Ottimizzazione avanzata della programmazione

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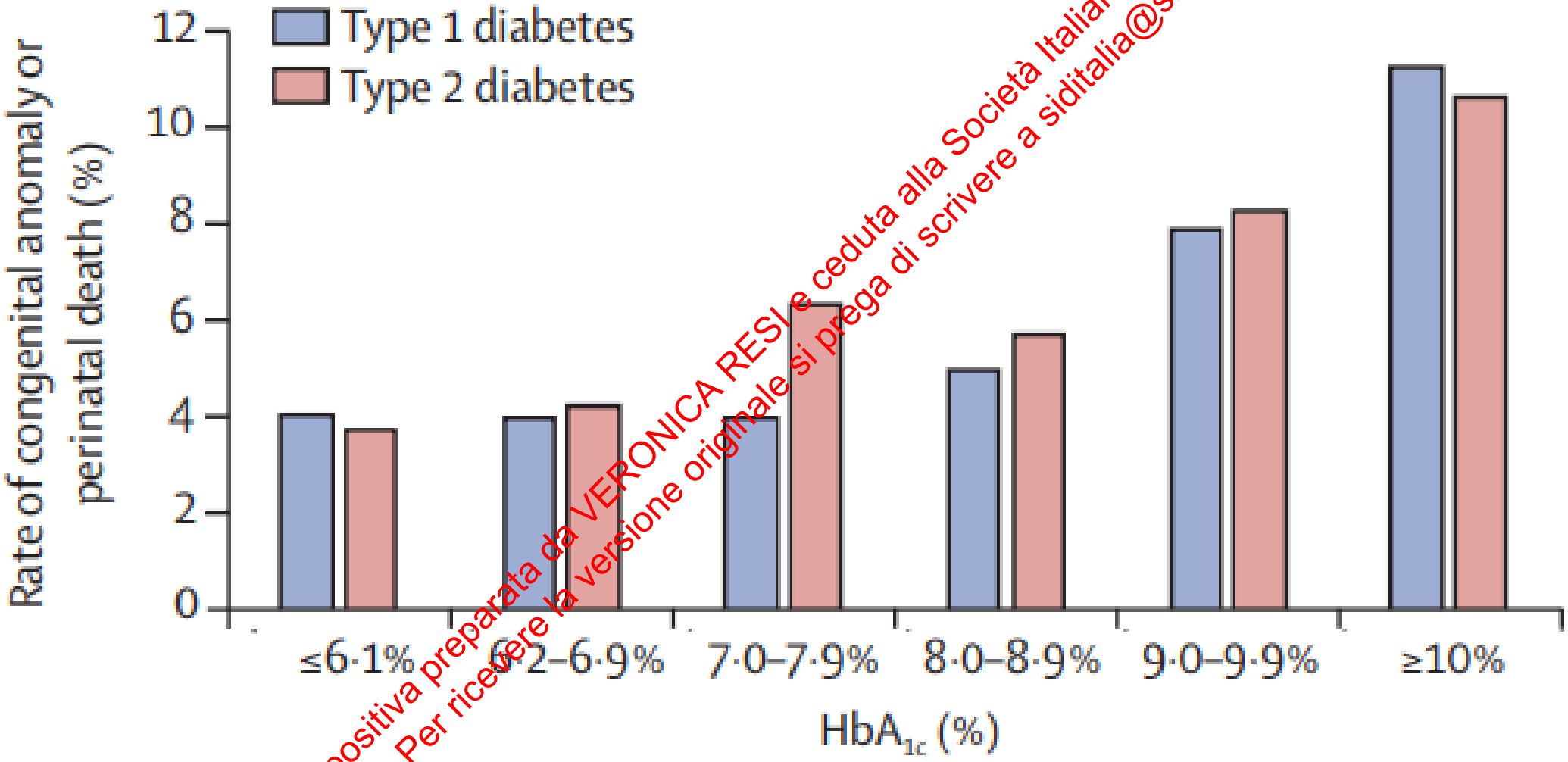
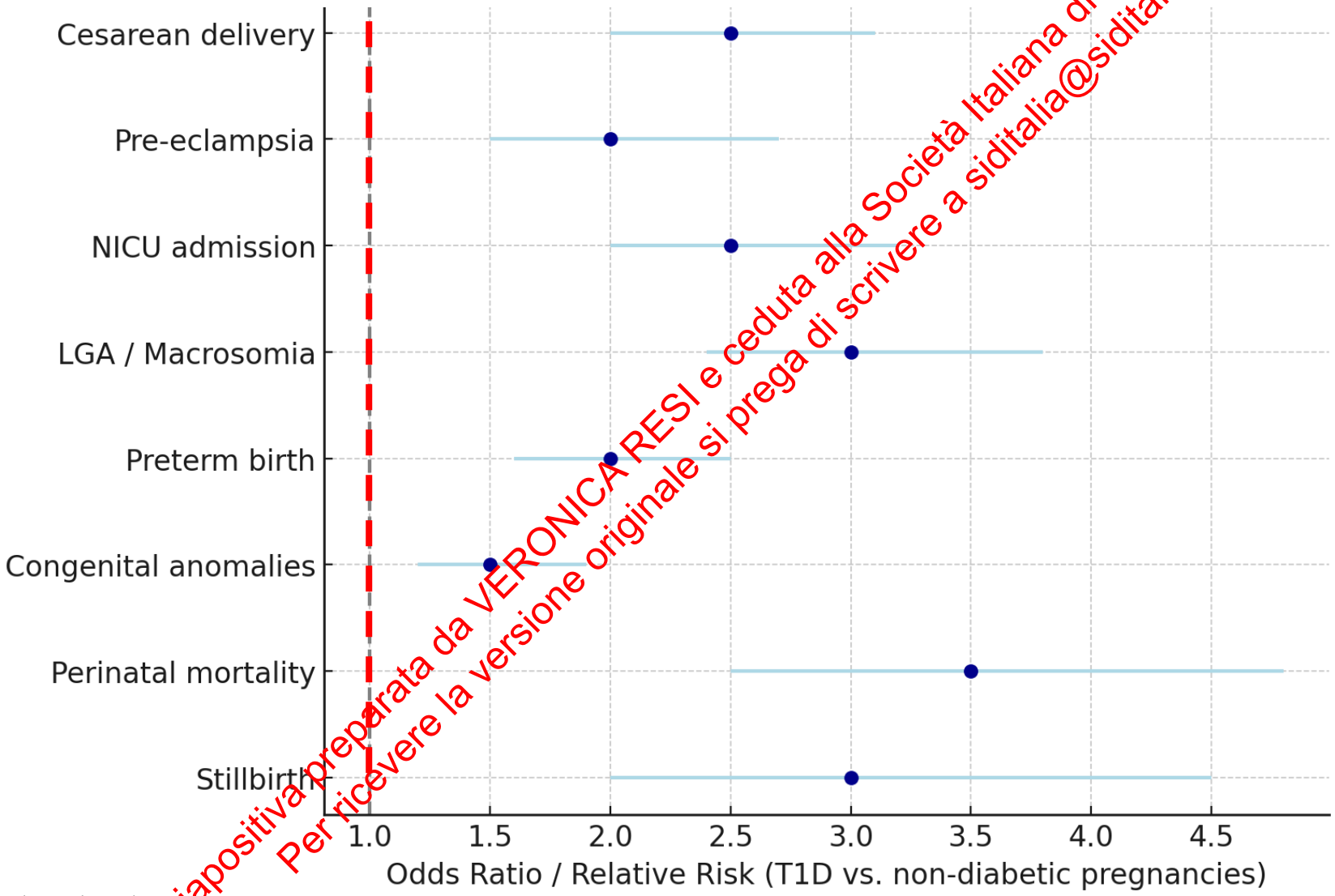
Why Preconception Still Matters



