ISPAD-Breakthrough T1D 2024 Fellowship Progress Report

Title: Menstrual Cycle Phases Effects on Glucose Metrics in Adolescents with Type 1 Diabetes: the MENSES (Monitoring and Enlightening glucose Sensor Excursions due to Sexual hormones) Study

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Summary:

Cecilia Nobili, M.D., is a paediatric-diabetes clinical researcher at the Regina Margherita Children's Hospital, University of Turin, and an ISPAD-Breakthrough T1D 2024 Research Grant winner. Her mentors are Prof. Luisa de Sanctis, Associate Professor of Paediatrics and Principal Investigator, and Davide Tinti, M.D., paediatric diabetologist.

Dr Nobili is investigating how the phases of the menstrual cycle affect continuous glucose monitoring (CGM) metrics in adolescent girls with type 1 diabetes (T1D), and whether automated insulin delivery (AID) can buffer this effect. The enrolled patients were 76 adolescent girls (57 on AID, 19 on multiple daily injections), spanning 283 menstrual cycles and 3,583 cycle phase-assigned CGM days drawn from more than six million sensor readings. CGM metrics were computed with the validated iglu R package. A multicentre expansion is ongoing to reach the powered sample size.

Background:

Type 1 diabetes management poses particular challenges in adolescent girls, and sex-related differences in diabetes care are increasingly recognised. Hormonal fluctuations across the menstrual cycle affect glycaemia and insulin sensitivity: in the luteal phase, characterised by high progesterone, insulin resistance and hyperglycaemia increase, often requiring therapy adjustment (Brown 2015). Yet the patient's own experience has rarely been linked to objective data. Fabris et al. (2025) reported, with a structured questionnaire, that most women with T1D identify the luteal phase as the worst for their control and consider current technology inadequate to handle the fluctuations related to the cycle. The largest objective evidence comes from the Type 1 Diabetes Exercise Initiative (T1DEXI; n = 179 women; Yardley/Li 2024): a modest but significant deterioration from the early-

follicular to the late-luteal phase — higher mean glucose, lower time in range (TIR), more time above range (TAR) — not explained by exercise, insulin or carbohydrates, pointing to a hormonal mechanism. Using CGM, Tatulashvili et al. (2022) confirmed a luteal TIR reduction and defined the five cycle phases used here (early-follicular EF, mid-follicular MF, peri-ovulatory PO, mid-luteal ML, late-luteal LL).

Current technology does not allow dynamic basal-rate modulation by cycle phase. Almost all clinical evidence on AID across the cycle comes from the MiniMed 780G advanced hybrid closed loop: Elhenawy (2024) found the open-loop luteal TIR fall abolished once the 780G was activated; the 780MENS study (Monroy 2025) and Mesa (2024) reported only a mild residual luteal deterioration with preserved TIR; and Levy (2022) found no significant phase differences under Tandem closed loop. This suggests AID may mitigate the cyclical effect — but these studies are small, single-system (780G or Control-IQ) and confined to adult women, and a recent systematic review concluded that conclusive evidence on the menstrual impact on glycaemia is lacking, underscoring the need for solid broader data. MENSES addresses this gap in adolescent girls and, uniquely, links the patients' reported experience to their objective CGM.

Objectives:

Primary objective: to evaluate the impact of the menstrual-cycle phases on glycaemic (CGM) metrics in adolescent girls with T1D, analysing how each phase influences the glucose profile.

Secondary objectives: (1) to compare the performance of the insulin-delivery modalities (advanced hybrid closed loop and CSII versus MDI) in glycaemic control across the cycle phases; (2) to capture the patients' perspective through qualitative data on their subjective experience and management difficulties during the cycle.

Study Design and Methods:

This was a monocentric, observational, cross-sectional study at the Regina Margherita Children's Hospital (AOU Città della Salute, Turin). Girls aged 12–17 years with T1D, regular menstruation for ≥ 2 years, CGM use ≥ 1 year with ≥ 80% sensor adherence, and last HbA1c < 10% were eligible. The protocol targets up to 40 patients per therapy group (MDI, MiniMed 780G, Tandem Control IQ, Omnipod 5) and is powered (90%) to detect a ≥ 5-percentage-point difference in TIR between the early-follicular and late-luteal phases.

