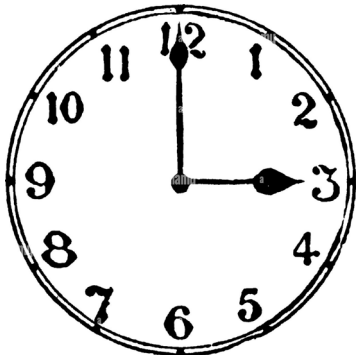
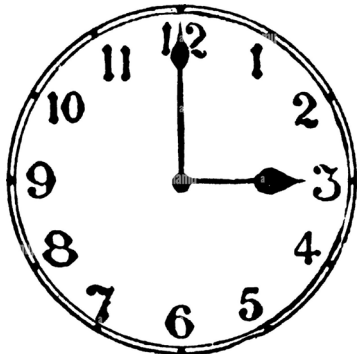
HOT TOPICS IN GRAVIDANZA

La gravidanza è sempre più tecnologica?





Il Dr. Andrea Tumminia dichiara di **non** aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Our primary aim

Diabetes Care and Research in Europe:
The St Vincent Declaration
1989

"Achieve pregnancy outcome in the diabetic woman that *approximates* that of the non-diabetic woman"

Glycemic goals for pregnant women with diabetes

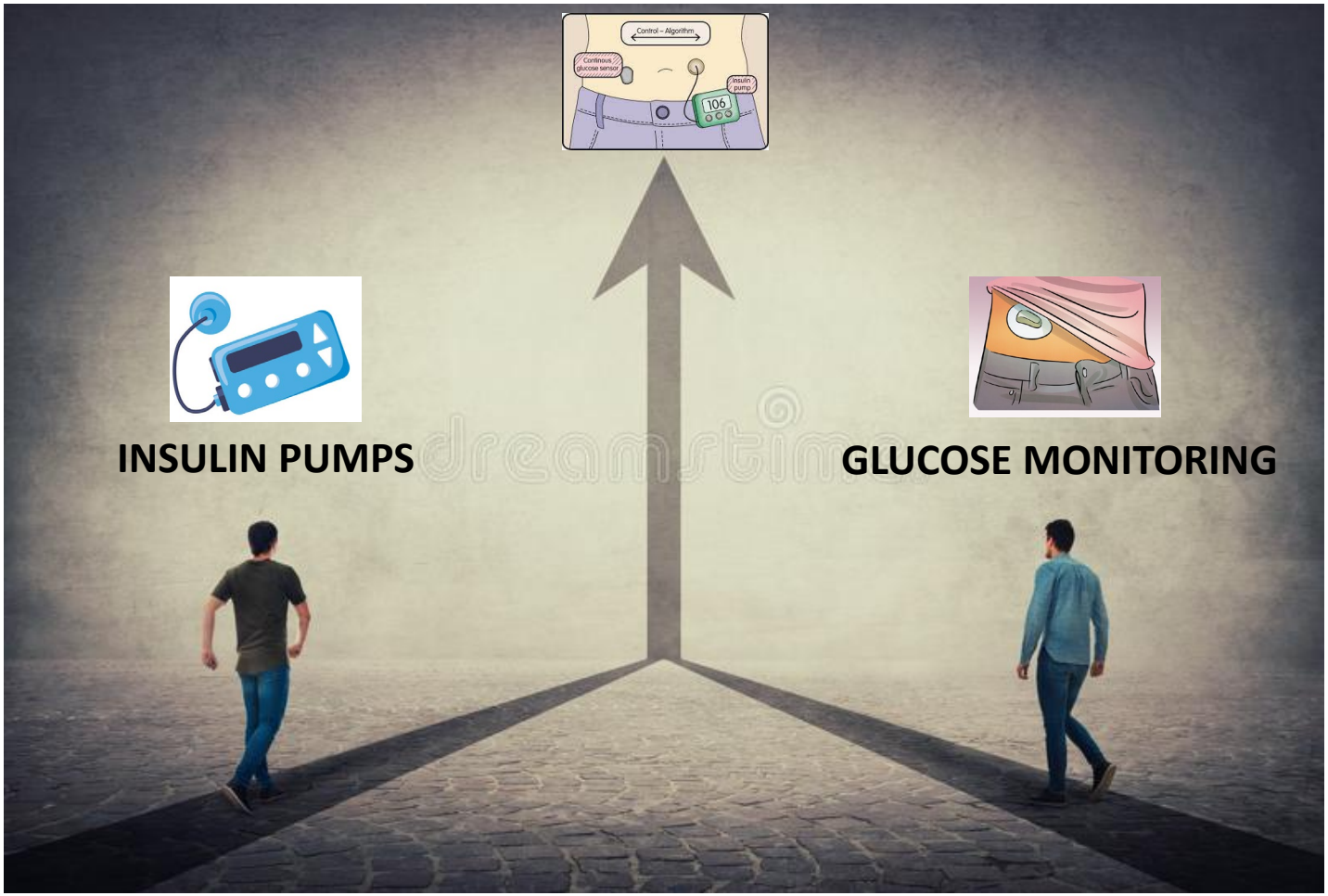
American Diabetes Association®

15. Management of Diabetes in Pregnancy: *Standards of Care in Diabetes—2024*

Similar to the targets recommended by ACOG (upper limits are the same as for GDM, described below), the ADA-recommended targets for women with type 1 or type 2 diabetes are as follows:

- Fasting glucose 70–95 mg/dL (3.9–5.3 mmol/L) and either
- One-hour postprandial glucose 110–140 mg/dL (6.1–7.8 mmol/L) or
- Two-hour postprandial glucose 100–120 mg/dL (5.6–6.7 mmol/L)

American Diabetes Association, Standard of Medical Care in Diabetes, 2024



- Different study designs
- Different populations
- Different primary outcomes
- Evolving technology

Journal of Perinatology (2020) 40:1145–1153
https://doi.org/10.1038/s41372-020-0698-x

ARTICLE

Time trends in pregnancy-related outcomes among women with type 1 diabetes mellitus, 2004–2017

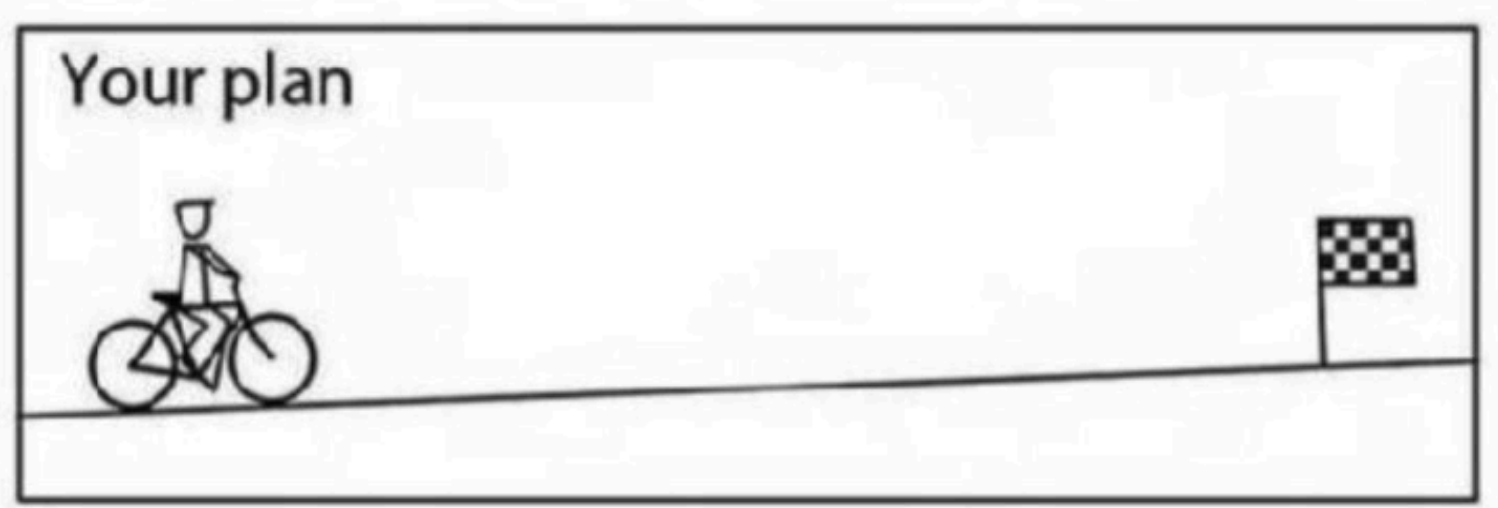
Objective: to examine time trends in US pregnant women with type 1 diabetes mellitus for maternal characteristics and pregnancy outcomes.

