Comparison of neonatal and maternal outcomes of anti-diabetic drugs in the treatment of gestational diabetes mellitus: Findings from Bayesian network meta-analysis

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Abstract

The safety and efficacy of different anti-diabetic drugs are not clear because of the lack of sufficiently powered clinical trials. This network meta-analysis was conducted to compare the efficacy and safety of three anti-diabetic drugs (insulin, glyburide, and metformin), and rank them as per their efficiency to control glucose levels, pregnancy, and neonatal outcomes. The study design is a systematic review, meta-analysis, and network meta-analysis. After a systematic search of existing databases, 34 randomized controlled trials were selected for inclusion in the analysis. We did pairwise network meta-analysis to calculate standardized mean difference and odds ratio (OR) as the summary measures for numerical and dichotomous variables, respectively, by using random-effects model. Our key outcomes were incidence of neonatal hypoglycemia, respiratory distress syndrome, macrosomia, C-section, admission to neonatal intensive care unit (NICU) and mean differences in the birth weight of neonates, gestational age at birth, HbA1C levels, fasting blood sugar, large at gestational age, and post-prandial glucose. It was found that metformin significantly lowered the post-prandial levels of glucose as compared with both glyburide and insulin in pairwise analysis (SMD = 14.11 [23–4.8]; SMD = 22.45 [30–14]), respectively. There was a significant reduction in birth weights of babies whose mothers were administered metformin as compared with either glyburide or insulin. The proportion of neonates admission to NICU was significantly lower for metformin when compared with insulin [Log OR = 0.334 (0.0184, 0.6814)]. Large at gestational age was significantly lower for metformin as compared with both glyburide and insulin [log OR = 0.393 (0.00179, 0.8218), respectively. Oral anti-diabetic drugs especially metformin performed better than both glyburide and insulin for all neonatal and maternal outcomes except that it significantly lowered the neonatal birth weight.

Keywords: Gestational diabetes mellitus, glyburide, insulin, metformin, oral anti-diabetic agents, randomized controlled trial

Introduction

Gestational diabetes mellitus (GDM) is the most common endocrinopathy affecting nearly 7–10% of all pregnancies worldwide. It is a condition of hyperglycemia that is recognized at any time in pregnancy based on defined thresholds. The risk factors of GDM include obesity, genetic influence, high-risk ethnicities, and pregnancy at late maternal age, previous history of GDM, and previous macrosomic infant.

There are many standardized screening and diagnostic guidelines such as american college of obstetricians and gynecologists...
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in terms of gestational age at birth, birth weight of neonate, the blood glucose levels of pregnant women as measured by which are administered among women diagnosed with GDM. To compare the efficacy and safety of various anti-diabetic drugs both by providing direct and indirect estimates. Therefore, we planned to carry out this network meta-analysis it could not present the summary findings to reach a conclusion. outcomes. A systematic review was conducted to present the as per their efficiency to control glucose levels and pregnancy population characteristics. There is no study that has attempted to carry out a three-arm RCT comparing only two drugs with each other. have been carried out to compare these drugs in terms of their safety and efficacy comparing only two drugs with each other. There is no study that has attempted to carry out a three-arm RCT to compare metformin, glyburide, and insulin with similar study population characteristics. Hence, there is no ranking available as per their efficiency to control glucose levels and pregnancy outcomes. A systematic review was conducted to present the comparative efficacy of these drugs but being the narrative review, it could not present the summary findings to reach a conclusion. Therefore, we planned to carry out this network meta-analysis to compare the efficacy and safety of metformin, glyburide, and insulin in controlling glucose levels among patients with GDM both by providing direct and indirect estimates.

Aim
To compare the efficacy and safety of various anti-diabetic drugs which are administered among women diagnosed with GDM.

Objectives
To compare the efficacy of anti-diabetic drugs in lowering the blood glucose levels of pregnant women as measured by hemoglobin A1c (HbA1c), fasting blood sugar levels, and Post-Prandial Glucose levels and incidence of cesarean section.

To compare the effect of these drugs on neonatal outcomes in terms of gestational age at birth, birth weight of neonate, large at gestational age, neonatal hypoglycemia, the incidence of macrosomia, ICU admission, and respiratory distress syndrome.

Methodology
We have used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines following population, intervention, comparators, outcomes, study design (PICOS) to report a meta-analysis of RCTs. Women having GDM were administered anti-diabetic drugs for controlling blood glucose levels during pregnancy. The outcome measures are lowering of blood glucose as measured by HbA1c, fasting blood sugar (FBS), and postprandial glucose (PPG) levels, Neonatal outcomes: gestational age at birth, birth weight of neonate, large at gestational age, neonatal hypoglycemia, the incidence of macrosomia, and respiratory distress syndrome. Secondary outcomes such as the proportion of mothers who had C-section and the number of neonates admitted to ICU after birth.

