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Oral Glucose-Lowering Agents vs Insulin for Gestational Diabetes
A Randomized Clinical Trial

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IMPORTANCE Metformin and glyburide monotherapy are used as alternatives to insulin in managing gestational diabetes. Whether a sequential strategy of these oral agents results in noninferior perinatal outcomes compared with insulin alone is unknown.

OBJECTIVE To test whether a treatment strategy of oral glucose-lowering agents is noninferior to insulin for prevention of large-for-gestational-age infants.

DESIGN, SETTING, AND PARTICIPANTS Randomized, open-label noninferiority trial conducted at 25 Dutch centers from June 2016 to November 2022 with follow-up completed in May 2023. The study enrolled 820 individuals with gestational diabetes and singleton pregnancies between 16 and 34 weeks of gestation who had insufficient glycemic control after 2 weeks of dietary changes (defined as fasting glucose >95 mg/dL [>5.3 mmol/L], 1-hour postprandial glucose >140 mg/dL [>7.8 mmol/L], or 2-hour postprandial glucose >120 mg/dL [>6.7 mmol/L], measured by capillary glucose self-testing).

INTERVENTIONS Participants were randomly assigned to receive metformin (initiated at a dose of 500 mg once daily and increased every 3 days to 1000 mg twice daily or highest level tolerated; n = 409) or insulin (prescribed according to local practice; n = 411). Glyburide was added to metformin, and then insulin substituted for glyburide, if needed, to achieve glucose targets.

MAIN OUTCOMES AND MEASURES The primary outcome was the between-group difference in the percentage of infants born large for gestational age (birth weight >90th percentile based on gestational age and sex). Secondary outcomes included maternal hypoglycemia, cesarean delivery, pregnancy-induced hypertension, preeclampsia, maternal weight gain, preterm delivery, birth injury, neonatal hypoglycemia, neonatal hyperbilirubinemia, and neonatal intensive care unit admission.

RESULTS Among 820 participants, the mean age was 33.2 (SD, 4.7) years). In participants randomized to oral agents, 79% (n = 320) maintained glycemic control without insulin. With oral agents, 23.9% of infants (n = 97) were large for gestational age vs 19.9% (n = 79) with insulin (absolute risk difference, 4.0%; 95% CI, −1.7% to 9.8%; *P* = .09 for noninferiority), with the confidence interval of the risk difference exceeding the absolute noninferiority margin of 8%. Maternal hypoglycemia was reported in 20.9% with oral glucose-lowering agents and 10.9% with insulin (absolute risk difference, 10.0%; 95% CI, 3.7%-21.2%). All other secondary outcomes did not differ between groups.

CONCLUSIONS AND RELEVANCE Treatment of gestational diabetes with metformin and additional glyburide, if needed, did not meet criteria for noninferiority compared with insulin with respect to the proportion of infants born large for gestational age.

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Visual Abstract

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Supplemental content

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Insulin has conventionally been used as the primary pharmacological agent for treatment of gestational diabetes and has been demonstrated to improve perinatal outcomes in persons with gestational diabetes who fail to maintain adequate glucose control with diet alone.[1,2] In the last 2 decades, oral glucose-lowering agents such as metformin and glyburide (glibenclamide) have emerged as potential alternatives to insulin treatment for gestational diabetes and preexisting diabetes as they are easier to administer, less costly, and have better acceptance among patients.[3-5] The American Diabetes Association cautions against the use of metformin and glyburide as first-line treatment agents for gestational diabetes because of concerns that these agents cross the placenta and have limited data on long-term safety in offspring.[6,7] Nonetheless, a study published in 2022 reported that 69% of pregnant individuals with gestational diabetes in the US receive either metformin or glyburide.[8] The National Institute for Health and Care Excellence in the UK recommends metformin as a primary pharmacological agent for gestational diabetes, and a 2023 study found that 59% of pregnant individuals with gestational diabetes in the UK initiate metformin when pharmacological treatment is needed.[9]

Treatment satisfaction is higher for metformin than insulin for gestational diabetes, although supplemental insulin is frequently needed, and early treatment with metformin does not reduce insulin initiation.[10,11] Glyburide monotherapy has demonstrated clinical efficacy comparable with insulin, with maternal hypoglycemia as the most frequently reported adverse effect.[12,13] A sequential combination of glucose-lowering agents could reduce the need for supplemental insulin while potentially increasing patient satisfaction and reducing costs.