Table 3 Delivery outcomes in women with type 1 diabetes over 14 years of follow-up.

	2004–2008 $n = 214$	2009–2012 $n = 215$	2013–2017 $n = 271$	P for trend
Birthweight (kg) ($n = 696$)	3.63 ± 0.74	3.62 ± 0.73	3.75 ± 0.78	$P = 0.07$
Birthweight percentiles ($n = 696$)	82.0 ± 24.9	79.4 ± 25.8	82.4% ± 25.1	$P = 0.77$
Macrosomia ($n = 696$)	67 (31.5%)	65 (30.2%)	100 (37.2%)	$P = 0.16$
LGA ($n = 696$)	121 (56.8%)	113 (52.8%)	166 (61.7%)	$P = 0.24$
SGA ($n = 696$)	7 (3.3%)	6 (2.8%)	5 (1.9%)	$P = 0.32$
Gestational age at delivery (weeks) ($n = 698$)	37.0 ± 2	37.1 ± 2	37.4 ± 2	$P = 0.01$
Preterm deliveries before 37 weeks ($n = 698$)	61 (28.6%)	54 (25.2%)	63 (23.2%)	$P = 0.18$
Preterm deliveries before 32 weeks ($n = 698$)	4 (1.9%)	3 (1.4%)	4 (1.5%)	$P = 0.74$
Vaginal deliveries ($n = 698$)	45 (21.1%)	52 (24.2%)	80 (29.6%)	$P = 0.03$
Primary cesarean delivery ($n = 368$)[a]	91 (81.3%)	86 (72.3%)	97 (70.8%)	$P = 0.06$
Neonatal hypoglycemia that required NICU ($n = 422$, during 2009–2016)[b]	–	34 (16.0%)	58 (27.8%)	$P = 0.004$

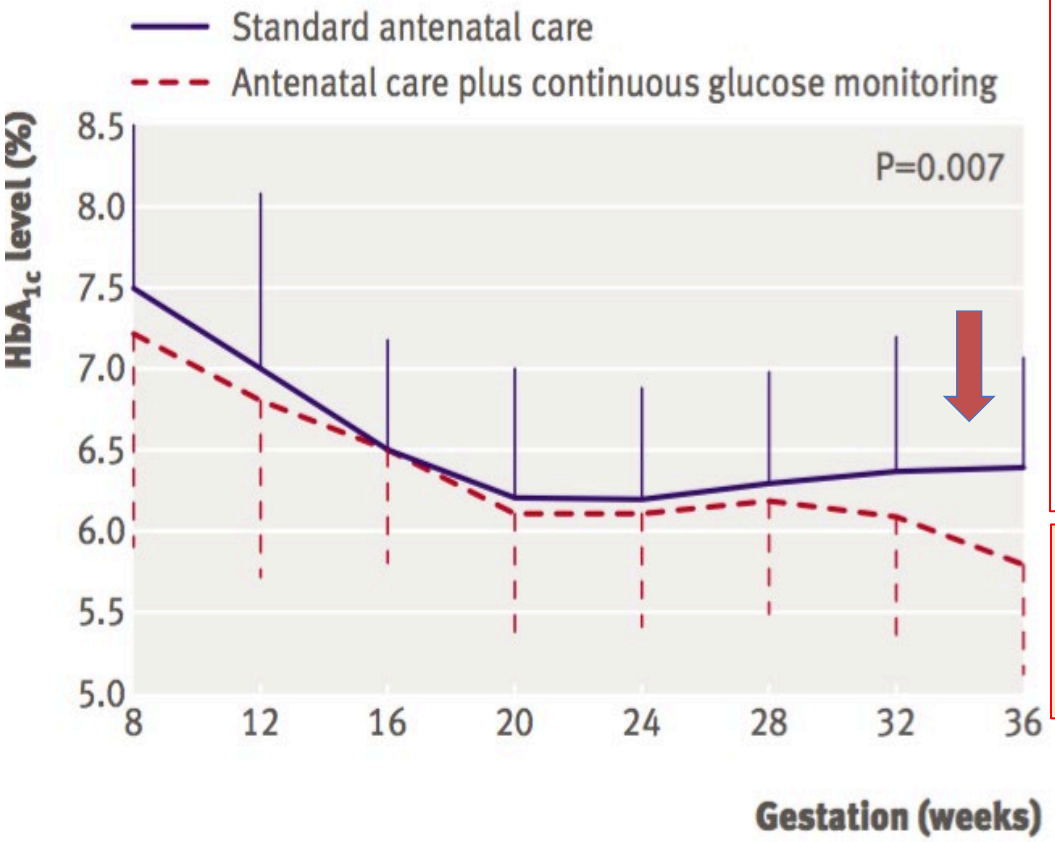
Helman et al, Journal of Perinatology, 2020

Use of diabetes technology during pregnancy



Retrospective (blinded) CGM

Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial



Intervention Continuous glucose monitoring was used as an educational tool to inform shared decision making and future therapeutic changes at intervals of 4-6 weeks during pregnancy. All other aspects of antenatal care were equal between the groups.

Main outcome measures The primary outcome was maternal glycaemic control during the second and third trimesters from measurements of HbA_{1c} levels every four weeks. Secondary outcomes were birth weight and risk of macrosomia using birthweight standard deviation scores and customised birthweight centiles. Statistical analyses were done on an intention to treat basis.

MACROSOMIA:

35% (intervention arm) P=0.05

60% (control arm)

Murphy HR et al, BMJ 2008

Real-Time (intermittent) CGM

The Effect of Real-Time Continuous Glucose Monitoring in Pregnant Women With Diabetes

	Real-time CGM	Control subjects	*P* value
N (% with type 1 diabetes)	79 (80)	75 (80)	
Live births	76 (96%)	73 (97%)	
Miscarriage	3 (4%)	2 (3%)	1.00
Males	34 (45%)	31(42%)	0.78
Weight gain in pregnancy (kg)	14.4 (−0.4 to 32.5)	13.9 (−2.0 to 31.0)	0.92
Preeclampsia	7 (9%)	6 (8%)	0.83
Caesarean section	28 (37%)	33 (45%)	0.30
Gestational age at birth (days)	263 (206–280)	264 (231–277)	0.14
Preterm delivery	16 (21%)	12 (16%)	0.47
Birth weight (g)	3,510 (1,070–4,356)	3,436 (2,045–4,424)	0.80
Birth weight z-score	1.07 (−2.32 to 3.78)	0.66 (−1.13 to 3.45)	0.20
Large-for-gestational-age infant	34 (45%)	25 (34%)	0.19
2-h plasma glucose (mmol/L)	2.8 (0.5–5.5)[a]	2.8 (1.1–6.7)	0.22
Neonatal hypoglycemia	25 (36%)[a]	29 (40%)	0.62
Severe neonatal hypoglycemia	9 (13%)[a]	10 (14%)	0.88
Preterm delivery and/or severe neonatal hypoglycemia	20 (29%)[a]	16 (22%)	0.36

INTERVENTION:
3-6 days RT-CGM
(8°, 12°, 21°, 27°, 33°)

<15% of total time

Comparable glucose control

Comparable outcomes

Secher A et al, Diabetes Care 2013

Cochrane Library

Cochrane Database of Systematic Reviews

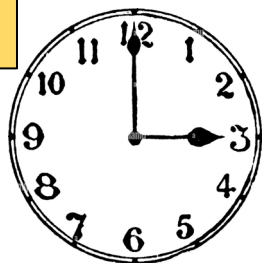
Techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes (Review)

Moy FM, Ray A, Buckley BS, West HM

Cochrane Database Syst Rev. 2017 Jun 11;6

This review found no evidence that any glucose monitoring technique is superior to any other technique among pregnant women with pre-existing type 1 or type 2 diabetes. The evidence base for the effectiveness of monitoring techniques is weak and additional evidence from large well-designed randomised trials is required to inform choices of glucose monitoring techniques.

