GESTATIONAL DIABETES: UDERSTANDING, MANAGING AND PREVENTING RISKS

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1

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2

Abbreviations for this presentation

- GDM: Gestational diabetes mellitus
- T1DM: Type 1 diabetes mellitus
- T2DM: Type 2 diabetes mellitus
- CGM: Continuous glucose monitor
- MDI: Multiple daily injections
- LGA: Large for gestational age
- SMBG: Self blood glucose monitoring
- TIR: Time in range

3

OBJECTIVES

- Define and diagnose GDM
- Review the pattern of gestational changes in insulin sensitivity
- Review the role of maternal dysglycemia on maternal and fetal outcomes
- Gain familiarity of the pregnancy-specific glycemic targets for SMBG and CGM
- Understand different treatment strategy options to help achieve the challenging glycemic goals during GDM

4

DEFINITION OF GDM

Carbohydrate Metabolism During Pregnancy

Joseph P. Hoet, M.D., Louvain, Belgium
Translation from the French by
P. D. W. Lukens, M.D., Philadelphia

Diabetes 1954;3:1-12

~~Any Degree Of Glucose Intolerance With Onset Or First Recognition During Pregnancy~~

ADA and ACOG:

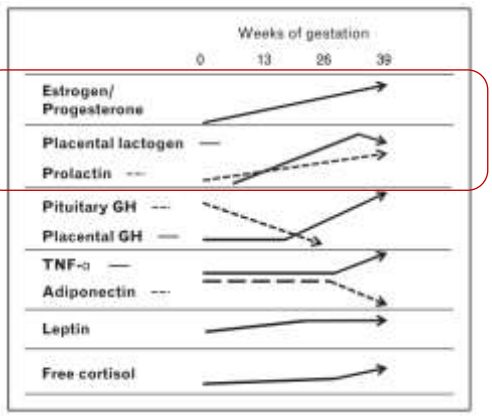
GDM is Diabetes that is First Diagnosed in the Second Or Third Trimester of Pregnancy that is Not clearly either preexisting Type 1 or Type 2 Diabetes

Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2024 |

5

METABOLISM IN PREGNANCY

GOAL IS TO DELIVER NUTRITION (GLUCOSE) TO FETAL PLACENTAL UNIT



Placental hormones and the control of maternal metabolism and fetal growth, D Newbern, Current Opinion in Endocrinology, Diabetes & Obesity 2011, 18:409–416

6

Early Pregnancy

E + P + Prl + hPL → ↑ β cell

Glucose demands for fetus are still low

- Increased Insulin demand met by
  - Estrogen and Progesterone stimulation of B cell hyperplasia/hypertrophy
  - Elevated prolactin and hPL drive β cell mass increase
- α cells and glucagon secretion unchanged
- Leptin levels increase

7

Late Pregnancy

Maternal metabolism switches to FFA use

- To maintain maternal blood glucose levels, insulin resistance ↑
- ↑lipolysis → ↑ fatty acid utilization and ↓ glucose uptake by skeletal muscle
  - IR in skeletal muscle mediated by ↑ hPGH and TNFα, ↓ adiponectin
  - Progesterone attenuates the insulin response in adipose tissue/skeletal muscles

8

DIAGNOSIS OF GDM: 2 STEP strategy @24-28w

- Screening: 50-g *non-fasting* OGTT, with plasma glucose measurement at 1 hour
- If plasma glucose after 1 h is >130 or >140 mg/dL, proceed to …
- Diagnostic: *Fasting* 3-hour 100g OGTT (F, 1, 2, 3 h values, ≥2 abn = GDM)
- Thresholds – CC or NDDG

	Carpenter-Coustan	NDDG
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)

Modified cutoffs: enzymatic glucose methods

Use of plasma/Serum – increased cutoffs

Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes*. American Diabetes Association
Diabetes Care Jan 2018, 41 (Supplement 1) S13-S27
ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstetrics & Gynecology Feb 2018 131(2):e49-e64.

9

Diagnosis of GDM: **One-step strategy** @24–28w

- 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h,
- The diagnosis of GDM is made 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)

Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2018*. American Diabetes Association
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ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstetrics & Gynecology Feb 2018 131(2):e49-e64.