For three consecutive cycles we obtained (i) CGM and pump exports (CareLink, Glooko, Clarity, LibreView); (ii) a clinical case-report form (demographics, age at menarche, last HbA1c, anthropometrics, sensor/pump type, coeliac/thyroid antibodies presence, oestroprogestin use, menstrual-onset dates); and (iii) a structured menstrual questionnaire

(dysmenorrhoea, perceived glycaemic change and insulin adjustment, visual-analogue distress, cycle characteristics). The case-report form also held the device-reported CGM metrics downloaded manually per phase, used here for validation.

The purpose-built questionnaire covered three domains: (i) cycle and gynaecological characteristics — age at menarche, flow duration, inter-cycle interval, pads per day, the dates of the last three menses, and oestroprogestin/contraceptive use; (ii) dysmenorrhoea and symptom burden — analgesic use, associated symptoms (headache, nausea, fatigue, irritability, hunger, diarrhoea) and, over the previous six months, severe menstrual pain, disruption of daily activities, bowel/bladder pain, school or placement absence, and a perceived menstrual abnormality (a validated 5-item questionnaire score called PIPPA - Period Impact Pain Assessment (Parker, 2022)); and (iii) perceived glycaemic change and self-management — whether glucose rises, falls or is unchanged and how the menstruating adolscent adjusts basal and rapid insulin, asked separately for the pre-menstrual and menstrual windows, each with a 1–10 visual-analogue score of the distress caused by glucose swings.

Statistical Analysis

Cycle phases were five 3-day windows relative to reported menses onset (Early Follicular - EF +1..+3; Mid Follicular - MF +6..+8; Periovulatory - PO −16..−14; ML Mid Luteal −9..−7; Late Luteal LL −3..−1), per Tatulashvili. CGM metrics were computed with the validated iglu R package. The primary contrast was the early-follicular vs late-luteal (EF vs LL) difference in TIR within each therapy group. Cycle-aggregated linear mixed models (metric ~ phase × therapy + age + diabetes duration + BMI-SDS + (1|patient)) were fitted; only days with ≥ 70% coverage were used.

Results

The analysable cohort comprised 76 girls (57 AID — MiniMed 780G, Tandem Control-IQ and Omnipod 5 — and 19 MDI) over 283 cycles.

Table 1. Patient characteristics.

Characteristic	All	AID	MDI	p
Age (years)	15.8 ± 1.7	15.8 ± 1.6	15.8 ± 1.8	0.751
T1D duration (years)	7.4 ± 4.1	7.2 ± 4.2	7.7 ± 4.0	0.601
BMI-SDS	0.6 ± 0.8	0.5 ± 0.8	0.9 ± 0.5	0.062
HbA1c (mmol/mol)	54.3 ± 10.8	52.4 ± 9.2	60.1 ± 13.3	0.017
HbA1c (%)	7.1 ± 1.0	6.9 ± 0.8	7.7 ± 1.2	0.017
Years since menarche	4.0 ± 2.9	3.9 ± 3.0	4.6 ± 3.0	0.297

AID duration (months, AID only)	—	51 ± 36	—	—
Hashimoto thyroiditis	23/76 (30%)	17/57 (30%)	6/19 (32%)	1.000
Coeliac disease	12/76 (16%)	9/57 (16%)	3/19 (16%)	1.000
Hormonal/cycle-inducing therapy	4/76 (5%)	4/57 (7%)	0/19 (0%)	0.567

Mean ± SD (Mann–Whitney) or n/N (%) (Fisher). HbA1c reported for description, not used for adjustment.

Primary objective

AID users had far higher TIR and less hyperglycaemia than MDI users across every metric (therapy $p \leq 0.001$), framing the cycle effect as a second-order modulation on top of therapy.

Regarding the primary endpoint (EF vs LL), the powered contrast did not reach significance in either group (AID TIR 68→67 (Δ-1.3, 0.227) pp; MDI TIR 51→48 (Δ-2.1, 0.274) pp). The only significant EF→LL change was a rise in moderate hyperglycaemia (TAR 180-250) among MDI users (26→28 (Δ+2.5, 0.040) pp), with AID users flat; hypoglycaemia (TBR, LBGI) was unchanged.

