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Reactive hypoglycaemia during the OGTT after gestational diabetes mellitus: Metabolic implications and evolution

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Abstract

Aims: Gestational diabetes (GDM) presents an increased cardio-metabolic risk and is diagnosed with an oral glucose tolerance test (OGTT). Reactive hypoglycaemia (RH) during the OGTT in pregnancy is associated with adverse outcomes. Although postpartum OGTT after GDM is recommended, the occurrence and implications of RH are unknown. We investigated the prevalence, metabolic implications and longitudinal evolution of RH at 6–8 weeks postpartum in women with a history of GDM.

Methods: Between 2011 and 2021, we consecutively followed 1237 women with previous GDM undergoing an OGTT at 6–8 weeks postpartum. RH was defined as 2-h glucose <3.9 mmoL/L after the OGTT. Metabolic outcomes were compared in women with and without RH (RH+/RH−). We also included a subcohort of 191 women with data on insulin sensitivity/secretion indices (MATSUDA, HOMA-IR, insulin-adjusted-secretion ISSI-2).

Results: The postpartum prevalence of RH was 12%. RH+ women had a more favourable metabolic profile including a 2-5-times lower prevalence of glucose intolerance and metabolic syndrome at 6–8 weeks postpartum compared to RH− (all $p \leq 0.034$). In the subcohort, women with RH+ had higher insulin sensitivity, higher ISSI-2 and an earlier glucose peak after OGTT ($p \leq 0.049$) compared to RH− women at the same time point. Insulin resistance increased and ISSI-2 decreased over the first year postpartum in both groups. These changes were associated with a 50% reduction in overall RH prevalence at 1-year postpartum. Some of the favourable profiles of RH+ persisted at 1-year postpartum, without group differences in the longitudinal metabolic changes.

Conclusions: At 6–8 weeks postpartum, RH was frequent in women after GDM and associated with a better metabolic profile including increased insulin sensitivity and higher insulin-adjusted-secretory capacity. RH might be a marker of favourable metabolic prognosis in women with a history of GDM.

KEYWORDS
gestational diabetes (GDM), glucose intolerance, insulin resistance, metabolic, postpartum, reactive hypoglycaemia (RH)

1 | INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most frequent pregnancy complications and is associated with adverse pregnancy and maternal cardio-metabolic outcomes in the postpartum.[1,2] International guidelines recommend oral glucose tolerance test (OGTT) during pregnancy and in the postpartum period for evaluation of persisting glucose intolerance.[3,4]

During pregnancy, up to 29% of patients experience hypoglycaemia during the OGTT.[5–9] Hypoglycaemia is generally defined as glucose concentration <3.9 mmol/L.[10] This threshold is set at a level where neuroendocrine responses are observed, whereas <3.0 mmol/L is defined as a threshold for neuroglycopenic symptoms.[10] Reactive hypoglycaemia (RH), mostly referred to as postprandial hypoglycaemia, is a condition of lower blood glucose levels that occurs after food intake or OGTT.[11] The post-OGTT RH during pregnancy has been associated with adverse neonatal complications such as low birth weight and frequent hospitalization.[6,8,12]

Although it is recommended to perform OGTT in women after GDM for postpartum re-evaluation of glucose tolerance, data regarding the occurrence of RH as well as their physiological correlates are lacking.[13] RH can carry significant morbidity in the general population. In addition to autonomous symptoms, deterioration in quality of life, attention deficit, and other neurological symptoms have been described.[14] In patients with diabetes, frequent episodes of hypoglycaemia may be associated with compensatory overeating and increased weight gain.[15,16] A link between hypoglycaemia and future obesity or type 2 diabetes has been evoked.[16,17] Therefore, RH in the postpartum might be associated with higher BMI, weight retention and features of metabolic syndrome (MetS) in women with GDM.

This study investigated the prevalence of RH at 6–8 weeks postpartum in women after GDM, the metabolic and physiological characterization of these subjects and described their longitudinal changes up to the 1-year postpartum in a prospective cohort of women with GDM.

What is already known?

- During pregnancy, reactive hypoglycaemia (RH) is associated with adverse neonatal complications.
- Despite recommendations to perfom an OGTT in the postpartum in women after gestational diabetes (GDM), data on RH and their metabolic characterization are lacking.

What this study found

- The prevalence of RH at 6–8 weeks postpartum was high, i.e., 12%.
- This early postpartum RH was associated with a favourable metabolic profile, increased insulin sensitivity and higher insulin-adjusted-secretory capacity.
- The RH prevalence was reduced by 50% at 1-year postpartum along with a reduction in insulin sensitivity.

What are the implications of this study?

- RH in the early postpartum period can be a marker of favourable metabolic prognosis in women with a history of GDM.

2 | METHODS

2.1 | Study design and patient population

This prospective clinical cohort consecutively followed women with GDM during pregnancy up to 1-year postpartum between 2011 and 2021[18–20] at the Lausanne University Hospital in Switzerland. The Lausanne University Hospital is affiliated to the University of Lausanne and is a tertiary hospital and referral centre in the Vaud province in Switzerland. The Human Research Ethics Committee of the Canton de Vaud (326/15) approved the study protocol.

