Management of Diabetes in Pregnancy

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PRECONCEPTION CARE

Preconception Care for Women With Established T1D or T2D

All Women of Child-Bearing Age

- Provide counseling on effective contraception for all who wish to avoid pregnancy
- Evaluate and treat diabetes-related complications

Women Seeking to Become Pregnant

- Review risks of uncontrolled diabetes during pregnancy
- Provide counseling on medications contraindicated during pregnancy
  - Statins, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and most non-insulin antihyperglycemic agents

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.
ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143.

Potential Contraindications to Pregnancy in Women with Established Diabetes

- Ischemic heart disease
- Untreated active proliferative retinopathy
- Renal insufficiency
- Severe gastroenteropathy

Jovanovic L, et al. *Mt Sinai J Med*. 2009;76:269-280.

Preconception Glucose Control for Women with T1D or T2D

	ADA	AACE
Preconception A1C goal	<7.0%*	<6.5%*
*Individualized target, with consideration of hypoglycemia risk.		

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.
ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143.

Management of Diabetes in Pregnancy

POST-CONCEPTION CARE

Diabetes in Pregnancy: Management Goals

- Educate patients to maintain adequate nutrition and glucose control before conception, during pregnancy, and postpartum
- Maintain close-to-normal glycemic control prior to and throughout pregnancy
  - Complication risk close to that of women without diabetes
  - Weekly A1C monitoring may be helpful to maintain goals (erythrocyte lifespan is 90 days during pregnancy)

Patient safety is first priority

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.
ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143.

Glucose Targets for Pregnant Women: AACE Recommendations

Condition	Treatment Goal
GDM	
Preprandial glucose, mg/dL	≤95*
1-Hour PPG, mg/dL	≤140*
2-Hour PPG, mg/dL	≤120*
Preexisting T1D or T2D	
Premeal, bedtime, and overnight glucose, mg/dL	60-99*
Peak PPG, mg/dL	100-129*
A1C	≤6.0%*

*Provided target can be safely achieved.

FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; PPG, postprandial glucose, T1D, type 1 diabetes; T2D, type 2 diabetes.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Glucose Targets for Pregnant Women: ADA Recommendations

Condition	Treatment Goal
GDM or Pre-existing T1D or T2D	
Preprandial glucose, mg/dL	≤95*
1-Hour PPG, mg/dL	≤140*
2-Hour PPG, mg/dL	≤120*
A1C	6.0% to 6.5%*†

*<6% may be optimal as pregnancy progresses.†
†If achievable without hypoglycemia.

FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; PPG, postprandial glucose, T1D, type 1 diabetes; T2D, type 2 diabetes.

ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143.

Glycemic Targets During Pregnancy: Expert Recommendations

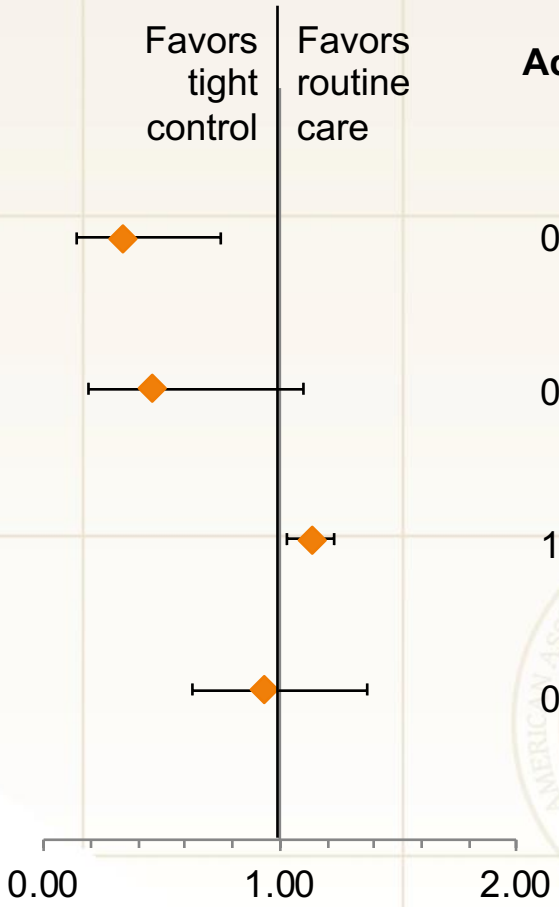
Some experts recommend more stringent goals (in particular, for patients on insulin therapy) to prevent maternal and fetal complications

