabetes," accounts for 90-95% of all diabetes. T2DM is due to a progressive loss of insulin secretion on the background of insulin resistance. Risk factors for developing T2DM include obesity, ethnicity, family history, physical inactivity, and history of gestational diabetes. Outside of pregnancy, T2DM is diagnosed based upon: (a) fasting blood glucose ≥ 126 mg/dL; (b) two-hour (2 h) plasma glucose ≥ 170 mg/dL during a 75 gm oral glucose tolerance test (oGTT); (c) HgA1c ≥ 6.5%; or (d) in a patient with symptoms of hyperglycemia or hyperglycemic crisis, a random glucose ≥ 200 mg/dL.

Though there may be a high suspicion for T2DM early in pregnancy and patients may meet diagnostic criteria during pregnancy, this diagnosis should be made definitively following a postpartum re-evaluation.

Complications. During pregnancy, T2DM is associated with both maternal and fetal risks. Maternal risks include worsening nephropathy and retinopathy, escalating insulin requirement, and development of hypertensive disorders. Fetal risks include congenital anomalies, growth abnormalities (both small for gestational age and macrosomia), stillbirth, operative delivery, birth trauma, shoulder dystocia, and neonatal hypoglycemia and hyperbilirubinemia. Despite adequate glycemic control and fetal surveillance, these complications are still increased among women with diabetes, in comparison to their healthy counterparts. Optimal diabetic management can reduce the incidence of some of these risks. For example, the risk for a major congenital malformation is 3.2% in the setting of first-trimester HgA1c value ≤ 7.9% and 23.5% among women with a HgA1c value > 10% (Table 1).

Table 1: Risk for major congenital malformation

INITIAL HGA1C VALUE (%)	MAJOR MALFORMATION
≤ 7.9	3.2
8.0 - 9.9	8.1
> 10.0	23.5

Preconception counseling. Ideally, all women with T2DM would have optimal glycemic control and consideration of medication exposures pre-conception. To this end, reliable contraception plus preconception counseling to discuss HgA1c goals is recommended. HgA1c < 7.0% is recommended to reduce the risk for congenital malformations. Many women with diabetes take an angiotensin converting enzyme inhibitor (ACE inhibitor) or angiotensin II receptor antagonist (ARB) for hypertension control or renal protection. These agents are contraindicated in pregnancy; a discussion about alternative agents or discontinuation due to different pregnancy blood pressure goals is needed. Finally, a search for underlying vasculopathy, including a retinal examination, renal function evaluation, and electrocardiogram (EKG) should be considered. NWP physicians are happy to provide this counseling.

Antepartum management. Establishing care early in pregnancy is important to address glucose goals, DM-related medications to achieve glycemic goals, and concomitant medication use. Baseline testing to assess underlying vasculopathy includes: (a) 24 hour collection to assess total protein and creatinine clearance; (b) comprehensive metabolic panel; (c) HgA1c; (d) 12-lead EKG if diabetes has been present > 10 years or if there is evidence of end-organ damage (such as chronic hypertension); and (e) referral for dilated eye examination unless one has been performed in the past year.

Table 2: Institute of Medicine weight gain recommendations (2009)

PRE-PREGNANCY CLASSIFICATION	PRE-PREGNANCY BMI (KG/M^2)	TOTAL WEIGHT GAIN RANGE SINGLETON	TOTAL WEIGHT GAIN RANGE TWINS
Underweight	< 18.5	28 - 40 lbs	
Normal weight	18.5 - 24.9	25 - 35 lbs	37 - 54 lbs
Overweight	25.0 - 29.9	15 - 25 lbs	31 - 50 lbs
Obese	> 30.0	11 - 20 lbs	25 - 42 lbs

During pregnancy, fasting and 2 h postprandial (PP) glucose checks are recommended, with the following goals: fasting < 95 mg/dL and 2 h PP < 120 mg/dL. Insulin is the preferred agent during pregnancy. It is prescribed based upon patient weight and dosed prior to breakfast, dinner, and bed. Some women inject a long-acting insulin outside of pregnancy (glargine (Lantus)). This insulin is safe in pregnancy; however, due to increased blood volumes and drug pharmacokinetics during pregnancy, twice daily dosing of this long-acting agent is often preferred. Exercise is encouraged, and review of weight gain goals is recommended (Table 2).