We decided to include all RCTs which have compared either of these three anti-diabetic drugs (glyburide, insulin, and metformin) from January 2000 to December 2019. The following data sources were searched for all RCTs: PubMed, EMBASE/ExcerptaMedica, Cochrane Central Register of Controlled Trials, Google Scholar, and Reference lists. Search strategies were independently designed and performed by two separate investigators. We used the following medical subject headings (MeSH) terms or Keywords indifferent combinations and permutations for searching studies from year January 2000 to December 2019 in advanced PubMed search: “gestational diabetes mellitus,” “oral hypoglycaemic,” “anti-diabetic drugs,” “glyburide,” “insulin,” “metformin,” and randomized controlled trials. The inclusion criteria were RCTs which had compared glyburide with insulin or metformin with insulin or glyburide with metformin, they provided information on one or more maternal or fetal outcomes, they were published as a full paper, Pregnant women diagnosed for GDM (ICD-10 codes 648.8-648.83) before delivery, they were continuously enrolled during the year before and 3 months after the delivery date and their first pharmacy claim for glyburide or insulin or metformin within 150 days of delivery. We excluded studies that had enrolled female patients: with diagnosis codes for type 1 or 2 diabetes, younger than 15 years or older than 45 years, with diagnosis or procedure codes for pregnancy with multiple gestations. Our analysis was restricted to the first eligible pregnancy with GDM for a given woman. The search strategies described above provided a list of studies. The titles and abstracts of all the retrieved studies were screened independently by two authors. The irrelevant studies were discarded in the first attempt. Later on, the full-text versions of the shortlisted studies were analyzed for the presence of a measurable outcome variable as described above. We extracted information on study characteristics, interventions, and outcomes as depicted in Table 1. Internal validity of RCTs was assessed using the Cochrane Risk of Bias tool. Extracted data were entered and analyzed using R version 3.3.1 (The R Foundation for Statistical Computing).
Before the analysis, data were standardized into equivalent units. As a basic step, we carried out a direct pairwise analysis. For continuous variables mean difference and 95% confidence interval (CI) were calculated. For dichotomous variables rates were expressed as rate ratio and 95% CI. Heterogeneity in the studies was evaluated by $I^2$ statistics to assess the degree of inter-study variation. $I^2$ values of $0–24.9\%$, $25–49.9\%$, $50–74.9\%$, and $75–100\%$ were considered as having no, mild, moderate, and significant thresholds for statistical heterogeneity.

The Bayesian network meta-analyses (NMA) works on the principle of pairwise meta-analysis that provides both direct and indirect comparisons. We selected a random-effects model to allow for heterogeneity among trials on the assumption that different treatment effects originated from a normal distribution.

We calculated summary measures of effect sizes (SMD or OR) and their 95% CI by the Markov Chain Monte Carlo method by running three Markov chains simultaneously with 1 lakh iterations.

In the network plot, the node size represents sample size, and the line thicknesses indicate the availability of direct comparisons between pairs of interventions. The surface under the cumulative ranking curve (SUCRA) is used to provide a hierarchy of the treatments. The larger the SUCRA value, the better the treatment or the lower the incidence of adverse effects. The presence of small-study effects or publication bias was assessed by funnel plot.

| Study ID | First Author, Y | Country | Sample period | Sample size | Median age | Mean or median intervention arm | Mean or median age control arm | Bias |
|----------|-----------------|---------|---------------|-------------|------------|-------------------------------|-------------------------------|------|
| 1        | O. Langer 2000  | USA     | NA            | 404         | 201        | 203                           | 29±7                         | 30±6 | L   |
| 2        | C. Anjalkashi 2007 | India  | NA            | 23          | 10         | 13                            | 24.9±3.73                    | 27.46±5.83 | H   |
| 3        | D. Oganyemi 2007 | USA     | 3 Y           | 97          | 48         | 49                            | NA                           | NA   | L   |
| 4        | T. Moore 2007   | USA     | NA            | 504         | 268        | 236                           | NA                           | NA   | U   |
| 5        | K. Lain 2009    | USA     | 3 Y           | 82          | 41         | 41                            | 32.2±5                       | 31.2±5.9 | H   |
| 6        | P. Mukhopadhyay 2012 | India  | 1 Y           | 60          | 30         | 30                            | 26.3±5.4                     | 26±4.3 | U   |
| 7        | A. Tempe 2013   | India   | 1 Y           | 64          | 32         | 32                            | 26.9±3.06                    | 27.5±3.04 | L   |
| 8        | M. Mirzamoredi 2014 | Iran   | 1 Y           | 96          | 37         | 39                            | 29.5±4.06                    | 31.18±5.01 | L   |
| 9        | M. Behrashi 2016 | Iran    | NA            | 249         | 120        | 129                           | 30.69±7                      | 29.98±7.033 | U   |
| 10       | P. Rao 2017     | India   | 22 M          | 100         | 50         | 50                            | 27.32±2.84                   | 26.3±3.01 | U   |
| 11       | M. Senat 2018   | France  | 4 Y           | 809         | 367        | 442                           | 32.5±5.1                     | 32.6±5.3 | U   |
| Glyburide vs Insulin |               |         |               |             |            |                               |                               |      |     |
| 12       | J. Rowan 2008   | New Zealand, Australia | NA | 733 | 363 | 370 | 33.5±5.4 | 33.5±5.1 | U |
| 13       | H. Ijas 2010    | Finland | 4 Y | 97 | 47 | 50 | 32.3±5.6 | 31.7±6.1 | U |
| 14       | E. Mesdaghnia 2012 | Iran   | 1 Y | 200 | 100 | 100 | 29.6±5.3 | 30.2±5.9 | L |
| 15       | J. Hassan 2012  | Pakistan | 2 Y | 150 | 75 | 75 | 30.29±3.06 | 30.88±3.6 | U |
| 16       | K. Terri 2012   | Finland | 4 Y | 217 | 110 | 107 | 31.9±5 | 32.1±5.4 | H |
| 17       | S. Niromanesh 2012 | Iran  | 2 Y | 160 | 80 | 80 | 30.7±5.5 | 31.8±5.1 | H |
| 18       | C. Spaulonci 2013 | Brazil | 3 Y | 92 | 46 | 46 | 31.93±6.02 | 32.76±4.66 | H |
| 19       | S. Raholamin 2014 | Iran   | 2 Y | 100 | 50 | 50 | 24.6±5.3 | 23.4±2.5 | L |
| 20       | H. Saleh 2016   | Egypt   | 2 Y | 137 | 67 | 70 | 31±3.42 | 29.8±2.18 | L |
| 21       | S. Ahoush 2016  | Egypt   | 11 M         | 95 | 47 | 48 | 31.6±2.8 | 32.1±3.2 | U |
| 22       | T. Wouldes 2016 | Australia | 18 M | 83 | 44 | 39 | 34.7±5 | 33.3±4.7 | U |
| 23       | T. Wouldes 2016 | New Zealand | 18 M | 128 | 64 | 64 | 34.1±4.8 | 34.2±4.7 | U |
| 24       | R. Arshad 2017  | Karachi | 2 Y | 50 | 25 | 25 | 29.7±3.41 | 31.6±3.27 | U |
| 25       | M. Mohammed 2018 | Iraq   | 1 Y | 150 | 75 | 75 | 35.1±4.3 | 33.7±2.6 | U |
| 26       | A. Ali 2018     | Egypt   | NA | 94 | 47 | 47 | 30.4±3.78 | 31.34±3.62 | U |
| 27       | A. Ahmed 2019   | Egypt   | 1 Y | 153 | 78 | 78 | 31.8±5.1 | 30.6±4.5 | U |
| 28       | N. Ghomian 2019 | Iran    | NA | 286 | 143 | 143 | 28.3±5.25 | 28.41±2.36 | U |
| 29       | S. Bukhari 2019 | Pakistan | 2 Y | 770 | 385 | 385 | 24.92±2.57 | 28.01±2.53 | L |
| 30       | T. Hatem 2019   | Iraq    | 15 M         | 100 | 50 | 50 | 34.2±5.2 | 33.9±5.0 | L |
| Metformin vs Insulin |               |         |               |             |            |                               |                               |      |     |
| 31       | L. Moore 2010   | USA     | 5 Y           | 149         | 75         | 74                            | 31±7                         | 29.6±2.78 | L |
| 32       | J. Silva 2010   | Brazil  | 16 M          | 72          | 32         | 40                            | 33.6±5.8                     | 31.5±5.4 | L |
| 33       | J. Silva 2012   | Brazil  | 26 M          | 200         | 104        | 96                            | 32.6±5.61                    | 31.29±5.36 | L |
| 34       | George 2015     | India   | 3 Y           | 159         | 79         | 80                            | 33.4±4.4                     | 33.6±4.6 | L |
| 35       | P. Pujara 2017  | India   | 1 Y           | 72          | 37         | 35                            | 29.59                        | 30.6 | U |
Results