Out of the consented cohort population of 1487 women followed in our clinic, those with known type 1 diabetes (n = 16), type 2 diabetes (n = 25), previous gastric bypass (n = 16) and those who did not attend the scheduled 6–8 weeks postpartum follow-up visit or were not yet due for the visit (n = 193/1487; 13%) were excluded. Overall, 83% of women who consented had GDM and valid postpartum data (n = 1237/1487). Figure 1 shows the detailed flow chart of the study. Our cohort included a nested subcohort of 191 women, participating in an intervention trial (MySweetHeart trial; NCT02890693) and had more detailed metabolic evaluation. This trial assessed the effect of a multidimensional interdisciplinary lifestyle and psychosocial intervention

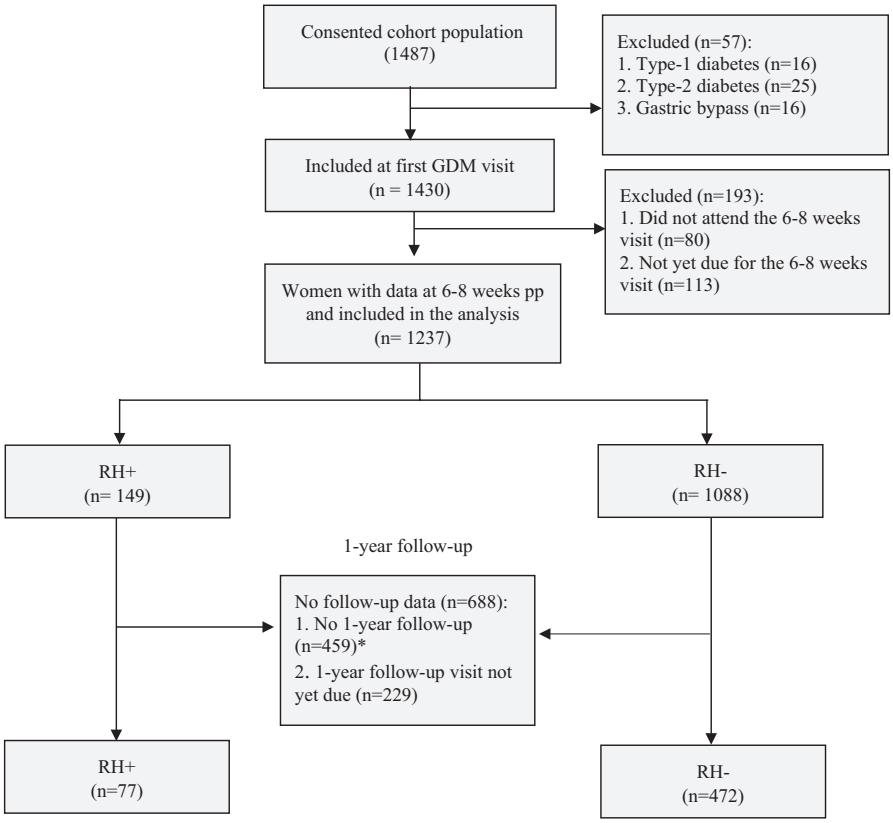

FIGURE 1 Flow of study participants. GDM denotes gestational diabetes mellitus. pp denotes postpartum. RH+ denotes women with reactive hypoglycaemia (had <3.9 mmoL/L of 2 h glucose during the 75-g oral glucose tolerance test at the 6–8 weeks postpartum) and RH− denotes women without reactive hypoglycaemia (had ≥3.9 mmoL/L 2 h glucose during the 75-g oral glucose tolerance test at the 6–8 weeks postpartum). The cohort included a subcohort of 191 women with detailed metabolic evaluation which consisted of 25 RH+ and 166 RH− women at the 6–8 weeks postpartum. Of these 191 women, 137 women who completed the 1-year follow-up had valid data for all measures (fasting and 2 h glucose, all indices of insulin secretion and sensitivity) at both time points. *1-year follow-up was only introduced in August 2015.

on metabolic and mental health in GDM women.[21] Of these 191 women, 93 and 98 were in the intervention and control groups respectively.

2.2 | GDM diagnosis and patient follow-up

All women were diagnosed with GDM at 24–28 weeks gestational age (GA) in accordance with international recommendations[3,4] and were followed accordingly.[3] Women had regular appointments every 1–3 weeks with a physician, diabetes-specialist nurse and/or a dietician. Insulin was initiated when glucose values remained above targets.[22] The postpartum follow-up visits included an assessment of the metabolic situation and counselling on lifestyle changes based on cardio-metabolic laboratory and anthropometric results.

2.3 | Measures

2.3.1 | Sociodemographic and anthropometric variables

Socio-demographic characteristics including age, nationality/ethnic origin, educational level, previous history of GDM, family history of diabetes, parity, breastfeeding and contraception use in the postpartum were collected during the first GDM clinic visit after diagnosis or follow-up visits. Women did not breastfeed during the OGTT, as this influences glucose and insulin values. Pre-pregnancy weight was extracted from participants' medical charts or, was self-reported if missing. We measured height and weight at the first and last GDM visit, and in the postpartum with electronic scales (Seca®). Waist circumference and blood pressure (OMRON® HEM-907) were also measured.

2.3.2 | Metabolic health characteristics

We measured HbA1c with a chemical photometric method (conjugation with boronate-Afinion®) at the first GDM visit and with a High-Performance Liquid Chromatography method (HPLC) in the postpartum according to international guidelines.[23] At 6–8 weeks postpartum, we performed a 75-g OGTT to measure FPG and 2-h glucose and at 1-year postpartum, only FPG was measured. OGTTs of women who did not have a correct overnight fasting were rescheduled. In the postpartum, we defined glucose intolerance (FPG ≥5.6 mmoL/L or HbA1c ≥39 mmol/mol [5.7%] or 2-h glucose ≥7.8 mmoL/L), prediabetes (FPG 5.6–6.9 mmoL/L or HbA1c 39–46 mmol/mol [5.7–6.4%] or 2-h glucose 7.8–11.0 mmoL/L) and diabetes (FPG ≥7.0 mmoL/L, 2-h glucose ≥11.1 mmoL/L or HbA1c ≥48 mmol/mol [6.5%]) according to the ADA criteria.[3] Prediabetes and diabetes were pooled together as glucose intolerance. We also measured fasting lipids.

