Closed Loop in Pregnancy
Where are we now and how did we get here?

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Women with T1DM have poor pregnancy outcomes

- 80 years since the first descriptions of macrosomia or large for gestational age (LGA) infants
- Pregnancy outcomes have barely changed ~60% of babies are born LGA
- LGA associated with increased risk of maternal and neonatal complications, and predisposes infant to developing obesity, type 2 diabetes and cardiovascular disease in adulthood
- Tight glucose control to prevent these outcomes is major focus of antenatal care

Nothmann M NEJM archive 1941;224: 275-280

Murphy HR et al. Lancet Diabetes and Endocrinology 2021; 9:153-164

Poor outcomes are common and not improving

LGA

1 in 2 women with **T1DM**

Caesarean section

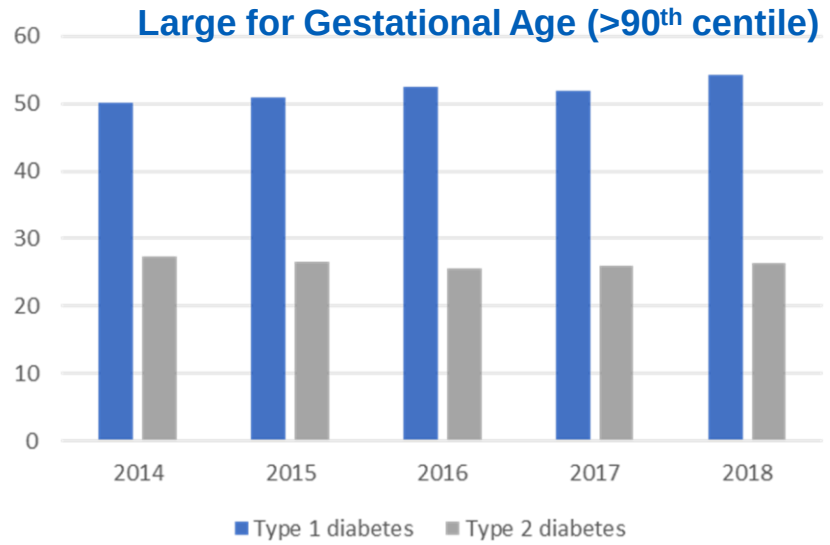
75% of babies of mums with **T1DM**

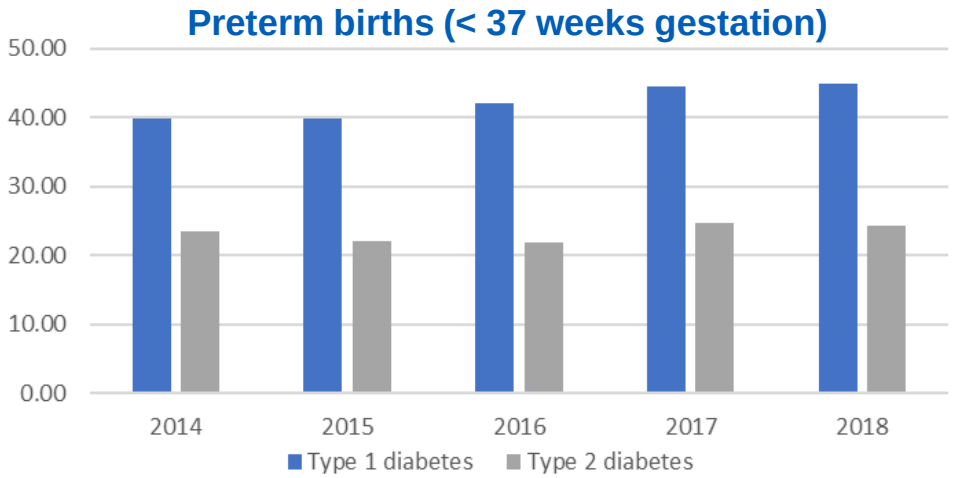
Preterm birth

1 in 2 women with **T1DM**

NICU

1 in 2 babies of mums with **T1DM**



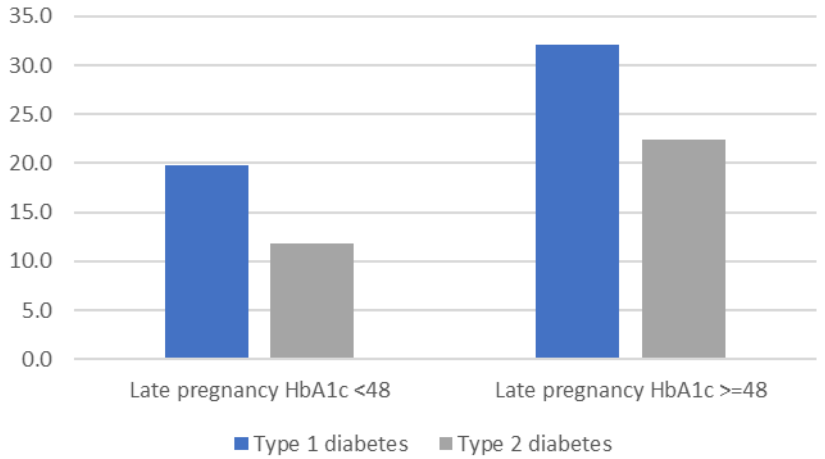


National Pregnancy in Diabetes Audit Report 2020 - NHS Digital

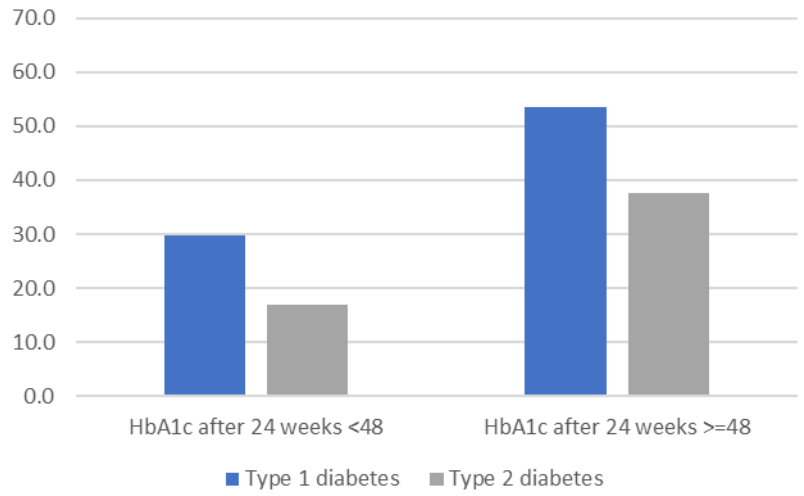
Poor glycaemic control is biggest risk factor for adverse outcomes

- Women with HbA_{1c} > 6.5% or 48 mmol/mol after 24 weeks have significantly higher rates of preterm birth, LGA and NICU admission

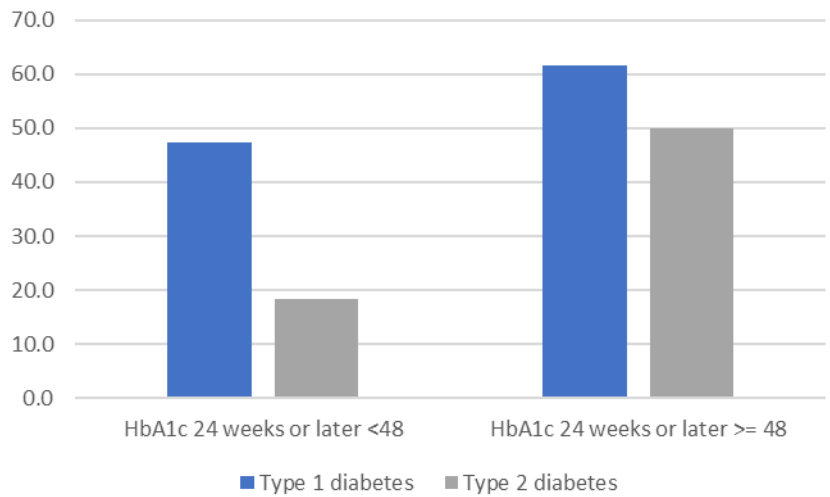
NICU admission



Preterm delivery



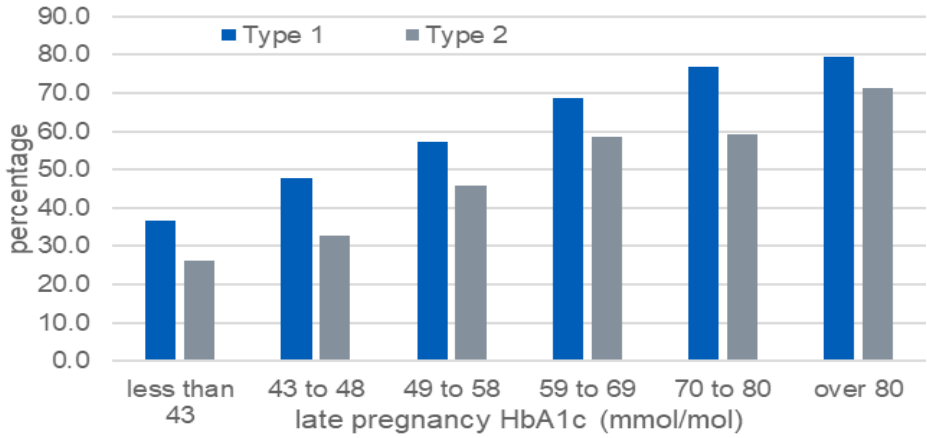
LGA



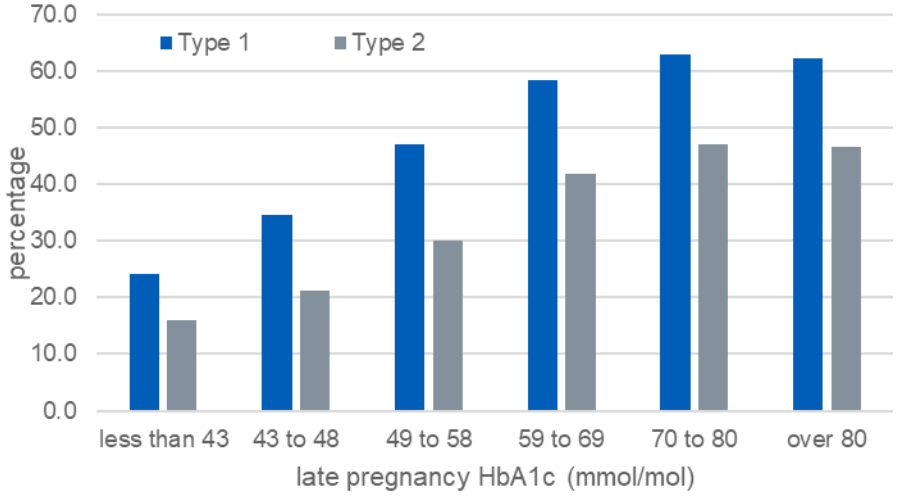
Need to aim for HbA1c <43 if we are to improve things

- Preterm births, LGA and neonatal care admissions were lowest in women with HbA1c <43mmol/mol after 24 weeks
- Thus to improve outcomes women need to aim for tighter glucose targets i.e. HbA1c 42mmol/mol (6.0%) during second/third trimesters