Section A. Selection of studies

The combined literature search identified around 638 studies. After reviewing the title, we included 122 studies for abstract review. Finally, only 34 studies matched the inclusion criteria [Figure 1].

There were 34 eligible studies conducted from year 2000 till 2019; 11 studies which compared glyburide and insulin,[12,13,16,18,19,20,23,27,30-32] 18 compared metformin with insulin,[6,8,13,15,20,24-26,33-35] and 5 assessed the efficacy of metformin with glyburide.[6,18,22,28,29] [Table 1] including a total of 6935 pregnant women having GDM.

Section B. Assessment of bias in selected studies

Low risk bias was found among 13 (37.1%) studies and 5 (14.3%) had high bias. However, bias was unclear in 17 (48.6%) studies [Table 1].

Section C: Results for Direct pairwise and Network Meta-analyses on Maternal and Neonatal Outcomes

Outcomes

The network plot for various maternal and neonatal outcomes has been presented in Supplementary File.

Mean Fasting Blood Sugar: Both direct pairwise and NMA revealed that there was no significant difference in the mean fasting blood glucose levels among the pregnant women who were administered any of the three drugs as indicated by the CrI of mean blood glucose levels [Tables 2 and 3].

Mean Post Prandial Glucose Levels: In the direct pairwise analysis, it was found that the mean PPG level was higher in the metformin group as compared with the insulin group. Hence, insulin significantly lowered the mean PPG as compared with metformin [SMD = −30.1 (−35.9 to −25.4)]. However, there was no significant difference in the mean PPG levels of glyburide vs. insulin and glyburide vs. metformin. However, results were significantly different for NMA. It was found that metformin significantly lowered the levels of glucose as measured by PPG as compared to both glyburide [14.11 (4.895, 23.47)] and insulin [SMD = 22.45 (14.55, 30.16)].

Mean HbA1c: Both pairwise and NMA analyses revealed that there was no statistically significant difference in the mean HbA1c levels of women belonging to three intervention groups [Tables 2 and 3].

C-section: As depicted by the log OR and CrI in Table 2, there was no difference in the proportion of pregnant women who underwent C-section during delivery among the three intervention groups. However, in NMA insulin group was found to have more incidence of C-section when compared to glyburide [log OR = −0.3893 (−0.7536, −0.02118)].

Neonatal hypoglycemia: The number of neonates who suffered from neonatal hypoglycemia was more among the insulin group as compared with the metformin group in pairwise analysis [log OR = −0.69 (−1.1, −0.34)]. In NMA, there was no statistically significant difference in the incidence of neonatal hypoglycemia among the three drugs [Table 3].

Birth weight: In pairwise analysis, metformin was found to significantly lower the birthweight of a neonate as compared with insulin [SMD = −69 (-1.4e + 02, −5.5)]. However, the neonatal birth weight was statistically similar for glyburide vs. insulin and glyburide vs. metformin. In NMA, metformin was found to significantly lower the birth weight of neonate as compared to both glyburide [SMD = 109.6 (33.34, 192.5)] and insulin [SMD = 59.72 (3.283, 121.4)] [Figure 2, Table 3].

