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Gestational reactive hypoglycaemia and adverse pregnancy outcomes: a systematic review and meta-analysis

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Abstract

Background Reactive hypoglycaemia is a condition where blood glucose drops after a glucose load, and may be associated with adverse pregnancy outcomes. This study aimed to determine the association between gestational reactive hypoglycaemia (GRH) and the risk of adverse pregnancy outcomes including those related to diabetes.

Methods We performed a systematic review and meta-analysis by searching 4 databases: Medline, Embase, Web of science, and Maternity & infant care database, from inception to 1 December 2023. The outcomes of interest were any reported adverse pregnancy outcomes including large for gestational age (LGA), macrosomia, small for gestational age (SGA), fetal growth restriction (FGR), low birth weight (LBW), caesarean delivery, neonatal intensive care unit (NICU) admission, neonatal hypoglycaemia, polyhydramnios, 5-min APGAR score < 7 and preterm delivery. Risk of bias assessment was performed with Newcastle Ottawa scale. Subgroup analysis was also performed.

Results From 14,746 records, 42 studies were selected for full-text assessment. Thirty studies reporting on 114,148 participants, including 18,878 women with GRH, fulfilled eligibility criteria. Pregnancies with observed GRH had higher risk of SGA (RR = 1.49, 95%CI = 1.33, 1.68), LBW (RR = 1.35, 95%CI = 1.13, 1.60), FGR (RR = 1.21, 95%CI = 1.05, 1.41), and NICU admission (RR = 1.23, 95%CI = 1.02, 1.49) compared to the euglycaemic group. At subgroup analyses, GRH diagnosed at postload glucose < 3 mmol/l was associated with an increased risk of NICU admission (RR = 3.39, 95%CI = 1.56, 7.34); and GRH limited to post glucose tolerance test (GTT) was associated with increased risk of polyhydramnios (RR = 1.93, 95%CI = 1.17, 3.20) and SGA (RR = 1.90, 95%CI = 1.01, 3.58).

Conclusions GRH is a condition not routinely diagnosed in pregnancy but associated with adverse fetal-neonatal outcomes as SGA, FGR, and NICU admission. At GTT, GRH is associated with the risk of polyhydramnios. More studies are still necessary to determine the threshold value for diagnosis of GRH and explore associations with other outcomes related to glucose dysmetabolism.

Keywords Gestational diabetes mellitus, Gestational reactive hypoglycaemia, Low birth weight, Pregnancy outcomes, Small for gestational age.

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Background

As part of normal physiological metabolic adaptation in pregnancy, increased maternal insulin resistance, lipolysis, and hepatic gluconeogenesis alongside reduced skeletal muscle glucose uptake is aimed for maintaining maternal glucose availability for the fetus [1–3]. Maternal and placental secreted hormones, particularly human placental lactogen, glucagon, cortisol, oestrogen, and progesterone all act in parallel to reduce maternal tissue sensitivity to insulin. Meanwhile, plasma insulin is elevated in mid-late gestation to maintain normal glucose homeostasis [3, 4]. Abnormal glucose tolerance that is detected for the first time in mid-late gestation can be clinically manifested as hyperglycaemia, and then diagnosed as gestational diabetes mellitus (GDM) according to various sets of criteria [5–7].

Hypoglycaemia during pregnancy is another condition of abnormal glucose values that mostly occurs due to the side-effect of tight glycaemic control in pregnancy diabetes [8–10]. However, pregnancy hypoglycaemia may also occur in women who have never been diagnosed with pregnancy diabetes and this condition may be an undiagnosed entity of impaired glucose tolerance. After a glucose load, some women might also exhibit hypoglycaemia considered as gestational reactive hypoglycaemia (GRH) [11, 12]. A previous meta-analysis by Mitta showed that 1-hour low glucose value following a 50-grams glucose challenge test (GCT) was associated with abnormal fetal growth [13]. Although the mechanism is not clearly understood, the asynchronous insulin response in GRH indicates a sign of glucose dysmetabolism, as akin to some form of impaired glucose tolerance or diabetes during pregnancy [14]. However, it is also not known if GRH in response to a glucose load as part of testing represents similar fluctuations in response to meals rich in simple carbohydrates in daily life.

Optimal screening of abnormal glucose tolerance during pregnancy is a part of essential maternity care to prevent impaired glucose tolerance-associated perinatal complications and postnatal progression of future morbidities in mother and child [15, 16]. Diagnostic criteria using a glucose loading test have been internationally adopted and modified to assess any glucose tolerance and insulin function in pregnant women population [6, 7, 15]. The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study found that values of 2-hour oral glucose tolerance testing (OGTT) predict adverse pregnancy outcomes related to pregnancy hyperglycaemia in a dose-response fashion [17, 18]. Nonetheless, the current interpretation of glucose loading tests only reflects hyperglycaemia and does not consider hypoglycaemia following a glucose loading test [12]. There is no current consensus established regarding the standards of glucose level to diagnose GRH and our understanding of its

association with adverse pregnancy outcomes is limited. The previous meta-analysis has shown that low glucose values following a 1-hour GCT are a potential predictor of LBW and SGA but it did not explore other possible pregnancy outcomes [13]. The objective of this study was to investigate the association between GRH after any glucose load and pregnancy outcomes, by meta-analysis of the published literature.

Methods

This study was registered on PROSPERO (<https://www.crd.york.ac.uk/prospero/>), a global registry of systematic review, that was funded by National Institutes of Health (CRD42023355124). This review was written in concordance with the guideline of Meta-Analysis of Observational Studies in Epidemiology [19], and the Preferred Reporting Items for Systematic Review and Meta-Analysis protocol [20].

Search strategy

Initial literature searching was conducted using the following databases: Medline, Embase, Web of Science, and Maternity & Infant Care Database (MIDIRS). To obtain additional papers not identified in the primary search, the snowball method was utilised by searching relevant cited articles within reference lists of included studies. The literature search included studies from inception to 1 December 2023, for case-control and cohort studies. The keywords for the search strategy were agreed with a medical librarian from the university faculty of population health science. The algorithm used for the search strategy was performed by combining MeSH and keyword terms in the databases. Detailed information on terms used in our search strategy for all databases is shown in Supplementary File 1.

Study selection and eligibility criteria

We reviewed studies that reported low glucose values following glucose ingestion during a GCT and/or a GTT as the exposure, which we defined as GRH in our meta-analysis. The study design considered appropriate for this systematic review was observational (case-control and cohort) studies that used either GCT or GTT for GDM screening/diagnosis ≥ 24 weeks. Published full-text articles and conference abstracts in any language regardless of publication year were collected. The population of interest for this systematic review and meta-analysis study was singleton pregnant women with GRH and not diagnosed with GDM or pregestational diabetes. Pregnancy with euglycaemia was determined as the control group. The outcomes of interests evaluated in this review were based on the adverse pregnancy outcomes in relation to glucose loading test and associated pregnancy outcomes [13, 17, 21], including small for gestational age

(SGA), large for gestational age (LGA), low birth weight (LBW), macrosomia, caesarean delivery, NICU admission, polyhydramnios, neonatal hypoglycaemia, neonatal hyperbilirubinaemia, low 5 min APGAR score (<7), fetal growth restriction (FGR), polyhydramnios, shoulder dystocia, perinatal mortality, preeclampsia (PE), and postpartum hemorrhage. Studies with confirmed pregestational diabetes, pre-existing type 1/2 diabetes mellitus, or diagnosed GDM in GRH cohort were excluded. Studies with incomplete information or evaluating low fasting glucose value, as opposed to post-load plasma glucose, were also excluded. Studies that were high in risk of bias assessment were also excluded.

Screening, data extraction, and risk of bias assessment

Article screening was independently completed by three review authors (MPMH, MJ, and MPMP) using Rayyan web platform for systematic reviews. Data extraction from eligible studies was independently performed by three review authors (MPMH, MJ, and MPMP). All studies extracted from each database were screened for their eligibility by title and abstract, according to the eligibility criteria. In cases where the title or abstract did not sufficiently indicate whether they met the inclusion criteria, the full-text was reviewed. Full-text articles for the studies were retrieved, reviewed, and analysed to see if they were suitable and relevant for qualitative analysis. We manually hand-searched reference lists for additional related studies. All studies that matched the selected eligibility criteria were extracted using a dedicated data sheet. We extracted relevant information from all studies meeting our eligibility criteria: first author, publication year, country of each study, the definition of exposure, method of giving exposure, sample size, outcome of interest, outcome definition (if any), and effect measure (number or proportion with and without outcomes). Any conflicting statements between reviewers were resolved by discussions with the senior reviewer.

Quality assessment

Measurement bias at study level for our review analysis was investigated using the Newcastle-Ottawa Scale for cohort and case-control studies [22]. Bias assessment was independently done by three reviewers (MPMH, MJ, and MPMP). According to the Newcastle-Ottawa Scale, the quality assessment is based on 3 criteria: study selection of participants (4 stars), study comparability (2 stars), and outcome assessment (3 stars). We considered studies with 7–9 stars as good, studies with 2–6 stars as fair, and studies with 0–2 stars as poor quality. Studies with poor scores in the Newcastle-Ottawa Scale were categorised as high risk of bias. Disagreements between the reviewers on the risk of bias assessment were resolved through discussion between the reviewers, and a third senior

reviewer (DS) was consulted in cases where they were unable to come to an agreed conclusion.

