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孕期糖尿病 24 週前之孕婦使用 metformin 的療效和安全性：系統性回顧、統合分析及臨床試驗計畫書

Efficacy and Safety of Metformin Use for Diabetes Mellitus in Pregnancy before 24 Weeks: a Systematic Review, Meta-Analysis and Clinical Trial Protocol

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口試委員會審定書

MASTER'S THESIS ACCEPTANCE CERTIFICATE
NATIONAL TAIWAN UNIVERSITY

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本論文係李佳謙（P12421409）在國立臺灣大學醫學院臨床醫學研究所完成之碩士學位論文，於民國 114 年 6 月 17 日承下列考試委員審查通過及口試及格，特此證明。

The undersigned, appointed by the Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University on 17 June 2025 have examined a Master's Thesis entitled above presented by Chia Chien Lee (P12421409) candidate and hereby certify that it is worthy of acceptance.

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系主任、所長：

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中文摘要

1. 研究背景

孕期糖尿病（diabetes mellitus in pregnancy）包括孕前糖尿病（preexisting diabetes mellitus, PDM）、孕期中新診斷糖尿病（undiagnosed diabetes mellitus）及妊娠糖尿病（gestational diabetes mellitus, GDM）。

在孕前糖尿病的患者中，大多數為第 2 型糖尿病（type 2 diabetes mellitus, T2DM）。Metformin 作為一種口服降血糖藥物，已被證實可改善胰島素敏感性、降低肝臟葡萄糖生成並減少腸道葡萄糖吸收。目前，大多數臨床指引建議 metformin 作為非懷孕 T2DM 患者的一線治療。然而，由於 metformin 會通過胎盤，加上安全性的資料相對有限，對於懷孕早期使用的安全性仍存在疑慮，目前並不建議在孕前糖尿病與妊娠糖尿病做為第一線的治療藥物，其適用性仍存在爭議。本研究的目的在於透過系統性回顧與統合分析，探討 metformin 在懷孕早期用於治療孕前糖尿病與早期妊娠糖尿病的療效與安全性。

2. 研究方法

透過檢索 PubMed、Embase 及 Cochrane 電子資料庫平台搜尋相關醫學文獻，共篩選出 152 篇文獻，其中符合納入與排除條件的 5 篇隨機對照試驗（RCT）被納入本系統性回顧與統合分析。評估指標包括：生產前最後一次糖化血色素（HbA1c）濃度、妊娠高血壓、子癇前症及剖腹產、早產、產傷、肩難產、出生體重、產下小於胎齡兒、產下大於胎齡兒、新生兒體脂肪量、新生兒黃疸、新生兒低血糖、呼吸窘迫症候群、入住新生兒加護病房、流產、胎死腹中及新生兒死亡。

3. 研究結果

本研究共納入 5 項研究，共 1522 受試者進行統合分析。使用 metformin 或 metformin 聯合胰島素與單獨使用胰島素相比，顯著降低：妊娠高血壓風險（OR 0.60 [95% CI 0.37–0.96]; p=0.03）、出生體重 Z 分數（差異 -0.36 [-0.50 – -0.22]; p<0.00001）、大於胎齡兒（LGA）比例（OR 0.71 [0.56 – 0.89]; p=0.003）、新生

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兒加護病房（NICU）住院率（OR 0.57 [0.35 – 0.95]; p=0.03）及胎死腹中風險（OR 0.36 [0.13 – 1.00]; p=0.05）；然而，使用 metformin 可能會增加小於胎齡兒（SGA）出生的風險（OR 1.87 [1.27 – 2.75]; p=0.002）。

進一步的次分組分析顯示，metformin 聯合胰島素與單獨使用胰島素相比，有較低的出生體重 Z 分數（差異 -0.36 [-0.50 – -0.22]; p<0.00001），並可顯著降低胎死腹中風險（OR 0.36 [0.13 – 1.00]; p=0.05）。此外，單獨使用 metformin 相較於單獨使用胰島素可顯著降低 NICU 住院率（OR 0.37 [0.14 – 0.99]; p=0.05）。

4. 研究結論

本統合分析顯示，在懷孕 24 週前使用 metformin 可降低妊娠高血壓、大於胎齡兒、出生體重 Z 分數、NICU 住院率及胎死腹中。然而，受限於研究數量有限，且不同亞組分析之間存在差異，仍需進一步研究來確認在孕前糖尿病與早期妊娠糖尿病使用 metformin 對母體及胎兒的長期影響。

關鍵詞：二甲雙胍類降血糖藥物、胰島素、第 2 型糖尿病、妊娠糖尿病、懷孕、系統性回顧、統合分析

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Abstract

1. Background

Diabetes mellitus in pregnancy includes pre-existing diabetes mellitus (PDM) and gestational diabetes mellitus (GDM). In pregnant patients with PDM, most have type 2 diabetes (T2DM)**.** Metformin is a well-established oral hypoglycemic agent that improves insulin sensitivity, decreases hepatic glucose production, and reduces intestinal glucose absorption. Most clinical guidelines recommend metformin as the first-line medication for the non-pregnant T2DM. However, because metformin can cross the placenta, there are safety concerns regarding its use in PDM and GDM in early pregnancy. The aim of this study is to explore the efficacy and safety of metformin use in early pregnancy for the treatment of PDM and early GDM through a systematic review and meta-analysis.

2. Method

A search of PubMed, Embase, and the Cochrane electronic database platform for relevant medical literature, a total of 152 articles was identified. Of these, five randomized clinical trials met the inclusion and exclusion criteria and were included in the systematic review and meta-analysis. The evaluated outcomes included final pre-delivery glycated hemoglobin (HbA1c) levels, gestational hypertension, preeclampsia, cesarean section, preterm birth, birth trauma, shoulder dystocia, birth weight, small for gestational age (SGA), large for gestational age (LGA), neonatal body fat mass, neonatal jaundice, neonatal hypoglycemia, respiratory distress syndrome, admission to the neonatal intensive care unit (NICU), miscarriage, stillbirth and neonatal death.

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3. Results

We identified five studies comprising 1522 participants which were included in this meta-analysis. Compared to insulin alone, metformin alone or metformin combined with insulin significantly reduces the risks of gestational hypertension (odds ratio [OR] 0.60 [95% CI 0.37-0.96]; p=0.03), birth weight Z score (difference -0.36 [-0.50 - -0.22]; p < 0.00001), LGA neonates (OR 0.71 [0.56 - 0.89]; p=0.003), NICU admissions (OR 0.57 [0.35 - 0.95]; p=0.03) and stillbirth (OR 0.36 [0.13 - 1.00]; p=0.05). However, this treatment is associated with an increased risk of delivering SGA neonates (OR 1.87 [1.27 - 2.75]; p=0.002). Subgroup analysis revealed that treatment with metformin combined with insulin group was significantly associated with reduced birth weight Z scores (difference -0.36 [-0.50 - -0.22]; p < 0.00001) and a lower the risk of stillbirth (OR 0.36 [0.13 - 1.00]; p=0.05), compared with insulin alone. Similarly, the metformin alone group significantly decreases the risk of NICU admission (rates OR 0.37 [0.14 - 0.99]; p=0.05) compared to the insulin alone group.

4. Conclusion

This meta-analysis reveals that metformin use before 24 weeks of gestation reduces the risks of gestational hypertension, stillbirth, LGA, birth weight Z score and NICU admission. However, limited study numbers and subgroup differences affect generalizability, warranting further research to confirm long-term effects.

Keywords: metformin, insulin, type 2 diabetes, gestational diabetes mellitus, systematic review, meta-analysis

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1. Introduction

Diabetes mellitus in pregnancy includes preexisting diabetes mellitus (PDM), undiagnosed diabetes, and gestational diabetes mellitus (GDM). According to the International Diabetes Federation (IDF) statistics in 2021, the global prevalence of diabetes mellitus in pregnancy is estimated to be 16.7%. Among these, PDM accounts for 10.6%, undiagnosed diabetes accounts for 9.1%, and GDM accounts for 80.3% [(1)]. Additionally, based on data from Taiwan's National Health Insurance database, the prevalence of diabetes mellitus in pregnancy in 2017 was 15.8%. In Taiwan, PDM accounted for 5.7%, undiagnosed diabetes for 2.5%, and GDM for 91.8% [(2)].

Pregnant women with hyperglycemia - including PDM, undiagnosed diabetes, and GDM are at higher risk of pregnancy complications compared to the general population [(3-7)]. These complications include miscarriage, preterm birth, stillbirth, gestational hypertension, preeclampsia, macrosomia, shoulder dystocia, and cesarean delivery [(4)]. Furthermore, neonates born to these mothers are also more likely to experience hypoglycemia, hypocalcemia, jaundice, neonatal intensive care unit (NICU) admission, and neonatal death [(5-7)]. Since early pregnancy is a critical period for embryonic development, elevated maternal blood glucose levels during this period can increase the risk of congenital anomalies in the fetus [(8)]. While GDM is typically diagnosed between 24 and 28 weeks of gestation and thus generally not associated with a higher risk of congenital malformations, some women may have undiagnosed diabetes or develop hyperglycemia earlier in pregnancy. Therefore, it is recommended that women with known diabetes or those diagnosed during pregnancy should achieve optimal glycemic control before conception or immediately after diagnosis to minimizing

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both maternal and neonatal risks [8, 10].

Metformin is a well-established oral hypoglycemic agent and is the first line treatment for type 2 diabetes mellitus (T2DM). However, for pregnant women with T2DM, insulin remains the preferred treatment due to its well-established safety profile. Since metformin crosses the placenta [11, 12], there are potential risks associated with its use during pregnancy, and thus it is not recommended as the first-line therapy for T2DM in pregnant women.

In women with GDM, studies have shown that metformin leads to better maternal weight control and lower risks of neonatal hypoglycemia and macrosomia compared to insulin treatment. However, approximately 23% of women in clinical trials failed to achieve glycemic targets with metformin alone, necessitating the addition of insulin. Additionally, metformin use has been associated with an increased risk of preterm birth [13-15]. Clinically, metformin may be considered an alternative treatment for women with GDM who cannot use insulin. Nonetheless, according to the American Diabetes Association (ADA) guidelines, metformin is not recommended for pregnant women at risk of gestational hypertension, preeclampsia, or intrauterine growth restriction [16, 17].

The efficacy and safety of metformin use in early pregnancy for women with diabetes mellitus remain controversial. Long term safety data and additional research are required to confirm its role in managing diabetes during pregnancy. To date, five randomized controlled trials (RCTs) [18-22] have explored the use of metformin in treating PDM, undiagnosed diabetes during pregnancy, and early GDM. However, the results have been inconsistent. Compared with insulin, two studies have shown that using metformin to treat PDM and early GDM resulted in less maternal weight gain and lower birth weights [20, 21]. One study found that

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glycemic control achieved by metformin or insulin did not differ significantly [22]. Nevertheless, patients with PDM and early GDM treated with metformin experienced fewer hypoglycemic episodes than those treated with insulin. Additionally, two studies showed no significant difference in the primary composite neonatal outcomes between the metformin and insulin groups for the treatment of PDM and early GDM [21, 22]. It is important to note that two of these trials had relatively small sample sizes, limiting their statistical power [18, 19]. Therefore, a systematic review and meta-analysis are warranted to evaluate the efficacy and safety of metformin use in early pregnancy for the treatment of PDM and early GDM.

2. Methods

2.1 Search methodology and study selection criteria

2.1.1 Developing a research question with PICO

We formulated our research question with population, intervention, comparator, and outcome (PICO). The target population (P) is women with diabetes mellitus in pregnancy during early pregnancy, including PDM, undiagnosed diabetes mellitus and early GDM; the intervention (I) includes treatment with metformin alone or metformin plus insulin; the comparator (C) is treatment with insulin; the outcomes (O) include last hemoglobin A1c (HbA1c) concentration in pregnancy, gestational hypertension, preeclampsia, caesarean section, birth trauma, shoulder dystocia, miscarriage, stillbirth, neonatal death, preterm birth, birth weight, SGA, LGA, neonatal body fat mas, neonatal hyperbilirubinemia, neonatal hypoglycemia, respiratory distress syndrome, and neonatal intensive care unit (NICU) admission.

2.1.2 Search strategy

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This study was conducted following the reporting items of the 2020 preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) statement. Searches were performed using PubMed, Embase, and Cochrane Library databases without language restrictions, covering data up to July 2024. In the PubMed database search, the following keywords and search strategy were used: metformin AND (pregnant OR pregnant women OR pregnancy) AND (type 2 diabetes OR diabetes mellitus) OR (gestational diabetes mellitus OR gestational diabetes). In the Embase database search, the following keywords and search strategy were used: metformin AND (pregnant OR pregnant women OR pregnancy) AND (type 2 diabetes OR diabetes mellitus OR gestational diabetes mellitus). In the Cochrane Library database search, the following keywords and search strategy were used: gestational diabetes AND type 2 diabetes AND pregnancy AND metformin (word variations have been searched).

2.1.3 Study selection criteria

Inclusion criteria: included (1) randomized controlled trials (RCTs); (2) pregnant women with T2DM or GDM; (3) diagnosis of T2DM or GDM before 24 weeks of gestation; (4) treatment with metformin alone or metformin plus insulin and (5) reporting at least one maternal or fetal outcome, such as gestational hypertension or neonatal hypoglycemia. We excluded studies in which: non-clinical studies, case reports, retrospective clinical analyses, review articles, duplicate publications or systematic reviews and meta-analysis.

2.2 Data Extraction

The information included the following: (1) characteristics of the studies, such as the name of the first author, the year of publication, the basic study design, the primary inclusion criteria for patients, the metformin and/or insulin

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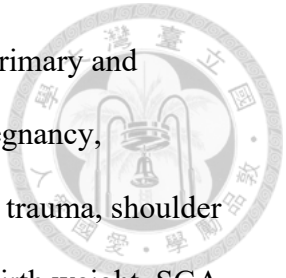

treatment regimens used, and the sample size; and (2) data on primary and secondary endpoints, including last HbA1c concentration in pregnancy, gestational hypertension, preeclampsia, caesarean section, birth trauma, shoulder dystocia, miscarriage, stillbirth, neonatal death, preterm birth, birth weight, SGA, LGA, neonatal body fat mas, neonatal hyperbilirubinemia, neonatal hypoglycemia, respiratory distress syndrome and NICU admission.

2.3 Risk of bias assessment

The Cochrane Risk of Bias (RoB) tool was used for four RCT studies, which were evaluated using the danger of bias tool covering six domains: (1) risk of bias arising from the randomization process, (2) risk of bias due to deviations from the intended interventions, (3) missing outcome data, (4) risk of bias in measurement of the outcome, (5) risk of bias in selection of the reported result, and (6) overall risk of bias.

2.4 The process of data synthesis and statistical analysis

Data were examined by Review Manager Web 8.20.1 The included RCTs were analyzed separately according to the treatment: metformin alone or metformin plus insulin, compared to insulin alone. The evaluated outcomes included last HbA1c concentration in pregnancy, gestational hypertension, preeclampsia, caesarean section, birth trauma, shoulder dystocia, miscarriage, stillbirth, neonatal death, preterm birth, birth weight, SGA, LGA, neonatal body fat mas, neonatal hyperbilirubinemia, neonatal hypoglycemia, respiratory distress syndrome and NICU admission.

Depending on the degree of heterogeneity among the studies, a fixed-effect model or a random-effect model was used for the analysis. Heterogeneity was tested using the Q test (chi-squared test) ($P < 0.10$ was considered statistically

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significant for heterogeneity) and the I^2 statistic (with I^2 values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively). A fixed-effect model was used when there was no significant heterogeneity ($I^2 < 50\%$); otherwise, a random-effect model was used. Dichotomous data were presented as odds ratios (ORs) with 95% confidence intervals (95% CIs), and continuous data were presented as mean values with standard deviations (SDs), with the mean difference and its 95% CI calculated. The p-value for the overall effect was tested using the Z test, with a P-value < 0.05 considered statistically significant. The analysis was performed using Review Manager Web 8.20.1 (https://revman.cochrane.org/).

