Pregestational Diabetes in Pregnancy

An Update

Disclosures

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- Nothing to disclose

Questions to Be Addressed

- What are risks factors for adverse pregnancy outcome in pre-gestational diabetes?
- Who should be screened for pre-gestational type 2 diabetes and how should this be done?
- How can one best attempt to achieve good control of diabetes?

Pre-gestational DM

Pre-conception Counseling

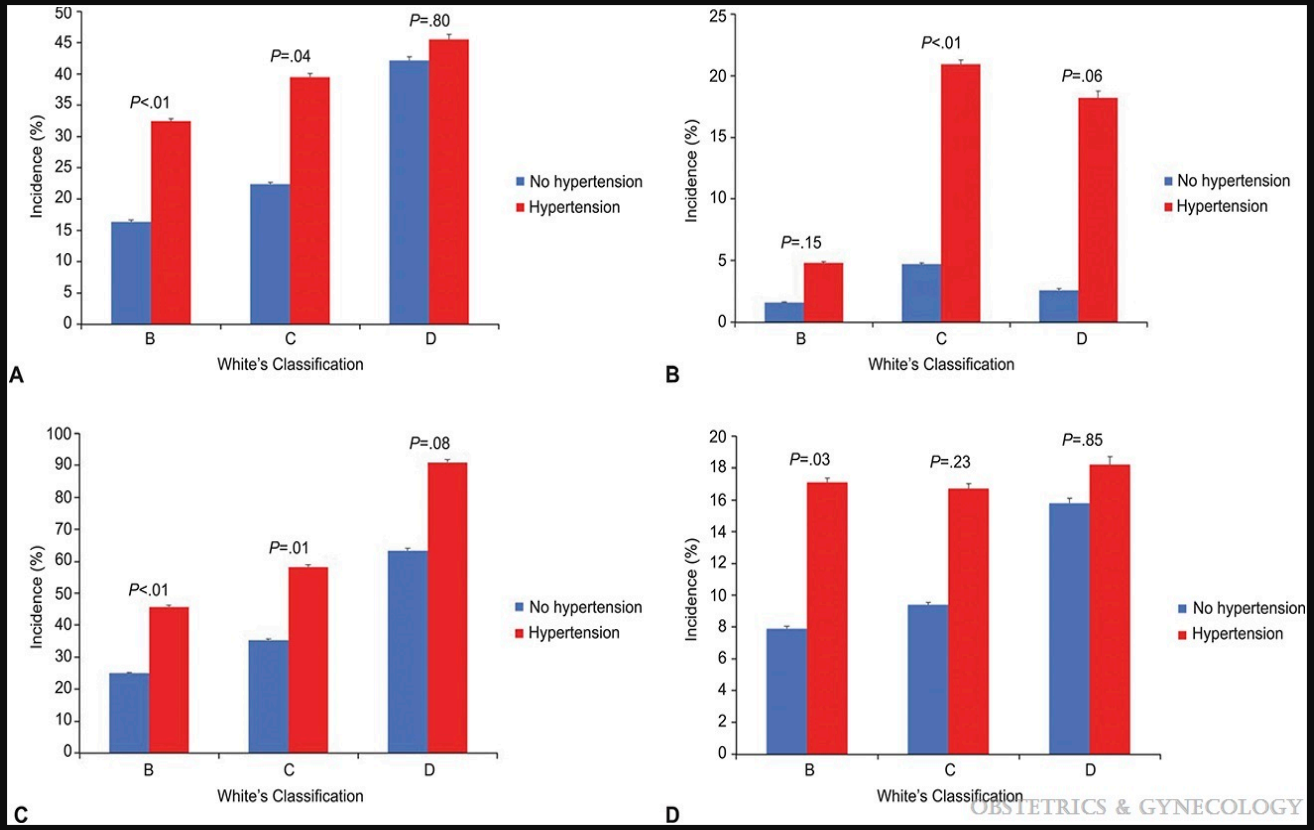
Adverse Outcomes in Pregnancy Among Type 1 Diabetics Data from 12 Population-based studies			
	Type 1 DM (N=14,099)	Background Population (N=4,035,373)	RR
Congenital malformations	5.0%	2.1%	2.4
Perinatal mortality	2.7%	0.72%	3.7
Preterm delivery	25.2%	6.0%	4.2
LGA	54.2%	10.0%	4.5