Statistical analysis

Meta-analysis and forest plot generation were conducted with Review Manager 5.4 and statistical significance was considered for any two-sided p -value less than 0.05. From each study the number of those with and without pregnancy complications in the two groups (GRH and normal glucose tolerance) was uniformly measured as a risk ratio (RR). Continuous data was collected and measured as standardized mean differences (SMD). A random-effect model and the Mantel-Haenszel method were used because of the high clinical heterogeneity across studies; each study used different criteria to define hypoglycaemia. I^2 statistic was used to determine statistical heterogeneity. Data with I^2 less than 40% were analysed using a fixed-effect model. Forest plots were employed to show the pooled estimates. To evaluate clinical heterogeneity, subgroup analysis explored different thresholds for GRH: < 5 mmol/l (90 mg/dl); < 4 mmol/l (70 mg/dl); and < 3 mmol/l (60 mg/dl). A further subgroup analysis evaluated the clinical manifestations of GRH, based on low value following either 1-hour GCT or GTT.

Results

Literature search

The PRISMA flow chart summarises the process to determine inclusion/exclusion for records and studies extracted from databases (Fig. 1). From the search strategy, 9607 of 14,746 records were yielded from all databases for the title and abstract screening, after removing duplicates. Throughout abstract screening, 42 full-text papers were obtained for eligibility assessment. After excluding 8 studies, 34 were included for the quality assessment, consisting of 29 full-text articles and 4 conference abstracts [23–26]. Based on the scoring under the Newcastle-Ottawa scale, three reviewers (MPMH, MPMP, and MJ) and the senior author excluded 4 studies [23, 27–29] with a high risk of bias for quantitative analyses (Table 1.). Reviewers' decision on the bias assessment can be seen in Supplementary File 2. Overall, the quantitative analyses included 30 studies with a total of 114,148 participants, comprising 18,878 women with GRH and 95,270 euglycaemic control women.

Study characteristics

Basic characteristics of 30 studies are summarized in Table 2. Most participants in the cohorts were recruited from the general pregnant population, except one article which included participants based on prior history of bariatric surgery [57]. The majority of studies performed 1-hour plasma glucose measurement after 50 g GCT. Nine studies performed GTT measurement [30, 57–64].

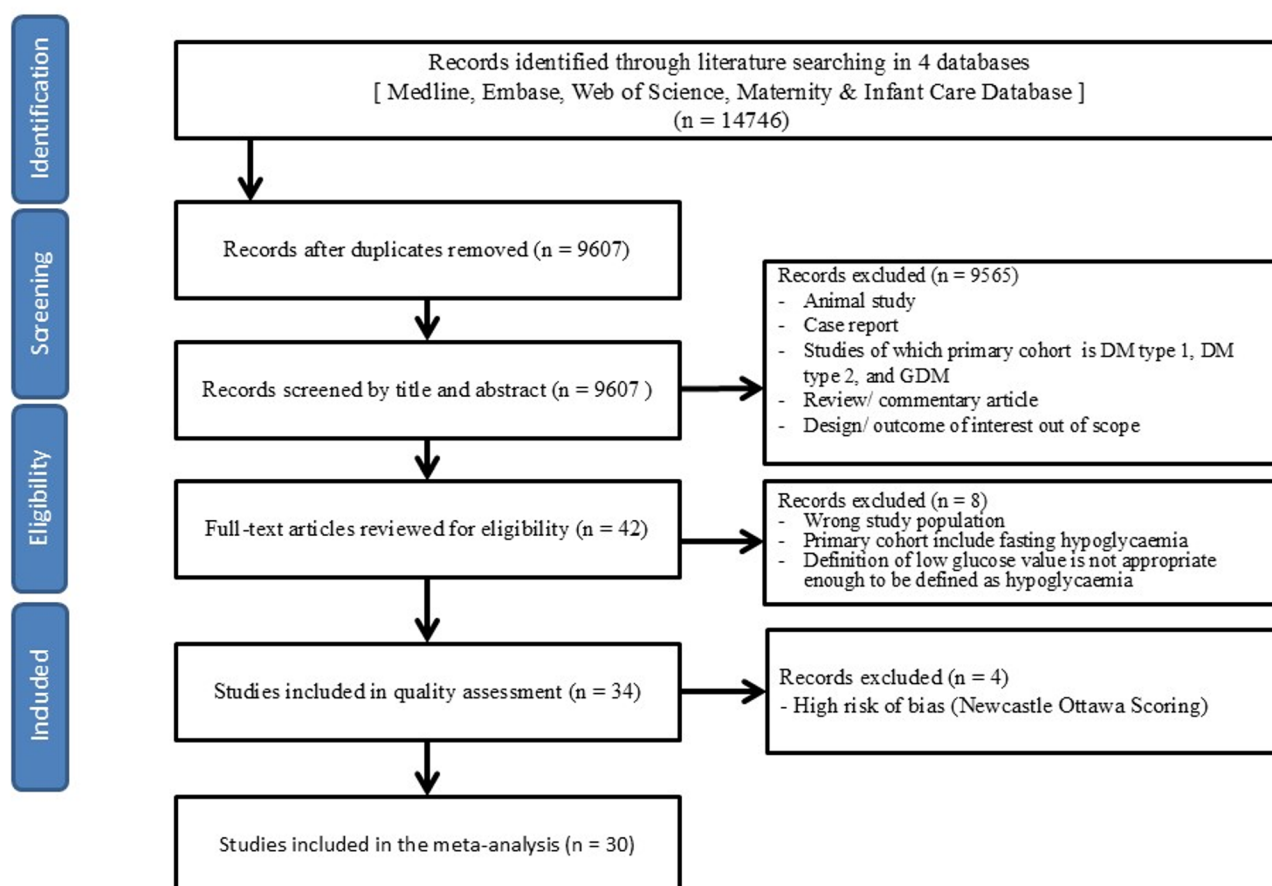


Fig. 1 Flow chart of study inclusion in systematic review and meta-analysis

Outcomes of interest in our meta-analyses included pregnancy outcomes associated with glucose dysmetabolism according to the HAPO study, the published GDM core outcome set, and the outcomes reported in a previous systematic review [13, 17, 18, 21]. All studies that were extracted from a full-text article had detailed the growth reference standards for criteria of neonatal birth weight, but the studies from conference abstracts did not explain the reference standards used for their cohorts.

Association between GRH and adverse pregnancy outcomes

Extracted data from included studies that reported adverse pregnancy outcomes were pooled to determine summary risk ratio (RR) for the associations between GRH and outcomes of interest (Table 3). Women with GRH were at a higher risk of delivering a baby that was SGA, LBW, and FGR (Fig. 2.) whilst they were at lower risk of delivering macrosomic/LGA infants as well as baby with hyperbilirubinaemia after birth. Neonates of women with GRH had a lower risk of delivered by caesarean section. This meta-analysis revealed no differences in the risk of other pregnancy outcomes related

to glucose dysmetabolism (NICU admission, neonatal hypoglycaemia, low 5-minute APGAR score, and perinatal mortality).

Subgroup analyses

Subgroup analysis was based on a pragmatic classification of the glucose threshold value ((postload glucose < 5 mmol/l, < 4 mmol/l, and < 3 mmol/l (Table 4.). Using a threshold for GRH diagnosis of glucose lower than 5 mmol/l, GRH was associated with an increased risk of SGA, LBW, FGR, and NICU admission. Using postload glucose < 4 mmol/l as a cutoff value for GRH, the risk of LBW still persisted. GRH using a threshold of postload glucose < 3 mmol/l was associated with an increased risk of NICU admission as well as LBW (Table 4.). GRH following 1-hour GCT was associated with increased risks of SGA (Fig. 3), LBW (Fig. 4), and FGR. GRH at GTT was associated with SGA, and polyhydramnios (Table 5; Figs. 5–6).

Table 1 Quality assessment for eligible studies

Author, Year	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Follow-up Long Enough for Outcomes to Occur	Adequacy of Follow-up of Cohorts	Total Score Selection Domain	Comparability Domain	Outcome/Exposure Domain	Quality
Bayraktar, 2020 [30]	*	*	*	*	**	*	*	*	4	2	3	Good
Bhat, 2012 [31]	*	*	no star	*	**	*	*	*	3	2	2	Good
Bienstock, 2008 [27]	no star	*	*	*	no star	*	*	*	3	0	3	Poor
Budak, 2018 [32]	*	*	*	*	**	*	*	*	4	2	3	Good
Calfee, 1999 [33]	*	*	no star	*	**	*	*	*	3	2	3	Good
Delibas, 2018 [34]	*	*	*	*	**	*	*	*	4	2	3	Good
Ding, 2023 [35]	*	*	*	*	**	*	*	*	4	2	3	Good
Duhl, 2000 [36]	*	*	*	*	*	*	*	*	4	1	3	Good
Feinberg, 2005 [37]	*	*	*	*	**	*	*	*	4	2	3	Good
Kerenyi, 2009 [28]	*	*	*	*	no star	*	*	no star	4	0	2	Poor
Kwon, 2015 [23]	no star	no star	no star	*	*	no star	*	*	1	1	2	Poor
Kwon, 2018 [38]	*	*	*	*	**	*	*	*	4	2	3	Good
Lurie, 1998 ± [39]	no star	*	no star	*	*	*	*	*	2	1	3	Fair
Ma, 1998 [40]	*	*	*	*	**	*	*	*	4	2	3	Good
Melamed, 2013 [41]	*	*	*	no star	**	no star	*	*	3	2	2	Fair
Nayak, 2019 [42]	*	*	*	*	*	*	*	no star	4	1	2	Good
Oawada, 2019 [43]	*	*	*	*	**	*	*	*	4	2	3	Good
Ong, 2008 [44]	no star	*	*	*	*	*	*	*	3	1	3	Good
Pugh, 2009 [45]	*	*	no star	*	*	*	*	*	3	1	3	Good
Raviv, 2021 [46]	*	*	*	*	*	*	*	no star	4	1	2	Good
Rehman, 2022 [47]	*	*	*	*	*	*	*	*	4	1	3	Good
Reicher, 2021 [48]	*	*	*	*	*	*	*	*	4	1	3	Good
Rottenreich, 2017 ± [49]	no star	*	*	*	*	*	*	*	3	1	3	Good
Scholl, 2021 [29]	no star	*	*	*	no star	*	*	*	3	0	3	Poor
Shinohara, 2015 [50]	*	*	*	*	*	*	*	no star	4	1	2	Good
Shinohara, 2016 [51]	*	*	*	*	*	*	*	no star	4	1	2	Good
Stivers, 2020 [26]	*	*	*	*	*	*	*	*	4	1	3	Good
Tanacan, 2020 [52]	*	*	*	*	*	*	*	*	4	1	3	Good
TopÇu, 2016 [53]	*	no star	*	*	*	*	*	no star	3	1	2	Good
Vadakekut, 2010 [54]	*	*	*	*	*	*	*	*	4	1	3	Good
Vemareddy, 2009 [25]	*	*	*	*	**	*	*	*	4	2	3	Good
Yoles, 2021 [24]	*	*	no star	*	*	no star	*	*	3	1	2	Good
Yuen, 2019 [55]	*	no star	*	*	*	*	*	no star	3	1	2	Good
Weissman, 2005 [56]	*	*	*	*	*	*	*	*	4	1	3	Good