3. Results

3.1 Included studies

A search conducted on the PubMed, Embase, and Cochrane electronic databases in a collection of 152 studies. After removing 31 duplicate articles, 121 articles remained. Of these, 108 articles were excluded after screening as they were not relevant to the objectives of this systematic review and meta-analysis. Additionally, 3 articles were excluded for having abstracts only, and 6 full-text articles were excluded for not meeting the inclusion criteria. Ultimately, 5 randomized controlled trials (RCTs) met the inclusion and exclusion criteria [18-22]. The selection process is displayed in Figure 1 (PRISMA flow diagram).

3.2 The characteristics of four RCTs

The summaries of five RCTs are presented in Table 1. All participants were pregnant women diagnosed with diabetes mellitus (PDM or GDM) before 24 weeks of gestation. A total of 1,522 participants were included, with ages ranging from 18 to 48 years. The sample sizes for each study ranged from 21 to 794

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participants.

In comparison to insulin alone, metformin alone or metformin plus insulin treatments were administered until delivery. The evaluated outcomes included last HbA1c concentration in pregnancy, gestational hypertension, preeclampsia, caesarean section, birth trauma, shoulder dystocia, miscarriage, stillbirth, neonatal death, preterm birth, birth weight, SGA, LGA, neonatal body fat mas, neonatal hyperbilirubinemia, neonatal hypoglycemia, respiratory distress syndrome and NICU admission, as indicated in the randomized controlled trials.

The dose adjustment criteria for metformin and insulin were generally consistent across the different RCTs, following the guidelines of the American College of Obstetricians and Gynecologists (ACOG) and the ADA. However, one study based its dose adjustment on the guidelines of the Diabetic Association of Pakistan, the International Association of Diabetes and Pregnancy Study Groups (IADPSG), and the ADA.

3.3 Quality assessment

The study analyzed selective reporting bias and other potential sources of bias. The bias assessment employed a color-coded system, categorizing performance as satisfactory (green) or unsatisfactory (red).

In the category of random sequence generation, an unclear risk of bias was identified, as one study only briefly mentioned that randomization was performed without providing further details. For other categories, including allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias, the risk was assessed as low. The summarized results and the graphical representation of the risk of bias are presented in Figures 2 and Figures

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3.4 Outcome for RCTs

This meta-analysis included five randomized controlled trials (RCTs) with a total of 1,522 participants. The trials compared the effects of metformin alone or metformin combined with insulin versus insulin alone on various maternal and neonatal outcomes. Table 2 provides a summary of the evaluated outcomes. For maternal outcomes, metformin or metformin combined with insulin showed a significant reduction in the risk of gestational hypertension (odds ratio [OR] 0.60 [95% CI 0.37-0.96]; p=0.03) and caesarean section (OR 0.76 [0.61 - 0.94]; p=0.01), compared to insulin alone (Figures 4 and Figures 5). However, no significant differences were observed in the last HbA1c concentration in pregnancy, preeclampsia, birth trauma and shoulder dystocia. For neonatal outcomes, the use of metformin was associated with lower birth weight (Difference -154.65 [-165.50 - -143.81]; p < 0.00001), birth weight Z score (difference -0.36 [-0.50 - -0.22]; p < 0.00001), LGA (OR 0.71 [0.56 - 0.89]; p=0.003), birthweight ≥ 4000 g (OR 0.57 [0.35 - 0.95]; p=0.03), neonatal hypoglycemia (OR 0.77 [0.60 to 0.97]; p=0.003), NICU admission (OR 0.55 [0.39 to 0.77]; p=0.0006), and stillbirth (OR 0.36 [0.13 - 1.00]; p=0.05) (Figures 6-12). However, metformin treatment was associated with an increased risk of delivering SGA neonates (OR 1.87 [1.27 - 2.75]; p=0.002) (Figures 13). Outcomes such as caesarean section, birth weight, SGA, neonatal hypoglycemia, and NICU admission showed considerable heterogeneity, indicating between-study variability and highlighting the need for cautious interpretation. No significant differences were observed in rates of preterm birth, neonatal body fat mass, hyperbilirubinemia, respiratory distress syndrome, miscarriage and neonatal

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death.

Subgroup analysis reveals that the effects of metformin combined with insulin versus insulin alone various maternal and neonatal outcomes. Table 3 provides a summary of the evaluated outcomes. For maternal outcomes, metformin combined with insulin showed a significant reduction in the risk of caesarean section (OR 0.74 [0.60 - 0.92]; p=0.007) (Figures 14). However, no significant differences were observed in gestational hypertension and preeclampsia. For neonatal outcomes, the use of metformin was associated with reduced birth weight (difference -155.10 [-165.95 - -144.24]; p < 0.00001), birth weight Z scores (difference -0.36 [-0.50 - -0.22]; p < 0.00001), hypoglycemia (OR 0.75 [0.59 - 0.95]; p=0.02), NICU admission (OR 0.55 [0.39 - 0.78]; p=0.007), and lower stillbirth (OR 0.36 [0.13 - 1.00]; p=0.05) (Figures 15-19). However, this treatment is associated with an increased risk of delivering SGA neonates (OR 1.72 [1.20 - 2.63]; p=0.004) (Figures 20). Outcomes such as caesarean section, SGA, neonatal hypoglycemia, and NICU admission showed considerable heterogeneity, indicating between-study variability and highlighting the need for cautious interpretation. No significant differences were observed in rates of preterm birth, birth trauma, shoulder dystocia, LGA, neonatal body fat mass, hyperbilirubinemia, respiratory distress syndrome, miscarriage, neonatal death and stillbirth.

Subgroup analysis reveals that the effects of metformin alone versus insulin alone on various maternal and neonatal outcomes. Table 4 provides a summary of the evaluated outcomes. For neonatal outcomes, the use of metformin was associated with lower NICU admission (rates OR 0.37 [0.14 - 0.99]; p=0.05) (Figures 21). However, no significant differences were observed in others

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maternal outcomes and neonatal outcomes.

3.5 Publication bias

In funnel plots, due to the low number of eligible RCTs (n=5) included in the meta-analysis, it is not recommended to assess the symmetry of the funnel plot because of insufficient statistical power.

4. Discussion

This is the first meta-analysis to evaluate the effects of metformin alone or in combination with insulin, compared to insulin alone, on maternal and neonatal outcomes. For maternal outcomes in pregnancies before 24 weeks of gestation, our results indicate that metformin significantly reduces the risk of gestational hypertension. Regarding neonatal outcomes, metformin use was associated with a lower risk of stillbirth, reduced birth weight Z scores, and decreased incidences of LGA neonates, and birthweight ≥ 4000 g. Subgroup analyses revealed that metformin combined with insulin significantly reduced both birth weight and birth weight Z scores, while metformin monotherapy was associated with a lower rate of NICU admissions.

The observed reduction in the risk of gestational hypertension among women treated with metformin aligns with previous studies demonstrating its vasoprotective and anti-inflammatory properties [23]. Given that insulin resistance and hyperinsulinemia contribute to endothelial dysfunction and elevated blood pressure, metformin's ability to enhance insulin sensitivity, reduce systemic inflammation, and improve endothelial function may underlie its protective effect against gestational hypertension [24].

Metformin was associated with a lower incidence of LGA neonates, reduced birth weight Z scores, and a decreased risk of macrosomia (birth weight ≥ 4000 g).

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These findings are consistent with previous clinical trials and observational studies demonstrating that metformin reduces excessive fetal growth compared to insulin therapy alone [15]. The mechanism underlying this effect may contribute to metformin's ability to lower maternal hyperglycemia, thereby reducing fetal hyperinsulinemia, which is a key driver of excessive fetal growth in GDM [25].

Moreover, our meta-analysis identified a potential reduction in stillbirth risk among metformin users. Although this finding reached only borderline statistical significance ($p = 0.05$), it is consistent with prior research suggesting that improved glycemic control and reduced fetal overgrowth contribute to a decreased risk of intrauterine fetal demise [13]. However, fetal and neonatal mortality, encompassing stillbirth, miscarriage, and neonatal death, is rare and results from multiple factors. The findings for miscarriage and neonatal death in our analysis were inconsistent with the stillbirth result and did not reach statistical significance, which were likely due to small sample sizes and residual confounding. Larger, well-designed studies are needed to confirm the association between metformin use and reductions in fetal and neonatal mortality.

NICU admission rates are primarily driven by fetal physiological compromise, including prematurity, hypoglycemia, respiratory distress syndrome, and neonatal jaundice. Our subgroup analysis found a significantly lower NICU admission rate in the metformin group compared to the insulin group, although statistical significance was marginal ($p = 0.05$). This finding aligns with previous meta-analyses on GDM [26, 27] and may reflect metformin's ability to provide more stable glycemic control, thereby reducing neonatal hypoglycemia - a key contributor to NICU admission. While insulin effectively controls maternal blood glucose, it may also lead to increased fetal adiposity and neonatal hypoglycemia,

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potentially elevating NICU admission rates.

Although our subgroup analysis identified a lower NICU admission rate in the metformin monotherapy group, this finding should be interpreted with caution. The rationale for conducting this subgroup analysis was to explore whether metformin alone could provide maternal and neonatal benefits, as reported in earlier studies. However, in real-world clinical practice, metformin is typically prescribed only for women with milder forms of hyperglycemia and is generally not recommended as first-line monotherapy for managing diabetes in pregnancy. This limitation narrows the generalizability of the subgroup findings, as patients receiving metformin monotherapy are likely to represent a lower-risk population.

Conversely, our meta-analysis revealed a statistically significant increase in the risk of SGA neonates with metformin treatment. However, this result showed substantial heterogeneity, suggesting considerable variability among the included studies. Differences in maternal characteristics - such as lower BMI, the presence of polycystic ovary syndrome (PCOS), or earlier initiation of treatment - may have influenced the overall effect estimates. Future research should consider stratified analyses to identify risk variations among different subpopulations.

This systematic review and meta-analysis provide compelling evidence supporting the use of metformin, either alone or in combination with insulin, for glycemic management in pregnancy before 24 weeks. Our findings suggest that metformin use is associated with meaningful maternal and neonatal benefits, including reductions in gestational hypertension, LGA neonates, birth weight Z scores, and NICU admissions. These results highlight metformin’s potential to enhance maternal metabolic control and reduce adverse pregnancy outcomes. From a clinical standpoint, metformin offers notable advantages as an oral agent,

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including ease of administration and improved patient adherence compared to insulin injections. In resource-limited settings where insulin may be inaccessible or difficult to administer, metformin represents a cost-effective and practical alternative. Broader adoption of metformin could enhance gestational diabetes care, improve health outcomes, and promote equitable healthcare access. Nonetheless, the slight increase in SGA neonates risk underscores the importance of individualized clinical assessment, particularly for pregnancies at risk of fetal growth restriction. Further research is needed to determine whether metformin exposure has long-term implications for offspring growth, metabolism, and development.

Additionally, our meta-analysis included limited data from Asian populations - only one study was conducted in Pakistan, with no representation from East, Southeast, or Northeast Asia. This limits the generalizability of our findings across diverse ethnic and geographic populations. Future randomized controlled trials should prioritize inclusion of underrepresented regions and ethnic groups to validate the safety, efficacy, and global applicability of metformin in pregnancy. Broader international adoption of metformin has the potential to reduce insulin dependency, improve pregnancy outcomes, and optimize resource utilization in maternal-fetal healthcare systems.

5. Conclusion

This meta-analysis demonstrates that metformin use before 24 weeks of gestation is associated with significant reductions in gestational hypertension, stillbirth, LGA, birth weight Z scores, and NICU admissions. These findings highlight metformin as a potentially valuable therapeutic option for early pregnancy diabetes management, offering both maternal and neonatal benefits.

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Given its oral administration, cost-effectiveness, and favorable safety profile, metformin may be especially advantageous in resource-limited settings and could help shape future clinical guidelines. However, the limited number of studies and heterogeneity among subgroups restrict the generalizability of these findings. Further high-quality, large-scale randomized trials are needed to validate the long-term safety and efficacy of metformin across diverse populations.

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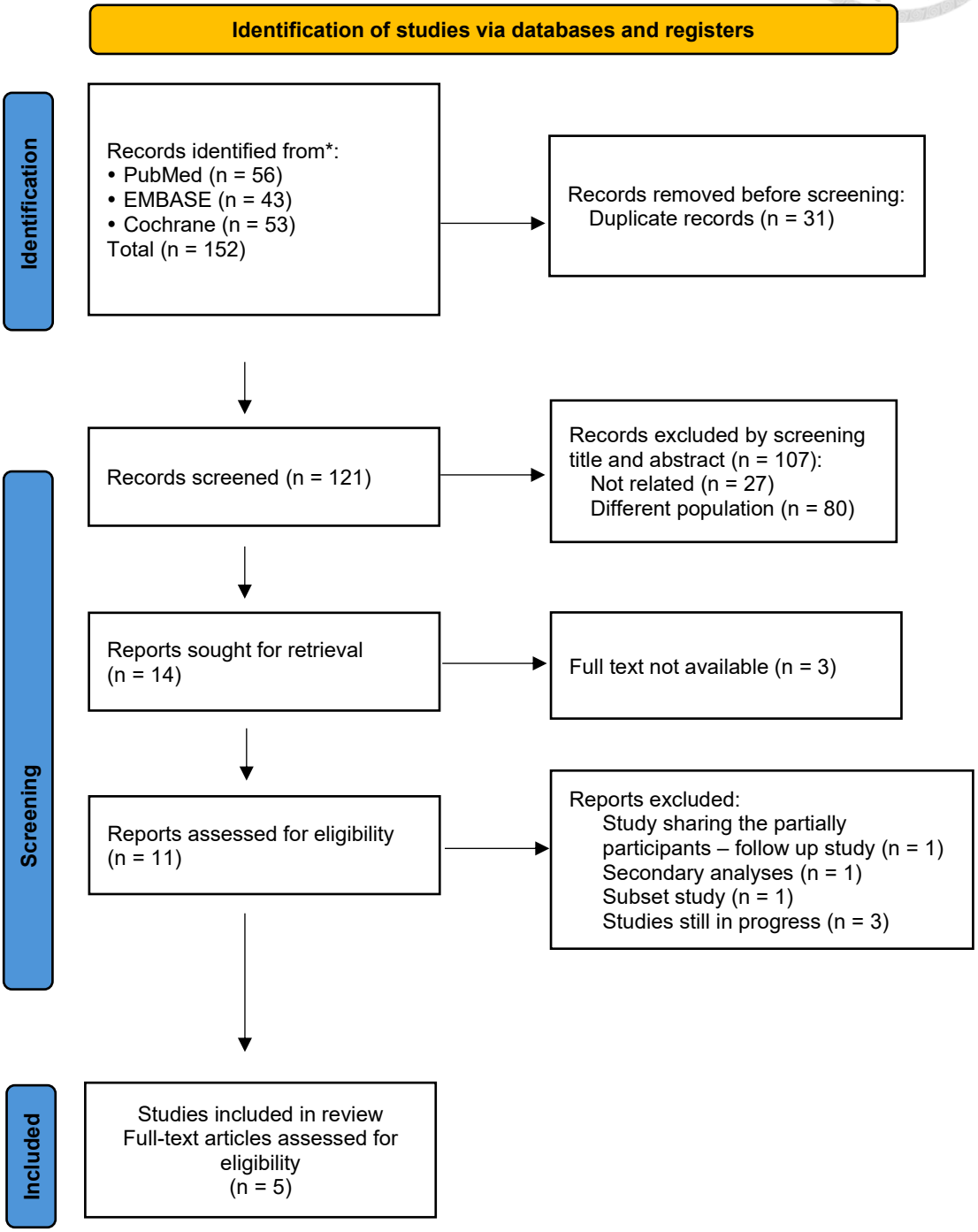
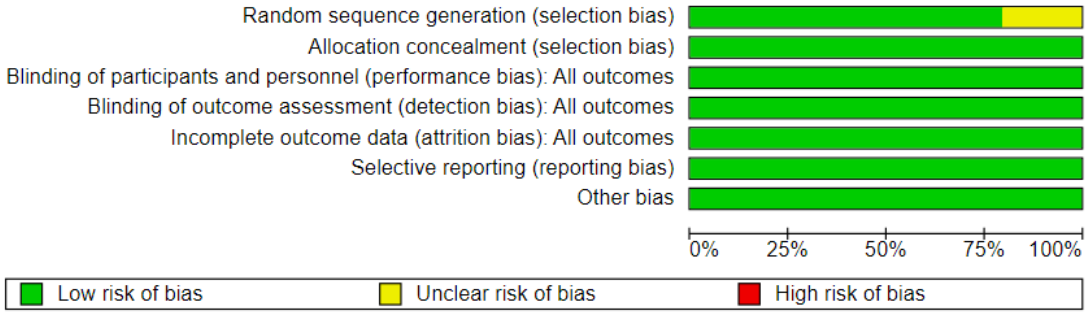
Figure 1. PROSMA flow diagram.



doi:10.6342/NTU202501547

Figure 2. Risk of bias graph.



doi:10.6342/NTU202501547

Figure 3. Summary for the risk of bias in the included studies.