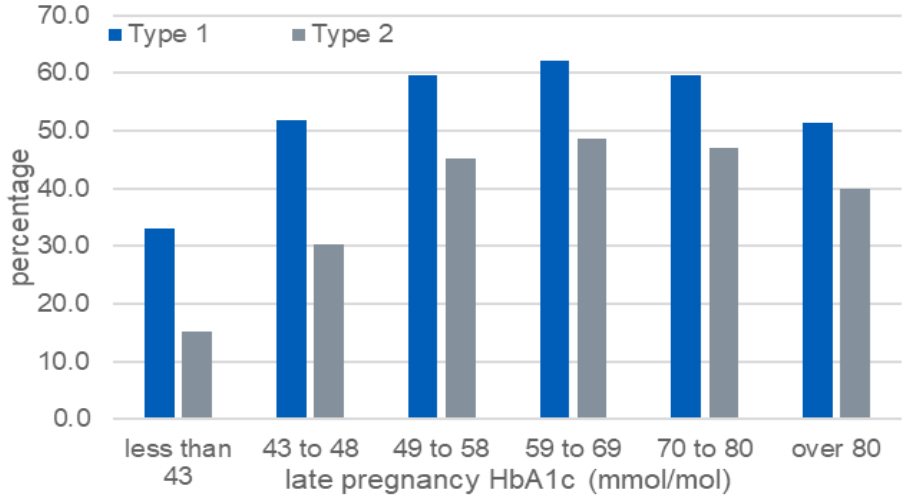
NICU admissions



Preterm births < 37 weeks



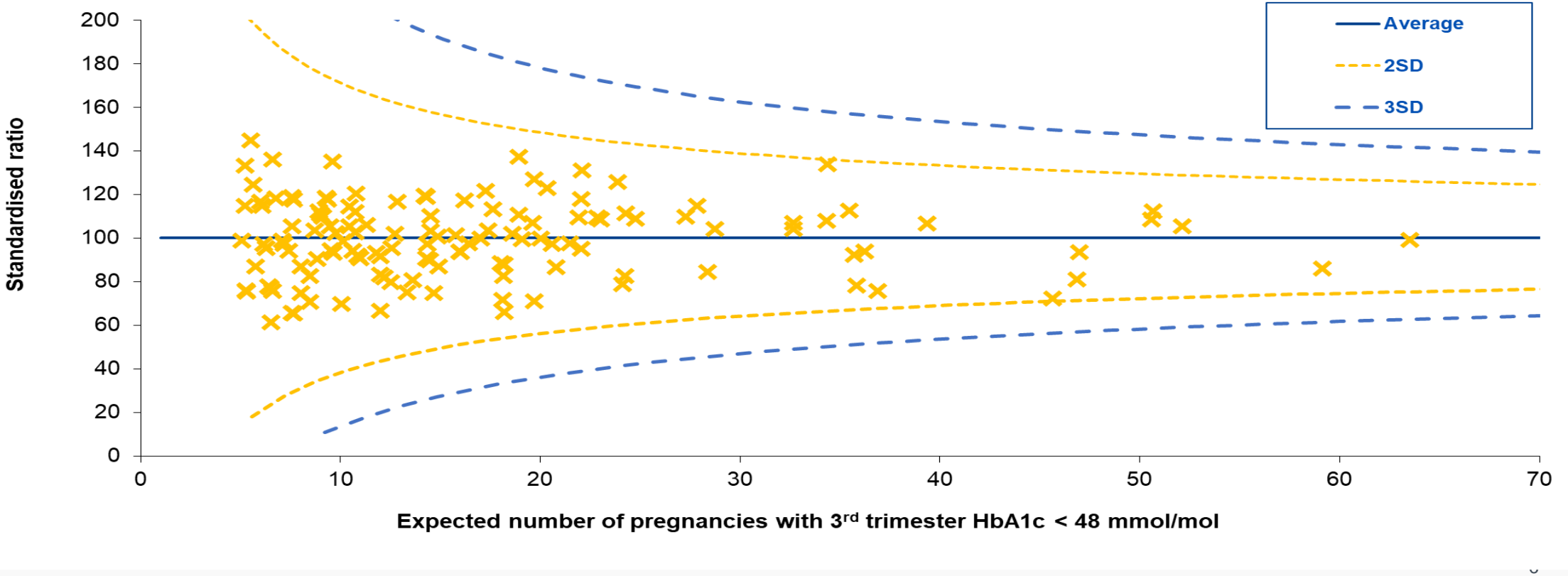
Large for gestational age (LGA) babies



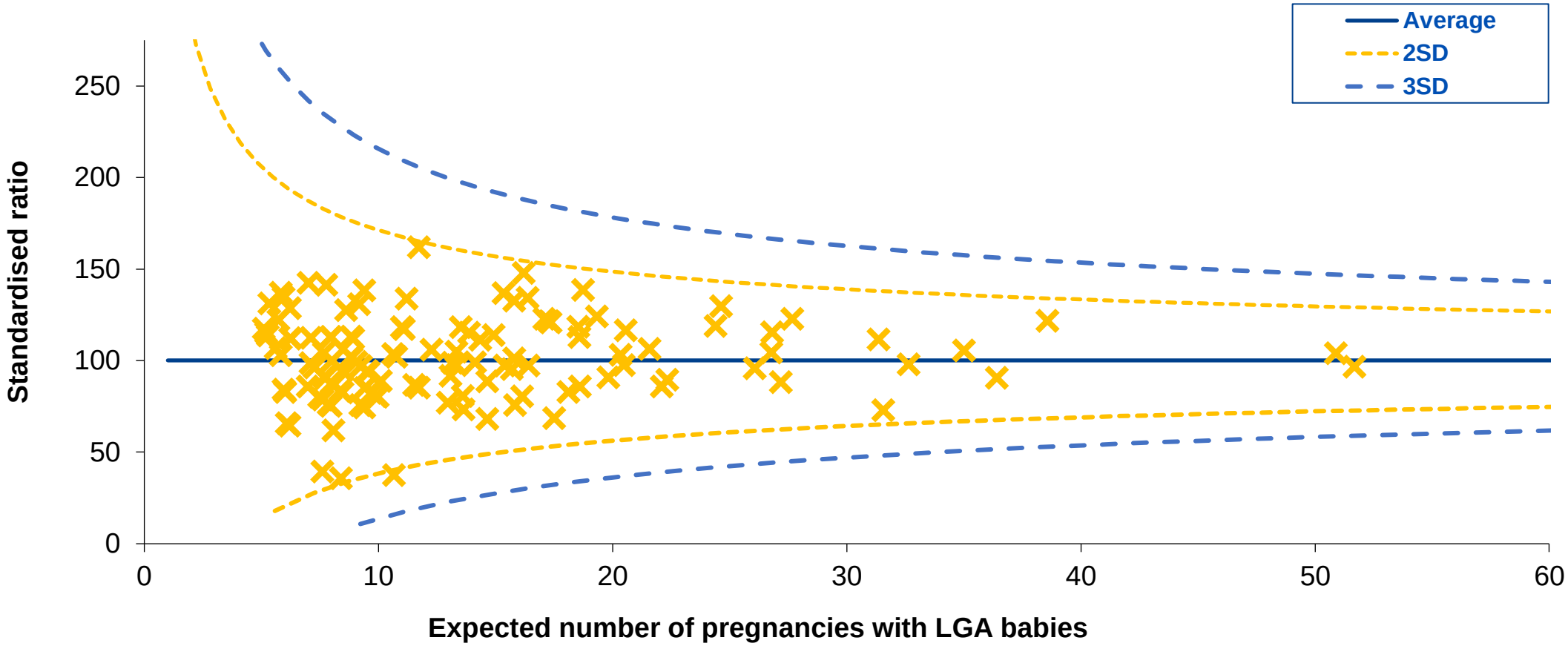
Differences are explained more by the characteristics of the women than by differences in clinical practice

New interventions are needed across all antenatal clinics to reach target HbA1c

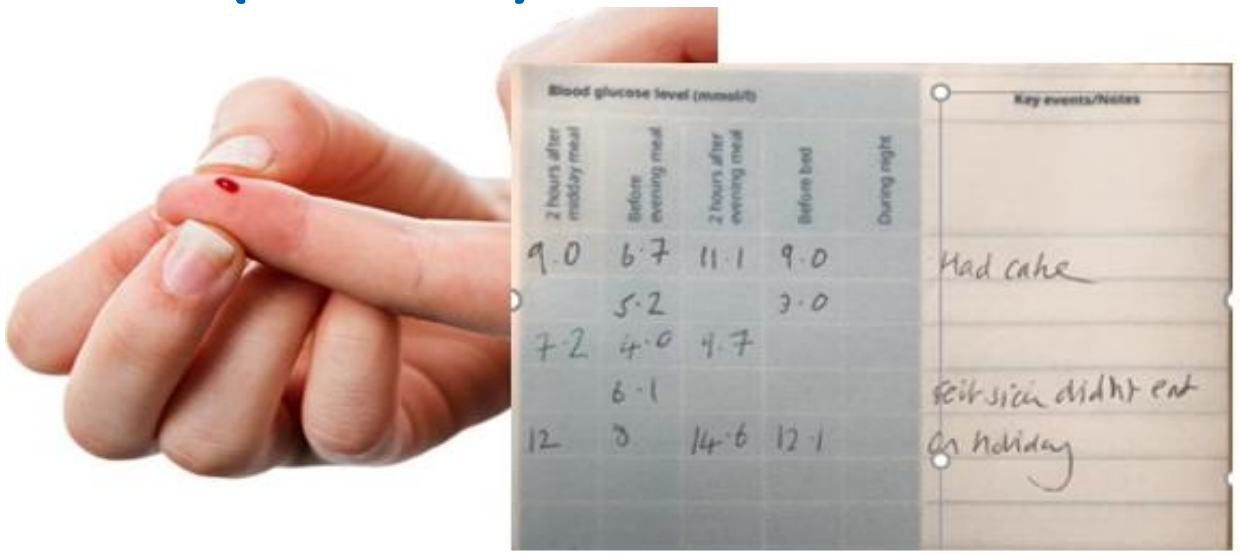
Funnel plot showing local variation in third trimester HbA_{1c} <6.5% (48 mmol/mol)



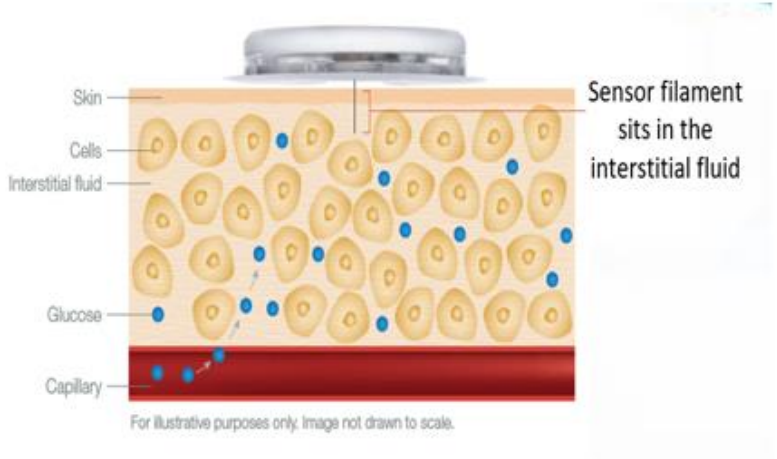
New interventions are needed across all antenatal clinics to reduce rates LGA in T1D