Glucose Increment	GDM	Preexisting T1D or T2D
Preprandial, premeal	≤90 mg/dL (5.0 mmol/L)	
Postprandial, post-meal	1-hour post-meal: ≤120 mg/dL (6.7 mmol/L)	
A1C	A1C <5.0%	A1C <6.0%

LeRoith D, et. al. *Endocrinol Metab Clin N Am.* 2011;40: xii-919. Castorino K et al. *Curr Diabetes Rep*, 2012;12:53-59. ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143.

Infant Outcomes With Tight Glucose Control During Pregnancy

	Intervention n (%)	Routine care n (%)	Adjusted relative risk (95% CI)	*P* value
Any serious perinatal complication*	7 (1)	23 (4)	0.33 (0.14-0.75)	0.01
Shoulder dystocia	7 (1)	16 (3)	0.46 (0.19-1.10)	0.08
Admission to neonatal nursery	357 (71)	321 (61)	1.13 (1.03-1.23)	0.01
Jaundice requiring phototherapy	44 (9)	48 (9)	0.93 (0.63-1.37)	0.72



*Death, shoulder dystocia, bone fracture, or nerve palsy.

Crowther CA, et al. *N Engl J Med*. 2005;352:2477-2486.

Diabetes in Pregnancy: Avoiding Complications

Preconception care	• Advances in diagnosis and treatment have dramatically reduced morbidity and mortality in both mothers and infants
Careful evaluations at each visit	• Renal impairment, cardiac disease, neuropathy
Regular ophthalmologic exams	• 1st trimester through 1st year postpartum • Examine active lesions more frequently
Hypertension management	• Target: systolic BP 110-129 mmHg; diastolic BP 65-79 mmHg • Lifestyle changes, behavior therapy, and pregnancy-safe medications (ACE inhibitors and ARBs contraindicated in pregnancy)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87. ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143.
Jovanovic L, et al. *Diabetes Care*. 2011;34:53-54.

Diabetes in Pregnancy: Management Approaches

- Early referral to a specialist is essential
- Collaborative effort among obstetrician/ midwife, endocrinologist, ophthalmologist, registered dietitian, and nurse educator
  - All team members should be engaged in patient education/care prior to and throughout pregnancy
- Individualized treatment plans, involving a combination of:
  - Glucose monitoring
  - Medical nutrition therapy (MNT)
  - Pharmacotherapy
  - Exercise
  - Weight management
  - Psychological support

Castorino K, Jovanovic L. *Clin Chem*. 2011;57:221-230.
Mathiesen ER, et al. *Endocrinol Metab Clin N Am*. 2011;40:727-738.

Glucose Monitoring in Pregnant Women with Diabetes: SMBG

Recommendations

- Insulin-requiring pregnant patients should perform SMBG ≥3 times daily
  - Morning fasting
  - Premeal (breakfast, lunch, and dinner)
  - 1-hour postprandial (breakfast, lunch, and dinner)
  - Before bed

Caveats and Limitations

- Potential for human error or inconsistencies in performing SMBG and/or self-reporting
- Hyper- or hypoglycemic episodes may go undetected when readings are intermittent

SMBG is the cornerstone of glucose management during pregnancy

SMBG, self-monitoring of blood glucose.