We defined gestational weight gain (GWG) as the difference between pre-pregnancy weight and weight at the end of pregnancy. Weight retention was defined as the difference between the pre-pregnancy weight and the postpartum weight (at 6–8 weeks/1-year postpartum). Metabolic syndrome (MetS) was defined according to the International Diabetes Federation guidelines.[24]

2.4 | Assessment of reactive hypoglycaemia at 6–8 weeks postpartum

We classified women to have RH+ if the 2-h glucose value during the 75-g OGTT at the 6–8 weeks postpartum visit was <3.9 mmol/L and RH− if 2-h glucose value was ≥3.9 mmoL/L in accordance with the ADA guidelines.[10] This cut-off has been used in most studies during pregnancy and in part of the non-pregnant literature.

2.5 | Insulin secretion/sensitivity indices

In the nested subcohort (191/1237, 15%), we performed a 75-g OGTT at 6–8 weeks and 1-year postpartum and measured glucose and insulin values every 30 min for 120 min. We calculated insulin secretion/sensitivity indices in this subcohort.

2.5.1 | Insulin sensitivity/resistance indices

Whole body insulin sensitivity was estimated with the Matsuda index.[25] The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was used as a measure of insulin resistance.[26]

2.5.2 | Insulin secretion indices

Area under the curve ($AUC_{ins/glu}$) was calculated according to the trapezoidal rule.[25]

Insulinogenic index (IGI) was used to estimate early-phase insulin secretion, and calculated below.[27]

$$IGI = \frac{(Ins30 - Ins0)\ (pmol)}{(Gluc30 - Gluc0)\ (mmol/l)}$$

Beta-cell function was assessed using the Insulin Secretion-Sensitivity Index-2 (ISSI-2), also known as the disposition index. The ISSI-2 informs about the insulin-adjusted secretory capacity of the beta-cell and expressed as the product of Matsuda index and $AUC_{ins/gluc}$.[28] We also determined the peak, i.e. highest level of the respective measured values of glucose/insulin during the 2 h OGTT measures in the postpartum.

2.6 | Statistical analysis

All statistical analyses were performed with Stata/SE 15.1 (StataCorp LLC, TX, USA). Socio-demographic and medical characteristics were presented as either means (±standard deviation) or in percentages (%). All variables including insulin sensitivity/secretion indices were normally distributed. We used ANOVA (continuous variables) and chi-square (categorical variables) tests to compare the differences in metabolic characteristics during pregnancy and at 6–8 weeks postpartum in women with RH+ and RH−.

In the subcohort ($n = 191$), we compared the cross-sectional relationship between insulin sensitivity/secretion indices and differences in peak glucose and insulin timing during the OGTT between RH+ and RH−. In this subcohort, we pooled women in the control and intervention groups in our analysis because the prevalence of prediabetes and their insulin sensitivity/secretion indices were similar at either time points.

To determine the change in outcomes associated with RH, we compared differences in metabolic characteristics at 1-year postpartum (longitudinal associations) in women with (RH+, $n = 77$) and without RH (RH−, $n = 472$) at 6–8 weeks postpartum (cross-sectional associations). We performed a paired t-test to determine the longitudinal changes in metabolic characteristics including measures of insulin sensitivity/secretion in the subcohort (this

was shown for the 137 participants who had valid data at 6–8 weeks and 1-year postpartum).

For all analyses performed in the subcohort, we also investigated if including group allocation (control vs. intervention) would influence the results. Group allocation did not influence the results, neither did age nor gestational age at the first GDM visit. As results remained similar compared to the non-adjusted results (including both differences in outcomes and the respective effect sizes), we present the non-adjusted data without group allocation or other adjustments. Regarding the entire cohort, adjusting for age or gestational age at the first GDM visit also yielded similar results and therefore unadjusted data were shown for all analyses. All statistical significances were two sided and accepted at $p < 0.05$.

3 | RESULTS

3.1 | Study participants and the prevalence of RH

Of the 1237 included GDM women, 149 had RH+ and 1088 had RH− at 6–8 weeks postpartum (Table 1). Thus, the prevalence of RH+ during the OGTT at the 6–8 weeks postpartum was 12%. The prevalence of RH+ at 6–8 weeks postpartum was similar (25/191;13%) in the nested subcohort (Table 3). When the cut-off of <3.0 mmoL/L was used, the prevalence was 2.3% (29/1237).

Out of the 1237 women, 549 (44%) completed the 1-year follow-up visit. Of these 549 women with follow-up data, 77 had RH+ (14%) at 6–8 weeks postpartum. The lower number of participants at 1-year postpartum is mostly because we introduced the 1-year follow-up visit in August 2015, 4 years after the start of the cohort.

3.2 | Metabolic health characteristics during and after pregnancy

RH+ women had lower pre-pregnancy weight and BMI, FPG and HbA1c during pregnancy and at 6–8 weeks postpartum (all $p \leq 0.034$; Table 2). At 6–8 weeks postpartum, the prevalence of obesity (BMI≥30.0 kg/m^2) was half as high in RH+ women compared to RH− women (OR 0.62, 95% CI; 0.49–0.79, $p < 0.001$). In addition, they had a 5-fold lower prevalence of prediabetes (OR 0.15, 95% CI: 0.06–0.36) and of glucose intolerance, i.e., prediabetes and diabetes together (OR 0.13, 95% CI: 0.05–0.34) (all $p \leq 0.001$). None of the RH+ women had diabetes. RH+ women also had a more favourable lipid profile and their prevalence of MetS-WC and MetS-BMI were over 40% or 1.7 and 2.7-times lower (OR 0.39, 95% CI: 0.25–0.63 and OR 0.23, 95% CI: 0.11–0.48, both $p \leq 0.001$) compared to RH− controls. However, GWG and weight retention at 6–8 weeks postpartum did not differ. These findings were similar in the subcohort. Particularly, no RH+ woman in the subcohort had glucose intolerance at 6–8 weeks postpartum (data not shown).