* >star symbol > fulfillment of eligibility criteria

± symbol > disagreement between reviewers, resolved by the senior author

Table 2 Characteristics of the included studies in the systematic review and Meta-Analysis

Author, Year	Study Design; Setting	Enrolment	Gestational Reactive Hypoglycaemia Definition		Euglycaemia Definition	Pregnancy Outcomes
			Glucose Loading Test	Threshold Value		
Bayraktar, 2020 [30]	Retrospective Cohort; Turkey	24–28 weeks	Glucose tolerance test	≤ 3.9 mmol/l	3.9–8.5 mmol/l	LBW, caesarean delivery, NICU admission, preterm birth, macrosomia, APGAR score < 7
Bhat, 2012 [31]	Prospective Cohort; India	24–28 weeks	1-hour Glucose challenge test	≤ 4.9 mmol/l	5–7.8 mmol/l	LBW, NICU admission
Budak, 2018 [32]	Retrospective Cohort; Turkey	24–28 weeks	1-hour Glucose challenge test	< 5 mg/dL	5–7.8 mmol/l	SGA, caesarean delivery, 5-minute APGAR score < 7, preterm birth
Calfee, 1999 [33]	Prospective Cohort; USA	≥ 24 weeks	1-hour Glucose challenge test	≤ 4.9 mg/dL	5–7.8 mmol/l	FGR
Delibas, 2018 [34]	Retrospective Cohort; Turkey	25–28 weeks	Glucose tolerance test	< 2.5 mmol/l	Carpenter and Coustan thresholds	SGA, LGA, 5-minute APGAR score < 7, NICU admission, preterm birth, PE
Ding, 2023 [35]	Retrospective Cohort; USA	≥ 24 weeks	1-hour Glucose challenge test	< 4.6 mmol/l	≥ 4.6 mmol/l	SGA, NICU admission, neonatal hypoglycaemia, neonatal hyperbilirubinaemia, perinatal death, PE, postpartum hemorrhage
Duhl, 2000 [36]	Retrospective Cohort; USA	26–29 weeks	1-hour Glucose challenge test	PG < 4 mmol/l	5–7.1 mmol/l	SGA
Feinberg, 2005 [37]	Retrospective Case Control Study; USA	24–28 weeks	1-hour Glucose challenge test	< 4.9 mmol/l	4.9–7.8 mmol/l	LBW, caesarean delivery, 5-minute APGAR score < 7, NICU admission, preterm birth, neonatal hypoglycaemia, neonatal hyperbilirubinaemia, postpartum hemorrhage
Kwon, 2018 [38]	Retrospective Cohort; Korea	24–28 weeks	1-hour Glucose challenge test	< 4.8 mmol/l	4.8–7.2 mmol/l	SGA, LGA, LBW, macrosomia, caesarean delivery, 5-minute APGAR score < 7, NICU admission, preterm birth, polyhydramnios, PE, perinatal mortality
Lurie, 1998 [39]	Retrospective Cohort; Israel	24–28 weeks	1-hour Glucose challenge test	< 3.3 mmol/l	3.3–6.1 mmol/l	Macrosomia, cesarean delivery, polyhydramnios, neonatal hyperbilirubinaemia, PE
Ma, 1998 [40]	Retrospective Cohort; USA	24–30 weeks	1-hour Glucose challenge test	< 5 mmol/l	5–6.7 mmol/l	SGA, LGA, cesarean delivery, NICU admission, neonatal hypoglycaemia, neonatal hyperbilirubinaemia, PE
Melamed, 2013 [41]	Retrospective Cohort; Israel	24–28 weeks	1-hour Glucose challenge test	< 3.9 mmol/l	3.9–6.7 mmol/l	SGA, LGA, LBW, macrosomia, FGR, caesarean delivery, 5-minute APGAR score < 7, NICU admission, preterm birth, neonatal hypoglycaemia, neonatal hyperbilirubinaemia, shoulder dystocia, perinatal mortality, PE, postpartum hemorrhage
Nayak, 2019 [42]	Retrospective Cohort; UK	24–28 weeks	Glucose tolerance test	< 3.6 mmol/l	3.6–7.7 mmol/l	LBW
Oawada, 2019 [43]	Retrospective Case Control Study; Japan	24–28 weeks	1-hour Glucose challenge test	< 4.2 mmol/l	4.2–7.8 mmol/l	SGA, LGA, LBW, macrosomia
Ong, 2008 [44]	Retrospective Cohort; UK	27–29 weeks	1-hour Glucose challenge test	< 4 mmol/l	4.1–7.8 mmol/l	-
Pugh, 2009 [45]	Prospective Cohort; USA	24–28 weeks	1-hour Glucose challenge test	< 4.9 mmol/l	4.9–7.8 mmol/l	LBW, macrosomia, FGR, caesarean delivery, 5-minute APGAR score < 7, NICU admission, preterm birth, PE
Raviv, 2021 [46]	Retrospective Cohort; Israel	24–28 weeks	Glucose tolerance test	< 3.3 mmol/l	Carpenter and Coustan thresholds	SGA, LGA, LBW, macrosomia, shoulder dystocia, PE
Rehman, 2022 [47]	Retrospective Cohort; UK	24–28 weeks	Glucose tolerance test	< fasting glucose value	Euglycaemia within all values (FPG < 95 mg/dL, 1-hour PG < 180 mg/dL, 2-hour PG < 140 mg/dL on modified IADPSG criteria)	SGA, polyhydramnios, shoulder dystocia, perinatal mortality
Reicher, 2021 [48]	Retrospective Cohort; Israel	24–28 weeks	Glucose tolerance test	< 3.3 mmol/l	Carpenter and Coustan thresholds	LGA, CS, 5-minute APGAR score < 7, polyhydramnios, PE

Table 2 (continued)

Author, Year	Study Design; Setting	Enrolment	Gestational Reactive Hypoglycaemia Definition		Euglycaemia Definition	Pregnancy Outcomes
			Glucose Loading Test	Threshold Value		
Rottenstreich, 2018 [49]	Retrospective Cohort; Israel	24–28 weeks	Glucose tolerance test	< 3.1 mmol/l	> 3.2 mmol/l	SGA, LGA, LBW, macrosomia, caesarean delivery, preterm birth,
Shinohara, 2015 [50]	Retrospective Cohort; Japan	24–28 weeks	1-hour Glucose challenge test	< 5 mmol/l	5–7.8 mmol/l	SGA, preterm birth, caesarean delivery
Shinohara, 2016 [51]	Retrospective Cohort; Japan	24–28 weeks	1-hour Glucose challenge test	< 5 mmol/l	5–7.8 mmol/l	SGA, caesarean delivery
Stivers, 2020 [26]	Retrospective Cohort; USA	24–28 weeks	1-hour Glucose challenge test	< 4.9 mmol/l	4.9–7.2 mmol/l	SGA, FGR, LGA
Tanacan, 2020 [52]	Retrospective Cohort; Turkey	24–28 weeks	1-hour Glucose challenge test	< 4.1 mmol/l	4.1–7.8 mmol/l	SGA
TopÇu, 2016 [53]	Retrospective Case Control Study; Turkey	24–28 weeks	1-hour Glucose challenge test	< 4.9 mmol/l	4.9–7.2 mmol/l	SGA, LGA, LBW, macrosomia, caesarean delivery, NICU admission, preterm birth, polyhydramnios, PE, perinatal mortality
Vadakekut, 2010 [54]	Retrospective Cohort; USA	24–28 weeks	1-hour Glucose challenge test	< 4.9 mmol/l	4.9–7.5 mmol/l	SGA
Vemareddy, 2009 [25]	Retrospective Cohort; USA	24–28 weeks	1-hour Glucose challenge test	< 5 mmol/l	5–7.2 mmol/l	-
Yoles, 2021 [24]	Retrospective Cohort; Netherlands	No information	1-hour Glucose challenge test	< 5 mmol/l	5–7.8 mmol/l	preterm delivery, LBW, macrosomia
Yuen, 2019 [55]	Prospective Cohort; Australia	24–28 weeks	Glucose tolerance test	< 3.6 mmol/l	Carpenter and Coustan thresholds	caesarean delivery, NICU admission, neonatal hypoglycaemia, perinatal mortality
Weissman, 2005 [56]	Retrospective Cohort; Israel	24–28 weeks	Glucose tolerance test	< 2.8 mmol/l	2.8–7.2 mmol/l	SGA, LGA, macrosomia, cesarean delivery