Murphy HR, Lancet Diabetes Endocrinol 2021; 9: 153–64 Published Online January 28, 2021

Maternal and Neonatal Adverse Outcome in Type 1 Diabetes Pregnancy



(approximate risk vs background population)

Effect Sizes From Meta-analyses Of Preconception Care On Outcomes.

Outcome	*Effect with preconception care*
Congenital malformations	RR ≈ 0.25 ↓ ~75%
Perinatal mortality	RR ≈ 0.35 ↓ ~65%
Preterm birth	RR ≈ 0.70 ↓ ~30%
First-trimester HbA1c	↓ ~2.4% (absolute)
NICU admission	RR ≈ 0.75 ↓ ~25%

Outcomes are relative to usual care without structured PCC
Risk Ratio (95% Confidance interval).

Wahabi HA PLOS ONE 15(8): e0237571.
Wahabi, H.A.,*BMC Pregnancy Childbirth* **10**, 63 (2010)
Wotherspoon ACDiabet Med. 2017 Sep;34(9):1303-1308.
Juza, A *Diabetology* **2025**, *6*, 75 .

Rates of pregnancy complications in preexisting diabetes in a United States cohort, (2004-2011) and in a United Kingdom cohort (2014-2018)

Table 1. Rates of pregnancy complications in preexisting diabetes in a United States cohort, 2004-2011

Adverse event	No diabetes N = 773 751	Type 1 diabetes N = 1125	Type 2 diabetes N = 10 136
Miscarriage, %	19.7%	17.9%	25.2%[a]
RR [95% CI]		0.91 [0.80-1.67]	1.28 [1.24-1.32]
Any congenital malformation, %	13.4%	18.5%[a]	19.0%[a]
RR [95% CI]		1.38 [1.15, 1.67]	1.42 [1.33, 1.51]
Any congenital heart defect, %	3.2%	8.9%[a]	6.9%[a]
RR [95% CI]		2.80 [2.10, 3.73]	2.16 [1.92, 2.41
Intrauterine fetal demise, %	0.3%	0.4%	0.8%[a]
RR [95% CI]		1.47 [0.55, 3.92]	2.5 [1.94, 3.26]
Hypertensive disorders of pregnancy, %	28.2%	47.4%[a]	55.4%
RR [95% CI]		1.68 [1.56, 1.81]	1.97 [1.92, 2.01]
Macrosomia, %	4.6%	11.0%[a]	6.6%[a]
RR [95% CI]		2.38 [1.85, 3.07]	1.43 [1.27, 1.61]
Cesarean delivery, %	35.4%	52.5%[a]	48.5%
RR [95% CI]		1.92 [1.79, 1.82]	1.37 [1.35, 1.38]

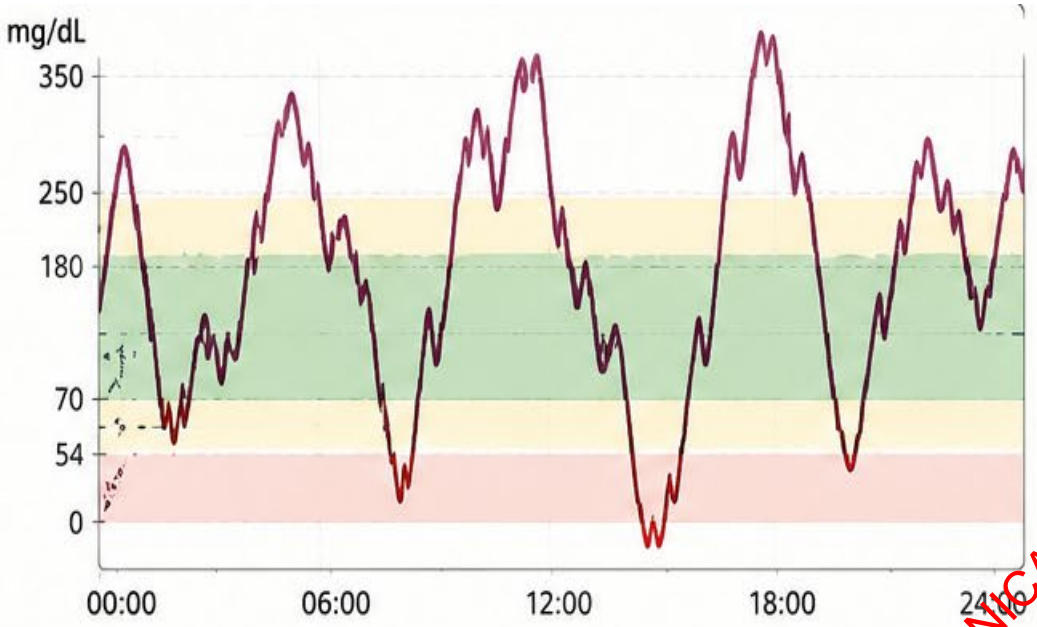
Table 2. Rates of pregnancy complications in preexisting diabetes in a United Kingdom cohort, 2014-2018

Adverse event	Type 1 diabetes N = 8690	Type 2 diabetes N = 8685	*P* value
Congenital malformation	4.5%	4.0%	.17
Stillbirth	1%	1.3%	.072
LGA	52.5%	26.2%	<.0001[a]
SGA	5.4%	14.1%	<.0001[a]

Abbreviations: LGA, large for gestational age; SGA, small for gestational age.
[a]Indicates statistical significance between type 1 and type 2 diabetes. (Modified from Murphy HR et al. *Lancet Diabetes Endocrinol.* 2021;9(3):153-164. ©Elsevier Ltd.[3]).