In this randomized, open-label noninferiority trial, we evaluated whether a strategy of starting metformin and adding, if needed, glyburide and then insulin was noninferior to initiating insulin treatment for prevention of large-for-gestational-age infants.

Key Points

Question In gestational diabetes, is a sequential oral glucose-lowering medication strategy of metformin and additional glyburide, if needed, noninferior to insulin treatment for prevention of large-for-gestational-age infants?

Findings Among 820 participants randomized to oral glucose-lowering medication, 23.9% of infants were large for gestational age compared with 19.9% randomized to insulin, a difference that did not meet the prespecified criteria for noninferiority.

Meaning Treatment of gestational diabetes with sequential oral glucose-lowering medication did not meet criteria for noninferiority compared with insulin with respect to the proportion of infants born large for gestational age.

Methods

Study Design

The trial was conducted at 25 centers in the Netherlands. The ethics review board of the University Medical Center Utrecht approved the study. All participants provided written informed consent. The trial protocol has been published previously[14] and is available in Supplement 1. Trial oversight and monitoring were provided by a trial steering committee. An independent data and safety monitoring board provided oversight. The Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials was followed.

Patients

Pregnant individuals who did not reach glycemic control (defined as fasting glucose >95 mg/dL [>5.3 mmol/L], 1-hour postprandial glucose >140 mg/dL [>7.8 mmol/L], or 2-hour postprandial glucose >120 mg/dL [>6.7 mmol/L], measured by capillary glucose self-testing) after approximately 2 weeks of dietary treatment were eligible if they were older than 18 years and between 16 and 34 weeks of gestation, had a singleton pregnancy, were diagnosed with gestational diabetes per local guidelines, were able to understand Dutch or English, and provided written informed consent. Individuals with prepregnancy diabetes, severe psychiatric or medical comorbidity, serious liver disease or kidney failure, or pregnant with a fetus affected by major congenital anomalies and/or known chromosomal abnormalities were not eligible for participation.

Trial Procedures

Participants were randomly assigned in a 1:1 ratio to initiate either metformin or insulin. Randomization was performed by a central computerized system using random permuted blocks of sizes 4, 6, and 8 and was not stratified.

Metformin was initiated at a dose of 500 mg once daily and increased every 3 days to 1000 mg twice daily or the highest level tolerated by the participant. If glycemic control was not achieved, glyburide, 2.5 mg, was added 30 to 60 minutes before each meal. A dose increase up to a maximum of 5 mg 3 times per day was possible. If glycemic control was not achieved with metformin and glyburide at maximum tolerated doses, glyburide was discontinued, insulin was initiated, and the maximum dose of metformin was continued. Insulin was prescribed according to local practice. The full treatment strategy for the intervention and control groups has been published previously.[14]

Outcomes

The primary outcome measure was infants born large for gestational age, defined as birth weight adjusted for gestational age and sex above the 90th percentile using the latest Dutch Perinatal Registry birth weight reference chart.[15] Secondary outcomes (evaluated for superiority) included maternal hypoglycemia (glucose <70 mg/dL [<3.9 mmol/L]), symptomatic hypoglycemia, or severe hypoglycemia prompting the need for help from another person), primary or secondary cesarean delivery, pregnancy-induced hypertension, preeclampsia, maternal weight gain, preterm delivery (<37 weeks of gestation), birth injury, neonatal hypoglycemia (moderate: serum glucose

<47 mg/dL [<2.6 mmol/L]; severe: serum glucose <36 mg/dL [<2.0 mmol/L]), neonatal hyperbilirubinemia requiring phototherapy, and neonatal intensive care unit admission.