10

Criteria for early screening

- BMI >25 AND

- First degree relative with GDM
- AA, Latino, Native American, Asian American, Pacific Islander
- Hypertension
- HDL <35, TG >250
- PCOS
- Physical Inactivity
- Acanthosis, severe obesity, NASH, etc.
- Prior GDM, macrosomia, stillbirth
- Pre-DM diagnosis

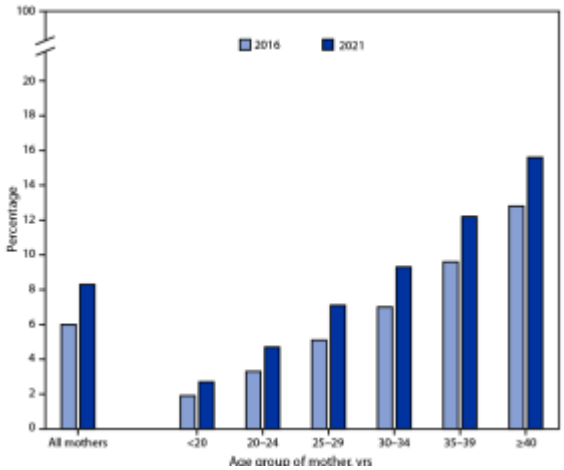
Diagnostic criteria same as those for adults for type 2 DM

Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2018.* American Diabetes Association Diabetes Care Jan 2018, 41 (Supplement 1) S13-S27
ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstetrics & Gynecology Feb 2018 131(2):e49-e64.

11

PREVALENCE

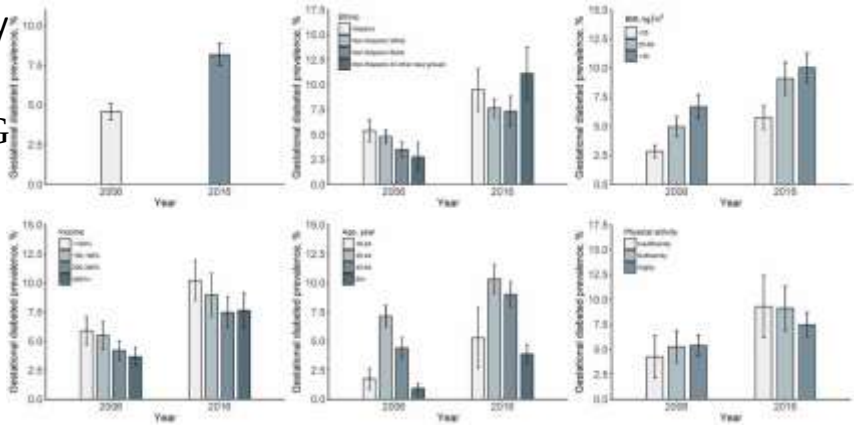
- The percentage of GDM has increased from 6.0% in 2016 to 8.3% in 2021.
- Increases in gestational diabetes were seen in each maternal age group, and rates rose steadily with maternal age; in 2021



12

RISK FACTORS

- Role of Ethnicity
- Obesity
- Excessive GWG
- Diet
- Birth-weight



13

What We Know About Pregnancies Complicated by Diabetes (Preexisting/GDM)

- Women with diabetes who are pregnant require tighter glycemic targets to reduce maternal and fetal health risks.
  - Fetal complications/risk: Fetal loss, fetal detah, premature delivery, delayed lung maturity, and macrosomia (>4 kg), birth defects (T1and T2DM)
  - Maternal complications/risk: Worsening hypolgycemia, pre-eclampsia, and Cesarean section delivery, progression of diabetic complications (e.g.,retinopathy: T1 and T2DM)
- Pregnancy outcomes have improved with the advent of newer insulins, SMBG and CGM, but remain suboptimal

14

Glycemic challenges during pregnancy for patients (and health care providers)

- Health risks for both mother and fetus
- Risks of hypoglycemia increased due to tighter glycemic targets 63-149 mg/dL (as opposed to standard goals of 70-180 mg/dL)
- Patient burden: glucose testing frequency (4-8x daily), food restrictions, stress, device alerts (for those wearing devices)
- Delays in onset of insulin action
- Delays in gastric emptying
- Limited geography: infusion sets/injections or CGM