Mean Gestational Age at Birth: The pairwise and NMA analyses showed no statistically significant difference in the mean gestational age at birth as depicted in Tables 2 and 3.

Large for gestational age: Direct pairwise analysis showed that metformin lowered the incidence of large for gestational age (LGA) as compared to glyburide [Log OR = −0.84 (−1.7, −0.013)]. Similarly, NMA also showed that the incidence of LGA was lower in the metformin group as compared to both glyburide and insulin [Figure 3, Tables 2 and 3].

Respiratory Distress Syndrome: there was no statistically significant difference in the incidence of RDS among neonates whose mother was administered either glyburide

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**Figure 1:** Flowchart showing selection of studies

**Figure 2:** Inconsistency Analysis of Birth Weight
or metformin or insulin both by pairwise and NMA analysis [Tables 2 and 3].

**Macrosomia**: Both pairwise and NMA revealed that there was no statistically significant difference in the incidence of macrosomia among neonates whose mother was administered either glyburide or metformin or insulin [Tables 2 and 3].

**ICU admission**: In the pairwise meta-analysis, it was observed that the metformin group had a lower incidence of admission to the NICU than insulin [log OR = −0.36 (−0.77, −0.024)] [Figure 4, Tables 2 and 3].

### Section D: Relative rankings of anti-diabetic drugs with respect to maternal and neonatal outcomes as per SUCRA values

As depicted in Table 4, metformin performed the best for reducing the risk of gestational age at birth, ICU admission, macrosomia, LGA, neonatal hypoglycemia, and RDS. Also, it

| Table 2: Direct Pairwise Summary measures for Maternal and Neonatal Outcomes | Table 3: Summary measures (log OR/SMD) of maternal and neonatal outcomes as per Network Meta-analysis |
|---------------------------------------------------------------|---------------------------------------------------------------|
| SMD/Log Odds Ratio (Grl)                                      | SMD/Log Odds Ratio                                           |
| Mean FBS                                                      | Mean Fasting Blood Sugar                                      |
| Glyburide.Insulin                                             | Glyburide                                                     |
| -0.3221 (-3.052, 2.302)                                       | -0.07837 (-2.869, 2.693)                                     |
| Glyburide.Metformin                                           | 0.2418 (-1.915, 2.487)                                       |
| -0.07837 (-2.869, 2.693)                                      | **SMD**                                                      |
| Insulin.Metformin                                             | Mean PPG                                                      |
| 0.2418 (-1.915, 2.487)                                        | -0.3893 (-0.7536, -0.02118)                                  |
| Mean PPG                                                      | 0.1065 (-0.1515, 0.3638)                                     |
| Glyburide.Insulin                                             | -0.2813 (-0.6717, 0.09856)                                   |
| -8.338 (-16.75, 0.1737)                                       | **SMD**                                                      |
| Glyburide.Metformin                                           | 0.1065 (-0.1515, 0.3638)                                     |
| 14.11 (4.895, 23.47)                                          | **SMD**                                                      |
| Insulin.Metformin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| Mean HbA1c                                                    | **SMD**                                                      |
| Glyburide.Insulin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| 0.0644 (-0.28, 0.43)                                          | **SMD**                                                      |
| Glyburide.Metformin                                           | 0.1065 (-0.1515, 0.3638)                                     |
| -0.0577 (-0.49, 0.37)                                         | **SMD**                                                      |
| Insulin.Metformin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -0.0700 (-0.25, 0.12)                                         | **SMD**                                                      |
| C section                                                     | 0.1065 (-0.1515, 0.3638)                                     |
| Glyburide.Insulin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| 0.30 (-0.21, 0.76)                                            | **SMD**                                                      |
| Glyburide.Metformin                                           | 0.1065 (-0.1515, 0.3638)                                     |
| 0.41 (-0.14, 1.0)                                             | **SMD**                                                      |
| Insulin.Metformin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -0.14 (-0.43, 0.14)                                           | **SMD**                                                      |
| Neonatal hypoglycaemia                                        | 0.1065 (-0.1515, 0.3638)                                     |
| Glyburide.Insulin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -0.28 (-0.78, 0.28)                                           | **SMD**                                                      |
| Glyburide.Metformin                                           | 0.1065 (-0.1515, 0.3638)                                     |
| -0.58 (-1.4, 0.21)                                            | **SMD**                                                      |
| Insulin.Metformin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -0.69 (-1.1, -0.34)                                           | **SMD**                                                      |
| Mean Birth weight                                             | 0.1065 (-0.1515, 0.3638)                                     |
| Glyburide.Insulin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -6.6 (-1.6e+02, 22.)                                          | **SMD**                                                      |
| Glyburide.Metformin                                           | 0.1065 (-0.1515, 0.3638)                                     |
| -8.1 (-2.0e+02, 34.)                                          | **SMD**                                                      |
| Insulin.Metformin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -6.9 (-1.4e+02, -5.5)                                         | **SMD**                                                      |
| Mean Gestational age at Birth                                 | 0.1065 (-0.1515, 0.3638)                                     |
| Glyburide.Insulin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -0.26 (-0.55, 0.051)                                          | **SMD**                                                      |
| Glyburide.Metformin                                           | 0.1065 (-0.1515, 0.3638)                                     |
| 0.0764 (-0.24, 0.42)                                          | **SMD**                                                      |
| Insulin.Metformin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -0.095 (-0.28, 0.11)                                          | **SMD**                                                      |
| LGA                                                           | 0.1065 (-0.1515, 0.3638)                                     |
| Glyburide.Insulin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -0.21 (-0.97, 0.38)                                           | **SMD**                                                      |
| Glyburide.Metformin                                           | 0.1065 (-0.1515, 0.3638)                                     |
| -0.84 (-1.7, -0.013)                                          | **SMD**                                                      |
| Insulin.Metformin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -0.35 (-0.85, 0.056)                                          | **SMD**                                                      |
| RDS                                                           | 0.1065 (-0.1515, 0.3638)                                     |
| Glyburide.Insulin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| 0.27 (-0.36, 0.95)                                            | **SMD**                                                      |
| Glyburide.Metformin                                           | 0.1065 (-0.1515, 0.3638)                                     |
| 0.30 (-0.99, 1.6)                                             | **SMD**                                                      |
| Insulin.Metformin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -0.40 (-0.95, 0.15)                                           | **SMD**                                                      |
| Macrosomia                                                    | 0.1065 (-0.1515, 0.3638)                                     |
| Glyburide.Insulin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -0.16 (-0.81, 0.40)                                           | **SMD**                                                      |
| Glyburide.Metformin                                           | 0.1065 (-0.1515, 0.3638)                                     |
| -0.63 (-1.9, 0.52)                                            | **SMD**                                                      |
| Insulin.Metformin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -0.34 (-0.80, 0.099)                                          | **SMD**                                                      |
| ICU admission                                                 | 0.1065 (-0.1515, 0.3638)                                     |
| Glyburide.Insulin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| 0.17 (-0.47, 0.85)                                            | **SMD**                                                      |
| Glyburide.Metformin                                           | 0.1065 (-0.1515, 0.3638)                                     |
| 0.051 (-0.69, 0.88)                                           | **SMD**                                                      |
| Insulin.Metformin                                             | 0.1065 (-0.1515, 0.3638)                                     |
| -0.36 (-0.77, -0.024)                                         | **SMD**                                                      |
controlled the mean blood glucose levels more efficiently as indicated by mean HbA1c and PPG. Glyburide ranked first for lowering the incidence of C-sections, and RDS. It also provided more glucose control in terms of mean Fasting blood sugar as compared to two other drugs [Table 4].

