Management of Diabetes in Pregnancy: New Guidelines and Practical Pointers

The Journal of Clinical Endocrinology & Metabolism, 2025, **110**, 2405–2452
https://doi.org/10.1210/clinem/dgaf288
Advance access publication 13 July 2025
Clinical Practice Guideline

ENDOCRINE SOCIETY

OXFORD

Preexisting Diabetes and Pregnancy: An Endocrine Society and European Society of Endocrinology Joint Clinical Practice Guideline

Jennifer A. Wyckoff,[1,*] Annunziata Lapolla,[2] Bernadette D. Asias-Dinh,[3] Linda A. Barbour,[4] Florence M. Brown,[5,6] Patrick M. Catalano,[7] Rosa Corcoy,[8,9,10] Gian Carlo Di Renzo,[11,12] Nancy Drobycki,[13] Alexandra Kautzky-Willer,[14] M. Hassan Murad,[15] Melanie Stephenson-Gray,[16] Adam G. Tabák,[17,18] Emily Weatherup,[1] Chloe Zera,[19,20] and Naykky Singh-Ospina[21]

Linda Barbour MD, MSPH, FACP
Professor of Endocrinology, Metabolism, and Diabetes and Maternal-Fetal Medicine
University of Colorado Anschutz Medical Campus
OB-Gyn Vail Conference
Feb 19, 2026

- No conflicts of interest
  - NIH R01s, R21s
  - ADA Pilot Grants
- Investigator-Initiated Pilot RCT Harold Hamm Diabetes Center/Presbyterian Health Foundation
- Investigator-Initiated Pilot RCT JAEB Center of Health Research and MannKind

Objectives—*perhaps a little something for everyone?*

- 1) Highlights of Endo Soc/European Endo Society Guidelines on Pre-existing Diabetes in Pregnancy
  - »Do Continuous Glucose Monitors (CGM's) improve outcomes in pregnancies complicated by T2DM? New data in GDM
  - »What is the optimal carb diet in Diabetes in pregnancy? Data in GDM
  - »Should metformin be added in T2DM? Implications for GDM
- 2) If not Metformin, is Inhaled Insulin an option?
  - » RCT Cross-over Trial on Afrezza for GDM
- 3) Pearls in Insulin Management of T2DM and GDM

Pre-existing Diabetes in Pregnancy Guideline

- Joint Guideline of the Endocrine Society and European Society of Endocrinology—2 years in the making
- **Co-Sponsoring Organizations:**
  - Association of Diabetes Care and Education Specialists,
  - American Pharmacists Association,
  - European Association for the Study of Diabetes
- **Supporting Organization:**
  - **Society for Maternal-Fetal Medicine**
- **Participating Organization:**
  - **American College of Obstetricians and Gynecologists**
- **Utilized GRADE evidence synthesis and recommendation development**

Guideline Development Panel-U.S./Europe

Endocrinologists, OB-Gyns, MFMs, Epidemiologists, Pharmacists, Dieticians, CDEs, Patient Rep (with no COIs)!!

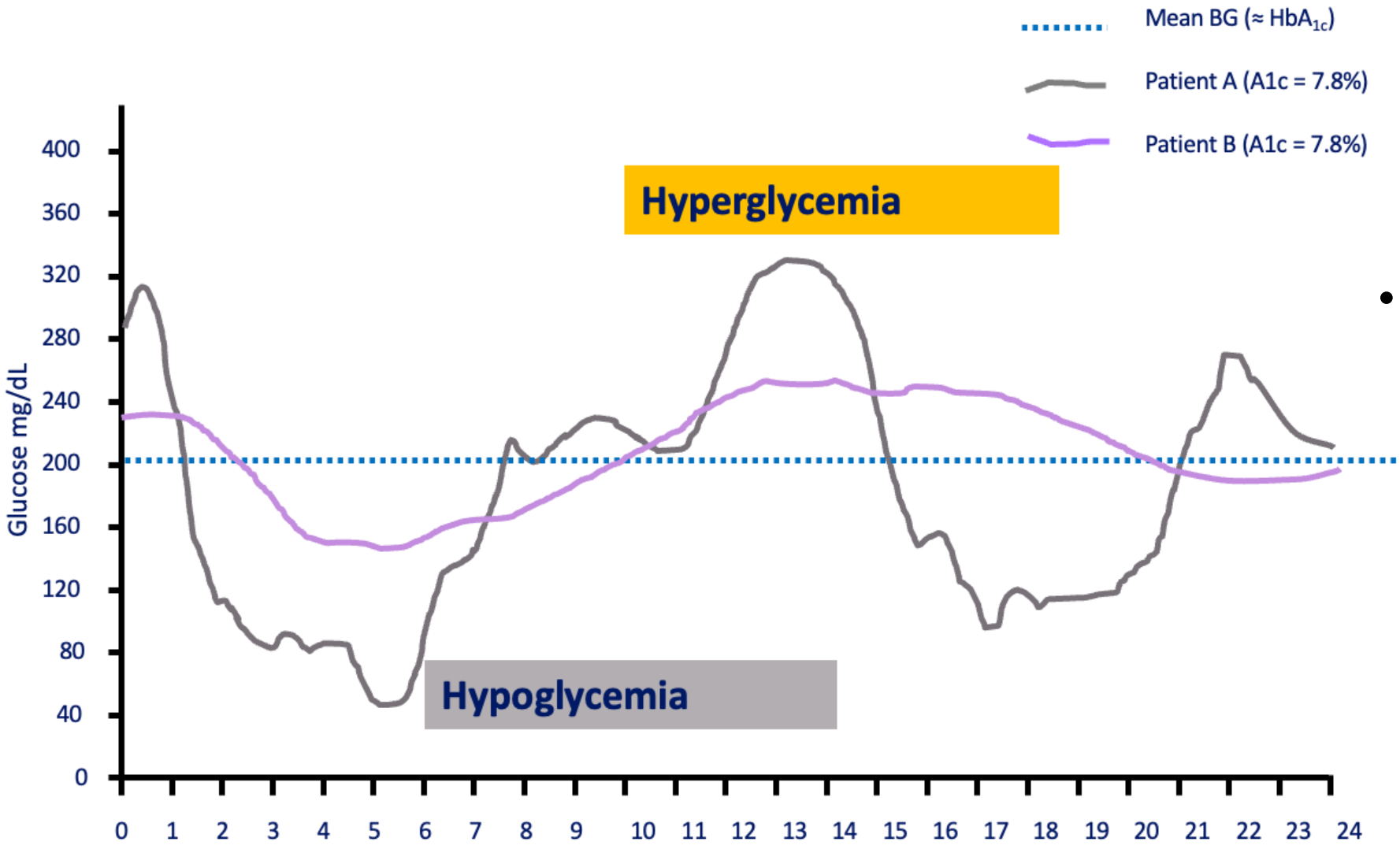
- Jennifer Wyckoff, MD
- Annunziata Lapolla, MD
- Bernadette Asias-Dinh
- Linda Barbour, MSPH, MD
- Florence Brown, MD
- Patrick Catalano, MD (ACOG)
- Rosa Corcoy, MD, PhD
- Gian Carlo Di Renzo, MD, PhD
- Nancy Drobycki, MSN, RN, CDCES
- Alexandra Kautzky-Willer
- Melanie Gray, BA Hons, BSc, MBDA
- Adam Tabák, MD, PhD
- Emily Weatherup, MS, RDN, CDCES
- Chloe Zera, MD, MPH (SMFM)

CGM in T2DM

Should a continuous glucose monitor (CGM) vs. no CGM (self-monitoring blood glucose [SMBG] as standard of care) be used in pregnant individuals with type 2 diabetes mellitus (T2DM)?

Outcome	Direct evidence	Indirect evidence
LGA infants	Yes	Yes
SGA infants	No	Yes
NN hypoglycemia	No	Yes
NICU admission	No	Yes
Glucometrics	No	Yes

Hgb A1c Does Not Reflect Blood Glucose Variability

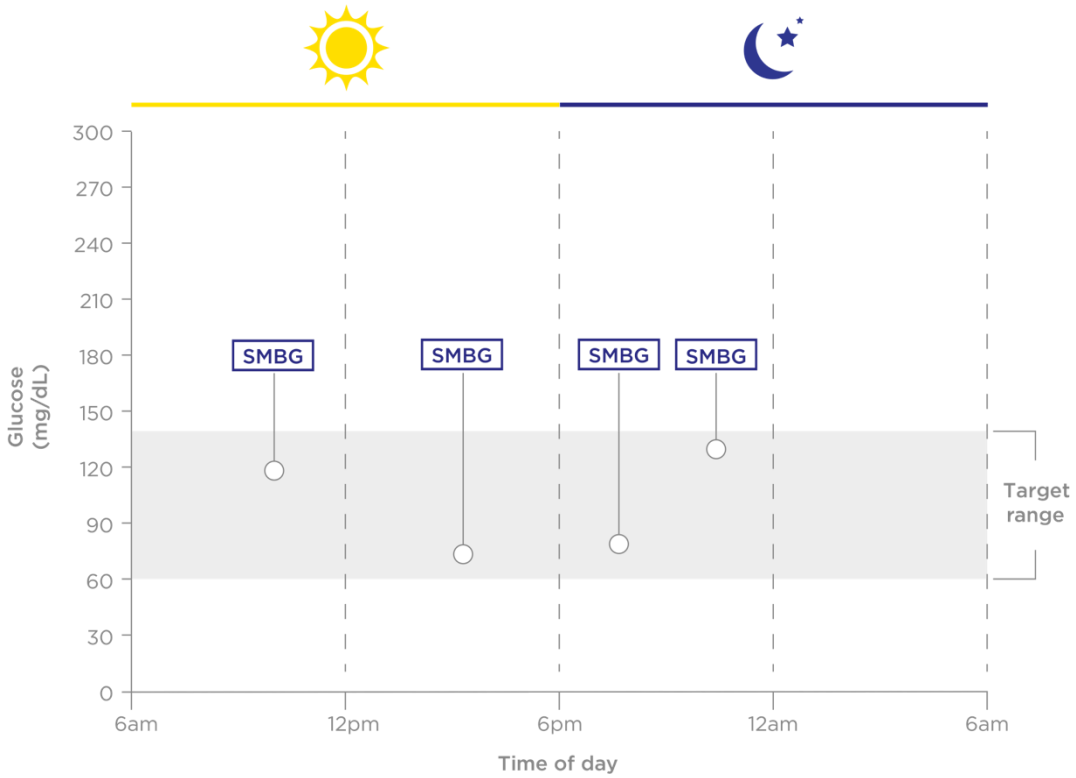


- ***How does Gluc variability and intermittent fetal hyperinsulinemia affect organogenesis, and fetal growth?***

