ORIGINAL ARTICLE

Systematic review of the use of metformin compared to insulin for the management of gestational diabetes: Implications for low-resource settings

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Abstract

Introduction: This systematic review examines the effectiveness of metformin treatment compared to insulin treatment for gestational diabetes within the context of a low-resource environment.

Methods: Electronic data searches of Medline, EMBASE, Scopus and Google scholar databases from 1 January, 2005 to 30 June, 2021 were performed using medical subject headings: *'gestational diabetes or pregnancy diabetes mellitus'* AND *'Pregnancy or pregnancy outcomes'* AND *'Insulin' AND 'Metformin Hydrochloride Drug Combination*/or *Metformin*/or *Hypoglycemic Agents'* AND *'Glycemic control or blood glucose'*.

Randomized controlled trials were included if: participants were pregnant women with gestational diabetes mellitus (GDM); the interventions were metformin and/or insulin. Studies among women with pre-gestational diabetes, non-randomised control trials or studies with a limited description of the methodology were excluded. Outcomes included adverse maternal outcomes: weight gain, C-section, pre-eclampsia and glycaemic control and adverse neonatal outcomes: birth weight, macrosomia, pre-term birth and neonatal hypoglycaemia. The revised Cochrane Risk of Bias Assessment for randomised trials was used for the evaluation of bias.

Results: We screened 164 abstracts and 36 full-text articles. Fourteen studies met the inclusion criteria. The studies provide moderate to high-quality evidence demonstrating the effectiveness of metformin as an alternative therapy to insulin. Risk of bias was low; multiple countries and robust sample sizes improved external validity. All studies were from urban centres with no rural data.

Conclusion: These recent high quality studies comparing metformin to insulin for the treatment of GDM generally found either improved or equivalent pregnancy outcome and good glycaemic control for most patients, although many required insulin supplementation. Its ease of use, safety and efficacy

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suggest metformin may simplify the management of gestational diabetes, particularly in rural and other low-resource environments.

Keywords: Gestational diabetes, metformin, rural, treatment

Résumé

Introduction: Cette revue systématique examine l'efficacité du traitement par metformine par rapport au traitement par insuline pour le diabète gestationnel dans le contexte d'un environnement à faibles ressources.

Méthodes: Des recherches de données électroniques ont été effectuées dans les bases de données Medline, Embase, Scopus et Google scholar du 1er janvier 2005 au 30 juin 2021 en utilisant les termes MeSH: *'gestational diabetes or pregnancy diabetes mellitus'* AND *'Pregnancy or pregnancy outcomes'* AND *'Insulin'* AND *'Metformin Hydrochloride Drug Combination/or Metformin/or Hypoglycemic Agents'* AND *'Glycemic control or blood glucose'.*

Les essais contrôlés randomisés ont été inclus si: les participantes étaient des femmes enceintes atteintes de diabète gestationnel (DG); les interventions étaient la metformine et/ou l'insuline. Les études portant sur des femmes atteintes de diabète prégestationnel, les essais contrôlés non randomisés ou les études dont la description de la méthodologie était limitée ont été exclus. Les résultats comprenaient des résultats maternels défavorables: prise de poids, césarienne, prééclampsie, contrôle glycémique et des résultats néonatals défavorables: poids de naissance, macrosomie, naissance prématurée et hypoglycémie néonatale. La version révisée de l'évaluation du risque de biais de Cochrane pour les essais randomisés a été utilisée pour l'évaluation du biais.

Résultats: Nous avons examiné 164 résumés et 36 articles complets. Quatorze études répondaient aux critères d'inclusion. Les études fournissent des preuves modérées à de haute qualité démontrant l'efficacité de la metformine comme thérapie alternative à l'insuline. Le risque de biais était faible; la multiplicité des pays et la taille robuste des échantillons ont amélioré la validité externe. Toutes les études provenaient de centres urbains, sans données rurales.

Conclusion: Ces études récentes de haute qualité comparant la metformine à l'insuline pour le traitement du DG ont généralement constaté une amélioration ou une équivalence de l'issue de la grossesse et un bon contrôle glycémique pour la plupart des patientes, bien que beaucoup d'entre elles aient eu besoin d'un supplément d'insuline. Sa facilité d'utilisation, son innocuité et son efficacité suggèrent que la metformine pourrait simplifier la prise en charge du diabète gestationnel, notamment en milieu rural et dans d'autres environnements à faibles ressources.