Section E: Inconsistency Analysis
Supplementary file represents the inconsistency analysis of all outcomes.

Section F: Assessment of Publication Bias
As indicated by the P value of Egger’s test and funnel plots, no publication bias was reported in the selection of studies [Supplementary File].

Discussion
A number of previous systematic reviews and meta-analyses have compared only a few maternal and/or neonatal outcomes by providing either narrative reviews or by using conventional meta-analysis which provides direct estimates only,[4,17,42,43] However, we have attempted to compare the efficacy and adverse effects of glyburide, metformin, and insulin by using Bayesian network meta-analysis.

NMA provides robust metrics (SUCRA values) for comparing the drugs, and also ranks the drugs in order of increasing efficacy and decreasing side effects. This may be considered as one of the methodological strengths of our study. The strength of our study is the inclusion criteria where we have selected only those studies where a single drug was administered for glucose control. For instance, we excluded the studies which used a combination of two or more anti-diabetic as a combination of drugs has different pharmacokinetics which can impact the magnitude of efficacy and thus, can lead to misinterpretation of findings.

Unlike in most of the RCTs and conventional meta-analysis, insulin has been documented to have more efficacy or at least par with other oral anti-diabetic agents in controlling blood glucose levels.[4,39,40] However, we have found that glyburide ranked first in controlling blood glucose as indicated by mean FBS [Table 4]; though statistically insignificant. Similarly, metformin ranked first for maintaining PPG [Table 4]. Hence, oral anti-diabetic drugs performed better than insulin for controlling GDM. Even the long-term glycemic control was well achieved with metformin (0.7) > glyburide (0.5) > insulin (0.3) as indicated by SUCRA values of HbA1c in Table 4. As clear in Table 4, glyburide performed the best in reducing the incidence of C-section followed by metformin and least being insulin and similar result was seen in a study by Sreelakshmi PR, the major cause for cesarean section was macrosomia which was seen among 10 of 26 women on insulin therapy.[44] However, all conventional meta-analyses in the past have concluded that insulin and oral anti-diabetic agents have the same efficacy in controlling blood glucose levels and is in contradiction to our findings because we have considered both direct and indirect estimates as already discussed in the previous paragraph. Our findings are congruent with a recent study by Krishankumar showing that insulin therapy and metformin have equal significant reduction in mean fasting and postprandial blood glucose level and achieve glycemic control and also suggested that metformin is a safe and efficacious oral antidiabetic agent in GDM in countries such as India being cost-effective and compliant.[45]

For neonatal outcomes, there was no significant difference for incidence of neonatal hypoglycemia, gestational age at birth, Table 4: SUCRA values for various maternal and neonatal outcomes

| Anti-Diabetic Drug | C section | Mean FBS | Birth wt | Gest age at birth | Mean HbA1c | ICU admission | LGA | Macrosomia | Neonatal | PPG | RDS |
|-------------------|-----------|----------|----------|------------------|------------|---------------|-----|-------------|----------|-----|------|
| Metformin         | 0.1       | 0.4      | 0.6      | 0.3              | 0.1        | 0.5            | 0.3 | 0.4         | 0.4      | 0.1 | 0.0  |
| Glyburide         | 1.0       | 0.2      | 0.6      | 0.3              | 0.1        | 0.5            | 0.4 | 0.0         | 0.0      | 0.0 | 0.7  |
| Insulin           | 0.4       | 0.5      | 0.6      | 0.3              | 0.0        | 0.4            | 0.4 | 0.1         | 0.1      | 0.1 | 0.7  |
macrosomia, and respiratory distress syndrome among the three drugs as depicted in Table 3. Metformin reduced the risk of both LGA and ICU admission in Table 3 (green font). The ranking of the drugs for these outcomes followed the hierarchy of metformin > insulin > glyburide as represented by SUCRA values in Table 4. The increasing order of SUCRA values for mean birth weight in Table 4 indicate the increasing order of adverse effect leading to reduction in mean birth weight that is, glyburide (least SUCRA – value most safe in terms of birth weight reduction) < Insulin < Metformin (highest SUCRA – Highest weight reduction risk).