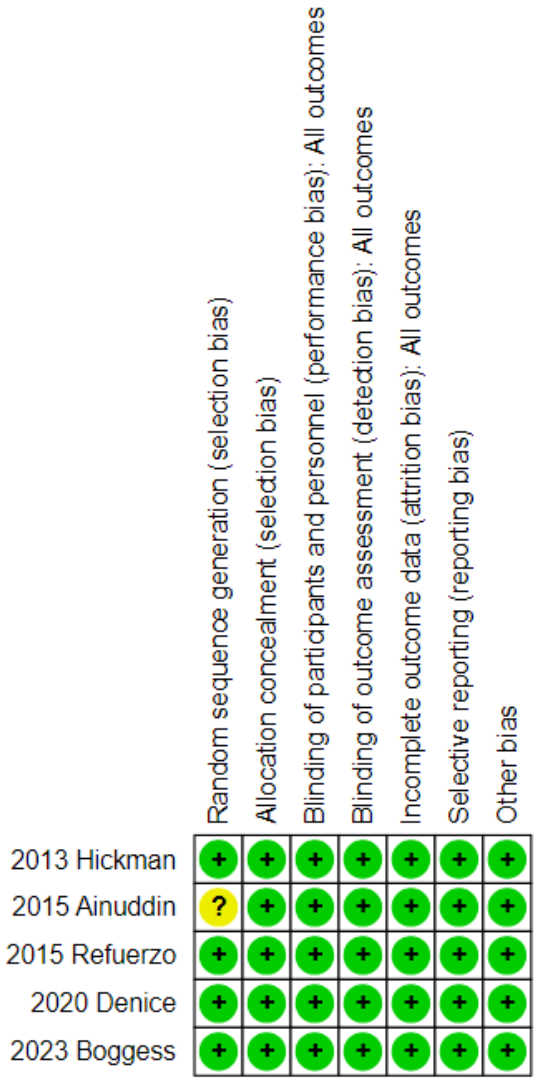


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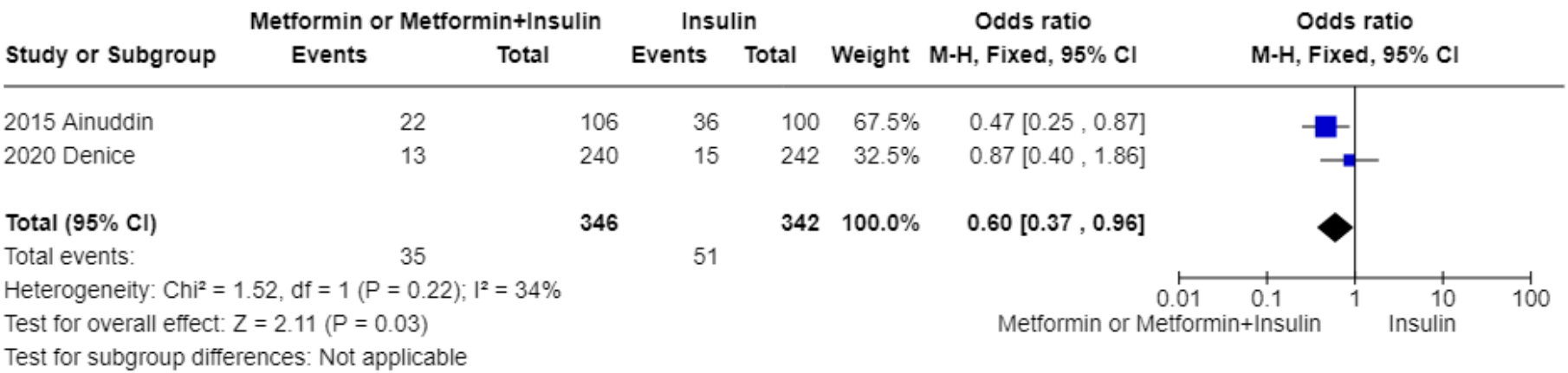
Figure 4. Forest plot comparing the effects of metformin alone or metformin combined with insulin versus insulin alone on gestational hypertension.



doi:10.6342/NTU202501547

Figure 5. Forest plot comparing the effects of metformin alone or metformin combined with insulin versus insulin alone on caesarean section.

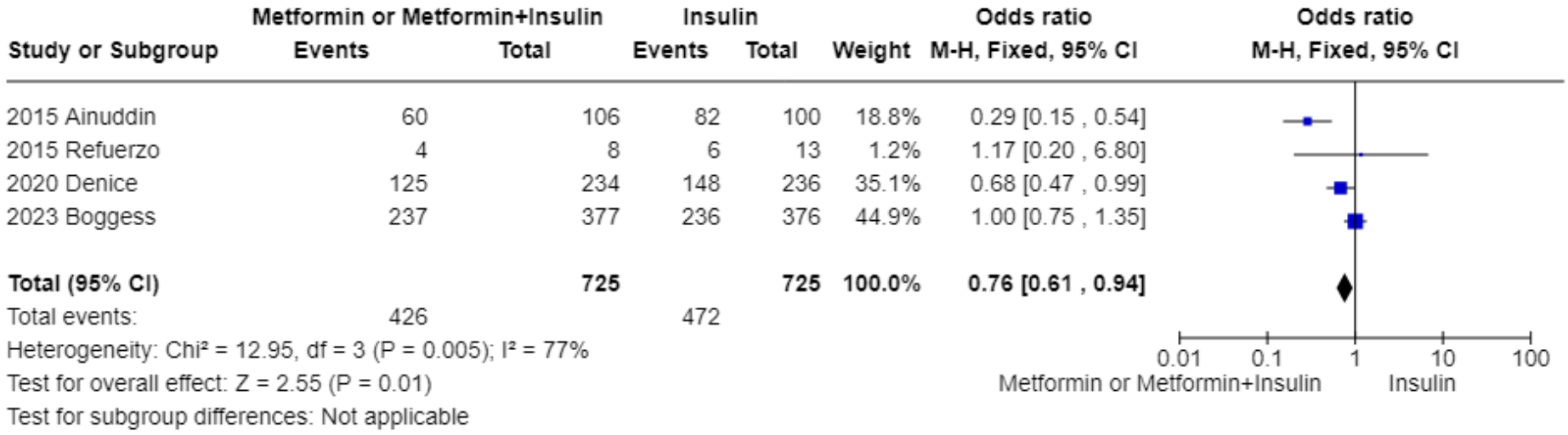


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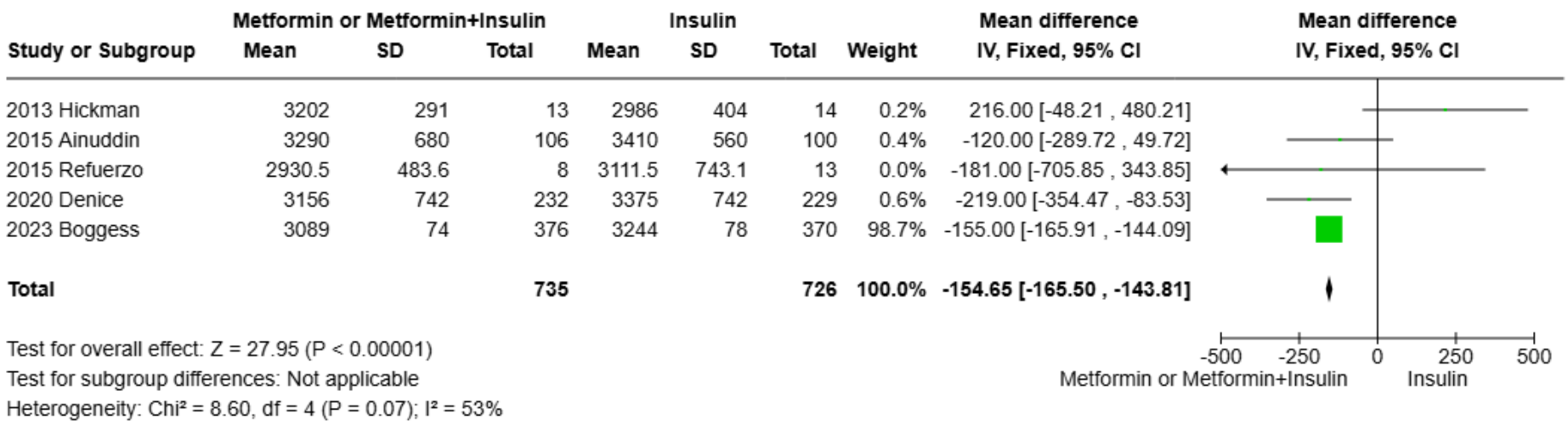
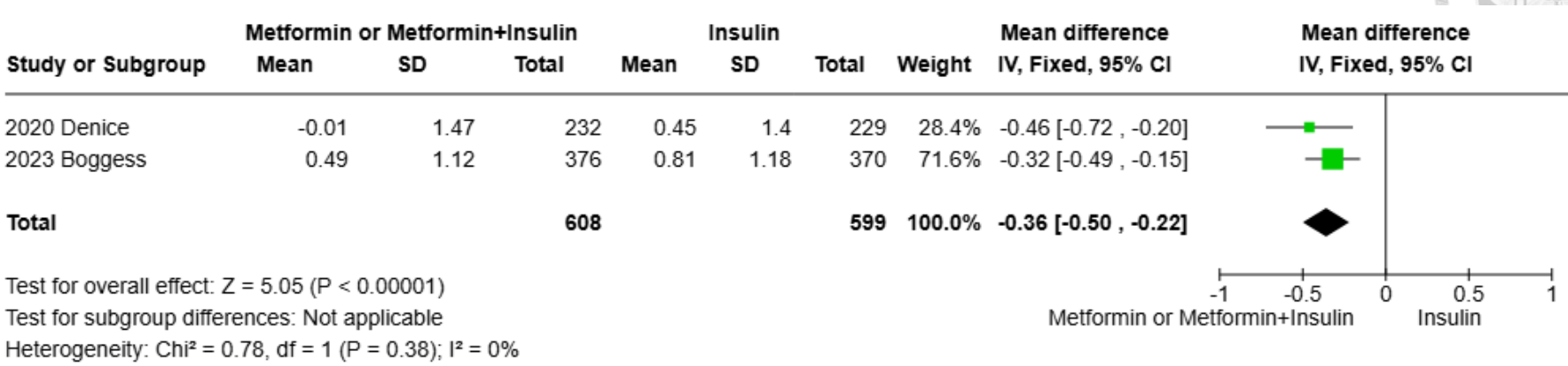
Figure 6. Forest plot comparing the effects of metformin alone or metformin combined with insulin versus insulin alone on birth weight.



doi:10.6342/NTU202501547

Figure 7. Forest plot comparing the effects of metformin alone or metformin combined with insulin versus insulin alone on birth weight Z score.



doi:10.6342/NTU202501547

Figure 8. Forest plot comparing the effects of metformin alone or metformin combined with insulin versus insulin alone on LGA.

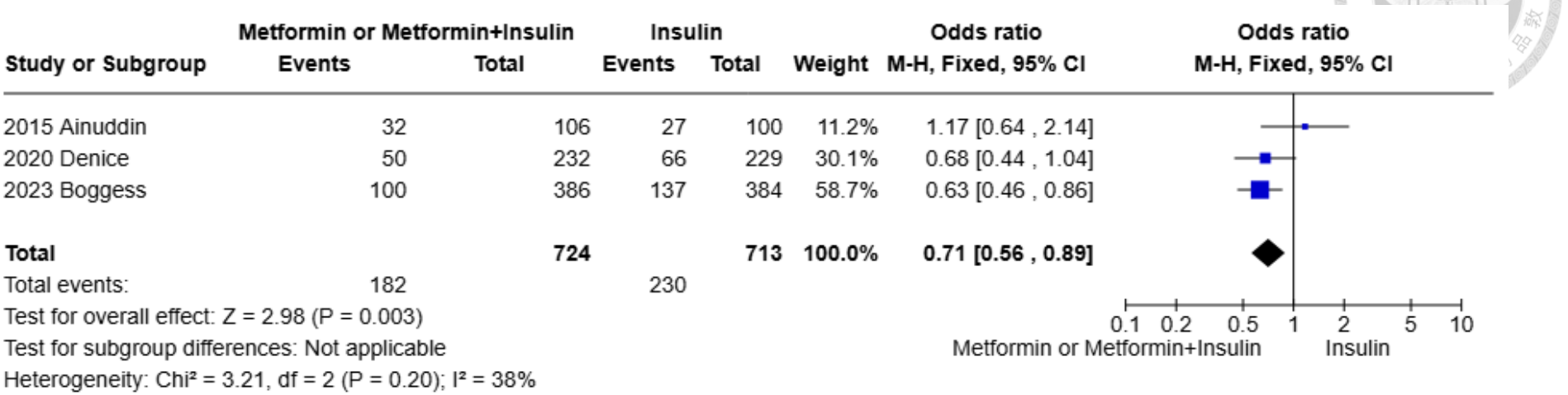


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Figure 9. Forest plot comparing the effects of metformin alone or metformin combined with insulin versus insulin alone on birthweight ≥ 4000 g.

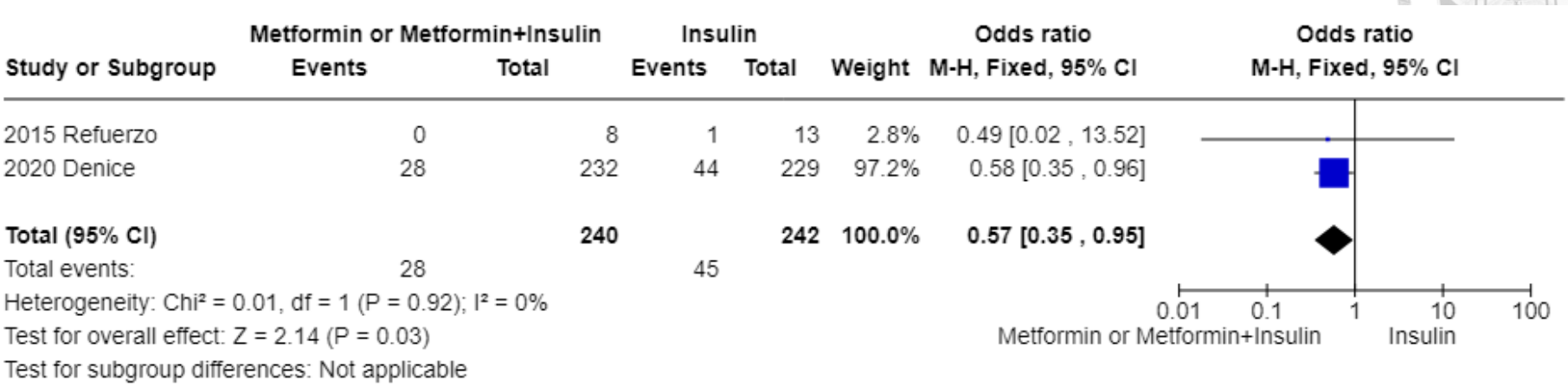

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Figure 10. Forest plot comparing the effects of metformin alone or metformin combined with insulin versus insulin alone on neonatal hypoglycemia.