Jovanovic L, et al. *Diabetes Care*. 2011;34:53-54. Castorino K, Jovanovic L. *Clin Chem*. 2011;57:221-230. Chitayat, L, et al. *Diabetes Technol Ther*. 2009;11:S105-111.

Glucose Monitoring in Pregnant Women with Diabetes: A1C

Recommendations

- Combine with SMBG to safely achieve target glucose levels
- Weekly A1C during pregnancy recommended
  - SMBG alone can miss certain high glucose values
  - SMBG + A1C yields more complete data for glucose control
  - Clinicians can further optimize treatment decisions with weekly A1C

Caveats and Limitations

- HAPO study suggests OGTT may predict adverse pregnancy outcomes better than A1C in women with diabetes

HAPO, Hyperglycemia and Adverse Pregnancy Outcomes; SMBG, self-monitoring of blood glucose.

Jovanovic L, et al. *Diabetes Care*. 2011;34:53-54. Castorino K, Jovanovic L. *Clin Chem*. 2011;57:221-230. Lowe LP, et al. *Diabetes Care*. 2012;35:574-580.

Glucose Monitoring in Pregnant Women with Diabetes: CGM

Recommendations

- CGM devices
  - Measure glucose concentration of interstitial fluid using subcutaneous sensor tip implanted in abdominal wall
  - Identify glycemic excursions that may go undetected with SMBG
- May be used as educational tool to improve treatment adherence

Caveats and Limitations

- Requires specialized knowledge (provider) and patient education

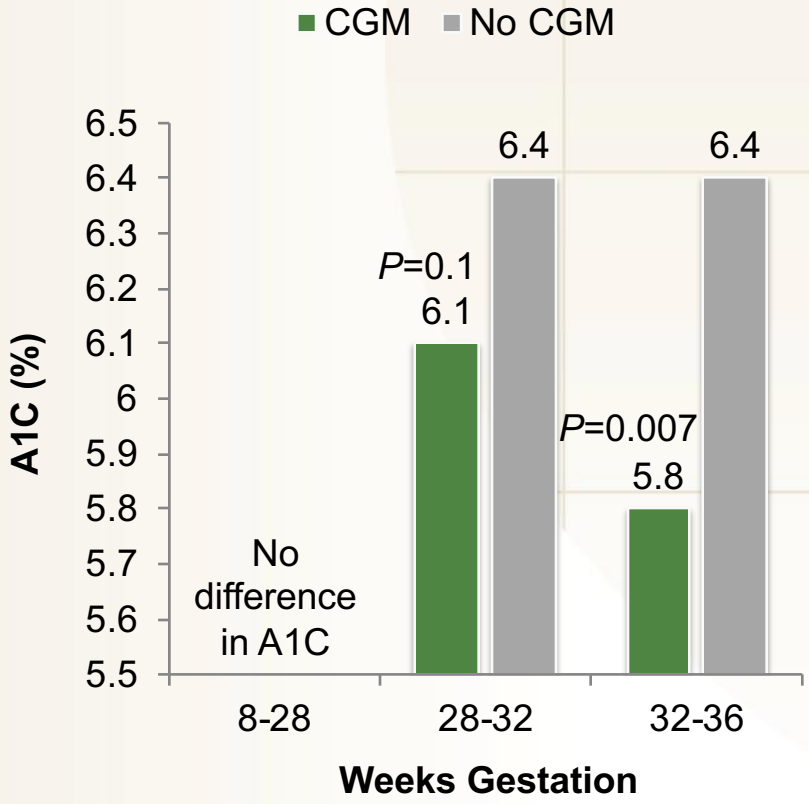
CGM may be useful in patients unable to achieve target glucose levels with SMBG alone