15

Diabetes During Pregnancy is a Balancing Act

- Optimizing glycemic control
- Risks of hyperglycemia
- Risk of hypoglycemia
- Quality of life
- Stress
- Nutritional restrictions
- Cost

16

Glucose Monitoring

- Fasting + Post Prandial (add preprandial if preexisiting on BB/pump)
  - 1 HOUR VS 2 HOUR
- Postprandial monitoring is associated with better glycemic outcomes and a lower risk of preeclampsia
- A1c is a secondary measure

rtCGM CONCEPTT

↑ TIR (68% vs 61%, p=0.003)
↓ Hyperglycemia (27% vs 32%, p=0.0028)
↓ LGA (50%) NICU admission (OR=0.48) N-hypoglycemia (OR=0.45)
1 day shorter length of hospital stay
Time spent in hypoglycemia/severe hypoglycemia were comparable

rtCGM GDM ?

FGM ?

17

Treatment goals GDM

- Fasting <95mg/dL
- 1 hour post-prandial <140 mg/dL
- 2 hour post-prandial <120 mg/dL
- HbA1c 6.0-6.5%
  - Less reliable
- Current recommendations for hypoglycemia thresholds include blood glucose <70 mg/dL and sensor glucose <63 mg/dL.

Management of Diabetes in Pregnancy: *Standards of Medical Care in Diabetes—2018*. American Diabetes Association
Diabetes Care Jan 2018, 41 (Supplement 1) S13-S27
ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstetrics & Gynecology Feb 2018 131(2):e49-e64.

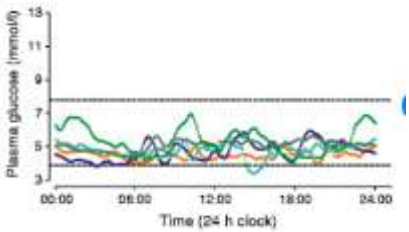
18

Continuous Glucose Monitoring (CGM)

19

Use of CGM during pregnancy

- CGM has an indication (CE mark) first for use during pregnancy and is covered for women with T1D during pregnancy in the UK since 2020
- Canada permitted the use of CGM during pregnancy during the COVID-19 pandemic
- The FDA has recently (2023) approved use of three CGMs during pregnancies complicated by diabetes
- Endocrine organizations including ADA, ENDO, AACE and others internationally support the use of CGM in pregnancies complicated by T1D.



20

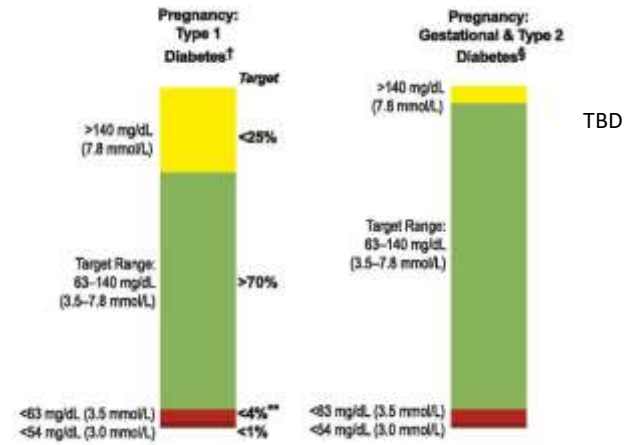
Flamingo Trial- Largest Published Trial in GDM at Present

- 100 participants with GDM
  - 50 experimental CGM, 50 SMBG
- Use of FLASH isCGM (Libre 14 day)
- Compared to the control group:
  - isCGM group reduced their fasting and postprandial hypoglycemia during the first 4 weeks following GDM diagnosis
  - No significant differences in progression to insulin therapy
  - Incidence of fetal macrosomia was significantly higher in SMBG as compared to FGM group

Majewska A. et al. Acta Diabetologica(2023)60:1171-1177

21

CGM TIR Goals During Pregnancies Complicated by Diabetes



TBD

- Outside of pregnancy, goal is >70% with target range of 70-180

Battelino et al. Diabetes Care 2019;42(8):1593–1603

22

Patient Considerations During Pregnancy

- Skin sensitivity
- Site selection
- Discuss regarding frequency of fingerstick testing for newer generations of CGM during pregnancy
- Education of patients about sensor lag when treating hyper or hypoglycemia
- Counsel re burden of device wear and alerts
- Insurance coverage depends on location
- TIR is likely not enough (mean glucose and CV matter)