Antenatal testing beginning at 32-33 weeks' gestation is recommended, with frequency of testing (1-2 times/week) dependent upon glycemic control and presence or absence of vascular disease. In addition to a detailed fetal anatomic survey at 20 weeks, a fetal echocardiogram is recommended at 21-22 weeks, plus growth assessment by ultrasound at 28-29 weeks, followed by interval growth ultrasound every 4-6 weeks.

Delivery timing. Timing of delivery is dependent upon glycemic control and weighing fetal risks (stillbirth) vs. early term neonatal risks (increased respiratory distress syndrome and hyperbilirubinemia). In addition, these neonates are at risk of hypoglycemia, especially if intrapartum glucose is suboptimal (goal 90-110 mg/dL). Delivery planning should include a discussion of shoulder dystocia risk, as well as an increased risk for cesarean section. For fetuses estimated to weigh > 4500 gms, consideration of C-section to prevent birth injury is recommended.

Postpartum. Many women managed with insulin during pregnancy can resume their pre-pregnancy oral hypoglycemic agents. In addition, for women who started pregnancy on insulin and had increased insulin dosing during pregnancy, they can often return to pre-pregnancy insulin dosing in the postpartum period. Some ACE inhibitors are compatible with lactation and can be resumed postpartum.

Gestational Diabetes

Gestational diabetes (GDM) is a condition of carbohydrate intolerance with onset or recognition during pregnancy. This diagnosis was used initially to identify women at increased risk for developing T2DM later in life; however, it is now appreciated that there are a number of maternal and fetal complications in affected pregnancies, in addition to long-term health implications.

Diagnosing GDM. Consistent with ACOG guidelines, we recommend the two-step approach for establishing a GDM diagnosis. This includes a screening test (50 gm, 1 h oGTT) for all women between 24 and 28 weeks' gestation, followed by a diagnostic test (100 gm, 3 h oGTT) when the 1 h result is > 135 mg/dL. Cut-off values for the 3 h test are: fasting > 95 mg/dL, and 1 , 2, and 3 h results > 179 mg/dL, > 154 mg/dL, and > 140 mg/dL, respectively, with two of four abnormal values leading to a diagnosis. For women with a 1 h result > 200 mg/dL, 75-90% will screen positive after the 3 h oGTT; referral for either the 3 h oGTT or initiating glucose checks and presuming a GDM diagnosis are both reasonable options.

Some women are considered high-risk for GDM and warrant early screening (Figure 1). For early screen-negative women, repeat screening between 24 - 28 weeks' ges-

Figure 1: Early screening strategy

RISK CRITERIA FOR EARLY SCREENING

BMI > 25 (> 23 in Asian Americans) and *one or more of the following:*

- **Physical inactivity**
- **First-degree relative with diabetes**
- **High-risk race or ethnicity**
- **Previous birth of infant weighing 9 lb or more**
- **Previous GDM**
- **Hypertension**
- **HDL < 35 mg/dL, triglycerides > 250 mg/dL**
- **PCOS**
- **HgA1c ≥ 5.7%, impaired glucose tolerance, or impaired fasting glucose**
- **Other indications of insulin resistance**
- **History of cardiovascular disease**

Adapted from ACOG Practice Bulletin 190, Feb. 2018.

tation is recommended. For GDM diagnosed prior to 20 weeks, obtaining a HgA1c, anomaly risk counseling, and a fetal echocardiogram is recommended. For women taking metformin for polycystic ovarian syndrome, discontinuing this agent after the first trimester, then proceeding with the 1 h early oGTT screening test is advised.