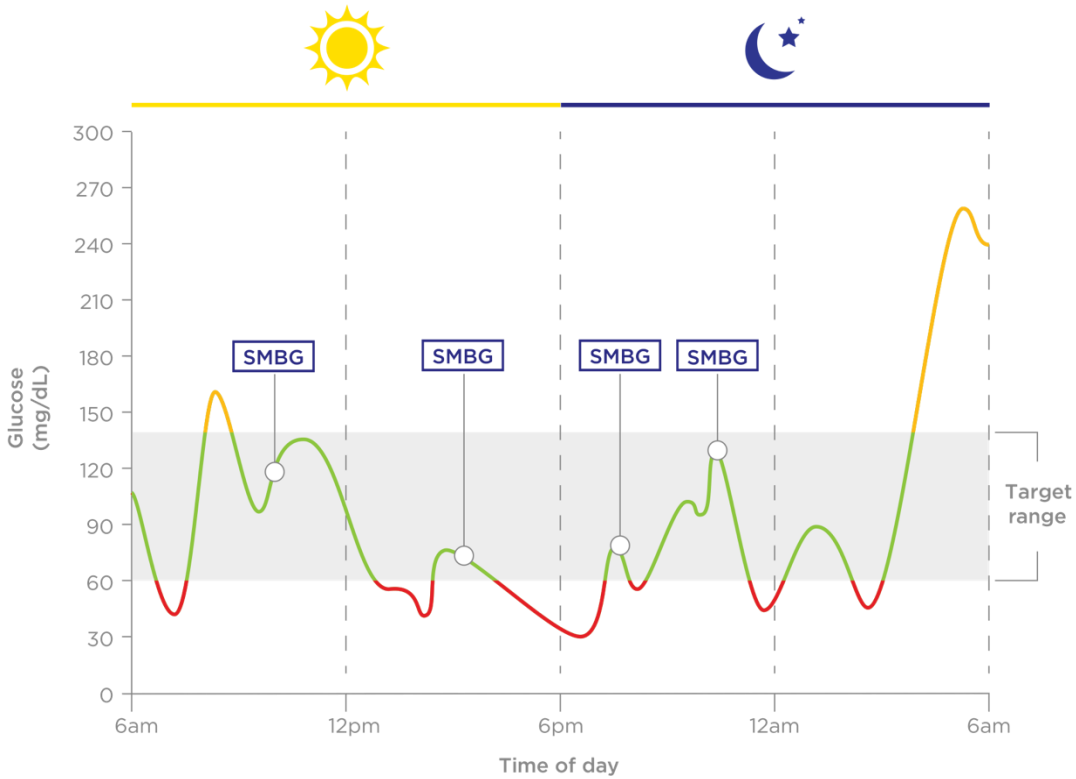
Image adapted from Penckofer S, Quinn L, et al. Does glycemic variability impact mood and quality of life? Diabetes Technol Ther. 2012 Apr;14(4):303-10.

SMBG Can Be Deceptive Compared to CGM

- All SMBG in range-4 time points



- CGM: 288 time points with significant glucose variability with hypoglycemia and hyperglycemia

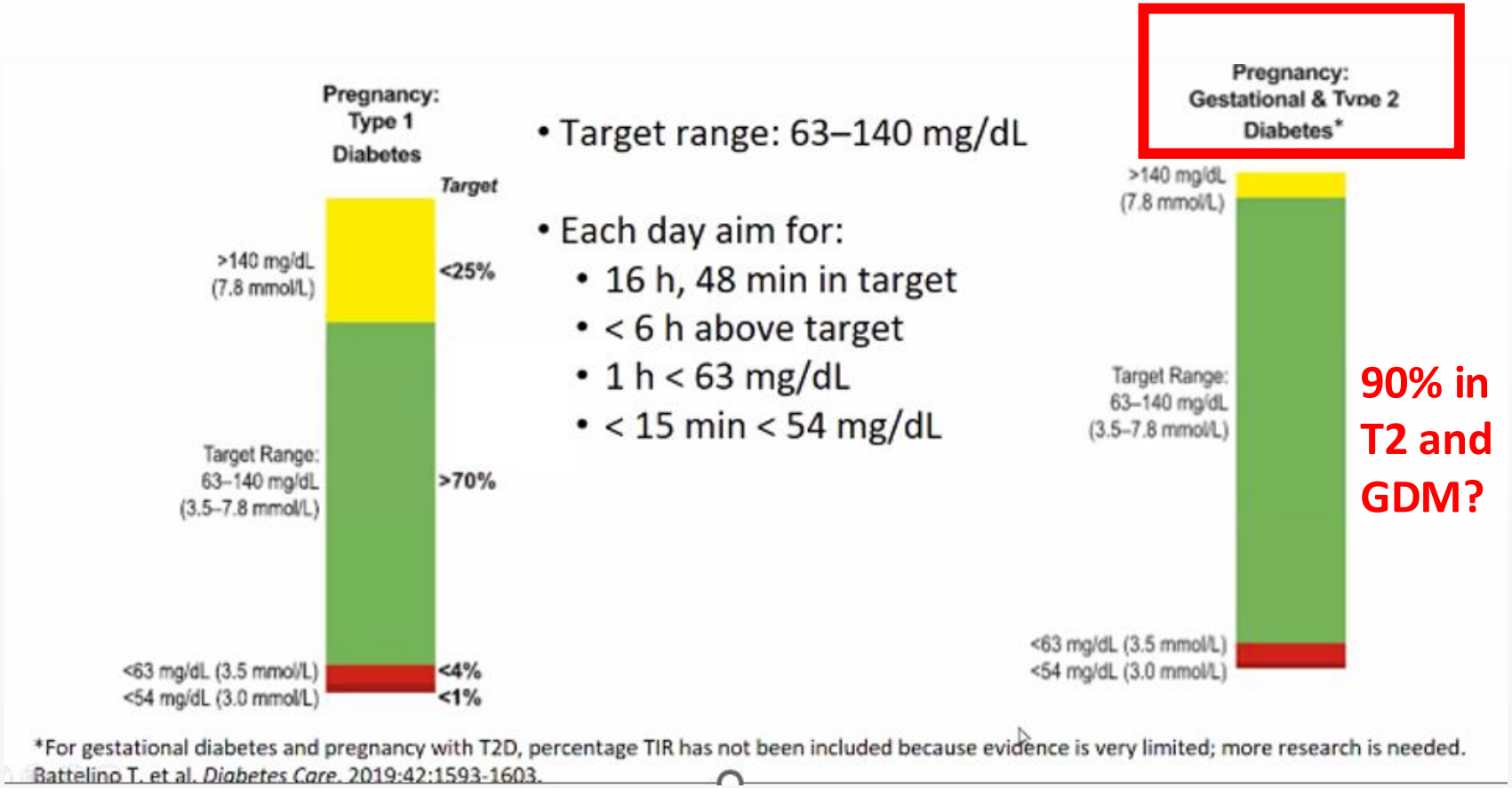


1. Janapala Rajesh Naidu, et al. "Continuous Glucose Monitoring Versus Self-monitoring of Blood Glucose in Type 2 Diabetes Mellitus: A Systematic Review with Meta-analysis." *Cureus* 11, no. 9 (September 2019):e5634.

TIR Goals for T1DM in Pregnancy: 70% TIR; <4% Low

Beneficial to improve pregnancy outcomes in T1DM (CONCEPTT) and in T2DM outside of pregnancy vs occasional SMBG or A1Cs.

Medicaid recently approved CGM in Jan 2026 for T2DM in pregnancy on 1 insulin injection/day and GDM (irrespective of insulin use)

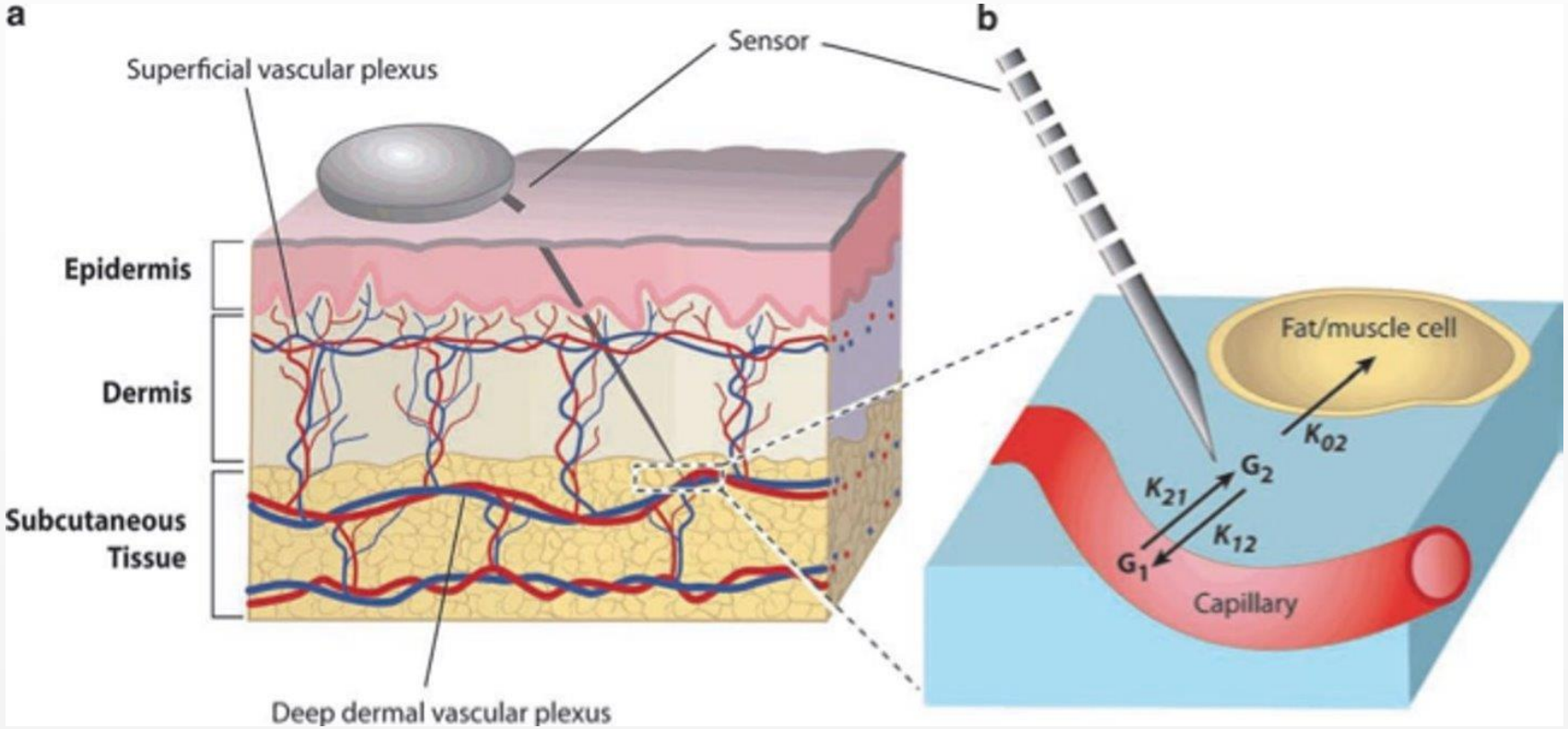


TIR Goals established for T1 DM but Not for T2DM or GDM: Ave gluc, TIR, or targets not established in T2DM or GDM but probably need to be much tighter

Mean and Noc Gluc more strongly assoc w/ LGA in GDM: Should Noc Range be 63-120 instead?