23

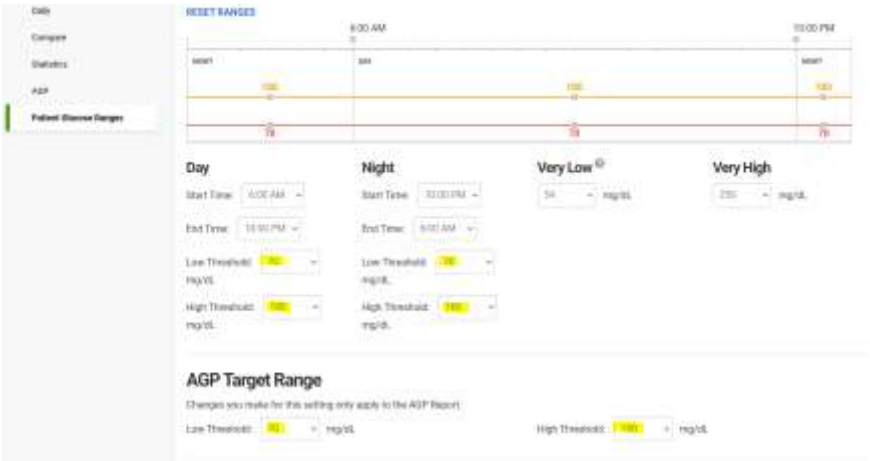
Changing Time in Range targets 65-140

Libreview adjusted targets will only appear on LibreView daily reports, **not** AGP

24

Changing Time in Range targets 65-140

For Clarity one needs to change different targets to view on overview and AGP



25

TREATMENT

26

Preconception Counseling/Optimization

- Ensure all individuals of childbearing potential are aware of the glycemic and health goals prior to pregnancy
- Educate on maternal and fetal risks of hypo and hyperglycemia
- Review overall health (retinopathy, nephropathy, HTN, cardiovascular disease, thyroid status, fertility status)
- Review meds and timeline for discontinuation of any with teratogenic potential
- Initiation of folic acid
- Review patient goals, self management tools, and potential for revisions of glucose management regimen.

27

Lifestyle Modifications

First Line: Diet Exercise and Weight Management

ACOG and ES → low carb diet
ADA – withdrawn any recommendation - ↫ RCTS

✓ (simple carbs 33-40%) Limit postprandial glucose excursions and excessive fetal growth

✗ Increase in fat → IR and has resulted in adiposity, NAFLD, metabolic syndrome in animal model offspring

- High Complex Carbs + fiber (low GI)
- Lower saturated fats

Maternal TG and FFA are strong predictors of fetal fat accretion

28

Medical Nutrition Therapy

- The recommended dietary reference intake for all pregnant people is a minimum of 175 g of carbohydrate (~35% of a 2,000-calorie diet), a minimum of 71 g of protein, and 28 g of fiber
- The nutrition plan should emphasize monounsaturated and polyunsaturated fats while limiting saturated fats and avoiding trans fats.
- Fasting urine ketone testing may be useful to identify those who are severely restricting carbohydrates to manage blood glucose

29

Weight gain

- Recommended weight gain during pregnancy for people with overweight is 15–25 lb (6.8–11.3 kg) and for those with obesity is 10–20 lb (4.5–9.1 kg) (67).
- There are no adequate data on optimal weight gain versus weight maintenance in pregnant people with BMI >35 kg/m2;, losing weight is not recommended because of the increased risk of small-for-gestational age infants

30

Conflicting Recommendations

American Diabetes Association	ACOG	Society for Maternal-Fetal Medicine	FIGO
Insulin first line	**Insulin preferred**	**Metformin and insulin both first line**	**Insulin, glyburide and metformin all first line**
Metformin and glyburide comparable, possible preference for metformin	Metformin second line Glyburide advised against	Acknowledge that half of patients on metformin will also require insulin	Preference for metformin and insulin over glyburide

31

What has been studied?