Wyckoff JA, European Journal of Endocrinology, 2025, Vol. 193, No. 1

From Thight Control To Safe Control



Grandi oscillazioni glicemiche

Ipoglicemie frequenti

Iperglicemie post-prandiali

TIR (63–140 mg/dL) 48%	TAR >140 mg/dL 44%
TBR <70 mg/dL 8%	CV 44%
TBR <54 mg/dL 3%	GMI 6.4%

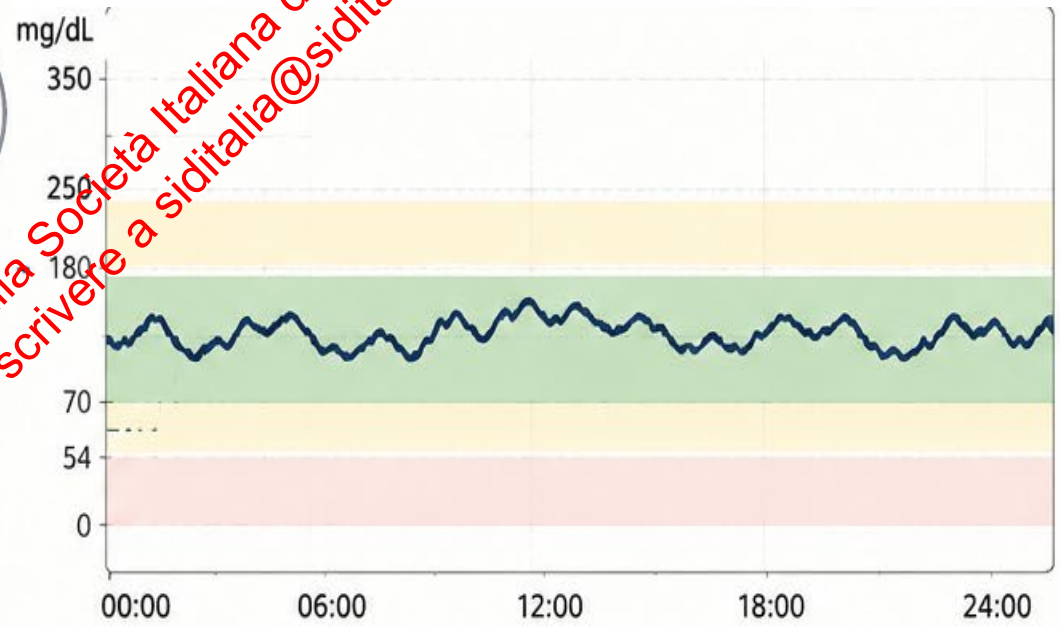
STESSA HbA1c 6.4%

Esiti di gravidanza influenzati da:

Tempo in range

Variabilità glicemica

Ipo e iperglicemie nelle prime settimane dello sviluppo fetale



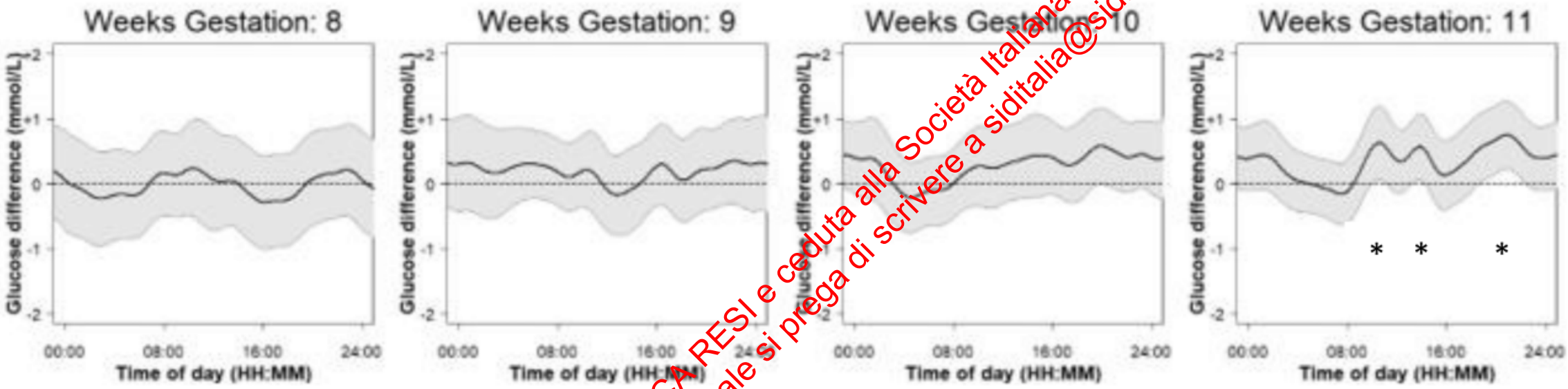
TIR (63–140 mg/dL) 82%	TAR >140 mg/dL 17%
TBR <70 mg/dL 1%	CV 24%
TBR <54 mg/dL 0.2%	GMI 6.4%

Glicemie stabili nel range

Ipoglicemie rare

Miglior profilo complessivo

CGM and Metrics –quantitative analysis

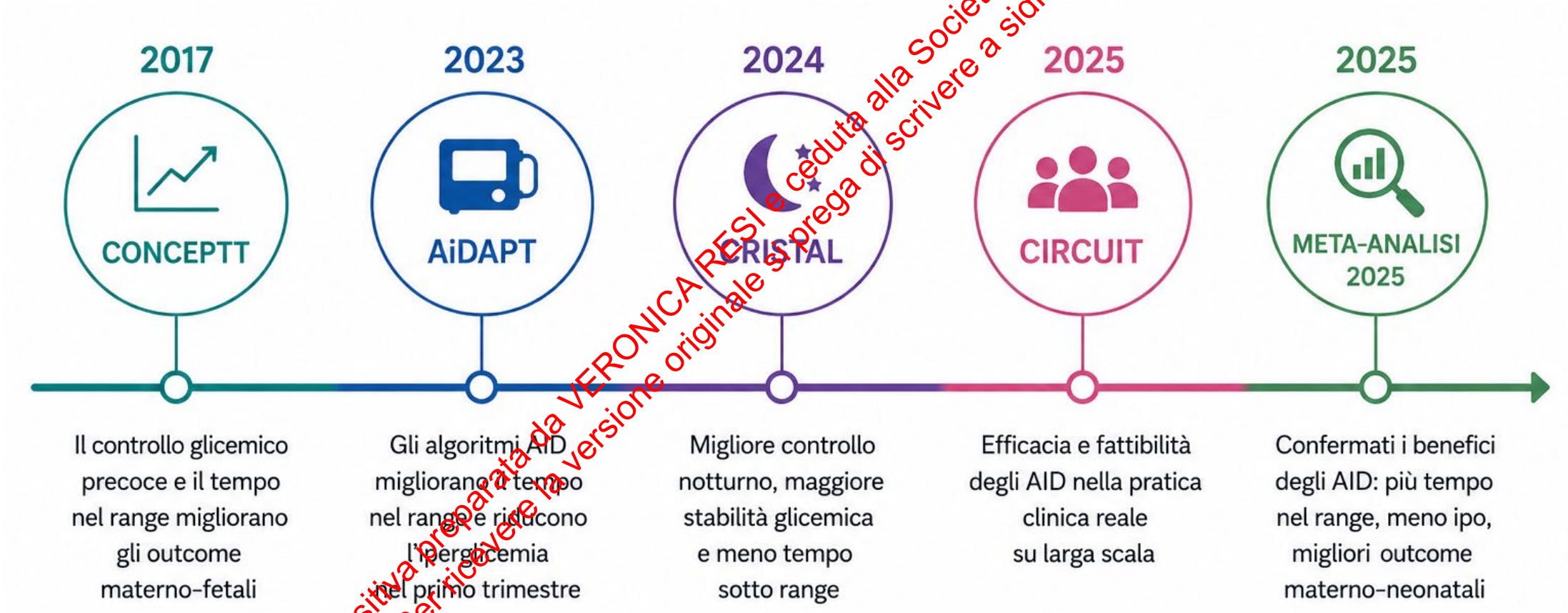


Normal birth weight is associated with achieving significantly lower mean CGM glucose concentration across the 24-h day and higher CGM time in range from before the end of the first trimester, emphasizing the need for a shift in clinical management, with increased focus on using weekly CGM glucose targets for optimizing maternal glycemia from early pregnancy.

