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Pregnancy outcomes in the different phenotypes of gestational diabetes mellitus based on the oral glucose tolerance test. A systematic review and meta-analysis

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ABSTRACT

Aims: To assess the prevalence variation in pregnancy outcomes of the different phenotypes of gestational diabetes mellitus (GDM).

Materials: Cohort, cross sectional and case control studies grouping together pregnant women with GDM, based on the results of oral glucose tolerance test(OGTT) and reporting pregnancy outcomes in each group, were included. The primary outcomes were (i)large for gestational age and ii)hypertensive disorders of pregnancy (HDP). The secondary outcomes included (i)insulin treatment, ii)admission to neonatal intensive care unit, iii) preterm birth, iv)small for gestational age and v)caesarean section. The pooled proportions of the outcomes of interest were calculated for each phenotype.

Results: 8 studies (n = 20.928 women with GDM) were included. The pooled prevalence of LGA, HDP and insulin treatment were 20 %, 8 % and 24 % respectively in women with abnormal fasting plasma glucose,10 %, 6 % and 9 % respectively in women with abnormal post-load plasma glucose and 14 %,14 % and 30 % in women with abnormal combined plasma glucose.

Conclusions: Pregnant women with abnormal fasting plasma glucose, present with the highest prevalence of LGA, while those with abnormal combined plasma glucose, present with the highest prevalence of HDP. Pregnant women with abnormal post-load plasma glucose present with the lowest need for insulin treatment.

1. Introduction

Gestational diabetes mellitus (GDM) develops during pregnancy in women whose beta cell function is insufficient to overcome the insulin resistance associated with the pregnant state [1]. The global prevalence of GDM is 17 % using the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [2].

GDM can be distinguished into three phenotypes based on the 75 g three time points oral glucose tolerance test (OGTT) results. Women presenting only with abnormal fasting glucose values, women presenting only with abnormal post-load glucose values, and women presenting with abnormal fasting and post-load glucose values. It has been previously reported that the different GDM phenotypes are associated with different maternal and fetal outcomes [3,4]. However, these phenotypes are not yet fully explored in terms of clinical outcomes and pathophysiological mechanisms.

Aim of the present *meta*-analysis of proportions is to investigate the prevalence of different maternal and fetal outcomes in the different phenotypes of GDM as defined by the OGTT.

2. Methods

This *meta*-analysis was conducted using a predetermined protocol established according to the Cochrane Handbook's recommendations. [5] The review adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and was registered to

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PROSPERO (CRD42023405429). [6].

2.1. Types of studies

Cohort, cross sectional and case control studies grouping together pregnant women with GDM, based on the results of O (abnormal fasting glucose OGTT values, abnormal post-load glucose values or combined abnormal fasting and post-load glucose values) and reporting pregnancy outcomes in each group, were included in this *meta*-analysis. No publication date restrictions were imposed, and only studies in European languages were included. Studies grouping pregnant women with GDM based on the number of abnormal OGTT components, without reporting which components were abnormal, were excluded.

2.2. Types of participants

Pregnant women diagnosed with GDM and sub-grouped into different phenotypes of GDM.

2.3. Types of outcome measures

The main outcomes were (1) large for gestational age and (2) hypertensive disorders of pregnancy prevalence. Additional outcomes included insulin treatment, admission to neonatal intensive care unit (NICU), preterm birth (delivery before the 37th gestational week), small for gestational age (SGA) and rate of caesarean section.

2.4. Search methods for identification of studies

PubMed, Cochrane Library, and Scopus databases were searched (up to March 31, 2023) for cohort, cross sectional, case control studies reporting pregnancy outcomes in women with different GDM phenotypes. The search and selection criteria were limited to European languages. A combination of the following terms was used: “gestational diabetes mellitus”, “GDM”, “oral glucose tolerance test”, “phenotypes”, “subgroups”, “pregnancy”, “outcomes”, “complications”. Two authors conducted the literature search independently; in case of disagreement, a consensus was reached after discussion. When a consensus could not be reached, a third author offered advice. All studies were compared to avoid duplicating or overlapping samples. In case of the latter, the study with the largest number of events was included. There was no limitation concerning the publication dates.

2.5. Study selection

Two authors assessed independently the eligibility of all identified citations according to the criteria mentioned above. After excluding ineligible studies, we searched https://retractiondatabase.org for any additional studies that may have been retracted. We have also checked interventional studies for obvious inconsistencies and implausibility in the characteristics and results of the participants; when such features were detected, the authors were contacted and, in the absence of explanatory information, these papers were excluded. Disagreements between authors were resolved by consensus.

2.6. Data extraction

Data extraction was performed independently by two authors. The study characteristics of each included study were assessed according to a predefined data extraction form included in the Cochrane Handbook for Systematic Reviews [5]. In case of disagreement, a consensus was reached after discussion between the two authors.