Additional exploratory outcomes included birth weight, birth weight above the 95th and 97th percentiles, gestational age at delivery, time from randomization to birth, sex, 5-minute Apgar score below 7 or below 4, small for gestational age, stillbirth, neonatal death, congenital defect/anomaly, umbilical artery pH level, need for respiratory support over 24 hours, culture-proven sepsis, and intravenous glucose therapy. At 36 weeks of gestation, patient satisfaction was assessed using 3 items from the Diabetes Treatment Satisfaction Questionnaire ("satisfaction with the current treatment," "Would you recommend the current treatment to somebody with the same diagnosis?," and "Are you satisfied to continue the current treatment?" rated on a scale from 0 [very dissatisfied] to 6 [very satisfied]), and health-related quality of life was assessed using the EuroQol 5-Dimension 5-Level (EQ-5D-5L) instrument.[16,17] Clinically important outcomes were also evaluated in individuals using metformin alone.

Race and ethnicity data were collected through participant self-report using prespecified categories.

Statistical Analysis

The analyses followed a prespecified statistical analysis plan (Supplement 2). The primary outcome was anticipated to occur in 20% of patients after treatment with insulin.[18] The noninferiority margin was prespecified at an 8% absolute risk difference based on the absolute risk difference for large for gestational age in 2 prior clinical trials.[19,20] With a 1-sided significance level of α = .025 and a power of 80%, the sample size was calculated at 393 patients in each group. Accounting for 3% loss to follow-up, 810 participants (405 per group) were needed. If the lower limit of the confidence interval of the absolute risk difference included or extended above the noninferiority margin of 8%, noninferiority was not proven. The Farrington-Manning test was used to calculate a *P* value for noninferiority.[21]

The primary outcome was estimated using the full analysis set containing the entire population as randomized to their treatment strategy irrespective of adherence, excluding participants who withdrew consent. The per-protocol population consisted of all participants randomized to the oral glucose-lowering agent strategy who received at least 1 dose of oral glucose-lowering treatment and continued to follow protocol. A comparison of the participants included vs not included in the per-protocol analysis is provided in eTable 1 in Supplement 3. No standardized mean differences that exceeded 0.10 SDs were found. Participants who had glyburide or insulin added according to protocol remained in the per-protocol analyses. Participants who were allocated to oral glucose-lowering agents but did not follow protocol (eg, those who were never prescribed glyburide and those who had insulin added to metformin) were excluded from the per-protocol analyses. Among participants allocated to insulin, only those who never took insulin were excluded from the per-protocol analyses. Results of both the full analysis set (primary analysis) and the per-protocol analysis were used for the noninferiority analysis of the primary outcome. The primary outcome was expected to be missing in less than 2%; therefore, use of multiple imputation was not planned. An "as-treated" table was constructed to show frequencies of effects and adverse effects for participants in whom metformin therapy was initiated. For dichotomous secondary outcomes, relative risks with 2-sided 95% CIs were estimated. Continuous secondary outcomes were analyzed using differences in means with 2-sided 95% CIs. Nonnormal continuous outcomes and ordinal data were described using medians with interquartile ranges. Kaplan-Meier curves were plotted to display the 2 treatment groups' time between randomization and delivery.

Prespecified subgroup analyses were performed for body mass index (calculated as weight in kilograms divided by height in meters squared) below or above 30, hemoglobin A_{1c} below or above the mean, age below or above the median, and gestational age before or after 28 weeks. Statistical testing for subgroup effects was done after testing for interaction. The subgroup analyses were prespecified and were considered exploratory.[14] As some of the initial subgroups such as infant sex and family history of diabetes were found to be clinically less relevant, we formally revised some of them in the final protocol and statistical analysis plan, prior to data lock and data analysis. An independent statistician conducted an interim safety review after 300 participants were enrolled, and inferential testing for efficacy was not conducted. SPSS version 28 (IBM) and SAS version 9.4 (SAS Institute Inc) were used for statistical analyses.

Results

Participant Characteristics

Between April 2017 and November 2022, among 1656 eligible participants, 820 provided informed consent and were randomized, 409 (50%) to the intervention group (oral glucose-lowering agents) and 411 (50%) to the control group (insulin) (**Figure 1**). Three participants allocated to oral glucose-lowering agents withdrew consent; none were lost to follow-up. Eight participants allocated to insulin withdrew consent, and 5 were lost to follow-up. At trial entry, the baseline characteristics of the remaining participants in the 2 groups (406 and 398) were similar (**Table 1**). The mean age was 33.2 (SD, 4.7) years, mean prepregnancy body mass index was 30.4 (SD, 6.2), and 35% of participants were nulliparous. Most participants (58%) were White.