Scott E CGM metrics and birt weight Diabetes Care 2022, 45:1724-1734

Come è cambiata l'evidenza?

Un percorso di 8 anni che ha ridefinito la gestione del T1D in gravidanza



Time in Range in Pregnancy: Is There a Role?

Jennifer A. Wyckoff[1] and Florence M. Brown[2]

[1]University of Michigan, Ann Arbor, MI; [2]Joslin Diabetes Center, Boston, MA

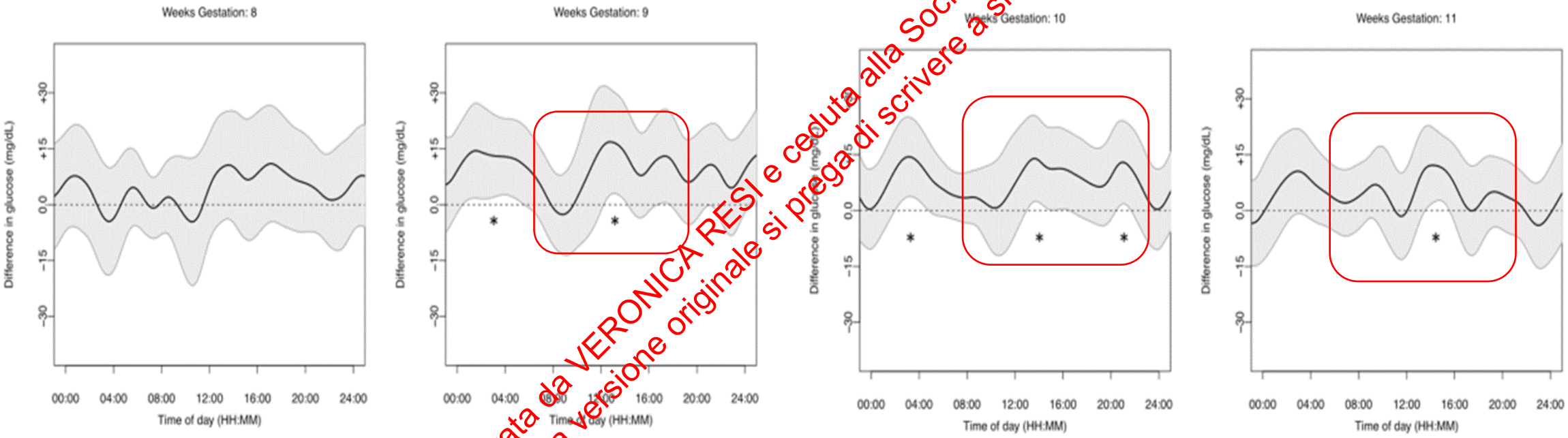
"However, the proposed TIR target of 63–140 mg/dL does not distinguish between optimal overnight/fasting/preprandial glucose targets and postprandial glucose targets that are necessary for data-driven basal and bolus insulin adjustments, respectively, that are required throughout pregnancy. For example, although meeting the TIR target, CGM glucose levels of 140 mg/dL overnight and 1- hour postprandial glucose levels of 63 mg/dL are both unacceptable. Thus, TIR cannot be used as a stand-alone metric."

The recommended TIR is being used as a target instead of a metric and this is critical due to evidence that glucose targets are stongly associated with maternal and neonatal outcome

Wyckoff JA, Diabetes Spectr. 2021 May;34(2):119-132

Traditional CGM Metrics Quantify Exposure.
Functional Glucose Analysis May Characterize Metabolic Behavior.

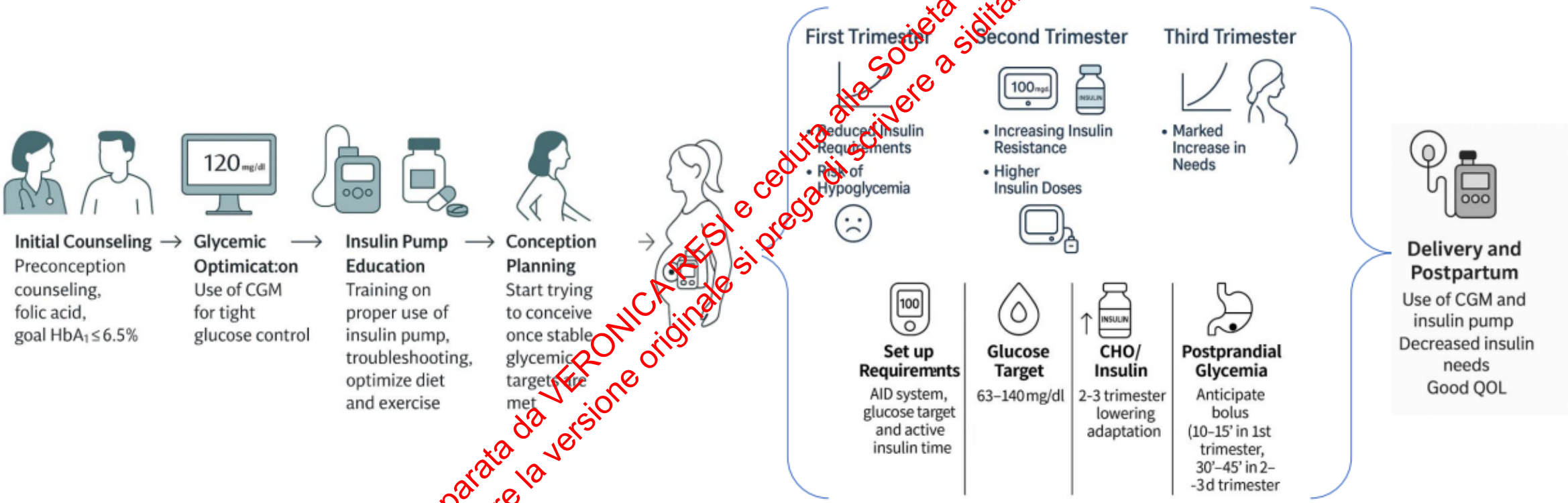
Despite optimal maternal HbA1c, 39% of neonates demonstrated LGA.



If clinically relevant glycemic trajectories diverge this early,optimization may need to begin before conception.