Metric (EF→LL)	**AID**	**MDI**
TBR2 <54	0.4→0.4 (Δ+0.0, 0.832)	0.8→0.8 (Δ+0.0, 0.985)
TBR 54-70	1.7→1.7 (Δ+0.0, 0.972)	3.3→2.9 (Δ-0.4, 0.236)
TIR 70-180	68.4→67.0 (Δ-1.3, 0.227)	50.6→48.5 (Δ-2.1, 0.274)
TITR 70-140	43.3→42.4 (Δ-0.9, 0.395)	30.2→29.1 (Δ-1.1, 0.563)
TAR 180-250	21.3→22.0 (Δ+0.7, 0.344)	25.9→28.4 (Δ+2.5, 0.040)
TAR2 >250	8.6→9.3 (Δ+0.7, 0.446)	20.2→20.3 (Δ+0.0, 0.983)
Mean glucose	159.9→161.6 (Δ+1.8, 0.389)	185.5→186.9 (Δ+1.4, 0.680)
CV	33.5→33.4 (Δ-0.1, 0.835)	34.6→35.6 (Δ+1.0, 0.266)
GMI	7.1→7.2 (Δ+0.0, 0.389)	7.7→7.8 (Δ+0.0, 0.680)
HBGI	6.9→7.2 (Δ+0.3, 0.415)	12.0→12.2 (Δ+0.2, 0.757)
LBGI	0.5→0.5 (Δ+0.0, 0.948)	0.8→0.8 (Δ+0.0, 0.818)

Table 2. EF→LL adjusted means; Δ = late-luteal minus early-follicular. Powered for a ≥ 5 pp EF-vs-LL TIR difference per group (target ≤ 40/group; single-centre MDI currently n = 19).

Considering the full cycle, therapy was by far the dominant determinant of every glycaemic metric (AID vs MDI, $p \leq 0.001$), consistent with the expected benefit of automated delivery. On top of this, a modest but significant effect of cycle phase emerged for time-in-range and moderate hyperglycaemia — TIR (phase $p = 0.040$), TITR ($p = 0.042$), TAR 180-250 ($p < 0.001$) — and for glycaemic variability (CV $p = 0.043$), whereas mean glucose/GMI ($p = 0.162$), severe hyperglycaemia TAR2 >250 ($p = 0.421$) and HBGI ($p = 0.259$) did not reach significance for the phase main effect. The hypoglycaemia indices showed no cyclical structure (TBR $p = 0.141$, TBR2 $p = 0.406$, LBGI $p = 0.147$, all

essentially flat), confirming that the menstrual effect in this cohort is a hyperglycaemic, not a hypoglycaemic, phenomenon. The deterioration was maximal at the mid-luteal phase for most metrics (worst-phase AID = ML for TIR, TITR, TAR2, mean glucose, GMI and HBGI; moderate hyperglycaemia TAR 180-250 peaked at late-luteal), consistent with peak progesterone and lowest insulin sensitivity, and had partly recovered by late-luteal. Crucially, a significant phase × therapy interaction for hyperglycaemia (TAR 180-250 p = 0.019; TAR2 >250 p = 0.011; HBGI p = 0.037; mean glucose p = 0.092, borderline) indicates that cyclical worsening was buffered by AID, whereas for overall TIR/TITR the interaction was non-significant (p = 0.215 and 0.654).

Metric	**p (phase)**	**p (phase×therapy)**	**Worst phase (AID)**
TBR2 <54	0.406	0.131	ML
TBR <70	0.141	0.170	MF
TIR 70-180	**0.040**	0.215	ML
TITR 70-140	**0.042**	0.654	ML
TAR 180-250	**<0.001**	**0.019**	LL
TAR2 >250	0.421	**0.011**	ML
Mean glucose	0.162	0.092	ML
CV	**0.043**	0.415	MF
GMI	0.162	0.092	ML
HBGI	0.259	**0.037**	ML
LBGI	0.147	0.270	MF