Interstitial Fluid Lag Time—Are Fingersticks Still Needed?

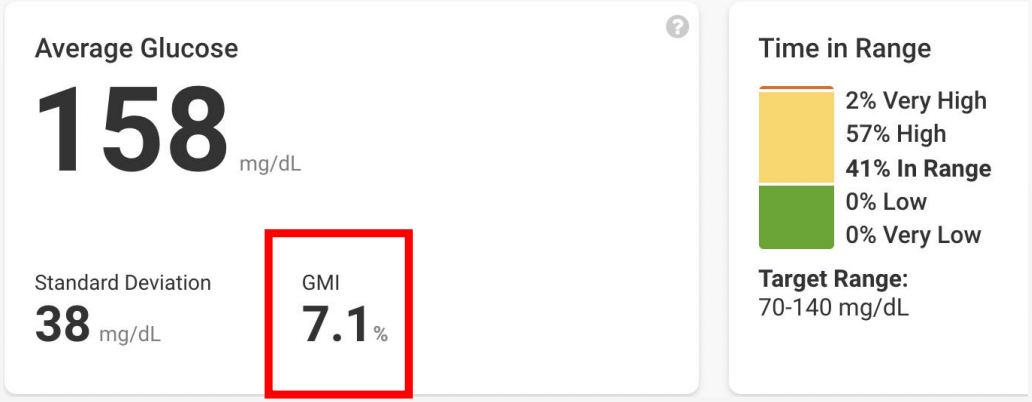
- The physiological **time lag** of glucose transport from the intravascular to subcutaneous interstitial fluid compartment is **~ 5-15 mins and longer when glucoses are rapidly falling or rising**.
- **If blood glucose is dropping fast, sensor readings will be higher than fingersticks. If blood sugar is rising fast, sensor readings will be lower than finger pricks**



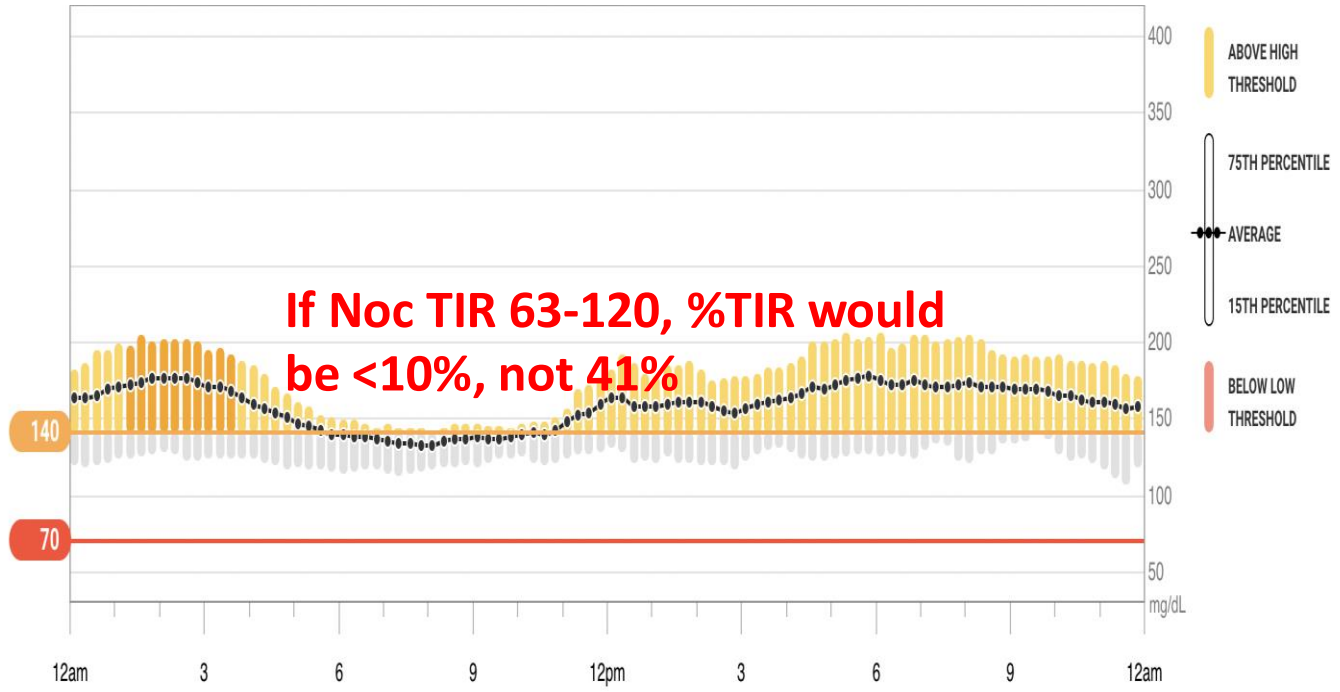
Cengiz E, Tamborlane WV. A tale of two compartments: interstitial versus blood glucose monitoring. Diabetes Technol Ther. 2009 Jun;11 Suppl 1(Suppl 1):S11-6.

Challenges with CGM in Interpretation: GMI vs A1C, Compression Lows, Sensor Inaccuracies first 12 hrs; Nocturnal Range <140

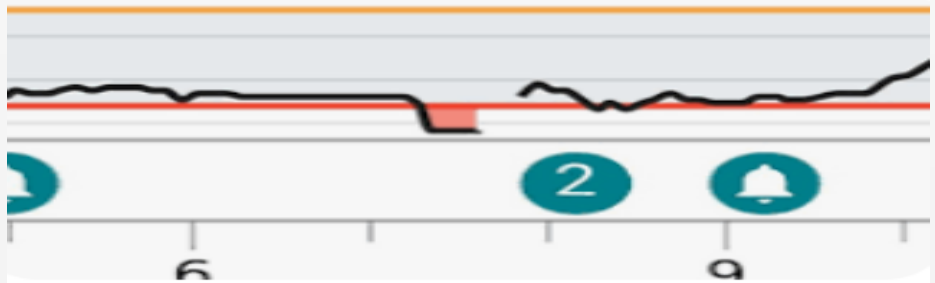
- 24 yo G2P1 at 7w2d with LADA
- **Hgb A1c at NOB 6.4% but CMI is 7.1**
- **Does pt need a Fetal Echo?**
- **Noct range is <140 so FBG of 139 still can be considered within TIR target**
- **First 12-24 hrs unreliable as sensor equilibrate**
- **Are Lows overnight Real or Compression lows**



GMI=Gluc Management Indicator
~Est A1C over 2 weeks



Are these Compression Lows Real?



CGM in T2DM

(Direct) evidence

- 3 RCTs, **none specific** for T2DM
- **intermittent CGM** (retrospective/ real-time)
- **separate analysis** for T2DM in 2 studies

Outcome	Trials	Participants	RR (95% CI)	Certainty
LGA infants	2	102 T2 alone	**0.88** (0.49 to 1.59)	Low ⨁⨁◯◯◯
SGA infants	2	361* (T1,T2)	**11% vs 0%** (Murphy 2008) **3 vs 5%** (Voormolen 2018)	Very low ⨁◯◯◯
NN hypoglycemia	3	515* (T1,T2)	**0.96** (0.75 to 1.23)	Very low ⨁◯◯◯
NICU admission	1	290* T1,T2)	**1.01** (0.65 to 1.59)	Very low ⨁◯◯◯
Glucometrics	2		≈ HbA_{1c} ≈severe hypo	Very low ⨁◯◯◯

* Not exclusively T2DM

(Murphy H, 2008; Secher A, 2012; Voormolen DN, 2018; Wilkie G, 2023)

CGM in T2DM

Indirect evidence: Observational in with T2D

Real-world, use vs no use

Continuous Glucose Monitoring for Management of Type 2 Diabetes and Perinatal Outcomes

Charles E. Padgett, MD, Yuanfan Ye, PhD, Macie L. Champion, MD, Rebecca E. Fleenor, MD, Vasiliki B. Orfanakos, MD, Brian M. Casey, MD, and Ashley N. Battarbee, MD, MSCR

Obstet Gynecol 144(5), NOV 2024

--Retrospective, 360 pregnancies in Alabama academic center

82 (22.7%) used CGM at mean gest age ~21 wks.

--CGM assoc with adjusted lower odds (0.48) of the primary composite neonatal morbidity (55.9% CGM vs 77.0% SMBG); Preterm birth (13.4% vs 25.2%, aOR 0.48) and NICU admission (33.8% vs 47.6%, aOR 0.36)

--However this 23% of the cohort was likely most motivated…

Recommendation- CGM in T2DM

In pregnant individuals with type 2 diabetes mellitus (T2DM), we suggest **either** continuous glucose monitor (CGM) or self-monitoring of blood glucose (SMBG). (2 | ⨁OOO), very low due to imprecision and indirectness
Conditional recommendation

Technical remarks

- **Both CGM and SMBG are considered reasonable alternatives; CGM may offer a potential advantage vs. SBGM in certain subgroups**
- **Ideal glycemic ranges, CGM metrics, and % Time in Range (TIR) for T2DM may be different** compared to those in T1DM that showed benefit. Those that achieve higher TIR have better pregnancy outcomes
- **Enormous resources and CDE support required** to include T2 DM pop; training of OB-Gyn providers; false alarms at night, sensor fatigue, education of pts on 15 min delay, poor accuracy when gluc rapidly falling/rising, compression lows, sensor failures, unreliability of sensor first 12 hrs

Real-Time Continuous Glucose Monitoring in Pregnancies With Gestational Diabetes Mellitus: A Randomized Controlled Trial

Amy M. Valent,[1] Michaela Rickert,[1] Christian Huerta Pagan,[1] Lucy Ward,[1] Emily Dunn,[2] and Monica Rincon[1]

Diabetes Care 2025;48:1581–1588 | https://doi.org/10.2337/dc25-0115

What about GDM? (not in Guidelines)

111 pts; 2:1 enrollment (Real time Dexcom vs Fingersticks and blinded Dexcom every 20 days)
90% dx 75 g 1 step (IADPSG); 10% CC 2 step
55% A2 GDM
Enrolled >20 wks; TIR 60-140 but 60-99 for noct TIR
Finger sticks qid also in CGM group. Ins based on Fingersticks

No diff in Ins Rx
Mod Diff %TIR 93 vs 88%; Mean gluc 103 vs 109
No diff in noct TIR, daytime gluc, noct gluc
No diff in FBG/1h PP Gluc (fingersticks)
No benefit in pregnancy outcomes
20-30% adverse outcomes to CGM (sensors, skin irritation)

24-h glucose (mg/dL)			
Mean	103 ± 8	109 ± 17	0.047
Individual SD	18 ± 4	20 ± 7	0.114
Individual CV (%)	17 ± 3	18 ± 4	0.341
Daytime glucose (mg/dL)	—	—	—
Mean	103 ± 9	110 ± 17	0.050
Individual SD	18 ± 4	20 ± 7	0.086
Individual CV (%)	17 ± 3	18 ± 4	0.237
Nocturnal glucose (mg/dL)			
Mean	102 ± 10	108 ± 18	0.058
Individual SD	12 ± 3	14 ± 5	0.180
Individual CV (%)	12 ± 3	12 ± 4	0.531
Fasting glucose (mg/dL)§	95 ± 9	100 ± 15	0.069

Question: OPTIMAL CARBOHYDRATE INTAKE
Should a carb restricted (< 175 g per day) diet v.s. usual diet (>= 175 g per day) during pregnancy be used in individuals with pre-existing type 2 diabetes?