Treatment Intensification and Crossover

Among participants allocated to oral glucose-lowering agents, 224 (55%) received metformin only and maintained euglycemia throughout the trial and 96 received additional glyburide without the need for insulin, for a total of 320 participants (79%) maintaining glycemic control using oral agents. Thirty-one participants (7.7%) allocated to oral agents required insulin, 15 participants (3.7%) used either metformin with insulin or insulin alone due to adverse effects, and 1 participant switched to metformin and insulin due to threatened preterm birth and administration of corticosteroids. These

367 participants (90%) were included in the per-protocol analyses. Participants not included in the per-protocol analyses (n = 39 [9.6%]) included 2 who never initiated metformin and started insulin instead, 27 who were not treated according to the study protocol and started insulin without starting glyburide for unknown reasons, and 1 who declined glyburide and was given insulin. In addition, in the last months of the trial, there were supply problems with glyburide. Therefore, 9 participants were not able to start glyburide and had to add insulin to metformin instead. They were omitted from the per-protocol analyses.

Among participants allocated to insulin, 1 started metformin and never used insulin and 1 declined pharmacological treatment altogether. These 2 participants (0.5%) were omitted from the per-protocol analyses.

Primary Outcome

Table 2 presents neonatal outcomes. Ninety-seven participants (23.9%) randomized to oral glucose-lowering agents had large-for-gestational-age infants compared with 79 (19.9%) of those randomized to insulin (absolute risk difference, 4.0%; 95% CI, −1.7% to 9.8%). The *P* value for noninferiority was .09. In the 764 participants included in the per-protocol analysis, noninferiority was also not reached (absolute risk difference, 3.4%; 95% CI, −2.5% to 9.3%; *P* = .06).

Secondary Outcomes

Neonatal secondary outcomes are summarized in Table 2 and maternal and obstetric outcomes are summarized in **Table 3**. Comparing participants randomized to oral agents vs insulin, there was more reported maternal hypoglycemia (20.9% vs 10.9%, respectively; absolute risk difference, 10.0%; 95% CI, 3.7%-21.2%) (Table 3). All other secondary outcomes did not differ between groups.

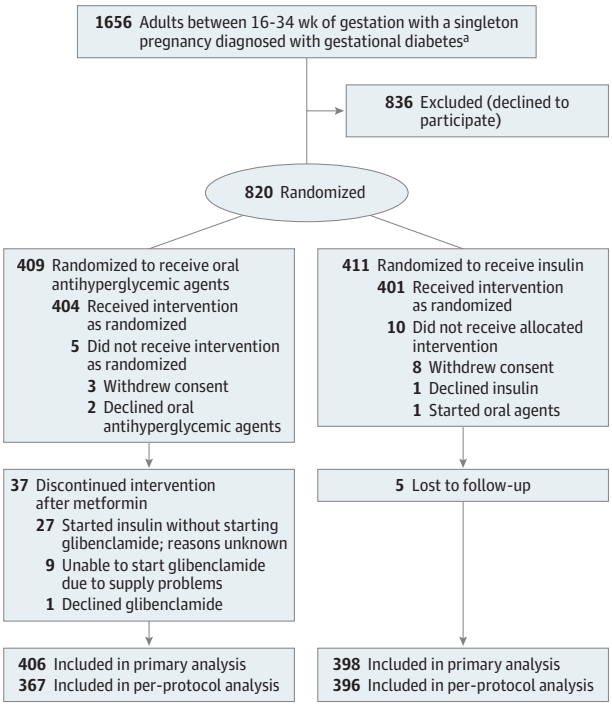
Adverse Effects

Questionnaires on drug-related adverse effects were returned by 493 participants (61%), 254 of 406 (63%) allocated to oral glucose-lowering agents and 239 of 398 (60%) allocated to insulin (Table 3). A higher proportion of participants allocated to oral agents reported adverse effects vs those allocated to insulin (78% vs 56%, respectively). Nausea (39% vs 13%) and diarrhea (39% vs 5%) were reported most frequently, followed by headaches (20% vs 13%) and vomiting (15% vs 1.7%).

