Pump (AID) use in Pregnancies with T1D

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Disclosures

- Research support: NIH, Helmsley Foundation, Abbott, Dexcom, Insulet, Tandem, Mannkind, NovoNordisk
- Advisory boards: Dexcom, Tandem Diabetes
- Portions of my talk will discuss non FDA approved (off label) use of devices
- This is **very** rapidly moving field with respect to data and publications

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

- Women with diabetes who are pregnant require tighter glycemic targets to reduce adverse maternal and fetal health risks
  - Fetal complications/risks: ALL: Fetal loss, fetal death, premature delivery, delayed lung maturity, hypoglycemia, macrosomia (> 4 kg), birth defects (T1&T2D)
  - Maternal complications/risks: Worsening hypoglycemia, pre-eclampsia, and Cesarean-section delivery, progression of diabetic complications (e.g., retinopathy:T1 and T2D)
- Pregnancy outcomes have improved with the advent of newer insulins, SMBG, and CGM, but remain suboptimal

  - Challenges for managing patients: Changing insulin requirements throughout pregnancy, patient burden of care, and others (like maternal comorbidities)

Kitzmiller JL, Cloherty JP, Younger MD, Tabatabaii A, Rothchild SB, Sosenko I, Epstein MF, Singh S, Neff RK. Diabetic pregnancy and perinatal morbidity. American Journal of Obstetrics and Gynecology. 1978 Jul 1;131(5):560-80.

Glycemic Challenges during Pregnancy for Patients (and Clinicians)

- Health risks for both the mother and fetus
- Risks of hypoglycemia increased due to tighter glycemic targets 63-140mg/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: insulin infusion sets/injections or CGM

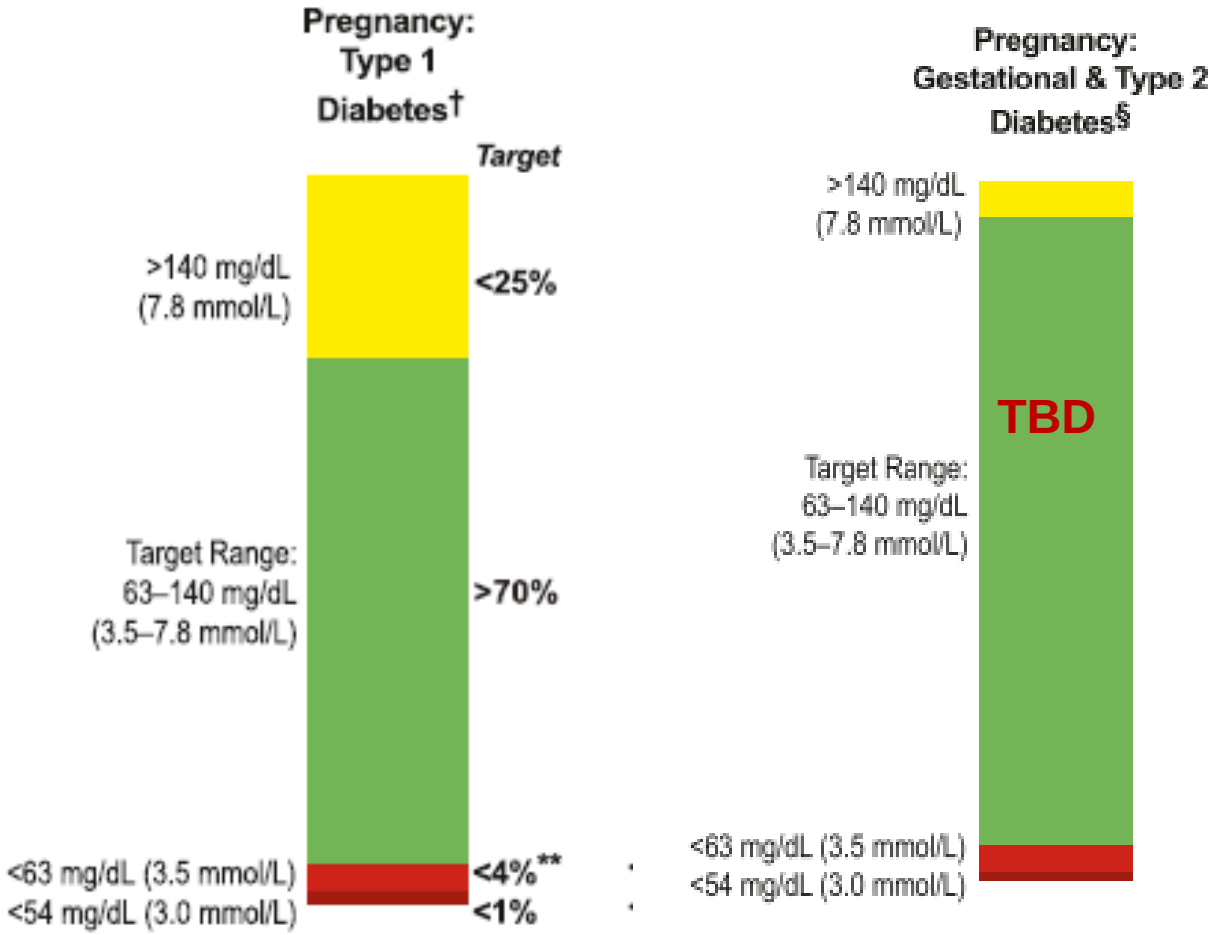
Jovanovic L, Peterson CM. Management of the pregnant, insulin-dependent diabetic woman. Diabetes Care. 1980 Jan 1;3(1):63-8.