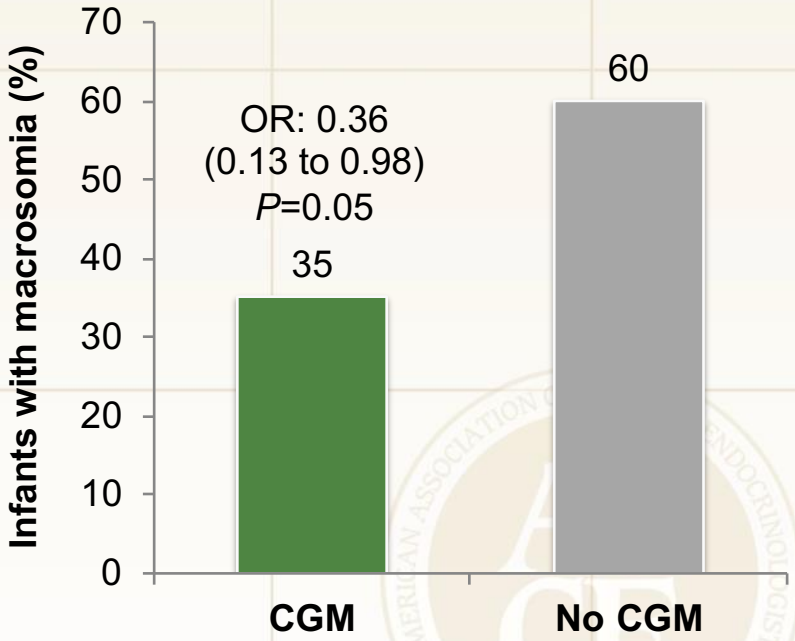
CGM, continuous glucose monitoring.

Hod M, Jovanovic L. *Int J Clin Pract Suppl*. 2010 Feb;(166):47-52. Castorino K, Jovanovic L. *Clin Chem*. 2011;57:221-230. Chitayat, L, et al. *Diabetes Technol Ther*. 2009;11:S105-111. Blevins TC, et al. *Endocr Pract*. 2010;16:1-16. Fonseca VA, et al. *Endocr Pract*. 2016;22:1008-1021.

Reduced Risk of Macrosomia With CGM

Pregnant Women With T1D or T2D (N=71)





CGM, continuous glucose monitoring; OR, odds ratio for reduced risk of macrosomia (95% confidence interval).

Murphy HR, et al. *BMJ*. 2008;337:a1680. doi: 10.1136/bmj.a1680.

CGM Devices: Professional vs Personal

Professional

- Owned by a health care professional
- Typically implanted for 3-5 days
- Data downloaded and analyzed by a health care professional

Personal

- Owned by the patient
- May be implanted for longer periods (eg, several weeks)
- Provide continuous feedback on glucose values, which may be read/interpreted by the patient in real time

Fonseca VA, et al. *Endocr Pract*. 2016;22:1008-1021..

Medical Nutrition Therapy During Pregnancy

- Refer patients for nutritional counseling with registered dietitian familiar with pregnancy
  - Provide a nutritionally adequate diet for pregnancy
  - Achieve normoglycemia
- Customize standard nutritional recommendations during pregnancy based on:
  - Height
  - Weight
  - Nutritional assessment
  - Level of glycemic control

- Key recommendations
  - Choose healthy low-carbohydrate, high-fiber sources of nutrition, with fresh vegetables as the preferred carbohydrate sources
  - Count carbohydrates and adjust intake based on fasting, premeal, and postprandial SMBG measurements
  - Avoid sugars, simple carbohydrates, highly processed foods, dairy, juices, and most fruits
  - Eat frequent small meals to reduce risk of postprandial hyperglycemia and preprandial starvation ketosis

MNT, medical nutrition therapy.

Handelsman YH, et al. Endocr Pract. 2015;21(suppl 1):1-87. ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143. Castorino K, Jovanovic L. Clin Chem. 2011;57:221-230. Jovanovic L, et al. Mt Sinai J Med. 2009;76:269-280. Mathiesen ER, et al. Endocrinol Metab Clin N Am. 2011;40:727-738.