Fifty-one percent (629/1237) were treated with glucose-lowering medication during pregnancy. While only 9% (57/629) of them had RH+ at 6–8 weeks postpartum, 15% (92/608) of non-treated women had RH+ ($p = 0.003$).

3.2.1 | Characterization of insulin sensitivity and secretion

In the subcohort, RH+ women were more insulin sensitive (MATSUDA) and had higher insulin-sensitivity-adapted insulin secretion than RH− (all $p \leq 0.002$), while IGI and $AUC_{ins/glu}$ did not differ (Table 3) at baseline (6–8 weeks postpartum). RH+ women had a 26% lower HOMA-IR (2.78 ± 1.8 vs. 3.75 ± 2.5) at baseline compared to RH−, but this difference was only borderline significant ($p = 0.049$). The timing of peak glucose was 11.38 ± 6.6 min earlier in RH+ women (or 9.28 ± 9.9 min earlier when we excluded the 9 women who had their highest glucose concentrations at T0). The time course of glucose, insulin and insulin/glucose ratios after OGTT are shown in Figure 2. At each time point, the respective values were either not different or lower in the RH+ group.

3.2.2 | Longitudinal change and consequences of hypoglycaemia

Table 4 shows the metabolic health outcomes at 1-year postpartum in the 549 women who completed the 1-year postpartum follow-up (RH−: $n = 472$, RH+: $n = 77$). Compared to RH− controls, women with RH+ at 6–8 weeks postpartum had a lower BMI and FPG at 1-year postpartum (both $p \leq 0.035$), but weight, weight retention or HbA1c were not significantly different. None of the RH+ women had diabetes at 1-year postpartum. The prevalence of prediabetes was 1.3-times (OR 0.58, 95% CI: 0.34–1.01, $p = 0.057$) lower and that of glucose intolerance, i.e., prediabetes and diabetes together was 3.6-times lower (OR 0.28, 95% CI: 0.09–0.79, $p = 0.016$) compared to RH− women. There were no differences in lipids and MetS between both groups.

In the nested subcohort, we investigated the differences in metabolic measures/indices between 6–8 weeks and 1-year postpartum in the 137 women with valid data for all measures and all indices at both time-point, ($n = 137/191$, Table 5). Although weight decreased by 1 kg

TABLE 1 Demographic and health characteristics in GDM women with and without reactive hypoglycaemia in the 6–8 weeks postpartum

Variable	All ($n = 1237$) Mean ± *SD*	RH− ($n = 1088$) Mean ± *SD*	RH+ ($n = 149$) Mean ± *SD*	*p* value
Characteristics during pregnancy				
Age (years)	33.10 ± 5.60	33.17 ± 5.51	32.54 ± 6.33	0.202
Age (years), median (IQR)	33.00 (8)	33.0 (8)	33.0 (6)	
Gestational age at first visit (weeks)	28.71 ± 3.57	28.68 ± 3.64	28.97 ± 2.94	0.353
Gestational age at delivery (weeks)	38.68 ± 3.69	38.66 ± 3.87	38.87 ± 1.78	0.518
Nationality/ethnic origin, *n* (%)				
Switzerland	343 (27.7)	303 (27.8)	40 (26.8)	0.104
Europe + North America	427 (34.5)	362 (33.3)	65 (43.6)	
Africa	211 (17.1)	188 (17.3)	23 (15.4)	
Asia + Western pacific	168 (13.6)	156 (14.3)	12 (8.1)	
Latin America	55 (4.4)	51 (4.7)	4 (2.7)	
Others	33 (2.7)	28 (2.6)	5 (3.4)	
Parity, *n* (%)				
0	579 (46.8)	506 (46.5)	73 (49.0)	0.896
1	388 (31.4)	342 (31.4)	46 (30.9)	
2	168 (13.6)	150 (13.8)	18 (12.1)	
≥3	102 (8.2)	90 (8.3)	12 (8.1)	
Previous history of GDM[a], *n* (%)				
Yes/No	80/1157 (6.5/93.5)	69/1019 (6.3/93.7)	11/138 (7.4/92.6)	0.800
Family history of diabetes[b], *n* (%)				
Yes/No	659/578 (53.3/46.7)	582/506 (53.5/46.5)	77/72 (51.7/48.3)	0.762
Characteristics at 6–8 weeks pp				
Breastfeeding at 6–8 weeks pp, *n* (%)				
Yes/No	1030/207 (83.3/16.7)	910/178 (83.6/16.4)	120/29 (80.5/19.5)	0.235
Mode of breastfeeding (*n*, %)				
Did not breastfeed	207 (16.7)	200 (18.4)	7 (4.7)	
Stopped before pp visit	196 (15.8)	153 (14.1)	43 (28.9)	0.487
Exclusive	565 (45.7)	496 (45.6)	69 (46.3)	
Mixed	269 (21.8)	239 (21.9)	30 (20.1)	
Contraception use at 6–8 weeks pp (*n*, %)				
Yes/No	359/878 (29.0/71.0)	320/768 (29.4/70.6)	39/110 (26.2/73.8)	0.839

Note: RH+ denotes women who had reactive hypoglycaemia, i.e., a 2 h glucose of <3.9 mmoL/L of during the 75-g OGTT at 6–8 weeks postpartum and RH− denotes women who had no reactive hypoglycaemia, i.e., a 2 h glucose of ≥3.9 mmoL/L. pp denotes postpartum period, and GDM denotes gestational diabetes mellitus.

[a]12.7% ($n = 91$) of multiparous had previous history of GDM.