Preconception Counseling/Optimization

Preconception Counseling/Optimization

- Ensure all individuals of childbearing potential are aware of the glycemic and health goals prior to pregnancy
- Educate on the 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 glucose management regimen

CGM TIR Goals During Pregnancies Complicated By Diabetes



Outside of pregnancy goal is >70% of time between 70-180 mg/dl

Battelino T, et al. Diabetes care. 2019 Aug 1;42(8):1593-603.

Other Metrics (A1C, SMBG)

Society	ADA	ENDO	AACE
HbA1c Target	<6.0 % ideal <7.0% if needed	<6.5% ideal < 7.0% if needed	<6.0%
Fasting BG mg/dL	≤ 95	60-99	GDM ADA goals T1&T2D ENDO goals
Post Prandial BG mg/dl	< 140 1 hr pp < 120 2 hr pp	100-129 mg/dl 1-2 hr pp	GDM ADA goals T1&T2DM ENDO goals

Management of Diabetes in Pregnancy: Standards of Care in Diabetes—2024. *Diabetes Care* 47, no. Supplement_1 (2024): S282-S294.
J Clin Endocrinol Metab, November 2016, 101(11):3922–3937
Endocrine Practice: August 2016, Vol. 22, No. 8, pp. 1008-1021

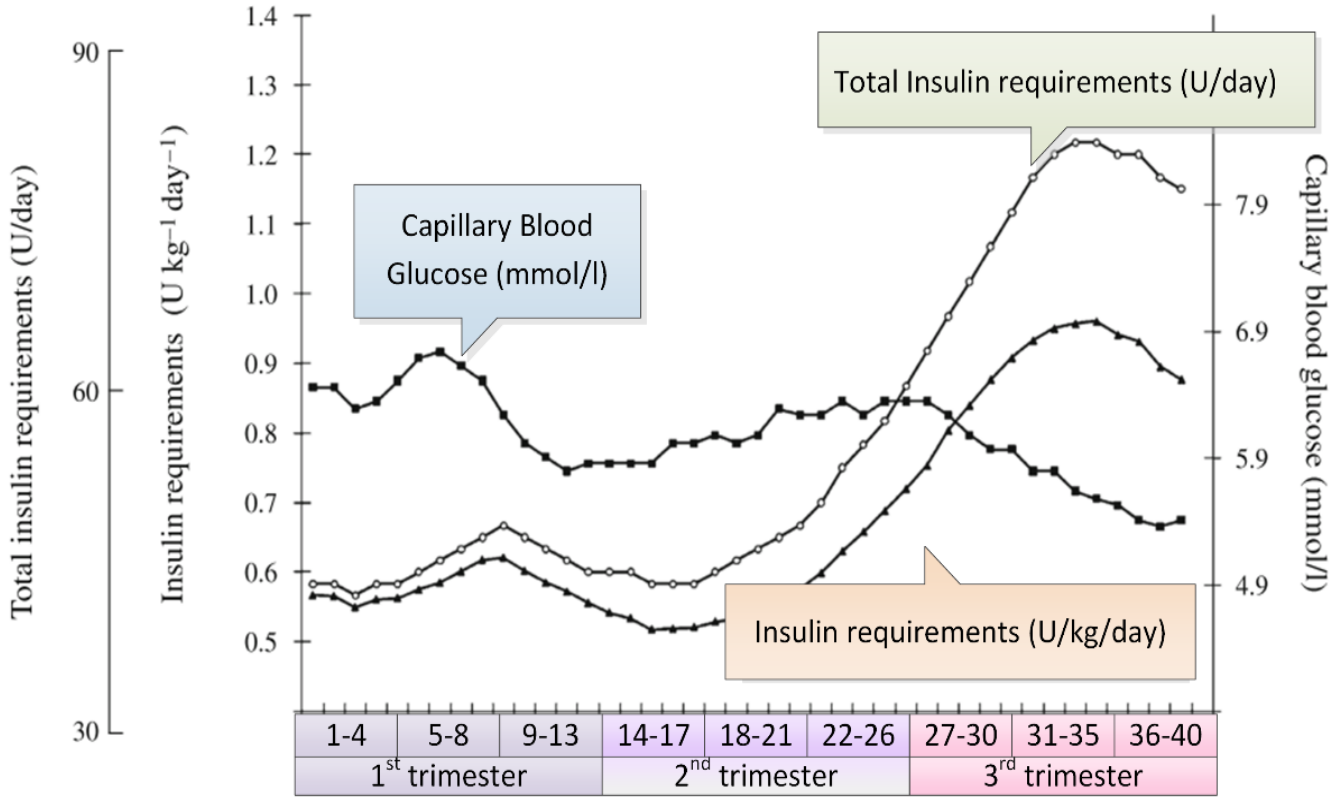
Patient Considerations During Pregnancy

- Skin sensitivity
- Site selection
- Discussion regarding frequency of finger stick 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 GV matter)

Management Challenges:

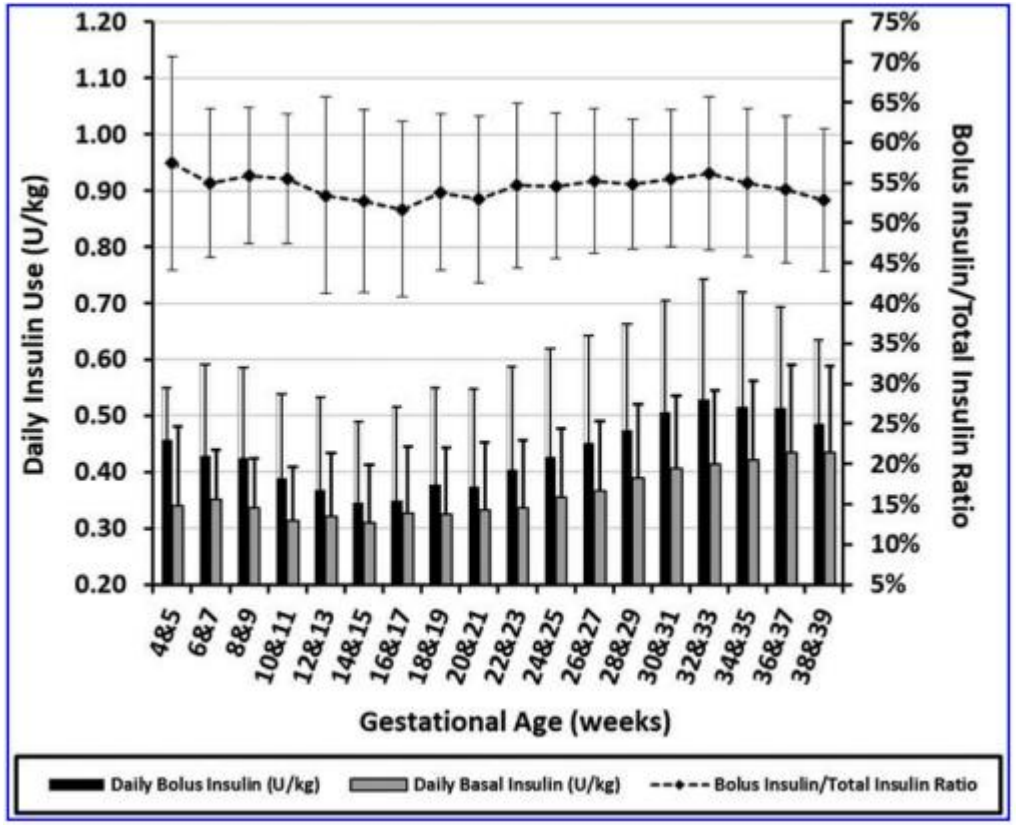
Why is managing pregnant people with diabetes so challenging?