Pharmacologic Treatment of Diabetes During Pregnancy

- Use insulin to treat hyperglycemia in T1D and T2D and when lifestyle measures do not control glycemia in GDM
  - Basal insulin: NPH or insulin detemir
  - Prandial insulin: insulin analogs preferred, but regular insulin acceptable if analogs not available

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.
ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143.

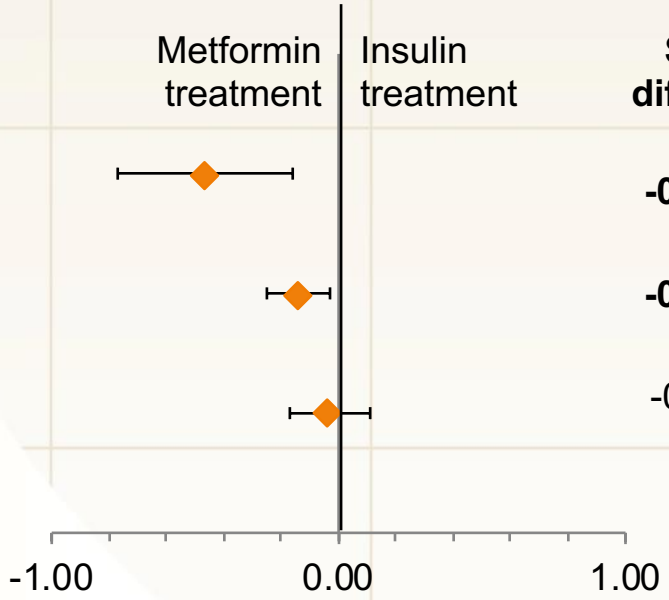
Oral Antihyperglycemic Therapy During Pregnancy

Medication	Crosses Placenta	Classification	Notes
Metformin	Yes	Category B	• Metformin and glyburide may be insufficient to maintain normoglycemia at all times, particularly during postprandial periods • Long-term safety of these agents during pregnancy is unknown
Glyburide	Minimal transfer	Some formulations category B (Micronase), others category C (Diaβeta)	

No other noninsulin antihyperglycemic agents are considered safe during pregnancy.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87. ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143. Poomalar GK. World J Diabetes. 2015;6:284-295. Micronase (glyburide) prescribing information. New York, NY: Pfizer Inc.; 2015. Diaβeta (glyburide) prescribing information. Bridgewater, NJ: sanofi-aventis U.S. LLC; 2009.

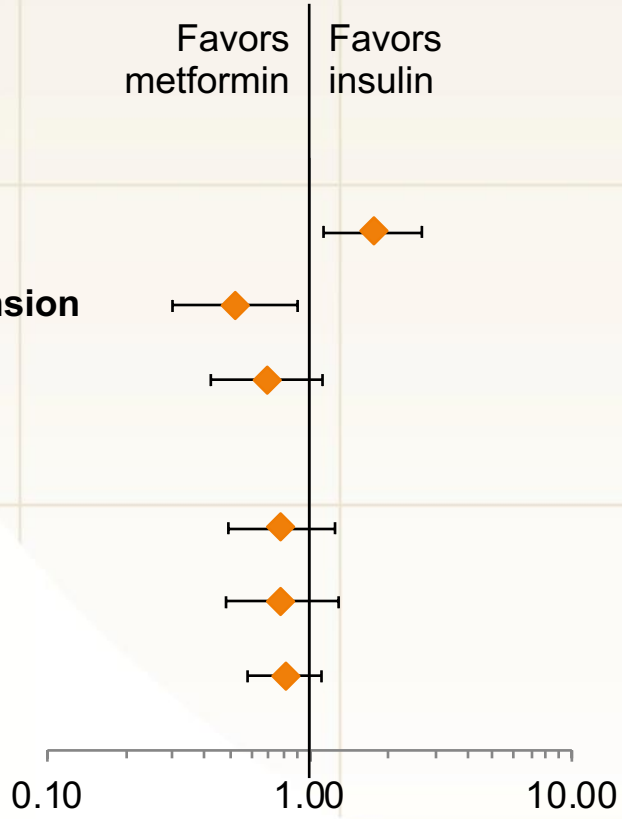
Effects of Metformin Therapy During Pregnancy



	Standard mean difference (95% CI)	*P* value
Maternal weight gain	**-0.47 (-0.77, -0.16)**	**0.003**
Gestational age at delivery	**-0.14 (-0.25, -0.03)**	**0.02**
Infant birth weight	-0.04 (-0.17, 0.09)	0.54

Gui J, et al. *PLOS One*. 2013;8(5):e64585.

