Département femme-mère-enfant

UNIL | Université de Lausanne

DIABETES AND PREGNANCY

POST ADA

Sybille Schenk – dietitian

Pr. Jardena Puder

31.08.2023

Interdisciplinary GDM Group Lausanne

Clinical care and research for mother and infant

AGENDA

- Breastfeeding
- Hypertension
- Metformin
- Nutrition – Low-carb : go/no go ?
- Glucose control, fetal insulin, growth, non-insulin-mediated factors and TG
- Tools & Algorithm (HCL)

BREASTFEEDING

LACTATION AND MATERNAL CVD RISK

Data from 8 Studies – 1.2 Million Parous Women (mean Age 51 y at entry) Pooled	10 Year Follow Up			
Breastfeeding	**CVD**	**CHD**	**Stroke**	**Fatal CVD**
HRs for Ever vs Never	0.89 (0.83, 0.95)	0.86 (0.78, 0.95)	0.88 (0.79-0.99)	0.83 (076-0.92)

Covariates: Demographics, CVD risk factors, Reproductive Lifestyle, SES, BMI),
Unknown APOs, At Baseline: self-report no CVD diagnosis or hospitalization in previous 6 years;
Average breastfeeding lifetime 15.6 mos

No studies accounted for a history of adverse pregnancy outcomes (APOs).

➔ Modest protective association for lactation and later life CVD may be overestimated.

Tschiderer L et al. J AM Heart Assoc

BREASTFEEDING – APO

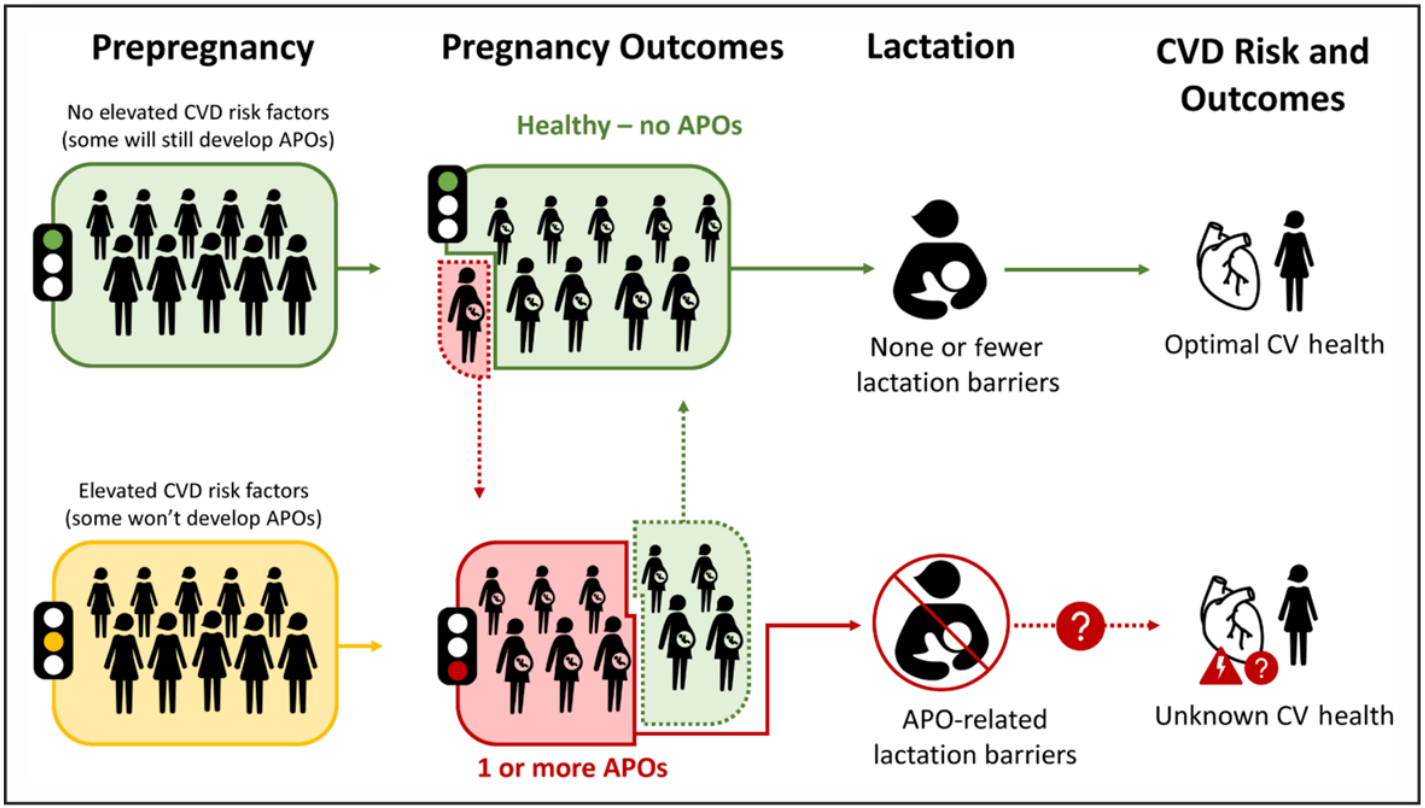


Figure. Prepregnancy risk profiles and adverse pregnancy outcomes could interfere with lactation: the missing reproductive links to future cardiovascular health.
APO indicates adverse pregnancy outcomes; CV, cardiovascular; and CVD, cardiovascular disease.