1



Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial

USAGE TIME

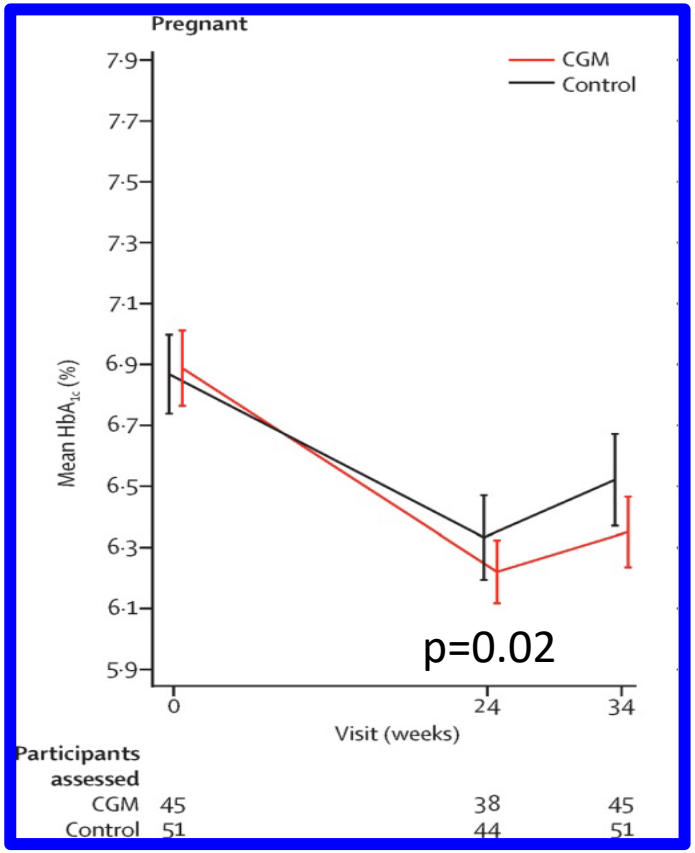
(> 6 days per week)

Primary Objective: if RT-CGM can improve glycemic control in women with T1DM who are pregnant or planning pregnancy

Results: 325 women (215 pregnant, 110 planning)

- **RT-CGM + SMBG** vs. **SMBG**
- **Lower HbA1c** in pregnant women using CGM (mean difference −0.19%; p=0.02
- CGM users spent **more time in target** and **less time hyperglycaemic**

- Lower incidence of: **LGA, neonatal intensive care admissions, neonatal hypoglycaemia**



Feig D. et al, The Lancet Diabetes Endocrinol, 2017

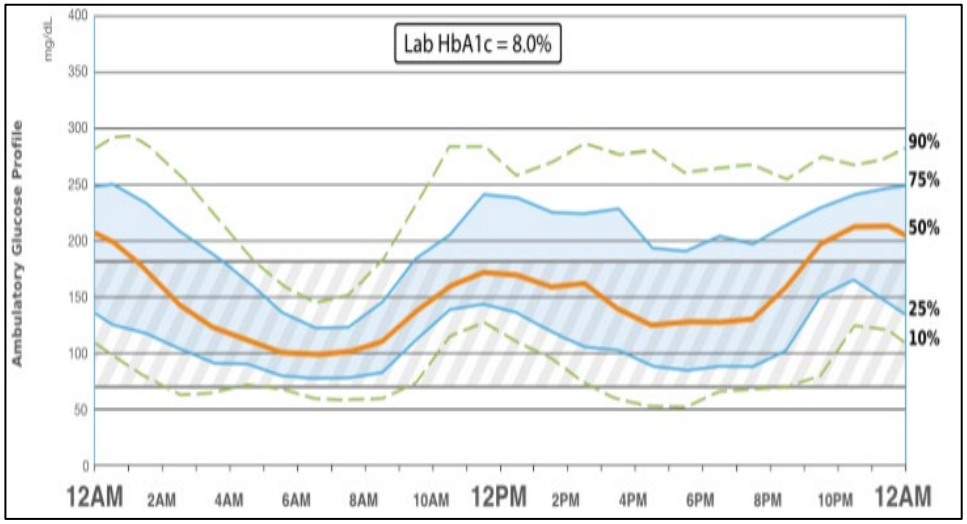
American Diabetes Association®

15. Management of Diabetes in Pregnancy: *Standards of Care in Diabetes—2024*

15.10 CGM is recommended in pregnancies associated with type 1 diabetes. **A** When used in addition to blood glucose monitoring, achieving traditional pre- and postprandial goals, real-time CGM can reduce the risk for large-for-gestational age infants and neonatal hypoglycemia in pregnancy complicated by type 1 diabetes. **A**

15.11 CGM metrics may be used in addition to but should not be used as a substitute for blood glucose monitoring to achieve optimal pre- and postprandial glycemic goals. **E**

- **CGM is recommended** in T1D during pregnancy
- **CGM metrics** may be helpful



American Diabetes Association, Standard of Medical Care in Diabetes, 2024

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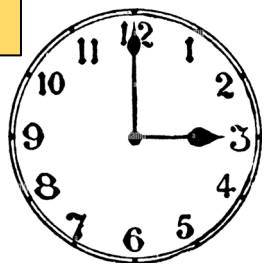
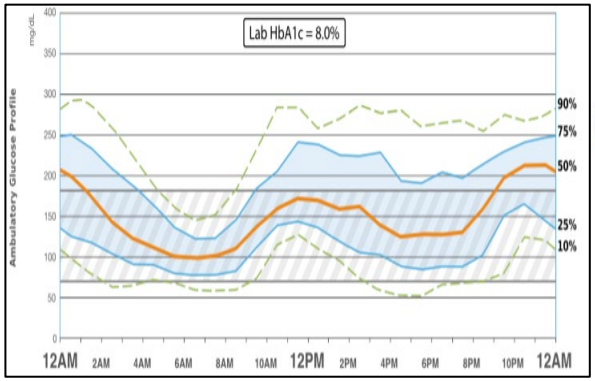
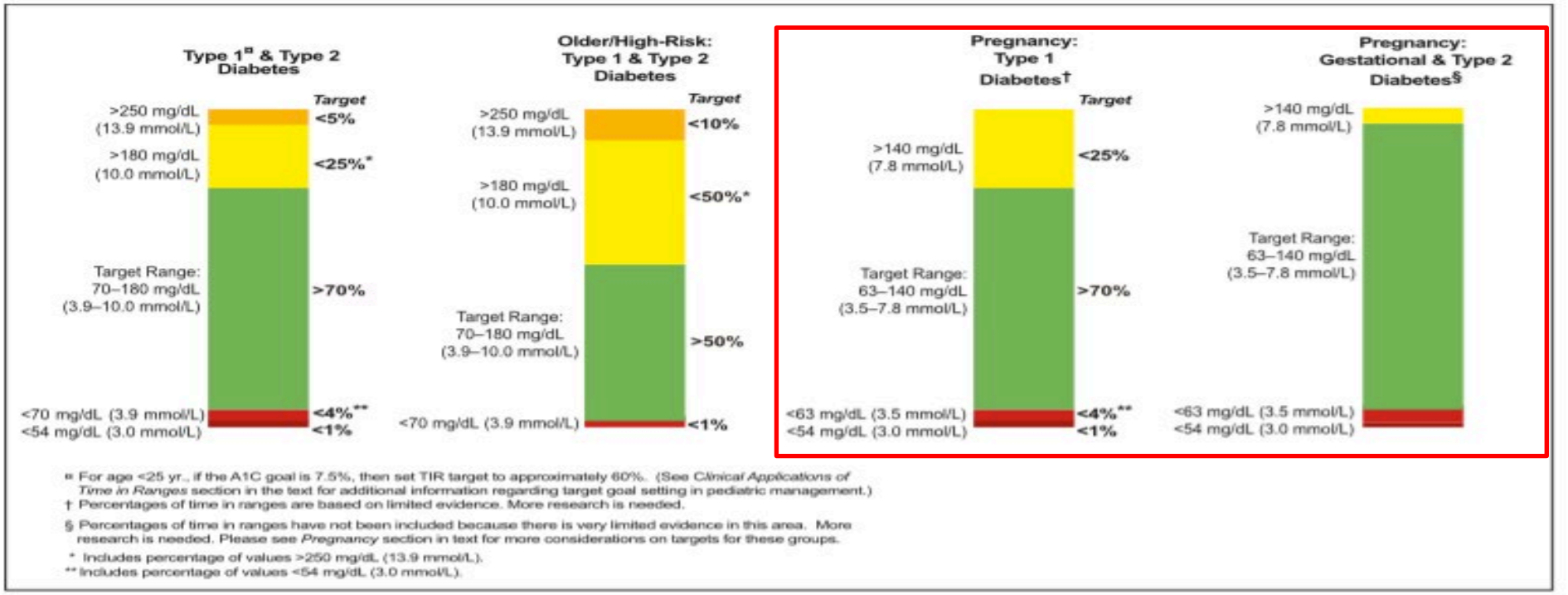


Time in target glucose ranges





¤ For age <25 yr., if the A1C goal is 7.5%, then set TIR target to approximately 60%. (See *Clinical Applications of Time in Ranges* section in the text for additional information regarding target goal setting in pediatric management.)
† Percentages of time in ranges are based on limited evidence. More research is needed.
§ Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please see *Pregnancy* section in text for more considerations on targets for these groups.
* Includes percentage of values >250 mg/dL (13.9 mmol/L).
** Includes percentage of values <54 mg/dL (3.0 mmol/L).