Benefits and Risks of Metformin Therapy During Pregnancy



	Odds ratio (95% CI)	*P* value
Maternal risks		
Preterm birth	**1.74 (1.13, 2.68)**	**0.01**
Pregnancy-induced hypertension	**0.52 (0.30, 0.90)**	**0.02**
Preeclampsia	0.69 (0.42, 1.12)	0.13
Infant risks		
Large for gestational age	0.78 (0.49, 1.25)	0.31
Small for gestational age	0.78 (0.48, 1.29)	0.34
Infant hypoglycemia	0.80 (0.58, 1.11)	0.19

Gui J, et al. *PLOS One*. 2013;8(5):e64585.

Insulin Use During Pregnancy

Insulin option	Pregnancy Category	Notes
Basal (control of fasting/preprandial glucose)		
NPH	B	
Detemir	B	
Glargine	C	Not formally studied in pregnancy
Degludec	C	Not formally studied in pregnancy
Pump therapy with rapid-acting analogs	B	
Bolus (control of postprandial hyperglycemia)		
Aspart, lispro	B	
Regular	B	
Glulisine	C	Not studied in pregnancy
Inhaled	C	Not studied in pregnancy
Components of patient education	• Insulin administration • Dietary modifications in response to SMBG • Hypoglycemia awareness and management	

NPH, Neutral Protamine Hagedorn; SMBG, self-monitoring of blood glucose

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87. ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143.
Jovanovic L, et al. *Mt Sinai J Med*. 2009;76:269-280. Castorino K, Jovanovic L. *Clin Chem*. 2011;57:221-230.

Pharmacokinetics of Insulins Safe for Use During Pregnancy

Name	Type	Onset	Peak Effect	Duration	Recommended Dosing Interval
Aspart	Rapid-acting (bolus)	15 min	60 min	2 hrs	Start of each meal
Lispro	Rapid-acting (bolus)	15 min	60 min	2 hrs	Start of each meal
Regular insulin	Intermediate-acting	60 min	2-4 hrs	6 hrs	60-90 minutes before meal
NPH	Intermediate-acting (basal)	2 hrs	4-6 hrs	8 hrs	Every 8 hours
Detemir	Long-acting (basal)	2 hrs	n/a	12 hrs	Every 12 hours

Following a positive pregnancy test, patients with preexisting diabetes being treated with insulin or oral antihyperglycemic medications should be transitioned to one of the above options

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87. ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143.

Initiation of Insulin in GDM

Initiate insulin when medical nutrition therapy fails to maintain glucose below the following thresholds

	Glucose level
Fasting	≤95 mg/dL
1-h postprandial	≤140 mg/dL
2-h postprandial	≤120 mg/dL

GDM, gestational diabetes mellitus.

ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143.

Insulin Dosing Guidelines During Pregnancy and Postpartum

Weeks gestation	Insulin TDD*
1-13 weeks	(0.7 x weight in kg) or (0.30 x weight [lbs])
14-26 weeks	(0.8 x weight in kg) or (0.35 x weight [lbs])
27-37 weeks	(0.9 x weight in kg) or (0.40 x weight [lbs])
38 weeks to delivery	(1.0 x weight in kg) or (0.45 x weight [lbs])
Postpartum (and lactation)†	(0.55 x weight in kg) or (0.25 x weight [lbs])

*Use 50% of TDD for basal insulin and 50% for premeal rapid-acting insulin boluses

†Decrease nighttime basal insulin by 50% in lactating women (to prevent severe hypoglycemia)

- Patients with T1D
  - 10-14 weeks gestation: period of increased insulin sensitivity; insulin dosage may need to be reduced accordingly
  - 14-35 weeks gestation: insulin requirements typically increase steadily
  - >35 weeks gestation: insulin requirements may level off or even decline
- Patients with obesity may require higher insulin dosages than those without obesity

TDD, total daily dose.