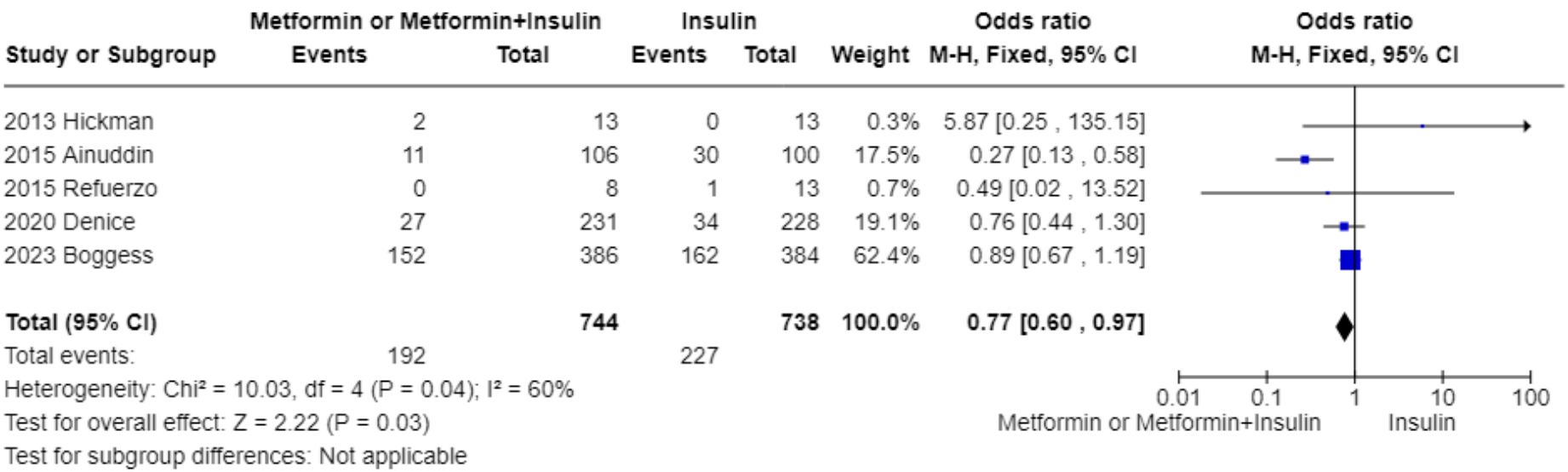

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Figure 11. Forest plot comparing the effects of metformin alone or metformin combined with insulin versus insulin alone on NICU admission.

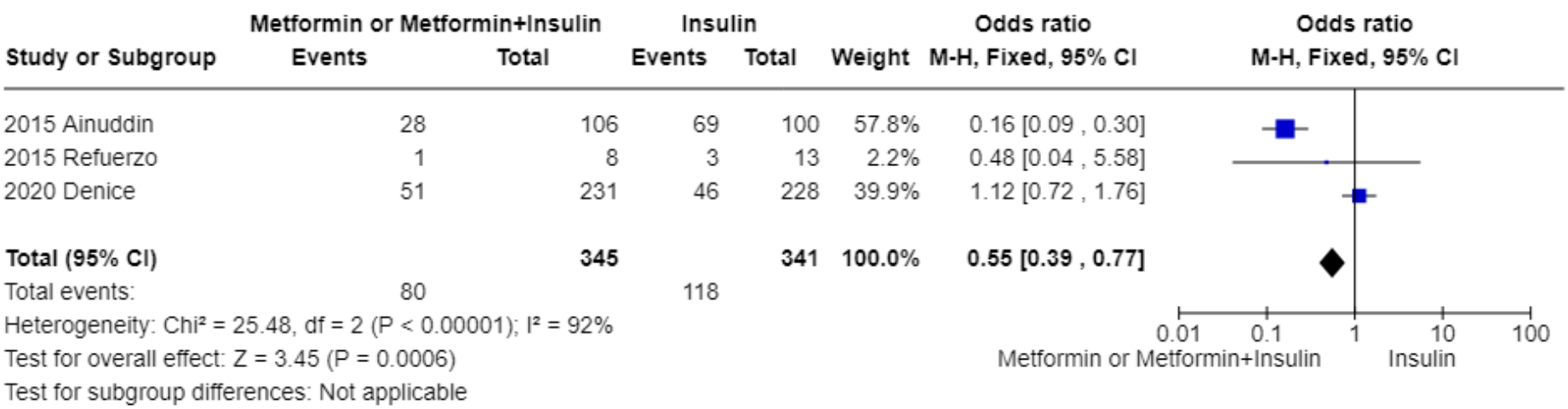

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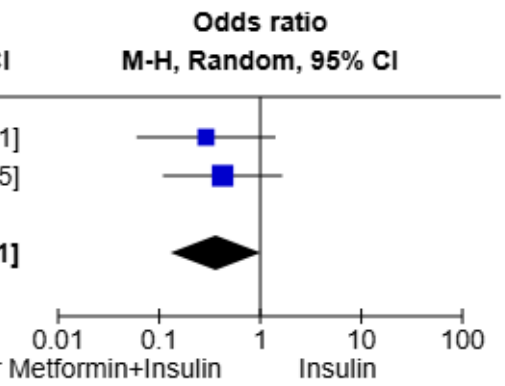
Figure 12. Forest plot comparing the effects of metformin alone or metformin combined with insulin versus insulin alone on stillbirth.



Study or Subgroup	Metformin or Metformin+Insulin Events	Total	Insulin Events	Total	Weight	Odds ratio M-H, Random, 95% CI
2020 Denice	2	227	7	236	42.5%	0.29 [0.06 , 1.41]
2023 Boggess	3	397	7	397	57.5%	0.42 [0.11 , 1.65]
Total (Wald[a])		**624**		**633**	**100.0%**	**0.36 [0.13 , 1.01]**
Total events:	5		14			

Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

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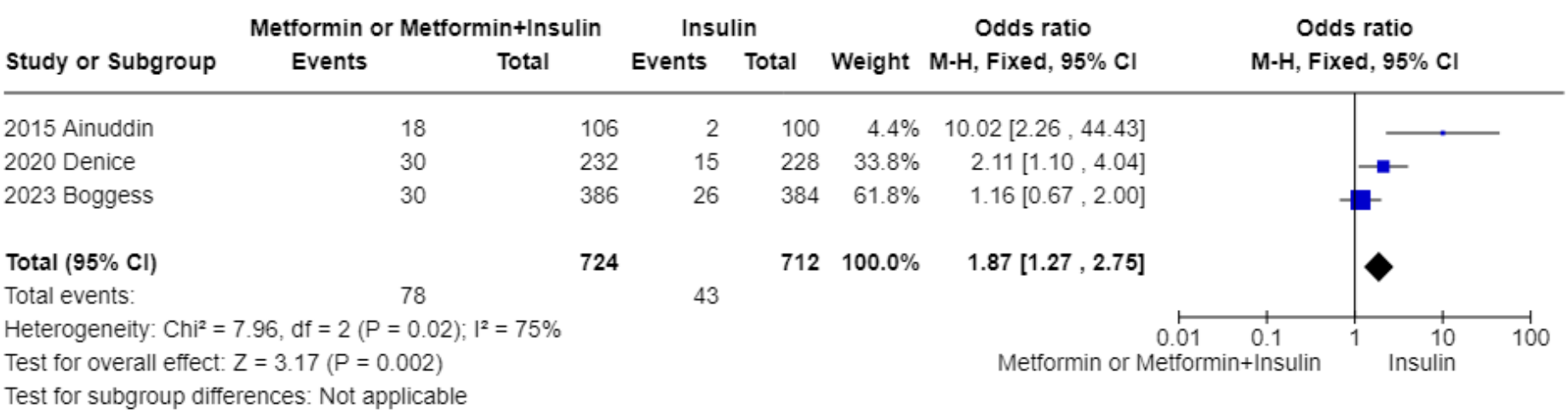
Figure 13. Forest plot comparing the effects of metformin alone or metformin combined with insulin versus insulin alone on SGA.



doi:10.6342/NTU202501547

Figure 14. Forest plot comparing the effects of metformin combined with insulin versus insulin alone on caesarean section.

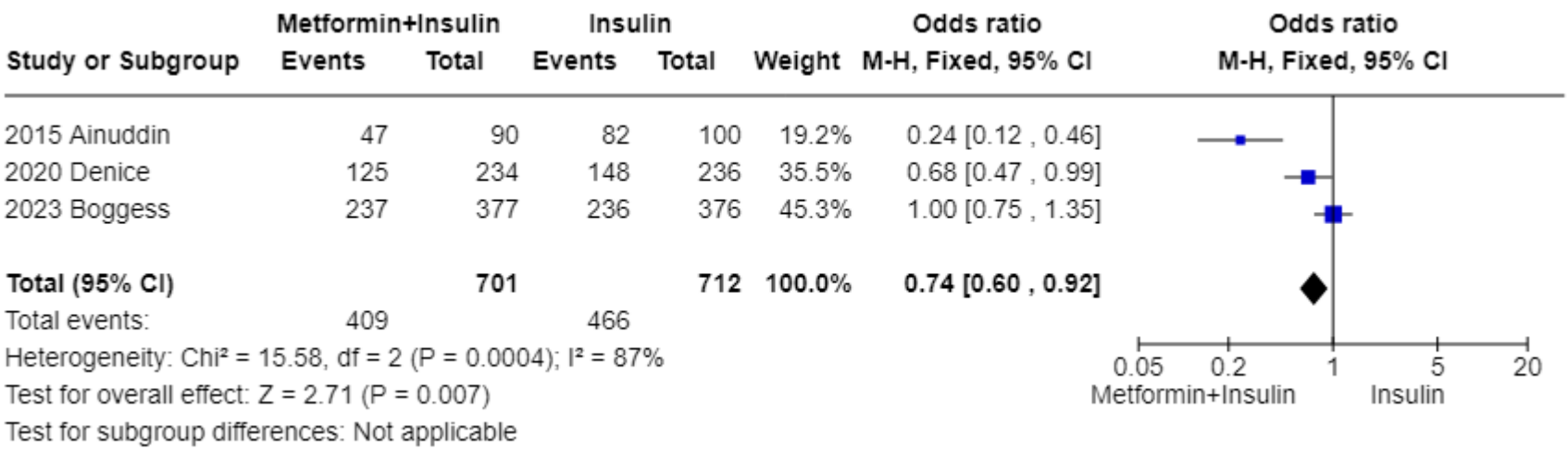


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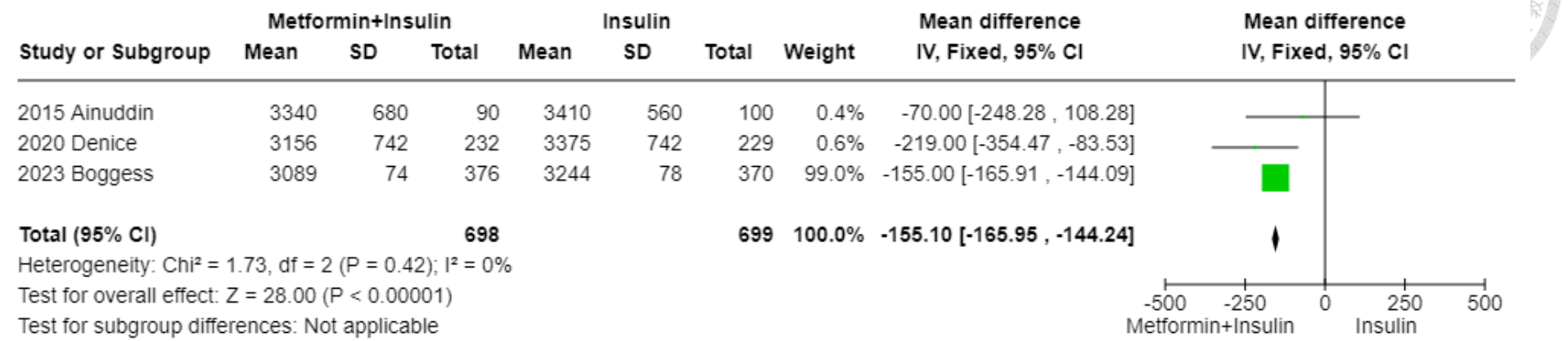
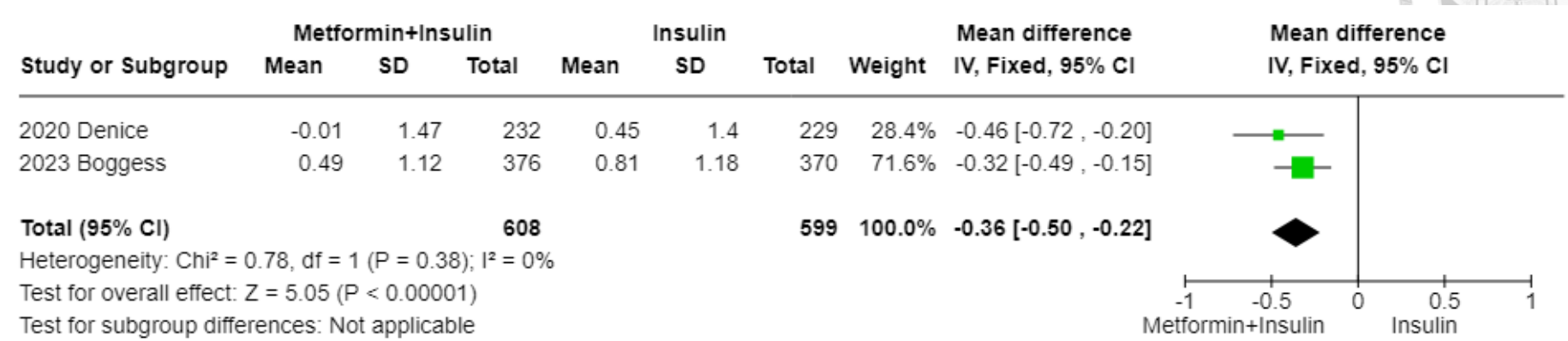
Figure 15. Forest plot comparing the effects of metformin combined with insulin versus insulin alone on birth weight.



doi:10.6342/NTU202501547

Figure 16. Forest plot comparing the effects of metformin combined with insulin versus insulin alone on birth weight Z scores.



doi:10.6342/NTU202501547

Figure 17. Forest plot comparing the effects of metformin combined with insulin versus insulin alone on neonatal hypoglycemia.