Glycemic Control and Birth Defects

- Nearly linear relationship between higher HgA1c levels and birth defects
- Rate of birth defects (Teratology 1989; 39:225)
  - ≤3% when HgA1c ~9% or less
  - 40% when HgA1c >14.4%
- No definite threshold for predicting birth defects

White's Classification of Diabetes in Pregnancy

- Class A: Diet alone, any duration or onset age.
- Class B: Onset age 20 years or older and duration less than 10 years.
- Class C: Onset age 10–19 years or duration 10–19 years.
- Class D: Onset age younger than 10 years, duration over 20 years, background retinopathy, or hypertension (not preeclampsia).
- Class R: Proliferative retinopathy or vitreous hemorrhage.
- Class F: Nephropathy with over 500 mg/day proteinuria.
- Class RF: Criteria for both classes R and F coexist.
- Class H: Arteriosclerotic heart disease clinically evident.
- Class T: Prior renal transplantation.



A comparison of select adverse outcomes across White's classification, B–D, in the presence and absence of chronic hypertension. Preeclampsia (A), small for gestational age (B), preterm delivery (C), and composite neonatal outcome (D). The P values above each diabetes class compare the incidence of the selected adverse outcome in the presence and absence of chronic hypertension. The error bars represent the 95% confidence interval of the incidence for each adverse outcome.Bennett. White's Class in Contemporary Population. Obstet Gynecol 2015.