Rafal Sibiak, Diabetes Research and Clinical Practice,Volume 207,2024,111088, ISSN 0168-8227

Empowering Pregnancy with Diabetes Technology: From Monitoring to Automated Care

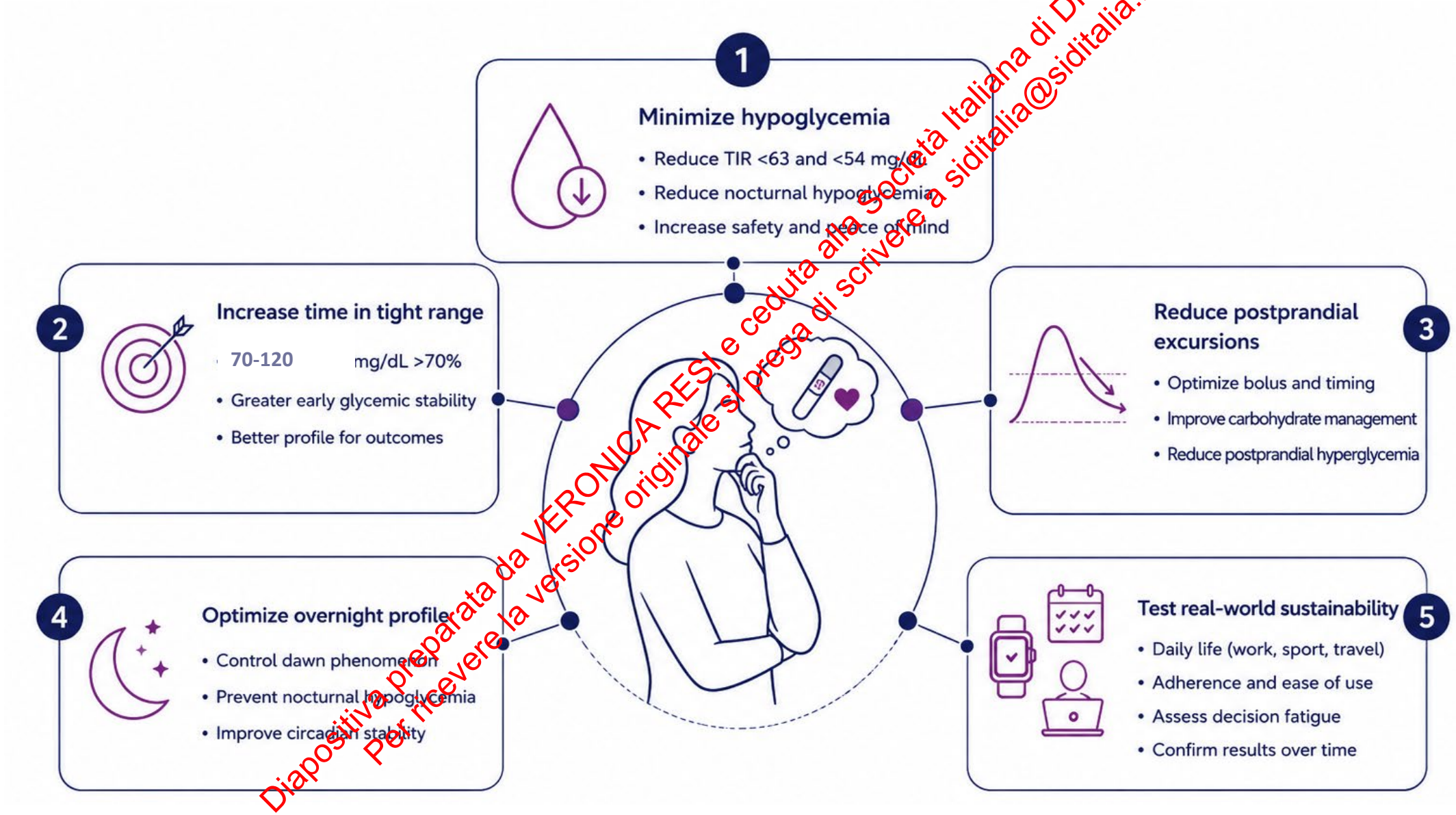


Resi V, on behalf Diabetes and Pregnancy Study Group, The Use of Technology

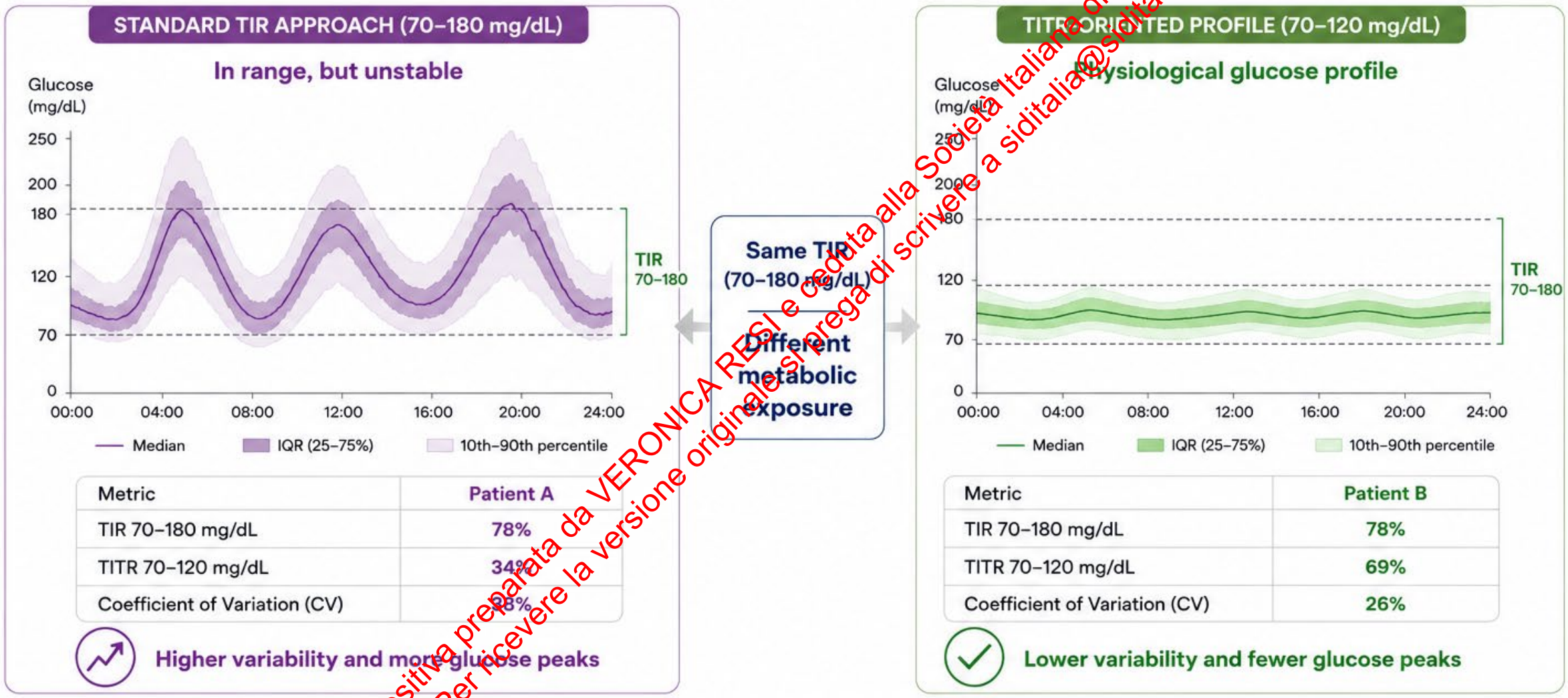
What Do These Studies Collectively Suggest?