Table 3. Cycle-aggregated mixed models

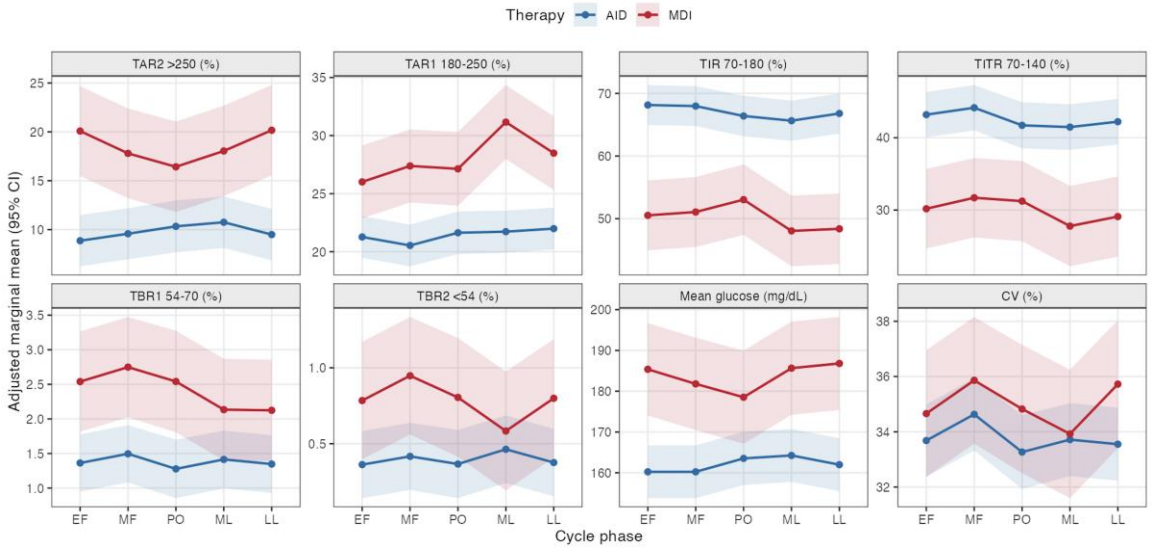

Figure 1. Adjusted marginal means (95% CI) across the five cycle phases, by therapy.

Secondary objective 1 — insulin-delivery modality across the cycle (AID vs MDI).

Automated delivery buffers the cycle effect: the residual cycle effect was smaller under automation, and the three closed-loop systems did not differ from one another in overall TIR ($p = 0.475$) nor in their cyclical pattern (phase × system $p = 0.159$).

AID system	n	Adjusted mean TIR (95% CI)
Medtronic 780G	7	71.7 (64.2–79.2)
Omnipod 5	19	66.6 (62.2–71.0)
Tandem Control-IQ	31	66.8 (63.3–70.4)

Table 4. Adjusted for age, diabetes duration, BMI-SDS. Small subgroups.

Secondary objective 2 — the patients' perspective.

The questionnaire dimensions (see Table 5 for the domains) that tracked glycaemic control were symptom burden and distress. The strongest correlates of lower TIR were distress related to menstrual cycle glycemic changes before and after the cycle onset (on a VAS scale from 0 to 10), functional impact (activity disruption, school absence) and the PIPPA dysmenorrhoea score (1 to 5); menarche age, flow and cycle length did not correlate. Perceived menstrual hyperglycaemia was corroborated by CGM (perceivers: TAR 40% vs 30%, TIR 58% vs 68%, $p < 0.001$). Importantly, girls with dysmenorrhoea had markedly lower TIR: a clinically actionable signal that dysmenorrhoea should be asked about at the diabetes visit, because it flags poorer glycaemic control.

Questionnaire item	n	ρ with TIR	p
VAS distress (during)	74	-0.42	**<0.001**
Perceived glucose change (during)	76	-0.37	**0.001**
Activity disruption	76	-0.31	**0.006**
School absence	76	-0.31	**0.007**
PIPPA score	76	-0.27	**0.020**
Dose action (during)	76	-0.26	**0.024**
VAS distress (pre)	75	-0.23	**0.049**
Age at menarche	68	+0.21	0.079
Perceived change (pre)	74	-0.20	0.090
Menstrual pain	76	-0.18	0.115
Pain medication	76	-0.14	0.213
Glucose improved since pump	54	+0.14	0.314
Intestinal/bladder pain	76	-0.08	0.494
Pads per day	75	-0.06	0.605

Table 5. Spearman correlation with mean TIR (patient-level).

Next Steps:

- Reach the planned sample size through a multicenter expansion.
- Perform the prespecified insulin analysis on the pooled dataset (total daily dose, bolus–basal distribution, automatic corrections across phases; AID vs MDI).
- Develop a predictor of the "cycle-sensitive" phenotype (which girls show a clinically meaningful luteal TIR dip) to target cycle-aware support.