2.7. Quality assessment of included studies

The risk of bias of the included studies was assessed independently by two authors using the Newcastle-Ottawa Scale (NOS). This scale is developed to assess the quality of cohort, case-control, cross-sectional studies. The studies are judged on eight items, categorized into three groups: selection of study groups; comparability of groups; and ascertainment of either the exposure or outcome of interest. A star is awarded for each quality item; the highest quality studies are awarded nine stars. The interpretation of the results is a follows, 7–9 stars low risk of bias, 4–6 stars moderate risk and 0–3 stars high risk of bias.

2.8. Synthesis of results

The data from each study were extracted, and the proportion of events for all outcomes [95 % confidence interval (CI)] was estimated for each study. The pooled estimate, weighted by the sample size of each study in each phenotype, was calculated using the *metaprop* function in open-source software R 2.15.1. Metaprop implements procedures which are specific to binomial data and allows computation of exact binomial confidence intervals. Given the inclusion of observational studies and their anticipated heterogeneity, the summary effect sizes were calculated using random-effects model. The latter assumes that the true effect size varies between the studies and that included studies represent a random sample of effect sizes that could have been observed. Therefore, we opted to use this model as it allows for variation within and between studies, providing a conservative estimate of the summary statistics with wider CIs. Pooled proportions were calculated, and the forest plots were illustrated. The heterogeneity between studies was assessed by the estimation of Cochrane’s Q and I^2 statistic. The unit of analysis for each outcome was the total number of pregnant women (or births) with GDM in each phenotype.

2.9. Sensitivity analysis

A sensitivity analysis was conducted including only studies which used the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria for the diagnosis of GDM. Included studies which used any other criteria for the diagnosis of the GDM, were not included in the sensitivity analysis.

3. Results

3.1. Study selection

The electronic search (PubMed, Cochrane, Scopus, Embase, Clinicaltrials.org) yielded 8.155 results. After exclusion of articles based on their title and/or abstract, 15 articles were left to be reviewed in full text. Of them, 7 were excluded with reasons (Table S1). 8 studies were included in the analysis (20,928 pregnant women with GDM) (Fig. 1) [3,4,7–12]. Seven were cohort studies [3,4,7–11], and one was a cross-sectional study [12]. The characteristics of the included studies are described in Table 1.

3.2. Risk of bias assessment

The risk of bias of the included studies is presented in Table S2. The NOS was used. Seven studies were marked with at least 7 stars (“low risk of bias”) [3,4,7–9,11,12], and one was marked with 6 stars[10]. Two studies lost stars due to comparability, 3 studies lost stars due to selection of the population of interest [7,8,10], and 6 studies due to assessment of the outcomes [3,4,7,9–11].

3.3. Primary outcomes

3.3.1. Large for gestational age

Data from 5 studies (n = 6,033) were used to assess the prevalence of Large for Gestational Age (LGA) in pregnant women with GDM [4,7,10–12]. The overall pooled prevalence of LGA was 14 % (95 % CI