Outcome	Direct Evidence	Indirect Evidence
LGA infants	No	Yes
SGA infants	No	Yes
Neonatal hypoglycemia	No	Yes
Development delay up to age 18 yrs	No	No
Offspring overweight up to age 18 yrs	No	No

- **In individuals with pre-existing diabetes mellitus (PDM), we <u>suggest</u> either a carbohydrate restricted diet (<175 g per day) or usual diet (>175 g per day) during pregnancy. (2 | ⊕◯◯◯)**

European Society of Endocrinology
ENDOCRINE SOCIETY

The American Journal of Clinical Nutrition 117 (2023) 227–234

The American Journal of CLINICAL NUTRITION

journal homepage: www.journals.elsevier.com/the-american-journal-of-clinical-nutrition

Narrative Review

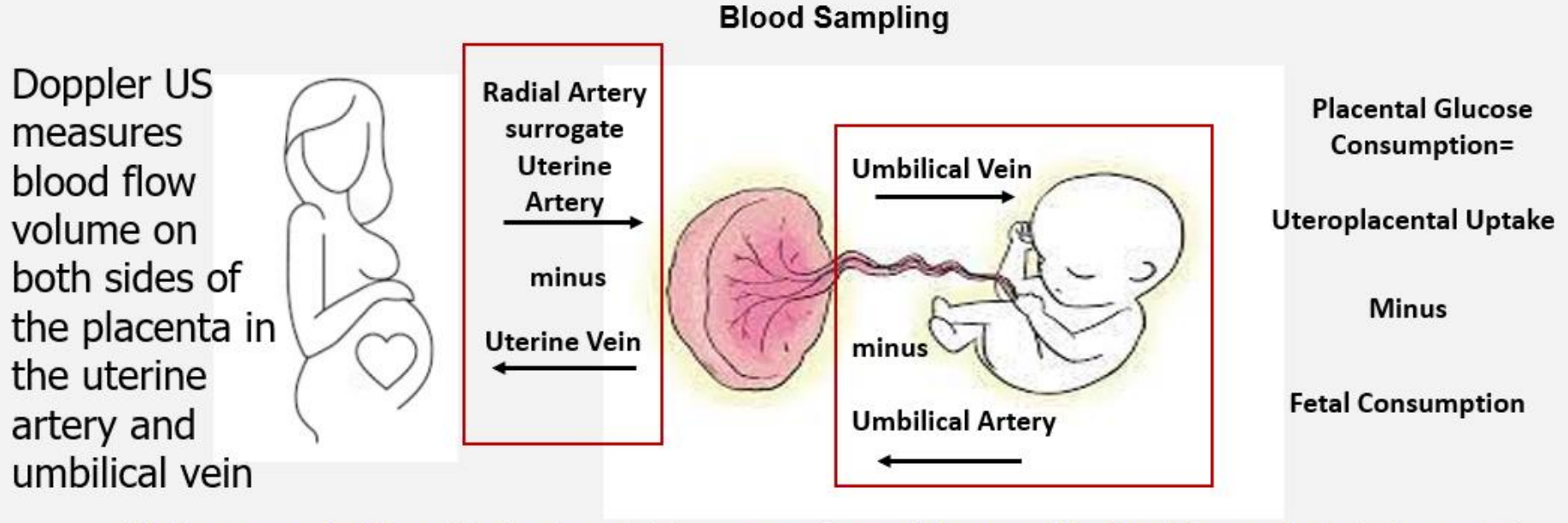
Re-examination of the estimated average requirement for carbohydrate intake during pregnancy: Addition of placental glucose consumption

Teri L. Hernandez [1,2,3,*], Paul J. Rozance [4]

Is ≥175g/d of carbs Enough or too much?

The RDA for Pregnancy does not account for the Placenta—perhaps it should be 210 g/day?

A.M. Holme, et al; The 4-vessel Sampling Approach to Integrative Studies of Human Placental Physiology in vivo, J Vis Exp 2017, 126.



We then converted the obligate placental glucose requirement to grams/day for dietary carbohydrate content:

([100g/day + 35g/day +36g/day] *15%) *2 +171 = 222 g/day

Adult Brain fetal brain placenta CV to convert EAR to RDA

~210g/day

No Clear Differences Across Diet RCTs for GDM

No RCTs Providing All Meals…

Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD009275.
DOI: 10.1002/14651858.CD009275.pub3.

Different types of dietary advice for women with gestational diabetes mellitus (Review)

Han S, Middleton P, Shepherd E, Van Ryswyk E, Crowther CA

High saturated fat results in increase in FFAs which prevent insulin signaling and cause Insulin Resistance—glycemic control may backfire when pregnant women replace carb calories with saturated fat

Diabetes Care
American Diabetes Association

Randomization to a Provided Higher-Complex-Carbohydrate Versus Conventional Diet in Gestational Diabetes Results in Similar Maternal 24-Hour Glycemia and Newborn Adiposity

Teri L. Hernandez, Sarah S. Farabi, Bailey K. Fosdick, Nicole Hirsch, Emily Z. Dunn, Kristy Rolloff, John P. Corbett, Elizabeth Haugen, Tyson Marden, Janine Higgins, Jacob E. Friedman, and Linda A. Barbour

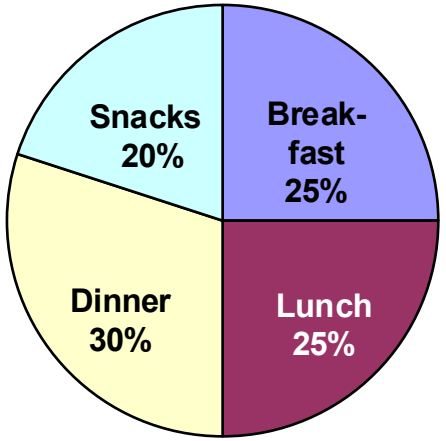
Diabetes Care 2023;46(11):1–10 | https://doi.org/10.2337/dc23-0617

Lower % Carbs-Not Low Absolute Carbs (25 kcal/kg) ALL Meals were Provided

- **CHOICE™ = Choosing Healthy Options In Carbohydrate Energy**
  - **60% carb, mostly complex**
  - **25% fat**
  - 15% protein
- **LC/CONV = Conventional Low Carbohydrate (adopted from Lois Jovanovic, Sansum)**
  - **40% carb**
  - **45% fat**
  - 15% protein
- Both diets
  - **Eucaloric**
  - SFA- 35-45%; MUFA- 35-45%; PUFA- 15-20%
  - **Simple Sugars: fixed at 70±5g in both diets**
  - **Carbs are 'complex:' low-moderate glycemic index**
  - Fiber is similar (~24g/day in LC, ~29g/day in CHOICE)