Mean Insulin Requirements and SMBG during Pregancies with T1D



A. García-Patterson,et al. "Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus : three changes of direction," *Diabetologia,* vol. 53, pp. 446-451, 2010

Insulin Delivery: The Lois P study



25 women with T1D followed longitudinally throughout pregnancy using CSII

O'Malley G, Ozaslan B, Levy CJ,et al. Longitudinal observation of insulin use and glucose sensor metrics in pregnant women with type 1 diabetes using continuous glucose monitors and insulin pumps: the LOIS-P Study. Diabetes technology & therapeutics. 2021 Dec 1;23(12):807-17.

Insulin Pumps vs MDI during Pregnancy

- Pump therapy has been shown to improve glycemic control, reduce severe hypoglycemic episodes, and improve quality of life in people with T1D outside of pregnancy
- Several small randomized trials from the 1980s showed no differences in glycemic control or pregnancy outcomes
- More recent cohort studies have found conflicting results, with some but not all finding differences in glycemic control (CONCEPTT sub-analysis favored MDI)

Pickup JC. Insulin-pump therapy for type 1 diabetes mellitus. N Engl J Med 2012;366:1616–1624
Feig, Diabetes Care 2018;41:2471–2479 | https://doi.org/10.2337/dc18-1437

Closed Loop Control (HCL Therapy during Pregnancy)

Currently Commercially Available HCL Systems in the US Target 70-180 mg/dl

HCL in Pregnancy Clinical use (off Label in US- FDA approved systems not customized for pregnancy)

- 670G, 780G: research-US (670G, PICLS) Europe (780G CRISTAL), off label use-equivalent outcomes
- Basal IQ/Control IQ: CIRCUIT (Canada) and off label use (results soon)
- Omnipod 5: off label, limited data
- i-Let:off label, limited data
- DIY Systems (Loop, open APS) changing quickly not currently available commercially- use currently predominantly savvy patients
- CamAPS (UK)- not yet available in the US (improved glycemic outcomes, but no M/F improvements, less than 70% TIR for many) with Ypsomed pump

Szmuilowicz ED, Levy CJ, Buschur EO, Polsky S. Expert Guidance on Off-Label Use of Hybrid Closed-Loop Therapy in Pregnancies Complicated by Diabetes. Diabetes Technology & Therapeutics. 2023 Mar 1.

Reported Glycemic Outcomes, Earlier HCL Studies in the UK

	Stewart et al, 2016 (overnight) N=16		Stewart et al, 2018 (day and night) N=16	
	CL	SAP	CL	SAP
Time in range	74.7%*	59.5%	62.3%	60.1%
Mean glucose (mg/dL)	119*	133	131.4	131.4
Standard deviation (mg/dL)	25	27	36	37.8
Time >140mg/dL	24%*	38.6%	36.1%	36.6%
Time >180mg/dL	7.4%*	15.7%	14.6%	14.8%
Time <63mg/dL	1.3%	1.9%	1.6%*	2.7%
Time <50mg/dL	0.3%	0.6%	0.2%*	0.5%
Median # of hypo events	3	2.5	8*	12.5

(*indicates P value<0.05)

Z. A. Stewart,, *et al.*, "Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes," *New England Journal of Medicine,* vol. 375, pp. 644-654, 2016.
Z. A. Stewart, *et al.*, "Day-and-Night Closed-Loop Insulin Delivery in a Broad Population of Pregnant Women With Type 1 Diabetes: A Randomized Controlled Crossover Trial," *Diabetes Care,* p. dc172534, Mar 2018.

Reported Maternal and Fetal Outcomes in UK Studies

	Overnight Stewart et al, 2016	Day and Night Stewart et al, 2018
Baseline HbA1c	6.8±0.6%	8.0±1.1%
Pre-eclampsia	31%	12.5%
Preterm	44%	NR
C-section	94%	81%
NICU admission	75%	69%
LGA	81%	44%
Congenital malformations	Not recorded	12.5%

Z. A. Stewart,, *et al.*, "Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes," *New England Journal of Medicine,* vol. 375, pp. 644-654, 2016.
Z. A. Stewart, *et al.*, "Day-and-Night Closed-Loop Insulin Delivery in a Broad Population of Pregnant Women With Type 1 Diabetes: A Randomized Controlled Crossover Trial," *Diabetes Care,* p. dc172534, Mar 2018.