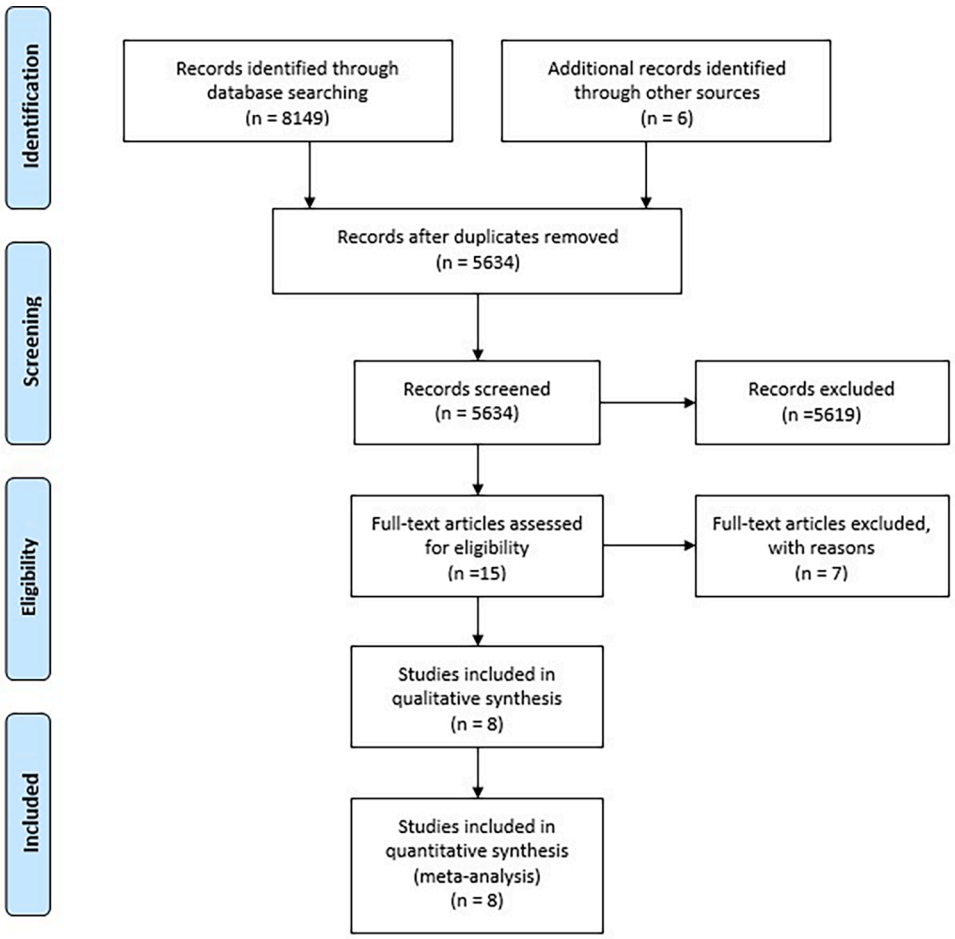

Fig. 1. Flow chart of the selection process of the included studies.

10 % to 19 %, I^2: 94 %). The pooled prevalence of LGA was 20 % [n = 399] (95 % CI 13 % to 29 %, I^2: 96 %) in 2612 pregnant women with abnormal fasting plasma glucose (5 studies) [4,7,10–12], 10 % [n = 205] (95 % CI 6 % to 17 %, I^2: 95 %) in 2341 pregnant women with abnormal post-load plasma glucose (5 studies) [4,7,10–12], and 14 % [n = 153] (95 % CI 9 % to 20 %, I^2: 86 %) in 879 pregnant women with abnormal combined plasma glucose (4 studies) (Fig. 2) [4,7,10,11].

3.3.2. Hypertensive disorders of pregnancy (HDP)

Data from 5 studies (n = 17,807) were used to assess the prevalence of HDP in pregnant women with GDM [3,7–9,12]. The overall pooled prevalence of HDP was 8 % (95 % CI 5 % to 13 %, I^2: 97 %). The pooled prevalence of HDP was 8 % [395] (95 % CI 4 % to 16 %, I^2: 85 %) in 3304 pregnant women with abnormal fasting plasma glucose (5 studies) [3,7–9,12], 6 % [952] (95 % CI 2 % to 16 %, I^2: 99 %) in 11,325 pregnant women with abnormal post-load plasma glucose (5 studies) [3,7–9,12], and 14 % [437] (95 % CI 7 % to 24 %, I^2: 96 %) in 3178 pregnant women with abnormal combined plasma glucose (4 studies) (Fig. 3)[3,7–9].

3.4. Secondary outcomes

3.4.1. Insulin treatment

Data from 4 studies (n = 2,545) were used to assess the need of insulin treatment in pregnant women with GDM [4,9,11,12]. The overall pooled prevalence of insulin treatment was 18 % (95 % CI 12 % to 26 %, I^2: 94 %). The pooled prevalence of insulin treatment was 24 % (95 % CI 17 % to 33 %, I^2: 79 %) in 420 pregnant women with abnormal fasting plasma glucose (4 studies) [4,9,11,12], 9 % (95 % CI 5 % to 16 %, I^2: 90 %) in 1743 pregnant women with abnormal post-load plasma glucose (4 studies) [4,9,11,12], and 30 % (95 % CI 25 % to 34 %, I^2: 0 %) in 382 pregnant women with abnormal combined plasma glucose (3 studies) (Figure S1)[4,9,11].

3.4.2. Admission to neonatal intensive care unit

Data from 2 studies (n = 1,274) were used to assess the prevalence of admission to neonatal intensive care unit (NICU) in neonates born from mothers with GDM [9,11]. The overall pooled prevalence of admission to NICU was 4 % (95 % CI 3 % to 5 %, I^2: 34 %). The pooled prevalence of admission to NICU was 5 % (95 % CI 2 % to 14 %, I^2: 53 %) in 109 neonates born from mothers with abnormal fasting plasma glucose (2 studies)[9,11], 3 % (95 % CI 3 % to 5 %, I^2: 8 %) in 1033 neonates born from mothers with abnormal post-load plasma glucose (2 studies) [9,11] and 5 % (95 % CI 3 % to 11 %, I^2: 3 %) in 132 neonates born from mothers with abnormal combined plasma glucose (2 studies) (Figure S2) [9,11].

3.4.3. Preterm birth

Data from 5 studies (n = 18,834) were used to assess the prevalence of preterm birth in pregnant women with GDM [7–11]. The overall pooled prevalence of preterm birth was 8 % (95 % CI 7 % to 9 %, I^2: 68 %). The pooled prevalence of preterm birth was 7 % (95 % CI 5 % to 9 %, I^2: 68 %) in 4064 pregnant women with abnormal fasting plasma glucose (5 studies) [7–11], 9 % (95 % CI 7 % to 11 %, I^2: 86 %) in 11,419 pregnant women with abnormal post-load plasma glucose (5 studies) [7–11], and 10 % (95 % CI 9 % to 11 %, I^2: 0 %) in 3351 pregnant women with abnormal combined plasma glucose (5 studies) (Figure S3) [7–11].