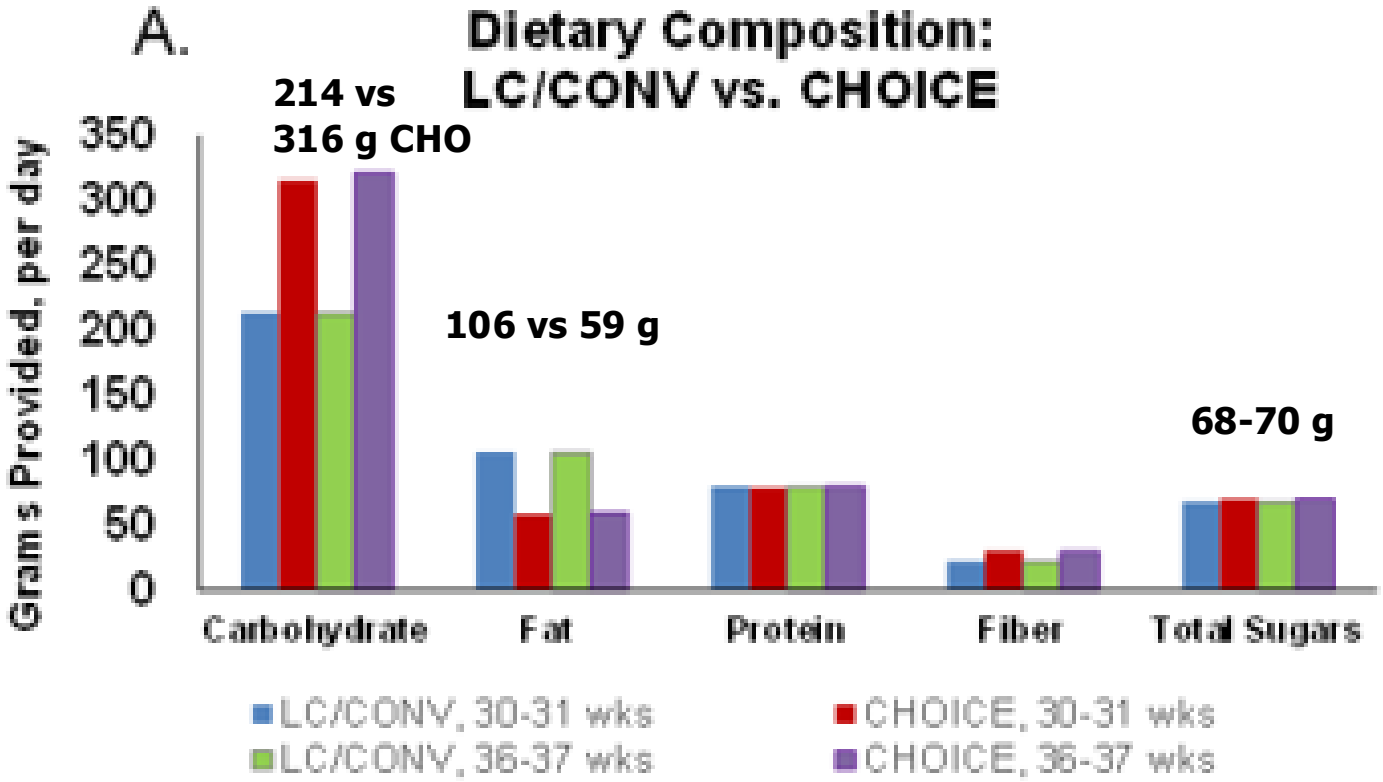
Food Preferences and Dislikes Solicited

Caloric Distribution



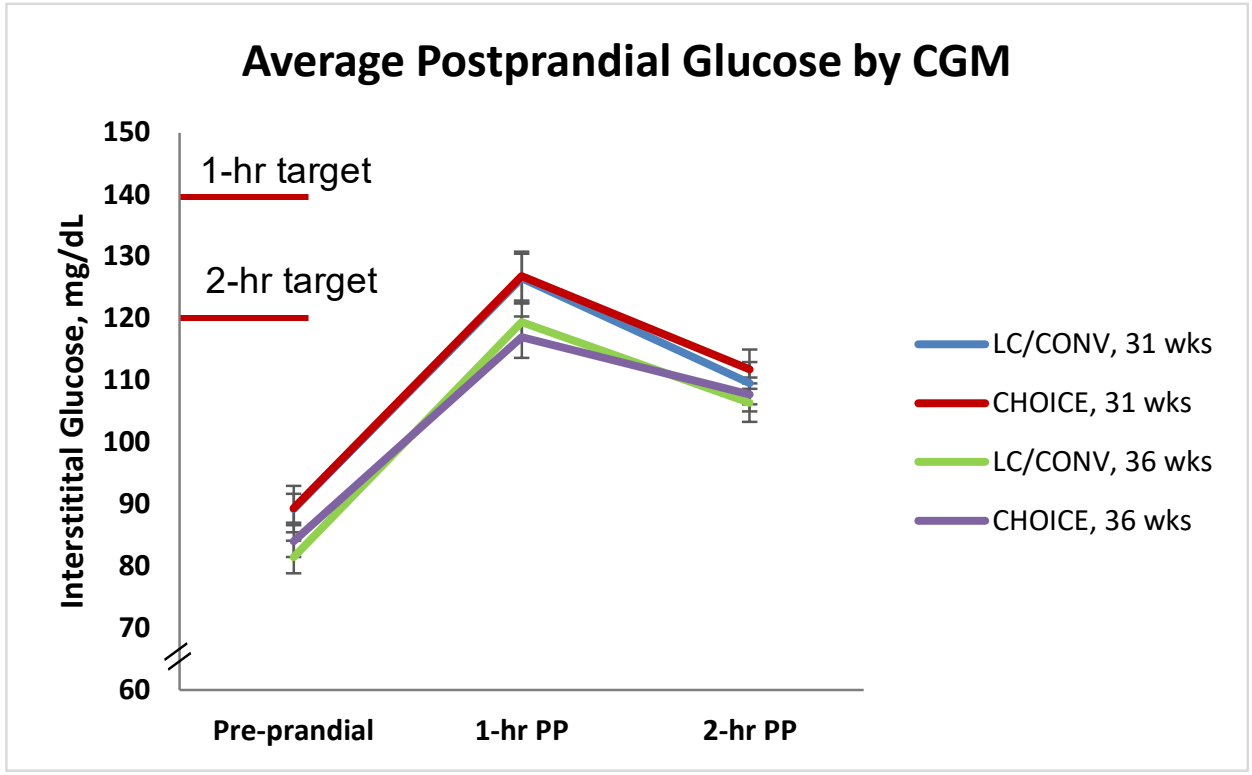
Subjects came to BioNutrition Kitchen every 3 days to pick up 9 meals Snack List provided

Carbs 316 vs 214 g; Fat 106 vs 59 g (n=59); Simple sugars the same BMI-matched, Eucaloric based on wt (2101 vs 2098 cal)



LC/CONV 40% total cal = 214 gm so NOT a Low Carb diet since based on BMI, not absolute carbs

Excellent Glycemic Control on Both Diets which Improved over Time Despite Increase in Insulin Resistance

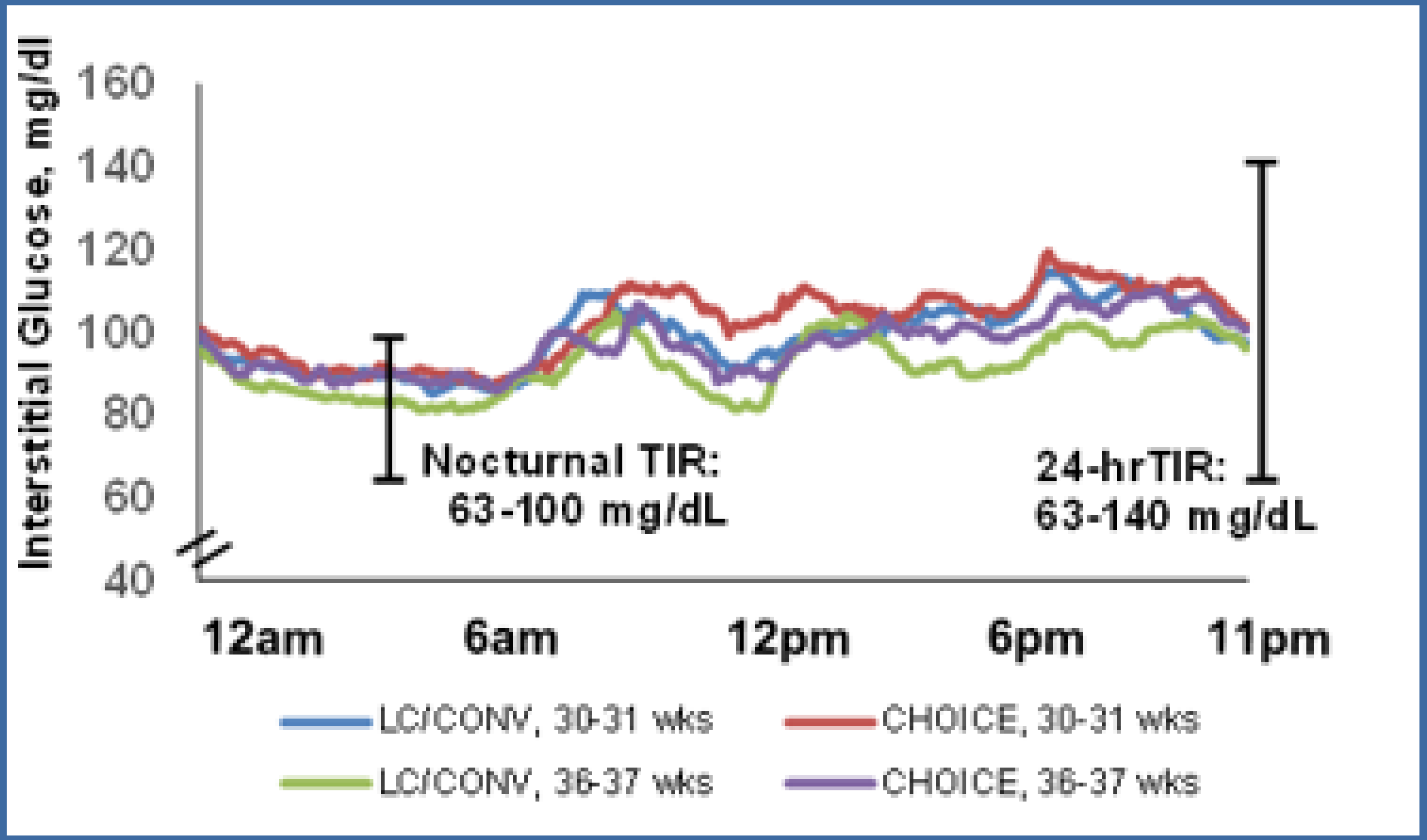


Mean ± SEM
All between-group comparisons
p>0.05

Within-group Comparisons	LC/CONV 30 wks	LC/CONV 37 wks	Choice 30 wks	Choice 36 wks
1-hr PP, mg/dL	127±4	119±3	124±5	*115±4
2-hr PP, mg/dL	106±4	106±3	108±4	106±3

*p=0.026

24-hour AUC Glucose No Different on Diets



However, Nocturnal AUC slightly lower on CONV

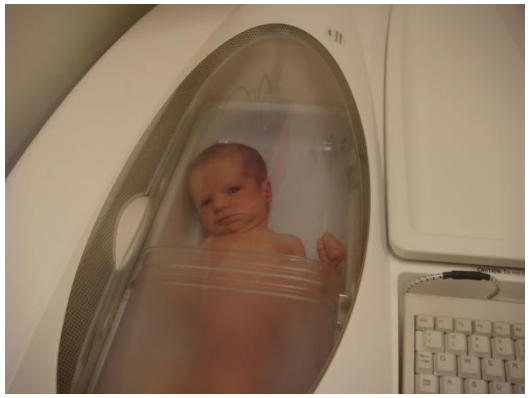
-One Diet May Not Fit All in A1GDM

-If calories are CONTROLLED, may be able to liberalize healthy carbs if fat is proportionally reduced

-Not applicable with A2GDM, T2DM, or T1DM where exogenous insulin is required

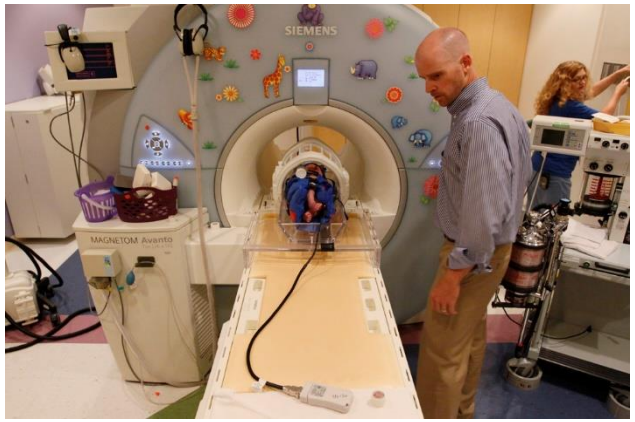
No Difference in Neonatal Adiposity

Conventional vs. CHOICE Diet



Neonatal Adiposity by PeaPod (Air Displacement) and MRI

- No difference in Cord Blood Insulin (Best biomarker of fetal exposure to Glu)
- Fasting and post-prandial (PP) TGs were strongly associated with neonatal liver lipid content at 31 wks by Newborn MRI



CAVEAT: 300 vs 200 grams of Carbs (complex) was tolerated due to CALORIES BEING FIXED, FOOD PROVIDED, SAT FAT BEING LIMITED, AND ONLY 2 KG WEIGHT GAIN ON DIET (Eucaloric)

RCT shows POTENTIAL FOR LIBERALIZATION OF COMPLEX CARBS IN GDM WOMEN CONTROLLED ON DIET ALONE who have ability to mount high insulin responses

DOES NOT APPLY TO TYPE 1 AND TYPE 2 WHO REQUIRE EXOGENOUS INSULIN TO COVER CARBS!!