Exploratory Analyses

Subgroup analyses showed no significant differences between groups (**Figure 2**). In the full analysis population, neonatal intravenous glucose therapy was administered more frequently to those randomized to oral agents (6.4% [26/407] vs 3.2% [13/403]). There were no other between-group differences in neonatal exploratory outcomes. In the exploratory analysis of participants treated with metformin alone without any additional glyburide or insulin, 19.7% had large-for-gestational-age infants (eTable 2 in Supplement 3). Patient satisfaction scores were similar between groups (median, 5 [IQR, 4-6] vs 5 [IQR, 4-6] on a 0- to 6-point scale), as shown in eTable 3 in Supplement 3.

Figure 1. Flow of Participants in the SUGAR-DIP Trial



[a]Screening logs were not kept.

However, participants allocated to oral agents would recommend their treatment to others with the same condition more often (median score, 5 [IQR 5-6] vs 4 [IQR, 3-6]) and would be more satisfied to continue their current treatment (median score, 5 [IQR, 4-6] vs 4 [IQR, 3-5]). In the per-protocol analyses, none of the secondary outcomes were significantly different between groups (eTables 4 and 5 in Supplement 3). Time between randomization and delivery did not differ between groups (eFigures 1 and 2 in Supplement 3).

Discussion

For pregnant individuals with gestational diabetes with an indication for pharmacological treatment, an initial treatment strategy of oral glucose-lowering agents was not noninferior to prevent large-for-gestational-age infants compared with insulin treatment, as the confidence interval of the risk difference exceeded the noninferiority margin of 8%.

These findings contribute to existing trial data regarding the use of metformin and glyburide as alternatives for insulin to manage gestational diabetes. Other trials of metformin and glyburide in pregnancy have shown favorable outcomes for oral medication compared with insulin; however, to our knowledge, none of these trials, except for a small feasibility trial, used a sequential combination of metformin and glyburide.[12,13,22,23] Although the current trial demonstrates that oral glucose-lowering agents are not noninferior to insulin, we also found that 21% of participants treated with metformin and glyburide needed insulin, either as hyperglycemic treatment

Table 1. Baseline Participant Characteristics

Characteristics	Oral glucose-lowering treatment (n = 406)	Insulin (n = 398)
Age, mean (SD), y	33.4 (4.7)	33.1 (4.6)
Prepregnancy body mass index, No. (%)[a,b]		
18 to ≤25	93 (22.9)	72 (18.1)
>25 to 30	111 (27.3)	110 (27.6)
>30	202 (49.8)	210 (52.8)
Mean (SD)	30.1 (6.1)	30.8 (6.4)
Body mass index at enrollment, mean (SD)[b]	33.7 (5.9)	32.9 (6.0)
Gestational age at randomization, wk, No. (%)		
16 to <28	120 (29.6)	104 (26.1)
28 to <34	286 (70.4)	294 (73.9)
Median (IQR)	30 (27-32)	30 (27-32)
Race and ethnicity, No. (%)[c]	n = 403	n = 398
African (sub-Saharan)	24 (6.0)	26 (6.5)
Asian	17 (4.2)	13 (3.3)
Indian, Pakistani, Bangladeshi, Hindu	39 (9.7)	36 (9.0)
Middle Eastern, North African	60 (14.9)	67 (16.8)
White	237 (58.8)	232 (58.3)
Other	26 (6.5)	24 (6.0)
Nulliparity, No. (%)	139 (34.2)	143 (35.5)
Polycystic ovarian syndrome, No. (%)	34 (8.4)	35 (8.7)
Hypothyroidism or hyperthyroidism, No. (%)	32 (8.0)	27 (6.7)
Chronic hypertension, No. (%)	19 (4.7)	21 (5.2)
Hemoglobin A_{1c} before randomization, mean (SD), %	5.5 (2.7)	5.5 (2.7)
Mean arterial pressure at study entry, mean (SD), mm Hg	86.2 (10.1)	86.4 (9.7)
Method of gestational diabetes diagnosis, No. (%)[d]	n = 401	n = 395
OGTT, 75 g	325 (81.0)	320 (81.0)
OGTT, 100 g	28 (7.0)	27 (6.8)
Daily glucose curve	41 (10.2)	35 (8.9)
Fasting glucose level	3 (0.7)	12 (3.0)
Other	4 (1.0)	1 (0.3)
OGTT result, mean (SD), mg/dL		
Fasting plasma glucose level	101 (16)	101 (16)
2-h Plasma glucose level after 75-g OGTT	167 (32)	169 (34)
Main reason for OGTT, No. (%)	n = 389	n = 378
Prior pregnancy with gestational diabetes	128 (32.9)	98 (25.9)
Obesity	101 (26.0)	121 (32.0)
Family history of diabetes	65 (16.7)	63 (16.7)
Ethnicity	46 (11.8)	38 (10.1)
Suspected macrosomia	17 (4.4)	18 (4.8)
Other	32 (8.2)	40 (10.6)