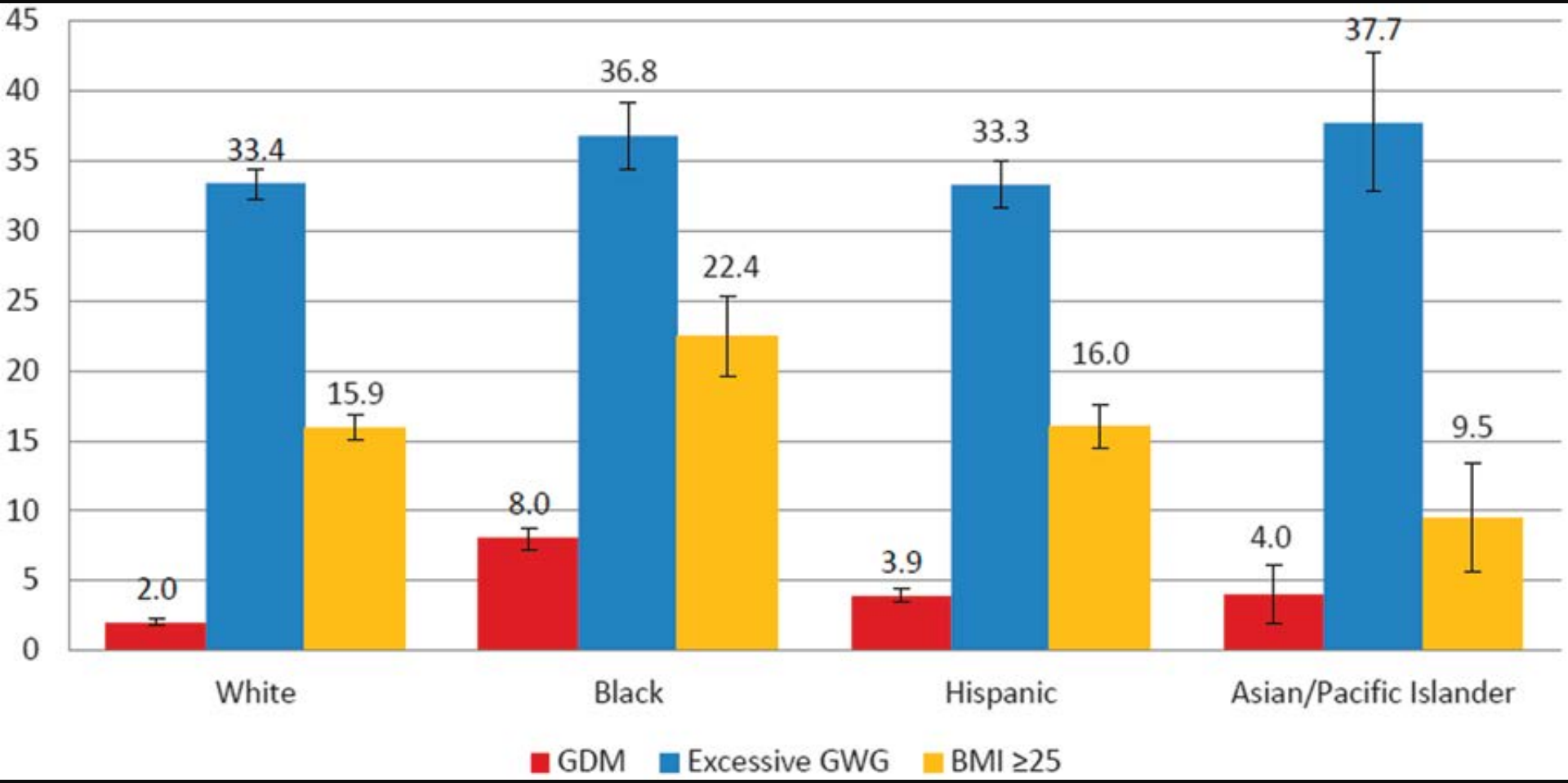
Wolters Kluwer

Bennet et al. Obstet Gynecol 2015;125:1217

So, it comes down to DM *with or without* microvascular disease, particularly as manifest by hypertension

Obesity?

Prevalence of LGA for Births at 37-41 Weeks



Kym et al. Obstet Gynecol 2014;123:737

Pre-Pregnancy BMI Category (Body Mass Index = BMI)	Recommended Total Weight Gain During Pregnancy	
BMI < 18.5 Underweight	12.5 – 18.0 kg	28.0 – 40.0 lbs
BMI 18.5 – 24.9 Normal Weight	11.5 – 16.0 kg	25.0 – 35.0 lbs
BMI 25.0 – 29.9 Overweight	7.0 – 11.5 kg	15.0 – 25.0 lbs
BMI ≥ 30 Obese	5.0 – 9.0 kg	11.0 – 20.0 lbs

$$\text{Body Mass Index (BMI)} = \text{Weight (kg)} / [\text{Height (m)}]^2$$

Pre-gestational DM

Pre-conception Counseling Recommendations

- Counsel patient regarding risks
- Assess renal status
- Assess other organ systems if indicated
  - Treat retinopathy before conception
- Switch from ACE inhibitors or AR blockers to acceptable med
- Achieve good glycemic control

Questions to Be Addressed

- What are risks factors for adverse pregnancy outcome in pre-gestational diabetes?
- **Who should be screened for pre-gestational type 2 diabetes and how should this be done?**
- How can one best attempt to achieve good control of diabetes?

Risk Factors for Diabetes

Modified from ACOG Practice Bulletin 180, July 2017

- Overweight-obesity
- Physical inactivity
- 1º relative with diabetes
- High-risk race/ethnicity
- Prior birth of infant >4000 g
- Previous GDM
- Hypertension
- HDL <35 or triglyceride >250
- PCOS
- Prior evidence of impaired glucose intolerance
- History of CVD

Screening for Pregestaional Diabetes

- ACOG “supports the two-step process….However, individual practices and institutions may choose to use the IADPSG’s recommendation, if appropriate, for the population they serve.”