[b]Yes consists of those with first-degree relationship of the participant (e.g., mother, father, brother, sister, daughter, son) and those with second-degree kinship with the participant (e.g., grandparents, grandchildren, nephews, niece, half-brother, half-sister). All values are expressed as mean ± *SD* or *n* (%) as indicated.

at 1-year postpartum, both FPG and HbA1c increased (all $p \leq 0.008$). In addition, insulin resistance (HOMA-IR & MATSUDA) increased by 36%–45%, $AUC_{ins/glu}$ increased and ISSI-2 decreased (all $p < 0.001$), the latter in the context of a substantial increase in insulin resistance. The time to peak glucose or peak insulin did not change. We found no differences between RH+ and RH− women when we compared their changes in anthropometric and other metabolic parameters including insulin resistance/secretion indices between 6–8 weeks and 1-year postpartum. Breastfeeding at this time did not influence the change in insulin resistance or secretion up to 1 year postpartum.

In the subcohort, 137 women had valid fasting and 2 h glucose data at 6–8 weeks and at1-year postpartum.

TABLE 2 Metabolic health characteristics during and after pregnancy in GDM women with and without reactive hypoglycaemia at the 6–8 weeks postpartum (baseline)

	All ($n = 1237$)	RH− ($n = 1088$)	RH+ ($n = 149$)	
Variable	**Mean ± *SD***	**Mean ± *SD***	**Mean ± *SD***	***p* value**
Characteristics during pregnancy				
Pre-pregnancy weight (kg)	69.74 ± 15.79	70.15 ± 15.93	66.78 ± 14.49	**0.015**
Pre-pregnancy BMI (kg/m^2)	26.08 ± 5.63	26.29 ± 5.68	24.53 ± 5.03	**0.001**
Pre-pregnancy BMI (kg/m^2), median (IQR)	24.97 (7.11)	25.15 (7.17)	23.51 (5.78)	
Fasting glucose at GDM diagnosis (mmol/l)	5.14 ± 0.71	5.16 ± 0.71	5.02 ± 0.73	**0.026**
1 h glucose at GDM diagnosis (mmol/l)	9.59 ± 1.81	9.63 ± 1.81	9.35 ± 1.84	0.145
2 h glucose at GDM diagnosis (mmol/l)	7.88 ± 1.80	7.99 ± 1.77	7.06 ± 1.87	**0.001**
HbA1c at first GDM visit (mmol/mol)	35.37 ± 4.57	35.48 ± 4.66	34.46 ± 3.76	**0.012**
HbA1c at first GDM visit (%)	5.38 ± 0.41	5.39 ± 0.42	5.30 ± 0.34	**0.012**
Gestational weight gain	12.57 ± 6.41	12.60 ± 6.41	12.32 ± 5.96	0.637
Characteristics at 6–8 weeks pp				
Fasting glucose (mmol/l)	5.01 ± 0.54	5.04 ± 0.54	4.80 ± 0.42	**0.001**
2 h glucose (mmol/l)	5.52 ± 1.64	5.83 ± 1.49	3.27 ± 0.46	**0.001**
HbA1c (mmol/mol)	34.72 ± 4.43	34.82 ± 4.45	33.99 ± 4.22	**0.034**
HbA1c (%)	5.32 ± 0.39	5.33 ± 0.38	5.26 ± 0.38	**0.034**
BMI (kg/m^2)	27.70 ± 5.41	27.92 ± 5.46	26.10 ± 4.78	**0.001**
Weight (kg)	74.08 ± 15.28	74.46 ± 15.35	71.30 ± 14.55	**0.019**
Weight retention at 6–8 weeks pp (kg)	4.34 ± 5.94	4.32 ± 5.93	4.45 ± 6.01	0.815
BMI status ($n = 1191$)[a]				
Normal weight (BMI≤24.9 kg/m^2)	401 (33.7)	337 (32.1)	64 (45.4)	**<0.001**
Overweight (BMI = 25.0–29.9 kg/m^2)	445 (37.4)	391 (37.2)	54 (38.3)	
Obese (BMI≥30.0 kg/m^2)	345 (29.0)	322 (30.7)	23 (16.3)	
Waist circumference (cm)	93.38 ± 12.0	93.73 ± 12.11	90.80 ± 10.85	**0.006**
Glucose tolerance status, (yes) (n, %)[b]				
Normal	1012 (81.8)	868 (79.8)	144 (96.6)	**<0.001**
Prediabetes	202 (16.3)	197 (18.1)	5 (3.4)	
Diabetes	23 (1.9)	23 (2.1)	0 (0)	
Total cholesterol (mmol/l)	5.18 ± 0.95	5.17 ± 0.95	5.24 ± 0.91	0.403
HDL (mmol/l)	1.50 ± 0.45	1.49 ± 0.46	1.57 ± 0.36	**0.033**
LDL (mmol/l)	3.12 ± 0.99	3.11 ± 1.01	3.13 ± 0.82	0.869
Triglycerides (mmol/l)	1.32 ± 0.87	1.34 ± 0.90	1.17 ± 0.61	**0.031**
SBP (mmHg)	112.68 ± 12.47	112.78 ± 12.61	111.98 ± 11.05	0.469
DBP (mmHg)	73.41 ± 9.85	73.54 ± 9.96	72.45 ± 8.97	0.211
Metabolic Syndrome (yes) (n, %)				
Waist circumference-defined	309 (25.0)	286 (26.3)	23 (15.4)	**0.002**
BMI-defined	147 (11.9)	140 (12.9)	7 (4.7)	**<0.001**

Note: RH+ denotes women who had reactive hypoglycaemia, i.e., a 2 h glucose of <3.9 mmoL/L during the 75-g oral glucose tolerance test at 6–8 weeks postpartum and RH− denotes women who had no reactive hypoglycaemia, i.e., a 2 h glucose of ≥3.9 mmoL/L.

Bold *p* values are significant ($p < 0.05$).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; pp, postpartum period; SBP, systolic blood pressure.