Abbreviation: OGTT, oral glucose tolerance test.

SI conversion: To convert glucose to mmol/L, divide by 18.

[a] Prepregnancy body mass index was assessed during the initial prenatal consultation.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Race and ethnicity data were collected through self-report. "Other" was a selectable response for race; it was not further specified.

[d] With 75-g OGTT, diagnosis was based on fasting glucose values >91.8 mg/dL (>5.1 mmol/L) and 2-hour values >153 mg/dL (>8.5 mmol/L) (World Health Organization [WHO] 2013 guidelines) or fasting glucose values >126 mg/dL (>7.0 mmol/L) and 2-hour values >140 mg/dL (>7.8 mmol/L) (WHO 1999 guidelines). A single fasting glucose value >110 mg/dL (>6.1 mmol/L) was considered abnormal.

or due to adverse effects, compared with 46% in the MiG:TOFU trial[22] comparing metformin alone with insulin. Thus, adding glyburide to metformin may reduce the number of patients requiring insulin, although this will also depend on population characteristics. The current population had less baseline obesity and was ethnically different from the population in the MiG:TOFU trial. Furthermore, in MiG:TOFU, a single fasting capillary blood glucose measurement exceeding 97 mg/dL (5.4 mmol/L) or 2-hour postprandial blood glucose measurements exceeding 121 mg/dL (6.7 mmol/L) was sufficient for drug initiation. In contrast, in the current trial, treatment initiation and treatment adaptation for insufficient glucose control was at the discretion of clinicians. A more stringent approach to initiating oral glucose-lowering agents could have yielded different effects on perinatal outcomes.

Consistent with prior trials, specific aspects of treatment satisfaction were higher in participants allocated to oral glucose-lowering agents.[12] This contrasts with an increased incidence of adverse effects, which were reported by 78% of those allocated to oral glucose-lowering agents and 56% of those

Table 2. Neonatal Outcomes[a]