Lane A, Lewis C and Gunderson E. J AM Heart

HYPERTENSION

HYPERTENSION NOMENCLATURE AND GUIDELINES

Guideline	Blood pressure, mm Hg				
	<120/80	120-129/<80	130-139/80-89	≥140/90	≥160/110
2019 American College of Obstetricians and Gynecologists	Normal			<20 weeks, mild chronic hypertension	**<20 weeks, severe chronic hypertension[a]**
2003 Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure	Normal	Pre-hypertension	**Pre-hypertension[b]**	**Stage 1 hypertension[a]**	**Stage 2 hypertension[a]**
2017 American College of Cardiology and American Heart Association	Normal	Elevated blood pressure	**Stage 1 hypertension[a]**	**Stage 2 hypertension[a]**	

Adapted from Sinkey RG, Oparil S. Lower blood pressure thresholds raise the bar in pregnancy. Circ Res 2019;125(2):195-7.
[a]Pharmacologic treatment recommended [b]Pharmacologic treatment only recommended if comorbid diabetes or renal disease

Battarbee, *AJOG*, 2020.
Sinkey, *Circ Res*, 2019.

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

Society for Maternal-Fetal Medicine Statement: Antihypertensive therapy for mild chronic hypertension in pregnancy The Chronic Hypertension and Pregnancy trial

Society for Maternal-Fetal Medicine; Publications Committee

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

- SMFM and ACOG recommend treatment with antihypertensive therapy for mild chronic hypertension in pregnancy to a goal blood pressure of <140/90 mm Hg
- Pregnant individuals with treated chronic hypertension should continue established antihypertensive therapy during pregnancy
- CHAP: The results support recommending pharmacologic treatment for mild chronic hypertension to a BP goal of <140/90 mm Hg, including continuing established antihypertensive therapy

Tita et al. NEJM 2022

METFORMIN

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

Denice S Feig, Lois E Donovan, Bernard Zinman, J J Sanchez, Elizabeth Asztalos, Edmond 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*

No difference in adverse neonatal composite outcome

We found several maternal and neonatal benefits in women using metformin:

- Reduced maternal weight gain
- Reduced insulin dose by 45 units per day! (105 units/day vs 155 units/day)
- Improved glycemic control (HbA1c 5.9% vs 6.1%)
- Reduced c-section rate (53% vs 63%)
- Reduced birthweight (218g), Extreme LGA (>97th centile), >4,000g
- Lower adiposity measures: SSF, fetal fat mass, abdo circumference

But also found increased SGA (12.9 vs 6.6%)

Normal SGA rate 10%!

Feig et al. Lancet DE 2020

Patients with Type 2 Diabetes Should NOT Take Metformin During Pregnancy

1. Metformin may cause HARM (SGA, childhood obesity, maternal side effects)
2. Metformin provides LIMITED or NO benefits to mom and baby
3. INSULIN is a safe and effective alternative (85% need insulin regardless)

Limited benefits do NOT outweigh risks

BALANCING REBUTTAL

Is it worth it?

FOR Metformin

1. Less maternal weight gain (2kg)
2. Less maternal insulin (40U)
3. Improved HbA1c (0.2% or 2mmol/mol)
4. ?Fewer cesarean deliveries
5. Smaller birthweight (200g)
6. ?Less LGA
7. Less adiposity at birth