[a]46 women had missing data.

[b]Glucose tolerance status defined according to ADA 2022 criteria based on fasting and 2 h glucose after oral glucose tolerance testing as well as on HbA1c. All values are expressed as mean ± *SD* or in %.

TABLE 3 Characterization of insulin sensitivity and secretion in GDM women with and without reactive hypoglycaemia at 6–8 weeks postpartum (nested subcohort)

Variable	RH− (166) Mean ± *SD*	RH+ (*n* = 25) Mean ± *SD*	*p*-value
Measures of insulin sensitivity/ secretion			
MATSUDA	6.63 ± 3.70	9.56 ± 4.43	**0.002**
HOMA-IR	3.75 ± 2.53	2.78 ± 1.83	**0.049**
ISSI-2	2.45 ± 0.92	3.32 ± 1.05	**0.001**
IGI	119.08 ± 339.45	122.64 ± 184.90	0.960
$AUC_{ins/glu}$	0.46 ± 0.26	0.41 ± 0.16	0.320
Glucose/insulin peak time			
Glucose peak time point (min)	40.22 ± 19.97	28.84 ± 13.36	**0.005**
Insulin peak time point (min)	58.62 ± 26.75	50.76 ± 29.10	0.169

Note: RH+ denotes women who had reactive hypoglycaemia, i.e., a 2 h glucose of <3.9 mmoL/L during the 75-g OGTT at 6–8 weeks postpartum and RH− denotes women who had no reactive hypoglycaemia, i.e., a 2 h glucose of ≥3.9 mmoL/L.

All values are expressed as mean ± *SD*.

Bold *p* values are significant ($p < 0.05$).

Abbreviations: AUC, Area under the insulin/glucose curve; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IGI, Insulinogenic index; ISSI-2, Insulin secretion-sensitivity index-2.

Compared to the 6–8 weeks postpartum, the prevalence of RH in all women in the subcohort was reduced by 50% at 1-year postpartum (1-year postpartum: 6.6% (9/137) versus 6–8 weeks postpartum: 13% (25/191), $p = 0.08$). Interestingly, 5% of previously RH− women newly developed RH at 1-year postpartum. In these women with newly developed RH, Matsuda (6.88 vs. 4.56, $p = 0.045$) and ISSI-2 (2.66 vs. 2.04, $p = 0.053$) at 1-year postpartum were higher compared to women who did not develop RH despite similar weight and breastfeeding frequency (data not shown).

4 | DISCUSSION

In this cohort of women with a history of GDM, we observed for the first time that 1 out of 8 women had reactive hypoglycaemia (RH+) at 6–8 weeks postpartum. In women after GDM, RH was associated with a lower BMI, FPG and HbA1c and a more favourable lipid profile. Compared to RH− women, RH+ had 2-5-times lower prevalence of glucose intolerance and metabolic syndrome (MetS). Some of these favourable metabolic characteristics (lower BMI, lower prevalence of glucose intolerance) persisted at 1-year postpartum. The longitudinal change in metabolic characteristics did not differ between both groups. A more detailed analysis of the subcohort revealed that RH+ women were more insulin sensitive, had a higher Insulin Secretion-Sensitivity Index-2 (ISSI-2) and an earlier glucose peak after OGTT. Insulin resistance increased and ISSI-2 decreased over the first year postpartum but these changes did not differ between groups. This evolution was associated with a 50% reduction in the prevalence of RH at 1-year postpartum.

Women with GDM are known for their disturbed underlying insulin secretion and higher insulin resistance. In this cohort of women with a history of GDM, the presence of RH+ was associated with a more beneficial metabolic profile. Even though postprandial RH has been shown in other contexts to be an expression of a less favourable metabolic and even prediabetes state,[11] the prevalence of prediabetes was 6-times lower. This suggests that RH+ was potentially protective of adverse metabolic outcomes at 6–8 weeks postpartum in our cohort of women after GDM.

In the subcohort, RH+ women had a combination of increased insulin sensitivity, an earlier glucose peak after OGTT and a higher ISSI-2 compared to RH− women. The higher ISSI-2 suggests that RH+ women might have a less impaired beta-cell function. Our findings regarding increased insulin sensitivity in RH+ women are consistent with a recent study in a healthy population that found lower HOMA-IR in RH+ subjects after OGTT compared to controls, albeit at much lower levels than in our study (1.2 ± 0.5 vs. 1.8 ± 0.8).[29] Other studies have observed a more rapid glucose clearing in healthy subjects with RH.[28] This rapid glucose clearing with a faster fall in glucose concentrations after the OGTT was also observed in our GDM population. A reduced glucagon secretion might contribute to RH and potentially the increased insulin sensitivity.[28]

The presence of RH within 2 h after glucose ingestion, often called early RH, is often attributed to an exaggerated