Outcomes	No. (%)		Risk difference, % (95% CI)	Relative risk (95% CI)
	Oral glucose-lowering treatment (n = 406)	Insulin (n = 398)		
Primary outcome				
Large for gestational age (as randomized)	97 (23.9)	79 (19.9)	4.0 (−1.7 to 9.8)[b]	
Large for gestational age (per protocol)	86/367 (23.4)	79/396 (20.0)	3.4 (−2.5 to 9.3)[b]	
Secondary outcomes				
<37 wk of gestation	39 (9.6)	33 (8.3)	−1.3 (−5.3 to 2.6)	1.16 (0.74 to 1.80)
Birth injury	4 (0.9)	0	0.9 (−0.6 to 0.8)	1.01 (1.00 to 1.02)
Neonatal blood glucose level, mg/dL				
<47	220 (54.1)	203 (50.4)	4.6 (−2.2 to 11.4)	1.09 (0.96 to 1.24)
<36	90 (22.1)	82 (20.3)	1.82 (−3.8 to 7.5)	1.10 (0.85 to 1.43)
Hyperbilirubinemia	20 (4.9)	13 (3.2)	1.7 (−1.0 to 4.4)	1.52 (0.77 to 3.01)
Hospital admission				
Neonatal intensive care unit	18 (4.4)	16 (4.8)	0.8 (−2.6 to 4.1)	1.14 (0.59 to 2.21)
Medium care	42 (10.3)	39 (11.0)	1.1 (−3.6 to 5.8)	1.10 (0.73 to 1.66)
Exploratory outcomes				
Birth weight				
>95th Percentile	61 (15.0)	53 (13.1)	1.7 (−3.1 to 6.5)	1.23 (0.80 to 1.59)
>97th Percentile	40 (9.8)	37 (9.3)	0.8 (−3.2 to 4.9)	1.06 (0.69 to 1.62)
Mean (SD), g	3358.3 (575)	3343.1 (503)	15 (−60 to 90)	
Gestational age at delivery, mean (SD), wk	37.6 (1.6)	37.7 (1.1)	−0.38 (−0.23 to 0.16)	
Time from randomization to birth, median (IQR), d	55 (42 to 76)	56 (43 to 72)	0 (−3 to 3)	
Female infant	196 (48.2)	187 (47.0)	1.5 (−5.4 to 8.5)	1.02 (0.90 to 1.17)
Apgar score[c]				
<7	16 (3.9)	12 (2.9)	1.0 (−1.6 to 3.5)	1.32 (0.63 to 2.75)
<4	3 (0.7)	3 (0.7)	−0.0 (−1.2 to 1.2)	0.99 (0.20 to 4.86)
Small for gestational age	20 (4.9)	26 (6.5)	−1.6 (−4.8 to 1.6)	0.75 (0.43 to 1.33)
Intrauterine fetal death	2 (0.4)	1 (0.2)	0.2 (−0.6 to 1.1)	1.00 (0.99 to 1.01)
Neonatal death	1 (0.2)	1 (0.2)	0.00 (−0.7 to 0.7)	1.00 (0.99 to 1.01)
Congenital defect/anomaly	13 (3.2)	12 (3.0)	0.2 (−2.2 to 2.6)	1.00 (0.97 to 1.02)
Umbilical artery pH, mean (SD)	7.22 (0.09)	7.21 (0.10)	NA	0.01 (−0.01 to 0.03)
Respiratory support >24 h[d]	11 (2.7)	11 (2.7)	0.0 (−2.3 to 2.2)	0.99 (0.43 to 2.25)
Culture-proven sepsis	3 (0.8)	0	0.8 (−0.1 to 1.6)	NA
Intravenous glucose therapy	26 (6.4)	13 (3.2)	3.2 (0.2 to 6.1)	1.98 (1.03 to 3.97)

Abbreviation: NA, not applicable.

SI conversion: To convert glucose to mmol/L, divide by 18.

[a] The noninferiority margin was prespecified at 8% absolute risk difference. Large for gestational age was defined as >90th percentile based on gestational age and sex.

[b] Risk difference (percentage points) and *P* value for Farrington-Manning test of noninferiority. For the primary outcome of large for gestational age, *P* = .09 for the as-randomized population and *P* = .06 for the per-protocol population.

[c] Apgar scores range from 0 to 10 and evaluate health of newborns at 1 and 5 minutes after birth. In healthy newborns, the Apgar score is 9 to 10.

[d] Respiratory support included continuous positive airway pressure and positive end-expiratory pressure.

allocated to insulin. Most notably, the incidence of self-reported maternal hypoglycemia was higher in the participants using oral glucose-lowering agents compared with participants using insulin. Glyburide's mechanism of interrupting the negative feedback of decreasing glucose on pancreatic insulin secretion may help to explain this finding. While our overall results do indicate limitations of treatment intensification of metformin with glyburide, the results of the exploratory analysis of those treated with metformin alone are in agreement with a recent meta-analysis supporting metformin as first-line pharmacological treatment of gestational diabetes.[24]

Limitations

This study has several limitations. First, it was an open-label trial, which introduces the possibility of bias in treatment allocation and outcome assessment. Second, the trial was conducted in the Netherlands. Generalizability to other populations with different demographics and health care systems may