Castorino K, Jovanovic L. *Clin Chem*. 2011;57:221-230. Kitzmiller JL, et al. *Diabetes Care*. 2008;31:1060-1079.

Continuous Subcutaneous Insulin Infusion During Pregnancy

Benefits

- Mimics physiologic insulin secretion
  - CSII devices use aspart or lispro
  - Safe and effective for management of GDM, T1D, or T2D
- No significant difference in glycemic control for pregnancy outcomes with CSII versus MDI therapy
- Can help address daytime or nocturnal hypoglycemia or a prominent dawn phenomenon

Limitations

- Complexity
  - Requires counseling and training
- Cost
- Potential for
  - Insulin pump failure
  - User error
  - Infusion site problems

CSII, continuous subcutaneous insulin infusion ; GDM, gestational diabetes mellitus; MDI, multiple daily injections; T1D, type 1 diabetes; T2D, type 2 diabetes.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87. Castorino K et al. *Curr Diab Rep*, 2012;12:53-59. Hod M. Jovanovic L. *Int J Clin Pract*, 2010;64:47-52. Kitzmiller JL, et al. *Diabetes Care*. 2008;31:1060-1079. Castorino K, Jovanovic L. *Clin Chem*. 2011;57:221-230.

Hypoglycemia in Pregnant Women With Diabetes

Pathophysiology

May be related to fetal absorption of glucose from the maternal bloodstream via the placenta, particularly during periods of maternal fasting

Risk Factors

- History of severe hypoglycemia before pregnancy
- Impaired hypoglycemia awareness
- Longer duration of diabetes
- A1C ≤6.5% at first pregnancy visit
- High daily insulin dosage

Causes of Iatrogenic Hypoglycemia

- Administration of too much insulin or other anti-hyperglycemic medication
- Skipping a meal
- Exercising more than usual

Clinical Consequences

- Minor: anxiety, confusion, dizziness, headache, hunger, nausea, palpitations, sweating, tremors, warmth, weakness
- Major: coma, traffic accidents, death
- Severe hypoglycemia: maternal seizures or hypoxia

Management

- Patient education on prevention and risks (especially during early pregnancy)
- Frequent SMBG
- Regular meal timing
- Accurate medication administration
- Exercise management

Mathiesen ER, et al. *Endocrinol Metab Clin N Am.* 2011;40:727-738. Inturrisi M, et al. *Endocrinol Metab Clin N Am.* 2011;40:703-726. Jovanovic L, et al. *Mt Sinai J Med*. 2009;76:269-280. Kitzmiller JL, et al. *Diabetes Care*. 2008;31:1060-1079. Hod M. Jovanovic L. *Int J Clin Pract*. 2010;64:47-52.

Treatment of Hypoglycemia

Hypoglycemia symptoms (BG <70 mg/dL)

Patient conscious and alert

- Consume glucose-containing foods (fruit juice, soft drink, crackers, milk, glucose tablets); avoid foods also containing fat
- Repeat glucose intake if SMBG result remains low after 15 minutes
- Consume meal or snack after SMBG has returned to normal to avoid recurrence

Patient severely confused or unconscious (requires help)

- Glucagon injection, delivered by another person
- Patient should be taken to hospital for evaluation and treatment after any severe episode

BG, blood glucose; SMBG, self-monitoring of blood glucose.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Physical Activity During Pregnancy

- Unless contraindicated, physical activity should be included in a pregnant woman's daily regimen
- Regular moderate-intensity physical activity can help to reduce glucose levels in patients with GDM, T1D, T2D
  - Walking
  - Cardiovascular training with weight-bearing, limited to the upper body to avoid mechanical stress on the abdominal region
- Monitor for hypoglycemia

GDM, gestational diabetes mellitus; T1D, type 1 diabetes; T2D, type 2 diabetes.