AiDAPT Study Cam-APS (UK)- % Time In Range 63-140 mg/dL

RCT in pregnant 118 individuals with T1D with mean A1c of 7.5% at enrollment in 1st trimester

End Points	Baseline		16 weeks' gestation until delivery		P-value[a]
	Closed loop (N=59)	Standard care (N=59)	Closed loop (N=59)	Standard care (N=61)	
% TIR 63-140 mg/dl (3.5-7.8 mmol/l)	47.8% ± 16.4%	44.5% ± 14.4%	68.2% ± 10.5%	55.6% ± 12.5%	NA
Change from baseline	NA	NA	20.4% ± 13.8%	11.0% ± 11.6%	NA
Adjusted difference[a] mean (95% CI)			10.5% (7.0%, 14.0%)		<0.001

Data are mean ± SD or median (IQR)

[a] Model adjusted for baseline % TIR, insulin delivery, and site as a random effect

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Lee TT, Collett C…& HM Murphy. New England Journal of Medicine. October, 2023.Slide Courtesy of H Murphy

Outcomes Maternal and Neonatal (AiDAPT Study)

	Closed loop (N=59)	Standard Care (N=60)	Adjusted difference (95% CI)	P-value
Hypertensive disorders (any)[a]	12 (20%)	25 (42%)	0.3 (0.1, 0.8)	0.02
worsening of existing hypertension	4 (7%)	2 (3%)		
new onset hypertension	6 (10%)	19 (32%)		
pre-eclampsia	4 (7%)	12 (20%)		
Maternal weight gain (kg) Mean ± SD[b]	11.1 ± 6.1	14.1 ± 6.1	3.7 (-6.8, -0.6)	0.02

	Closed loop	Standard Care	Adjusted difference (95% CI)	P-value
Serious Birth Injury	1 (2%)	4 (7%)		
Respiratory distress[a]	5 (8%)	8 (13%)	0.5 (0.1, 2.1)	0.37
Hypoglycaemia (treated with IV or oral glucose)[a]	26 (44%)	25 (42%)	1.0 (0.4, 2.7)	0.95
Hyperbilirubinemia[b]	40 (68%)	37 (62%)	1.3 (0.5, 3.3)	0.49
Readmission within 7 days	8 (14%)	3 (5%)		
NICU Stay ≥1 day[b]	**13 (22%)**	**15 (25%)**	**0.8 (0.3, 2.4)**	**0.60**
Length of stay (days) Median (IQR)[c]	6 (3, 10)	5 (3, 7)	1.5 (1.3, 1.8)	<0.001

No statistically significant differences if fetal size were noted between groups

[a] Based on a mixed effects logistic regression model adjusting for insulin modality and site as a random effect
[b] Based on a mixed effects logistic regression model adjusting for site as a random effect
[c] Based on a mixed effects poisson regression model adjusting for insulin modality and site as a random effect

Lee TT, Collett C…& HM Murphy. New England Journal of Medicine. October, 2023. Slide Courtesy of H Murphy

Neonatal Outcomes (AiDAPT Study)

Birth weight	Closed loop N=59	Standard Care N=60	Adjusted difference (95% CI)	P-value
Weight (kg) Mean ± SD	3.3 ± 0.6	3.5 ± 0.5		
Centile Mean ± SD[a]	73 ± 27	79 ± 26	-5.8 (-17.1, 5.5)	0.37
Median customized centiles (IQR)[b]	81 (53-97)	90 (71-99)		
Small for gestational age <10th centile[c]	3 (5%)	1 (2%)	3.1 (0.2, 48.6)	0.41
Large for gestational age >90th centile[c]	23 (39%)	30 (50%)	0.7 (0.3, 1.6)	0.39
Extremely large for gestational age >97.7th centile	13 (22%)	19 (32%)		
Macrosomia >4.0kg	4 (7%)	9 (15%)		

Fetal/meonatal outcome				
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Lee TT, Collett C…& HM Murphy. New England Journal of Medicine. October, 2023. Slide Courtesy of H Murphy