Abbreviations: FGR fetal growth restriction, LBW low birth weight, LGA large for gestational age, NICU neonatal intensive care unit, PE preeclampsia, RR risk ratio, SGA small for gestational age

Discussion

In the meta-analysed literature, pregnant women with GRH value < 5 mmol/l had a high risk of having small babies, either diagnosed with SGA, LBW, or FGR while the risk of delivering LGA or macrosomia was reduced. Of outcomes associated with diabetes, only polyhydramnios was associated with GRH in this meta-analysis. Our meta-analysis agrees with the previous meta-analysis by Mitta [13]. Their meta-analysis showed an increased risk of SGA in women with a 1-hour GCT value < 5 mmol/l. However, they did not examine studies with GRH following GTT. Hypoglycaemia is typically defined in pregnant women with diabetes using a glucose level < 4 mmol/l in which neuroendocrine response is more observed and may need immediate treatment [47]. In a subgroup analysis, LBW still persisted with GRH threshold < 4 mmol/l. Published studies have used different cut-offs to define GRH. Physiological glucose in non-diabetic subjects may be lower, although precise limits are debated. Our meta-analysis suggests that in GRH with glucose value < 3 mmol/l (the most severe), there is an increased risk for baby to be admitted to NICU. Quansah et al. found that women with GDM and subsequent postpartum RH < 3.9 mmol/l have a better metabolic profile, with better insulin response than women with typical GDM and no

Table 3 Key findings of the Meta-Analysis

Pregnancy Outcomes	Heterogeneity (I ²)	Model	Pooled RR (95% CI)
SGA	59%	Random-effect	1.49 (1.33, 1.68)**
LGA	25%	Fixed-effect	0.74 (0.76, 0.82)**
LBW	67%	Random-effect	1.35 (1.13, 1.60)**
Macrosomia	0%	Fixed-effect	0.69 (0.61, 0.77)**
NICU admission	60%	Random-effect	1.23 (1.02, 1.49)*
APGAR score < 7	63%	Random-effect	1.88 (0.96, 3.68)
Caesarean section	76%	Random-effect	0.90 (0.79, 0.96)**
Shoulder dystocia	0%	Fixed-effect	0.50 (0.24, 1.05)
FGR	0%	Fixed-effect	1.21 (1.05, 1.41)*
Polyhydramnios	71%	Random-effect	0.94 (0.42, 2.12)
Neonatal hypoglycaemia	95%	Random-effect	1.54 (0.37, 6.44)
Neonatal hyperbilirubinaemia	0%	Fixed-effect	0.82 (0.72, 0.92)**
Perinatal mortality	12%	Fixed-effect	1.06 (0.73, 1.55)
Preterm delivery	89%	Random-effect	1.16 (0.88, 1.54)
PE	57%	Random-effect	0.90 (0.71, 1.16)
Postpartum hemorrhage	84%	Random-effect	0.59 (0.29, 1.20)

Abbreviations: FGR fetal growth restriction, LBW low birth weight, LGA large for gestational age, N/A non-applicable, NICU neonatal intensive care unit, PE preeclampsia, RR risk ratio, SGA small for gestational age. Asterisk (*) symbol indicates significant value

* = p -value < 0.05; ** = p -value < 0.01

Table 4 Subgroup analysis based on plasma glucose threshold value

Pregnancy Outcomes	Postload glucose < 5 mmol/l	Postload glucose < 4 mmol/l	Postload glucose < 3 mmol/l
	Pooled RR (95% CI)	Pooled RR (95% CI)	Pooled RR (95% CI)
SGA	1.49 (1.33, 1.68)**	1.38 (1.09, 1.74)**	2.20 (0.49, 9.87)
LGA	0.74 (0.76, 0.82)**	0.83 (0.71, 0.97)*	0.57 (0.28, 1.18)
LBW	1.35 (1.13, 1.60)**	1.45 (1.22, 1.72)**	5.08 (1.16, 22.23)*
Macrosomia	0.69 (0.61, 0.77)**	0.80 (0.64, 1.01)	0.54 (0.25, 1.15)
NICU admission	1.23 (1.02, 1.49)*	1.40 (0.92, 2.12)	3.39 (1.56, 7.34)**
APGAR score < 7	1.88 (0.96, 3.68)	1.88 (0.96, 3.68)	N/A
Caesarean section	0.90 (0.79, 0.96)**	0.90 (0.79, 1.02)	0.80 (0.56, 1.15)
Shoulder dystocia	0.50 (0.24, 1.05)	0.50 (0.24, 1.05)	N/A
FGR	1.21 (1.05, 1.41)*	N/A	N/A
Polyhydramnios	0.94 (0.42, 2.12)	N/A	N/A
Neonatal hypoglycaemia	1.54 (0.37, 6.44)	7.10 (0.06, 823.09)	N/A
Neonatal hyperbilirubinaemia	0.82 (0.72, 0.92)**	N/A	N/A
Perinatal mortality	1.06 (0.73, 1.55)	2.46 (0.28, 21.28)	N/A
Preterm delivery	1.16 (0.88, 1.54)	1.17 (0.82, 1.68)	1.71 (0.38, 7.76)
PE	0.90 (0.71, 1.16)	0.93 (0.67, 1.30)	N/A
Postpartum hemorrhage	0.59 (0.29, 1.20)	N/A	N/A

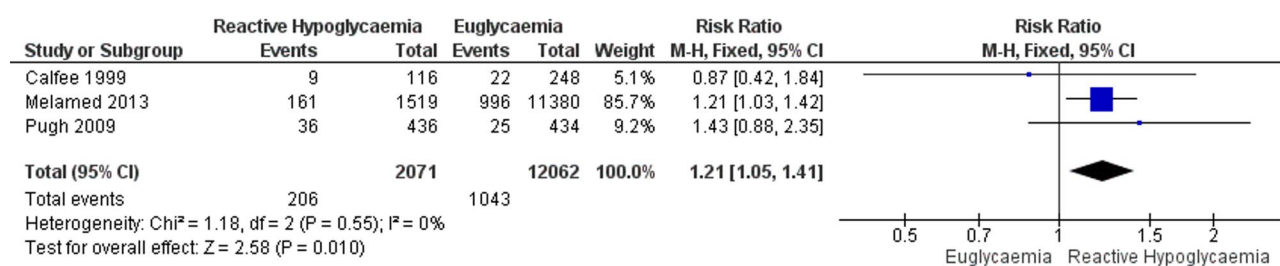
Abbreviations: FGR fetal growth restriction, LBW low birth weight, LGA large for gestational age, N/A not applicable, NICU neonatal intensive care unit, PE preeclampsia, RR risk ratio, SGA small for gestational age. Asterisk (*) symbol indicates significant value.

*= p -value < 0.05; **= p -value < 0.01

postpartum RH [65]. Whereas it is possible that even severe GRH represents a milder and/or earlier form of undiagnosed glucose intolerance, there are no long-term studies of women with GRH alone without diagnosis of GDM. Women with GDM in pregnancy display a less sensitive maternal insulin response to a glycaemic stimulus compared to otherwise normal pregnancies [66]. GRH may reflect the first phase of glucose dysmetabolism before overt diabetes, a suboptimal primary insulin response to glucose loads, but this remains speculative. When the first-phase insulin response is insufficient, there may be a late and excessive second-phase insulin secretion, leading to reactive hypoglycaemia [14, 67]. In other words, GRH may be caused by a delay in the peak of first-phase insulin secretion in response to plasma glucose levels, followed by excessive secondary insulin response [68]; insulin response to glucose loads can also be biphasic or triphasic [69]. The phenomenon may very well have multiple aetiologies. Altered gut transit or glucose absorption, abnormally increased insulin sensitivity,

reduced insulin clearance, and changes in the hypothalamus-hypophysis axis also merit consideration. Maternal hypoglycaemia may decrease glucose availability to fetus [70] but that would not explain why GRH and FGR co-exist in women with insulin resistance or obesity or in women subsequently diagnosed with diabetes. Disorders in placental function may be key to untangling, at least in part, the pathophysiology leading to placental dysfunction and abnormal fetal growth [71, 72]. Although no studies have reported to date placental abnormalities in GRH, some reports have improved our understanding of how during pregnancy can affect the placenta [48]. Placental histopathology findings associated with diagnosed or suspected glucose dysmetabolism, including possibly GRH, include villous thrombosis and maturation disorders (fetal vascular malperfusion, delayed villous maturation), in turn associated with outcomes such as FGR and stillbirth [49, 56, 73–76].

