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Review

Metformin versus insulin for gestational diabetes: The reporting of ethnicity and a meta-analysis combining English and Chinese literatures

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ABSTRACT

Conclusive information is lacking regarding the safety and efficacy of using metformin versus insulin in the treatment of gestational diabetes (GDM), with existing reviews providing conflicting conclusions for key outcomes. This updated and comprehensive meta-analysis is the first to include randomised controlled trials (RCTs) published in both English and Chinese. The increased coverage of the literature will help inform clinical decisions regarding the use of metformin to treat GDM. This study will also summarise the reporting of ethnicity by RCTs as there appears to be ethnic disparities in the rates of adverse pregnancy outcomes associated with GDM as well as response to metformin. PubMed, Embase, CENTRAL and China National Knowledge Infrastructure were searched for RCTs that compared metformin versus insulin for the treatment of GDM. Twenty-nine RCTs were included. Metformin was found to be at least comparable to insulin for key pregnancy outcomes, and lower in cost. 2/29 studies reported the number of participants from each ethnic group. The short-term data suggests that metformin is safe and effective for the management of GDM. Further follow-up studies are required to elucidate the longer-term effects of metformin exposure in-utero. We recommend that future RCTs discuss ethnicity when reporting baseline characteristics and results.

1. Introduction

The prevalence of gestational diabetes mellitus (GDM) has been increasing significantly over the past 2 decades, with figures ranging widely between countries and ethnic groups (Beischer et al., 1991; Rossi et al., 2000; Ferrara, 2007). Women with GDM are at increased risk of adverse pregnancy outcomes including preeclampsia (and other hypertensive complications during pregnancy), preterm labour, and operative delivery (Beyuo et al., 2015; Lindsay et al., 2015; Gonzalez-Quintero et al., 2007; Yogev et al., 2004; Hyperglycemia and Adverse, 2010; Carpenter, 2007; Vambergue and Fajardy, 2011). A history of GDM increases the risk of developing cardiovascular disease (Retnakaran and Shah, 2009; Harreiter et al., 2014; Shah et al., 2008; Li et al., 2014; Carr et al., 2006) and was also shown to be a risk factor (independent of pre-pregnancy BMI, age, ethnicity, and parity) for developing early subclinical atherosclerosis among women who had not yet developed type 2 diabetes or metabolic syndrome post-delivery (Gunderson et al., 2014). Around 30–60% of women diagnosed with GDM during the index pregnancy will experience GDM in a subsequent pregnancy (Getahun et al., 2010; Kim et al., 2007; MacNeill et al., 2001; Moses, 1996; Nohira et al., 2006; Philipson and Super, 1989; Schwartz et al., 2015; England et al., 2015). Neonatal complications in offspring born to women with GDM include most commonly macrosomia (and its complications), as well as prematurity, hyperinsulinemia, hypoglycaemia, hypoxaemia, respiratory distress syndrome, asphyxia, polycythaemia, and postpartum hyperbilirubinaemia (Beyuo et al., 2015; Lindsay et al., 2015; Gonzalez-Quintero et al., 2007; Vambergue and Fajardy, 2011; Cordero et al., 1998; Becerra et al., 1990; Correa et al., 2008; Persson et al., 2013; Wendland et al., 2012; Mitanchez et al., 2014, 2015; Robert et al., 1976; Widness et al., 1990).

Insulin has traditionally been the gold standard treatment for GDM when conservative measures such as diet and lifestyle modifications fail to achieve satisfactory blood glucose control (The American College of Obstetricians and Gynecologists, 2013; Nahuis et al., 2014; Cheung, 2009). Around 15–30% of women with GDM cannot be managed with diet and lifestyle modification alone and will require pharmacological therapy (Nahuis et al., 2014; Gilmartin et al., 2008). Insulin is costly, requires multiple-daily injections; and the need for refrigeration and

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careful handling can be cumbersome particularly in developing regions (Berggren and Boggess, 2013; Kavitha et al., 2013; Magon and Seshiah, 2011; Norman et al., 2004; Jiang et al., 2015). Hypoglycaemia occurs in approximately 70% of women who use insulin some time during their pregnancy (Refuerzo, 2011). Oral anti-hyperglycaemic drugs (OADs) (such as metformin and glyburide) are an attractive alternative to insulin, and are increasingly used to treat GDM.

Metformin crosses the placenta freely and foetal serum levels are comparable with maternal values (Vanky et al., 2005; Eyal et al., 2010; Charles et al., 2006; Kovo et al., 2008). Metformin is classified as Category B by the FDA (American Diabetes Associa, 2015) and as Category C by the Australian Therapeutic Goods Administration (TGA) (Helseth et al., 2013) during pregnancy. The American Diabetes Association (ADA) recommends insulin as first-line treatment for GDM, but acknowledges that the evidence so far suggests that metformin may be an acceptable alternative though long-term safety is unknown (American Diabetes Associa, 2016).