Complications. Women with GDM are at increased risk for developing gestational hypertension and preeclampsia, plus C-section and its associated morbidities. Fetal/neonatal complications include macrosomia, neonatal hypoglycemia and hyperbilirubinemia, operative delivery, shoulder dystocia, and birth trauma. Fifty percent of women with GDM will develop T2DM during their lifetimes.

Management during pregnancy. During pregnancy, fasting and 2 h PP glucose checks are recommended, with fasting goal < 95 mg/dL and 2 h PP goal < 120 mg/dL. Referral for diabetic education with attention to the role of exercise and weight gain goals is recommended (Table 2). Adherence to an American Diabetic Association diet is the first step in managing women with GDM. Criteria for starting therapy includes: (a) fasting value > 95 mg/dL on 3 h oGTT or (b) over 2 weeks of 20% of values above goals.

If diet alone does not achieve optimal glucose control, insulin initiation is recommended, consistent with recent ACOG updated guidelines. The choice of first-line agent for control of GDM is not without controversy. Using similar research studies to formulate recommended guidelines, the opinion endorsed by ACOG is that insulin should be the first-line prescribed agent. The opinion endorsed by the Society for Maternal Fetal Medicine is that either insulin or metformin can be offered for medical management of GDM. After review of recommendations provided by ACOG and SMFM—and because there is equivalent glycemic control with glibenclamide and insulin but different neonatal outcomes (increased neonatal complications seen in women treated with this oral agent and no long-term outcome data published), **NWP providers have opted to endorse the opinion of ACOG.** Weight-based insulin dosing is advised, and NWP referral can be considered for insulin initiation or for patients with a complicated course.

For women who decline insulin therapy, metformin should be considered a first-line oral agent option. Twice daily dosing with meals (start 500 mg) is recommended. The dose can be titrated upward to 1000 mg by mouth twice daily. Gastrointestinal intolerance is a known associated side effect. For many women, the extended release formulation is better tolerated. Once medication is started, diagnosis changes to GDM A2 with implications for both antenatal surveillance and delivery timing.

With GDM A1, there is no role for antenatal testing in the absence of other morbidities (such as hypertension or BMI > 35). In addition, there is no indication for an early term delivery. For women with GDM A2, antenatal testing beginning at 32-33 weeks' gestation is recommended with frequency dependent upon glycemic control, plus growth assessment by ultrasound at 28-29 weeks followed by interval growth ultrasound every 4-6 weeks.

Delivery timing. Similar to delivery timing in the setting of T2DM, delivery timing is dependent upon degree of glycemic control, weighing fetal risk (stillbirth) with neonatal risks associated with an early term delivery. For well-controlled GDM A2, delivery prior to 39 weeks' gestation not indicated.

Postpartum. Agents started in pregnancy (insulin or oral agent) should be discontinued. A single fasting glucose test on postpartum day one can be considered, with additional fasting and 2 h PP checks if the fasting value is >

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126 mg/dL. For persistent hyperglycemia despite an ADA diet, initiation of metformin or restarting insulin at half of third-trimester dosing is reasonable, plus referral to a primary care physician for lifelong diabetes management.

For women diagnosed with GDM, a 2 h, 75 gm oGTT is recommended at 6-12 weeks postpartum. Fasting glucose > 125 mg/dL or a 2 h result > 199 mg/dL is consistent with diabetes mellitus, and referral to a primary care provider for ongoing management is recommended. Fasting glucose 100-125 mg/dL or a 2 h result 140-199 mg/dL is consistent with impaired fasting glucose or impaired glucose tolerance, which puts the individual at lifetime increased risk for diabetes mellitus and warrants attention. Care may include weight loss, increased physical activity and metformin. Referral to a primary care physician should also be considered. Women with normal results (fasting < 100 mg/dL and 2 h glucose < 140 mg/dL) still have a lifetime risk for developing diabetes mellitus and reassessment of glycemic status every 1 to 3 years is warranted.

Conclusion

With a worsening obesity epidemic in this country, all reproductive care providers will manage women who either have pregestational diabetes or are at risk for developing T2DM or GDM. This *Perinatal Progress* outlines associated complications, diagnosis, and management of these conditions during pregnancy. There are opportunities both prior to pregnancy (via contraception counseling and preconception counseling), as well as during pregnancy to optimize reproductive outcomes. NWP welcomes the opportunity to partner with you in the care of these women.