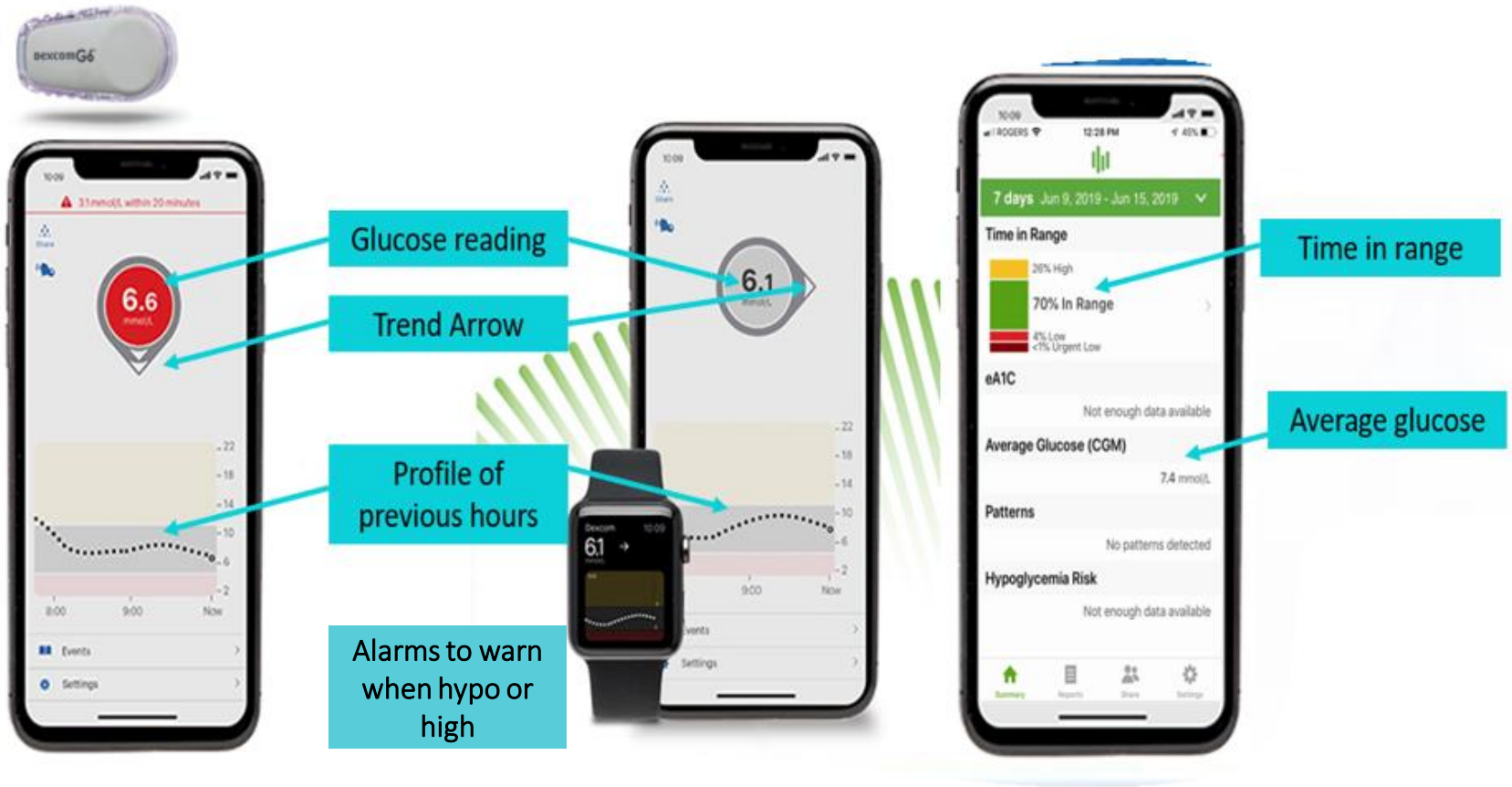


Standard Care: ‘fingerprick’ Self Monitored Blood Glucose (SMBG)

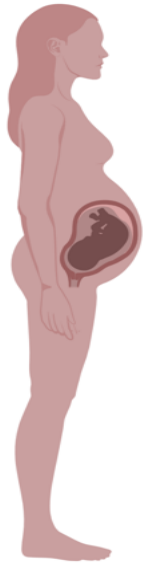


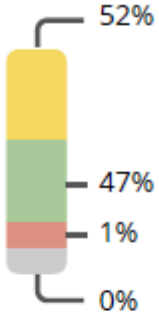
Continuous glucose monitoring (CGM) is revolutionising diabetes clinical practice





CGM helps in pregnancy (CONCEPTT study)

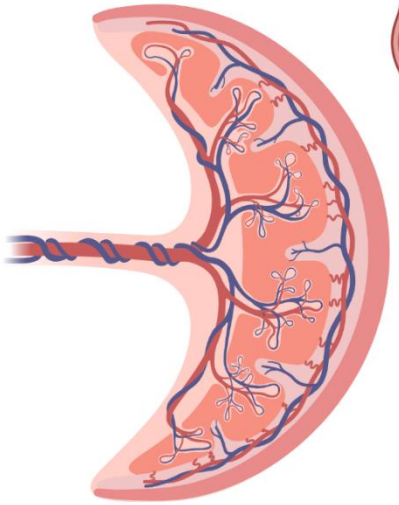


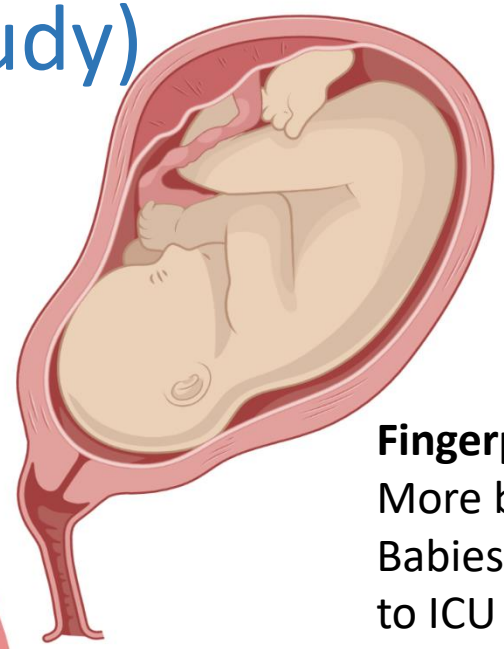


Time in range

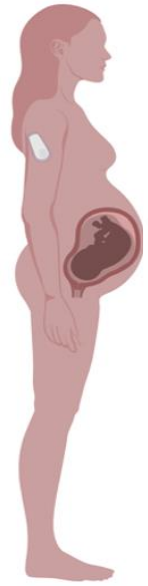
Fingerprick users
Higher HbA1c at 34 weeks
Less able to keep glucose in pregnancy range

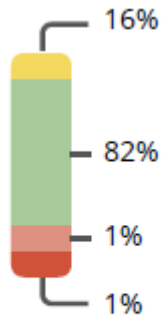
Mum's glucose





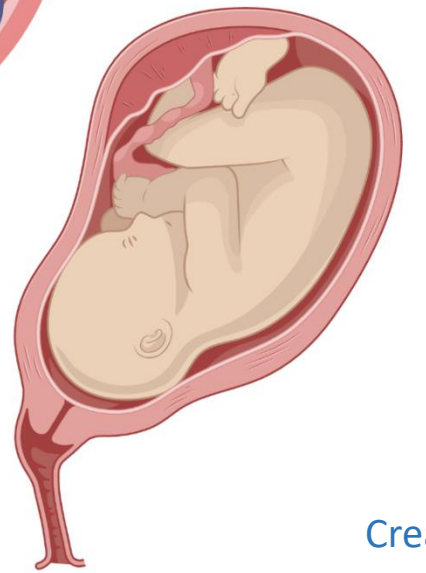
Fingerprick users
More big babies
Babies needed to go to ICU





Time in range

CGM users
Lower HbA1c at 34 weeks
Were able to maintain glucose in normal pregnancy range



CGM users
Fewer big babies
Babies didn't need to go to ICU

Feig DS et al. Lancet 2017

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CONCEPTT

Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial

Improved glucose control in pregnant CGM group

- **Lower HbA1c at 34 weeks**

  (6.3 vs 6.4% p=0.021)

- **More time in target range (3.5-7.8mmol/l)**

  (68% vs 61% p=0.003) ~1.7 hour/day

- **Less time hyperglycemic**

  (27% vs 32% p=0.028) ~ 1.2h/day

Feig DS et al. Lancet 2017

CONCEPTT

Improved neonatal outcomes in pregnant CGM group

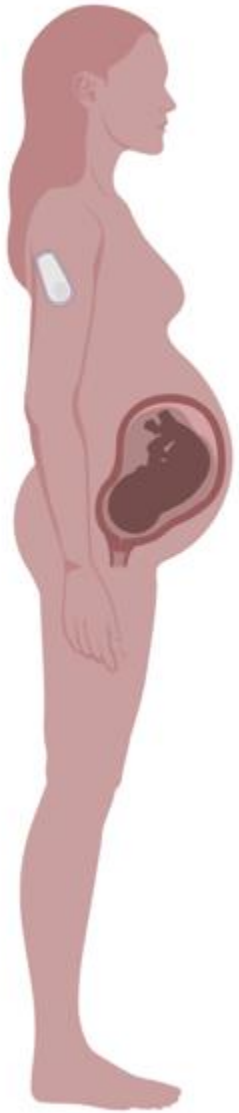
- ✓ lower LGA (53% vs 69% p=0.02)
- ✓ fewer neonatal ICU (27% vs 43% p=0.025)
- ✓ less neonatal hypoglycaemia (15% vs 28% p=0.016)
- ✓ reduced infant length of hospital stay (3.1 vs 4.0 days p=0.009)

- ✓ NNT = 6 to prevent 1 LGA or 1 neonatal hypoglycaemia
- ✓ NNT = 8 to prevent 1 NICU admission

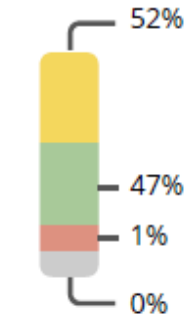
- ✓ Cost effective (predicted to save NHS £9.5 million/year)

Feig DS et al. Lancet 2017

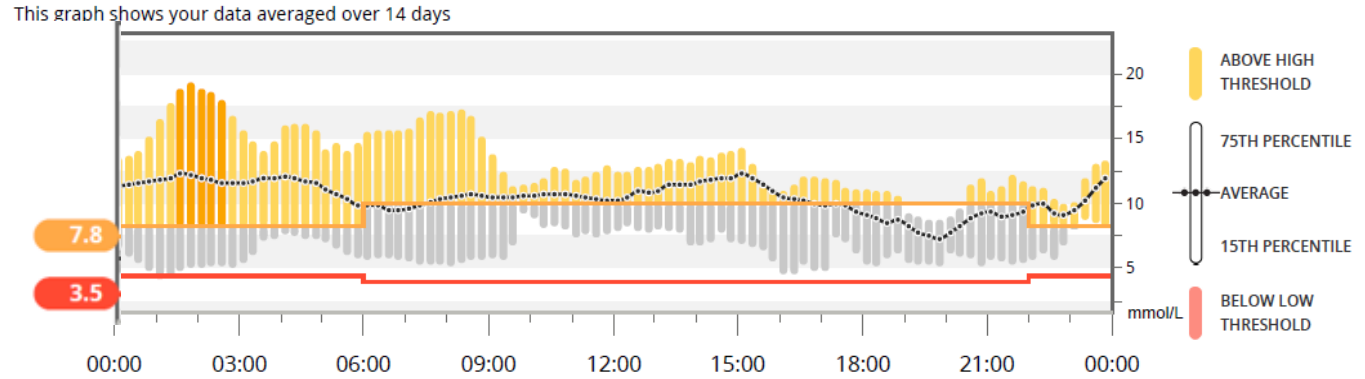
Different way of thinking about glucose



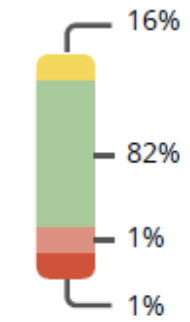
More time **outside** of pregnancy range 3.5-7.8