For all maternal outcomes, that is, for effectively controlling mean FBS, PPG, mean HbA1c, and reducing the C-section incidence, oral anti-diabetic agents performed the best, and insulin performed the worst. For neonatal outcomes, metformin performed the best for all indicators except that it leads to a reduction in the mean birth weight of neonates. Other reviews have also found that glyburide increases the risk of macrosomia, LGA, increased gestational at birth which is in sync with other findings too.[4,17] We also found that regarding NICU admission, metformin significantly reduced the incidence followed by glyburide and insulin gave the worst results. In other reviews, they also found similar findings but could not comment on the effectiveness of glyburide as direct evidence was not available. Albeit, owing to the merits of NMA, we could derive this summary estimate for glyburide as well.

The latest guidelines for diagnosis and management of GDM by the Maternal health division of the Ministry of Health and Family welfare by the government of India recommends the use of oral metformin after 20 weeks of gestation in contrast to tedious parental administration which makes insulin therapy costly and causes adherence issue especially in low resource country such as India leading to a better and more sustainable patient-centric care.[46-48] ACOG recommends that in those women who decline insulin therapy or there is concern regarding the safety of insulin, metformin is a reasonable alternative choice.[49,50] This is the first largest network meta-analysis that has attempted to explore eleven outcome variables (5 maternal + 6 neonatal) thus providing comprehensive summary measures for effectiveness and efficacy of oral anti-diabetics and insulin.

However, there are a few limitations as well which strongly warrant the conscious interpretation of findings such as a possibility of regional bias from studies of different geographic locations making it difficult to comment on a single setting or a population, systematic reviews and meta-analysis are of sample size for each pair of intervention may not be sufficient to estimate all outcome measures, also NMA involves both direct and indirect estimates from different studies and individual studies address different confounders like age, ethnicity, genetics, differential health services among various countries which can also impact the outcomes.

What is already known about the subject?

• The incidence of gestational diabetes mellitus is increasing in India which is a rising public healthcare problem.
• Gestational diabetes mellitus has varied impacts on maternal and neonatal outcomes.
• Variety of oral antidiabetic drugs and insulin formations are available in the market but which has a better impact on the treatment of gestational diabetes mellitus (GDM) is still not known.

What does this meta-analysis add to this subject?

• This is a network meta-analysis considering the risk-benefit ratio of oral anti-diabetic drugs and insulin in the treatment of gestational diabetes mellitus.
• It has public health implications as 70% of the Indian population resides in the rural area where the medical facility is catered through primary healthcare. Primary physician does not know about the efficacy of the drugs and which is the better treatment of GDM.
• This network meta-analysis is important as it shows that oral antidiabetics perform better than insulin for all neonatal and maternal outcomes. Oral anti-diabetic drugs especially metformin provide both fast and long-term glucose control over insulin.
• In a country such as India where there are adherence issues with an injectable form of insulin, oral antidiabetic drug increases patient compliance and can help primary care physicians to provide care via a patient-centric approach.

Conclusion

To conclude, this network meta-analysis clearly states that oral anti-diabetic drugs especially metformin provide both the fastest and long-term glucose control over insulin. Glyburide significantly reduces the chances of C-section and provided good short-term glucose management. However, in terms of neonatal outcomes, metformin was found to be the best performer, insulin performed at second rank and glyburide was found to be the worst. Hence, the findings of this NMA need to be gelled with clinical experience and individual response.

Key message

• The strength of this systematic review is the inclusion criteria where those studies were selected where a single drug was administered for glucose control. The combination of drugs has different pharmacokinetcis which can impact the magnitude of efficacy and thus, can lead to misinterpretation of findings.
• This is the first largest network meta-analysis that has attempted to explore 11 outcome variables (5 maternal + 6 neonatal) thus providing comprehensive summary measures for effectiveness and efficacy of oral anti-diabetes and insulin.

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In India, no study has attempted to carry out a three-arm randomized controlled trial to compare metformin, glyburide, and insulin with similar study population characteristics.

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Conflicts of interest
There are no conflicts of interest.