AGAINST Metformin

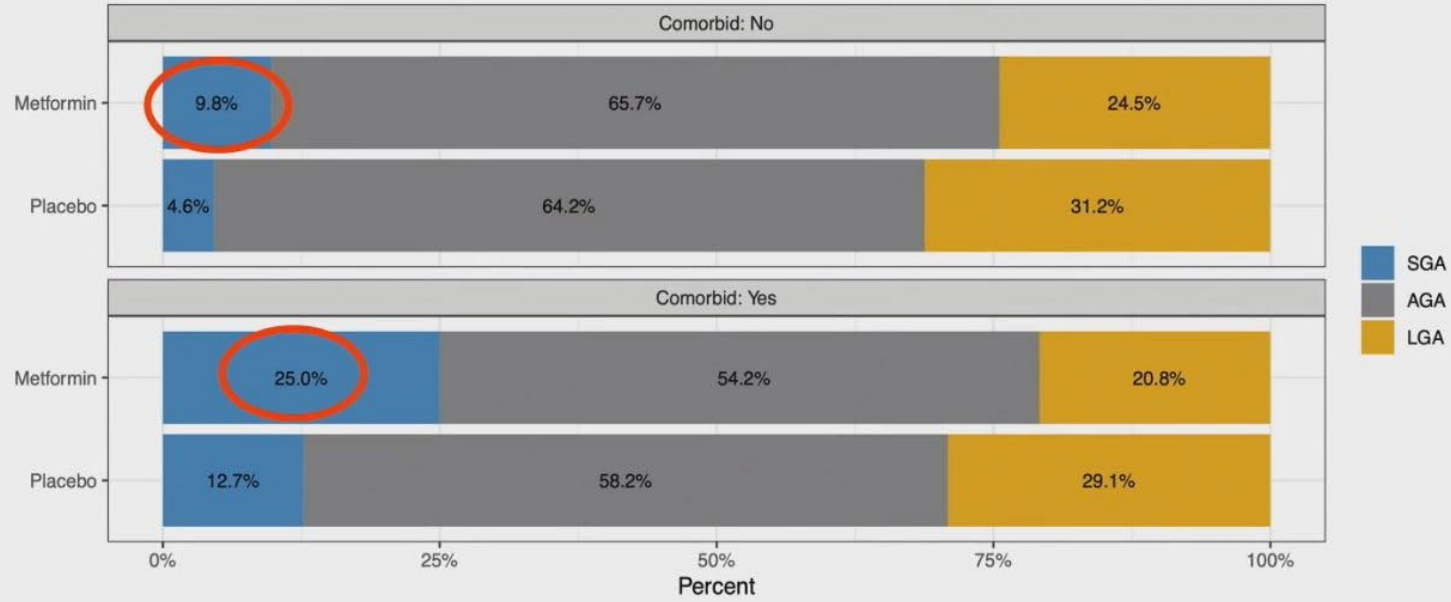
1. More SGA at birth
2. No difference in BMI or adiposity at 2yo
3. Higher fasting glucose at 2yo
4. ?More adiposity in childhood
5. No difference in neonatal morbidity (pregnancy loss, preterm birth, birth injury, RDS, hypoglycemia, hyperbilirubinemia, LGA, SGA, LBW, NICU admission)
6. No difference in preeclampsia
7. GI side effects
8. Burden of another medication
9. More episodes of maternal hypoglycemia

BALANCING REBUTTAL: WHEN TO BE VERY CAREFUL

Determinants of Small for Gestational Age in Women With Type 2 Diabetes in Pregnancy: Who Should Receive Metformin?

https://doi.org/10.2337/dc22-0013

Denice S. Feig,[1–3] Bernard Zinman,[1–3] Elizabeth Asztalos,[4] 6Lois E. Donovan,[4,7] Prakesh S. Shah,[5,6] J. Johanna Sanchez,[4,5] George Tomlinson,[1,3] and Kellie E. Murphy,[1–3,10] on behalf of the MiTy Collaborative Group*



Feig et al. Diabetes Care 2022

NUTRITION – LOW-CARB?

LOW-CARB : GO/NO GO ?

Pregnancy nutritional recommendations

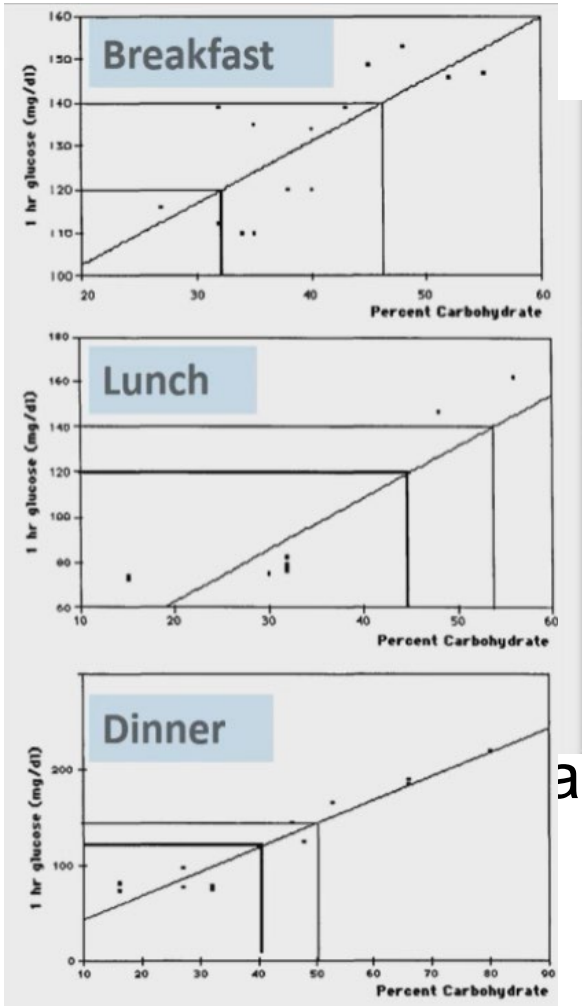
	Carbohydrate	Fiber	Total Fat	Protein
Pregnant (IOM 2005)	175g*	28g	'Not Determined'	71g*
Pregnant (USDA 2020-2025)	175g*	25-34g (increase by trimester)	20-35 (%kcal)**	71g*
Non-Pregnant	130g	25g	'Not Determined'	45g
% of total calories	45-65%		20-35%	10-35%
Low CHO Very Low CHO	<130g (<26%) 20-50g (<10%)	--	55-60 (%kcal) 70-90 (%kcal)	0.8-1.5g/kg IBW)