Screening for Pregestational Diabetes

Practical Options

- 2-step approach (50 g 1 hr screen→ 3 hour OGTT)
- 1 step approach (75 g, 2 hr OGTT)
- Hemoglobin A1c
- Fasting plasma glucose
- Home BG monitoring

Questions to Be Addressed

- What are risks factors for adverse pregnancy outcome in pre-gestational diabetes?
- Who should be screened for pre-gestational type 2 diabetes and how should this be done?
- **How can one best attempt to achieve good control of diabetes?**

Necessary Components of Good Glycemic Control

- Patient buy in / ownership
- Nutrition / dietary measures
- Activity measures
- Provider coaching, including taking time to coach
- Medications
- Coordination of the above

Diabetes Management 101
(aka “Coaching”)

- Insist on patient self blood glucose monitoring - “you manage what you measure”
- Review the results at every patient visit – talk about it!
- Suggest ways to improve – coach!
- Establish reliable, responsive, outcome-oriented referral services

Diet and Carbs in DM

Total Calories	Carbohydrate Calories (40% of total) / g of carbs	Carbohydrate Distribution
2000 calories per day (1st 6 months of pregnancy)	800 calories 200 g	35-45 g @ breakfast 45-60 g @ lunch and dinner 15-20 g @ snacks x 2
2200 calories per day (last 3 months of pregnancy)	880 calories 220 g	Add 20 g per day

Diet and Carbs in DM

Examples of Carbohydrate Selections	Be Very Cautious With or Avoid
Special K cereal, 1 level cup - 23 g 1 cup whole milk – 12 g Labeled foods with 20-30 g 1 medium fruit – 20 - 25 g 1 average bread slice - 20 g 1 medium size potato - 35 g ½ cup of rice/potatoes/pasta - 25 g	Pasta dishes Heavy breads Pizza Smoothies Fruit juices, salads, cocktails Carbohydrate-containing soda

Activity in DM

- **30 minutes of moderate-to-vigorous intensity aerobic exercise at least 5 days a week (150 min per week)**
  - **You can talk but not sing**
  - **You cannot say more than a few words without pausing for a breath**

http://www.diabetes.org/food-and-fitness/fitness/types-of-activity/?loc=DropDownFF-typesofactivity

ADA, 2013

Activity in DM

- **I recommend 10,000 steps per day, *every* day @ consistent times**
  - **About 3.5 - 4 miles**
  - **A sedentary person: 2,000 steps per**
    Average person: 3,000 – 5,000 steps per day
  - **It takes about 20 minutes to walk 3,000 steps**

Tools for DM Care

- Oral agents for type 2 DM
  - Metformin
  - Glibenclamide
- Insulin agents
  - Rapid-acting
  - Short-acting
  - Intermediate-acting
  - Long-acting

Tools for DM Care

- Glucose monitors
- More rapid acting insulins
- Insulin pumps
- “Peakless” insulins
- Continuous glucose monitors
- Closed loop systems


ОБУВЬ

Oral Anti-Diabetic Medications in Pregnancy

- **Cochrane meta-analysis of 8 adequate RCTs, metformin v. glibenclamide**
  - **GHTN:** **RR 0.70 (NS) (med quality)**
  - **CS:** **RR 1.20 (NS) (low quality)**
  - **Induction:** **RR 0.81 (NS) (low quality)**
  - **Perineal trauma:** **RR 1.67 (NS) (low quality)**
  - **LGA:** **RR 0.67 (NS) (low quality)**
  - ***Neo composite:*** ***RR 0.54 (Sig) (low quality)***
  - **Neo hypoglycemia:** **RR 0.86 (NS) (low quality)**

Cochrane Database Syst Rev. 2017 Jan 25;1:CD011967. doi: 10.1002/14651858.CD011967

Metformin (Glucophage®)

- MOA: ↓ hepatic glucose production, ↓ intestinal absorption of glucose, ↑ insulin sensitivity via ↑ glucose uptake and utilization
- Contraindications: Significant renal disease (SCr >1.3), cardiac or hepatic disease
- Common side effects: gi upset, flatulence, and diarrhea (leads to discontinuation in 5-10% of patients)

Metformin (Glucophage®)