Another very interesting and novel finding in the subgroup analysis of this study is the unusual combination

**Fig. 2** Forest plot of the pooled effect of estimate (RR) of FGR when GRH was compared with euglycaemia

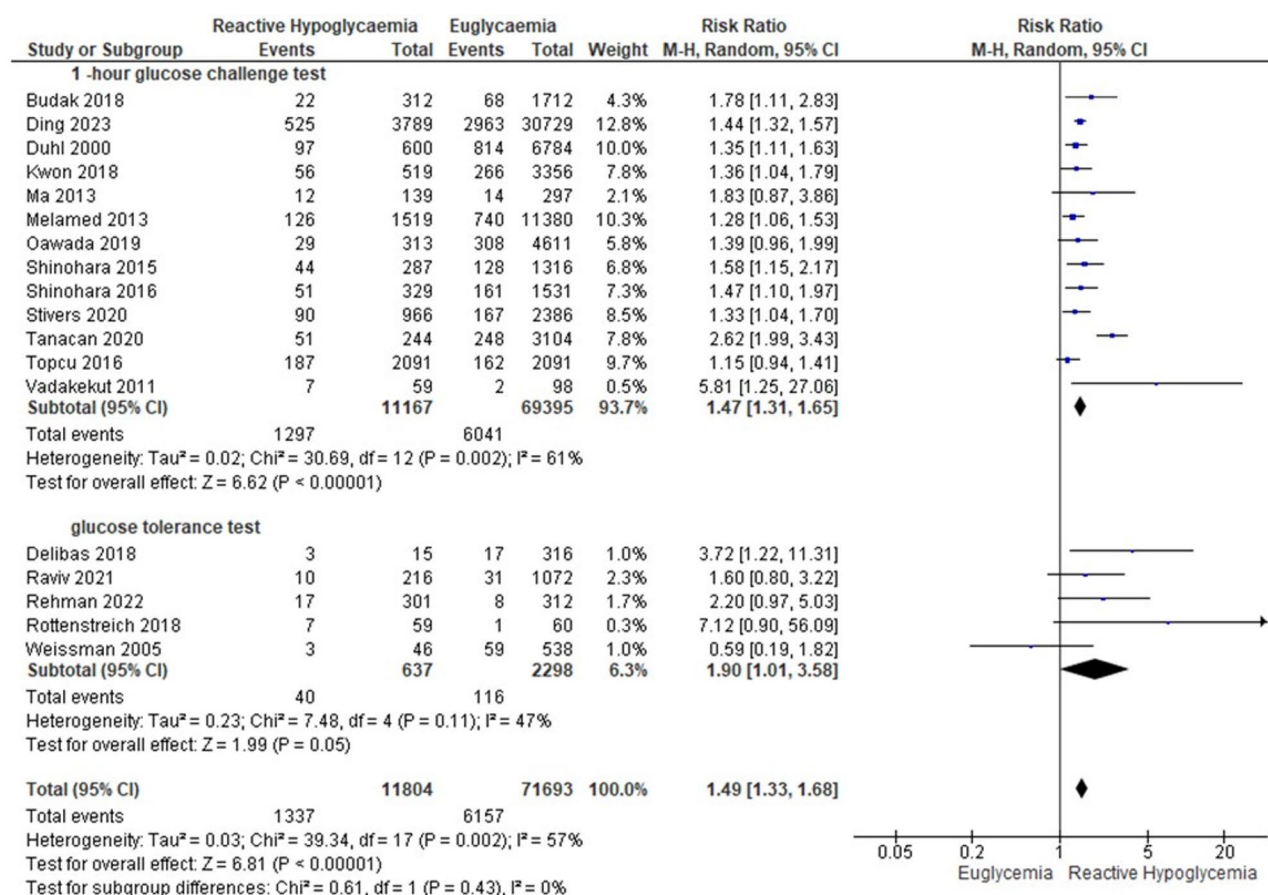


Fig. 3 Forest plot of the subgroup analysis for GRH at 1-hour GCT and GTT to the risk of small for gestational age

of SGA with polyhydramnios in women with GRH after GTT. Although its incidence is low, the co-existence of polyhydramnios and SGA in pregnancies in the absence of any fetal congenital malformation has been reported previously [34, 55]. A study in two UK hospitals, published recently [61] found that GRH, defined as 2-hour GTT value lower than or equivalent to fasting level, was associated with polyhydramnios and mean birth-weight similar to pregnancies complicated by diabetes, with babies overall heavier than controls. Outcomes typically related to diabetes such as abdominal circumference >95th centile, induction of labour, perinatal infection, hypertensive disorders of pregnancy, neonatal hypoglycaemia, and ambiguous genitalia were also higher with GRH in preliminary analyses of data from one hospital alone [77] but this did not persist in the combined dataset. Some of the pregnancy complications that are relevant to diabetes are multifactorial and the associated pathophysiology is not always clearly understood [42, 78–80]. Other pre-existing maternal conditions such as obesity and dyslipidaemia often found in women with GDM may contribute to the occurrence of these outcomes and other complications typically related to pregnancy diabetes and hyperglycaemia [46, 81, 82].

Our study could have been limited by the fact that there is no agreed recommendation on the glucose value threshold and tests to diagnose women with GRH. The authors in the included studies applied different tests (GCT/GTT), criteria, and glucose value thresholds to diagnose GRH following glucose loading test, according to each study setting, resulting in considerable clinical heterogeneity. Moreover, Rottenstreich's study included women with a history of post-bariatric surgery [57]. We acknowledge this clinical heterogeneity in the considered studies, including in adjustment for confounders in. To address the study heterogeneity, the meta-analysis was performed using a random effect model. Since there are no agreed thresholds to define GRH, our meta-analyses help elucidate the impact of different thresholds on outcomes, to inform future research. How and when GRH affects pregnancies remains to be determined, but this meta-analysis, including the subgroup analyses, shows that GRH is associated with adverse neonatal outcomes, regardless of the test or threshold used to diagnose GRH. Some analyses not included in PROSPERO protocol for this systematic review and meta-analysis were performed post-hoc at the request of the peer-reviewers.

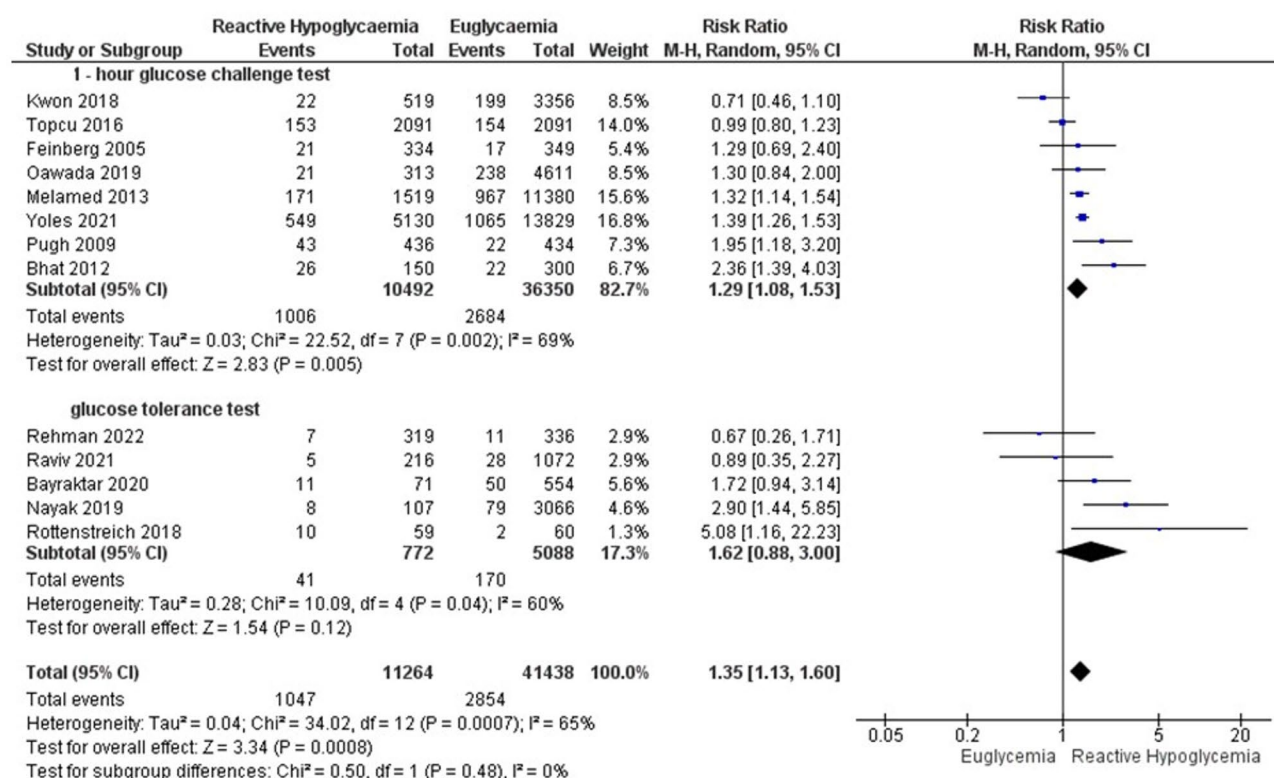


Fig. 4 Forest plot of the subgroup analysis for GRH at 1-hour GCT and GTT to the risk of low birth weight

Table 5 Subgroup analysis based on glucose loading test (1-hour glucose challenge test vs. glucose tolerance test)

Pregnancy Outcomes	1-hour Glucose challenge test	Glucose tolerance test
	Pooled RR (95% CI)	Pooled RR (95% CI)
SGA	1.47 (1.31, 1.65)**	1.90 (1.01, 3.58)*
LGA	0.72 (0.65, 0.81)**	0.90 (0.69, 1.18)*
LBW	1.29 (1.08, 1.53)**	1.62 (0.88, 3.00)
Macrosomia	0.69 (0.62, 0.78)**	0.64 (0.43, 0.94)*
NICU admission	1.14 (0.96, 1.36)	2.16 (0.92, 5.10)
APGAR score < 7	1.46 (0.73, 2.89)	1.98 (0.47, 8.24)
Caesarean section	0.86 (0.77, 0.96)*	1.01 (0.83, 1.22)
Shoulder dystocia	0.11 (0.01, 1.77)	0.69 (0.32, 1.49)
FGR	1.21 (1.05, 1.41)*	N/A
Polyhydramnios	0.71 (0.27, 1.88)	1.93 (1.17, 3.20)**
Neonatal hypoglycaemia	1.64 (0.28, 9.74)	1.05 (0.36, 2.97)
Neonatal hyperbilirubinaemia	0.82 (0.72, 0.92)**	N/A
Perinatal mortality	1.04 (0.71, 1.52)	3.16 (0.13, 77.27)
Preterm delivery	1.10 (0.81, 1.50)	1.59 (0.70, 3.58)
PE	0.90 (0.71, 1.16)	0.99 (0.61, 1.61)
Postpartum hemorrhage	0.59 (0.29, 1.20)	N/A