*RDA = recommended dietary allowance; **Acceptable Macronutrient Distribution Range; IBW = ideal body weight; CHO = carbohydrates

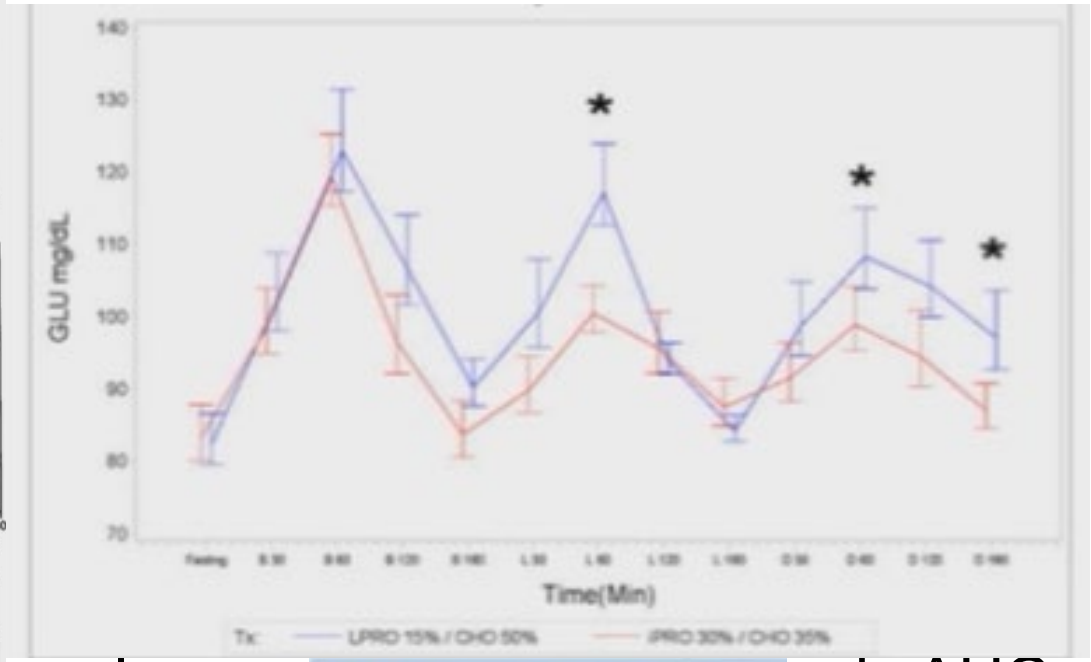
Otten JJ, IOM 2006
Valent AM, Oral presentation

LOW-CARB

Low CHO	<130g (<26%)
Very Low CHO	20-50g (<10%)



Small studies



ans lower p emic AUC

15% Pro/ CHO 50%

30% Pro/ CHO 35%

Pro

Contra

Landon MB, N Engl J Med 2009 Trout KK, Womens Health Rep 2022.
Crowther CA, N Engl J Med 2005 Mijatovic J, AJCN 2020

LOW-CARB

Low CHO	<130g (<26%)
Very Low CHO	20-50g (<10%)

- *« Ketones are harmful for fetal development »* theoretically and biologically makes sense but there is only a trend, hard to see a correlation or a difference.

GDM

n=75 CHO 55% 203-237g

n=75 CHO 40% 177-187g

	Control group		Low-CHO diet group		
	n	Value	*n*	Value	*P* value
Gestational age at delivery (weeks)	75	38.9 ± 1.8	75	39.0 ± 2.1	0.37
Insulin treatment, *n* (%)	75	41 (54.7)	75	41 (54.7)	1
Final insulin dose/kg body weight (units)	41	0.28 ± 0.19	41	0.24 ± 0.15	0.44
Maternal weight gain (kg)	72	2.3 ± 2.3	73	1.4 ± 2.0	0.017
Ketonuria (%)	68		70		0.837
Moderate or high, *n* (%)		14 (20.6)		16 (22.9)	
Absent or mild, *n* (%)		54 (79.4)		54 (77.1)	
Maternal hypertension, *n* (%)	75	10 (13.3)	75	4 (5.3)	0.16
Cesarean sections, *n* (%)	75	20 (26.7)	74	25 (33.8)	0.38
SGA, *n* (%)	75	12 (16.0)	74	8 (10.8)	0.47
LGA, *n* (%)	75	6 (8.0)	74	3 (4.1)	0.49
Macrosomia, *n* (%)	75	5 (6.7)	74	1 (1.4)	0.21
Newborn hypoglycemia, *n* (%)	75	10 (13.2)	74	9 (12.2)	1

Moreno-Castilla, Diabetes Care 2015

LOW-CARB

Low CHO	<130g (<26%)
Very Low CHO	20-50g (<10%)