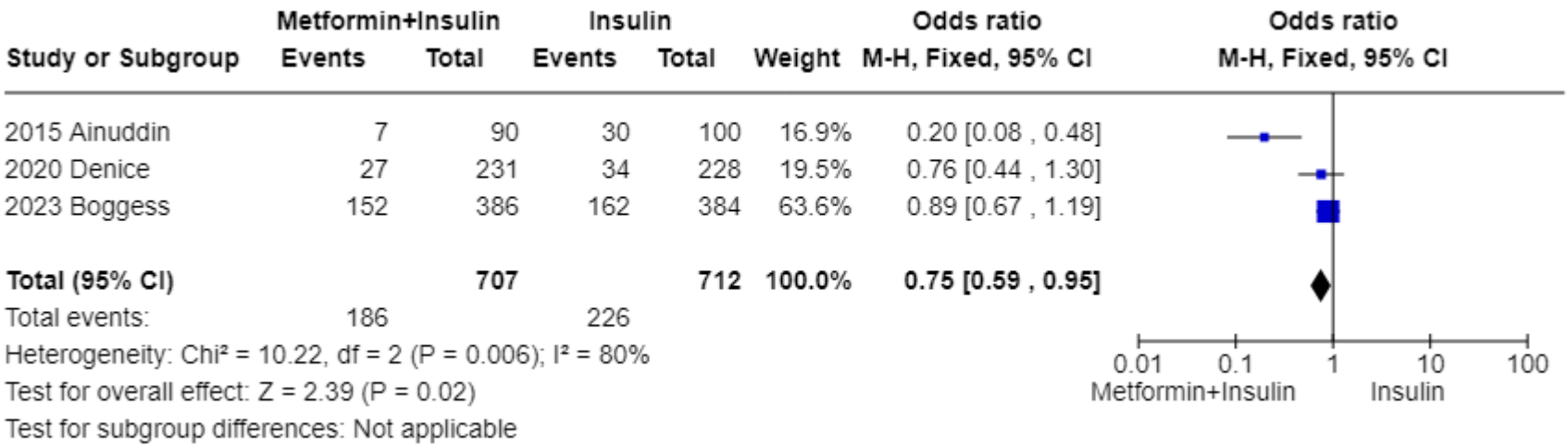


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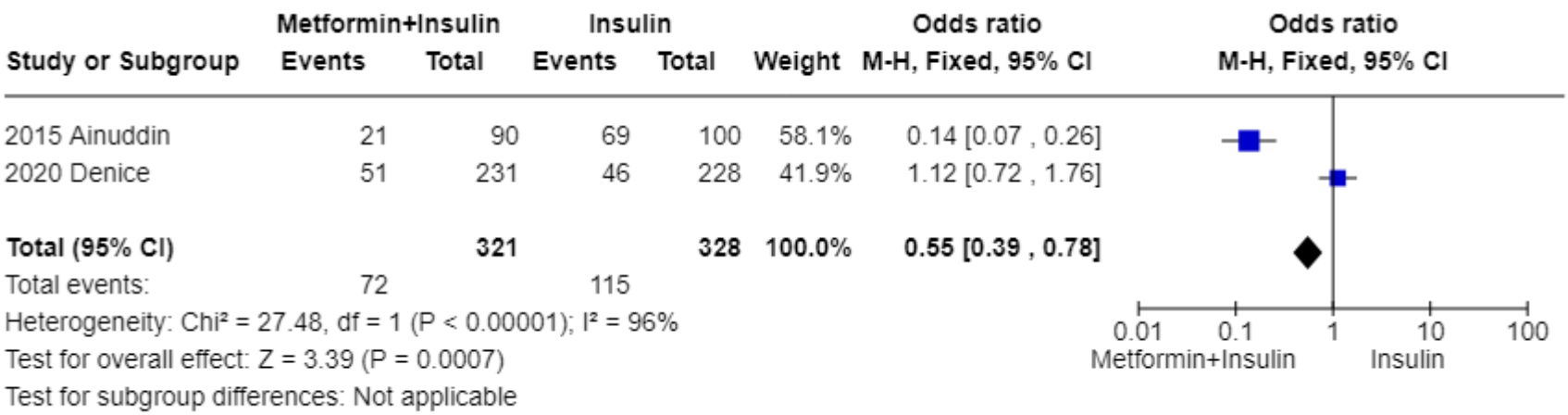
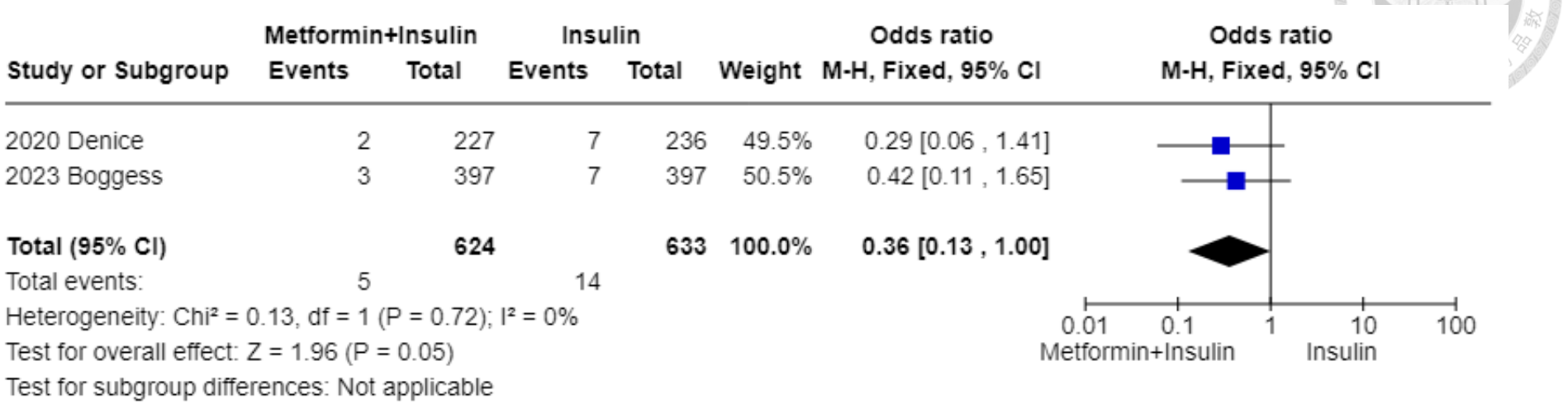
Figure 18. Forest plot comparing the effects of metformin combined with insulin versus insulin alone on NICU admission.



doi:10.6342/NTU202501547

Figure 19. Forest plot comparing the effects of metformin combined with insulin versus insulin alone on stillbirth.



doi:10.6342/NTU202501547

Figure 20. Forest plot comparing the effects of metformin combined with insulin versus insulin alone on SGA.

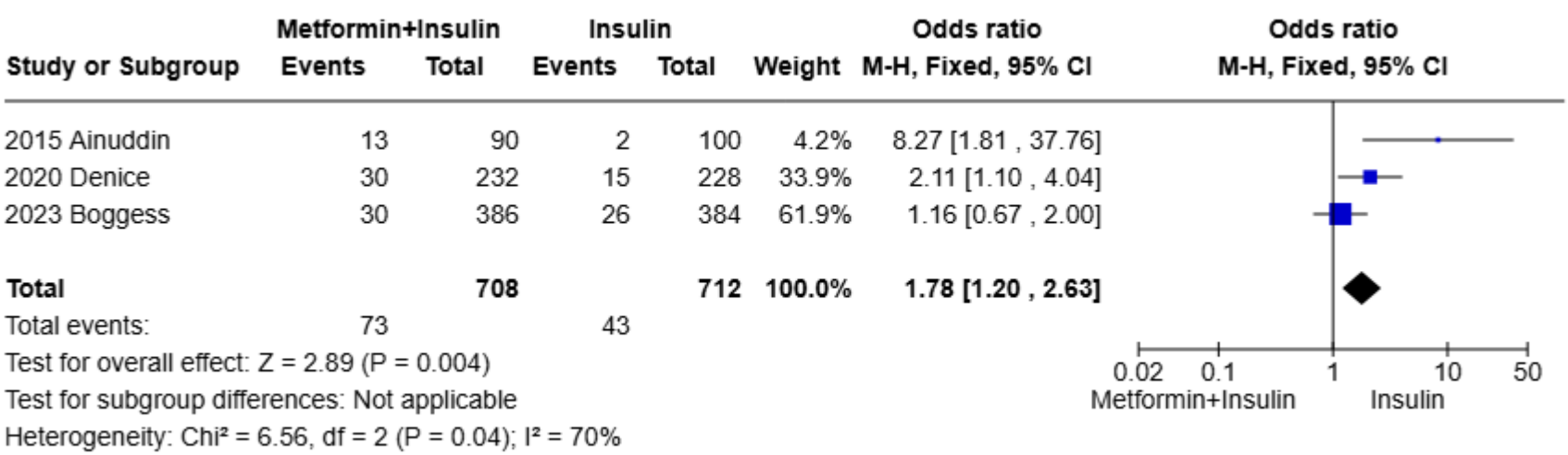


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Figure 21. Forest plot comparing the effects of metformin versus insulin on NICU admission.

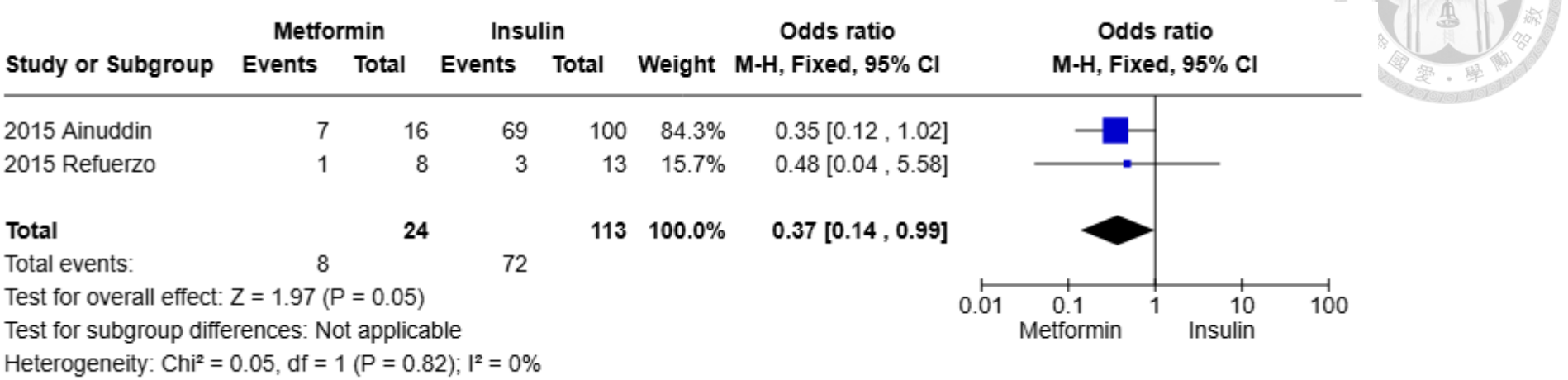

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Table 1. Summary of the five randomized controlled trials included in this meta-analysis.

Authors (Year)	Country	No. of subjects		Dose of metformin	Dose of Insulin	Outcomes
Kim A. Boggess et al (2023)	USA	397	397	Started at dose of 500 mg twice a day for 1 week, then if tolerated, to increase to 1000 mg twice a day	Combination of rapid/short and intermediate/long-acting insulin: - Fasting glucose: 70–95 mg/dL - 1 h postprandial: < 140 mg/dL - 2 h postprandial: < 120 mg/dL	No significant difference in the primary composite Neonatal outcome between the two groups - Lower proportion of LGA infants in the metformin group
Denice S Feig et al (2020)	Canada and Australia	233	240	1000 mg twice daily	Adjusted to meet glucose targets: - Fasting: < 95 mg/dL - 2-h postprandial: < 120 mg/dL	No significant difference in the primary composite Neonatal outcome between the two groups - Better glycemic control - Required less insulin - Gained less weight - Lower cesarean rate - Infants weighed less - Fewer above the 97th percentile for birth weight - More SGA babies
Jahan Ara Ainuddin et al (2015)	Pakistan	106 (Metformin alone: 16)	100	Started at dose of 500 mg/daily and increased up to 2500 mg	Target blood glucose levels were: Fasting ≤ 100 mg/dL and 1.5 h postprandial ≤ 126 mg/dL Insulin regimen (twice daily): - 1st trimester: 0.6 units/kg/day - 2nd trimester: 0.7 units/kg/day - 28–36 weeks: 0.8–0.9 units/kg/day - 36 weeks+: 1 unit/kg/day	- Less neonatal hypoglycemia - More SGA babies - Pregnancy induced hypertension - Less NICU stay of >24 hours - Less neonatal jaundice
Jerrie S. Refuerzo et al (2015)	USA (Texas)	8	13	500 mg daily was initiated, increased by 500 mg as needed for a maximum dose of 2500 mg a day	Adjusted by trimester and doses split AM and PM - 1st trimester-0.7 units/kg/day - 2nd trimester-0.8 units/kg/day - 3rd trimester-Third trimester—0.9 to 1.0 units/kg/day	- Similar rates of cesarean delivery, birth weights, NICU admissions, respiratory distress syndrome, and neonatal dextrose treatment - 1 case of fetal macrosomia (insulin group) 1 case of shoulder dystocia (metformin group)
M. Ashley Hickman et al (2013)	North Carolina	14	14	Started at dose of 500 mg once or twice per day and increased up to 2500 mg/daily	The starting insulin dose was 0.7 units/kg/day, divided as follows: - AM dose: 2/3 NPH and 1/3 Regular insulin - PM dose: Half NPH and half Regular insulin	- Similar glucose control between groups - Metformin users had fewer hypoglycemia

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Table 2. Effect of metformin combined with insulin or metformin alone vs insulin alone on several maternal and neonatal outcomes.

Outcome	No of Study	Metformin or Metformin + Insulin (N)	Insulin (N)	Effect size (95% CI)	p value	I^2
Maternal Outcomes						
Last HbA1c concentration in pregnancy	3	245	260	Difference -0.09 (-0.22 to -0.04)	0.17	73
Gestational hypertension	2	346	342	OR 0.60 (0.37 to 0.96)	0.03	34
Preeclampsia	3	354	355	OR 0.99 (0.65 to 1.50)	0.96	45
Caesarean section	4	725	725	OR 0.76 (0.61 to 0.94)	0.01	77
Neonatal Outcomes						
Preterm birth	4	639	640	OR 0.95 (0.75 to 1.21)	0.7	47
Birth trauma	2	492	484	OR 0.99 (0.51 to 1.93)	0.97	0
Shoulder dystocia	4	640	643	OR 1.13 (0.50 to 2.52)	0.77	0
Birth weight, g	5	735	726	Difference -154.65 (-165.50 to -143.81)	< 0.00001	53
Birth weight Z score	2	608	599	Difference -0.36 (-0.50 to -0.22)	< 0.00001	0
Small for gestational age	3	724	712	OR 1.87 (1.27 to 2.75)	0.002	75
Large for gestational age	3	724	713	OR 0.71 (0.56 to 0.89)	0.003	38
Birth weight >=4000 g	2	240	242	OR 0.57 (0.35 to 0.95)	0.03	0
Neonatal body fat mass	2	459	439	Difference -0.01 (-0.09 to 0.01)	0.09	85
Hyperbilirubinemia	3	719	711	OR 0.95 (0.74 to 1.22)	0.67	80
Neonatal hypoglycemia	5	744	738	OR 0.77 (0.60 to 0.97)	0.03	60
Respiratory distress syndrome	3	345	341	OR 0.87 (0.46 to 1.64)	0.66	0
NICU admission	3	345	341	OR 0.55 (0.39 to 0.77)	0.0006	92
Fetal and Neonatal Death	2	624	633	OR 0.89 (0.50to 1.6)	0.7	0
Miscarriage	2	624	633	OR 1.41 (0.56 to 3.52)	0.47	0
Stillbirth	2	624	633	OR 0.36 (0.13 to 1.00)	0.05	0
Neonatal death	2	624	633	OR 2.06 (0.51 to 8.21)	0.31	52

doi:10.6342/NTU202501547

Table 3. Effect of metformin combined with insulin vs. insulin alone on several maternal and neonatal outcomes.