Table 1
Characteristics of the included studies.

Study	Type of study / Patients	Criteria for diagnosis of GDM and gestational age at diagnosis	Maternal age / Preconceptional BMI / Mode of Conception / Obesity %/ Gestational age at birth	Outcomes
Black (2010)	Retrospective cohort study / 1691 women with GDM Abnormal fasting blood glucose 886 pregnant women Abnormal post-load blood glucose 474 pregnant women Abnormal combined blood glucose 331 pregnant women	IADPSG (24–28 weeks of gestation)	Abnormal fasting group 30.4 years / 30.8/ NA/ 48.2 %/ 38.8 gestational weeks Abnormal post-load group 32.1 years / 28.1/ NA/ 30.4 %/ 38.3 gestational weeks Abnormal combined group 32.0 years / 31.8/ NA/ 52.9 %/ 38.7 gestational weeks	LGA (sex-, race-, and gestational age–specific birth weight > 90th percentile), primary caesarean section, preterm delivery, shoulder dystocia/birth injury, gestational hypertension, hyperbilirubinemia
Feng (2017)	Retrospective cohort study / 2927 women with GDM Abnormal fasting blood glucose 1370 pregnant women Abnormal post-load blood glucose 1100 pregnant women Abnormal combined blood glucose 457 pregnant women	IADPSG (24–28 weeks of gestation)	Not reported	Caesarean section, macrosomia, LGA (birth weight > 90th percentile based on gender and gestational age), preterm birth, neonatal complication, SGA
Ketumarn (2017)	Cross-sectional study / 415 women with GDM Abnormal fasting blood glucose 120 pregnant women Abnormal post-load blood glucose 295 pregnant women	American College of Obstetricians and Gynecologists (ACOG), American Diabetes Association (ADA) (mean gestational age at diagnosis was 19.2 ± 8 weeks of gestation)	All women with GDM 32.9 years / 24.5/ NA/ 12.3 %/ NA	Insulin treatment caesarean section, Preeclampsia
Kalok (2020)	Retrospective cohort study / 1105 women with GDM Abnormal fasting blood glucose 53 pregnant women Abnormal post-load blood glucose 963 pregnant women Abnormal combined blood glucose 89 pregnant women	NICE (mean gestation age at diagnosis was 24.6 weeks of gestation)	All women with GDM 32.2 years / NA/ NA/ 13.2 %/ 38.3 gestational weeks Abnormal fasting group 31.1 years / NA/ NA/ 18.9 %/ 38.2 gestational weeks Abnormal post-load group 32.1 years / NA/ NA/ 13.1 %/ 38.3 gestational weeks Abnormal combined group 33.2 years / NA/ NA/ 23.6 %/ 37.8 gestational weeks	Insulin treatment, caesarean delivery, preeclampsia (defined as any hypertension with proteinuria, which developed after 20 weeks of gestation), stillbirth, preterm delivery, macrosomia, shoulder dystocia LGA (defined as a birth weight of more than 4000 g), neonatal hypoglycemia, neonatal jaundice, NICU admission
Papachatzopoulou (2020)	Prospective cohort study / 831 pregnant women with GDM Abnormal fasting blood glucose 180 pregnant women Abnormal post-load blood glucose 402 pregnant women Abnormal combined blood glucose 249 pregnant women	IADPSG (24–28 weeks of gestation)	Abnormal fasting group 33.0 years / 26.1/ NA/ 8.3 % ART/ 38.6 gestational weeks Abnormal post-load group 33.7 years / 23.9/ NA/ 15.9 % ART/ 38.5 gestational weeks Abnormal combined group 34.3 years / 27.3/ NA/ 12 % ART/ 38.4 gestational weeks	LGA (defined as birth weight greater than the 90th centile), SGA, birth weight, Insulin treatment
Ryan (2020)	Retrospective cohort study / 12,942 pregnant women with GDM Abnormal fasting blood glucose 1699 pregnant women	Diabetes Canada Criteria	Abnormal fasting group 32.0 years / NA/ NA/ NA/ NA Abnormal post-load group 32.5 years / NA/ NA/ NA/ NA	LGA (defined by a birth weight over the 90th percentile for each sex and gestational age group for the Canadian population), HDP (defined as gestational hypertension, pre-clampsia and eclampsia, diagnosed based on ICD-9 and ICD-10 codes), composite adverse outcome, preterm delivery, caesarean section, induction of labor

(*continued on next page*)

Table 1 (*continued*)