- Immediate release
  - Initial dose 500 mg BID or 850 once daily
  - Increase in 500 mg increments at one week or 850 mg increments in 1-2 weeks
  - Usual dose 2000 mg daily in divided doses
  - Maximum dose 2550 mg per day
- Extended release
  - Initial dose 500 to 1000 mg once daily
  - Increase in 500 mg increments at weekly
  - Usual dose 2000 mg daily in divided doses
  - Maximum dose 2500 mg per day

RCT of Detemir versus NPH in Pregnant Women with Diabetes

- RCT (non-inferiority) of 87 women ≤34 wks gestation with GDM and type 2 DM to compare:
  - NPH and fast-acting insulins
  - Detemir and fast-acting insulins
- Primary outcome – mean glucose until delivery

Herrera et al. Am J Obstet Gynecol 2015;213:426

RCT of Detemir versus NPH in Pregnant Women with Diabetes

Per Protocol Analysis of Glucose Concentrations			
Mean BG	**Detemir**	**NPH**	**P**
Overall	109.5 (10.0)	107.4 (7.1)	0.2937
Fasting	100.7 (10.1	97.3 (7.4	0.1093
Postprandial	114.2 (10.2)	112.9 (8.9)	0.3204
Median BG			
Overall	103.3 (100.0-116.3)	103.7 (99.6-108.6)	0.8542
Fasting	92.2 (88.5-100.3)	91.3 (87.0-95.3)	0.5476
Postprandial	108.8 (104.0-120.6)	108.7 (103.0-115.4)	0.9550

Herrera et al. Am J Obstet Gynecol 2015;213:426

Dosing Paradigms

- Calculate total insulin dose
  - Wt in kg x 0.7, 0.8, or 0.9 (by trimester)
- Allot 60% of total to morning and 40% to evening
- Of morning dose - 2/3 long-acting and 1/3 rapid-acting
- Of evening dose – 1/2 dose long-acting and 1/2 dose rapid-acting