		CURRENT GAP
AiDAPT^	Improved pregnancy-specific TIR, reduced hyperglycemia, lower management burden	Conducted during pregnancy, not in preconception
CRISTAL°	Better overnight control and improved glucose stability	No dedicated data on preconception optimization
CIRCUIT§	Reinforced efficacy and feasibility of AID in real-world pregnancy care	No evidence on timing of AID initiation before conception
Collective evidence	Earlier stability, less hypoglycemia, better overnight control, higher achievable psTIR	Lack of randomized trials specifically designed for the preconception period

Goals of Preconception AID Optimization



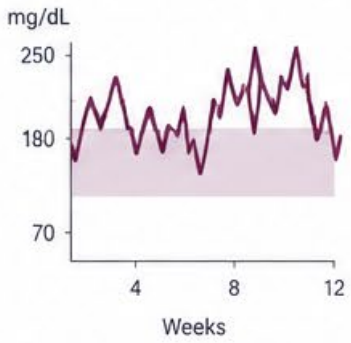
Beyond Standard TIR? Could TITR Matter Before Conception?



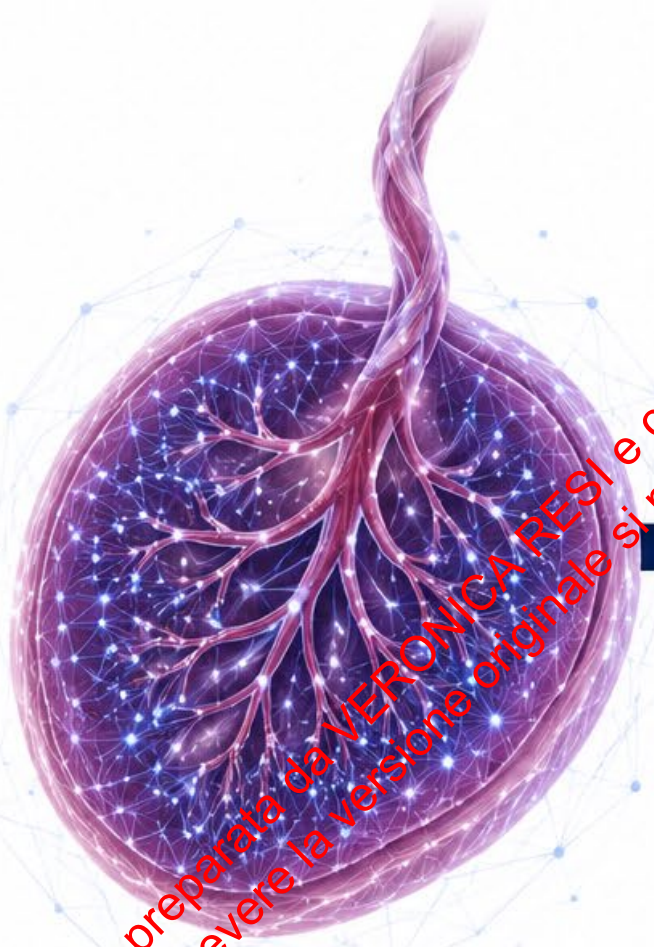
The goal of preconception care may not only be reaching range, but reaching stability before organogenesis begins.

Does The Placenta Remember?

EARLY GLYCEMIC EXPOSURE



- Hyperglycemia
- Glycemic variability
- Hyperinsulinemia
- Inflammation / oxidative stress



PLACENTAL EPIGENETIC AND FUNCTIONAL CHANGES

DNA METHYLATION CHANGES
Altered methylation of key genes

HISTONE MODIFICATIONS
Chromatin remodeling and altered gene expression

ALTERED miRNA EXPRESSION
Post-transcriptional regulation

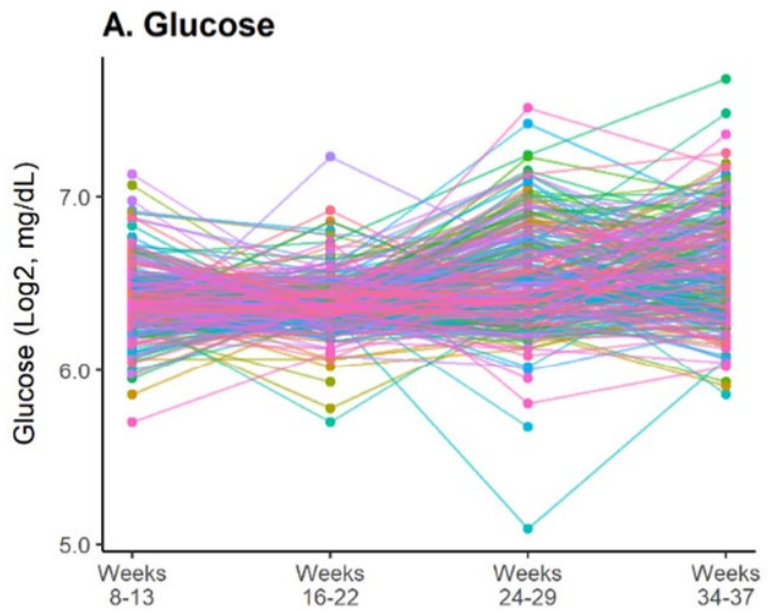
INFLAMMATION & OXIDATIVE STRESS PATHWAYS
Persistent pro-inflammatory state and redox imbalance

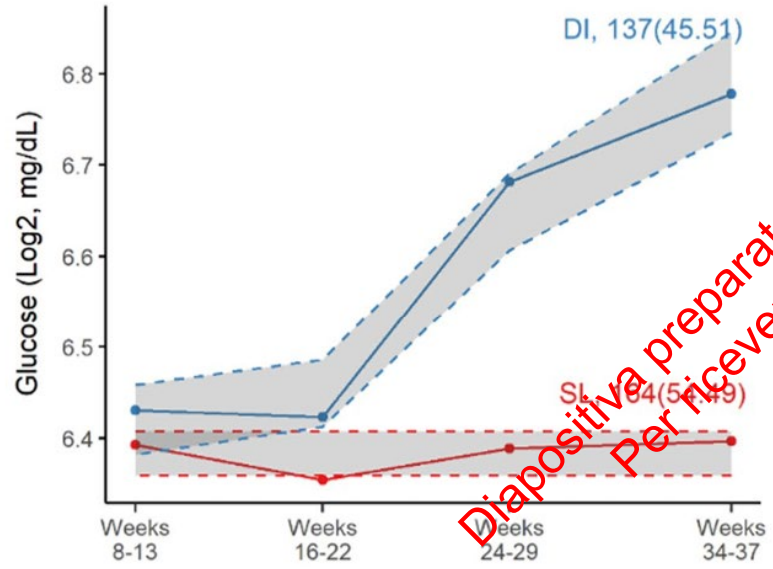
ALTERED NUTRIENT TRANSPORT AND HORMONAL SIGNALING
Modified placental efficiency and endocrine function