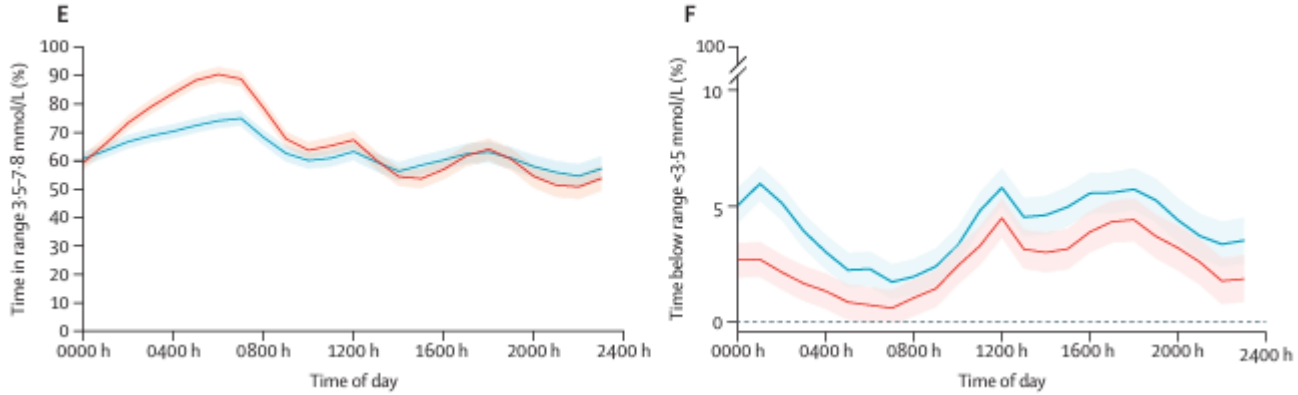
Comparing Advanced Hybrid Closed Loop Therapy And Standard Insulin Therapy in Pregnant Women with Type 1 Diabetes (CRISTAL), April 2024

- Double-arm, parallel-group, open-label, randomized controlled trial conducted in secondary and tertiary care specialist endocrinology centers at 12 hospitals (11 Belgium, 1 Holland)
- 95 randomly assigned to control arm or Medtronic 780G (AHCL)
- 43 patients assigned to AHCL therapy and 46 assigned to their standard of care therapy completed the study.
- Mean a1c at enrollment 6.5%
- System set to 100 for all participants when feasible, assistive tools (fake carb entry) used by many
- The mean proportion of time spent in the target range (averaged over four time periods) was **66·5%** (SD 10·0) in the AHCL therapy group compared with **63·2%** (12·4) in the standard insulin therapy group (adjusted mean difference 1·88 percentage points [95% CI –0·82 to 4·58], p=0·17).

Benhalima, Katrien, et al. "Comparing advanced hybrid closed loop therapy and standard insulin therapy in pregnant women with type 1 diabetes (CRISTAL): a parallel-group, open-label, randomised controlled trial." *The Lancet Diabetes & Endocrinology* (2024).

CRISTAL study Cont'd

- Overnight time in the target range was higher (adjusted mean difference 6·58 percentage points p=0·0026), and time below range overall (adjusted mean difference –1·34 percentage points, p=0·0020) and overnight (adjusted mean difference –1·86 percentage points p=0·0005) were lower with AHCL therapy than with standard insulin therapy.
- In pregnant women starting with tighter glycemic control, AHCL therapy did not increase overall time in target range, but increased overnight time in target range, reduced time below range, and improved treatment satisfaction.