Abbreviations: FGR fetal growth restriction, GCT glucose challenge test, GTT glucose tolerance test, LBW low birth weight, LGA large for gestational age, N/A not applicable, NICU neonatal intensive care unit, PE preeclampsia, PG plasma glucose, RR risk ratio, SGA small for gestational age. Asterisk (*) symbol indicates significant value

* = p -value < 0.05; ** = p -value < 0.01

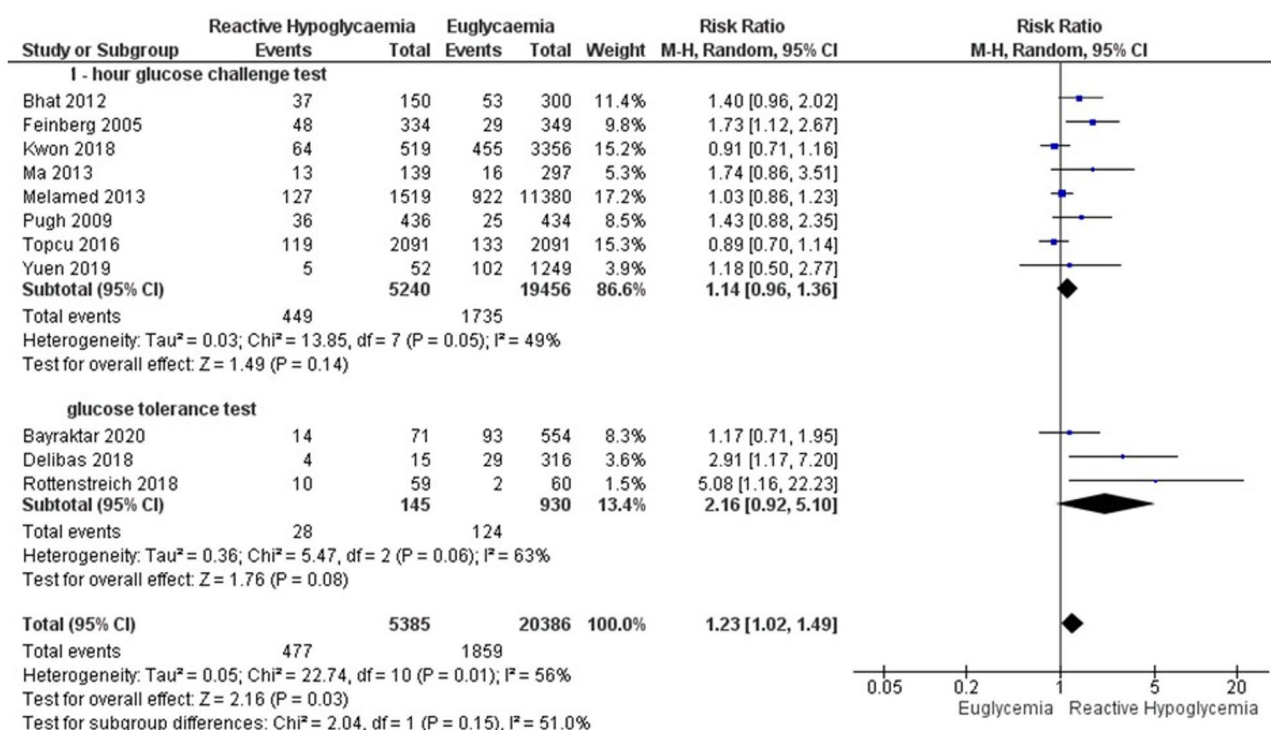


Fig. 5 Forest plot of the subgroup analysis for GRH at 1-hour GCT and GTT to the risk of NICU admission

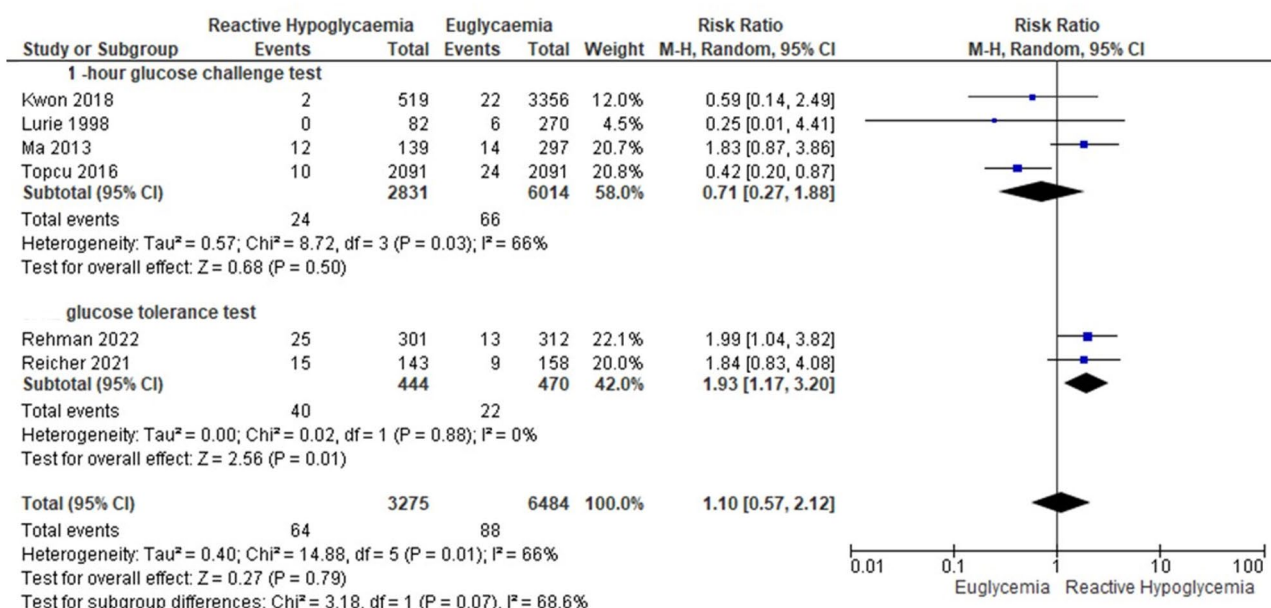


Fig. 6 Forest plot of the subgroup analysis for GRH at 1-hour GCT and GTT to the risk of polyhydramnios

Some of the pregnancy outcomes related to glucose dysmetabolism and/or insulin resistance were not reported well or at all in the published literature, so they could not be examined in the meta-analyses. Existing studies are also potentially severely limited by the possible inclusion of women with undiagnosed milder glucose dysmetabolism, sufficient to cause placental dysfunction but not to

be diagnosed formally as diabetes, in the controls, particularly when less sensitive criteria are used. A well-powered study with well-defined controls is needed to elucidate differences in insulin secretory and function, mechanistic pathophysiology, and adverse outcomes in pregnancy with GRH, compared to both GDM and to controls with normal glucose tolerance more narrowly defined.

Conclusions

This meta-analysis has shown that regardless of the glucose loading test used to define GRH, this typically undiagnosed maternal condition poses risks to pregnancy. The risks include small baby and polyhydramnios were higher in GRH at GTT. However, the combination of a small baby with polyhydramnios, seen with GRH, may confuse clinicians and preclude appropriate intervention.

Further studies will be key to determining the best cut-off value to diagnose GRH and intervene if needed. We must balance the need to eliminate preventable harm, with the imperative to avoid alarming women unnecessarily, at least until we know more about the underlying maternal metabolic associations. Whereas it might be too early to change clinical practice, it is clear that GRH in pregnancy should be studied further, including with regards to longer term outcomes in the offspring.

Abbreviations

FGR	fetal growth restriction
HAPO	hyperglycaemia and adverse pregnancy outcomes
LBW	low birth weight
LGA	large for gestational age
N/A	not applicable
NICU	neonatal intensive care unit
PE	preeclampsia
PG	plasma glucose
GRH	reactive hypoglycaemia
RR	risk ratio
SGA	small for gestational age

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12884-025-08016-x>.

Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.
Supplementary Material 5.
Supplementary Material 6.