Table 3. Obstetric and Maternal Outcomes in the Full Analysis Set

Outcomes	No. (%)		Risk difference, % (95% CI)	Relative risk (95% CI)
	Oral glucose-lowering treatment (n = 406)	Insulin (n = 398)		
Secondary outcomes				
Maternal hypoglycemia[a]	53 (20.9)	26 (10.9)	10.0 (3.7-21.2)	2.16 (1.30-3.59)
Primary cesarean delivery	77 (19.0)	68 (17.1)	1.9 (−11.9 -12.8)	1.01 (0.82-1.24)
Secondary cesarean delivery	56 (13.8)	50 (12.6)	2.5 (−3.5 to 8.5)	1.14 (0.85-1.51)
Pregnancy-induced hypertension	48 (11.8)	46 (11.6)	0.2 (−4.2 to 4.7)	0.99 (0.68-1.46)
Preeclampsia/HELLP syndrome	28 (6.9)	22 (5.5)	1.4 (−2.0 to 4.7)	1.25 (0.73-2.14)
Gestational weight gain, mean (SD), kg	9.3(6)	10.4 (7)	1.1 (−0.03 to 2.14)	
Exploratory outcomes				
Drug-related adverse effects[b]	n = 280	n = 261		
Individuals with any adverse effects	218 (77.9)	146 (55.9)		
Nausea	100 (39.4)	31 (13.0)		
Diarrhea	98 (38.6)	12 (5.0)		
Fatigue	73 (28.7)	51 (21.3)		
Headache	51 (20.1)	31 (13.0)		
Hypoglycemia	53 (20.9)	26 (10.9)		
Vomiting	37 (14.6)	4 (1.7)		

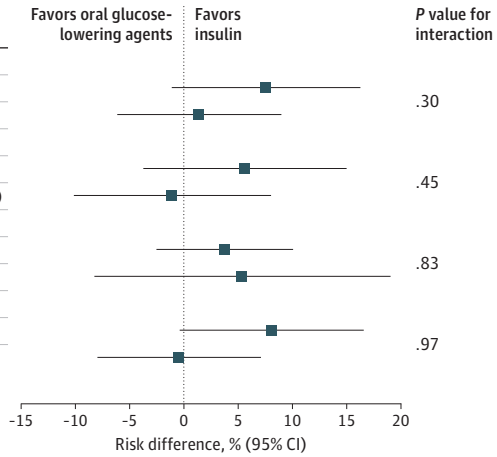
Abbreviation: HELLP, hemolysis elevated liver enzymes and low platelets.

[a] Defined as glucose <70 mg/dL, symptomatic hypoglycemia, or severe hypoglycemia prompting the need for help by another person.

[b] All participants received a questionnaire about drug-related adverse effects; 493 completed the questionnaire, 254 in the oral glucose-lowering treatment group and 239 in the insulin group. The denominators in the table are for questionaires that may not have been fully completed but that had information about adverse effects.

Figure 2. Subgroup Analyses of Incidence of Large-for-Gestational-Age Infants

	No. with large-for-gestational-age infants/total No. (%)		Risk difference, % (95% CI)
	Oral glucose-lowering agents	Insulin	
Age, y			
<33	44/173 (25.6)	31/172 (18.0)	7.56 (-1.13 to 16.25)
≥33	53/233 (22.7)	48/226 (21.2)	1.41 (-6.15 to 8.97)
Glycemic control			
Hemoglobin A_{1c} above mean	45/165 (27.3)	34/159 (21.4)	5.62 (-3.75 to 14.98)
Hemoglobin A_{1c} below mean	30/152 (19.7)	31/147 (21.1)	-1.07 (-10.15 to 8.02)
Admission to study			
<28 wk of gestation	81/340 (23.8)	64/320 (20.0)	3.75 (-2.54 to 10.05)
≥28 wk of gestation	16/65 (24.6)	15/78 (19.2)	5.38 (-8.26 to 19.03)
Prepregnancy body mass index[a]			
≥30	61/202 (30.2)	46/208 (22.1)	8.08 (-0.40 to 16.56)
<30	14/90 (15.6)	12/76 (15.8)	-0.44 (-7.98 to 7.09)



[a] Calculated as weight in kilograms divided by height in meters squared.

be limited,[25] although the study population was ethnically diverse. Third, the study population included individuals with a gestational diabetes diagnosis as early as 16 weeks of gestation, whose findings may not be applicable to individuals diagnosed after 20 weeks of gestation, as recommended by the US Preventive Services Task Force.[26] Fourth, there was differential loss to follow-up between the 2 groups.

Conclusions

Treatment of gestational diabetes with metformin and additional glyburide, if needed, did not meet criteria for noninferiority compared with insulin with respect to the proportion of infants born large for gestational age.

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