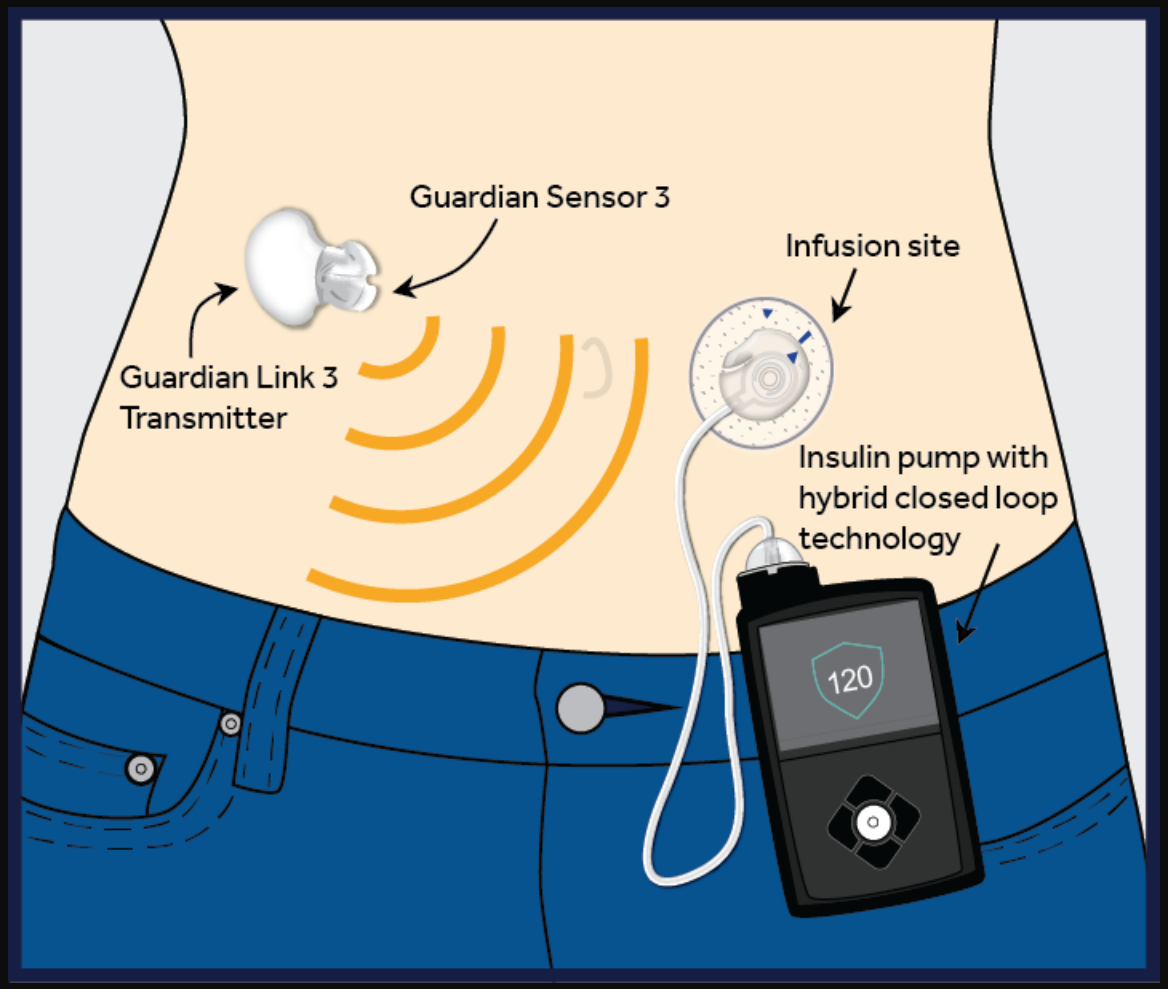
Dosing Paradigms

- Morning NPH regimen
  - Both NPH and rapid-acting pre-breakfast
- Morning detemir regimen
  - Determir before breakfast
  - 1/2 of rapid-acting before breakfast; 1/2 before lunch

Dosing Paradigms

- Evening NPH regimen
  - Both NPH and rapid-acting pre-dinner
- Evening detemir regimen
  - Same as for NPH

Closed Loop Systems



Closed Loop Insulin Delivery Systems

- Goals
  - Limit dangerous BG excursions
    - Threshold (low BG) suspend system
  - Maintain BG within an appropriate range
    - Control-to-range system
    - Control-to-target system
    - Dual-hormone systems