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Authors' contributions

Muhammad Pradhiki Mahindra (MPMH) and Dimitrios Siassakos (DS) designed the study concept. MPMH, DS, Sara Hillman (SH), and Anna L David (AD) contributed to the design of systematic review and meta-analysis. MPMH, Michelle Jie (MJ), Muhammad Pradhika Mapindra (MPMP), and DS performed the independent record screening from the databases. MPMH, MPMP, Sana Rehman (SR), and DS performed data extraction and analysis. MPMH, AD, SH, Owen Vaughan (OV), and DS contributed to data interpretation. MPMH was responsible for drafting the manuscript. AD, SH, OV, and DS were supervising and validating the research outputs. All authors were contributing to the visualization and draft finalisation.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Buchanan T. Glucose metabolism during pregnancy: normal physiology and implications for diabetes mellitus. *Isr J Med Sci*. 1996;27(8-9):432–41. <https://pubmed.ncbi.nlm.nih.gov/1960041/>.
2. Díaz P, Powell TL, Jansson T. The role of placental nutrient sensing in maternal-fetal resource allocation, vol. 91. *Biology of Reproduction*. Society for the Study of Reproduction; 2014.
3. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The pathophysiology of gestational diabetes mellitus, vol. 19. *International Journal of Molecular Sciences*. MDPI AG; 2018.
4. Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EAH. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. *Am J Obstet Gynecol*. 1991;165(6 PART 1):1667–72.
5. National Institute for Health and Care Excellence. Diabetes in pregnancy : management from preconception to the postnatal period. NICE. 2015;(February):2–65. Available from: <http://www.ncbi.nlm.nih.gov.ez.srv.meduniwien.ac.at/pubmed/25950069>
6. Metzger BE. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010;33:676–82.
7. Minschart C, Beunen K, Benhalima K. An update on screening strategies for gestational diabetes mellitus: A narrative review, vol. 14. *Dove Medical Press Ltd*; 2021. p. 3047–76.
8. Rosenn BM, Miodovnik M. Glycemic control in the diabetic pregnancy: is tighter always better? *J Matern-Fetal Med*. 2000. [https://doi.org/10.1002/\(SICI\)1520-6661\(200001/02\)9:1%3C;29::AID-MFM7%3E;3.0.CO;2-Z](https://doi.org/10.1002/(SICI)1520-6661(200001/02)9:1%3C;29::AID-MFM7%3E;3.0.CO;2-Z).
9. Parikh RM, Joshi SR, Menon PS, Shah NS. Intensive glycemic control in diabetic pregnancy with intrauterine growth restriction is detrimental to fetus. *Med Hypotheses*. 2007;69(1):203–5.
10. Mohan N, Banerjee A. Metabolic emergencies in pregnancy. *CME: OBSTETRIC MEDICINE Clin Med*. 2021;21(5):438–78. Available from: <https://www.nice.org.uk/>.
11. Anderson JW, Herman RH. Classification of reactive hypoglycemia. *Am J Clin Nutr*. 1969;22(5):646–50. Available from: <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med1&NEWS=N&AN=4894611>.
12. Chandler PT. An update on reactive hypoglycemia. *Am Fam Physician*. 1977;16(5):113–6. Available from: <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med1&NEWS=N&AN=920567>.
13. Mitta M, Sanchez-Ramos L, Roeckner JT, Bennett S, Kovacs A, Kaunitz AM. A low 50-gram, 1-hour glucose challenge test value predicts neonatal birth weight less than the 10th percentile: a systematic review and meta-analysis. *Am J Perinatol*. 2021;38(8):841–7.
14. Sussman KE, Stimmiller L, Birenboim H. Plasma insulin levels during reactive hypoglycemia. *Diabetes*. 1966;15(1):1–4. Available from: <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med1&NEWS=N&AN=5907146>.
15. Sweeting A, Wong J, Murphy HR, Ross GP. A clinical update on gestational diabetes mellitus. *Endocr Rev*. 2022;43(5):763–93.
16. Stacey T, Tennant PWG, McCowan LME, Mitchell EA, Budd J, Li M, et al. Gestational diabetes and the risk of late stillbirth: a case-control study from england, UK. *BJOG*. 2019;126(8):973–82.
17. HAPO Study Cooperative Research Group. The hyperglycemia and adverse pregnancy outcome(HAPO)study. *Int J Gynecol Obstet*. 2002;78:69–77.

18. Boyd EM, Lynn PL, Alan RD, Elisabeth RT, Udom C, Donald RC, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008;365:687–96.
19. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D et al. Meta-analysis of Observational Studies. 2022.
20. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. *BMJ*. 2015;349(January):1–25. Available from: <https://doi.org/10.1136/bmj.g7647>.
21. Egan AM, Bogdanet D, Griffin TP, Kgosidialwa O, Cervar-Zivkovic M, Dempsey E, et al. A core outcome set for studies of gestational diabetes mellitus prevention and treatment. *Diabetologia*. 2020;63(6):1120–7.
22. Wells G, O'Connell BS, Peterson D, Welch J, Losos V et al. M., The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
23. Kwon HY, Park HS, Shin AS, Kim YH, Park YW. Association between neonatal outcomes and low value of 50 G glucose challenge test. 43, *J Perinat Med*. 2015.
24. Yoles I, Vaisbuch E, Wainstock T, Barak O, Schiller T. How low can it get? How low can it get? Prenatal outcomes of women with low 50 gr oral glucose challenge test results. In: 33rd Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research. 2021.
25. Vemareddy K, Burgess T, Minkoff H. 95: The relationship between low maternal values on GCT and pregnancy outcomes. *Am J Obstet Gynecol*. 2009;201(6):S51. Available from: <https://doi.org/10.1016/j.ajog.2009.10.110>.
26. Stivers SL, Thomas M, Devaiah G, Lambers D. Association of maternal hypoglycemia on the glucose challenge test and small for gestational age infants. 2022.
27. Bienstock JL, Holcroft CJ, Althaus J. Small fetal abdominal circumference in the second trimester and subsequent low maternal plasma glucose after a glucose challenge test is associated with the delivery of a small-for-gestational age neonate. *Ultrasound Obstet Gynecol*. 2008;31(5):517–9.
28. Kerényi Z, Tamás G, Kivimäki M, Péterfalvi A, Madarász E, Bosnyák Z, et al. Maternal glycemia and risk of large-for-gestational-age babies in a population-based screening. *Diabetes Care*. 2009;32(12):2200–5.
29. Scholl TO, Sowers M, Chen X, Lenders C. Maternal glucose concentration influences fetal growth, gestation, and pregnancy complications. *Am J Epidemiol*. 2001;154(6):514–20.
30. Bayraktar B, Balıkoğlu M, Kanmaz AG. Pregnancy outcomes of women with hypoglycemia in the oral glucose tolerance test. *J Gynecol Obstet Hum Reprod*. 2020. <https://doi.org/10.1016/j.jogoh.2020.101703>.
31. Bhat RG, Bhagya KV, Kumar P. Association of low maternal plasma glucose after oral glucose challenge test with small for gestational age neonate. *International Journal of Infertility & Fetal Medicine*. 2012;3(1):22–5.
32. Budak MŞ, Araç E. Maternal hypoglycaemia on the 50 g oral glucose challenge test - evaluation of obstetric and neonatal outcomes. *Ginekol Pol*. 2018;89(7):370–4.
33. Calfee EF, Rust OA, Boffill JA, Ross EL, Morrison JC. Maternal Hypoglycemia: Is It Associated with Adverse Perinatal Outcome? Current Concepts. Vol. 19, *Journal of Perinatology*. 1999. Available from: <http://www.stockton-press.co.uk>
34. Delibas IB, Tanrıverdi S, Cakmak B. Does reactive hypoglycemia during the 100 g oral glucose tolerance test adversely affect perinatal outcomes? *Ginekol Pol*. 2018;89(1):25–9.
35. Ding JJ, Lundsberg LS, Culhane JF, Patridge C, Milley L, Son M. The association between a low 50-gram, 1-hour glucose challenge test value and neonatal morbidity. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2023. <https://doi.org/10.1080/14767058.2023.2245527>.
36. Duhi AJ, Ural SH, Witer FR. Low 1-Hour Glucose Screens and Small for Gestational Age Infants. *J Perinatol*. 2000;5:288–90. available from: http://kiss.kstudy.com/journal/thesis_name.asp?tname=kiss2002&key=3183676.
37. Feinberg JH, Magann EF, Morrison JC, Holman JR, Polizzotto MJ. Does maternal hypoglycemia during screening glucose assessment identify a pregnancy at-risk for adverse perinatal outcome? *J Perinatol*. 2005;25(8):509–13.
38. Kwon H, Lee J, Lee BW, Kwon JY, Kim YH. The association between low 50 g glucose challenge test values and adverse pregnancy outcomes. *J Womens Health*. 2018;27(6):801–7.
39. Lurie S, Levy R, Weiss R, Boulton G, Hagay ZJ. Low values on 50 gram glucose challenge test or oral 100 gram glucose tolerance test are associated with good perinatal outcome. *J Obstet Gynaecol (Lahore)*. 1998;18(5):451–4.
40. Ma KK, Mele L, Landon MB, Spong CY, Ramin SM, Casey B, et al. The obstetric and neonatal implications of a low value on the 50-g glucose screening test. *Am J Perinatol*. 2013;30(9):715–21.
41. Melamed N, Hirsch L, Peled Y, Hod M, Wiznitzer A, Yogev Y. The association between low 50 g glucose challenge test result and fetal growth restriction. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2013;26(11):1107–11.
42. Nayak AU, Vijay AMA, Indusekhar R, Kalidindi S, Katreddy VM, Varadhan L. Association of hypoglycaemia in screening oral glucose tolerance test in pregnancy with low birth weight fetus. *World J Diabetes*. 2019;10(5):304–10.
43. Oawada N, Aoki S, Sakamaki K, Obata S, Seki K, Hirahara F. Clinical significance of low result of 1-h 50-g glucose-challenge test in pregnant women. *J Maternal-Fetal Neonatal Med*. 2019;32(1):58–61.
44. Ong KK, Diderholm B, Salzano G, Wingate D, Hughes IA, MacDougall J, et al. Pregnancy insulin, glucose, and BMI contribute to birth outcomes in nondiabetic mothers. *Diabetes Care*. 2008;31(11):2193–7.
45. Pugh SK, Doherty DA, Magann EF, Chauhan SP, Hill JB, Morrison JC. Does hypoglycemia following a glucose challenge test identify a high risk pregnancy? *Reprod Health*. 2009;6(1):1–7.
46. Raviv S, Wilkof-Segev R, Maor-Sagie E, Naeh A, Yoeli Y, Hallak M, et al. Hypoglycemia during the oral glucose tolerance test in pregnancy—maternal characteristics and neonatal outcomes. *Int J Gynecol Obstet*. 2021;158(June):1–7. <https://doi.org/10.1002/ijgo.14037>.
47. Rehman S, Kazi S, Shah H, Wallis N, Mahindra P, Al Wattar BH, Whitten M, Lattey K, Parrington M, Turner R, Burden C, Siassakos D. Reactive Hypoglycaemia at Glucose Tolerance Test—Another Presentation of Gestational Diabetes: A Multicentre Retrospective Study. *BJOG*. 2025;132(7):927–34. <https://doi.org/10.1111/1471-0528.18105>. Epub 2025 Feb 25. PMID: 40000446; PMCID: PMC12051243.
48. Reicher L, Lavie A, Attali E, Fouks Y, Feinmesser L, Landesberg I et al. Low glucose at 3-hour 100 gram oral glucose tolerance test: implications for glucose control. 2021; Available from: <https://www>
49. Rottenstreich A, Elazary R, Ezra Y, Kleinstern G, Beglaibter N, Elchahal U. Hypoglycemia during oral glucose tolerance test among post-bariatric surgery pregnant patients: incidence and perinatal significance. *Surg Obes Relat Dis*. 2018;14(3):347–53.
50. Shinohara S, Hirai M, Hirata S, Suzuki K. Relation between low 50-g glucose challenge test results and small-for-gestational-age infants. *J Obstet Gynaecol Res*. 2015;41(11):1752–6.
51. Shinohara S, Uchida Y, Hirai M, Hirata S, Suzuki K. Relationship between maternal hypoglycaemia and small-for-gestational-age infants according to maternal weight status: a retrospective cohort study in two hospitals. *BMJ Open*. 2016;6: 13749. <https://doi.org/10.1136/bmjopen-2016-013749>.
52. Tanacan A, Zengin Y, et al. Use of the 50-g glucose challenge test to predict small-for-gestational-age neonates. *J Diabetes*. 2020;12:792–7.
53. Topçu HO, Iskender CT, Çelen Ş, Oskovi A, Uygun D, Erkaya S. Maternal hypoglycemia on 50 g glucose challenge test: outcomes are influenced by fetal gender. *J Perinat Med*. 2016;44(4):369–76.
54. Vadakekut ES, McCoy SJ, Payto ME. Association of maternal hypoglycemia with low birth weight and low placental weight: a retrospective investigation. *J Am Osteopath Assoc*. 2011;111(3):148–52.
55. Yuen L, Bontempo S, Wong VW, Russell H. Hypoglycaemia on an oral glucose tolerance test in pregnancy – is it clinically significant? *Diabetes Res Clin Pract*. 2019;147:111–7.
56. Weissman A, Solt I, Zloczower M, Jakobi P. Hypoglycemia during the 100-g oral glucose tolerance test: incidence and perinatal significance. *Obstet Gynecol*. 2005;105(6):1424–8.
57. Huynh J, Dawson D, Roberts D, Bentley-Lewis R. A systematic review of placental pathology in maternal diabetes mellitus. *Placenta*. 2015;36(2):101–14.
58. Rezaiee M, Aghaei M, Mohammadbeigi A, Farhadifar F, Zadeh Ns, Mohammadalehi N. Fetal macrosomia: risk factors, maternal, and perinatal outcome. *Ann Med Health Sci Res*. 2013;3(4):546.
59. Woltamo DD, Meskele M, Workie SB, Badacho AS. Determinants of fetal macrosomia among live births in southern Ethiopia: a matched case–control study. *BMC Pregnancy Childbirth*. 2022. <https://doi.org/10.1186/s12884-022-04734-8>.
60. Sertsu A, Nigussie K, Eyeberu A, Tibebe A, Negash A, Getachew T, et al. Determinants of neonatal hypoglycemia among neonates admitted at Hiwot Fana comprehensive specialized university hospital, Eastern Ethiopia: a retrospective cross-sectional study. *SAGE Open Med*. 2022;10: 205031212211418.
61. Mitchell NA, Grimbley C, Rosolowsky ET, O'Reilly M, Yaskina M, Cheung PY, et al. Incidence and risk factors for hypoglycemia during Fetal-to-Neonatal transition in premature infants. *Front Pediatr*. 2020;8(February):1–6.