	CHO 135g (165±7g) 20% compliant 71% baseline <175g		CHO 180-200g (190±9g) 65% compliant 57% baseline <175g		
Infant outcomes					
Sex	23		19		0.98†
Male, *n* (%)	23	12 (52.2)	19	11 (57.9)	
Female, *n* (%)	23	11 (47.8)	19	8 (42.1)	
Birthweight, g	24	3125 ± 101	20	3278 ± 79	0.25
Within vs. outside normal range	24		20		0.41†
SGA, *n* (%)	24	6 (25.0)	20	3 (14.3)	0.25†
LGA, *n* (%)	24	0 (0)	20	1 (4.8)	0.28†
Macrosomia, *n* (%)	24	1 (4.2)	20	1 (4.8)	0.55†
Fat mass, %	7	7.2 ± 2.2	8	10.1 ± 1.0	0.23
Fat-free mass, %	7	92.8 ± 2.2	8	89.9 ± 1.0	0.23
Length (cm)	16	47.9 ± 0.7	10	49.2 ± 0.4	0.20
Head circumference (HC) (cm)	22	33.9 ± 0.3	17	34.9 ± 0.3	<0.05
HC percentiles[1]	22	43.7 ± 7.2	17	66.2 ± 7.2	0.08

- Primary outcome = 0.04 mmol/L difference in urine ketones (power n=50)
- **GDM Diagnosis ~20 weeks but intervention ~28 weeks gestation (6wk)**
- No difference in macronutrient intake within or between groups (38% CHO; 21% protein; 37% fat)
- No differences in A1C, fasting glucose, postprandial glucose, insulin use

OHSU

Mijatovic J, AJCN 2020

LOW-CARB

Low CHO	<130g (<26%)
Very Low CHO	20-50g (<10%)

There is no role for reduced-carbohydrate meal plans in the treatment of GDM – Hernandez T, Oral presentation

- Multiple definitions of low-carb (grams/day, %CHO...)
- In 2005 the theoritical ≥175g reco ➔ maternal and fetal brain glucose requirements
- Low-carb = not inferior, not superior. Any dietary modification (high carb, DASH diet, calorie restriction, high fiber/low GI) after GDM resulted in improved maternal glucose, lower birthweight…
- Compliance is a challenge, methods to assess are limited…Inadequate power because small studies…
- BMI inconsistently reported, GWG during the diet exposure not reported, no blinding possible

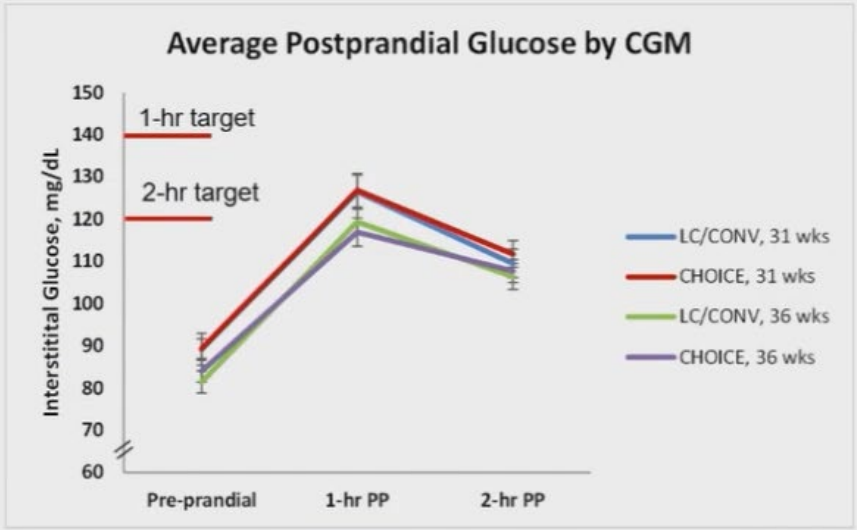
Yamamoto JM, Diabetes Care 2018
Han S, Cochrane 2017

Low CHO	<130g (<26%)
Very Low CHO	20-50g (<10%)

LOW-CARB

Conventional: 40% CHO, 45% Fat, 15% Pro
CHOICE: 60% CHO, 25% Fat, 15% Pro

Excellent Glycemic Control on Both Diets which Improved over Time



40% CHO-45% Fat (214g/d) vs. 60% CHO-25% fat (316g/d)

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

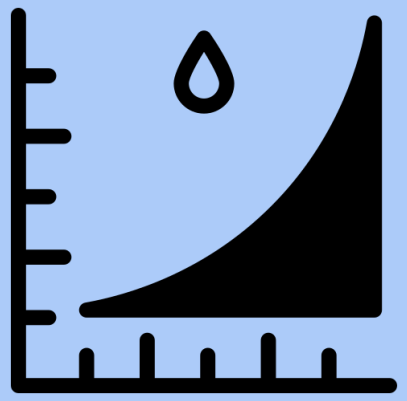
R01 DK101659, under review

LOW-CARB – TAKE HOME MESSAGE

- Reduction of simple sugars.
- Be flexible in complex carb content (ketones).
- Quality of, fats, proteins…
- Fibers