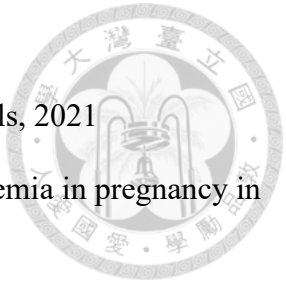
Outcome	No of Study	Metformin + Insulin (N)	Insulin (N)	Effect size (95% CI)	p value	I^2
Maternal Outcomes						
Gestational hypertension	2	330	342	OR 0.66 (0.40 to 1.07)	0.09	0
Preeclampsia	2	330	342	OR 1.02 0.66 to 1.57)	0.94	65
Caesarean section	3	701	712	OR 0.74 (0.60 to 0.92)	0.007	87
Neonatal Outcomes						
Preterm birth	2	618	613	OR 0.99 (0.78 to 1.26)	0.93	65
Birth trauma	2	476	484	OR 0.89 (0.4 to 1.76)	0.74	0
Shoulder dystocia	2	618	616	OR 1.00 (0.43 to 2.32)	0.99	0
Birth weight, g	3	698	699	Difference -155.10 (-165.95 to -144.24)	< 0.00001	0
Birth weight Z score	2	608	599	Difference -0.36 (-0.50 to -0.22)	< 0.00001	0
Small for gestational age	3	708	712	OR 1.78 (1.20 to 2.63)	0.004	70
Large for gestational age	3	708	713	OR 0.72 (0.57 to 0.90)	0.09	58
Neonatal body fat mass	2	459	439	Difference -0.01 (-0.09 to 0.01)	0.09	85
Hyperbilirubinemia	3	703	711	OR 0.95 (0.74 to 1.23)	0.71	79
Neonatal hypoglycemia	3	707	712	OR 0.75 (0.59 to 0.95)	0.02	80
Respiratory distress syndrome	2	321	328	OR 0.87 (0.44 to 1.73)	0.69	52
NICU admission	2	239	241	OR 0.55 (0.39 to 0.78)	0.0007	96
Fetal and Neonatal Death	2	624	633	OR 0.89 (0.50to 1.6)	0.7	0
Miscarriage	2	624	633	OR 1.41 (0.56 to 3.52)	0.47	0
Neonatal death	2	624	633	OR 2.06 (0.51 to 8.21)	0.31	52
Stillbirth	2	624	633	OR 0.36 (0.13 to 1.00)	0.05	0

doi:10.6342/NTU202501547

Table 4. Effect of metformin vs. insulin on maternal and neonatal outcomes.

Outcome	No of Study	Metformin (N)	Insulin (N)	Effect size (95% CI)	p value	I^2
Maternal Outcomes						
Last HbA1c concentration in pregnancy	2	18	25	Difference 0.12 (-0.10 to 0.34)	0.28	51
Preeclampsia	2	24	113	OR 0.90 (0.30 to 2.69)	0.85	60
Caesarean section	2	24	113	OR 1.03 (0.35 to 3.02)	0.96	0
Neonatal Outcomes						
Preterm birth	2	21	27	OR 1.09 (0.03 to 1.32)	0.1	0
Shoulder dystocia	2	22	27	OR 5.40 (0.19 to 149.78)	0.32	NA
Neonatal hypoglycemia	3	37	126	OR 0.7 (0.26 to 1.88)	0.48	0
Respiratory distress syndrome	2	24	113	OR 0.86 (0.22 to 3.34)	0.83	0
NICU admission	2	24	113	OR 0.37 (0.14 to 0.99)	0.05	0

doi:10.6342/NTU202501547



References

1. Magliano DJ, Boyko EJ. In IDF DIABETES ATLAS, 10th ed. Brussels, 2021
2. Lin SY, Wu YL, Kuo CH, et al. Trends in epidemiology of hyperglycemia in pregnancy in Taiwan, 2008-2017. Front Endocrinol (Lausanne) 2022;13:1041066
3. Egan AM, Dow ML, Vella A: A Review of the Pathophysiology and Management of Diabetes in Pregnancy. Mayo Clin Proc 2020;95:2734-2746
4. Battarbee AN, Venkatesh KK, Aliaga S, Boggess KA: The association of pregestational and gestational diabetes with severe neonatal morbidity and mortality. J Perinatol 2020;40:232-239
5. Ye W, Luo C, Huang J, Li C, Liu Z, Liu F: Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. BMJ 2022;377:e067946
6. Lai FY, Johnson JA, Dover D, Kaul P: Outcomes of singleton and twin pregnancies complicated by pre-existing diabetes and gestational diabetes: A population-based study in Alberta, Canada, 2005-11. J Diabetes 2016;8:45-55
7. Alexopoulos AS, Blair R, Peters AL: Management of Preexising Diabetes in Pregnancy: A Review. JAMA 2019;321:1811-1819
8. Jovanovic L, Liang Y, Weng W, Hamilton M, Chen L, Wintfeld N: Trends in the incidence of diabetes, its clinical sequelae, and associated costs in pregnancy. Diabetes Metab Res Rev 2015;31:707-716
9. Battarbee AN, Venkatesh KK, Aliaga S, Boggess KA: The association of pregestational and gestational diabetes with severe neonatal morbidity and mortality. J Perinatol 2020;40:232-239
10. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol 2018;131:e49-e64
11. Kuo CH, Li HY: Diagnostic Strategies for Gestational Diabetes Mellitus: Review of Current Evidence. Curr Diab Rep 2019;19:155
12. Vanky E, Zahlsen K, Spigset O, Carlsen SM: Placental passage of metformin in women with

doi:10.6342/NTU202501547

polycystic ovary syndrome. Fertility and sterility 2005;83:1575-1578

13. Balsells M, Garcia-Patterson A, Sola I, Roque M, Gich I, Corcoy R: Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ 2015;350:h102
14. Tarry-Adkins JL, Aiken CE, Ozanne SE: Comparative impact of pharmacological treatments for gestational diabetes on neonatal anthropometry independent of maternal glycaemic control: A systematic review and meta-analysis. PLoS Med 2020;17:e1003126
15. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP: Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med 2008;358:2003-2015
16. Barbour LA, Scifres C, Valent AM, Friedman JE, Buchanan TA, Coustan D, Aagaard K, Thornburg KL, Catalano PM, Galan HL, Hay WW, Jr., Frias AE, Shankar K, Simmons RA, Moses RG, Sacks DA, Loeken MR: A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes. American journal of obstetrics and gynecology 2018;219:367.e361-367
17. Barbour LA, Feig DS: Metformin for Gestational Diabetes Mellitus: Progeny, Perspective, and a Personalized Approach. Diabetes Care 2019;42:396-399
18. M. Ashley Hickman, Ryan McBride, Kim A. Boggess, Robert Strauss: Metformin Compared with Insulin in the Treatment of Pregnant Women with Overt Diabetes: A Randomized Controlled Trial. Am J Perinatol 2013;30:483–490
19. Jerrie SR, Rose G, Claudia P, Maria H, Sean CB, Susan R: A pilot randomized, controlled trial of metformin versus Insulin in women with type 2 diabetes mellitus during pregnancy. Am J Perinatol 2015;32:163-170
20. Jahan AA, Nasim K, Sidra Z, Syed SA, Anjum AH: Metformin treatment in type 2 diabetes in pregnancy: an active controlled, parallel-group, randomized, open label study in patients with type 2 diabetes in pregnancy. Journal of Diabetes Research 2015; 2015; pp 1-11

doi:10.6342/NTU202501547

21. Denice SF, Lois ED, Bernard Z, J Johanna S, Elizabeth A, Edmond AR, I George , Eileen H, Anthony BA, Lorraine LL, David S, Jon F RB, Paul JK, Siobhan T, H David M, Simon YT, George T, Kellie EM, on behalf of the MiTy Collaborative Group: Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo controlled trial. Lancet Diabetes Endocrinol 2020; 8: 834-844

22. Kim AB, Arielle, Jerrie SR, Noelia Z, Ashley NB, Kacey E, Gladys AR, Gayle O, Celeste D, Mark BL, Kjersti MA, Kedra W, Christina S, Todd R, Wadia M, Amy Va, Sherri L, Laura Y, M. Alison M, Sonia T, Ashley B, Diane B: Metformin plus insulin for preexisting diabetes or gestational diabetes in early Pregnancy the MOMPOD randomized clinical trial. JAMA 2023;330(22):2182-2190

23. Argyro S, Kypros H. N, Jyoti B, Steve H, Ranjit A, Reena K, Alice P, Hassan S: Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus. N Engl J Med 2016; 374:434-443

24. Leena PB, Barbara SN: The intersection of metformin and inflammation. Am J Physiol Cell Physiol 2021; 10; 320 (5): C873–C879

25. Crowther CA, Hiller JE, Moss JR, Andrew JM, William SJ, Jeffrey SR: Effect of treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes. N Engl J Med 2005; 352(24), 2477-2486

26. Le-xin B, Wan-ting S, u-xin H: Metformin versus insulin for gestational diabetes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2021; 34(16), 2741–2753

27. Bo Sheng, Juan Ni, Bin Lv, Guoguo Jiang, Xuemei Lin, Hao Li: Short-term neonatal outcomes in women with gestational diabetes treated using metformin versus insulin: a systematic review and meta-analysis of randomized controlled trials. Acta Diabetol 2023; 60(5):595-608

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Appendix: Clinical Trial Protocol

Protocol title:

A Randomized, Double-blind, Multicenter Trial to Assess Efficacy and Safety of Metformin for Pregnant Women with PDM, Undiagnosed Diabetes Mellitus, or Early GDM

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LIST OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AE	Adverse Event
ALT	Alanine Aminotransferase
ART	Assisted Reproductive Technology
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
BPP	Biophysical Profile
CBG	Capillary Blood Glucose
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CRF	Case Report Form
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
DSMB	Data and Safety Monitoring Board
EDC	Estimated Date of Confinement
FPG	Fasting Plasma Glucose
GA	Gestational Age
GDM	Gestational Diabetes Mellitus
GI	Gastrointestinal
HDL	High-Density Lipoprotein
HbA1c	Hemoglobin A1c
IBS	Irritable Bowel Syndrome
IDF	International Diabetes Federation
IRB	Institutional Review Board
ITT	Intention-to-Treat
LDL	Low-Density Lipoprotein
LGA	Large for Gestational Age
LMP	Last Menstrual Period
NICU	Neonatal Intensive Care Unit
NST	Non-tress Testing
OCT	Optical Coherence Tomography
OGTT	Oral Glucose Tolerance Test
OR	Odds ratio
PCOS	Polycystic Ovary Syndrome
PDM	Pregestational Diabetes Mellitus

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PP	Per-Protocol
RCT	Randomized Controlled Trials
RDS	Respiratory Distress Syndrome
RR	Relative Risk
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SGA	Small for Gestational Age
SMBG	Self-monitoring of Blood Glucose
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
UACR	Urine Albumin to Creatinine ratio
ULN	Upper Limit of Normal

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1. Study Synopsis

Title	A Randomized, double-blind, multicenter trial to assess efficacy and safety of metformin for pregnant women with PDM, undiagnosed diabetes mellitus, or early GDM
Phase	Phase III clinical trial
Study Type	Intervention
Purpose	To compare the safety and efficacy of metformin plus insulin versus insulin for treatment women with diabetes mellitus in pregnancy during early pregnancy
Primary Objectives	To evaluate whether the combination of metformin and insulin improves fetal and neonatal outcomes compared to insulin monotherapy in pregnant women diagnosed before 20 weeks of gestation with pregestational diabetes mellitus (PDM), undiagnosed diabetes mellitus, or early gestational diabetes mellitus (GDM).
Secondary Objectives	1 To evaluate the individual fetal and neonatal outcomes that comprise the primary composite endpoint. 2 To assess maternal glycemic control and insulin requirements throughout pregnancy. 3 To evaluate maternal outcomes related to pregnancy and delivery. 4 To assess the safety and tolerability of metformin use during pregnancy. 5 To compare additional neonatal outcomes not included in the primary endpoint.
Study Design	This is a randomized, double-blind, multicenter trial to assess the efficacy and safety of metformin plus insulin versus insulin alone for the treatment of women with diabetes mellitus during early pregnancy. Enrolled subjects will be assigned to either a placebo or metformin in a 1:1 ratio, stratified by study site and timing of diabetes diagnosis/baseline gestational age.
Number of Subjects	A total of approximately 638 subjects (319 per treatment arm) will be enrolled to yield an estimated 574 evaluable participants. This sample size incorporates a 10% anticipated dropout rate and provides 80% power to detect a clinically meaningful difference in the incidence of composite fetal and neonatal outcomes between the metformin plus insulin group and the insulin monotherapy group.
Primary Endpoint	Large for gestational age (LGA).
Secondary Endpoints	Included hypertensive disorders, preeclampsia, caesarean section, glycemic control, maternal hypoglycemia, gestational weight gain, miscarriage, stillbirth,

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	neonatal death, preterm birth, small for gestational age (SGA), major congenital malformations, cord blood C-peptide > 90th percentile, neonatal hypoglycemia, hyperbilirubinemia, respiratory distress syndrome (RDS), and neonatal intensive care unit (NICU) admission.
Inclusion Criteria	1. Maternal age 18-50 years at enrollment. 2. Women with diabetes mellitus during early pregnancy include PDM, undiagnosed diabetes mellitus, and early GDM. 2.1. PDM is defined as diabetes mellitus (DM) diagnosed before pregnancy. 2.2. Undiagnosed diabetes mellitus is defined when DM is first diagnosed during pregnancy (usually at first prenatal visit) either fasting plasma glucose (FPG) ≥126 mg/dL, or hemoglobin A1c (HbA1C) ≥6.5%. 2.3. Early GDM is defined when GDM was diagnosed before 20 weeks of gestational age (GA) by the one-step approach and two-step approach. • The one-step approach: 75 gm oral glucose tolerance test (OGTT) with at least one abnormal value: FPG ≥ 92 mg/dL, 1 hour ≥ 180 mg/dL, or 2-hour ≥ 153 mg/dL • The two-step approach: Step 1: 50g glucose challenge test (non-fasting), and if blood glucose is ≥140 mg/dL after 1 hour, proceed to Step 2. Step 2: 100g OGTT, measuring fasting, 1-hour, 2-hour, and 3-hour blood glucose; diagnose GDM if two or more of the following thresholds are met: fasting ≥95 mg/dL, 1-hour ≥180 mg/dL, 2-hour ≥155 mg/dL, 3-hour ≥140 mg/dL. 3. Gestational age at randomization between 10 weeks 0 days and 20 weeks 6 days by menstrual dating confirmed by ultrasound or ultrasound alone. 4. Singleton fetus without known or suspected anomalies before randomization. 5. Willingness to follow the study protocol to control PDM, undiagnosed or GDM. 6. Willing to give informed written consent.
Exclusion Criteria	1. Type 1 diabetes 2. Multiple gestation. 3. Suspected or known fetal structural or chromosomal abnormality before randomization. 4. Known medical contraindications to metformin (history of lactic acidosis).

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	5. Known intolerance to metformin. 6. Known pre-existing renal disease (creatinine > 1.5 mg/dL). 7. Acute liver disease or known liver abnormalities (acute viral hepatitis, Aspartate Aminotransferase (AST)/ Alanine Aminotransferase (ALT) > 2x Upper Limit of Normal (ULN)). 8. Known medical conditions that predispose a woman to GI distress (Crohn's disease, ulcerative colitis, irritable bowel syndrome (IBS), celiac disease). 9. Current or past history of alcohol abuse. 10. Current or past history of smoking. 11. Participation in another study that could affect the primary outcome. 12. Unwilling or unable to follow the study protocol. 13. Other significant chronic medical or psychiatric illness that, in the investigator's opinion, would prevent participation in the study.
Data Analysis	The primary efficacy analysis will compare the incidence of the composite fetal and neonatal outcome between the metformin plus insulin group and the insulin monotherapy group. Relative risks (RRs) and 95% confidence intervals (CIs) will be estimated using appropriate generalized linear models. All analyses will be performed under the intention-to-treat (ITT) principle. A two-sided p-value <0.05 will be considered statistically significant. Secondary and safety outcomes will be analyzed using standard statistical methods appropriate for binary and continuous variables. Secondary and safety outcomes will be analyzed using appropriate statistical methods for binary and continuous variables, including chi-square for categorical variables and t-tests or non-parametric tests for continuous variables as appropriate. Sensitivity analyses and per-protocol (PP) analyses will be performed to assess the robustness of primary results.

2. Introduction

2.1 Background

Diabetes mellitus in pregnancy encompasses PDM, undiagnosed diabetes mellitus, and GDM. According to the International Diabetes Federation (IDF), the global prevalence of diabetes in pregnancy was 16.7% in 2021, comprising 10.6% PDM, 9.1% undiagnosed diabetes, and 80.3% GDM [(1)]. In Taiwan, national insurance data from 2017 estimated the overall prevalence at 15.8%, including 5.7% PDM, 2.5% undiagnosed diabetes, and 91.8%

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GDM [2].