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Supplementary Files
The network plot for various maternal and neonatal outcomes

Inconsistency Analysis for all neonatal and maternal outcomes

Funnel plots for all neonatal and maternal outcomes

PRISMA guidelines

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

| Section/Topic | Item # | Checklist Item                                                                                                                                                  | Reported on Page # |
|---------------|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| TITLE         | 1      | Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).                                             | 1                  |
| ABSTRACT      | 2      | Provide a structured summary including, as applicable:                                                                                                          | 1                  |
| Structured summary |       | Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis.       |                    |
| INTRODUCTION  | 3      | Describe the rationale for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted.            | 3-4                |
| Rationale     | 4      | Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4                  |
| METHODS       | 5      | Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number. | NA                |
| Eligibility criteria | 6   | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification). | 5,6                |
| Information sources | 7   | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6,7                |
| Search        | 8      | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                            |                    |
| Study selection | 9    | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).   | 7                  |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 8,9                |
| Data items    | 11     | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                      |                    |
| Geometry of the network | S1  | Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers. | Figure 2           |
| Risk of bias within individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 10, TABLE 1 |
| Summary measures | 13  | State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses. | 9-10              |
| Planned methods of analysis | 14 | Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: Handling of multi-arm trials; Selection of variance structure; Selection of prior distributions in Bayesian analyses; and Assessment of model fit. | 9-10              |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 9-10              |
| Additional analyses | 16 | Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: Sensitivity or subgroup analyses; Meta-regression analyses; Alternative formulations of the treatment network; and Use of alternative prior distributions for Bayesian analyses (if applicable). | NA                |
RESULTS†

Study selection 17 Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.

Presentation of network structure S3 Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.

Summary of network geometry S4 Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.

Study characteristics 18 For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.

Risk of bias within studies 19 Present data on risk of bias of each study and, if available, any outcome level assessment.

Results of individual studies 20 For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks.

Synthesis of results 21 Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g., placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.

Exploration for inconsistency S5 Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.

Risk of bias across studies 22 Present results of any assessment of risk of bias across studies for the evidence base being studied.

Results of additional analyses 23 Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).

DISCUSSION

Summary of evidence 24 Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policymakers).

Limitations 25 Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).

Conclusions 26 Provide a general interpretation of the results in the context of other evidence, and implications for future research.

FUNDING

Funding 27 Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.

PICOS=Population, intervention, comparators, outcomes, study design. *Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

†Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.
Box. Terminology: Reviews With Networks of Multiple Treatments

Different terms have been used to identify systematic reviews that incorporate a network of multiple treatment comparisons. A brief overview of common terms follows.

Indirect treatment comparison: Comparison of 2 interventions for which studies against a common comparator, such as placebo or a standard treatment, are available (i.e., indirect information). The direct treatment effects of each intervention against the common comparator (i.e., treatment effects from a comparison of interventions made within a) may be used to estimate an indirect treatment comparison between the 2 interventions (Appendix Figure 1, A). An indirect treatment comparison (ITC) may also involve multiple links. For example, in Appendix Figure 1, B, treatments B and D may be compared indirectly on the basis of studies encompassing comparisons of B versus C, A versus C, and A versus D.

Network meta-analysis or mixed treatment comparison: These terms, which are often used interchangeably, refer to situations involving the simultaneous comparison of 3 or more interventions. Any network of treatments consisting of strictly unclosed loops can be thought of as a series of ITCs (Appendix Figure 1, A and B). In mixed treatment comparisons, both direct and indirect information is available to inform the effect size estimates for at least some of the comparisons; visually, this is shown by closed loops in a network graph (Appendix Figure 1, C). Closed loops are not required to be present for every comparison under. “Network meta-analysis” is an inclusive term that incorporates the scenarios of both indirect and mixed treatment comparisons.

Network geometry evaluation: The description of characteristics of the network of interventions, which may include use of numerical summary statistics. This does not involve quantitative synthesis to compare treatments. This evaluation describes the current evidence available for the competing interventions to identify gaps and potential bias. Network geometry is described further in Appendix Box 4.

Appendix Box 1: The Assumption of Transitivity for Network Meta-Analysis

Methods for indirect treatment comparisons and network meta-analysis enable learning about the relative treatment effects of, for example, treatments A and B through use of studies where these interventions are compared against a common therapy, C.

When planning a network meta-analysis, it is important to assess patient and characteristics across the studies that compare pairs of treatments. These characteristics are commonly referred to as effect modifiers and include traits such as average patient age, gender distribution, disease severity, and a wide range of other plausible features.

For network meta-analysis to produce valid results, it is important that the distribution of effect modifiers is similar, for example, across studies of A versus B and A versus C. This balance increases the plausibility of reliable findings from an indirect comparison of B versus C through the common comparator A. When this balance is present, the assumption of transitivity can be judged to hold.

Authors of network meta-analyses should present systematic (and even tabulated) information regarding patient and characteristics whenever available. This information helps readers to empirically evaluate the validity of the assumption of transitivity by reviewing the distribution of potential effect modifiers across trials.

Appendix Box 2: Differences in Approach to Fitting Network Meta-Analyses

Network meta-analysis can be performed within either a frequentist or a Bayesian framework. Frequentist and Bayesian approaches to statistics differ in their definitions of probability. Thus far, the majority of published network meta-analyses have used a Bayesian approach.

Bayesian analyses return the posterior probability distribution of all the model parameters given the data and prior beliefs (e.g., from external information) about the values of the parameters. They fully encapsulate the uncertainty in the parameter of interest and thus can make direct probability statements about these parameters (e.g., the probability that one intervention is superior to another). Frequentist analyses calculate the probability that the observed data would have occurred under their sampling distribution for hypothesized values of the parameters. This approach to parameter estimation is more indirect than the Bayesian approach.

Bayesian methods have been criticized for their perceived complexity and the potential for subjectivity to be introduced by choice of a prior distribution that may affect findings. Others argue that explicit use of a prior distribution makes transparent how individuals can interpret the same data differently. Despite these challenges, Bayesian methods offer considerable flexibility for statistical modeling. In-depth introductions to Bayesian methods and discussion of these and other issues can be found elsewhere.