Mots clés: Diabète gestationnel, traitement, metformine, rural

INTRODUCTION

Rural Canadians are estimated to have higher rates of diabetes, complications and undiagnosed diabetes.[1-5] This difference extends to pregnancy where increased rates of gestational diabetes mellitus (GDM) contribute to higher maternal and neonatal morbidity.[6-8] While GDM affects approximately 6% of Canadian pregnancies, rates are much higher (12%) in Northwest Ontario with a large First Nations population.[9]

Treatment of GDM decreases the risk of adverse pregnancy outcomes.[10] For decades, insulin has been the recommended treatment but requires self-administration by injection and regular monitoring of glucose levels.[11] This can be challenging in rural areas where physician and dietary resources are limited and weather and geography can make frequent follow up impractical.

Metformin, an oral biguanide hypoglycaemic, has recently been introduced as a more user-friendly alternative to insulin in the treatment of GDM.[12,13] It improves glucose metabolism by suppressing hepatic glucose production and increases gut metabolism and peripheral glucose uptake.[14] Unlike other hypoglycaemics, there is no associated risk of hypoglycemia.[15]

This review of recent literature compares the effectiveness of metformin to insulin in improving pregnancy outcomes and achieving glycaemic control in women with diabetes in pregnancy.

METHODS

Data sources

Electronic data searches of Medline, Embase, Scopus and Google Scholar databases from 1 January, 2005

to 30 June, 2021 were performed using medical subject headings terms: '*gestational diabetes or pregnancy diabetes mellitus'* AND '*Pregnancy or pregnancy outcomes'* AND *'Insulin' AND 'Metformin Hydrochloride Drug Combination*/or *Metformin*/or *Hypoglycemic Agents'* AND *'Glycemic control or blood glucose'*.

Study selection

Studies were included if they met 3 criteria: participants were pregnant women with GDM; the interventions were metformin with or without supplemental insulin, and insulin alone; studies were randomized controlled trials reporting on the outcomes of interest. Studies among women with pre-gestational diabetes, non-randomised control trials or studies with a limited description of the methodology, non-English language and abstracts/posters were excluded.

Outcomes studied were adverse maternal outcomes: Weight gain, C-section, pre-eclampsia and glycaemic control and adverse neonatal outcomes: Birth weight, macrosomia, pre-term birth and neonatal hypoglycaemia.

Data extraction and quality assessment

Data included authors, year published, number of subjects, study design, results. The revised Cochrane Risk of Bias Assessment for randomised trials was used for the evaluation of bias.[16]

RESULTS

The review included 14 randomised controlled trials on the use of metformin as a treatment for GDM.[17-30] All studies compared the pregnancy outcomes of metformin-treated patients with insulin-treated patients, and all examined the effectiveness of metformin in achieving glycaemic control. Eleven countries were represented with 60–751 participants (average 180) [Figure 1].

Pregnancy outcomes

Maternal outcomes for women treated with metformin compared to insulin, experienced lower maternal weight gain in 7 studies[17,18,22-25,29][Table 1].

All but two studies found C-section rates were unaffected by metformin use. A 2011 study (n = 97) identified a tendency towards

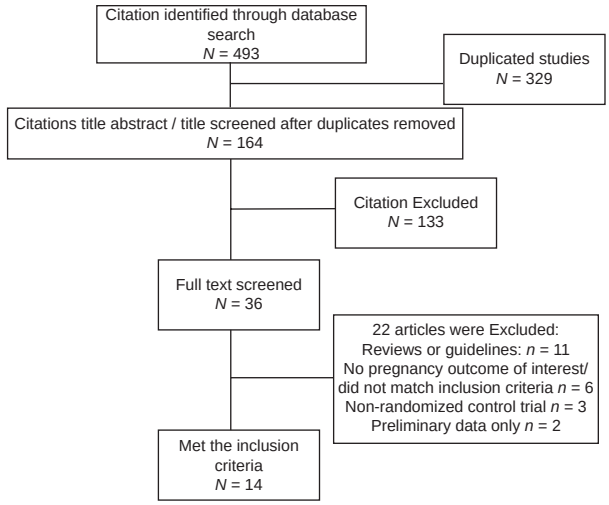

Figure 1: Study selection flow chart.

increased C-sections, while a larger 2021 study (n = 200) found a lower incidence.[21,24]

Neonatal outcomes were favourable: 4 studies have found less hypoglycaemia in the metformin-treated group.[17,25,27,29] Neonatal birth weight was found to be significantly lower in the metformin group compared to insulin in four different studies.[17,20,21,23] Rates of pre-term birth were lower in the metformin group in 1 study which excluded women who required insulin supplementation.[28] Two studies found an increase in pre-term births (P = 0.04), but no increased incidence of either neonatal respiratory distress or neonatal intensive care unit (NICU) admission.[25,27]

Other pregnancy outcomes not assessed across all studies found a positive metformin profile associated with severe maternal hypoglycaemia, mean neonatal glucose level at birth, neonatal jaundice, respiratory distress and NICU admission[17,22-25,29] [Table 2].