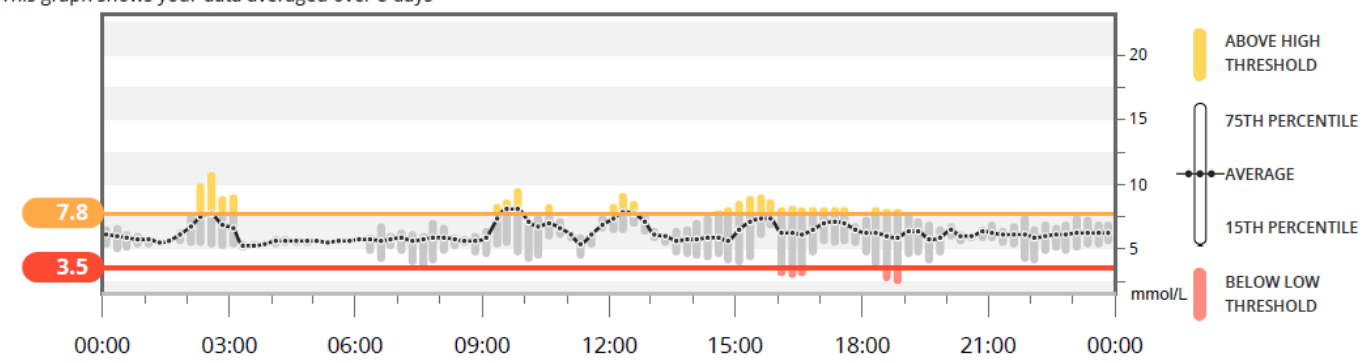
Time in range



Big baby



Time in range



More time **inside** of pregnancy range 3.5-7.8

Normal sized baby

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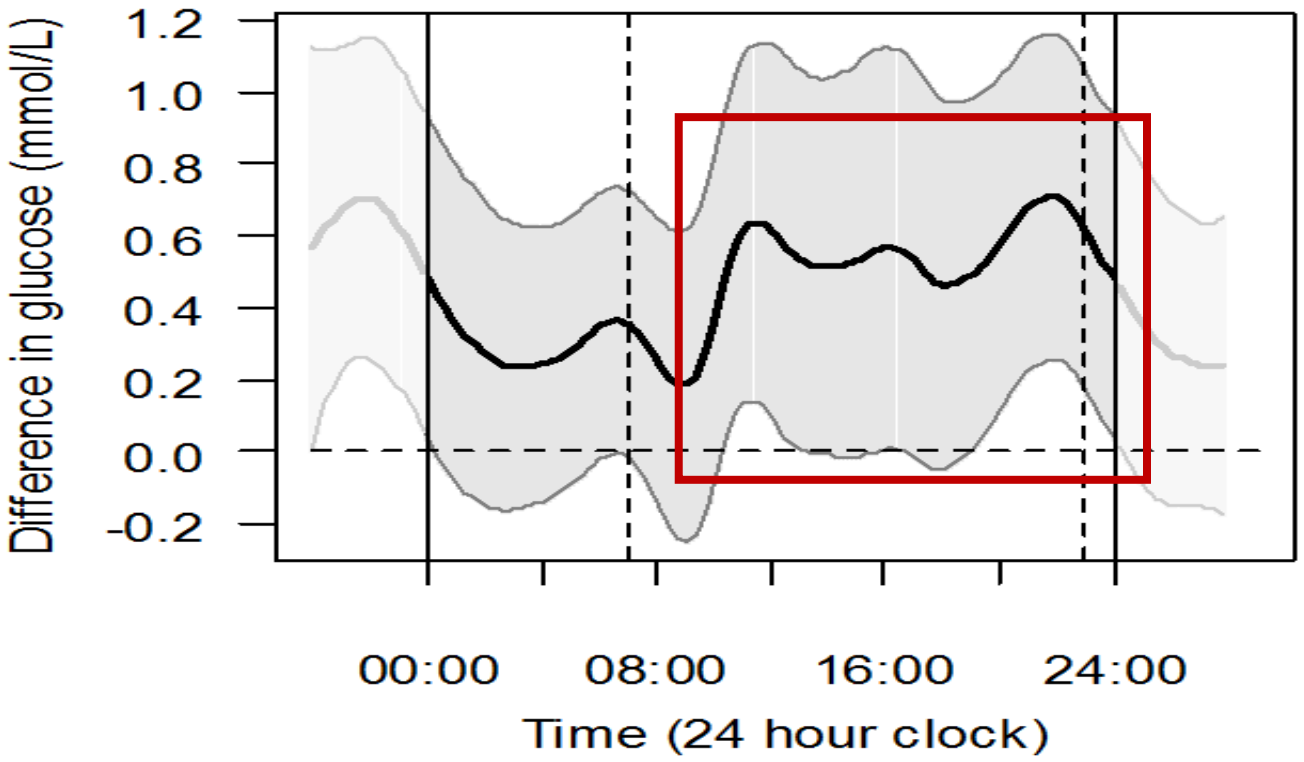
CGM profiles show when glucose is related to LGA

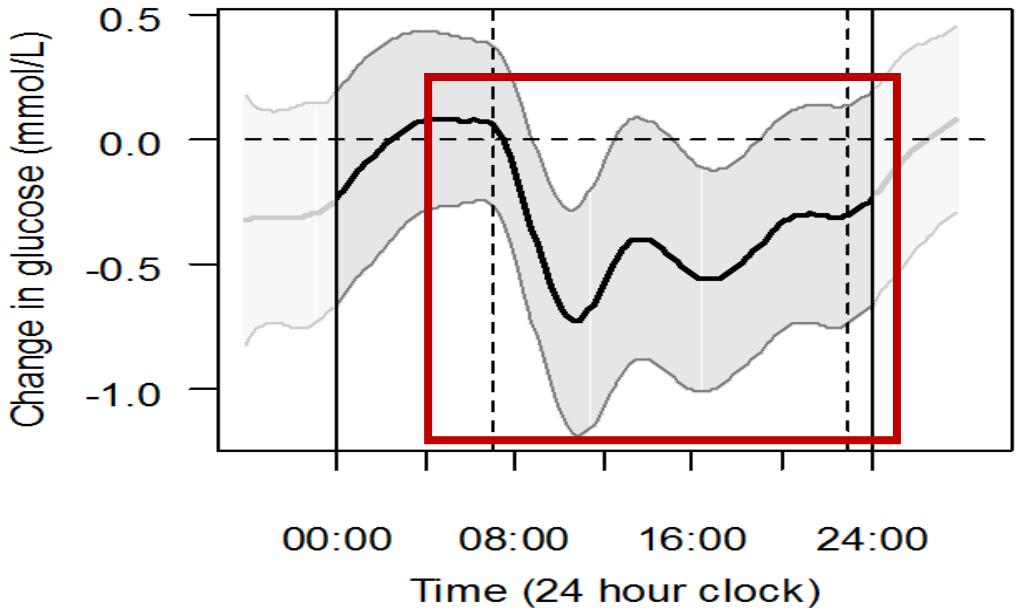
Women who had an LGA infant ran a significantly higher glucose for 14 hours a day – especially **mealtimes/snacks**



Scott EM et al. Continuous Glucose Monitoring in Pregnancy: Importance of Analyzing Temporal Profiles to Understand Clinical Outcomes. Diabetes Care 2020 Jun; 43(6): 1178-1184.

CGM improves daytime (mealtime) glucose control

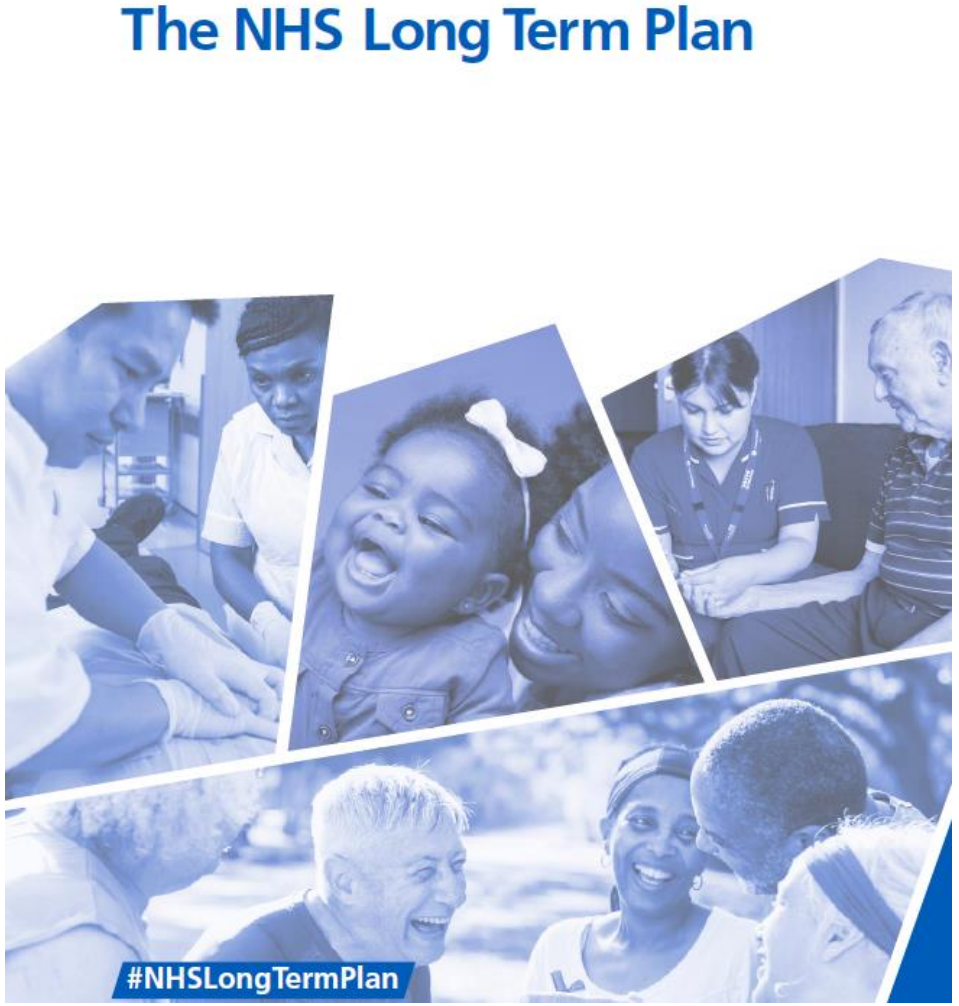
Pregnant CGM users ran a significantly lower glucose for a total of 7 hours a day



Scott EM et al. Continuous Glucose Monitoring in Pregnancy: Importance of Analyzing Temporal Profiles to Understand Clinical Outcomes. Diabetes Care 2020 Jun; 43(6): 1178-1184.

NHS Long term plan

- Committed that by 2020/2021 all pregnant women with Type 1 diabetes will be offered continuous glucose monitoring to improve neonatal outcomes
- NHS England have funded it and supported its rollout nationally through Local Maternity Systems



NICE NG3 updated guidance December 2020

Intermittently scanned CGM and continuous glucose monitoring

1.3.17 Offer continuous glucose monitoring (CGM) to all pregnant women with type 1 diabetes to help them meet their pregnancy blood glucose targets and improve neonatal outcomes. **[2020]**

1.3.18 Offer intermittently scanned CGM (isCGM, commonly referred to as flash) to pregnant women with type 1 diabetes who are unable to use continuous glucose monitoring or express a clear preference for it. **[2020]**

1.3.19 Consider continuous glucose monitoring for pregnant women who are on insulin therapy but do not have type 1 diabetes, if:

- they have problematic severe hypoglycaemia (with or without impaired awareness of hypoglycaemia) **or**
- they have unstable blood glucose levels that are causing concern despite efforts to optimise glycaemic control. **[2015, amended 2020]**

1.3.20 For pregnant women who are using isCGM or continuous glucose monitoring, a member of the joint diabetes and antenatal care team with expertise in these systems should provide education and support (including advising women about sources of out-of-hours support). **[2020]**

Diabetes Technology Network Top tips leaflets for women using CGM

https://abcd.care/resource/top-tips-using-dexcom-g6-real-time-cgm-pregnancy

GETTING BREAKFAST RIGHT

Breakfast is the most challenging meal for keeping the post meal glucose in target; carbohydrate is not well tolerated at this time of day. Most women have to spread their breakfast over 2 smaller meals containing 15-20g.

Good breakfast choices:

- 1 slice whole-wheat toast (C15g) with a topping e.g. poached or scrambled eggs / mushrooms / tomato / cheese / ham / bacon / avocado.
- 1 small pot yoghurt (C13g) with one small chopped fruit or cup of berries (C7g) topped with nuts / seeds
- 25g jumbo porridge oats (C15g) soaked overnight in crème fraiche and 1 cup berries (C7g), top with nuts / seeds
- 40g jumbo porridge oats (C25g) cooked with water and single cream added to taste

ACTION DONE (TICK BOX): ☐

BULKING UP MEALS WITH MORE PROTEIN AND VEGETABLES / SALAD

Eating more protein foods such as meat, fish, chicken, cheese, eggs, tofu, Quorn, pulses and vegetables will fill you up more and stop you feeling hungry. These foods also flatten out the post meal glucose rise and so help achieve the post meal glucose targets whilst avoiding dips in glucoses later.

ACTION DONE (TICK BOX): ☐

BEING ACTIVE AFTER EATING

Being active for 10-15 minutes after eating can make your post meal glucose level as much as 2 mmols/L lower and so help achieve the post meal glucose target.

This can be going for a walk or being active around the house or work place.

AVOID BEING INACTIVE IMMEDIATELY AFTER EATING

ACTION DONE (TICK BOX): ☐

AVOID EATING CARBOHYDRATE LATE IN EVENING

Overnight can be as much as a third of your day so getting glucose levels as near normal pre bed and overnight can really help optimise glucose levels for pregnancy.

Eating your evening meal before 7.30 pm and keeping evening snacks to minimal carbohydrate or carbohydrate free (unless eaten to avoid a hypo) can make all the difference to achieving the pre-bed, overnight and even fasting glucose targets.