Study	Type of study / Patients	Criteria for diagnosis of GDM and gestational age at diagnosis	Maternal age / Preconceptional BMI / Mode of Conception / Obesity %/ Gestational age at birth	Outcomes
	Abnormal post-load blood glucose 8812 pregnant women Abnormal combined blood glucose 2431 pregnant women			
Kotzaeridi (2021)	Prospective cohort study / 194 pregnant women with GDM Abnormal fasting blood glucose 67 pregnant women Abnormal post-load blood glucose 83 pregnant women Abnormal combined blood glucose 44 pregnant women	IADPSG (24–28 weeks of gestation)	• Abnormal fasting group 32.0 years / 27.7/ NA/ NA/ NA Abnormal post-load group 33.1 years / 25.4/ NA/ NA/ NA Abnormal combined group 33.3 years / 25.4/ NA/ NA/ NA	Induction of fetal lung maturation, vacuum extraction, GAD, birth weight, caesarean section, admission to NICU, preterm delivery, LGA (bodyweight above the 90th percentile)
Chatzakis (2023)	Prospective cohort study / 1654 women with GDM Abnormal fasting blood glucose 546 pregnant women Abnormal post-load blood glucose 781 pregnant women Abnormal combined blood glucose 327 pregnant women	IADPSG (24–28 weeks of gestation)	Abnormal fasting group 33.0 years / 26.1/ NA/ 9.8 % ART/ NA Abnormal post-load group 33.7 years / 24.3/ NA/ 13.8 % ART/ NA Abnormal combined group 34.3 years / 27.8/ NA/ 12.2 % ART/ NA	pregnancy-associated plasma protein A (PAPP-A), uterine arteries pulsatility index, preeclampsia (de- fined as the new onset of hypertension with systolic blood pres- sure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and proteinuria (300 mg/24 h) or the new onset of hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation in a previously normotensive patient)

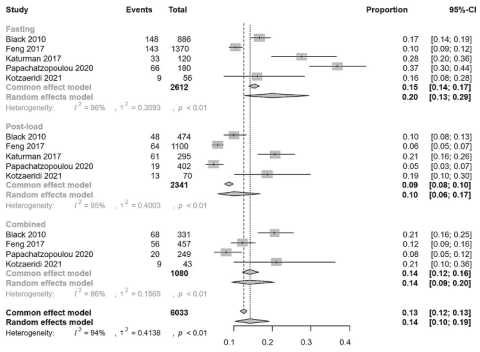

Fig. 2. Forest plot for the primary outcome of Large for Gestational Age (LGA). Proportions (95% CIs) for each study are denoted by black boxes (black lines). The combined proportion estimate for all studies is represented by a black diamond, where diamond width corresponds to 95% CI bounds. Box and diamond heights are inversely proportional to precision of the OR estimate. The P-value for heterogeneity (P-het) is shown. For each phenotype there is a separate diamond which summarizes the proportion estimate for all studies in that phenotype. At the bottom of the figure, the last diamond combines the proportion estimates of all phenotypes.

3.4.4. Small for gestational age

Data from 2 studies (n = 3,758) were used to assess the prevalence of SGA in pregnant women with GDM [4,10]. The overall pooled prevalence of SGA was 4 % (95 % CI 3 % to 4 %, I^2: 18 %). The pooled prevalence of SGA was 3 % (95 % CI 3 % to 4 %, I^2: 64 %) in 1550 pregnant women with abnormal fasting plasma glucose (2 studies) [4,10], 5 % (95 % CI 4 % to 6 %, I^2: 0 %) in 1502 pregnant women with abnormal post-load plasma glucose (2 studies) [4,10] and 3 % (95 % CI 2 % to 5 %, I^2: 0 %) in 706 pregnant women with abnormal combined plasma glucose (2 studies) (Figure S4) [4,10].

3.4.5. Caesarean section

Data from 6 studies (n = 14,890) were used to assess the rate of caesarean section in pregnant women with GDM [7–12]. The overall pooled rate of caesarean section was 36 % (95 % CI 30 % to 43 %, I^2: 97 %). The pooled rate of caesarean section was 39 % (95 % CI 30 % to 49 %, I^2: 97 %) in 4184 pregnant women with abnormal fasting plasma glucose (6 studies) [7–12]. 31 % (95 % CI 22 % to 42 %, I^2: 97 %) in 8735 pregnant women with abnormal post-load plasma glucose (5 studies) [7–11] and 39 % (95 % CI 28 % to 52 %, I^2: 95 %) in 1971 pregnant women with abnormal combined plasma glucose (5 studies) (Figure S5) [7–11].

3.5. Sensitivity analysis

A sensitivity analysis was carried out, including only studies which used the IADPSG criteria for the diagnosis of GDM. Five studies were included in the analysis [3,4,7,10,11].