Glycaemic control

All 14 studies concluded that metformin was effective in the management of GDM, but in 12 studies, between 3% and 46% of patients started on the metformin required supplemental insulin to maintain glycaemic control [Table 2]. Patient satisfaction with metformin use was high.[25,29] Rowan's 2008 study (n = 751) found more women would choose to receive their assigned metformin treatment again (76.6% vs. 27.2%, P < 0.001) compared to insulin-treated women.[25]

Patients on combination therapy had lower median dose of insulin (42 vs. 50 units. P = 0.002)

Table 1: Maternal outcomes for metformin use compared to insulin for the treatment of gestational diabetes

Author (year)	Weight gain	C-sections	Pre-eclampsia	Glycemic control	Women in the metformin group who required insulin supplementation, *n* (%)
Ainuddin *et al.*, (2015)[17]	↓	↔	↓	↔	32 (43)
Ashoush *et al.*, (2016)[18]	↓	↔	↔	↔	11 (23)
Ghomian *et al.*, (2019)[19]	↔	↔	↔	↔	30 (17)
Hamadani *et al.*, (2017)[20]	↔	↔	N/A	↔	N/A
Ijäs *et al.*, (2011)[21]	↔	↑	N/A	↔	15 (32)
Mesdaghinia *et al.*, (2013)[22]	↓	↔	↔	↔	22 (22)
Niromanesh *et al.*, (2012)[23]	↓	↔	↔	↔	11 (14)
Picon-Cesar *et al.*, (2021)[24]	↓	↓	↔	↔	24 (21)
Rowan *et al.*, (2008)[25]	↓	↔	↔	↔	168 (46)
Ruholamin *et al.*, (2014)[26]	N/A	↔	↔	↔	2 (3)
Saleh *et al.*, (2016)[27]	N/A	↔	↔	↔	N/A
Somani *et al.*, (2016)[28]	↔	↔	↔	↔	8 (25)
Spaulonci *et al.*, (2013)[29]	↓	↔	↔	↔	12 (26)
Tertti *et al.*, (2013)[30]	↔	↔	↔	↔	23 (21)

↔: No significant difference between metformin group and insulin group, ↑: Significantly higher in metformin group compared to insulin group, ↓: Significantly lower in metformin group compared to insulin group, N/A: Not available

Table 2: Neonatal outcomes for metformin use compared to insulin for the treatment of gestational diabetes

Author (year)	Birth weight	Neonatal hypoglycemia	Preterm birth	LGA/macrosomia
Ainuddin *et al.*, (2015)[17]	↓	↓	↔	↔
Ashoush *et al.*, (2016)[18]	↔	↔	↔	↔
Ghomian *et al.*, (2019)[19]	↔	↔	↔	↔
Hamadani *et al.*, (2017)[20]	↓	N/A	N/A	N/A
Ijäs *et al.*, (2011)[21]	↓	↔	N/A	↔
Mesdaghinia *et al.*, (2013)[22]	↔	↔	↓	↔
Niromanesh *et al.*, (2012)[23]	↓	↔	↔	↓
Picon-Cesar *et al.*, (2021)[24]	↔	↔	↔	↔
Rowan *et al.*, (2008)[25]	↔	↓	↑	↔
Ruholamin *et al.*, (2014)[26]	↔	↔	↔	↔
Saleh *et al.*, (2016)[27]	↔	↓	↑	↔
Somani *et al.*, (2016)[28]	↔	↔	↔	↔
Spaulonci *et al.*, (2013)[29]	↔	↓	↔	↔
Tertti *et al.*, (2013)[30]	↔	↔	↔	↔

↔: No significant difference between metformin group and insulin group, ↑: Significantly higher in metformin group compared to insulin group, ↓: Significantly lower in metformin group compared to insulin group, N/A: Not available, LGA: Large for gestational age

and had similar pregnancy outcomes to those treated with metformin alone.[25] The group of patients requiring insulin supplementation had distinct baseline characteristics: higher body

mass index, glucose levels and gestational age at diagnosis and had a higher proportion of Maori or Pacific Islander Indigenous patients (30% vs. 13%, $P < 0.001$).[25]

The study with the highest proportion of participants requiring supplemental insulin (46%), occurred in 10 urban obstetrical hospitals in New Zealand and Australia, and enrolled 363 patients in the metformin group.[25] They defined adequate control as <30% of glycaemic measurements in the reference range (fasting <5.5 mmol/L; 2-h pc <7.0 mmol/L). These target levels are less stringent than present recommended Canadian values of 5.3 mmol/L and 6.7 mmol/L.[4] Insulin supplementation commenced at a median of 20.4 days (interquartile range 12.4–27.5) after beginning metformin.