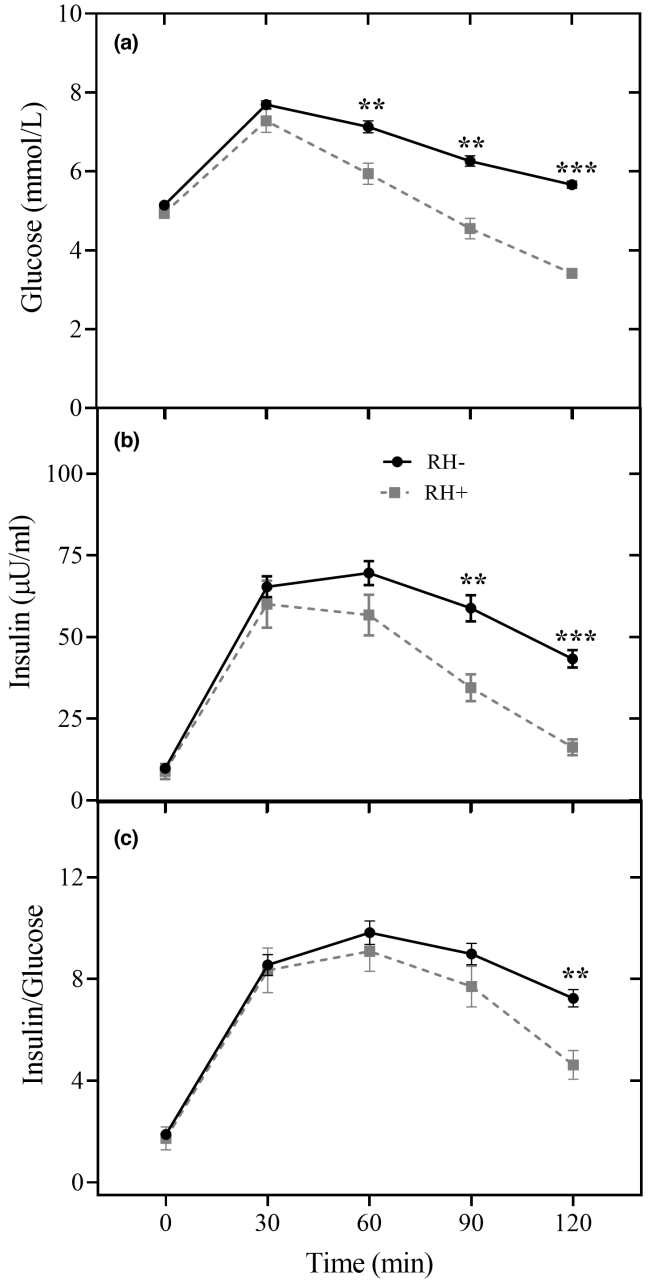

FIGURE 2 Time course of glucose, insulin and insulin/glucose ratio concentration in women with and without reactive hypoglycaemia (RH) in the nested subcohort. Time course of (a) glucose, (b) insulin and (c) insulin/glucose ratio concentration in women with reactive hypoglycaemia (RH+) (■) and without reactive hypoglycaemia (RH−) (●) during the 2 h, 75 g oral glucose tolerance test (OGTT) at 6–8 weeks postpartum after gestational diabetes in the nested subcohort. $^{**}p < 005$; $^{***}p < 0.001$ for significant differences between groups at a given time point.

insulin response to elevated plasma glucose levels due to a rapid gastric emptying.[14] Insulin sensitivity may also play a role in early RH as reflected by higher insulin sensitivity in healthy subjects with RH occurring 2–3.5 h after an OGTT compared to those without RH.[30,31] In contrast, late RH occurs between 4–5 h of glucose ingestion in the setting of increased insulin resistance and disturbed insulin secretion. An inhibition of early-phase insulin secretion leading to increased plasma glucose and to a delayed and/or exaggerated late-phase insulin secretion may result in late RH.

The presence of RH+ at 6–8 weeks postpartum continued to be associated with more favourable metabolic outcomes at 1-year postpartum, although differences were less pronounced. Changes in metabolic health outcomes over the postpartum period were similar in both groups. We are only aware of longitudinal studies regarding hypoglycaemia in patients with diabetes, but not of RH in relatively healthy subjects. It has been postulated that relative increases in insulin release and subsequent hyperinsulinaemia might further augment insulin resistance or even lead to a potential exhaustion of beta-cells due to insulin over-secretion. The only long-term data regarding the impact of hypoglycaemia exist in patients with type 1 or type 2 diabetes, although the overall CV risk is very different between our cohort and these patient groups. In these patients with diabetes, hypoglycaemia was associated with a worsened weight trajectory,[15] and even a higher risk of CV events and mortality.[32] Importantly, the glucose concentrations in these studies were mostly lower than those mentioned in our cohort and patients were treated with insulin or other hypoglycaemic agents. The changes in cardio-metabolic outcomes over the 1-year postpartum in our cohort were not associated with a worsened trajectory in RH+ women with GDM and their metabolic profile remained healthier.

Despite a small decrease in weight of a mean of 1 kg during the 1-year postpartum, insulin resistance increased substantially in the subcohort (by 36%–45%) and ISSI-2 decreased and failed to compensate for this increase. The observed changes were associated with a 50% reduction in the overall prevalence of RH+ at 1-year postpartum which occurred without differences in the timing of the glucose peak during the OGTT. This shows the primordial role of insulin sensitivity and of adjusted insulin secretion in RH in these women.

The strengths of our study include its prospective design with longitudinal follow-up and the detailed metabolic evaluation in the subcohort. It is the first study to determine the prevalence of RH, its metabolic characterization and longitudinal evolution and consequences in the postpartum in women after GDM. There are however some limitations, such as the lack of a comparable control group, i.e., women without GDM and the reduced number of women in the 1-year follow-up. The lack of glucagon data and the length of observation after the OGTT could also be a potential limitation. The threshold (<3.9 mmoL/L) chosen to define RH,[10] can be controversially discussed, but is consistent with previous

TABLE 4 Metabolic outcomes at 1-year (late) postpartum in GDM women with and without reactive hypoglycaemia at 6–8 weeks postpartum