ACTION DONE (TICK BOX): ☐

Diabetes Technology Network support videos and user stories for using CGM during pregnancy

https://abcd.care/dtn-education/diabetes-tech-in-pregnancy

ABCD/DTN Best Practice Guide: Using diabetes technology in pregnancy

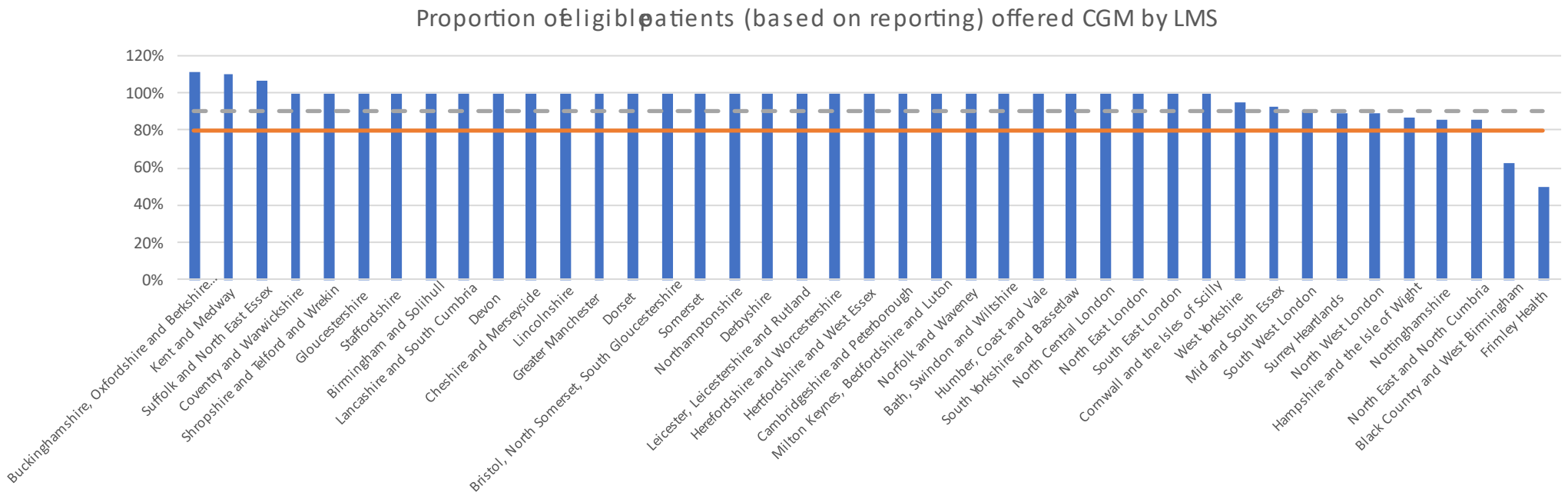
ABCD

DTN UK
collaborate · evolve · support

BEST PRACTICE GUIDE:
Using diabetes technology in pregnancy

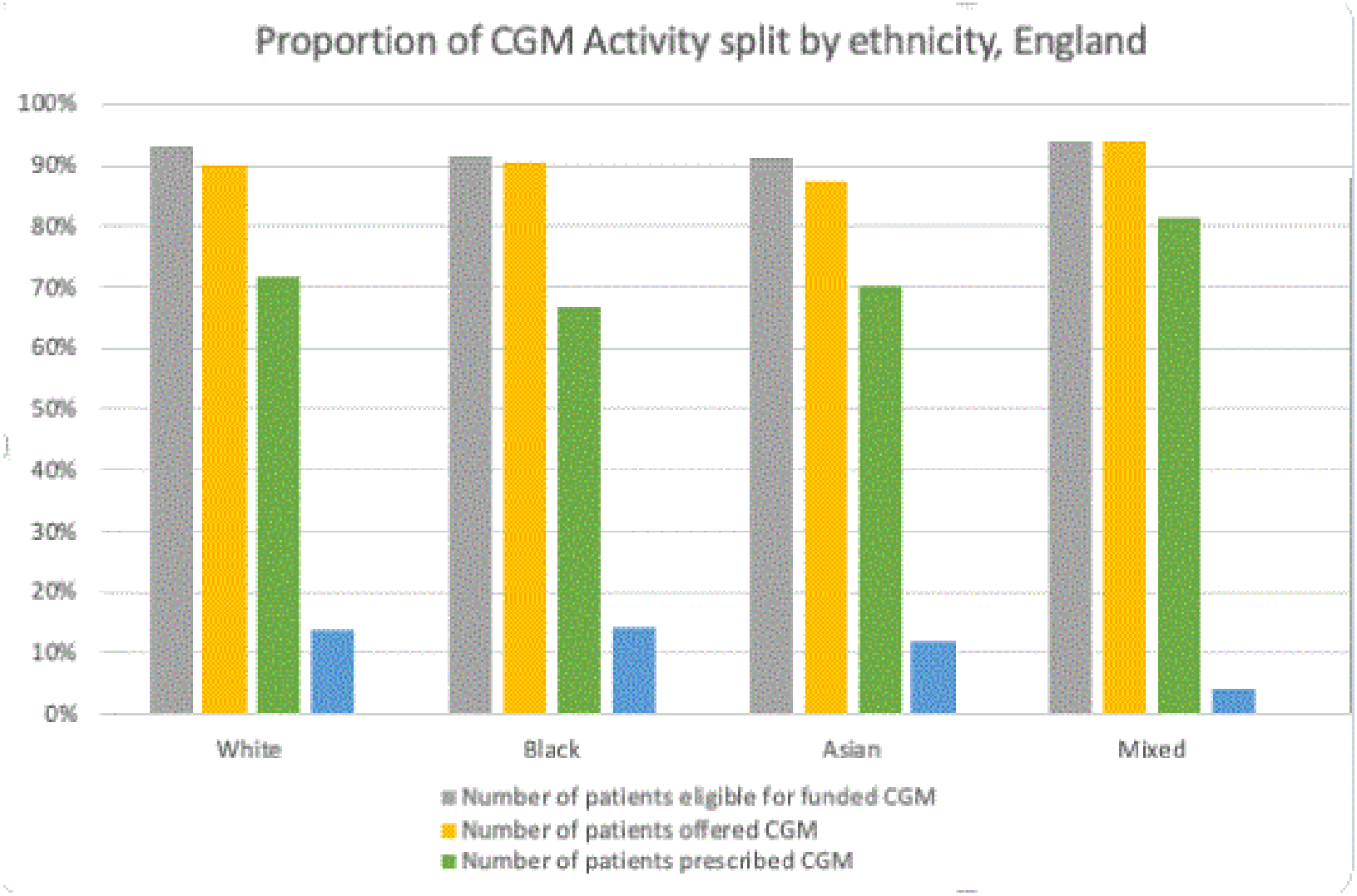
https://abcd.care/dtn/CGM

NHS England and Local Maternity Systems data - 98% uptake of CGM offer across pregnancy



NHS England and NHS Improvement

No healthcare inequalities with CGM implementation based on ethnicity (or social deprivation)



LGA rates are still high even in women using CGM

- Even in CONCEPTT, LGA rates are still occurring in ~50% of women using CGM
- So, is there more that we can learn about trends in glucose across pregnancy that will help us to use CGM more effectively?

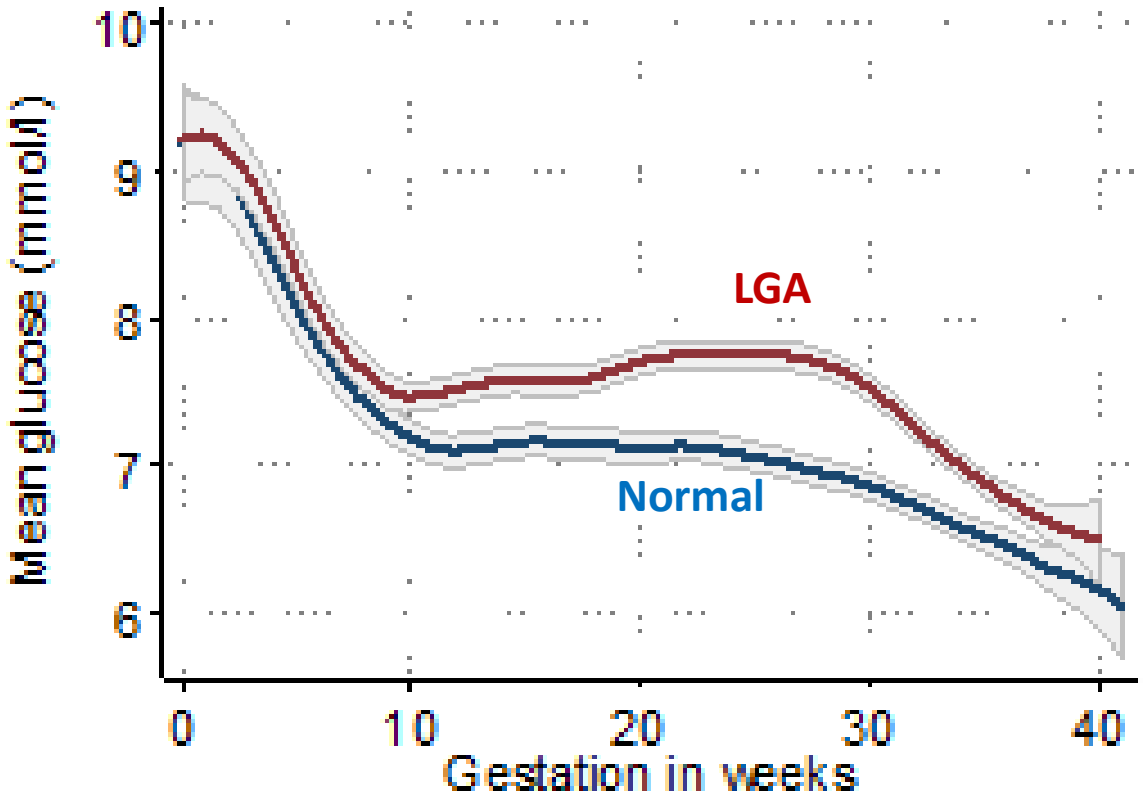
What do we do in clinical practice when using CGM

- Pregnant women with type 1 diabetes are reviewed frequently and therapeutic decisions are made based on the previous week's mean CGM glucose data (a combination of glucose summary metrics and 24hr glucose profiles)
- Pregnancy is a dynamic state of continuous metabolic adaptation with changes in insulin sensitivity and glucose tolerance throughout
- Weekly CGM glucose metrics and 24hr profiles associated with a normal birthweight baby are unknown
- Thus, despite widespread CGM use, international diabetes guidelines do not include gestationally appropriate CGM glucose targets

Scott EM, Murphy HR et al. Diabetes Care 2022 45 (8): 1724–1734

CGM metrics and birthweight

Mean Glucose (mmol/l)

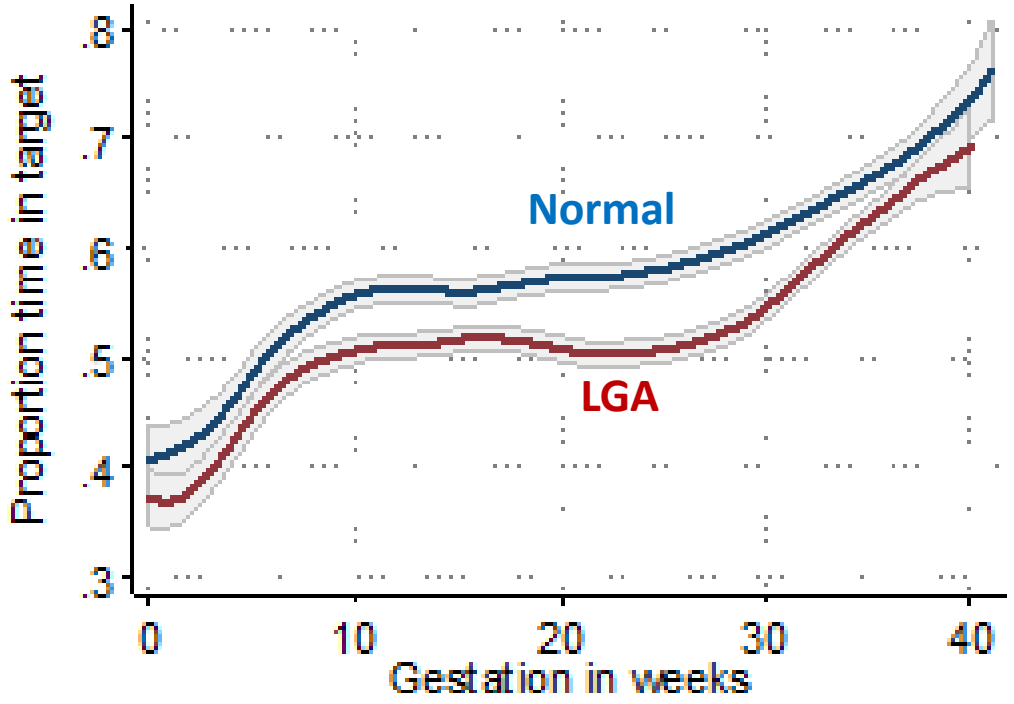


- Irrespective of baseline maternal glycemia, first trimester glucose levels decrease rapidly without initial differences between women who go onto have a normal sized or LGA infant
- However, maternal glucose trajectory achieved by 10 weeks gestation determines the relationship to birthweight for the rest of pregnancy
- Demonstrates central role of maternal glucose to the pathogenesis of LGA from early gestation
- Normal growth associated with mean glucose of 7 mmol/l (from 10 weeks)