- Percentage of readings (%)
- Time per day (hours)

Time In Range (TIR)
Time Above Range (TAR)
Time Below Range (TBR)

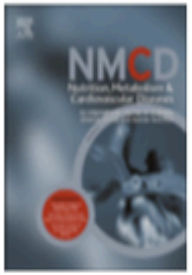
Battelino T. et al, Diabetes Care, 2019

Flash Glucose Monitoring during pregnancy

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

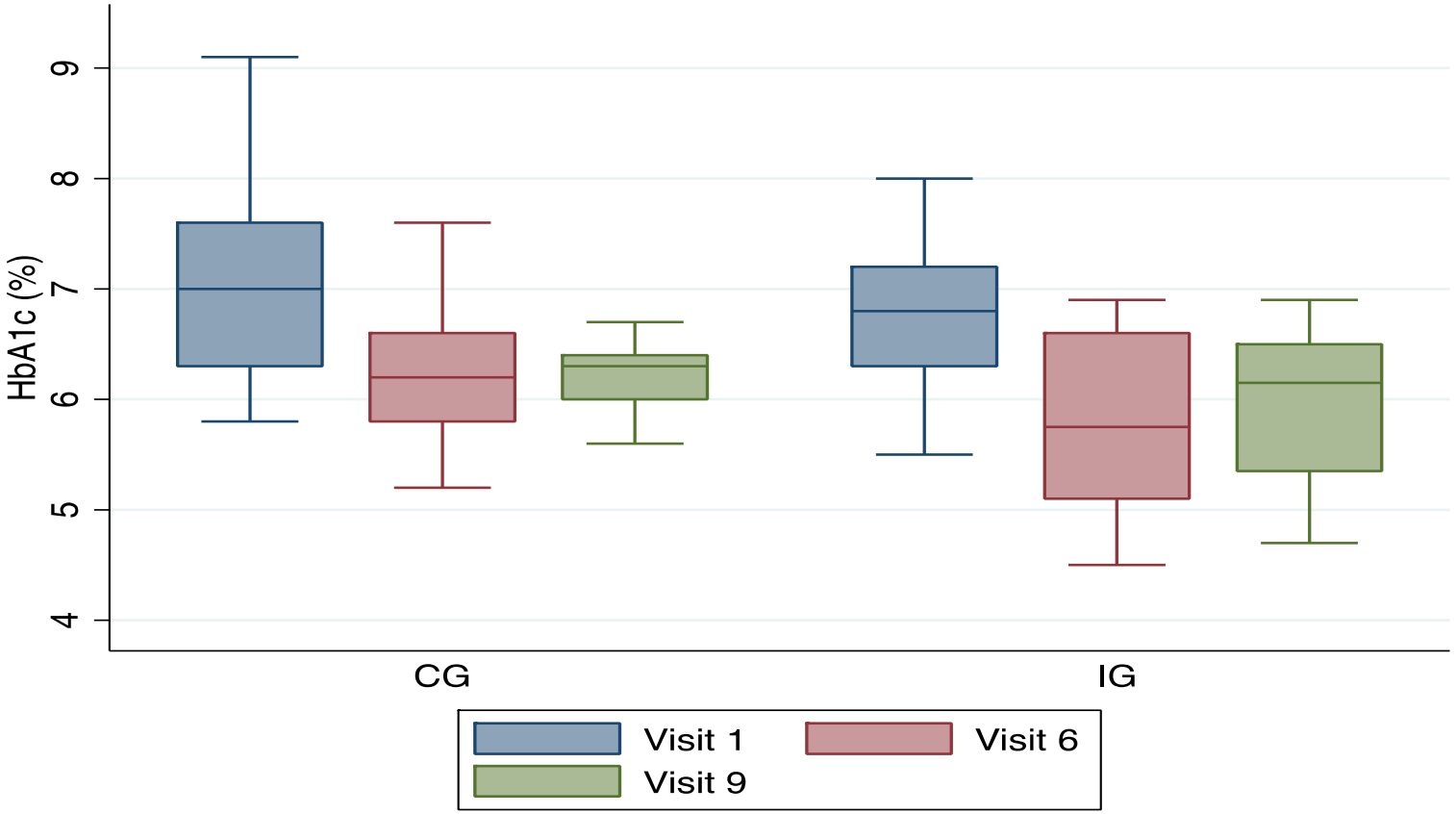
journal homepage: www.elsevier.com/locate/nmcd



Efficacy of flash glucose monitoring in pregnant women with poorly controlled pregestational diabetes (FlashMom): A randomized pilot study

Andrea Tumminia [a], Agostino Milluzzo [a,*], Camilla Festa [b], Raffaella Fresa [c], Basilio Pintaudi [d], Marina Scavini [e], Ester Vitacolonna [f], Angela Napoli [g], Laura Sciacca [a]

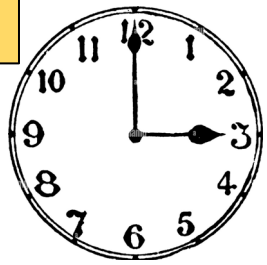
Efficacy of flash glucose monitoring in pregnant women with poorly controlled pregestational diabetes (FlashMom): A randomized pilot study



- In <u>both study arms</u>, <u>HbA1c decreased significantly</u> ($p<0.01$) during pregnancy, with no statistically significant differences in the two groups (-0.65±0.7 vs. -0.67±0.8 for IG and CG, p=0.89)