Pregnant women with hyperglycemia - including PDM, and GDM are higher risk of pregnancy complications compared to the general population [3-7]. These complications include miscarriage, preterm birth, stillbirth, gestational hypertension, preeclampsia, macrosomia, shoulder dystocia, and cesarean delivery [4]. Furthermore, neonates born to these mothers are also more likely to experience hypoglycemia, hypocalcemia, jaundice, NICU admission, and neonatal death [5-7]. Since early pregnancy is a critical period for embryonic development, elevated maternal blood glucose levels during this period can increase the risk of congenital anomalies in the fetus [8]. While GDM is typically diagnosed between 24 and 28 weeks of gestation and thus generally not associated with a higher risk of congenital malformations, some women may have undiagnosed diabetes or develop hyperglycemia earlier in pregnancy. Therefore, it is recommended that women with known diabetes or those diagnosed during pregnancy should achieve optimal glycemic control before conception or immediately after diagnosis to minimizing both maternal and neonatal risks [8, 10].

2.2 Rationale

Metformin is a widely used oral antidiabetic agent and is considered first-line therapy for type 2 diabetes mellitus (T2DM). However, in pregnancy, insulin has traditionally remained the standard treatment due to its proven safety and long-standing clinical experience. Since metformin can cross the placenta [11,12], concerns about potential fetal effects have limited its routine use during pregnancy, especially in early gestation.

Evidence from studies in women with GDM suggests that metformin may offer advantages over insulin, such as lower maternal weight gain and reduced rates of neonatal hypoglycemia and macrosomia. However, approximately 23% of women treated with metformin monotherapy fail to achieve adequate glycemic control and require supplemental insulin. Furthermore, some trials have reported increased risk of preterm birth among

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metformin users [13–15]. While metformin may be a reasonable option for women who cannot tolerate or access insulin, it is not universally recommended—particularly in those at high risk for hypertensive disorders or intrauterine growth restriction [16,17].

Currently, the role of metformin in early pregnancy, especially among women with PDM, undiagnosed diabetes, or early GDM, remains uncertain. Although five randomized controlled trials (RCTs) have explored this issue, variations in study design and outcomes have led to inconsistent conclusions regarding its efficacy and safety [18–22]. In our recent meta-analysis of these five RCTs, we found that metformin use before 24 weeks of gestation - either as monotherapy or in combination with insulin - was associated with significantly lower risks of gestational hypertension, stillbirth, LGA, birth weight ≥ 4000 g, and NICU admissions. These findings suggest that metformin may offer additional metabolic and vascular benefits beyond glycemic control. However, an increased risk of SGA was also observed, highlighting the need for careful individual risk assessment. Moreover, one of the included RCTs defined a primary composite outcome that combined directionally opposite outcomes such as LGA and SGA[22], which may have diluted the treatment effect and contributed to the non-significant result in the primary endpoint, thereby obscuring the potential benefits of metformin.

Moreover, most existing studies lack adequate representation of Asian populations, limiting the generalizability of current evidence. Therefore, this randomized, double-blind, multicenter clinical trial is designed to evaluate whether initiating metformin in combination with insulin before 20 weeks of gestation can improve maternal and neonatal outcomes compared to insulin monotherapy. The study aims to fill current evidence gaps and clarify the potential role of metformin in the early management of diabetes during pregnancy.

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3. Study Objective

3.1 Primary objective

The primary objective of this study is to evaluate whether the combination of metformin and insulin improves fetal and neonatal outcomes compared to insulin monotherapy in pregnant women diagnosed before 20 weeks of gestation with PDM, previously undiagnosed diabetes mellitus, or early GDM.

3.2 Secondary objectives

The secondary objectives of the study are as follows:

- To evaluate each individual fetal and neonatal outcome that comprises the primary composite endpoint.
- To assess maternal glycemic control and insulin requirements throughout the course of pregnancy.
- To evaluate maternal outcomes associated with pregnancy and delivery, including but not limited to preeclampsia, cesarean delivery, and maternal weight gain.
- To assess the safety and tolerability of metformin use during pregnancy, including adverse maternal and fetal events.
- To compare additional neonatal outcomes not included in the primary composite endpoint, such as neonatal hypoglycemia, respiratory distress, and need for NICU admission.

4. Study Design

4.1 General Design

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter clinical trial designed to evaluate the efficacy and safety of metformin in combination with insulin, compared to insulin monotherapy, for the treatment of pregnant women with PDM, previously undiagnosed diabetes mellitus, or early GDM, diagnosed before 20 weeks of

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gestation.

Participants will be randomized between 10 weeks 0 days and 20 weeks 6 days of gestation and followed through pregnancy, delivery, and up to 30 days postpartum. Neonatal outcomes will be followed until 30 days of age.

The trial aims to determine whether the addition of metformin to insulin therapy reduces the incidence of a composite adverse neonatal outcome, and to evaluate maternal metabolic, obstetric, and safety outcomes.

4.1.1 Randomization and Blinding

Eligible participants will be randomized in a 1:1 ratio to receive either metformin or matching placebo, in addition to standard insulin therapy. Randomization will be stratified by study site and by baseline gestational age/timing of diabetes diagnosis. A permuted block randomization scheme will be used and centrally managed by an independent data coordinating center. The randomization sequence will be generated by an independent statistician and implemented through a secure, web-based electronic data management system.

The trial will be conducted under double-blind conditions. Study participants, investigators, care providers, and outcome assessors will be blinded to treatment allocation. In the event of a medical emergency, unblinding may be performed through a predefined emergency unblinding procedure via the data system by authorized personnel only.

4.1.2 Informed Consent

Prior to participation, written informed consent will be obtained from all participants. Each site will use a site-specific consent form based on the standardized project-level consent template. Informed consent must be approved by the Institutional Review Board (IRB) at each participating center. Participants will receive a signed copy of the consent form for their records.

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4.2 Study Outcomes

Primary Study Outcomes

- LGA: Infant birthweight >90th percentile for gestational age and sex, based on standardized growth charts.

Secondary Outcomes

- Hypertensive disorders of pregnancy: Includes gestational hypertension, preeclampsia, and eclampsia, diagnosed according to American college of obstetricians and gynecologists (ACOG) criteria.
- Preeclampsia: New-onset hypertension (systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg) after 20 weeks' gestation with proteinuria (≥300 mg/24h or protein/creatinine ratio ≥0.3), or other systemic signs (e.g., thrombocytopenia, impaired liver function).
- Cesarean section: Delivery by operative abdominal route.
- Maternal glycemic control: Assessed by fasting and postprandial blood glucose logs and/or HbA1c at predefined intervals during pregnancy.
- Maternal hypoglycemia: Capillary blood glucose <60 mg/dL, regardless of symptoms.
- Gestational weight gain: Total weight gain from randomization to delivery, adjusted for gestational age, and compared to ACOG guidelines [23].
- Miscarriage: Fetal loss before 20 weeks of gestation.
- Stillbirth: Intrauterine fetal death occurring at ≥20 weeks of gestation.
- Neonatal death: Death of a liveborn infant before 28 completed days of life.
- Preterm birth: Delivery before 37 weeks 0 days of gestation.
- SGA: Birthweight <10th percentile for gestational age and sex, based on standardized growth charts.

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- Major congenital malformations: Structural anomalies diagnosed prenatally or postnatally, confirmed by clinical examination or imaging, and classified as major based on centers for disease control and prevention (CDC) definitions [24, 25].
- Cord blood C-peptide >90th percentile: Measured from umbilical cord blood at delivery; elevated levels may reflect fetal hyperinsulinemia.
- Neonatal hypoglycemia: Capillary blood glucose (CBG) < 40 mg/dL within the first 24 hours of life, or any hypoglycemia requiring clinical intervention (e.g., intravenous glucose, glucose gel).
- Neonatal hyperbilirubinemia: Total serum bilirubin exceeding age-specific treatment threshold requiring phototherapy, per Taiwan society of neonatology guidelines [26].
- RDS: Clinical diagnosis requiring supplemental oxygen and/or mechanical ventilation with compatible chest imaging in the first 72 hours of life.
- NICU admission: Admission to a neonatal intensive care unit for >24 hours within the first 72 hours of life.

5. Subject Selection and Withdrawal

5.1 Inclusion Criteria

5.1.1 Maternal age 18-50 years at enrollment.

5.1.2 Women with diabetes mellitus during early pregnancy include PDM, undiagnosed diabetes mellitus, and early GDM.

5.1.2.1 PDM is defined as DM diagnosed before pregnancy.

5.1.2.2 Undiagnosed diabetes mellitus is defined when DM is first diagnosed during pregnancy (usually at the first prenatal visit) either FPG ≥126 mg/dL, or HbA1C ≥6.5%.

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5.1.2.3 Early GDM is defined when GDM was diagnosed before 20 weeks of GA by the one-step approach and two-step approach.

- The one-step approach:

  75 gm OGTT with at least one abnormal value: FPG ≥ 92 mg/dL, 1 hour ≥ 180 mg/dL, or 2-hour ≥ 153 mg/dL

- The two-step approach:

  Step 1: 50g glucose challenge test (non-fasting), and if blood glucose is ≥140 mg/dL after 1 hour, proceed to Step 2.

  Step 2: 100g OGTT, measuring fasting, 1-hour, 2-hour, and 3-hour blood glucose; diagnose GDM if two or more of the following thresholds are met: fasting ≥95 mg/dL, 1-hour ≥180 mg/dL, 2-hour ≥155 mg/dL, 3-hour ≥140 mg/dL.

5.1.3 Gestational age at randomization between 10 weeks 0 days and 23 weeks 6 days by menstrual dating confirmed by ultrasound or ultrasound alone.

5.1.4 Singleton fetus without known or suspected anomalies before randomization.

5.1.5 Willingness to follow the study protocol to control PDM, undiagnosed or early GDM.

5.1.6 Informed written consent.

5.2 Exclusion Criteria

5.2.1 Type 1 diabetes.

5.2.2 Multiple gestation.

5.2.3 Suspected or known fetal structural or chromosomal abnormality before randomization.

5.2.4 Known medical contraindications to metformin (history of lactic acidosis).

5.2.5 Known intolerance to metformin.

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5.2.6 Known pre-existing renal disease (creatinine > 1.5 mg/dL).

5.2.7 Acute liver disease or known liver abnormalities (acute viral hepatitis, AST/ALT > 2x ULN).

5.2.8 Known medical conditions that predispose a woman to GI distress (Crohn's disease, ulcerative colitis, irritable bowel syndrome (IBS), celiac disease).

5.2.9 Current or past history of alcohol abuse.

5.2.10 Current or past history of smoking.

5.2.11 Participation in another study could affect the primary outcome.

5.2.12 Unwilling or unable to follow the study protocol.

5.2.13 Other significant chronic medical or psychiatric illnesses that, in the investigator's opinion, would prevent participation in the study.

5.3 Study Gestational Age Determination

Study gestational age is used to define eligibility criteria and to calculate the Estimated Date of Confinement (EDC), commonly referred to as the estimated due date. The EDC is determined based on a reliable last menstrual period (LMP) or the earliest available dating ultrasound. Gestational age must be established prior to randomization, and participants must be between 10 weeks 0 days and 20 weeks 6 days of gestation, as determined by standardized dating methods.

The following algorithm will be used to determine Study Gestational Age:

5.3.1 Establish whether the participant has a reliable LMP date. A sure LMP date refers to a date that the participant confidently recalls, with regular menstrual cycles and no hormonal contraceptive use prior to conception.

5.3.2 If the LMP is considered reliable, Study gestational age will be determined by comparing:

- The gestational age calculated from the LMP, and

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- The earliest dating ultrasound performed before 22 weeks 6 days of gestation.

If the ultrasound agrees with the LMP within the ranges specified in the table below, the LMP-based gestational age will be used:

Gestational age by LMP at first ultrasound	Ultrasound agreement with LMP
≤ 13 weeks 6 days	±5 days
14 weeks 0 days to 22 weeks 6 days	±7 days

If the difference is outside the acceptable range, then the gestational age will be based on the ultrasound measurement.

However, the subject must still meet the inclusion criterion of being ≤ 20 weeks 6 days of gestation based on the ultrasound. If this threshold is exceeded, the subject will be ineligible for enrollment.

5.3.3 If the LMP is unreliable or unknown, the Study Gestational Age will be based on the first dating ultrasound, which must be performed on or before 20 weeks 6 days of gestation.

5.3.4 For pregnancies conceived via assisted reproductive technology (ART), the gestational age will be calculated based on the embryo transfer date and embryo age.

5.4 Early Study Agent Discontinuation or Study Withdrawal of Subjects

Subjects may choose to stop the double-blind study agent or withdraw from the study at any time and for any reason. If the subject stops the study drug after titration to the therapeutic dose, then the subject may be restarted on the study medication at the discretion of the PI unless the patient meets one of the specific stopping rules below. If a subject permanently discontinues the study agent, the site will still collect the blood specimens, fetal measurements, and outcome data. In rare instances, a subject may be withdrawn from the study if, in the opinion of the investigator, it is not in the subject's best interest to continue study participation.

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Specific rules to stop the study agent for an individual subject:

- Maternal side effects that cannot be managed with oral medication. Subjects may experience nausea, vomiting, or diarrhea as a result of the study agent. It will be challenging to distinguish symptoms of pregnancy from the side effects of metformin. Women will be instructed to take the study agent with meals to reduce the potential for side effects. Those who experience gastrointestinal (GI) symptoms will be offered routine medication management (anti-emetics). If the subject is unable to tolerate the study agent after 21 days on one pill twice a day or after 21 days on two pills twice a day, she will discontinue the study agent. However, study participation and data collection will continue until study completion.
- Maternal or fetal complications believed to be related to the study agent.
- The study agent may also be discontinued in cases of unmanageable, irreversible, or serious adverse events (SAEs).
- The study agent will be continued from randomization until delivery, even if the subject requires home bed rest or hospitalization for medical or obstetrical reasons, unless medical contraindications develop (e.g., acute renal insufficiency defined as creatinine > 1.5 mg/dL or liver disease defined as AST/ALT > 3x ULN).

Data collection and follow-up for subjects who discontinue the study agent:

Subjects who discontinue the double-blind study agent will continue to have maternal and neonatal data collected through study completion. Every effort will be made to collect the blood specimens, neonatal measurements, and maternal and neonatal outcome data on all randomized subjects, even if they discontinue the study agent or deliver at a non-study hospital.

6. Analysis Plan

All statistical analyses will be performed using the R statistical software. All tests will be

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two-sided, and a p-value of <0.05 will be considered statistically significant unless otherwise specified. The main analysis will follow the ITT principle, with a PP analysis conducted as a sensitivity analysis.

6.1 Baseline Characteristics and Group Comparability

Descriptive statistics will be used to summarize baseline characteristics, including means (± standard deviations) for continuous variables and proportions for categorical variables. Between-group comparisons will be conducted to assess balance and potential confounding.

6.2 Primary Outcome

The primary endpoint is the incidence of LGA. This is a binary endpoint.

The primary analysis will compare the proportion of subjects experiencing the composite outcome between the metformin plus insulin group and the insulin monotherapy group using a log-binomial model to estimate the RR and its 95% CI. The study is powered to detect a reduction in the event rate from 30% in the control group to 21% in the treatment group (odds ratio (OR) = 0.71) with 80% power, at a two-sided significance level of 0.05.

6.3 Secondary Outcomes

- Binary outcomes (e.g., preeclampsia, cesarean delivery, miscarriage, neonatal death, SGA) will be analyzed with estimation of RR and 95% CI.
- Continuous outcomes (e.g., HbA1c, insulin dose, birth weight, gestational weight gain) will be summarized using means, medians and standard deviations. Between-group differences will be assessed using mean differences with 95% CIs and tested using independent t-tests or non-parametric alternatives if normality assumptions are not met.