Scott EM, Murphy HR et al. Diabetes Care 2022 45 (8): 1724–1734

CGM metrics and birthweight

% Time in pregnancy target range (3.5-7.8 mmol/l)

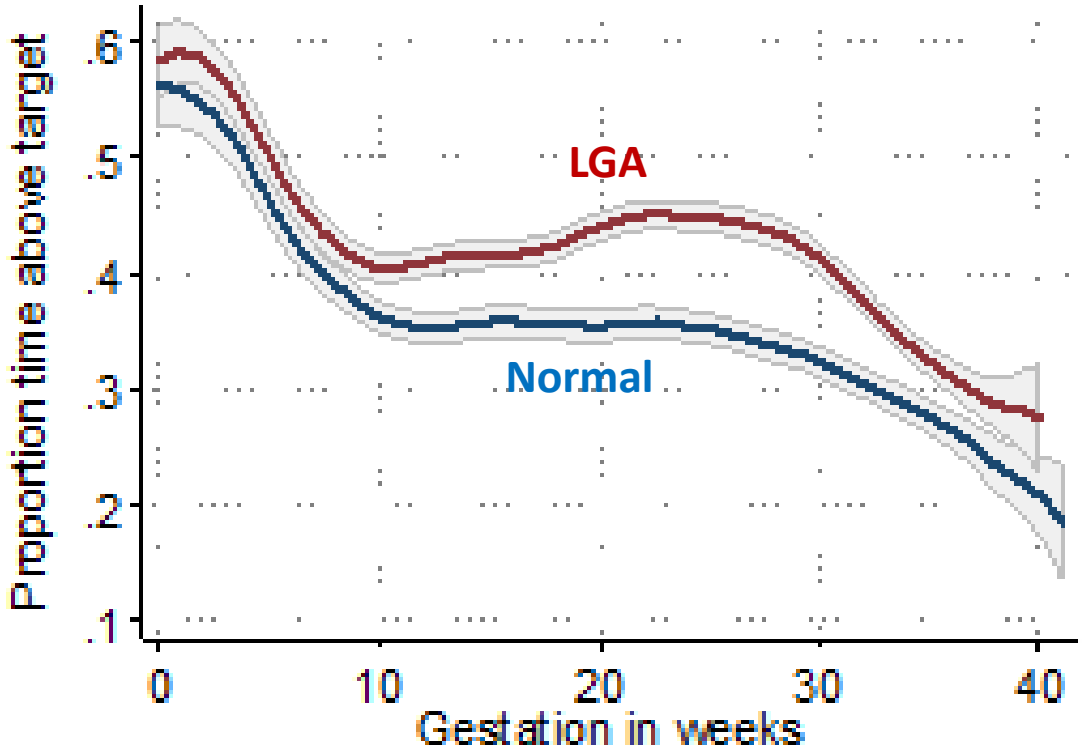


- International consensus that a TIR target of >70% is recommended in pregnancy
- Majority of women using CGM and intensive insulin therapy only reach this after 34 weeks
- Normal growth is associated with a TIR of 55-60% from 10 weeks
- Aiming to achieve 70% where possible thereafter

Scott EM, Murphy HR et al. Diabetes Care 2022 45 (8): 1724–1734

CGM metrics and birthweight

% Time above pregnancy target range (3.5-7.8 mmol/l)



- Normal growth associated with spending no more than 35% time above range from 10 weeks gestation
- Given that >50% of women had LGA despite using CGM and intensive insulin therapy, it suggests that new advances such as closed-loop insulin delivery is likely to be required for widespread attainment of the time in range targets for pregnancy

Scott EM, Murphy HR et al. Diabetes Care 2022 45 (8): 1724–1734

So how can we improve further?

In CONCEPTT, CGM improved rates of LGA from 70% to 50% and gained almost 2 hours extra time spent in glucose pregnancy range

Still some way to go……

Closed Loop or Automated insulin delivery (AID) is a way of delivering insulin through an insulin pump that communicates with a continuous glucose monitor (CGM) and an algorithm

Closed Loop in pregnancy pioneers in UK……

Professor Roman Hovorka

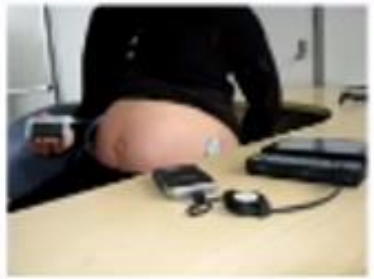
Professor Helen Murphy

CamAPS FX

HCL in T1D pregnancy timeline

CLIP-02
Murphy et al. (2011)

Crossover RCT
n = 12
24hr closed-loop vs. SAP
2 x 24hr inpatient admissions
Snacks, meals and exercise



CLIP-04
Stewart et al. (2018)

Crossover RCT
n = 16
4 weeks 24hr
HCL vs. SAP
Home setting

Commercialised HCL (2020)

CamAPS Fx
Licensed in pregnancy

CLIP-01
Murphy et al. (2011)

Exploratory safety study
n = 10
2 x 24hr inpatient admissions
1st : early pregnancy (12-16 weeks)
2nd : late pregnancy (28-32 weeks)
High carbohydrate meals

CLIP-03
Stewart et al. (2016)

Crossover RCT
n = 16
4 weeks overnight
HCL vs. SAP
Home setting
Optional continuation

Adaptability in labour and delivery
Stewart et al. (2018)

n = 27
Continuation phase of CLIP-03 and CLIP-4 for rest of pregnancy including **home and hospital settings**

Closed loop in pregnancy (CLIP-03)
= better glucose control/TIR than Sensor Augmented Pump

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes

Zoe A. Stewart, M.D., Malgorzata E. Wilinska, Ph.D., Sara Hartnell, B.Sc., Rosemary C. Temple, M.D., Gerry Rayman, M.D., Katharine P. Stanley, M.D., David Simmons, M.D., Graham R. Law, Ph.D., Eleanor M. Scott, M.D., Roman Hovorka, Ph.D., and Helen R. Murphy, M.D.

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ABSTRACT

BACKGROUND
In patients with type 1 diabetes who are not pregnant, closed-loop (automated) insulin delivery can provide better glycemic control than sensor-augmented pump therapy, but data are lacking on the efficacy, safety, and feasibility of closed-loop therapy during pregnancy.

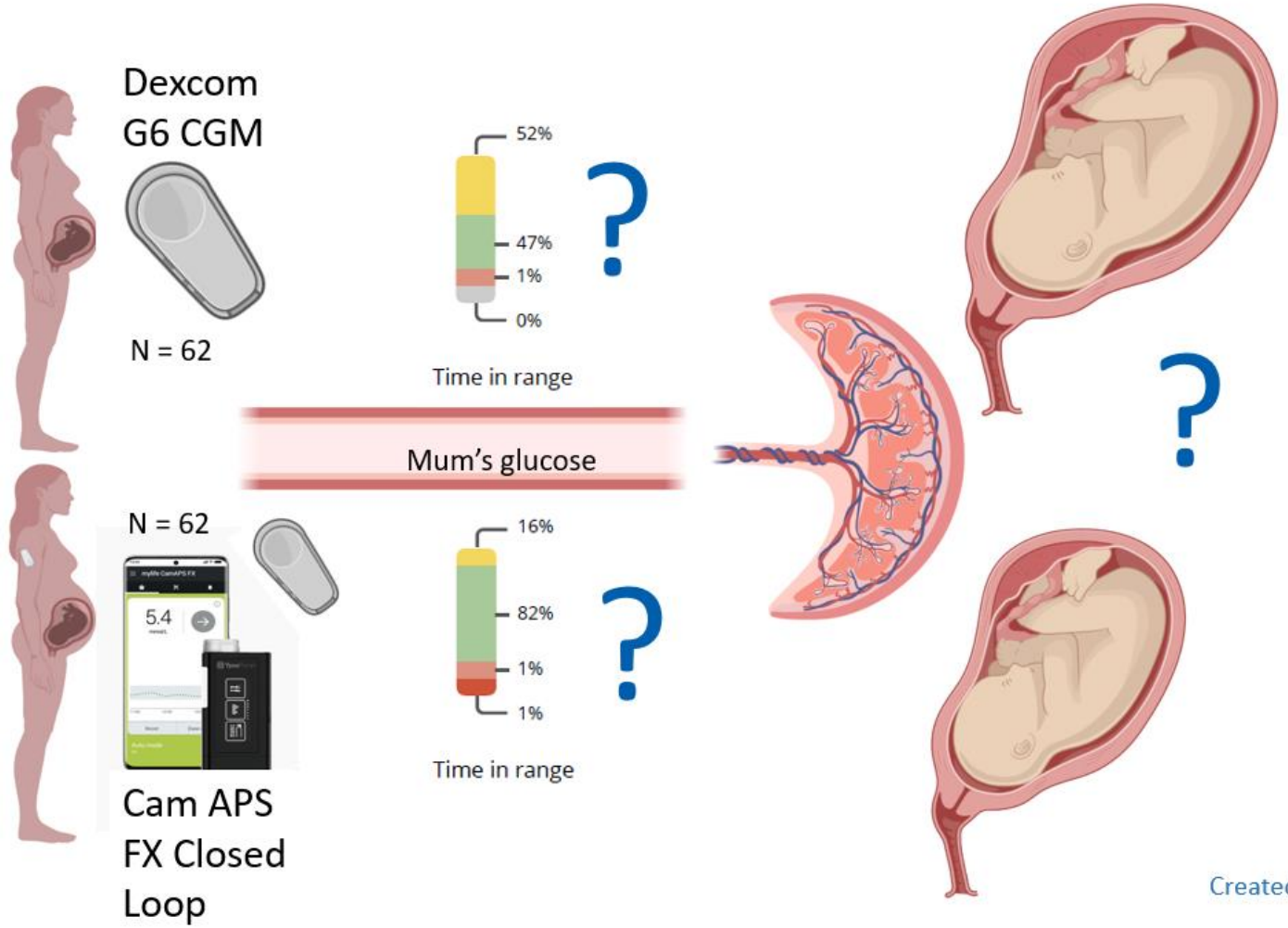
METHODS
We performed an open-label, randomized, crossover study comparing overnight closed-loop therapy with sensor-augmented pump therapy, followed by a continuation phase in which the closed-loop system was used day and night. Sixteen pregnant women with type 1 diabetes completed 4 weeks of closed-loop pump therapy (intervention) and sensor-augmented pump therapy (control) in random order. During the continuation phase, 14 of the participants used the closed-loop system day and night until delivery. The primary outcome was the percentage of time that overnight glucose levels were within the target range (63 to 140 mg per deciliter [3.5 to 7.8 mmol per liter]).

RESULTS
The percentage of time that overnight glucose levels were in the target range was higher during closed-loop therapy than during control therapy (74.7% vs. 59.5%; absolute difference, 15.2 percentage points; 95% confidence interval, 6.1 to 24.2; P=0.002). The overnight mean glucose level was lower during closed-loop therapy than during control therapy (119 vs. 133 mg per deciliter [6.6 vs. 7.4 mmol per liter], P=0.009). There were no significant differences between closed-loop and control therapy 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 (up to 14.6 additional weeks, including antenatal hospitalizations, labor, and delivery), glucose levels were in the target range 68.7% of the time; the mean glucose level was 126 mg per deciliter (7.0 mmol per liter). No episodes of severe hypoglycemia requiring third-party assistance occurred during either phase.