62. Callaghan WM, Chu SY, Kim YS, Schmid CH, Lau J, England JL. Maternal obesity and risk of gestational. *Diabetes Care*. 2007;30(8):2070–6.
63. O'Malley EG, Reynolds CME, Killalea A, O'Kelly R, Sheehan SR, Turner MJ. Maternal obesity and dyslipidemia associated with gestational diabetes mellitus (GDM). *Eur J Obstet Gynecol Reprod Biol*. 2020;246:67–71.
64. Mahindra MP, Sampurna MTA, Mapindra MP, Sutowo Putri AM. Maternal lipid levels in pregnant women without complications in developing risk of large for gestational age newborns: a study of meta-analysis. *F1000Res*. 2021;9:1–23.
65. Rehman S, Kazi S, Shah H, Wallis N, Mahindra P, Al Wattar BH, et al. Reactive hypoglycaemia at glucose tolerance test—another presentation of gestational diabetes: a multicentre retrospective study. *BJOG*. 2025. <https://doi.org/10.1111/1471-0528.18105>.
66. Brett KE, Ferraro ZM, Yockell-Lievre J, Gruslin A, Adamo KB. Maternal–fetal nutrient transport in pregnancy pathologies: the role of the placenta. *Int J Mol Sci*. 2014;15(9):16153–85.
67. Ehlers E, Talton OO, Schust DJ, Schulz LC. Placental structural abnormalities in gestational diabetes and when they develop: A scoping review. *Placenta*. 2021;116(April):58–66. Available from: <https://doi.org/10.1016/j.placenta.2021.04.005>.
68. Basnet KM, Bentley-Lewis R, Wexler DJ, Kilic F, Roberts DJ. Prevalence of intervillous thrombi is increased in placentas from pregnancies complicated by diabetes. *Pediatr Dev Pathol*. 2016;19(6):502–5.
69. Stanek J. Decidual arteriopathy with or without associated hypertension modifies the underlying histomorphology in placentas from diabetic mothers. *J Obstet Gynaecol Res*. 2017;43(5):839–47.
70. Higgins M, McAuliffe FM, Mooney EE. Clinical associations with a placental diagnosis of delayed villous maturation: a retrospective study. *Pediatr Dev Pathol*. 2011;14(4):273–9.
71. El-Tarhoury SA, Almasry SM, Elfayomy AK, Baghdadi H, Habib FA. Placental growth factor and soluble Fms-like tyrosine kinase 1 in diabetic pregnancy: A possible relation to distal villous immaturity. *Histol Histopathol*. 2014;29(2):259–72. Available from: <https://pubmed.ncbi.nlm.nih.gov/23939615/>.
72. Arizawa M, Nakayama M, Kidoguchi K. Correlation of placental villous immaturity and dysmaturity with clinical control of maternal diabetes. *Nihon Sanka Fujinka Gakkai Zasshi*. 1991;43(6):595–602.
73. Furman B, Erez O, Senior L, Shoham-Vardi I, Bar-David J, Maymon E, et al. Hydramnios and small for gestational age: prevalence and clinical significance. *Acta Obstet Gynecol Scand*. 2000;79(1):31–6.
74. Altuntas Y. Postprandial reactive hypoglycemia. *Med Bull Sisli Etfal Hosp*. 2019;53:215–20.
75. American Diabetes Association. Glycemic targets: standards of medical care in diabetes—2022. *Diabetes Care*. 2022;45:S83–96.
76. Quansah DY, De Giorgi S, Le Dizes O, Camponovo C, Benhalima K, Cosson E, et al. Reactive hypoglycaemia during the OGTT after gestational diabetes mellitus: metabolic implications and evolution. *Diabet Med*. 2022. <https://doi.org/10.1111/dme.14920>.
77. Kuhl C, Hornnes PJ, Andersen O. Review Etiology and Pathophysiology of Gestational Diabetes Mellitus. Vol. 34, *DIABETES*. 1985. Available from: <http://diabetesjournals>
78. Erez O, Shoham-Vardi I, Sheiner E, Dukler D, Bashiri A, Mazor M. Hydramnios and small for gestational age are independent risk factors for neonatal mortality and maternal morbidity. *Arch Gynecol Obstet*. 2005;271(4):296–301.
79. Hofeldt FD, Lufkin EG, Hagler L, Block MB, Dippe SE, Davis JW, et al. Are abnormalities in insulin secretion responsible for reactive hypoglycemia? *Diabetes*. 1974;23(7):589–96. Available from: <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med1&NEWS=N&AN=4841143>.
80. Tura A, Morbiducci U, Sbrignadello S, Winhofer Y, Pacini G, Kautzky-Willer A. Shape of glucose, insulin, C-peptide curves during a 3-h oral glucose tolerance test: any relationship with the degree of glucose tolerance? *Am J Physiol Regul Integr Comp Physiol*. 2011. <https://doi.org/10.1152/ajpregu.00650.2010>.
81. Dalfrà MG, Pacini G, Parretti E, Ragazzi E, Mello G, Lapolla A. Elevated insulin sensitivity and-cell function during pregnancy in mothers of growth-restricted newborns. *Am J Physiol Endocrinol Metab*. 2011;301:25–30. Available from: <http://www.ajpendo.org>.
82. Winterhager E, Gellhaus A. Transplacental nutrient transport mechanisms of intrauterine growth restriction in rodent models and humans. *Front Physiol*. 2017;8(NOV):1–13.

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