Infant GOLD

What are the Options when Diet Fails?

And if I already have T2DM, can Metformin reduce my need for insulin?

Question: Should insulin v.s. metformin + insulin be used in pregnant individuals with pre-existing type 2 diabetes?

In GDM: **ADA and ACOG—Insulin is Preferred**

SMFM: Metformin is Safe and Reasonable first line alternative to insulin

Outcome	Direct Evidence	Indirect Evidence
LGA infants	Yes	Yes
SGA infants	Yes	Yes
NICU admission	Yes	Yes
Preeclampsia	Yes	Yes
Offspring overweight	No	Yes

Metformin Actions

Foretz M Nature Reviews Endocrinol 2019 15:569
Swenson KS, Wesolowski SR Diab 2023;72(9):1214
Carroll DT Trends Dev Biol 2021; 14:1-17

- Metformin directly crosses by OCT3 (Organic Cation Tx); No 1st pass liver metabolism; Fetal ≥Maternal Concentrated placenta/fetal mitochondria 1000X; OGT liver, pancreas, kidney, Skel muscle
- Met ↑AMPK and ↓mTOR –placenta nutrient sensor-nutrient restrict
- ↓Gluc prod, ↓ Cell Cycle prolif (anti-cancer effect)
- **Embryo/Placenta has few OCT3 transporters in 1st Trim so safe**

Viewpoint Obstet Gynecol. 2018 Aug;132(2):496-505 ajog.org

A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes

Linda A. Barbour, MD; Christina Scifres, MD; Amy M. Valent, DO; Jacob E. Friedman, PhD; Thomas A. Buchanan, MD; Donald Coustan, MD; Kjersti Aagaard, MD, PhD; Kent L. Thornburg, PhD; Patrick M. Catalano, MD; Henry L. Galan, MD; William W. Hay Jr, MD; Antonio E. Frias, MD; Kartik Shankar, PhD; Rebecca A. Simmons, MD; Robert G. Moses, MD; David A. Sacks, MD; Mary R. Loeken, PhD

Pleiotropic Effects acting on Multiple Tissues: Variety of Molecular Effects debated

Inhibits Mito Complex 1 Resp to activate AMPK→ ↓ cAMP→↓Gluconeogenesis (anti-cancer effect)

Activates AMP Kinase→↓mTOR → ↓ proliferation, ↑apoptosis and cell-cycle arrest (anti-cancer effect)

Changes gene expression: Activated AMP Kinase can phosphorylate epigenetic enzymes changing methylation, MicroRNAs

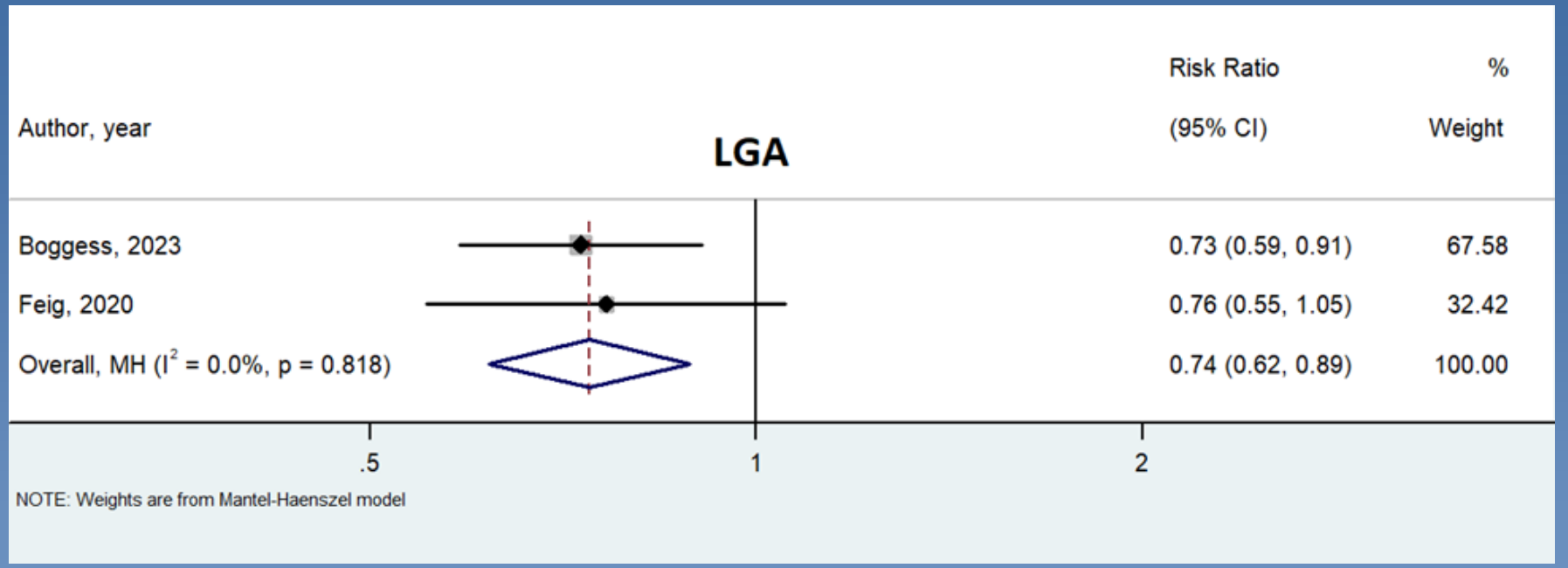
Microbiome Effects: ↓ Bile acid absorption; ↑ GLP-1, ↑ Gut utilization Gluc→↓ **Gluc when not absorbed: Metformin DR**

Decreases inflammation

Does not lower TGs unlike insulin or glyburide

Metformin: Direct Evidence

- In metanalysis, the RR of LGA was 0.74 [0.62-0.89] with high certainty of evidence (MiTy and MOMPOD)
- SGA, NICU, Offspring BW, and preeclampsia were not diff but SGA was higher in MiTy but not MOMPOD



Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo-controlled trial

No diff in 1° Outcome; ↓LGA but ↑SGA

Slight ↓ GWG ↓Insulin Dose

Denice S Feig, Lois E Donovan, Bernard Zinman, JJ Sanchez, Elizabeth Asztalos, Lanfona A Ryan, I G Fantus, Eileen Hutton, Anthony B Armson, Lorraine L Lipscombe, David Simmons, Jon F R Barrett, Paul J Karanicolas, Siobhan Tobin, H David McIntyre, Simon Yu Tian, George Tomlinson, and Kellie E Murphy, on behalf of the MiTy Collaborative Group*

Lancet Diabetes Endocrinol 2020; 8: 834-44

Summary

Background Although metformin is increasingly being used in women with type 2 diabetes during pregnancy, little data exist on the benefits and harms of metformin use on pregnancy outcomes in these women. We aimed to

JAMA | Original Investigation

Metformin Plus Insulin for Preexisting Diabetes or Gestational Diabetes in Early Pregnancy
The MOMPOD Randomized Clinical Trial

No diff in 1° Outcome; ↓LGA

No diff GWG or Ins Dose

Kim A. Boggess, MD; Arielle Valint, MS; Jerrie S. Refuerzo, MD; Noelia Zork, MD; Ashley N. Battarbee, MD, MSCR; Kacey Eichelberger, MD; Gladys A. Ramos, MD; Gayle Olson, MD; Celeste Durnwald, MD; Mark B. Landon, MD; Kjersti M. Aagaard, MD, PhD; Kedra Wallace, PhD; Christina Scifres, MD; Todd Rosen, MD; Wadia Mulla, MD; Amy Valent, DO; Sherri Longo, MD; Laura Young, MD, PhD; M. Alison Marquis, MStat; Sonia Thomas, DrPH; Ashley Britt, MS; Diane Berry, PhD

Long-Term (5-10 yrs) Offspring Exposed to Metformin vs Insulin (GDM) or Metformin vs Placebo (PCOS) May Have Higher Risk Overweight

Rowan JA, (MiG TOFU) *BMJ Open Diabetes Res Care 2018*
--Inc BMI in Auckland but not Adelaide children exposed in GDM

Engen LG (Preg Met) *Lancet Child & Adol Health March 2019*
--Inc BMI in children exposed in PCOS

Paavilainen E (Finland; 2RCTs GDM) *Diab Obes Metab 2022*
--No difference in BMI

Some but not all long-term data on 5-10 y.o. children suggest a higher risk of childhood overweight in those exposed in-utero (MiG and PCOS RCTs)

Too early to look at effect at 2 yrs (catch-up vs catch-down) in SGA and LGA infants; Males > Females

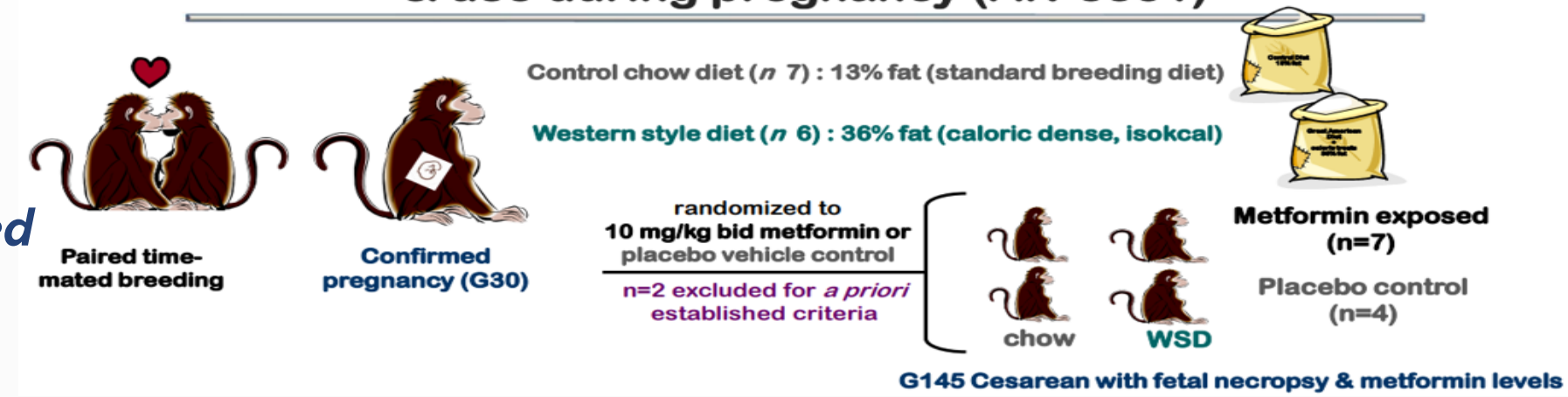
Growth Restriction in utero mismatched with overnutrition in infancy/childhood →→Obesity

What happens to fetuses when NHP moms with similar placentas are given metformin at doses achieved in humans? Not good….