CONCLUSIONS
Overnight closed-loop therapy resulted in better glucose control than sensor-augmented pump therapy in pregnant women with type 1 diabetes. Women receiving day-and-night closed-loop therapy maintained glycemic control during a high proportion of the time in a period that encompassed antenatal hospital admission, labor, and delivery. (Funded by the National Institute for Health Research and others; Current Controlled Trials number, ISRCTN71510001.)

Stewart Z et al. NEJM 2016; 375: 644-654

Automated Insulin Delivery Amongst Pregnant women with Type 1 diabetes



- Maternal glucose (time in range)
- Neonatal outcomes (NICU, LGA)
- Qualitative data outcomes
- Health economic outcomes
- Data submitted to NICE HTA
- Being presented at ADA (publication on its way)

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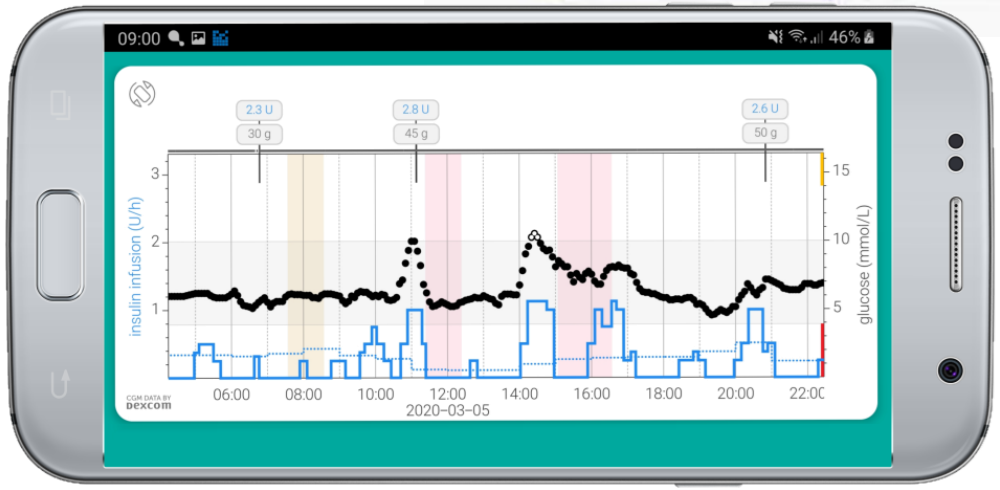
NIHR | National Institute for Health Research

How does CamAPS FX work?

Modulates basal insulin delivery by:

- Adjusting insulin every 8-12 minutes

- Causes for no delivery (occlusion, low reservoir) will result in pump alarm / vibrate
- **Hybrid closed-loop → still requires insulin boluses for carbohydrates**



How does CamAPS FX work?

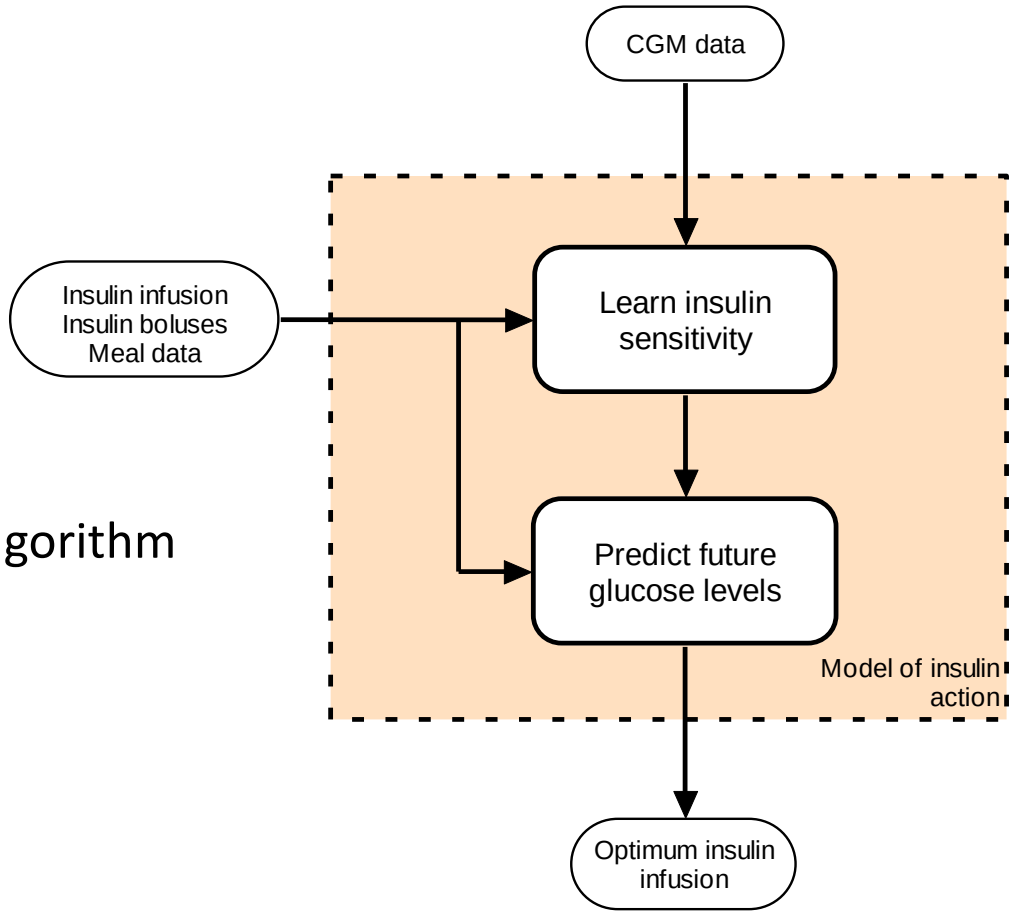
What are the **inputs** to the algorithm?

Starting the system

- ✓ **Body weight & Total Daily Dose (TDD)**
- ✓ Insulin sensitivity and active insulin time calculated by algorithm

Ongoing

- ✓ Real-time CGM
- ✓ Carbohydrates and pre-meal insulin boluses



Understanding CamAPS FX settings

Adjustable settings to optimise outcomes

✓Insulin to Carbohydrate ratio

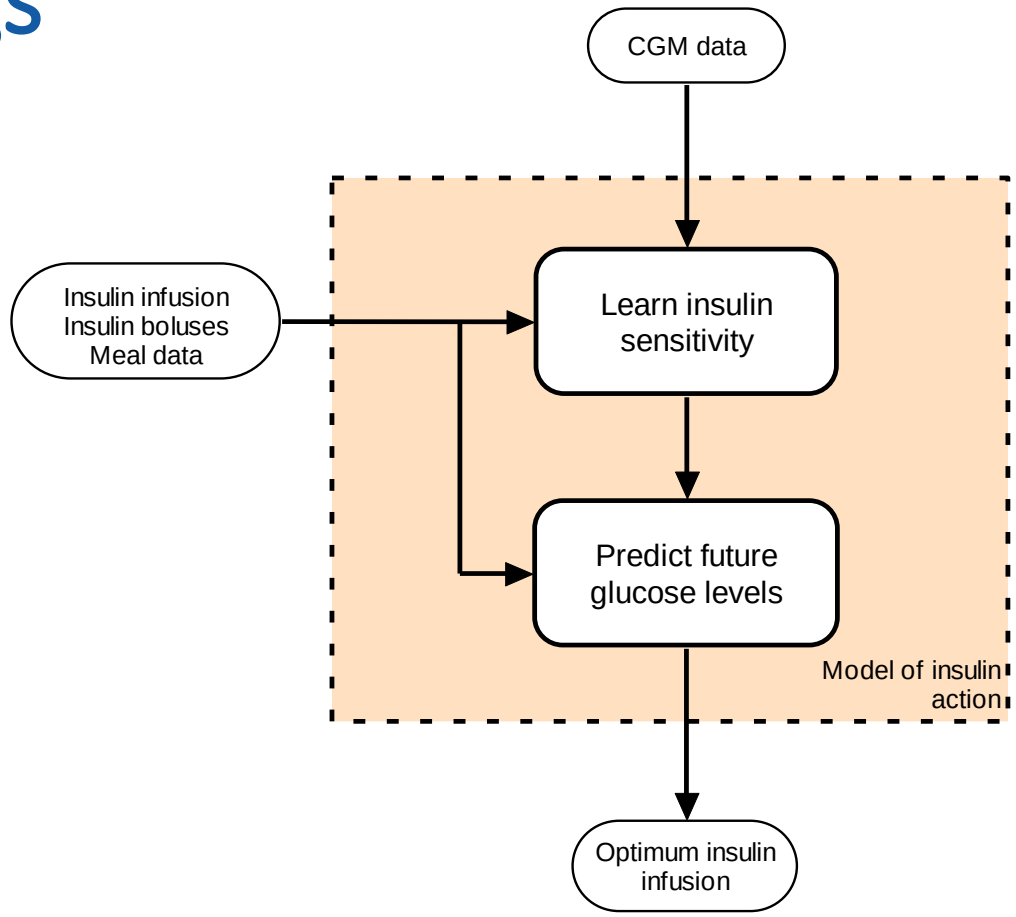
✓Glucose Target – default ~5.8mmol/l

Settings not affecting closed-loop operation

x Active insulin time

x Insulin sensitivity

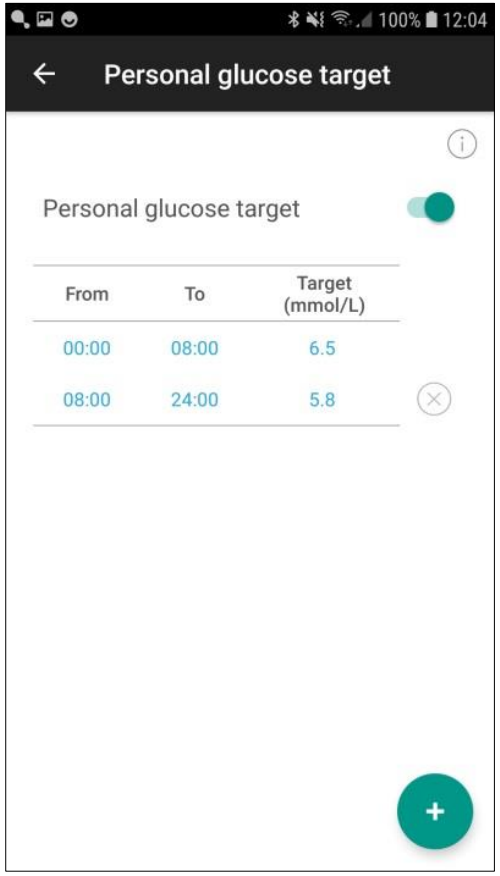
x Pre-programmed basal rates



NB: Basal rates, insulin sensitivity and active insulin time are important if Auto Mode is not available.