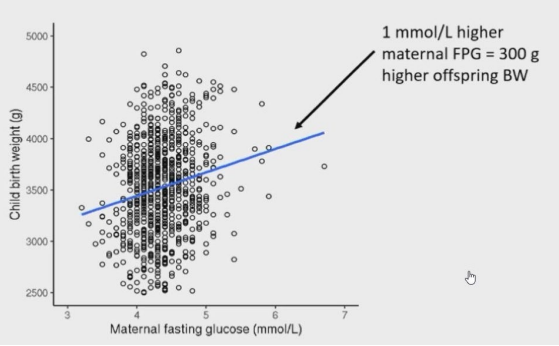
➔ It's not all sugar…

GLUCOSE CONTROL, FETAL INSULIN, GROWTH, NON-INSULIN-MEDIATED FACTORS AND TG



GLUCOSE CONTROL, FETAL INSULIN & WEIGHT

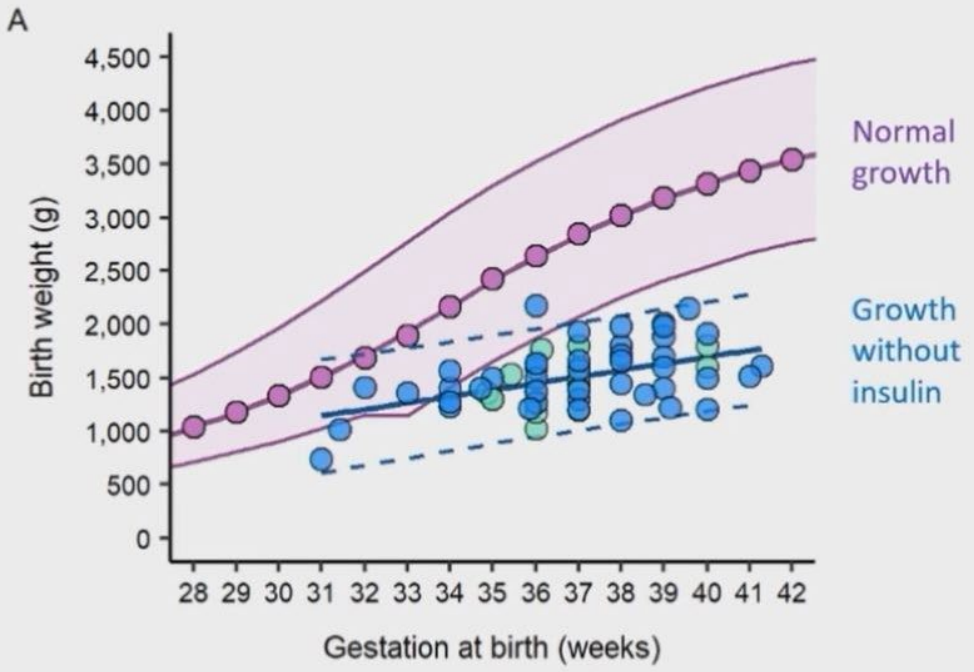
- Maternal glucose is the primary regulator of fetal insulin
- Fetal insulin – influences 50% growth (adipose)
- Non-insulin-mediated components of fetal growth are similarly important



Hughes AE, JCI

GLUCOSE CONTROL, FETAL INSULIN & WEIGHT

Fetal insulin accounts for half of birth weight by term gestation in humans



Hughes AE, JCI

NON-INSULIN-MEDIATED AND TG ORAL PRESENTATION

& late (30 wks GA)

- **Early pregnancy triglyceride levels (not HbA1c) have independent effect on birth weight and LGA**
- **Small proportion of this is mediated by glucose below the threshold of diagnosis of GDM**
- **Need strategies to improve triglyceride levels**

Saravanan P, PRiDE study, oral presentation

PHYSIOLOGICAL GLYCEMIC CHANGES IN PREGNANCY

CHANGES IN MATERNAL GLUCOSE METABOLISM DURING PREGNANCY

	Change
Insulin sensitivity	Decreased
Fasting insulin	Increased
Insulin secretion	Increased
Fasting glucose	Decreased
Hepatic insulin sensitivity	Decreased
Hepatic glucose production	Increased