Initiation of Metformin in Early Pregnancy Results in Fetal Bioaccumulation, Growth Restriction & Renal Dysmorphology in a Primate Model

Erin BOLTE, Ph.D., Tyler DEAN, BSc, Brandon GARCIA, BSc, Maxim D. SEFEROVIC, Ph.D., Kristin SAUTER, Ph.D., Gwendolynn HUMMEL, MSc, Matthew BUCHER, BSc, Feng Li, Ph.D., John HICKS, M.D., Ph.D., Xuan QIN, Ph.D., Melissa A. SUTER, Ph.D., Enrico R. BARROZO, Ph.D., Michael JOCHUM, Ph.D., Cynthia SHOPE, MS, Jacob E. FRIEDMAN, Ph.D., Maureen GANNON, Ph.D., Stephanie R. WESOLOWSKI, Ph.D., Carrie E. MCCURDY, Ph.D., Paul KIEVIT, Ph.D., Kjersti M. AAGAARD, M.D., Ph.D.

Novel Rhesus macaque model of maternal metformin initiation & use during pregnancy (AN-8851)



Am J Obstet Gyn Sept 2024; 231:e1-16

Key findings.

Among the n=11 G145 pregnancies with confirmed exposure to drug or vehicle and normal fetal necropsy, we observed significant metformin bioaccumulation in kidney, liver, gut, placenta, amniotic fluid, serum and urine of drug-exposed fetuses. Levels in fetal urine neared biomolar equivalence to maternal levels following initiation by G30. Bioaccumulation of metformin in the fetus was associated with growth restriction in liver, skeletal muscle, heart and retroperitoneal fat masses, driving lower fetal body weight. Sagittal sections of fetal kidneys demonstrated delayed maturation, with disorganized glomerular generations and increased cortical thickness.

R4- Metformin: Justification

Direct Data: Decreased LGA in insulin plus metformin (RR, 0.74 [0.62–0.89]) SGA: RR, 1.43 [0.98–2.10]).

Indirect Data:

•Fetal Metformin = maternal in 2nd, 3rd (minimal 1st); concentrated in fetal mitochondria 1000-fold; decreases cell cycle proliferation (Inc in SGA in MiTY)

• Some offspring exposed in GDM and PCOS pregnancies have a higher risk of overweight at 5 to 10 yrs. Adverse impact on skeletal muscle, growth, and kidney development NH primates

- Panel judged benefit of adding metformin to decrease LGA did not, **on average**, outweigh potential harm of increasing SGA or adverse childhood body composition. Metformin usually ineffective alone.
- Conditional Rec requiring clinical judgement. Metformin **may be useful** when insulin is not affordable, safe to use, or if substantial benefit shown (less wt gain, much lower insulin needs).
- Other populations in which **metformin should be avoided are** those at high risk for SGA due to hypertension, renal disease, and placental insufficiency
- In pregnant individuals with pre-existing diabetes already on insulin, we suggest against routine addition of metformin. (2 | ⨁OOO)

If Metformin is not going to save moms from insulin injections, what about Inhaled Insulin in GDM?

Received: 29 January 2025 | Revised: 28 May 2025 | Accepted: 18 June 2025

DOI: 10.1002/pmf2.70065

PREGNANCY

BRIEF REPORT

Inhaled insulin in pregnancy: A case series supporting feasibility and clinical potential for pregnant people with diabetes

Michaela C. Rickert[1] | Linda A. Barbour[2] | Bruce W. Bode[3] | Amy Wehbe[4] | Ernest O. Asamoah[5] | Benito Lopez[6] | Amy M. Valent[1]

Inhaled Technosphere Insulin (TI) Compared With Rapid-acting Analog Insulin (RAA) In Gestational Diabetes (GDM): Preliminary data submitted to ADA 2026

Author Block: AMY VALENT, ROY W. BECK, CELESTE DURNWALD, CAROL LEVY, KRISTIN CASTORINO, GRENYE O'MALLEY, IRL HIRSCH, DONLA Y. GYALNUB, CAMILLA M. LEVISTER, KATRINA C. RUEDY, LAUREN KANAPKA, LYNN BARBOUR, *Portland, OR, Tampa, FL, Philadelphia, PA, Santa Barbara, CA, Seattle, WA, New York, NY, Denver, CO* *Also Claire Ingram, Jocelyn Phipers*

If Not Metformin, Afrezza for GDM? 5-Site RCT Crossover Breakfast Pilot

Inclusion: Humalog or Novolog <20 U at Breakfast (Afrezza 2:1 with 4-8 unit cartridges)

CTRC: Glucometer testing q 15 mins X1 hr then q 30 mins for 2 hrs while wearing CGM

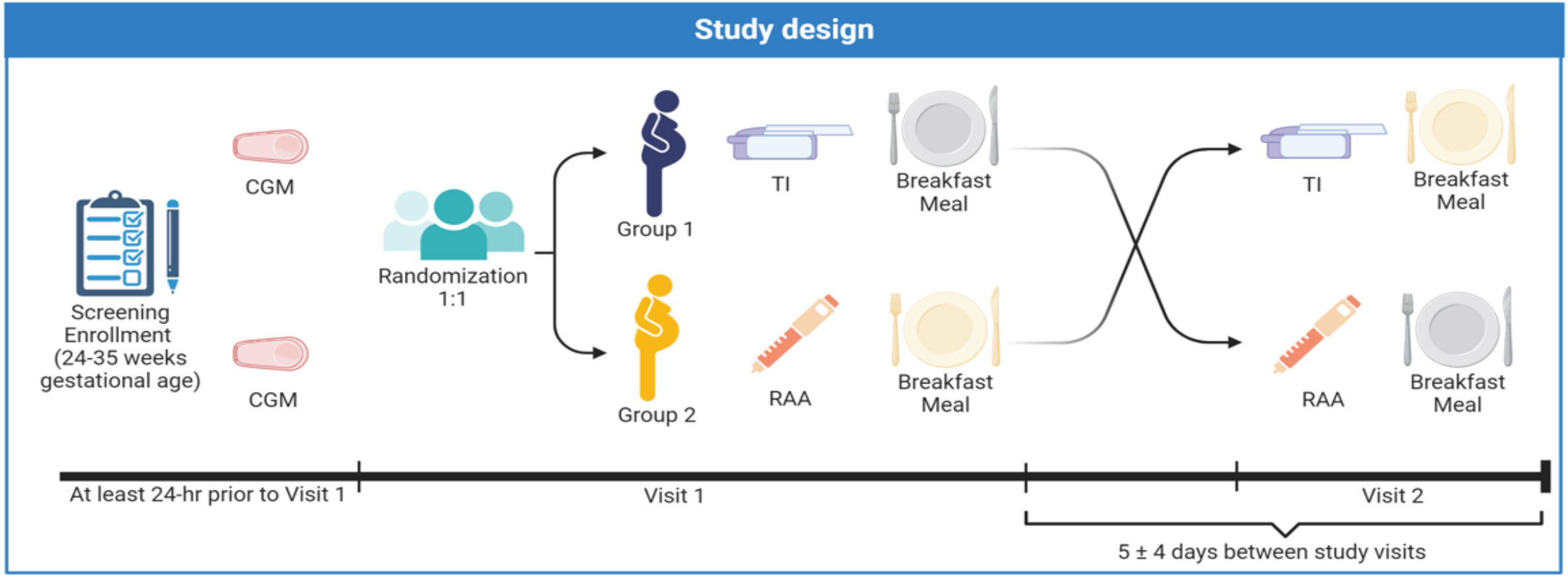


Figure 1. Potential participants will be screened and enrolled after informed consent. A blinded CGM will be placed after informed consent is signed at least 24 hours prior to Visit 1. Participants will be randomized 1:1 at Visit 1 to start with TI vs. home RAA (referent) medication for the meal challenge intervention. Visit 2 will occur within 5 ± 4 days of Visit 1 and participants will crossover their intervention. Study duration is from enrollment to end of Visit 2. CGM: continuous glucose monitor; TI: inhaled Technosphere Insulin; RAA: rapid acting insulin analog.

Valent (OHSU); Barbour, Ingram, Phipers (CU AMC); Durnwald (Penn); Levy (Mount Sanai); Castorino (Sansum)