Variable	RH− ($n = 472$) Mean ± *SD*	RH+ ($n = 77$) Mean ± *SD*	*p* value
Weight (kg)	73.36 ± 16.92	70.75 ± 16.01	0.199
BMI (kg/m^2)	27.47 ± 6.13	25.88 ± 5.55	**0.035**
Weight retention at 1 year pp (kg)	3.46 ± 5.96	3.24 ± 6.37	0.802
Fasting glucose (mmol/l)	5.43 ± 0.63	5.22 ± 0.6	**0.007**
HbA1c (mmol/mol)	34.70 ± 5.15	34.02 ± 2.96	0.250
HbA1c (%)	5.32 ± 0.47	5.26 ± 0.27	0.250
Total cholesterol (mmol/l)	4.42 ± 0.80	4.44 ± 0.73	0.855
HDL (mmol/l)	1.36 ± 0.36	1.39 ± 0.33	0.521
LDL (mmol/l)	2.55 ± 0.72	2.57 ± 0.71	0.809
Triglycerides (mmol/l)	1.17 ± 0.76	1.30 ± 1.20	0.206
Glucose tolerance status (yes) (*n*, %)[a]			
Normal	286 (60.6)	56 (72.7)	**0.016**
Prediabetes	169 (35.8)	21 (27.3)	
Diabetes	17 (3.6)	0 (0)	
SBP (mmHg)	112.49 ± 10.92	111.70 ± 10.90	0.558
DBP (mmHg)	72.27 ± 9.58	72.14 ± 9.57	0.434
Metabolic syndrome (yes) (*n*, %)			
Waist circumference-defined	142 (30.3)	18 (23.4)	0.751
BMI-defined	74 (15.8)	7 (9.1)	0.295
Breastfeeding, *n* (%)			
Yes	218 (46.2)	33 (42.9)	0.587
No	254 (53.8)	44 (57.1)	
Mode of breastfeeding, (*n*, %) ($n = 218$)			
Did not breastfeed	254 (53.8)	44 (57.1)	
Stopped before visit	149 (31.6)	17 (22.1)	0.092
Exclusive	7 (1.5)	5 (6.5)	
Mixed	62 (13.1))	11 (14.3)	
Contraception use, yes, (*n*, %)	88 (18.6)	10 (13.0)	0.229

Note: Data are shown for women who completed both the early (6–8 weeks) and late (1 year) postpartum follow-up.

RH+ denotes women who had reactive hypoglycaemia, i.e., a 2 h glucose of <3.9 mmoL/L during the 75-g OGTT at 6–8 weeks postpartum and RH− denotes women who had no reactive hypoglycaemia, i.e., a 2 h glucose of ≥3.9 mmoL/L.

p value from logistic regression analysis.

Bold *p* values are significant ($p < 0.05$).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HbA1c denotes glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; pp, postpartum period; SBP, systolic blood pressure.

aGlucose tolerance status defined according to ADA 2022 criteria based on fasting glucose and HbA1c (no OGTT performed).

studies during pregnancy that revealed adverse outcomes.[6,9] Furthermore, it is a cut-off where a physiological response to neuroendocrine hormones is observed and has been used in previous studies.[7,10] Although surrogate markers are useful to determine insulin resistance, there are limitations underlying each method and the glucose clamp remains the gold standard for direct measurement of insulin sensitivity. Although the use of insulin in pregnancy could be a confounder, women stopped insulin treatment immediately after delivery. It is thus a marker of less favourable metabolic health similar to BMI. In that context, it does not differ from

TABLE 5 Longitudinal changes in metabolic outcomes including measures of insulin sensitivity and secretion between the 6–8 weeks and 1-year postpartum (nested subcohort; $n = 137$)

Variable	6–8 weeks postpartum ($n = 137$) Mean ± *SD*	1-year postpartum ($n = 137$) Mean ± *SD*	*p* value
Weight (kg)	72.20 ± 14.80	71.20 ± 16.81	**0.001**
Fasting glucose (mmol/l)	4.94 ± 0.46	5.32 ± 0.61	**<0.001**
HbA1c (mmol/mol)	34.05 ± 4.28	34.64 ± 4.89	**0.008**
HbA1c (%)	5.22 ± 0.39	5.30 ± 0.44	**0.008**
Measures of insulin sensitivity/secretion			
MATSUDA	7.37 ± 4.07	5.13 ± 3.01	**<0.001**
HOMA-IR	1.98 ± 2.04	3.12 ± 2.74	**<0.001**
ISSI-2	2.66 ± 1.01	2.18 ± 0.85	**<0.001**
$AUC_{ins/glu}$	0.44 ± 0.24	0.56 ± 0.33	**<0.001**
IGI	159.57 ± 347.07	134.73 ± 292.20	0.943
Glucose/insulin peak time			
Glucose peak time point (min)	40.50 ± 17.60	44.14 ± 23.31	0.113
Insulin peak time point (min)	56.54 ± 26.31	59.35 ± 27.37	0.328

Note: HbA1c denotes glycated haemoglobin. 6–8 weeks postpartum denotes clinic visit at 6–8 weeks after delivery and 1-year postpartum denotes 1-year visit after delivery.

All values are expressed as mean ± *SD*.

Bold *p* values are significant ($p < 0.05$).

Abbreviations: AUC, Area under the insulin/glucose curve; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IGI, Insulinogenic index; ISSI-2, Insulin secretion-sensitivity index-2.

other patient high-risk characteristics that reduce the prevalence of RH. Another potential limitation might be the inclusion of 191/1237 women participating in a trial that may have reasons and characteristics that are distinct from the main cohort.

5 | CONCLUSIONS

In our cohort of women after GDM, the prevalence of RH at 6–8 weeks postpartum was 12%. The presence of RH+ at 6–8 weeks postpartum was associated with more favourable metabolic outcomes and several of these beneficial outcomes including a lower prevalence of glucose intolerance persisted over time. RH+ was associated with a more rapid glucose peak and possibly absorption, increased glucose clearing, higher insulin sensitivity and higher insulin-adjusted secretory capacity of the beta-cell (ISSI-2), which could be a sign of fitter beta-cells. The latter two decreased substantially during the first year postpartum, and this was accompanied with a 50% decreased prevalence of RH. This highlights the essential role of insulin sensitivity and the concomitant increased insulin-adjusted secretory capacity of the beta-cell in the occurrence of RH in these women with a history of GDM.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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