3.6. Large for gestational age

Data from 4 studies (n = 5,618) were used to assess the prevalence of Large for Gestational Age (LGA) in pregnant women with GDM [4,7,10,11]. The overall pooled prevalence of LGA was 13 % (95 % CI 10 % to 18 %, I^2: 94 %). The pooled prevalence of LGA was 18 % (95 % CI 11 % to 29 %, I^2: 96 %) in 2492 pregnant women with abnormal fasting 2 glucose (4 studies) [4,7,10,11], 8 % (95 % CI 5 % to 13 %, I^2: 88 %) in 2046 pregnant women with abnormal post-load plasma glucose (4 studies) [4,7,10,11], and 14 % (95 % CI 9 % to 20 %, I^2: 86 %) in 1080

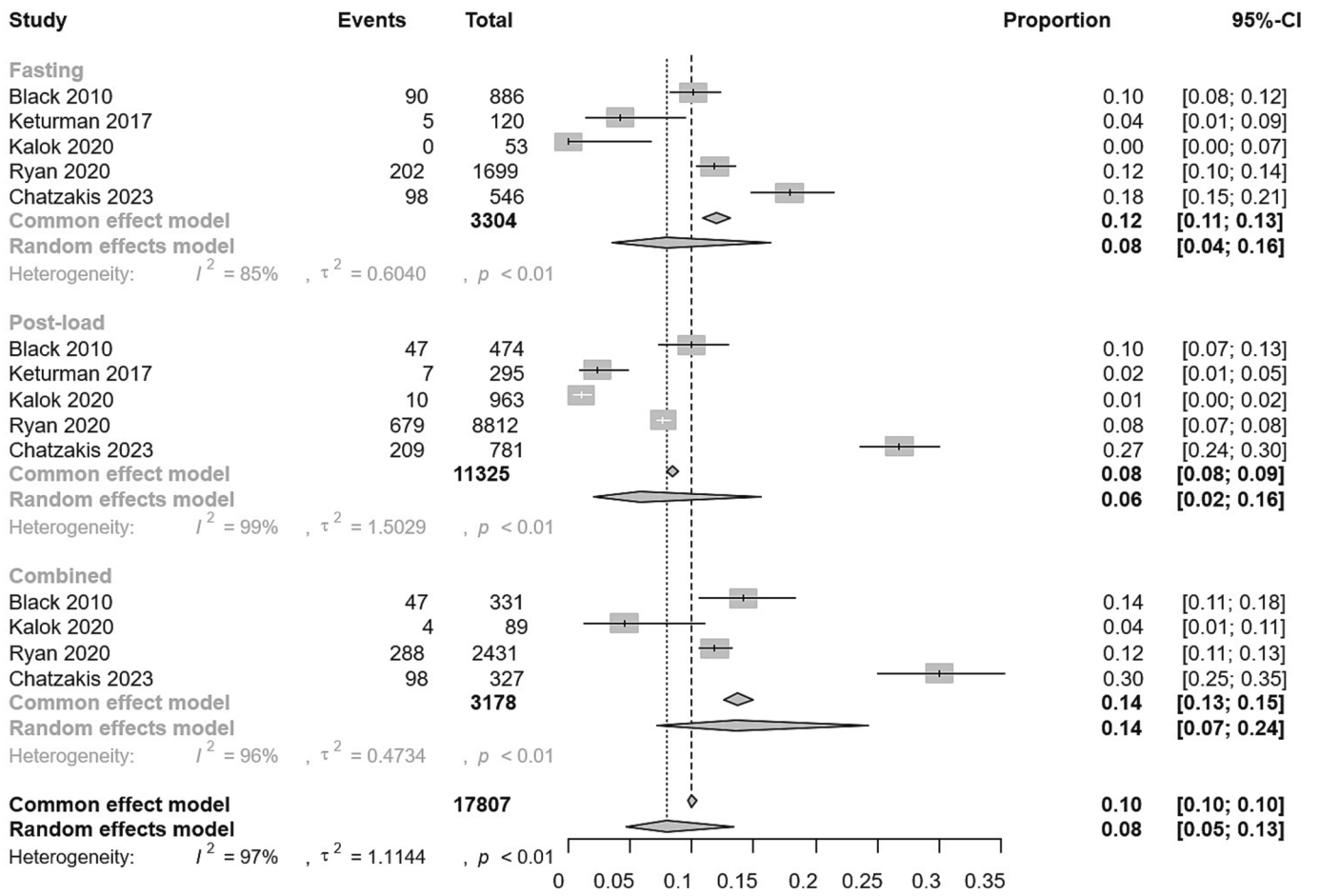

Fig. 3. Forest plot for the primary outcome of Hypertensive Disorders of Pregnancy (HDP). Proportions (95% CIs) for each study are denoted by black boxes (black lines). The combined proportion estimate for all studies is represented by a black diamond, where diamond width corresponds to 95% CI bounds. Box and diamond heights are inversely proportional to precision of the OR estimate. The P-value for heterogeneity (P-het) is shown. For each phenotype there is a separate diamond which summarizes the proportion estimate for all studies in that phenotype. At the bottom of the figure, the last diamond combines the proportion estimates of all phenotypes.

pregnant women with abnormal combined plasma glucose (4 studies) [4,7,10,11].