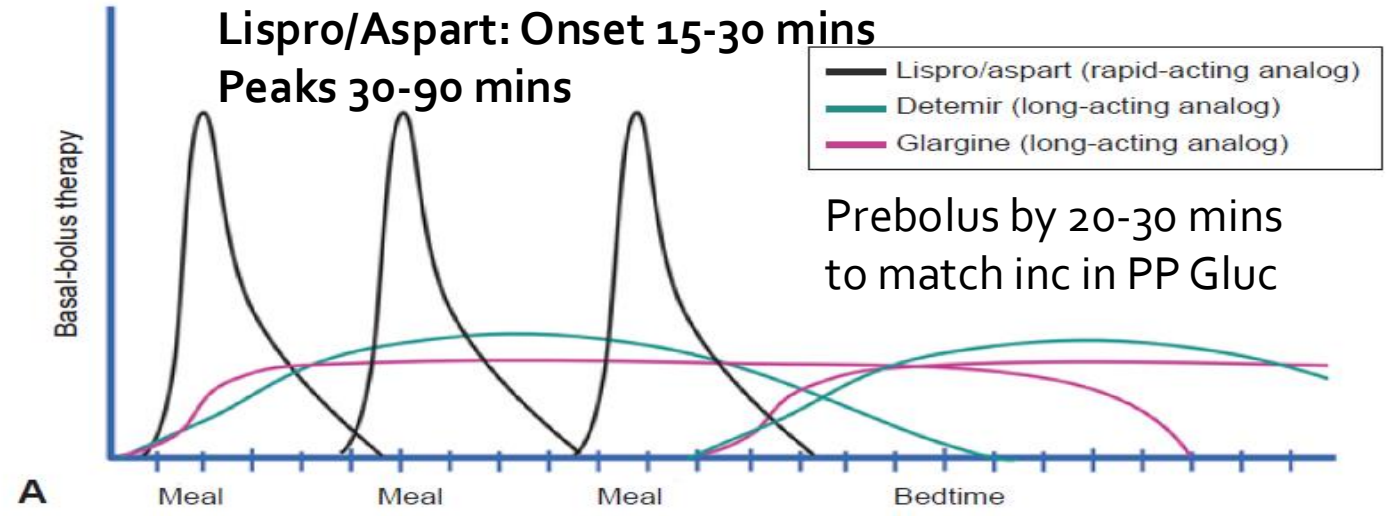
Clinical Expert Series CME

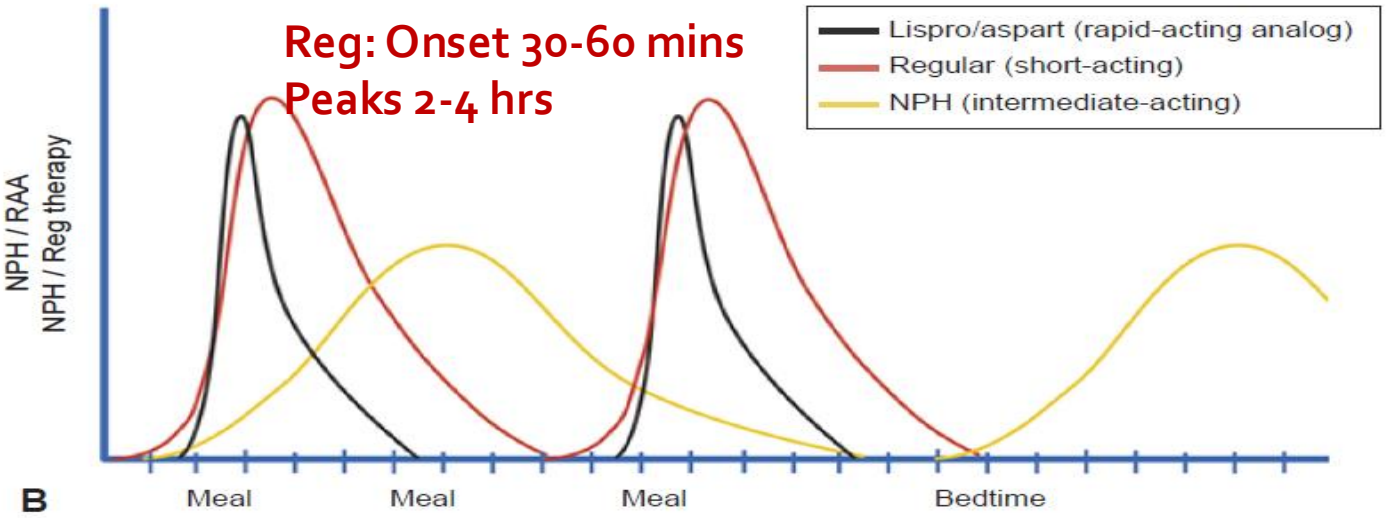
Insulin Management for Gestational and Type 2 Diabetes in Pregnancy

Amy M. Valent, DO, MCR, and Linda A. Barbour, MD, MSPH

Boster Gynecol 2024, Nov 1;144(5):633-647.

And When We Are Stuck Using Insulin, How Can we Optimize Effectiveness??





-Newer insulins have more flexibility to accommodate different lifestyles, schedules, erratic eating behaviors

-Empower by up-titration self-management

-Give bolus according to variable carb intake

-Correction factor if necessary

Basal-bolus regimen: Fasting and PP hyperglycemia with variable sleep schedule and/or variable mealtimes
E.g. 90 kg patient 3rd trimester

90 kg X 0.7 = 63 units TDD

- 40% of TDD as basal insulin (glargine) = 25 Units (can give as single or divided dose every 12 hrs.)
- 60% of TDD as bolus (RAA)= 38 Units divided in breakfast, lunch & dinner (13 Units) or according to size of meal (e.g. 12 Units breakfast; 10 Units lunch; 16 Units dinner)

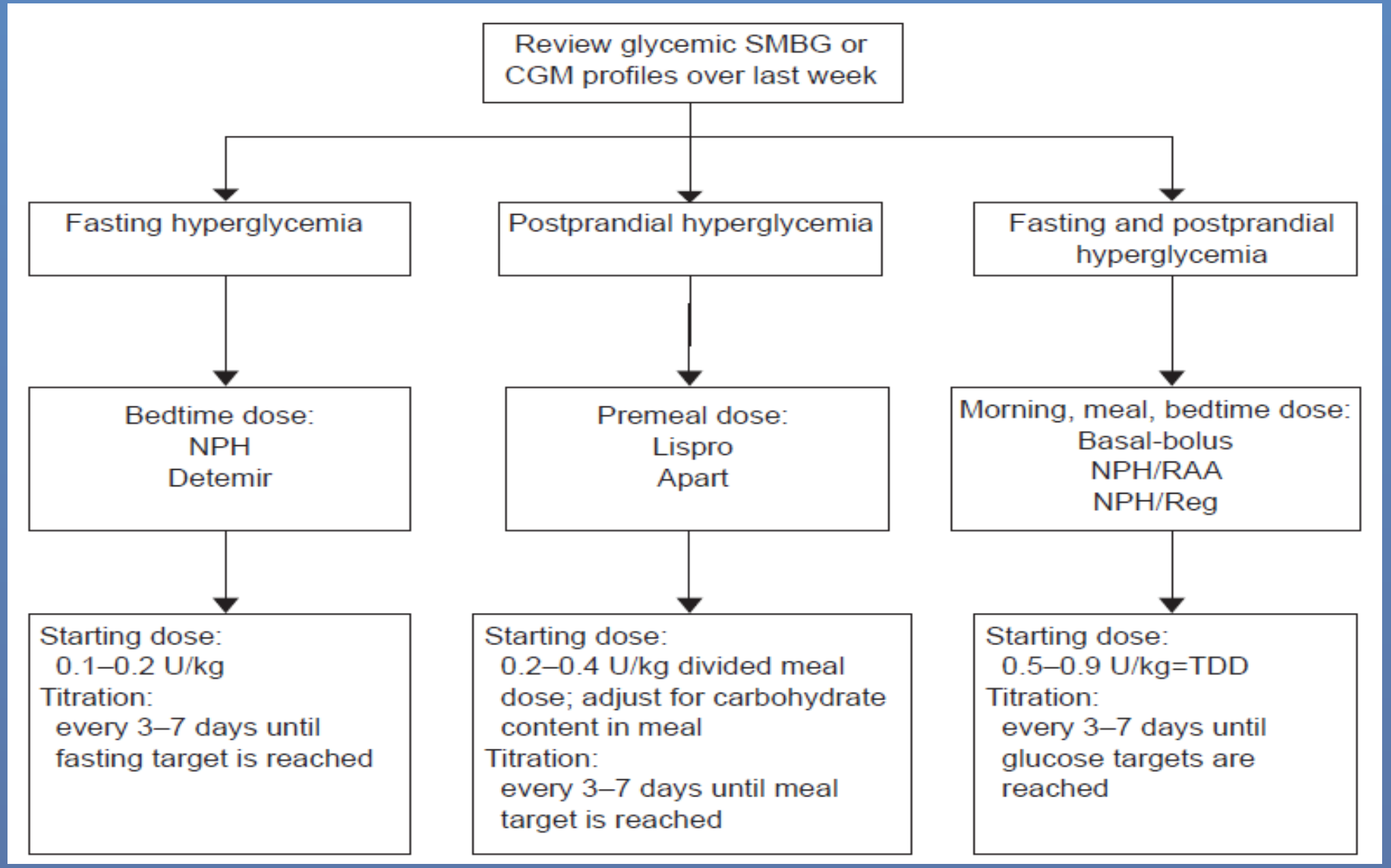
It's all in the Hx and Individual Gluc Profile; Universal Dosing by U/kg Unlikely to Work Well

Table 2. Key Questions to Consider When Using Insulin Therapy

Key Questions	Possible Insulin Solutions
Does the patient have predominant fasting hyperglycemia without eating in the middle of the night?	NPH at bedtime
Does the patient have significant fasting hyperglycemia with intermittent postprandial hyperglycemia after larger meals?	NPH before bedtime; rapid-acting insulin analogs before largest meals
Does the patient have fasting and postprandial hyperglycemia, but the cost of insulin is limiting access?	Morning and bedtime NPH along with regular insulin administered 60 min before breakfast and dinner may be an option. Patients must be instructed on the importance of consistent meal timing and carbohydrate quantity with meals.
Does the patient have postprandial hyperglycemia, but meals have variable timing and carbohydrate content?	Rapid-acting insulin analogs 15–20 min before each meal with a range for smaller- vs higher-carbohydrate meals
Does the patient have variable daytime and nighttime schedules (ie, eating, sleeping, work)?	Long-acting basal insulin once a day or in divided doses (every 12 h) with rapid-acting insulin analogs before meals
Does the patient exercise irregularly or have variable intensities of physical activity?	Encourage patients to time exercise before or after a meal; consider decreasing rapid-acting insulin analogs before a meal in close proximity to exercise
Is the patient struggling with nausea and vomiting?	Provide medications to improve nausea and vomiting or workup for other causes. Consider taking half of the rapid-acting insulin analogs dose 15–20 min before eating to determine whether entire meal can be consumed and bolus remainder just at the start of the meal
Does the patient want more autonomy for self-management and ownership of their diabetes care?	Long-acting basal insulin at 40–50% of TDD with rapid-acting insulin analogs using an ICR or ICF
Is the patient skipping or missing insulin doses?	Inquire about the reasons for missing or skipping doses to determine whether insulin regimen needs to be altered. Insulin pens do not require refrigeration (ie, can be taken to work or when running errands).
Does the patient continue to have significant postprandial hyperglycemia despite uptitration of rapid-acting insulin analogs?	Inquire about timing of administration before meals. With advancing gestation and increasing insulin resistance, the insulin absorption with higher doses can be more delayed, and patients may need to administer rapid-acting insulin analogs 15–45 min before meals to have the same peak effect.

NPH, neutral protamine Hagedorn; TDD, total daily dose; ICR, insulin/carbohydrate ratio; ICF, insulin correction factor.

Personalized Approach to Optimal Treatment



Rarely start TDD more than 0.6 U/kg; for a 100 kg mom, that is already 60 units!! Focus Diet-eating up to insulin dose is not good!

Juggling the Benefits and Risks of Treatments Without Consensus

- **CGMs:** Clearly a benefit in T1DM—unclear T2DM and GDM; lack of RCTs showing better pregnancy outcomes. Intensive resources/training—many trials ongoing.
- **GDM Diet:** May be able to liberalize high quality, complex carbs if calories eucaloric in A1GDM, NOT in A2GDM, T1 or T2DM. Low carb diets (<100 g) of unproven safety, ketogenic; placenta/fetal brain require ~70 g 3rd trim
- **Metformin not so fast**—at least not in T2DM. Possible dec in skeletal mass, SGA, and long-term offspring consequences in GDM/PCOS and Primate Models
- **GLP-1RAs (not discussed):** Unlikely to cross; need more safety data. Potential benefits to ↓ preeclampsia and prevent excess GWG; need data continuing them at lowest dose… Semaglutide no detectable in breast milk *Nutrients 2024 (16):2886*
- **Afrezza as a substitute for prandial injectable insulin** (or metformin) in GDM requiring modest insulin? We will see!
- **Insulin Management:** Focus on which insulin the patient actually needs to match insulin dose with glycemic excursion; rarely is long duration of Reg useful
- **Enormous need for more DM providers in OB-Gyn** (40% women child bearing age with prediabetes and 2-5% with DM)!!!

Questions???