Closed Loop Insulin Delivery Systems

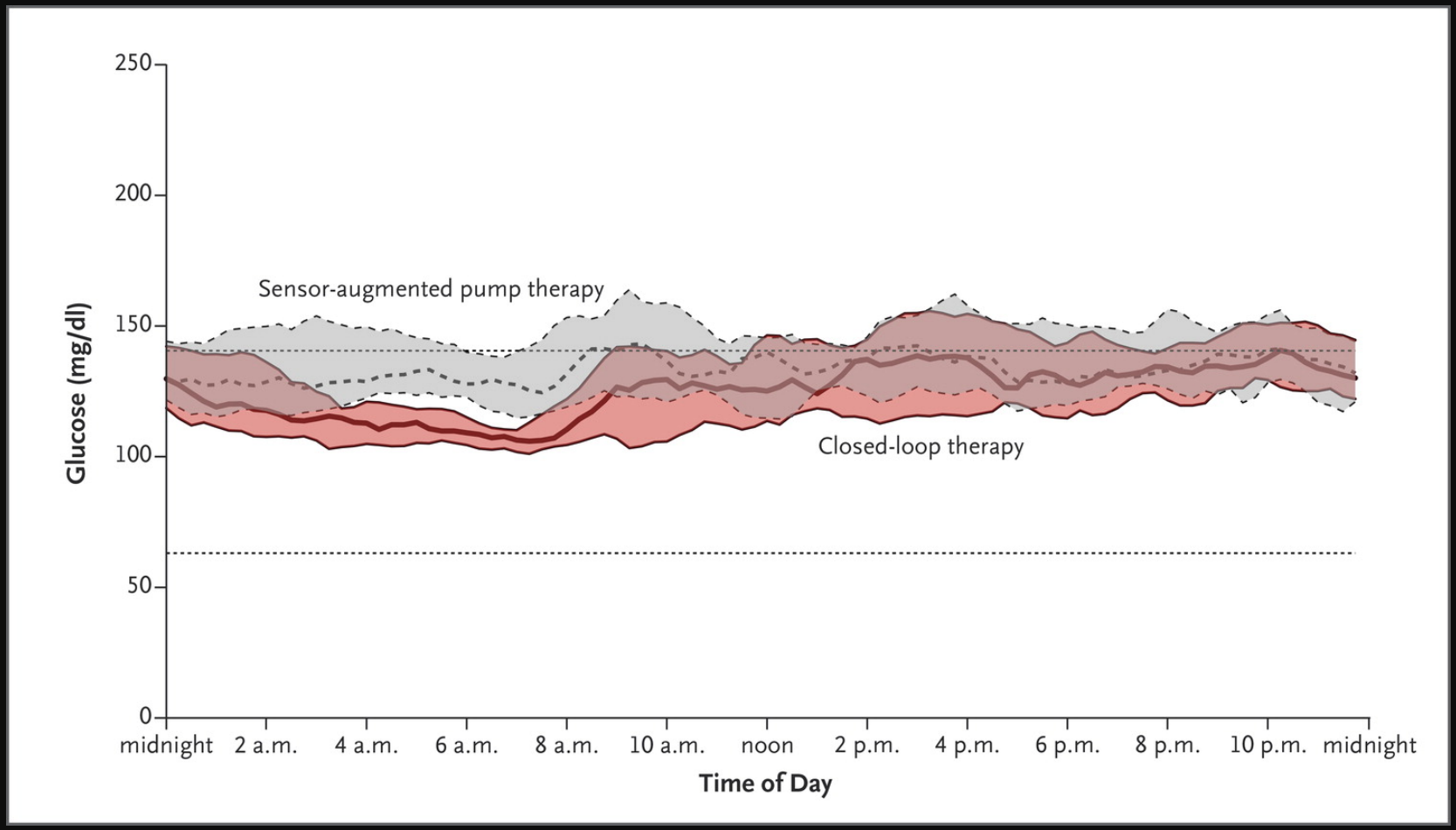
- Components
  - Insulin (or dual hormone) pump
  - Continuous glucose monitor (interstitial)
    - Finger stick glucose meter
  - Control system-algorithm
    - Model predictive control
    - Proportional-integral-derivative control
    - Fuzzy logic

Closed Loop Insulin System in Pregnancy

- Open-label, randomized, crossover study comparing overnight closed-loop therapy (CLT) with sensor-augmented pump therapy (SaPT) → continuation phase with CLT
  - 16 patients with type 1 diabetes completed 4 weeks of CLT (intervention) and SaPT (control) in random order
  - 14 patients used the CLT day and night until delivery
- The primary outcome - % time that overnight glucose levels were within the target range (63 to 140 mg per deciliter [3.5 to 7.8 mmol per liter]

Stewart ZA et al. N Engl J Med 2016;375:644-654.

Median Sensor-Recorded Glucose Values over a 24-Hour Period with Sensor-Augmented Pump Therapy and Closed-Loop Insulin Delivery