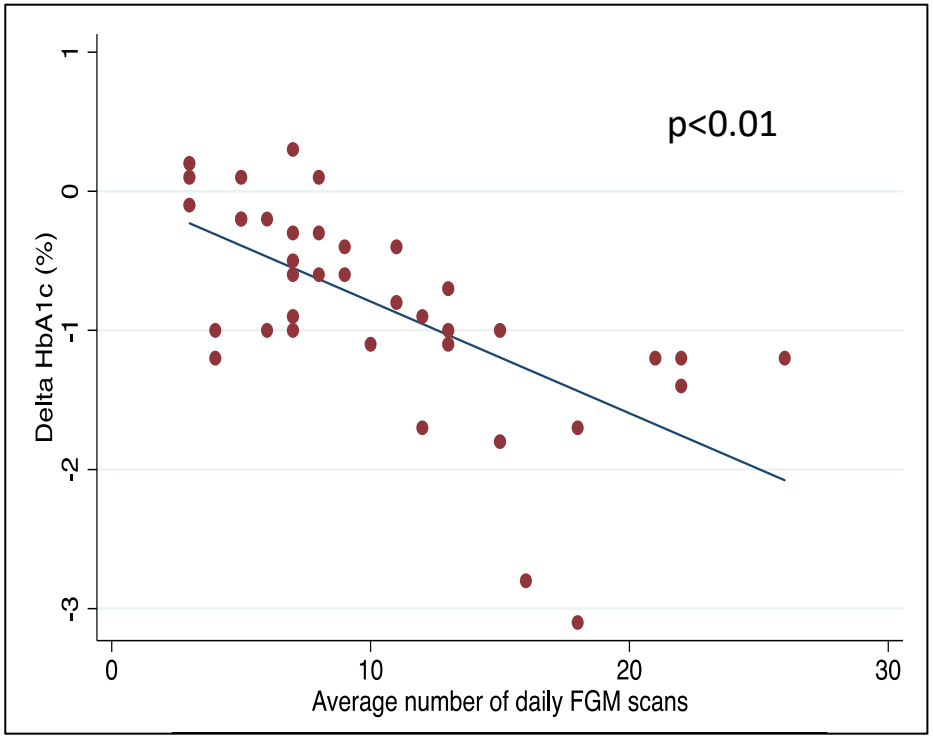
Tumminia A. et al, NMCD, 2021

3

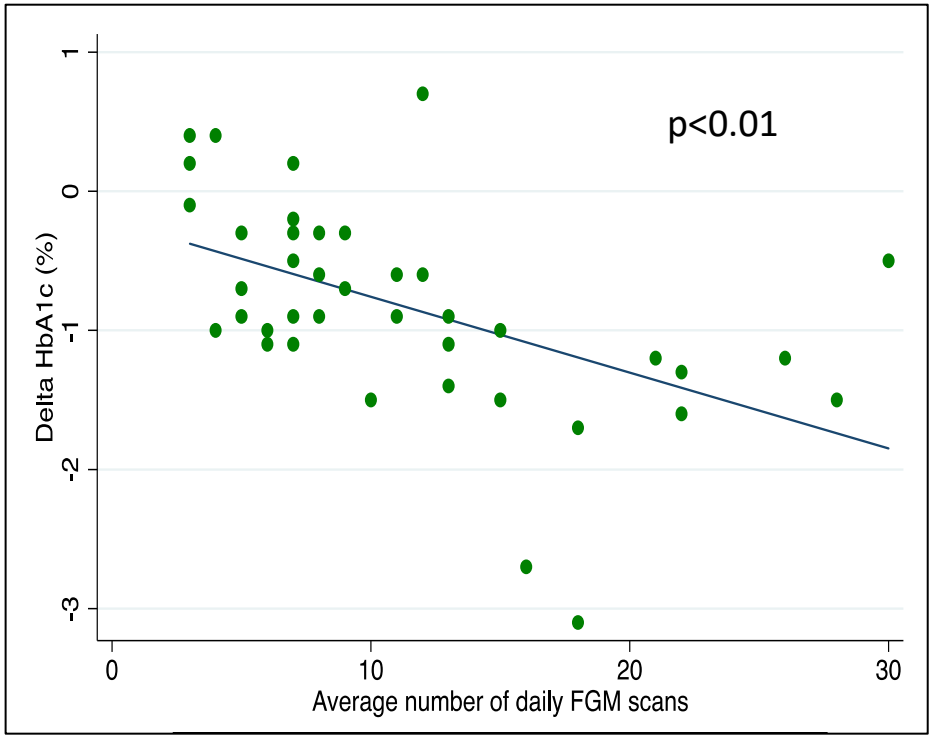


Time for education and patient's commitment

VISIT 6 (21st - 24th GESTATIONAL WEEK)



VISIT 9 (32th - 35th GESTATIONAL WEEK)



- The average number of daily FGM scans was positively associated to a better glucose control across gestation (HbA1c reduction at II and III trimester)

Tumminia A. et al, NMCD, 2021

Continuous subcutaneous insulin infusion vs multiple daily injections in pregnant women with type 1 diabetes mellitus: a systematic review and meta-analysis of randomised controlled trials and observational studies

Przemyslaw M Rys[1,*], Agnieszka H Ludwig-Slomczynska[2,*], Katarzyna Cyganek[3] and Maciej T Malecki[3,4]

European Journal of Endocrinology
(2018) **178**, 545–563

Conclusions:

- In T1DM-complicated pregnancy, **CSII compared to MDI therapy resulted in <u>better first trimester glycaemic control</u>**; this difference decreased in subsequent trimesters
- CSII therapy was associated with lower insulin requirements, **<u>higher gestational weight gain</u>** and **higher risk for infants being LGA**

American Diabetes Association®

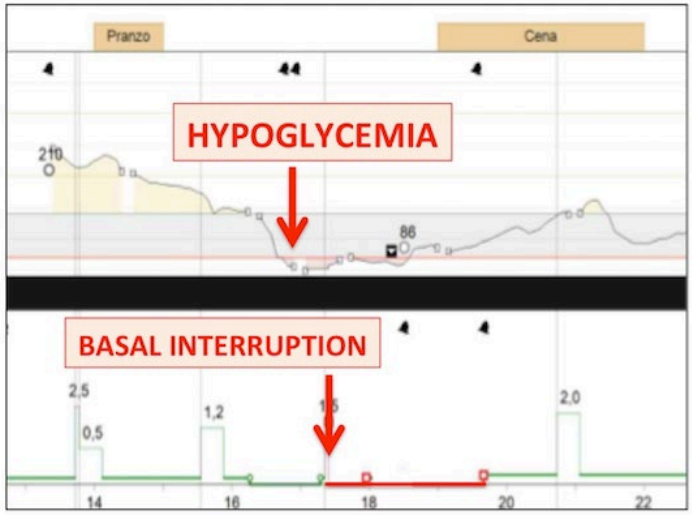
It is <u>not clear</u> that they are superior to multiple daily injections

American Diabetes Association, Standard of Medical Care in Diabetes, 2024

Diabetologia
Journal of the European Association for the Study of Diabetes (EASD)

Risk for ketonaemia in type 1 diabetes pregnancies with sensor-augmented pump therapy with predictive low glucose suspend compared to low glucose suspend: a crossover RCT

K. Benhalima[1], F. van Nes[2], P. Gillard[1], C. Mathieu[1];

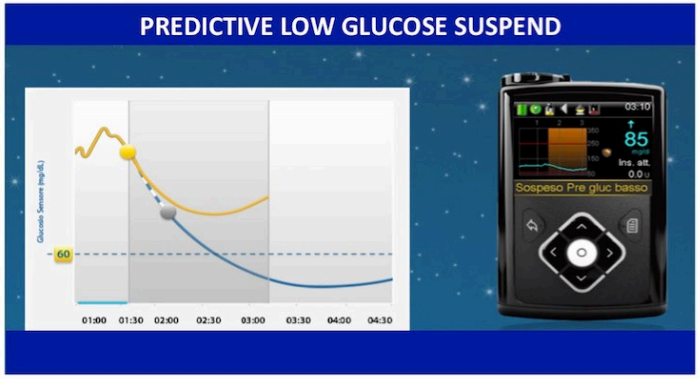


Conclusion: SAP therapy with PLGS mode is a safe alternative to LGS in pregnancy since the increased suspension time of insulin was associated with similar TIR with less time in hypoglycaemia, and without increased risk for significant ketonaemia. Treatment satisfaction and fear for hypoglycaemia were similar when using PLGS and LGS mode.

- Similar TIR
- Less time in hypoglycaemia
- Without increased risk of ketonemia

PLGS

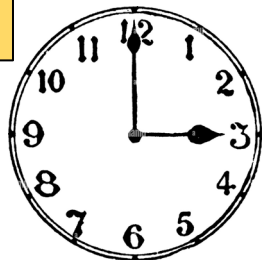
HOW DOES IT WORK…



ALGORITHM TO PREDICT HYPOGLYCEMIA BEFORE IT OCCURS

Benhalima K, et al., Diabetologia 2021

4



Randomized Trial of Assisted Hybrid Closed-Loop Therapy versus Sensor-Augmented Pump Therapy in Pregnancy