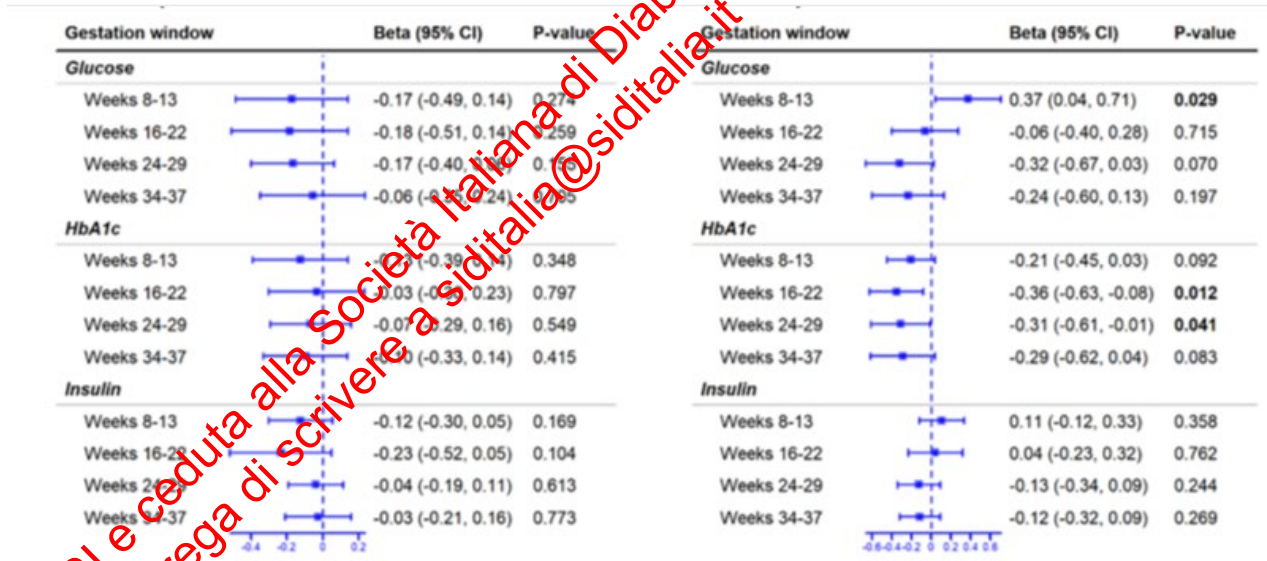
FETAL PROGRAMMING AND LONG-TERM IMPACT

- Altered growth trajectories (LGA / SGA)
- Metabolic programming (obesity, insulin resistance, type 2 diabetes)
- Neurodevelopmental outcomes
- Cardiometabolic risk in later life

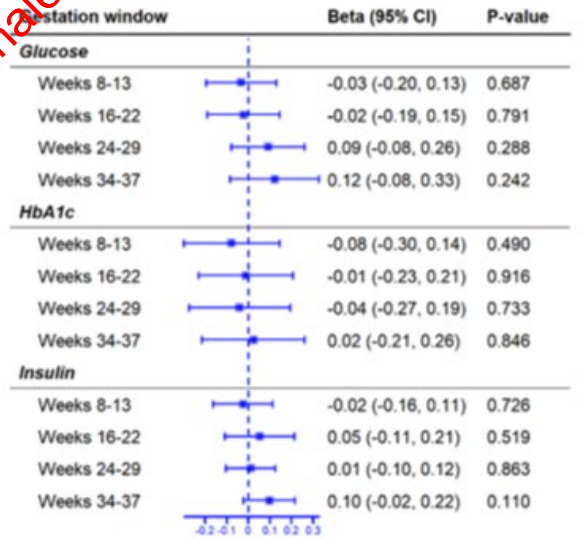
Longitudinal maternal glycemia during pregnancy and placental epigenetic age acceleration