Assessment of risk of bias

Bias risk was assessed using the Cochrane risk-of-bias tool for randomised trials (RoB 2)[16] which assesses studies across 7 fields including randomisation process, deviation from intervention, missing data outcomes, measurement of outcomes, selection of results reported and overall bias risk. Thirteen of the included studies had a low risk of bias and 1 study had minimal bias concerns [Figure 2].

DISCUSSION

All 14 studies found metformin-treated patients had improved, or equivalent, pregnancy outcomes. Metformin was protective of neonatal hypoglycemia, macrosomia and maternal weight gain. Two studies documented a higher number of pre-term births in patients using metformin, but no increase in neonatal respiratory distress or NIU admission.[24,26] Nine studies found no difference.[17-20,22-25,27-30] This finding is supported by a 2021 meta-analysis of 4545 subjects (including type 2 diabetes mellitus patients) that found an equivalent incidence of pre-term birth.[31]

Metformin was effective for glycaemic control, but 3%–46% of patients required supplemental insulin for glycaemic control in eight studies[17-19,23-25,29,30] [Table 1].

Diabetes Canada supports the use of metformin or insulin for the treatment of GDM when diet and physical activity fail to achieve adequate glycaemic control, but counsels that metformin crosses the placenta.[32] While follow-up studies have not shown developmental concerns, longer-term studies are needed.[32,33] The literature generally compares an intervention to 'routine care' and assumes insulin therapy is accompanied by adequate monitoring and follow up. This may not be the case in all rural practices, where metformin may be more manageable than insulin therapy.

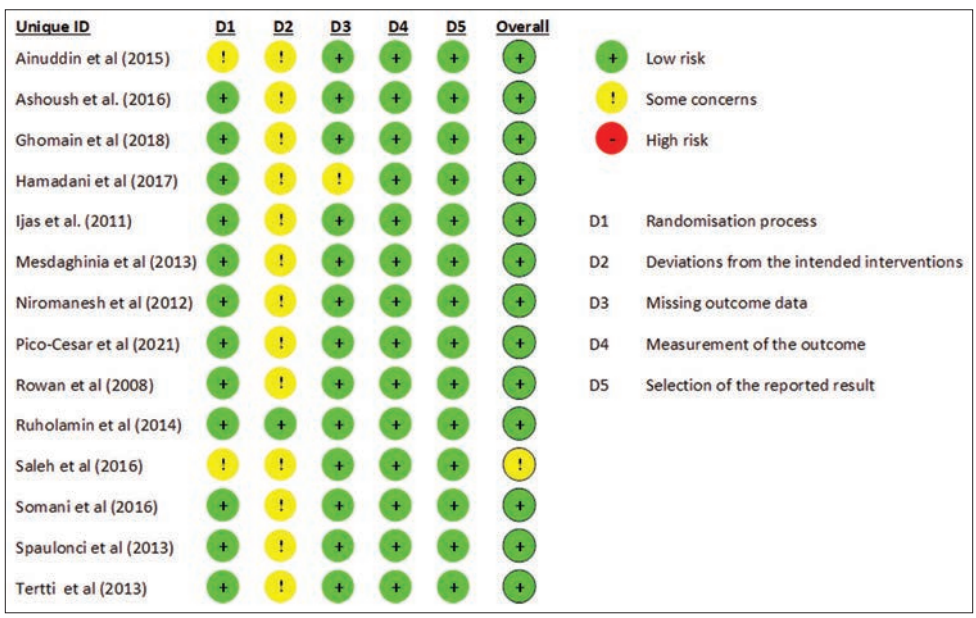

Figure 2: Assessment of the risk of bias in the included studies Version 2 of the Cochrane risk-of-bias tool for randomised trials.

Adopting practical and effective treatment approaches is particularly important in primary care and rural and remote communities where access to specialist care is limited.

Limitations

There was no direct rural context in the reviewed studies. They were in large urban centres and no rural population subsets were identified. It was assumed that adequate dietary and clinical support and monitoring existed. Patient performance of glycaemic monitoring or insulin administration was not measured.

CONCLUSION

Recent high quality studies comparing metformin to insulin for the treatment of GDM generally found either improved or equivalent pregnancy outcome and good glycaemic control for most patients, although many required insulin supplementation. Its ease of use, safety and efficacy suggest metformin may simplify the management of gestational diabetes, particularly in rural and remote communities.

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Conflicts of interest: There are no conflicts of interest.

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