Trimester of gestation

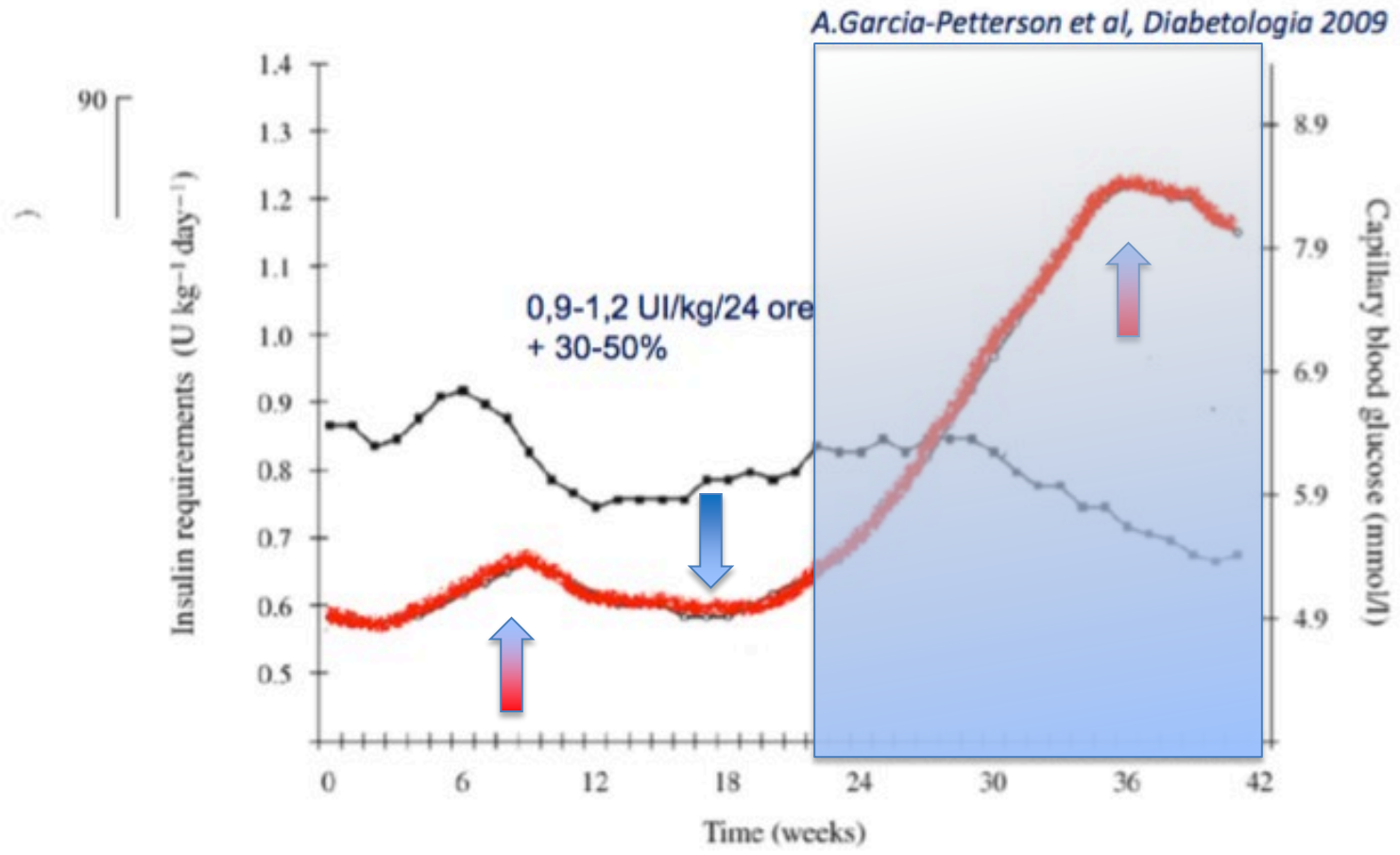
- SAP vs HCL from 14-18 weeks gestation until 4-6 weeks post-partum
- n=11 HCL, n=12 SAP
- Time spent <63 mg/dL decreased in both groups, significantly in the HCL group (2.82% vs 7.92%)
- Third trimester pTIR increased with SAP (68.2% vs 64.3%)

Table 2. Glycemic Outcomes by Randomization Group, Adjusted for Clinic

	SAPT (n=12)	HCL (n=12)[ab]	p-value
Average HbA1c (%)			
First trimester (%)	6.69 (0.188)	6.65 (0.184)	0.8811
Second trimester (%)	6.14 (0.188)[c]	6.24 (0.184)[c]	0.6936
Third trimester (%)	6.09 (0.188)[c]	6.66 (0.187)[d]	**0.0406**
Post-partum (%)	6.20 (0.188)[c]	6.71 (0.191)[d]	0.0659
CGM Measures in the Third Trimester			
Average sensor glucose (mg/dL)	119 (4.16)	132 (4.26)	**0.0475**
Glucose management index (%)	6.16 (0.10)	6.45 (0.10)	0.0515
Time spent <54 mg/dL	2.02 (0.74)[c]	1.25 (0.76)[c]	0.4747
Time spent <63 mg/dL	5.08 (1.26)	2.82 (1.29)[c]	0.2237
Time spent 63-140 mg/dL	68.2 (3.09)[d]	61.9 (3.16)	0.1667
Time spent >140 mg/dL	27.9 (3.40)	36.3 (3.48)	0.0987
Time spent >180 mg/dL	8.49 (2.32)	13.65 (2.38)	0.1346

Polsky S, et al., DTT 2024

FABBISOGNO INSULINICO NEL DM1 IN GRAVIDANZA



Commercially available AHCL systems (except for one) use glucose targets
not appropriate for pregnancy

Insulin requirement displayed a peak in week 9, a nadir in week 16, a second peak in week 37. For the change in insulin requirement the sharpest slope was observed from 16 to week 37.

Full title: Expert Guidance on Off-Label Use of Hybrid-Closed Loop Therapy in Pregnancies Complicated by Diabetes

Principle	Possible Adaptations to Assist HCL Therapy in Pregnancy
Practice individualized medicine	• Use MDI+CGM before and during pregnancy and/or • Use SAPT therapy before and during pregnancy: ➢ Discontinue AID use prior to pregnancy or ➢ Discontinue AID use at discovery of pregnancy and/or • Use partial closed-loop therapy before and during pregnancy and/or • Select appropriate candidates for AID use in pregnancy
Know data on AID use in and outside of pregnancy	• Glycemic outcomes with AID use • Health outcomes with AID use
Use AID systems in non-pregnant individuals first	• Gain knowledge, comfort, and expertise with system in non-pregnant individuals prior to using in pregnant women • Understand AID systems: ➢ Algorithm ➢ Glucose target level/range ➢ Alternate modes (e.g., exercise mode, sleep mode) ➢ Modifiable pump settings in and outside of automated mode • Know how to upload and view AID system data
Assess/re-assess AID use throughout pregnancy	• Examine glucose control at each pregnancy visit • Examine psychosocial burdens at each pregnancy visit • Consider continuing current therapy or changing to alternate therapy at each visit (e.g., AID → SAPT, SAPT → AID)
Assist commercial AID system for use in pregnancy	• Use lowest glucose level/range for AID system • Correct for hyperglycemia often ➢ Use bolus calculator, when possible ➢ Provide pregnant women with glucose threshold above which corrections should be initiated • Enter manual boluses or "fake carbs" when required (when using the bolus calculator will not allow a bolus) ➢ Consider marking "fake carbs" with an event marker label (e.g. "other") ➢ Provide a range for manual bolus or "fake carb" input (start conservatively, watch for treatment effect, adjust as needed) ➢ Avoid stacking insulin by limiting frequency of these boluses to once every 2 hours • Avoid over-correction for hypoglycemia ➢ Consume fewer carbohydrates for corrections ➢ Check capillary glucose (not sensor glucose) before treatment and re-treatment • Adjust pump settings to avoid prolonged basal insulin suspensions and thereby reduce rebound hyperglycemia • Advise proper nutrition and bolusing techniques ➢ Adhere to recommended carbohydrate consumption levels for pregnancy ➢ Alter premeal bolus time with stage of pregnancy ➢ Split boluses for high-fat/high-carbohydrate meals • Alter pump settings around meal times ➢ Adjust carbohydrate-to-insulin ratios frequently ➢ "Steal" from basal 2-3 hours after meal times • Consider exiting automated mode overnight and re-initiating each morning ➢ SAPT over night and AID during the day ➢ Partial-closed loop over night and AID during the day