Appendix Box 3: Network Meta-Analysis and Assessment of Consistency

Network meta-analysis often involves the combination of direct and indirect evidence. In the simplest case, we wish to compare treatments A and B and have 2 sources of information: direct evidence via studies comparing A versus B, and indirect evidence via groups of studies comparing A and B with a common intervention, C. Together, this evidence forms a closed loop, ABC.

Direct and indirect evidence for a comparison of interventions should be combined only when their findings are similar in magnitude and interpretation. For example, for a comparison of mortality rates between A and B, an odds ratio determined from studies of A versus B should be similar to the odds ratio comparing A versus B estimated indirectly based on studies of A versus C and B versus C. This assumption of comparability of direct and indirect evidence is referred to as consistency of treatment effects.

When a treatment network contains a closed loop of interventions, it is possible to examine statistically whether there is agreement between the direct and indirect estimates of treatment effect.

Different methods to evaluate potential differences in relative treatment effects estimated by direct and indirect comparisons are grouped as local approaches and global approaches. Local approaches (e.g., the Bucher method or the node-splitting method) assess the presence of inconsistency for a particular pairwise comparison in the network, whereas global approaches (e.g., inconsistency models, measure for inconsistency) consider the potential for inconsistency in the network as a whole.

Tests for inconsistency can have limited power to detect a true difference between direct and indirect evidence. When multiple loops are being tested for inconsistency, one or a few may show inconsistency simply by chance. Further discussions of consistency and related concepts are available elsewhere.

Inconsistency in a treatment network can indicate lack of transitivity (see Appendix Box 1).
Appendix Box 4: Network Geometry and Considerations for Bias

The term network geometry is used to refer to the architecture of the treatment comparisons that have been made for the condition under. This includes what treatments are involved in the comparisons in a network, in what abundance they are present, the respective numbers of patients randomly assigned to each treatment, and whether particular treatments and comparisons may have been preferred or avoided.

Networks may take on different shapes. Poorly connected networks depend extensively on indirect comparisons. Meta-analyses of such networks may be less reliable than those from networks where most treatments have been compared against each other.

Qualitative description of network geometry should be provided and accompanied by a network graph. Quantitative metrics assessing features of network geometry, such as diversity (related to the number of treatments assessed and the balance of evidence among them), co-occurrence (related to whether comparisons between certain treatments are more or less common), and homophily (related to the extent of comparisons between treatments in the same class versus competing classes), can also be mentioned.

Although common, established steps for reviewing network geometry do not yet exist, however examples of in-depth evaluations have been described related to treatments for tropical diseases and basal cell carcinoma and may be of interest to readers. An example based on 75 trials of treatments for pulmonary arterial hypertension (Appendix Figure 5) suggests that head-to-head studies of active therapies may prove useful to further strengthen confidence in interpretation of summary estimates of treatment comparisons.

Appendix Box 5: Probabilities and Rankings in Network Meta-Analysis

Systematic reviews incorporating network meta-analyses can provide information about the hierarchy of competing interventions in terms of treatment rankings.

The term treatment ranking probabilities refers to the probabilities estimated for each treatment in a network of achieving a particular placement in an ordering of treatment effects from best to worst. A network of 10 treatments provides a total of 100 ranking probabilities—that is, for each intervention, the chance of being ranked first, second, third, fourth, fifth, and so forth).

Several techniques are feasible to summarize relative rankings, and include graphical tools as well as different approaches for estimating ranking probabilities. Appendix Figure 6 shows 2 approaches to presenting such information, on the basis of a comparison of adjuvant interventions for resected pancreatic adenocarcinoma.

Robust reporting of rankings also includes specifying median ranks with uncertainty intervals, cumulative probability curves, and the surface under the cumulative ranking (SUCRA) curve.

Rankings can be reported along with corresponding estimates of pairwise comparisons between interventions. Rankings should be reported with probability estimates to minimize misinterpretation from focusing too much on the most likely rank.

Rankings may exaggerate small differences in relative effects, especially if they are based on limited information. An objective assessment of the strength of information in the network and the magnitude of absolute benefits should accompany rankings to minimize potential biases.
Mean Fasting Blood Sugar

C-SECTION

Mean Postprandial Glucose

NEONATAL HYPOGLYCEMIA

Mean HbA1c

BIRTH WEIGHT
GESTATIONAL AGE AT DIABETES

LARGE FOR GESTATIONAL AGE

RESPIRATORY DISTRESS SYNDROME

MACROSOMIA

NICU ADMISSION

Mean Fasting Blood Sugar

| Study               | P-value | Mean Difference (95% CrI)      |
|---------------------|---------|--------------------------------|
| Insulin vs Glyburide|         |                                |
| direct              | 0.4529  | 1.1 (-2.2, 4.3)                |
| indirect            |         | -1.0 (-5.5, 3.7)               |
| network             |         | 0.34 (-2.3, 3.0)               |
| Metformin vs Glyburide|       |                                |
| direct              | 0.4618  | -0.89 (-4.7, 3.1)              |
| indirect            |         | 1.2 (-3, 5.1)                  |
| network             |         | 0.075 (-2.7, 2.9)              |
| Metformin vs Insulin|         |                                |
| direct              | 0.4498  | 0.14 (-2.4, 2.5)               |
| indirect            |         | -2. (-7, 3.2)                  |
| network             |         | -0.28 (-2.5, 1.9)              |
A. Mean Fasting Blood Sugar

B. Mean Postprandial Glucose

C. Mean HbA1c

D. C- section
E: Neonatal Hypoglycaemia

G: Mean Gestational Age at Birth

F: Mean Birth Weight

H: LARGE FOR GESTATIONAL AGE
I: Respiratory Distress Syndrome

K: NICU Admission

J: Macrosomia