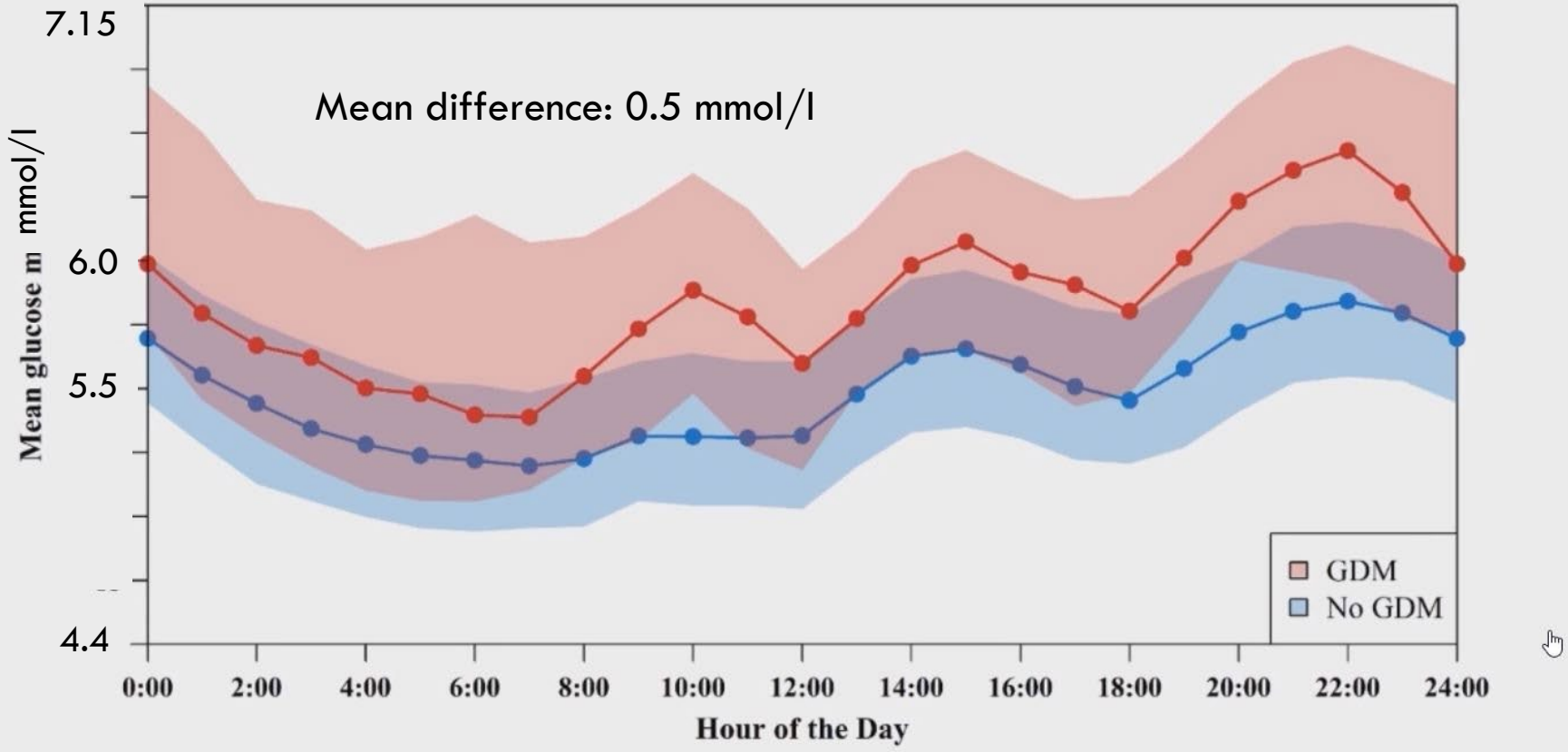
GLAM

Glucose Levels Across Maternity

Glycemic profiles of uncomplicated pregnancies, overall and by trimester

	Entire gestational period	1st trimester	2nd trimester	3rd trimester
Number of participants	413	118	413	355
Days with CGM readings Median	123	18	69	53
Mean glucose mmol/l Mean	5.39	5.66	5.39	5.39
Glucose Coefficient of Variation (%) Mean	19%	18%	19%	20%
% Time 3.5-6.7 mmol/l Mean	85%	83%	85%	84%
%Time 3.5-7.8 mmol/l Mean	94%	95%	95%	94%
%Time <3.5 mmol/l Median	1.8%	0.8%	1.5%	2.0%

MEAN GLUCOSE BY HOUR OF THE DAY AND GDM STATUS



Dots in the middle of shaded bands represent medians, shaded bands represent interquartile ranges. Only includes CGM data prior to OGTT test date.

Carlson A, Oral presentation

Metric	Gestational Weeks 18-22 and Weeks 32-34
Number of participants	157
Number of meals	3747
Mean fasting glucose	4.9 mmol/l
Mean glucose level prior to meal	5.05 mmol/l
Mean postprandial glucose level	
30 min after meal time	5.7 mmol/l
1 hour after meal time	6.0 mmol/l
2 hours after meal time	5.7 mmol/l
3 hours after meal time	5.4 mmol/l
Mean post-prandial peak	7.0 mmol/l
Mean glucose meal excursion	2.0 mmol/l
Median time to peak glucose	62 min

Carlson A, Oral presentation. Healthy controls

TOOLS & ALGORITHM (HCL)

TOOLS & ALGORITHM

For Pumps that are not Camaps (Camaps not in US)

Off-Label "Assisted" HCL Therapy in Pregnancy

Approach for "Assisted" HCL Therapy in Pregnancy:

- Use the lowest glucose target level/range for the system.
- Correct often for hyperglycemia
  - Bolus calculator
  - Provide glucose threshold

- Enter extra boluses (manual or "fake carbohydrates") when needed
  - Provide a range for manual boluses or "fake carb" input
  - Limit frequency to once every 2 hours