- Sulfonylureas:
  - Glyburide less placental transfer than glipizide, so preferred
    - Category C
- Biguanides
  - Metformin-Category B
- A-glucosidase inhibitors
  - Acarbose –Category B
- Insulin
  - Most human and analog insulins Category B, glargine Category C
- No studies: GLP-1 (C), DPP-4 (B), SGLT-2 (⃠assigned), thiazolidinediones (C)

Coustan, Donald R. "Pharmacological management of gestational diabetes: an overview." *Diabetes Care* 30.Supplement 2 (2007): S206-S208.

32

Medications

- Insulin: ideal in capable patients, especially early GDM, older women, higher FBG, as those patients more likely to fail oral
- Metformin: perhaps better in patients at high risk of hypoglycemia
  - Avoid in placental insufficiency
  - Concerns about increased preterm birth
  - Higher failure rates-more women will require insulin
- Glyburide: ideal for more post-prandial hyperglycemia
  - Can be dosed HS to control fasting hyperglycemia
  - Concerns about increased macrosomia and birth weight
  - Lower failure rates-less likely to require insulin
- Both oral medications cross placenta and co-administration may increase placental transport and therefore fetal exposure
- Long-term effects on children still unclear
- As with all diabetes treatment, “right” answer will be different for each patient

33

Insulin pump therapies

34

Insulin pump therapies

- Advantages:
  - Less glycemic variability
  - Lower risk of hypoglycemia
  - Higher TIR
  - Potential for better quality of life
- Disadvantages
  - Not licensed for pregnancy
  - Glycemic targets not appropriate for pregnancy
  - Insufficient data
  - Insufficient flexibility to adapt to increasing insulin needs in pregnancy

35

Some useful tips..

- Continue to reassess whether HCL is working or whether we should switch to manual mode
- Use the lowest glucose target
- Actively adjust carb ratios
- Consider even adding supplemental long-acting insulin as the pregnancy advances
- Consider boluses and fake carbs

36

Insulin pump therapies

Selected studies of hybrid closed loop in pregnancy

	Year of publication	Location	System	Study design	No. of participants
CLIP-3 (38)	2016	UK	CamAPS FX with FreeStyle Navigator II sensor	Randomized crossover trial	16
CLIP-4 (39)	2018	UK	CamAPS FX with FreeStyle Navigator II sensor	Randomized crossover trial	16
AiDAPT (40)	2024	UK	CamAPS FX with Dexcom G6 sensor	RCT	124
CRISTAL (41)	2024	Belgium and Netherlands	Medtronic MiniMed 780G with Guardian 3 → 4 sensor[b]	RCT	95
PICLS (42)	2024	USA	Medtronic MiniMed 670G with Guardian 3 sensor	RCT	24

37

Risk of developing T2DM

- Increased lifetime maternal risk for diabetes estimated at 50–60%
- 10-fold increased risk of developing type 2 diabetes compared with those without GDM
- People with BMI >25 kg/m2, weight loss is associated with lower risk of developing GDM in the subsequent pregnancy
- Development of type 2 diabetes is 18% higher per unit of BMI increase from prepregnancy BMI at follow-up, highlighting the importance of effective weight management after GDM

38

Preeclampsia and Aspirin

- Diabetes in pregnancy is associated with an increased risk of preeclampsia
- Individuals with GDM may be candidates for aspirin therapy for preeclampsia prevention if they have a single high risk factor, such as chronic hypertension or an autoimmune disease, or multiple moderate risk factors, such as being nulliparous, obesity, being age ≥35 years.

39

Areas for further evaluation

- TIR and other factors impacting adverse maternal and fetal outcomes including LGA babies
- How to best use CGM
- Use CGM and CLC systems and pregnancy outcomes in all types of pregnancies complicated by diabetes
- What is the optimal glycemic targets (is 70% TIR achievable and adequate), different goals for GDM and T2DM?
- Role of A1c, mean glucose, glycemic variability?
- Insulin Analogs (ultra rapid, inhaled?)

40

In closing

- Pregnancies complicated by diabetes are associated with an increased risk of adverse maternal outcomes and neonatal complications
- Gestational changes in insulin resistance confer an increased risk of hypoglycemia and hyperglycemia
- CGM use in pregnancy improves glycemic control and maternal and neonatal outcomes while lowering self-care burden in a cost saving fashion
- Individuals with GDM should undergo oral glucose tolerance testing between 4 and 12 weeks postpartum due to 10-fold greater risk of developing T2DM

41

Thank you!

42