Szmuilowicz E et al, DTT, 2023

The NEW ENGLAND JOURNAL of MEDICINE

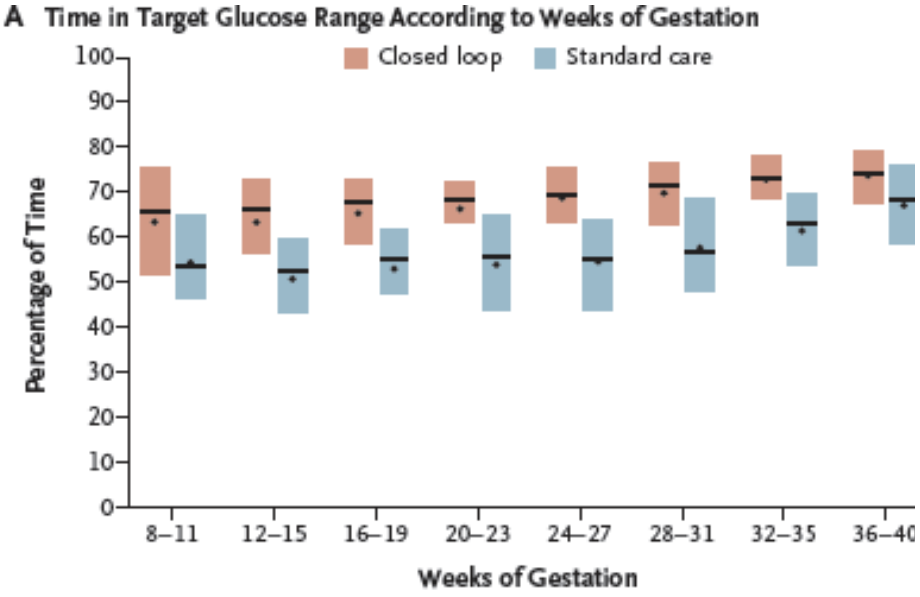
ORIGINAL ARTICLE

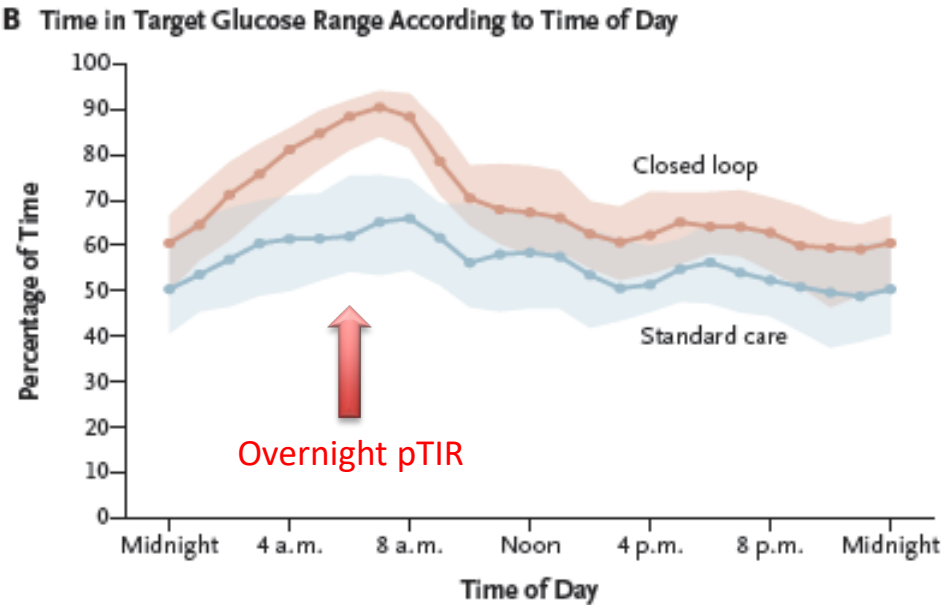
Automated Insulin Delivery in Women with Pregnancy Complicated by Type 1 Diabetes

- N=124 from nine sites in UK
- Standard insulin therapy (N=63) or hybrid closed-loop therapy (N=61) both with CGM
- Primary outcome: TIRp (63-140 mg/dl) from 16 GW until delivery

Table 2. Primary and Secondary Maternal Glucose Outcomes.*

Outcomes	Baseline†			Antenatal Intervention Phase‡		
	Closed Loop (N=59)	Standard Care (N=59)		Closed Loop (N=59)	Standard Care (N=61)	Adjusted Treatment Difference (95% CI)§
Primary outcome						
Percentage of time with glucose level in range 63–140 mg/dl	47.8±16.4	44.5±14.4	pTIR	68.2±10.5	55.6±12.5	10.5 (7.0 to 14.0)¶
Key secondary outcomes						
Percentage of time with glucose level >140 mg/dl	48.7±18.0	51.8±16.2	pTAR	29.2±10.6	41.4±13.2	−10.2 (−13.8 to −6.6)
Percentage of overnight time with glucose level in range 63–140 mg/dl (11 p.m. to 7 a.m.)†	47.4±20.8	44.5±16.6		70.8±11.2	56.7±13.6	12.3 (8.3 to 16.2)





Lee T. et al, NEJM 2024

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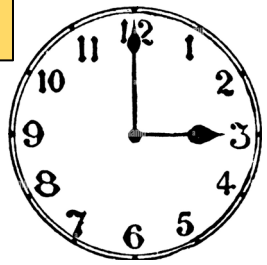
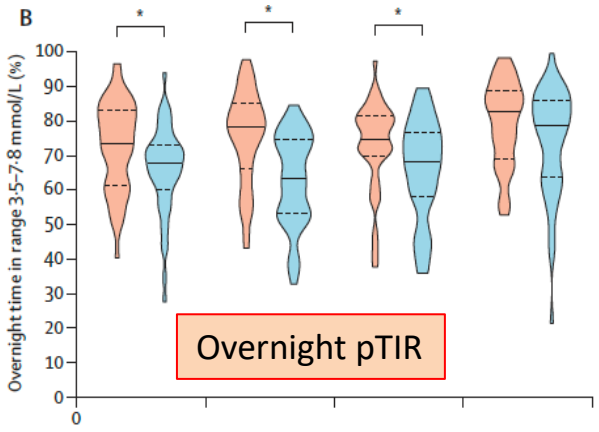


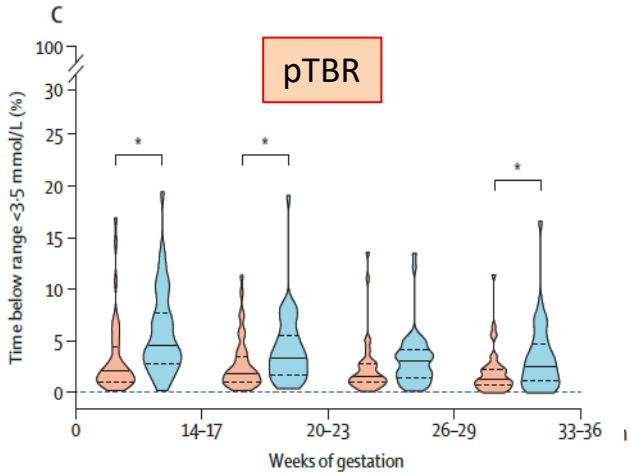
Time of the day

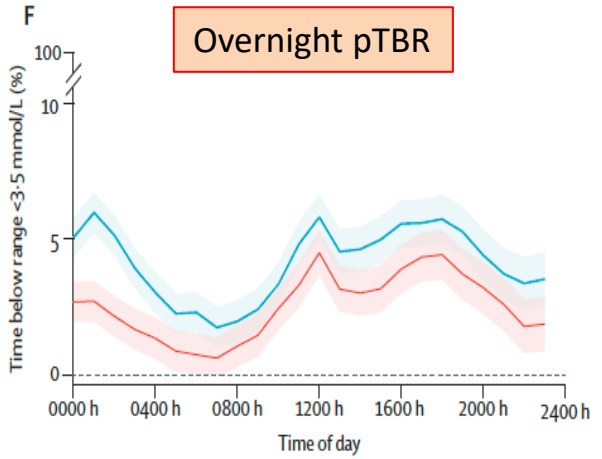
Comparing advanced hybrid closed loop therapy and standard insulin therapy in pregnant women with type 1 diabetes (CRISTAL): a parallel-group, open-label, randomised controlled trial

- 95 women
- AHCL vs. standard insulin therapy
- Primary outcome: pTIR across gestation
- Secondary outcomes: overnight pTIR, pTBR overall and overnight

	Baseline		Antenatal period (over four visits)*		Adjusted mean difference (95% CI)†
	Advanced hybrid closed loop therapy (n=46)	Standard insulin therapy (n=49)	Advanced hybrid closed loop therapy (n=46)	Standard insulin therapy (n=49)	
Primary outcome					
Proportion of time with glucose concentration in range 3·5–7·8 mmol/L	60·5% (14·2)	57·6% (13·7)	66·5% (10·0)	63·2% (12·4)	1·88% (–0·82 to 4·58)
Key secondary outcomes					
Proportion of overnight time with glucose concentration in range 3·5–7·8 mmol/L (2400 h to 0600 h)‡	64·8% (17·6)	60·4% (21·9)	75·1% (13·1)	67·2% (14·6)	6·58% (2·31 to 10·85)§
Proportion of time with glucose concentration <3·5 mmol/L	5·3% (4·9)	5·1% (3·2)	2·5% (2·8)	4·1% (3·4)	–1·34% (–2·19 to –0·49)§
Proportion of overnight time with glucose concentration <3·5 mmol/L (2400 h to 0600 h)‡	5·3% (6·8)	4·0% (3·9)	1·9% (3·2)	4·2% (4·7)	–1·86% (–2·90 to –0·81)§







Benhalima K. et al., The Lancet Diabetes Endocrinology, 2024

LA GESTIONE METABOLICA DURANTE IL PARTO NELLE DONNE CON DIABETE TIPO 1

GUIDA PRATICA

Il documento è a cura di:
Raffaella Fresa, Andrea Tumminia, Roberto Dodesini, Basilio Pintaudi, Cristina Lencioni, Teresa Marcone, Ester Vitacolonna ed Angela Napoli

È un prodotto del gruppo di studio SID-AMD "Diabete e Gravidanza", coordinato da Angela Napoli

- cerca di rispondere ad un bisogno clinico che alla fine di un lungo iter di cura, rischia di essere trascurato.
- riguarda tutti gli attori della sala parto ad iniziare dalla partoriente.