Mostly for Tandem
Avoid stalking, mark fakes

- Avoid over-correcting for hypoglycemia
  - Consume fewer carbohydrates given basal suspensions
  - Check blood glucose before treatment and re-treatment

Szmuilowicz E et al. DTT 2023
Sarit Polsky, Oral presentation

TOOLS & ALGORITHM

- Avoid prolonged basal insulin suspensions by adjusting pump settings

- Proper nutrition and bolusing techniques
  - Recommend carbohydrate consumption per guidelines
  - Split high-fat/high-carbohydrate meal boluses
  - Change pre-meal bolus timing per stage of pregnancy

Trimester	Pre-Meal Bolus Timing
First	15 ± 10 minutes
Second	30 ± 12 minutes
Third	45 ± 15 minutes

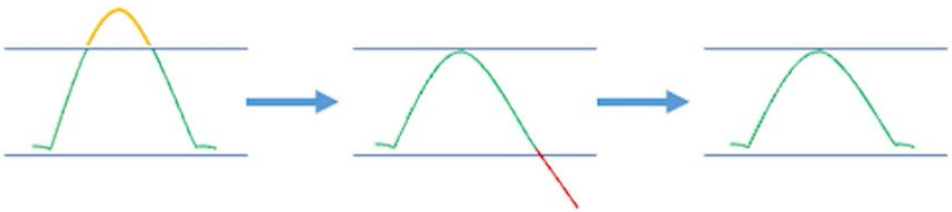
Hypo corrections: 4-8 g /carbs

Szmuilowicz E et al. DTT 2023

TOOLS & ALGORITHM

Especially Tandem Control-IQ

- Adjust pump settings to "super bolus" around meal times[1,2]
  - Carbohydrate-to-insulin ratio adjustments frequently
  - "Steal" from basal 2-3 hours after meal times[3]



- Consider using HCL during the daytime only (exiting each night)
  - SAPT over night (or partial closed-loop therapy) with HCL during the day

Tandem: use almost always sleep modus (6.1-6.7 mmol/l): cave: no automated hyper correction boli , agressive basal insulin adjustment , strong ISF: 90/TDI (affects both correction bolus and basal modulation)
780G 5.5 mmol/l, DBLG1 6.1 mmol/l
Camaps: 4.4-11.1 mmol/l, up to 350 U/d

Szmuilowicz E et al. DTT 2023
Wang, Diabetes Medicine 2023

Current Studies with HCL Therapy in Pregnancy

Study Title / Clinical Trials #	PI	Location (# of sites)	Study Design	System	Study Start/ Completion
PICLS (Pregnancy Intervention with a Closed-Loop System) [NCT03774186]	Sarit Polsky	Colorado and Ohio, USA (2)	•Parallel RCT to commercial system (HCL) or SAPT with same system •N=23 completers	Medtronic 670G pump, Guardian CGM, PID algorithm	3-21-2019/ 3-8-2022
AiDAPT (Automated Insulin Delivery Among Pregnant women with T1D) [NCT04938557]	Helen R. Murphy	United Kingdom (10-12)	•Parallel RCT to investigational system (HCL) or CSII/MDI •N=124	DANA Diabecare RS pump, Dexcom G6 CGM, MPC algorithm	9-26-2019/ 6-30-2023
Automated Insulin Delivery in Pregnant Patients With T With Extension Into Outpatient at Home	Eyal Dassau	California, Minnesota, and New York, USA (3)	•48-60 hour supervised session with investigational system, option to continue •N=21	iAPS platform, Zone-MPC and HMC	7-27-2020/ 5-31-2022
Closed-Loop Insulin Delivery in Pregnant Women with T1D (CRISTAL) [NCT04520971]	Katrien Benhalima	Belgium and Netherlands (11)	•RCT to commercial system (HCL) or standard care	Medtronic 780G pump, Guardian CGM	1-15-21/ 6-2023
Closed-loop Insulin Delivery In T1D Pregnancies (CIRCUIT) [NCT04902378]	Denice Feig and Lois Donovan	Canada (2)	•RCT to commercial system (HCL) or SAPT	Tandem Control IQ, Dexcom G6 CGM, MPC algorithm	6-15-2021/ 1-2024

Lois-P Consortium

Barbara Davis Center for Diabetes

Abbreviations: HMC, Health Monitoring System; MPC, Model Predictive Control;

Szmuilowicz E et al. DTT 2023
Sarit Polsky, Oral presentation

TRANSLATING CGM DATA TO OPTIMIZE OUTCOMES

- %TIR ideal? Different for different outcomes?
- Should there be a different overnight TIR vs daytime?
- Should we have trimester-specific TIR's?
- What should the mean glucose be in pregnancy to get the best outcomes? Is it different for different outcomes? For women with type 1 vs type 2?

Target 1st T: 5.5 mmol/l
2nd/3rd T: 5 mmol/l

- Evtl more relaxed targets in women with severe hypo

Szmuilowicz E et al. DTT 2023
Benhalima K, Lancet Endo, 2023

THANK YOU FOR YOUR ATTENTION