6.4 Sensitivity and Subgroup Analyses

To evaluate the robustness of the primary findings, multiple sensitivity analyses will be conducted. These analyses will adjust for key baseline covariates that may influence maternal

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or neonatal outcomes, including:

- Timing of diabetes diagnosis (PDM vs. undiagnosed diabetes vs. early GDM)
- Time of treatment initiation
- Pre-pregnancy weight
- Polycystic ovary syndrome (PCOS) status
- Baseline glycemic control (e.g., HbA1c at enrollment)

The primary analysis will also be repeated using a PP population, defined as participants who completed the study intervention as assigned with no major protocol deviations. Comparison of ITT and PP results will allow assessment of the impact of treatment adherence on outcomes.

In addition, prespecified subgroup analyses will be conducted to explore potential effect modification by the following baseline maternal characteristics:

- Pre-existing renal disease
- Chronic hypertension
- Body Mass Index (BMI) categories are defined according to the Ministry of Health and Welfare (MOHW), Taiwan, as follows: <18.5-23.9, 224.0-26.9, 27-29.9, and ≥30 kg/m
- Maternal age at enrollment (<35 vs. ≥35 years)
- PCOS status
- Timing of metformin initiation (10-14 weeks vs. 15-20 weeks gestation)

These subgroup analyses will be performed by including interaction terms between treatment allocation and each covariate in the regression model. A p-value <0.10 for interaction will be considered suggestive of heterogeneity in treatment effect and will be interpreted cautiously.

All sensitivity and subgroup analyses will be considered supportive and interpreted in the

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context of the overall trial results.

6.5 Per-Protocol Population Definition

The PP population will include all randomized participants who:

- Received the assigned intervention (metformin or placebo) for at least 21 consecutive days at the target dose.
- Did not discontinue treatment for non-clinical reasons.
- Had no major protocol violations, such as: Incorrect eligibility (e.g., GA >20+6 at randomization, multiple gestation), unblinding or use of non-study diabetes medications and missing key baseline or outcome data.

6.6 Safety Analysis

Adverse events (AEs) and serious adverse events (SAEs) will be summarized by treatment group using counts and percentages. Between-group comparisons will be conducted to evaluate differences in event rates across groups.

6.7 Handling of Missing Data

The extent and patterns of missing data will be assessed and reported. If the amount of missing data is minimal (<5%), a complete case analysis may be performed as the primary approach. For variables with a greater degree of missingness, multiple imputation will be used to address the missing data.

6.8 Sample Size Calculation

The study is designed to detect a statistically significant difference in the incidence of LGA between the metformin plus insulin group and the insulin monotherapy group. Based on prior studies and pooled data from our meta-analysis, the expected event rate in the control group (insulin only) is estimated at 30%, while the event rate in the metformin combined with insulin group is expected to be 21%, corresponding to a OR of 0.71, with 80% power and a two-sided significance level of 0.05.

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Using these assumptions, a total of 638 participants (319 per group) are required. This calculation includes a 10% allowance for dropout or loss to follow-up. This sample size provides sufficient power to detect a clinically meaningful reduction in LGA incidence with the use of metformin during early pregnancy.

7. Safety assessment

Safety oversight will be conducted under the direction of the Data and Safety Monitoring Board (DSMB), which includes study investigators and representatives of the sponsor. The Safety Monitoring Committee (SMC) will evaluate safety-related data on an ongoing basis, including but not limited to AEs, SAEs, physical examinations, vital signs, and relevant laboratory parameters throughout the study.

7.1 Definition

An AE is any untoward medical occurrence in a participant who has received study treatment, whether or not it is considered related to the treatment.

A SAE is defined as any event that results in one or more of the following outcomes:

- Death
- Life-threatening condition
- Hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Any event deemed medically significant by the investigator

7.2 Recording of Adverse Events

All AEs reported by the participant or observed by the investigator will be recorded in the case report form (CRF), regardless of their suspected relationship to study treatment. Each AE will be assessed for:

- Severity (mild, moderate, severe)

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- Duration
- Outcome
- Relationship to study drug (not related, possibly related, probably related, definitely related)

7.3 Reporting of Serious Adverse Events

All SAEs must be reported to the sponsor and regulatory authorities within 24 hours of site awareness. The investigator will provide a detailed written report, including event description, onset and resolution dates, treatment required, and investigator assessment of causality.

All SAEs must be reported to the sponsor and regulatory authorities within 24 hours of site awareness. The investigator will provide a detailed written report, including event description, onset and resolution dates, treatment required, and investigator assessment of causality.

7.4 Stopping Rules

The DSMB may recommend early termination of the trial in part or in full if:

- An excess of SAEs is observed in one treatment arm, particularly those related to maternal or neonatal outcomes
- A clear benefit or harm is established based on interim safety and efficacy data
- New information becomes available that significantly affects the risk–benefit assessment

7.5 Medical Monitoring

A qualified medical monitor will oversee the clinical safety of the trial and review all reported SAEs. The medical monitor will:

- Ensure timely evaluation of safety events
- Communicate with investigators and sponsor regarding significant concerns

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- Participate in DSMB reviews if needed
- Maintain confidentiality unless unblinding is necessary for safety

7.6 Unblinded Medical Monitor

In case of safety concerns requiring unblinded assessment, an unblinded medical monitor (independent from the blinded study team) will be designated. This individual will have access to treatment allocation and can evaluate whether an AE or SAE may be related to study drug without compromising study blinding for the rest of the team.

7.7 Independent Data Safety Monitoring Board

An independent DSMB will be established to monitor participant safety and review unblinded data periodically. The DSMB will consist of experts in obstetrics, neonatology, biostatistics, and clinical trials. Responsibilities include:

- Reviewing cumulative safety and efficacy data
- Recommending trial continuation, modification, or termination
- Ensuring participant safety without bias

The DSMB will operate under a separate DSMB charter, outlining its scope, frequency of review, and communication procedures.

Reference

1. Magliano DJ, Boyko EJ. In IDF DIABETES ATLAS, 10th ed. Brussels, 2021
2. Lin SY, Wu YL, Kuo CH, et al. Trends in epidemiology of hyperglycemia in pregnancy in Taiwan, 2008-2017. Front Endocrinol (Lausanne) 2022;13:1041066
3. Egan AM, Dow ML, Vella A: A Review of the Pathophysiology and Management of Diabetes in Pregnancy. Mayo Clin Proc 2020;95:2734-2746
4. Battarbee AN, Venkatesh KK, Aliaga S, Boggess KA: The association of pregestational and gestational diabetes with severe neonatal morbidity and mortality. J Perinatol 2020;40:232-239

doi:10.6342/NTU202501547

5. Ye W, Luo C, Huang J, Li C, Liu Z, Liu F: Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. BMJ 2022;377:e067946
6. Lai FY, Johnson JA, Dover D, Kaul P: Outcomes of singleton and twin pregnancies complicated by pre-existing diabetes and gestational diabetes: A population-based study in Alberta, Canada, 2005-11. J Diabetes 2016;8:45-55
7. Battarbee AN, Venkatesh KK, Aliaga S, Boggess KA: The association of pregestational and gestational diabetes with severe neonatal morbidity and mortality. J Perinatol 2020;40:232-239
8. Jovanovic L, Liang Y, Weng W, Hamilton M, Chen L, Wintfeld N: Trends in the incidence of diabetes, its clinical sequelae, and associated costs in pregnancy. Diabetes Metab Res Rev 2015;31:707-716
9. Alexopoulos AS, Blair R, Peters AL: Management of Preexising Diabetes in Pregnancy: A Review. JAMA 2019;321:1811-1819
10. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol 2018;131:e49-e64
11. Kuo CH, Li HY: Diagnostic Strategies for Gestational Diabetes Mellitus: Review of Current Evidence. Curr Diab Rep 2019;19:155
12. Vanky E, Zahlsen K, Spigset O, Carlsen SM: Placental passage of metformin in women with polycystic ovary syndrome. Fertility and sterility 2005;83:1575-1578
13. Balsells M, Garcia-Patterson A, Sola I, Roque M, Gich I, Corcoy R: Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ 2015;350:h102
14. Tarry-Adkins JL, Aiken CE, Ozanne SE: Comparative impact of pharmacological treatments for gestational diabetes on neonatal anthropometry independent of maternal glycaemic control: A systematic review and meta-analysis. PLoS Med 2020;17:e1003126

doi:10.6342/NTU202501547

15. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP: Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med 2008;358:2003-2015

16. Barbour LA, Scifres C, Valent AM, Friedman JE, Buchanan TA, Coustan D, Aagaard K, Thornburg KL, Catalano PM, Galan HL, Hay WW, Jr., Frias AE, Shankar K, Simmons RA, Moses RG, Sacks DA, Loeken MR: A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes. American journal of obstetrics and gynecology 2018;219:367.e361-367

17. Barbour LA, Feig DS: Metformin for Gestational Diabetes Mellitus: Progeny, Perspective, and a Personalized Approach. Diabetes Care 2019;42:396-399

18. M. Ashley Hickman, Ryan McBride, Kim A. Boggess, Robert Strauss: Metformin Compared with Insulin in the Treatment of Pregnant Women with Overt Diabetes: A Randomized Controlled Trial. Am J Perinatol 2013;30:483–490

19. Jerrie SR, Rose G, Claudia P, Maria H, Sean CB, Susan R: A pilot randomized, controlled trial of metformin versus Insulin in women with type 2 diabetes mellitus during pregnancy. Am J Perinatol 2015;32:163-170

20. Jahan AA, Nasim K, Sidra Z, Syed SA, Anjum AH: Metformin treatment in type 2 diabetes in pregnancy: an active controlled, parallel-group, randomized, open label study in patients with type 2 diabetes in pregnancy. Journal of Diabetes Research 2015; 2015; pp 1-11

21. Denice SF, Lois ED, Bernard Z, J Johanna S, Elizabeth A, Edmond AR, I George , Eileen H, Anthony BA, Lorraine LL, David S, Jon F RB, Paul JK, Siobhan T, H David M, Simon YT, George T, Kellie EM, on behalf of the MiTy Collaborative Group: Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo controlled trial. Lancet Diabetes Endocrinol 2020; 8: 834-844

22. Kim AB, Arielle, Jerrie SR, Noelia Z, Ashley NB, Kacey E, Gladys AR, Gayle O,

doi:10.6342/NTU202501547

Celeste D, Mark BL, Kjersti MA, Kedra W, Christina S, Todd R, Wadia M, Amy Va, Sherri L, Laura Y, M. Alison M, Sonia T, Ashley B, Diane B: Metformin plus insulin for preexisting diabetes or gestational diabetes in early Pregnancy the MOMPOD randomized clinical trial. JAMA 2023;330(22):2182-2190

23. https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=1143&pid=6601&sid=6597
24. https://www.cdc.gov/birth-defects/about/types.html
25. https://archive.cdc.gov/www_cdc_gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-4/chapter4-1.html
26. http://www.tsn-neonatology.com/health/content.php?id=21

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Appendix 1. Schedule of Activities (SOA)

	Baseline	Treatment Period					Pollow-up Period	
Visit number	V1	V2	V3	V4	V5	V6	V7	V8
Week	10 weeks 0 days to 20 weeks 6 days	24 Weeks	28 Weeks	32 Weeks	36 Weeks	40 Weeks	Delivery	Postpartum Contact (4 weeks)
Informed Consent	X							
Eligibility Assessment	X							
Demographics and Medical History	X							
Physical Examination	X							
Randomization	X							
Dose Escalation		X	X	X	X			
Dispense Study Agent	X	X	X	X	X			
Collect Study Agent Count of Returned Bottles			X	X	X	X		
Record Daily Insulin Dosing	X	X	X	X	X	X	X	
Ultrasound for Fetal Growth and Anomalies	X	X	X	X	X	X		
Fetal Monitoring (NST/BPP)[1]			X	X	X	X		
Maternal Height, Weight, BMI, BP	X	X	X	X	X	X		
Electrocardiogram (ECG)	X							
Blood Chemistry Tests[2]	X	X		X		X		
Fasting Blood Glucose	X	X	X	X	X	X	X	X

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Glycated Albumin	X	X	X	X	X	X	X	X
HbA1c	X	X		X		X		
SMBG[3]	X (Training)	Daily	Daily	Daily	Daily	Daily	Daily	
Urinalysis and UACR	X	X	X	X	X	X	X	X
Eye Examinations[4, 5, 6, 7]	X							
Foot examination[6]	X							
Maternal AE		X	X	X	X	X	X	X
Neonatal AE							X	X
Neonatal Adiposity Measurement							X	
Cord Blood C-peptide Collection							X	
Postpartum Follow-up[8]							X	X

1 Fetal monitoring includes both non-stress testing (NST) and biophysical profile (BPP).
2 Blood chemistry tests include lipid profile (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG)) and serum creatinine.
3 Self-monitoring of blood glucose (SMBG) training is conducted at baseline. Daily logs should include fasting, postprandial (after breakfast, lunch, and dinner), and bedtime glucose values.
4 Eye examination: Visual acuity, intraocular pressure, and optical coherence tomography (OCT) will be performed.
5 For participants with pre-existing diabetic retinopathy, ophthalmologic evaluation will be repeated once per trimester or as recommended by the ophthalmologist.
6 Eye and foot examinations are not required for participants with early GDM.
7 Participants with diabetic retinopathy should be monitored once per trimester.
8 Postpartum Follow-up include weight, BP, glucose, etc.

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Appendix 2. ACOG Diagnostic Criteria for Hypertensive Disorders of Pregnancy

Category	Diagnostic Criteria
Gestational Hypertension	New-onset hypertension after 20 weeks of gestation (systolic ≥140 mmHg or diastolic ≥90 mmHg on two occasions at least 4 hours apart), without proteinuria or severe features.
Preeclampsia	Hypertension after 20 weeks of gestation with one or more of the following: 1. Proteinuria: ≥300 mg in 24-hour urine, or protein/creatinine ratio ≥0.3, or dipstick ≥1+ (if quantitative not available). 2. In absence of proteinuria: any of the following severe features – • Thrombocytopenia (platelets <100,000/μL) • Elevated liver transaminases (AST or ALT twice normal) • Serum creatinine >1.1 mg/dL or doubling of baseline • Pulmonary edema • New-onset headache or visual disturbances
Preeclampsia with Severe Features	Preeclampsia plus any of the following severe features: 1. Systolic BP ≥160 mmHg or Diastolic BP ≥110 mmHg (confirmed twice) 2. Platelet count <100,000/μL 3. Elevated liver enzymes with right upper quadrant or epigastric pain 4. Progressive renal insufficiency 5. Pulmonary edema 6. Persistent headache or visual symptoms
Eclampsia	The onset of seizures in a woman with preeclampsia, with no other attributable neurological cause.
Chronic Hypertension	Hypertension diagnosed before 20 weeks of gestation, or known prior to pregnancy, or that persists after delivery.
Chronic Hypertension with Superimposed Preeclampsia	A woman with chronic hypertension who develops any of the following: 1. New-onset proteinuria 2. Sudden increase in BP or proteinuria 3. Development of severe features 4. Organ dysfunction attributable to preeclampsia

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Appendix 3. Comparison of BMI Classifications and Gestational Weight Gain Recommendations

BMI Category	MOHW Pre-pregnancy BMI (kg/m^2)	ACOG Pre-pregnancy BMI (kg/m^2)	Recommended Total Weight Gain (kg)
Underweight	< 18.5	< 18.5	12.5 – 18
Normal weight	18.5 - 23.9	18.5 - 24.9	11.5 – 16
Overweight	24.0 - 26.9	25.0 - 29.9	7 – 11.5
Mild obesity	27.0 - 29.9	-	-
Moderate to severe obesity	≥ 30.0	≥ 30.0	5 – 9

*BMI categories defined by MOHW (Taiwan) reflect higher cardiometabolic risk in Asian populations. Gestational weight gain recommendations follow ACOG guidelines, which are based on WHO BMI categories.

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