Personal glucose target – customisable for pregnancy

Algorithm target (default 5.8 mmol/L) adjustable at different times of day & night



Suggested algorithm targets in pregnancy:

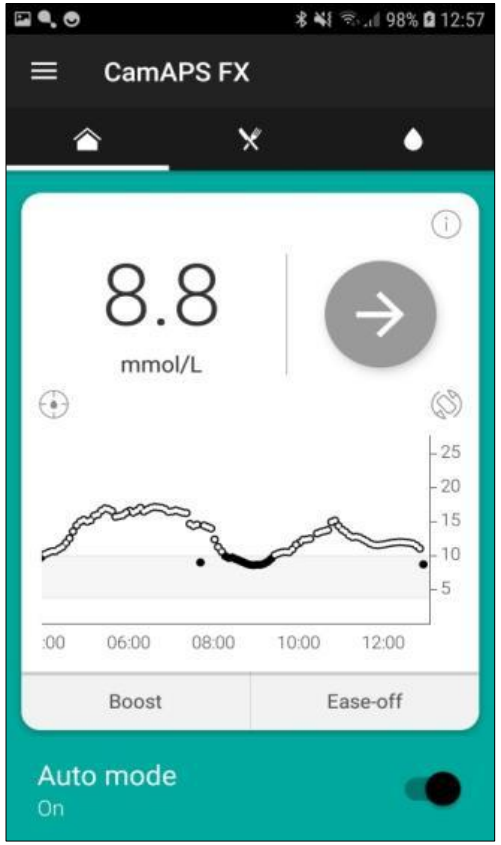
- 1st trimester: 5.5 mmol/L
- 2nd trimester (or earlier if hypo risk low): 4.5-5.0 mmol/L

Treat to target:

- TIR (3.5-7.8 mmol/L): 70%
- mean glucose: 6.0-6.5 mmol/L

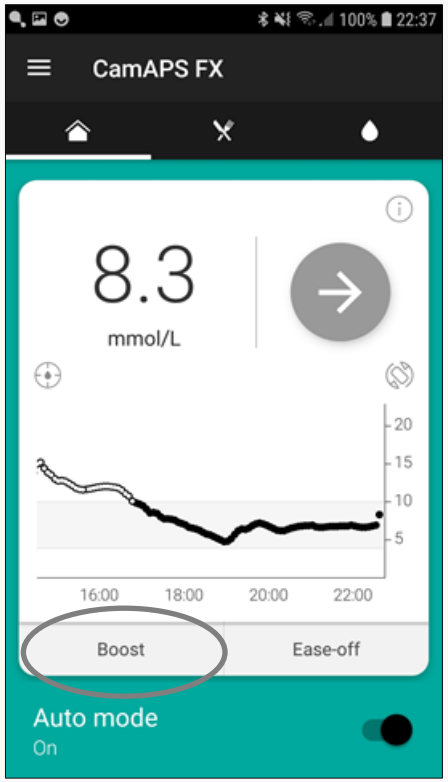
When to adjust target

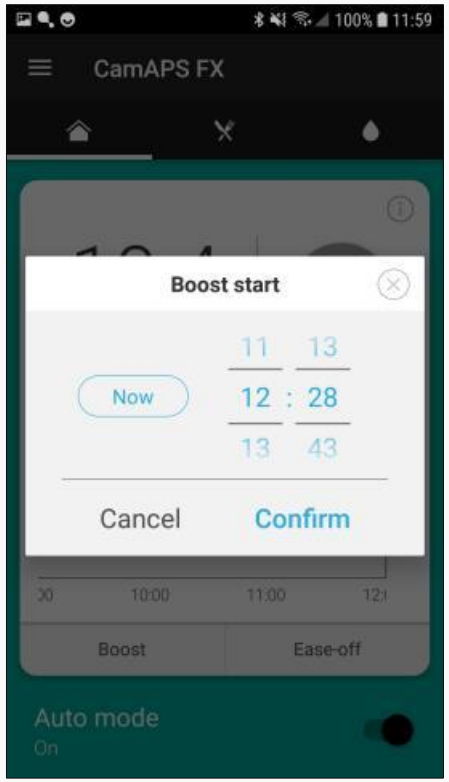
- Lower target if glucose variability low
- Raise target if period of frequent hypoglycaemia

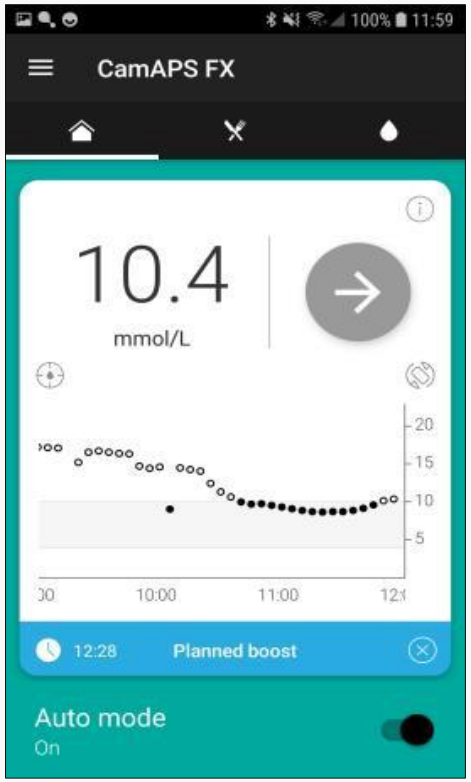


Boost

- Increases basal insulin delivery by ~35%
- Once glucose reaches target, boost **will not** continue to increase insulin delivery





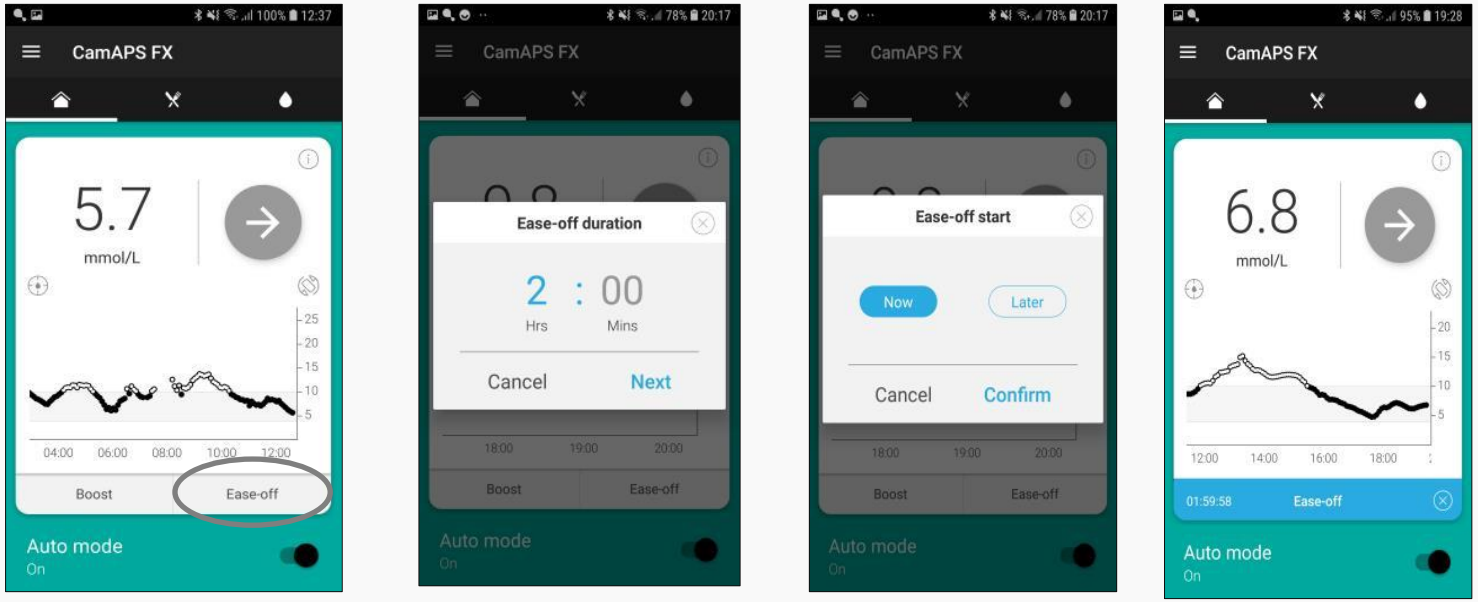


When to use Boost?

- Post prandial hyperglycaemia
- Low grade illness (not requiring sick day rules)

Ease Off

- Substantially reduces basal insulin delivery
- Raises glucose target temporarily by 2.5mmol
- Insulin delivery stops if glucose < 7 mmol/L
- Tries to prevent glucose falling below 6.1mmol – depending on the fall rate, the system may suspend insulin delivery earlier.



When to use Ease Off?

- Before, during and/or after exercise/activity
- Following hypoglycaemia
- Hot weather

Pregnancy Intervention With a Closed-Loop System (PICLS)

- Pilot RCT Sensor augmented pump vs. hybrid CL (**Medtronic 670G)**
- **N=47 women** ≤11 weeks gestation
- 2 USA centers (Colorado & Ohio)
- SAPT birth until 3-7 days post-partum then CL
- Primary outcome severe hypoglycemia

https://clinicaltrials.gov/ct2/show/NCT03774186

PI Sarit Polsky

CRISTAL

- RCT Standard care vs. **780G Medtronic Guardian 3/4**
- **N=92** (52 recruited) stratified center/pump vs MDI/HbA1c
- 12 centers (11 Belgium, 1 Netherlands)
- Masked CGM at ~ 14, 20, 26, 33/40
- Primary outcome TIR 14-36 weeks
- Planned health economic analsyes

https://clinicaltrials.gov/ct2/show/NCT04520971

PI Katrien Benhalima

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Closed-loop Insulin delivery by glucose Responsive Computer algorithms In Type 1 diabetes pregnancies – Pilot:

- CIRCUIT N=**66** (18 recruited) Diab Canada 300k x 3yrs Feb 2022
- Tandem t:slim X2 with Control IQ vs CGM DexcomG6
- Primary outcomes CGM TIR 3.5-7.8mmol/L

- LOIS-P Modified zone MPC with t:slim
- N=21 48-60hr supervised studies USA
- www.liebertpub.com/doi/10.1089/dia.2021.0521

https://clinicaltrials.gov/ct2/show/NCT04902378

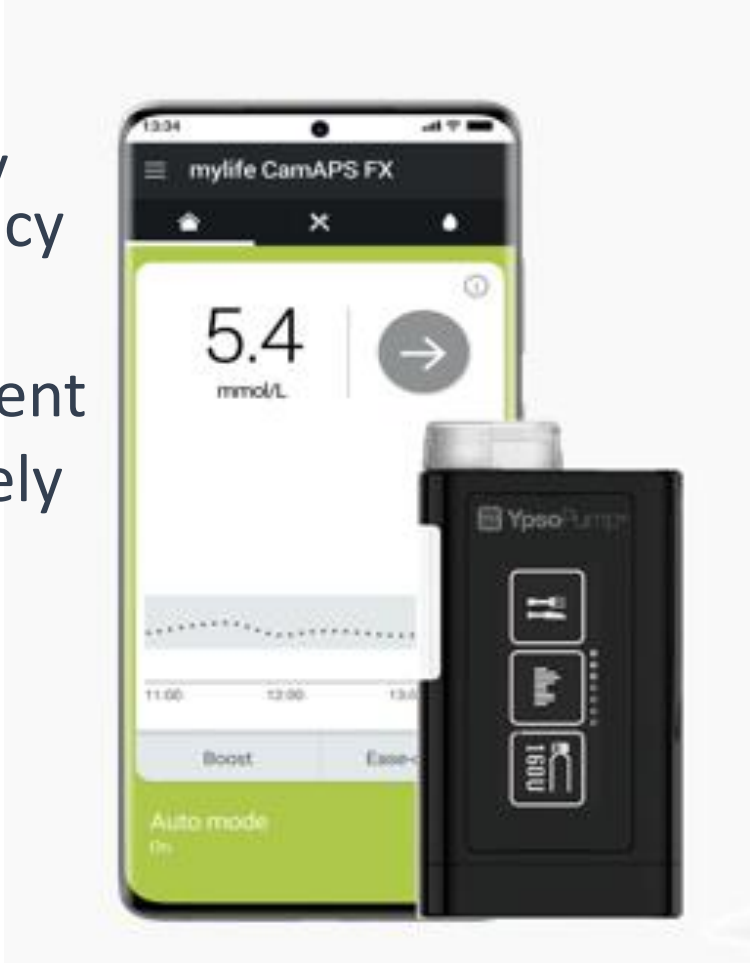
PIs Lois Donovan & Denice Feig

Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

In development [GID-TA10845] Expected publication date: TBC Register as a stakeholder

Take home messages

- ✓Closed Loop is the future for T1DM in pregnancy
- ✓CamAPS is the one that has received CE Mark for pregnancy and has customisable glucose targets necessary for pregnancy
- ✓It's not complicated - Have a go!
- ✓Diet carb quality/quantity is key for diabetes self-management
- ✓It allows more aggressive carb insulin ratio adjustments safely
- ✓Continue CL during antenatal admissions, labour/birth, postnatal
- ✓Stop CL during VRIII
- ✓Aim for 70% TIR mean glucose 6-6.5mmol/L but every little helps



Thank you.....

Prof Graham Law

Prof Helen Murphy

Prof Denice Feig

All women and their babies who've taken part in our research

DTN UK
collaborate · evolve · support

NHS England

MRC Medical Research Council

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