3.6.1. *Hypertensive disorders of pregnancy (HDP)*

Data from 2 studies (n = 3,345) were used to assess the prevalence of HDP in pregnant women with GDM [3,7]. The overall pooled prevalence of HDP was 17 % (95 % CI 12 % to 24 %, I^2: 96 %). The pooled prevalence of HDP was 14 % (95 % CI 9 % to 20 %, I^2: 94 %) in 1432 pregnant women with abnormal fasting plasma glucose (2 studies) [3,7], 17 % (95 % CI 8 % to 32 %, I^2: 98 %) in 1255 pregnant women with abnormal post-load plasma glucose (2 studies) [3,7], and 21 % (95 % CI 12 % to 34 %, I^2: 96 %) in 658 pregnant women with abnormal combined plasma glucose (2 studies) [3,7].

3.6.2. *Insulin treatment*

Data from 2 studies (n = 1,025) were used to assess the need of insulin treatment in pregnant women with GDM[4,11]. The overall pooled prevalence of insulin treatment was 23 % (95 % CI 15 % to 32 %, I^2: 90 %). The pooled prevalence of insulin treatment was 23 % (95 % CI 12 % to 38 %, I^2: 91 %) in 247 pregnant women with abnormal fasting plasma glucose (2 studies) [4,11], 15 % (95 % CI 9 % to 23 %, I^2: 85 %) in 485 pregnant women with abnormal post-load plasma glucose (2 studies) [4,11], and 31 % (95 % CI 26 % to 36 %, I^2: 0 %) in 293 pregnant women with abnormal combined plasma glucose(2 studies) [4,11].

3.6.3. *Preterm birth*

Data from 3 studies (n = 4,787) were used to assess the prevalence of preterm birth in pregnant women with GDM[7,10,11]. The overall pooled prevalence of preterm birth was 8 % (95 % CI 7 % to 10 %, I^2: 80 %). The pooled prevalence of preterm birth was 7 % (95 % CI 5 % to 10 %, I^2: 83 %) in 2312 pregnant women with abnormal fasting plasma glucose (3 studies) [7,10,11], 10 % (95 % CI 6 % to 15 %, I^2: 91 %) in 1644 pregnant women with abnormal post-load plasma glucose (3 studies) [7,10,11], and 8 % (95 % CI 7 % to 11 %, I^2: 0 %) in 831 pregnant women with abnormal combined plasma glucose (3 studies) [7,10,11].

3.6.4. *Caesarean section*

Data from 3 studies (n = 4,298) were used to assess the rate of caesarean section in pregnant women with GDM [7,10,11]. The overall pooled rate of caesarean section was 37 % (95 % CI 26 % to 48 %, I^2: 98 %). The pooled rate of caesarean section was 38 % (95 % CI 23 % to 57 %, I^2: 99 %) in 2312 pregnant women with abnormal fasting plasma glucose (3 studies) [7,10,11]. 31 % (95 % CI 17 % to 49 %, I^2: 98 %) in 1356 pregnant women with abnormal post-load plasma glucose (3 studies) [7,10,11] and 41 % (95 % CI 23 % to 62 %, I^2: 98 %) in 630 pregnant women with abnormal combined plasma glucose (3 studies) [7,10,11].

For the outcome of admission to NICU the sensitivity analysis was not possible as only one study using the IADPSG criteria contributed to this outcome [11]. For the outcome of SGA both studies which

contributed to this outcome in the main analysis used the IADPSG criteria, thus there was no need for sensitivity analysis [4,10].

4. Discussion

4.1. Main findings

In this study we showed that different phenotypes of GDM, based on the results of OGTT, present with different proportions of maternal and fetal outcomes. More specifically, we showed that pregnant women with abnormal fasting plasma glucose, present with the highest prevalence of large for gestational age (20 %), while those with abnormal combined plasma glucose, present with the highest prevalence of HDP (13 %), Pregnant women with abnormal post-load plasma glucose present with the lowest need for insulin treatment (9 %).

4.2. Interpretation

The increase prevalence of large for gestational age in the pregnant women with abnormal fasting plasma glucose, can be explained by the pathophysiological mechanisms which characterize those women. Abnormal fasting plasma glucose indicates hepatic insulin resistance, as in the fasting state, glucose levels are primarily regulated by the liver [13,14]. The liver plays a critical role in maintaining glucose homeostasis by producing glucose through glycogenolysis and gluconeogenesis [15,16]. In normal physiology, insulin suppresses those processes and thereby reduces the plasma glucose levels [17]. However, in the case of hepatic insulin resistance, the hepatocytes proceed with glycogenolysis and gluconeogenesis, continuing to produce glucose, which results in fasting hyperglycemia [18].