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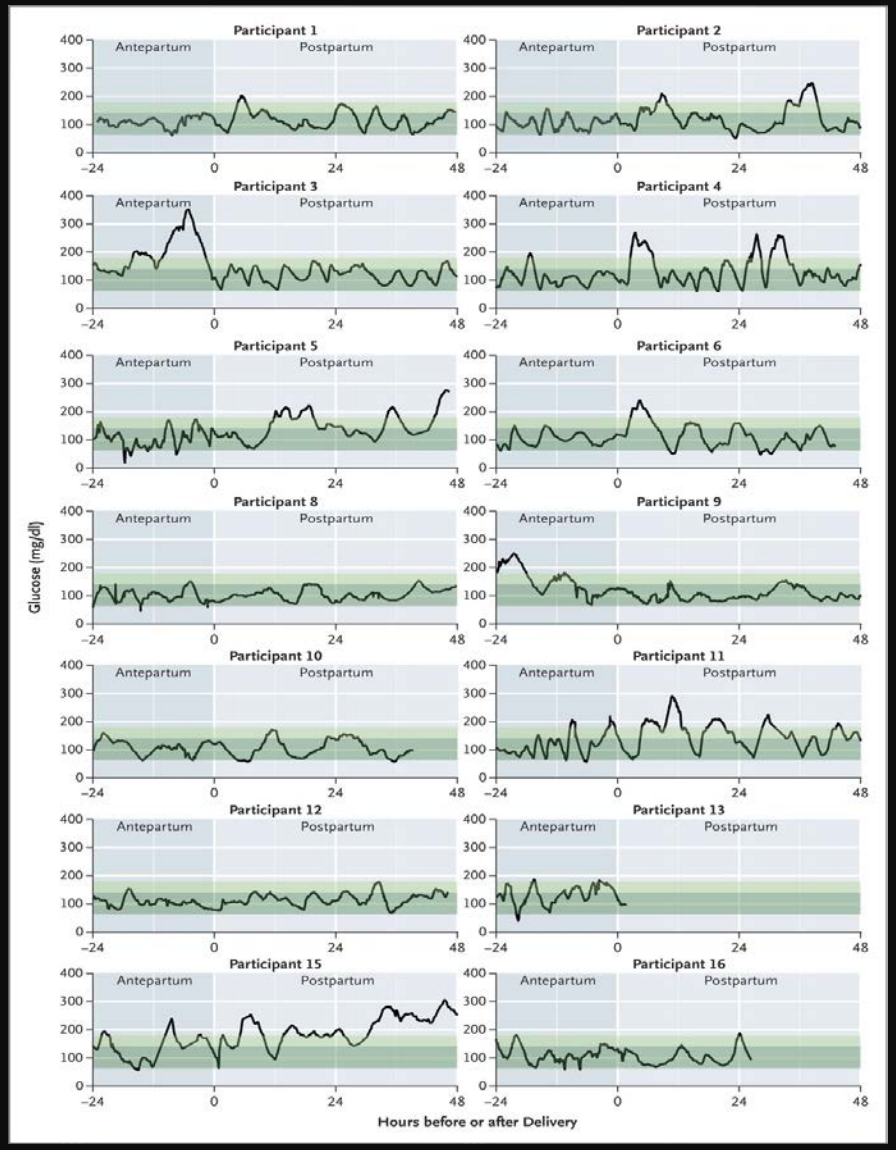
The NEW ENGLAND JOURNAL of MEDICINE

Glycemic Control during Labor and Delivery in the 14 Participants Who Continued to Use Closed-Loop Insulin Delivery



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Closed Loop Insulin System in Pregnancy

- Percentage of time that overnight glucose levels were in the target range was higher during CLT (74.7% vs. 59.5%; 95% CI, 6.1 to 24.2; P=0.002)
- Overnight mean glucose level was lower during CLT (119 vs. 133 mg per deciliter [6.6 vs. 7.4 mmol per liter], P=0.009)
- There were no significant differences in the percentage of time in which glucose levels were below the target range (1.3% and 1.9%, respectively; P=0.28), in insulin doses, or in adverse-event rates
- During the continuation phase, glucose levels were in the target range 68.7% of the time; mean glucose level = 126 mg per deciliter. No episodes of severe hypoglycemia requiring third-party assistance occurred during either phase

Stewart ZA et al. N Engl J Med 2016;375:644-654.

Timing of Delivery in Pre-gestational DM

- Induction of labor for suspected macrosomia does not reduce the likelihood of birth trauma
- Early delivery may be indicated in poorly controlled patients or for comorbidities
- Patients with well-controlled DM and no comorbid conditions “may be allowed to progress to their [EDD]”

ACOG Practice Bulletin 60, March 2005