Castorino K, Jovanovic L. *Clin Chem*. 2011;57:221-230. ADA. *Diabetes Care*. 2004;27(suppl 1):S88-S90. Jovanovic L, et al. *Mt Sinai J Med*. 2009;76:269-280.

Weight Management in Pregnant Women With Diabetes

- Healthy weight gain targets based on prepregnancy BMI
  - Minimal weight gain for patients with BMI >30 kg/m^2
- Independent of maternal glucose levels, higher maternal BMI associated with increased risk of:
  - Caesarean delivery
  - Infant birth weight >90th percentile
  - Cord-blood serum C-peptide >90th percentile
- Achieve weight objectives by maintaining a balanced diet and exercising regularly

BMI, body mass index.

Castorino K, Jovanovic L. *Clin Chem*. 2011;57:221-230. Metzger BE, et al. *BJOG* 2010;117:575-584.

Labor and Delivery for Women With Diabetes

- Increased risk of transient neonatal hypoglycemia during the 4-6 hours prior to delivery
- Monitor blood glucose levels closely during labor to determine patient's insulin requirements
  - Most women with GDM will not require insulin once labor begins
  - Endocrinologist or diabetes specialist should manage glycemia in women with T1D during labor and delivery

GDM, gestational diabetes mellitus; T1D, type 1 diabetes.

Castorino K, Jovanovic L. *Clin Chem*. 2011;57:221-230.

Psychological Support During Pregnancy in Women With Diabetes

- Individualized psychosocial interventions are likely to help improve both pregnancy outcomes and patient quality of life
  - Mental health professionals with expertise in diabetes should be included in multidisciplinary healthcare team
  - Healthcare teams can help manage patients' stress and anxiety before and during pregnancy
  - Identify and address barriers to effective diabetes management, such as fear of hypoglycemia and an inadequate social support network

Snoek SJ, et al. *Psychology in Diabetes Care*, 2nd Ed. West Sussex, England: John Wiley & Sons Inc., 2005:54.
Jovanovic L, et al. *Mt Sinai J Med*. 2009;76:269-280.

Diabetes in Pregnancy: Postpartum and Lactation

- Metformin and glyburide are secreted into breast milk and are therefore contraindicated during lactation
- Breastfeeding plus insulin therapy may lead to severe hypoglycemia
  - Women with T1D at greatest risk
  - Preventive measures
    - Reduce basal insulin dosage
    - Carbohydrate intake prior to breastfeeding
- Bovine-based infant formulas are linked to increased risk of T1D
  - Avoid in offspring of women with diabetes or at risk for diabetes (eg, history of gestational diabetes, family history of diabetes)
  - Soy-based products are a potential substitute

Castorino K, Jovanovic L. *Clin Chem*. 2011;57:221-230.

Management of Diabetes in Pregnancy

POSTPARTUM CARE

Postpartum Care

- Psychosocial assessment and support
- Lactation support and education
  - Breastfeeding may confer metabolic benefits to mother and child
- Women with GDM
  - Test for persistent diabetes 4-12 weeks postpartum with 75-g OGTT
  - Screen for T2D every 3 years after GDM
- Women with pre-existing T1D or T2D
  - Monitor closely for hypoglycemia and implement prevention tactics as insulin sensitivity returns to normal 1-2 weeks after delivery
  - Discuss family planning options to avoid unplanned future pregnancies

GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; T1D, type 1 diabetes; T2D, type 2 diabetes.

ADA. *Diabetes Care*. 2018;41(suppl 1):S137-S143.