Selective references

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Diabetes Mellitus Quick Reference Guide

Northwest Perinatal Center

	PRECONCEPTION COUNSELING	SCREENING AND DIAGNOSIS	MANAGEMENT DURING PREGNANCY	ANTENATAL TESTING AND ULTRASOUND	TIMING OF DELIVERY	POSTPARTUM
Pregestational T1DM	*MFM primary management or consultation if diabetes is being managed by endocrinology.*					

Pregestational T2DM	• Goal HgA1c < 7.0%
	• ACE inhibitor and ARB cessation timing
	• Search for underlying vasculopathy
		Diagnosis must be made outside of pregnancy	• Counsel on glucose goals, medication, exercise, and weight gain
			• Baseline studies:
			  • 24 h urine collection for protein
			  • CMP
			  • HgA1c
			  • 12-lead EKG (if disease for > 10 yrs or end-organ damage)
			  • dilated eye exam
			• Goal glucose (mg/dL):
			  • fasting < 95
			  • 2 h postprandial < 120
			• Weight-based insulin given multiple times daily
				• Fetal testing: 1-2x/week (depending on glycemic control and vascular disease) beginning at 32-33 wks
				• Detailed anatomic survey: 20 wks
				• Fetal echocardiogram: 21-22 wks
				• US for growth: 28-29 wks and then every 4-6 wks
					Depends upon glycemic control	• Return to pre-pregnancy oral agent (if applicable)
						• If pre-pregnancy insulin, return to first trimester dosing
						• ACE inhibitor safe with lactation

Diabetes Mellitus Quick Reference Guide, cont.

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	PRECONCEPTION COUNSELING	SCREENING AND DIAGNOSIS	MANAGEMENT DURING PREGNANCY	ANTENATAL TESTING AND ULTRASOUND	TIMING OF DELIVERY	POSTPARTUM

GDM A1	N/A	Two-step approach for diagnosis:
		• 50 gm, 1 h oGTT at 24-28 weeks > 135 mg/dL, followed by:
		• 100 gm, 3 h oGTT with 2 out of 4 abnormal results (mg/dL):
		  • fasting > 95
		  • 1 h > 179
		  • 2 h > 154
		  • 3 h > 140
		• Consider diagnosis with 1 h result > 200 mg/dL (see *Perinatal Progress* Vol. 11 No. 1)
		• Screen prior to 24 weeks if risk factors present (see *Perinatal Progress* Vol. 11 No. 1)
		• Repeat screen at 24-28 wks if no early diagnosis
			• Counsel on glucose goals, medication, exercise, and weight gain
			• Diabetic education
			• Goal glucose (mg/dL):
			  • fasting < 95
			  • 2 h PP < 120
				No antenatal testing for isolated GDM A1	No role for delivery prior to 39 weeks	• 75 gm 2 hr oGTT to diagnose type 2 diabetes vs impaired glucose tolerance at 6 wks post delivery

GDM A2			Begin weight-based insulin therapy when:
			• Fasting glucose > 105 mg/dL on 3 h oGTT OR
			• More than 2 weeks of 20% of:
			  • fasting values > 100 mg/dL
			  OR
			  • 2 h PP > 120 mg/dL
			
			If insulin is declined, may consider metformin alternative agent (*Perinatal Progress*)
				• Fetal testing: Weekly beginning at 32-33 wks
				• US for growth: 28-29 wks and then every 4-6 wks
					Depends upon glycemic control; for well-controlled GDM A2, no role for delivery prior to 39 weeks	• Discontinue insulin or metformin
						• Assess postpartum day 1 fasting glucose; ongoing testing if glucose > 126 mg/dL
						• For persistent hyperglycemia, consider metformin and referral to PCP
						• 75 gm 2 hr oGTT to diagnose type 2 diabetes vs impaired glucose tolerance at 6 wks post delivery