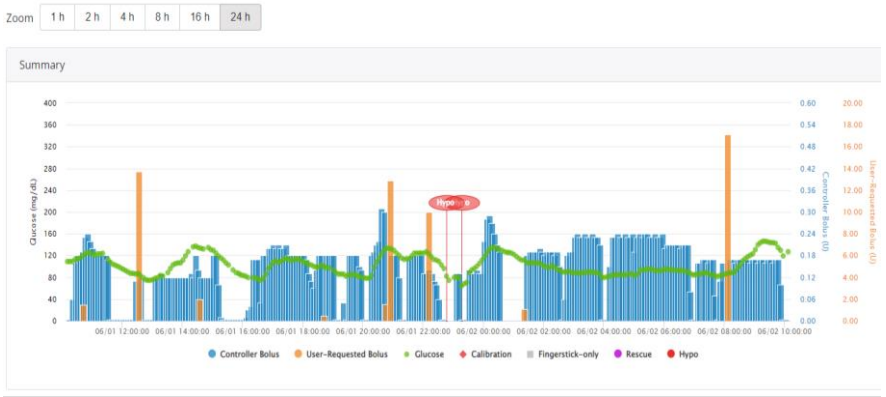


Red= 780G Blue = Standard care

Benhalima, Katrien, et al. "Comparing advanced hybrid closed loop therapy and standard insulin therapy in pregnant women with type 1 diabetes (CRISTAL): a parallel-group, open-label, randomised controlled trial." *The Lancet Diabetes & Endocrinology* (2024).

At-home Use of a Pregnancy-specific Hybrid Closed-loop Algorithmn

- The iAPS is a smartphone-based artificial pancreas platform using the Harvard designed zone-MPC algorithm integrating the Dexcom G6 continuous glucose monitor, Tandem t:AP insulin pump
- Every five minutes, the controller computes an optimal insulin microbolus to target glucose zones set at **80-110 mg/dL during the day** and **80-100 mg/dL overnight (12:00AM-6:00AM)**
- Setting adjustments to optimize delivery could be performed by study team as pregnancy progressed: Basal rates, I:C ratios, and ISF



Deshpande S,…& Dassau E. Diabetes Technol Ther 2019;21:35-43
Ozaslan B,…& Dassau E. Front Endocrinol 2021;12:12:768639

Levy CJ, Kudva YK…& Dassau E. Diabetes Care, 2023, doi.org/10.2337/dc23-0173

CGM outcomes for run-in period vs CLC-P use (N=10)

Sensor Glucose Metrics	Run-in§ 7 days prior to CLC	CLC-P	Absolute Difference (95% CI)	P value
Primary Outcome:				
Time 63-140 mg/dL	64.5% ± 16.3	78.6% ± 9.2	14.1 (6.6 to 21.7)	0.002
Secondary Outcomes:				
Overnight time in 63-140 mg/dL	61.3% ± 20.7	84.8% ± 7.7	23.5 (9.0 to 37.9)	0.005
Postprandial time 63-140 mg/dL	NA	73.4% ± 11.0	NA	NA
Time <63 mg/dL	3.7% [IQR 1.5 to 6.4]	1.6% [IQR 1.4 to 2.1]	-2.8 (-8.3 to -0.3)	0.037
Time <54 mg/dL	1.0% [IQR 0.3 to 2.2]	0.4% [IQR 0.3 to 0.4]	-0.9 (-3.7 to -0.02)	0.037
Time >140 mg/dL	29.8% ± 19.5	19.7% ± 9.5	-10.1 (-19.2 to -1.0)	0.033
Time >180 mg/dL	7.2% [IQR 4.0 to 13.6]	3.4% [3.0 to 8.0]	-5.3 (-13.6 to -1.2)	0.002
Mean glucose —mg/dL	123.1 ± 24.1	115.1 ± 10.6	-8.0 (-19.1 to 3.1)	0.139
Hypoglycemic events per week	4.0 ± 4.7	0.7 ± 0.6	-5.4 (-7.7 to -3.7)	<0.001

Plus minus values are means ± standard deviation. CI denotes confidence interval, and IQR denotes interquartile range.
NA indicates not applicable.
To convert values for glucose to millimoles per liter, multiply by 0.05551.
Hypoglycemic events were defined as time <54 mg/dL for fifteen consecutive minutes followed by time >70 mg/dL for fifteen consecutive minutes

Levy CJ, Kudva YK…& Dassau E. Diabetes Care, 2023,
doi.org/10.2337/dc23-0173

For patients planning pregnancy/become pregnant unexpectedly

- Review the data on off label use of HCL system use off label and the targets of the currently available systems
- Discuss the benefits and risks of off-label HCL system use in pregnancy and strategize with the patient re benefits and limitations of AHCL therapy
- Consider additional strategies to optimize control with assistive tools (fake carbs, sleep mode, options for exercise, breast feeding and iteratively evaluate risks and benefits of use weekly as pregnancy progresses
- Discuss post partum management

Szmuilowicz ED, Levy CJ, Buschur EO, Polsky S. Expert guidance on off-label use of hybrid closed-loop therapy in pregnancies complicated by diabetes. Diabetes Technology & Therapeutics. 2023 May 1;25(5):363-73.