Maternal hyperglycemia leads to increased glucose concentration in the fetus, causing hypertrophy of the fetal pancreatic islet and overproduction of insulin [19]. Insulin serves as a growth-promoting factor in controlling the size of the developing fetus and is strongly associated with fetal macrosomia [20,21].

Furthermore, in the general population it was found that diabetes increased hepatic synthesis of cholesterol and triglycerides [22,23]. Triglycerides cross the placenta by hydrolysis to free fatty acids, which become incorporated into fetal lipids. Maternal triglyceride concentrations have a significant positive correlation with birth weight [24].

Increased prevalence of HDP in the women with abnormal combined plasma glucose can be explained by the combination of pathophysiological mechanisms which characterize those women. Abnormal fasting plasma glucose indicate hepatic insulin resistance, while abnormal post-load plasma glucose indicate mostly muscle tissue and adipose tissue insulin resistance [13,14]. Thus, women with abnormal combined plasma glucose may present with hepatic, muscle and adipose tissues insulin resistance. Indeed, a recent study showed that pregnant women with abnormal fasting and post-load.

plasma glucose present with a higher degree of insulin resistance, compared to pregnant women with isolated abnormal fasting or post-load plasma glucose [11]. Insulin resistance contribute to the development of hypertensive disorders through a plethora of mechanisms, including limited production of the beneficial NO and induction of pathogenic molecules PAI-1, ICAM-1, VCAM-1, and E-selectin, which result in the endothelial dysfunction which is noted in the women with GDM [25–28]. Off note, a large study in the general population, assessing the associations among the different stages of impaired glucose metabolism and hypertension, showed that participants with impaired fasting plasma glucose plus impaired glucose tolerance had higher prevalence of hypertension compared to participants with isolated impaired fasting plasma glucose or isolated impaired glucose tolerance [29].

Abnormal post-load plasma glucose levels indicate abnormal glucose homeostasis post-prandially. Medical nutrition therapy has been proven sufficient to reduce post-prandial hyperglycemia by utilizing the appropriate amount and selecting the right type of carbohydrates, using specific types of dietary protein, manipulating the meal timing and orders [30]. In addition, mild to moderate physical activity could significantly improve post-prandial glucose levels, as Insulin sensitivity is increased through the amelioration of inflammation, oxidative stress and endothelial dysfunction [31–33]. Thus, the muscle cells are better able to use any available insulin to take up glucose during and after physical activity. When the muscles contract during activity, the cells are able to take up glucose and use it for energy whether insulin is available or not [34,35]. Therefore, pregnant women with abnormal post-load plasma glucose could achieve their glycemic targets without the need of insulin treatment in the majority of the patients.

There were no discernible distinctions among the GDM phenotypes in the secondary outcomes of cesarean section rates and preterm births. The choice of delivery method and its timing is significantly influenced by the protocols and guidelines followed by different medical departments. Furthermore, glycemic control plays a substantial role, which can also be influenced by regional medical practices. Consequently, the variability in the management of GDM may account for the lack of disparities observed in these outcomes among the phenotypes.

Furthermore, in addition to the valuable insights into the associations between GDM phenotypes, pathological mechanisms and pregnancy outcomes that this study provides, it also opens up intriguing avenues for future research. These avenues call for the investigation of the interplay of various risk factors and their potential interactions with phenotypes [36–40].

The present study demonstrates different phenotypes of GDM are linked to distinct pregnancy outcomes and as a result, attending physicians should be prepared to anticipate these variations.

This finding, in conjunction with prior studies that have established diverse pathophysiological mechanisms underlying these phenotypes [3,11]. Therefore, the present study initiates a discussion regarding the potential adaptation of distinct therapeutic approaches based on these phenotypes and a tighter follow up in the women with phenotypes associated with higher risk for adverse pregnancy outcomes.

4.3. Strengths and limitations

This is the first *meta*-analysis assessing the effect of different GDM phenotypes on the maternal and fetal outcomes. In addition, a sensitivity analysis was conducted in order to tackle the potential heterogeneity introduced in the study by the different criteria used for the diagnosis of GDM. A limitation of the study is that given the small number of the available studies on the topic, a *meta*-regression analysis, accounting for potential confounders, was not feasible. However, the potential confounders are presented in the Table 1 for each study. Furthermore, due to the inability to perform *meta*-regression analysis, a statistical assessment of the differences between the phenotypes is not feasible.

5. Conclusion

Pregnant women with abnormal fasting plasma glucose, present with the highest prevalence of large for gestational age, while those with abnormal combined plasma glucose, present with the highest prevalence of hypertensive disorders of pregnancy. Pregnant women with abnormal post-load plasma glucose present with the lowest need for insulin treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110913.

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