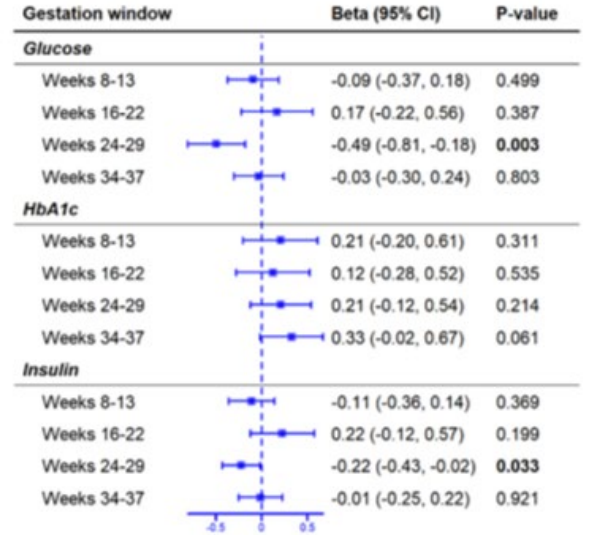




C. Hispanic

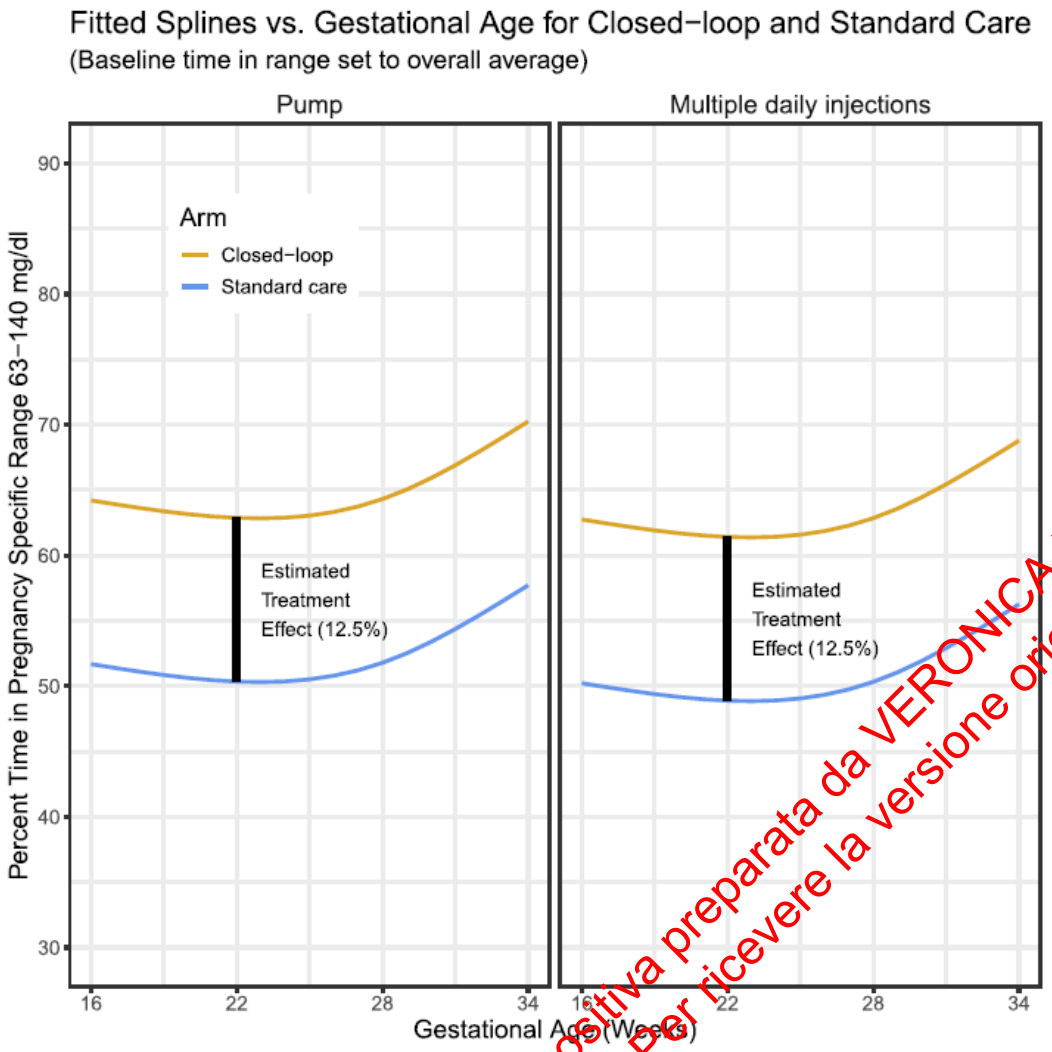


D. Asian/Pacific Islander

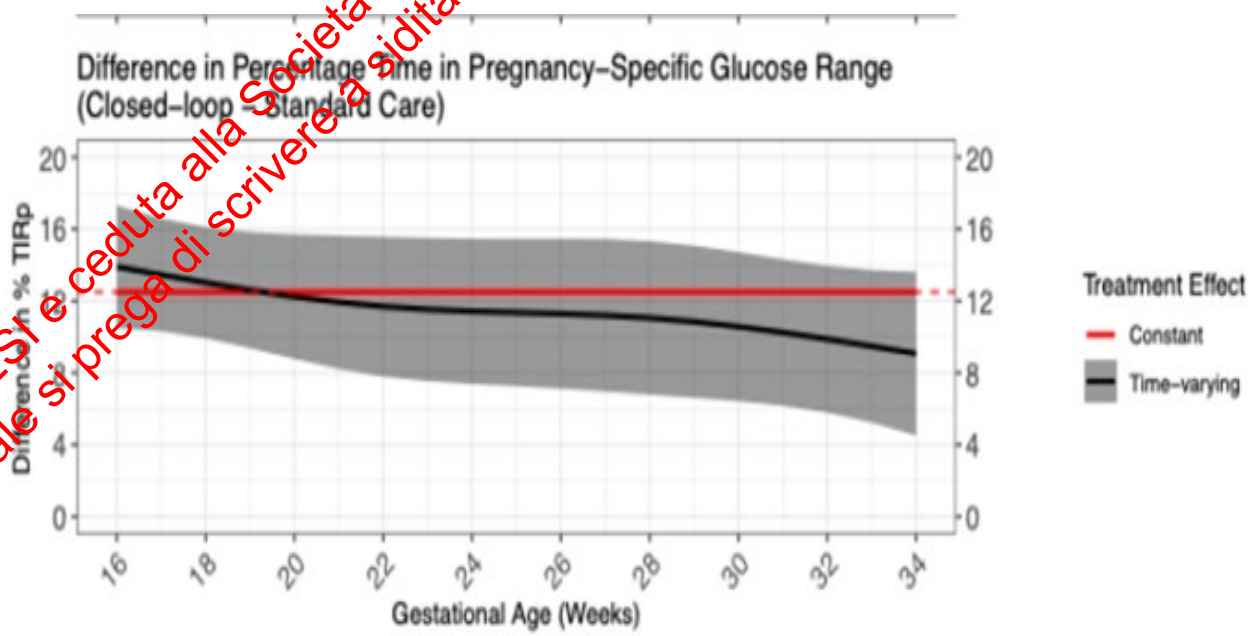


Habtewold et al. Clinical Epigenetics 2025 17:19 BMC

Closed-loop therapy changes the entire gestational glycemic trajectory, not simply average glucose values



The left panel is for a patient using insulin pump and the right panel for a patient using multiple daily insulin injections at baseline. The primary analysis model estimated a constant treatment effect for any given week in the follow-up period (16-34 weeks). This effect is equal to the vertical difference between the two curves and is shown on the figure as a solid black line. The modeled mean for closed-loop is shown in gold and the mean for standard care is shown in blue.



- week-to-week exposure matters
- variability and stability may carry biological relevance
- longitudinal metrics may better capture fetal exposure

Donovan LE, the CIRCUIT randomized clinical trial. *JAMA*. 2025;334(24):2176-2185. doi:10.1001/jama.2025.19578.

Why Preconception Matters Even More Than Pregnancy

BEFORE CONCEPTION
Metabolic preparation window

EARLY PREGNANCY
Weeks 0–8

ORGANOGENESIS
Weeks 3–10

CONTINUING PREGNANCY
Weeks 10–birth

BEYOND BIRTH
Lifelong impact

The metabolic foundation is set before conception

- Glycemic stability
- Hypoglycemia reduction
- Overnight control
- Time in range optimization
- Reduced variability

Better starting point = better placental environment from day one

THE PLACENTA HAS A MEMORY

Early metabolic exposure induces persistent epigenetic, inflammatory and functional changes

EPIGENETIC MODIFICATIONS
DNA methylation
histone changes
miRNA alterations

INFLAMMATION & OXIDATIVE STRESS
Pro-inflammatory milieu and redox imbalance

ALTERED NUTRIENT TRANSPORT
Modified glucose, amino acid and lipid transfer

PERSISTENT PROGRAMMING
Potential impact on fetal growth and lifelong health

WHY EARLY MATTERS

PLACENTA MEMORY
The placenta "remembers" metabolic exposures through epigenetic and functional changes

EARLY EXPOSURE
The earliest weeks are critical for placental development and signaling

ORGANOGENESIS
Maternal glycemia influences cell proliferation, differentiation and organ formation

CUMULATIVE GLYCEMIC BURDEN
The total exposure over time matters more than isolated measurements

AID AS STABILIZATION TOOL
Helps minimize peaks, variability and hypoglycemia — creating a more favorable intrauterine environment

POTENTIAL LONG-TERM IMPACT

- Optimal fetal growth and development
- Lower risk of metabolic and cardiovascular disease
- Better neurodevelopmental outcomes
- Stronger foundation for lifelong health