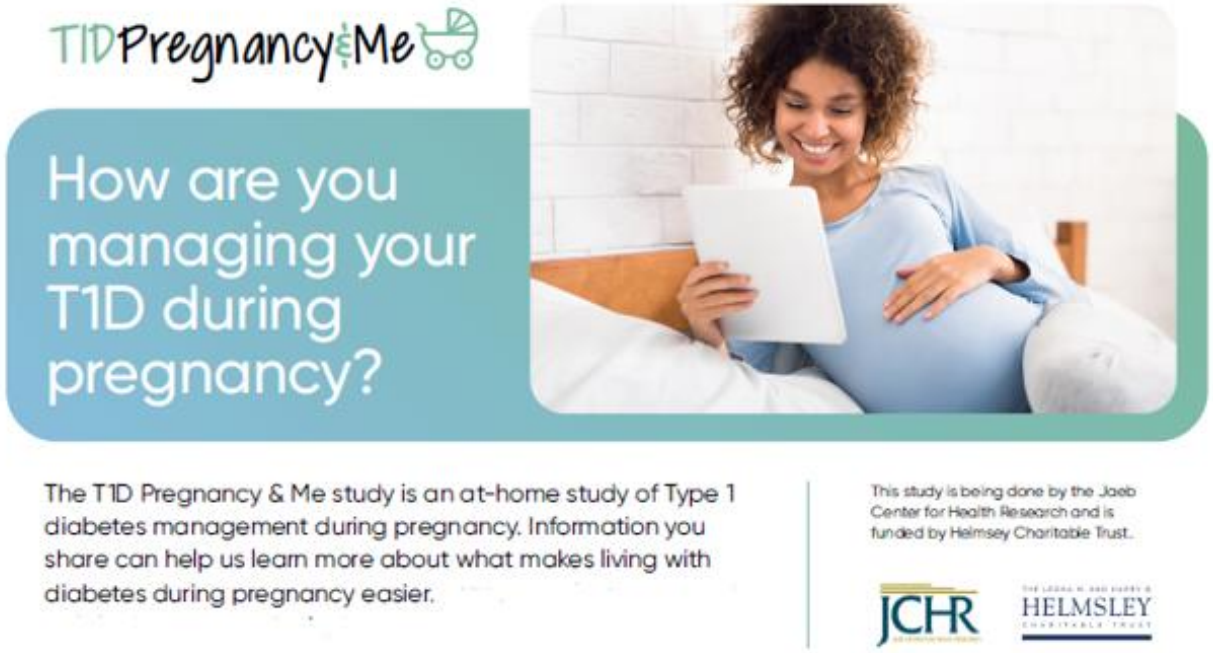
Areas for Further Evaluation

- TIR and other factors impacting adverse maternal and fetal outcomes including LGA babies
- How to best use CGM
- Use CGM, CLC systems and associated pregnancy outcomes in all pregnancies complicated by diabetes
- What are the optimal glycemic targets (is 70% TIR achievable and adequate), different goals for GDM and T2D?
- Role of A1c, mean glucose, glycemic variability?
- Insulin Analogs (ultra rapid, inhaled?)
- Future use of systems with customized targets and how to maximize outcomes now
- Pre-pregnancy planning
- Engagement of industry

In Closing

- Pregnancies complicated by diabetes have an increased risk of maternal and neonatal complications
- Gestational changes in insulin resistance increase the risk of hypoglycemia and hyperglycemia.
- Preconception counseling is crucial to ensure that individuals of childbearing potential understand glycemic and health goals before pregnancy
- CGM use in pregnancy improves glycemic control and maternal and neonatal outcomes while lowering self-care burden in a cost-saving fashion.
- Commercially available HCL systems can be considered for off-label use in select pregnant individuals with experienced providers after careful discussion of risks, benefits, and alternatives, as well as strategies to optimize pump use and algorithms until approved systems are available.

How can we and our patients help?
2 upcoming studies….



Follow up trial evaluating a larger cohort with a system able to meet pregnancy targets

Will be enrolling at Sinai end of Q1 of early Q2 2025

Opening late1st Quarter 2025

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Thank You

Patients
Clinical colleagues
Research participants
Funding organizations
Collaborators

Icahn School of Medicine at Mount Sinai

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I wish we had 6 more hours in every day!