Experiences of Continuous Subcutaneous Insulin Infusion in Pregnant Women with Type 1 Diabetes During Delivery from Four Italian Centers: A Retrospective Observational Study

PROTOCOLLO PER LA GESTIONE DEL MICROINFUSORE DURANTE E DOPO IL PARTO

Il protocollo parte
» dal momento del ricovero in caso di parto spontaneo o cesareo;
» 2 ore dopo la somministrazione di prostaglandine in caso di parto indotto.

Operazioni preliminari

- Mantenere terapia insulinica ed alimentazione abituali fino alla partenza del protocollo
- Da quel momento non assumere cibo
- Per coloro che utilizzano il sistema integrato, microinfusore-sensore, applicare un nuovo sensore il giorno precedente, in caso di parto programmato; altrimenti prima di recarsi in ospedale, laddove possibile.
- In prossimità del parto verificare la correttezza dei profili basali preimpostati sulla pompa da attivare singolarmente in base alla glicemia del momento, seguendo gli algoritmi del protocollo:
  - » **Profilo A:** quello in uso
  - » **Profilo B:** con velocità basale dimezzata (50% del Profilo A)
  - » **Profilo C:** di sicurezza, con velocità basale pari a 0.1 -0,2 unità/ora

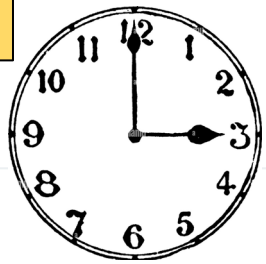
PROFILO "A"
Basale adottata fino a quel momento
_____ U/h

PROFILO "B"
Basale dimezzata
_____ U/h

PROFILO "C"
Profilo di "sicurezza" da adottare per glicemie <70mg/dl
0,1-0,2 U/ora

- CSII is possible and safe in selected and educated women
- RT-CGM helps to obtain better glucose control

Fresa R. et al, DTT 2013



Peripartum and early postpartum

Advanced Hybrid Closed-Loop Therapy Compared With Standard Insulin Therapy Intrapartum and Early Postpartum in Women With Type 1 Diabetes: A Secondary Observational Analysis From the CRISTAL Randomized Controlled Trial

CRISTAL

Double-arm, parallel-group, open-label, randomized controlled trial in Belgium and the Netherlands

↓

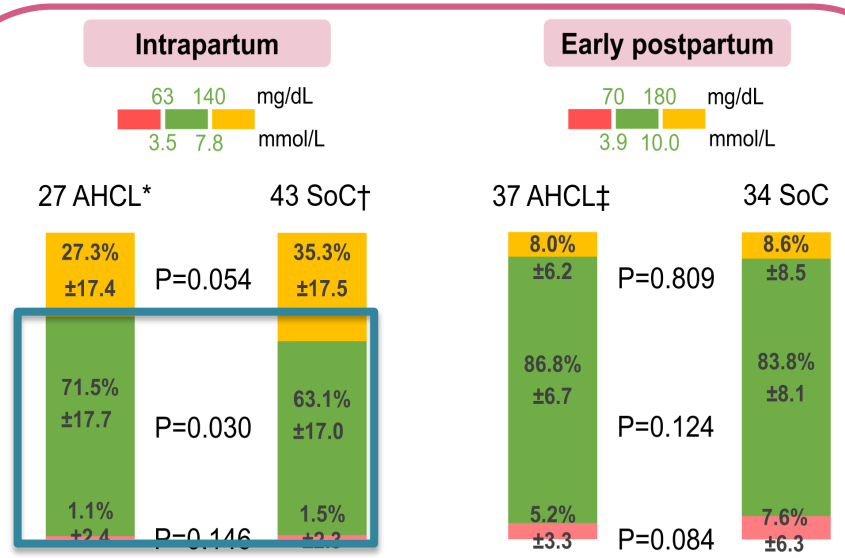
95 pregnant participants with T1D

1:1

- 46 in AHCL group (intervention) → 43 gave birth
- 49 in SoC group (control) → 46 gave birth

Secondary observational analysis on **differences in glycemic control and safety outcomes** intrapartum and early postpartum

27 (62.8%) used AHCL	**Intrapartum**	45 (97.8%) used SoC
37 (86.0%) used AHCL	**Early postpartum**	34 (73.9%) used SoC



➔ Improved glycemic control with AHCL ➔ Similar tight glycemic control

- ✓ This was achieved without increased time below range.
- ✓ No severe hypoglycemia or diabetic ketoacidosis was reported intrapartum and early postpartum in either group.
- ✓ AHCL performed well during both vaginal and cesarean deliveries.

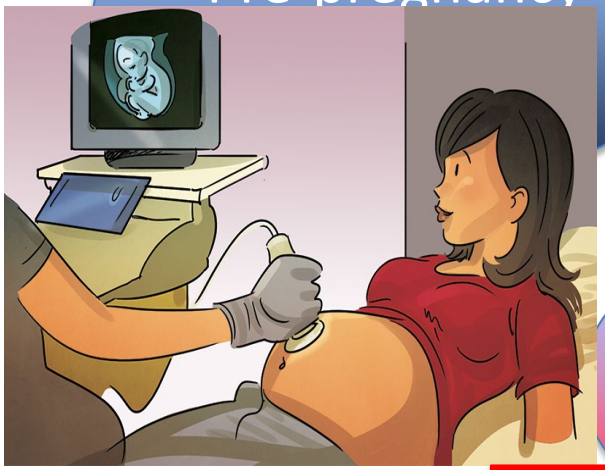
AHCL therapy is safe and effective for maintaining glycemic control intrapartum and early postpartum.

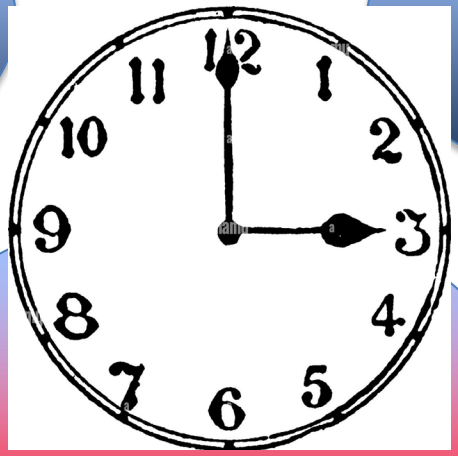
Beunen K, et al. Diabetes Care 2024

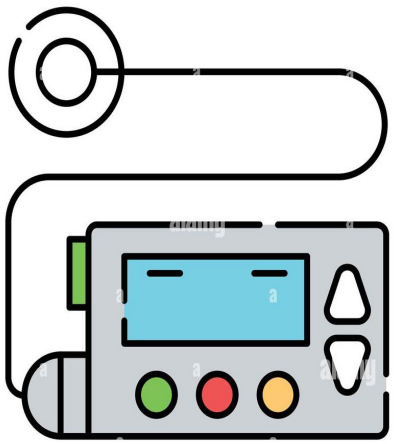
La gravidanza è sempre più tecnologica?

YES,
but we should always consider the Time…

- Usage time
- Time in target glucose ranges
- Time for education and patient's commitment
- Trimester of gestation
- Time of the day
- Peripartum and early postpartum time







ALGORITHM and TARGETS !!!

Thanks for the attention