Currently, there is some evidence to suggest that use of metformin in women with GDM is relatively safe and effective when compared to insulin with respect to short-term maternal and offspring outcomes (Jiang et al., 2015; Gui et al., 2013; Kitwitee et al., 2015; Lautatzis et al., 2013; Li et al., 2015; Singh et al., 2015; Su and Wang, 2014; Zhao et al., 2015; Zhu et al., 2016; Dhulkotia et al., 2010; Poolsup et al., 2014; Balsells et al., 2015). However, existing reviews on the topic are limited by the small number of randomised controlled trials (RCTs) included and the lack of long-term follow-up data (Jiang et al., 2015; Gui et al., 2013; Kitwitee et al., 2015; Lautatzis et al., 2013; Li et al., 2015; Singh et al., 2015; Su and Wang, 2014; Zhao et al., 2015; Zhu et al., 2016; Dhulkotia et al., 2010; Poolsup et al., 2014; Balsells et al., 2015). The conclusions of currently published systematic reviews and meta-analyses comparing metformin versus insulin in the treatment of GDM are inconsistent for some key pregnancy outcomes including mean birth weight, the rates of preeclampsia, pregnancy-induced hypertension, preterm birth, neonatal hypoglycaemia, and admission to the neonatal intensive care unit (NICU) (Jiang et al., 2015; Gui et al., 2013; Kitwitee et al., 2015; Lautatzis et al., 2013; Li et al., 2015; Singh et al., 2015; Su and Wang, 2014; Zhao et al., 2015; Zhu et al., 2016; Dhulkotia et al., 2010; Poolsup et al., 2014; Balsells et al., 2015). The inconsistencies in the literature are a concern and any increase in the risk of adverse short-term outcomes may be associated with an increased risk of a range of long-term complications.

1.1. Ethnicity and its significance in the management of GDM

Ethnicity is potentially a complex marker of many difficult-to-quantify influences on GDM-affected pregnancies (Nguyen et al., 2012). Ethnicity has been shown to influence response to treatment in women with GDM (Schwartz et al., 2015; Bentley-Lewis et al., 2014; Berggren et al., 2012; Esakoff et al., 2011; Moore et al., 2010; Mukerji et al., 2012; Silva et al., 2006; Sridhar et al., 2013; Williams et al., 2014; Wong, 2012; Xiang et al., 2011). Certain ethnicities including Asian, Indigenous Australian, Torres Strait Islander, Pacific Islander, Maori, Middle Eastern, and non-white African are at increased risk of GDM (Cheung et al., 2001; Erem et al., 2015; Cypryk et al., 2008; Moses and Cheung, 2009). Even when controlled for demographic, anthropometric, and socioeconomic factors, studies have reported ethnic disparities in the rates of adverse GDM-associated perinatal outcomes, GDM recurrence, and risk of diabetes post-partum (Schwartz et al., 2015; Nguyen et al., 2012; Bentley-Lewis et al., 2014; Berggren et al., 2012; Esakoff et al., 2011; Mukerji et al., 2012; Silva et al., 2006; Sridhar et al., 2013; Wong, 2012; Xiang et al., 2011).

Evidence from a study by Moore et al. suggested that African-American individuals may have a better glycaemic response to metformin (lower HbA1c levels) in comparison to European Americans (Williams et al., 2014). Moore et al. also speculated that one possible explanation may be an ethnic difference in response to metformin (Moore et al., 2010). Moore et al. found that the failure rate of metformin was much higher in a study involving mainly Hispanic women with GDM (Moore et al., 2010) whereas a previous study involving mostly African-Americans showed that all patients achieved adequate glycaemic control with metformin (Moore et al., 2007). These findings are particularly interesting, as ethnicity is not universally reported by RCTs and possible ethnic disparities in response to metformin therapy for GDM should be considered when comparing treatment options for GDM.

The present study will search both English language and Chinese language databases for RCTs that compared metformin versus insulin for the management of GDM. A large number of RCTs are published in Chinese only and represent a ready source of potentially valuable data that is often overlooked. It is expected that the expanded coverage of the literatures will enable clarification of current inconsistencies in the literature and support clinicians in making informed clinical decisions regarding the use of metformin in the management of GDM. The reporting of ethnicity by RCTs comparing metformin versus insulin for the treatment of GDM is crucial as possible ethnic disparities in pregnancy outcomes and response to treatment need to be taken into account when interpreting study results. This review will summarise the reporting of ethnicity by the included RCTs.

2. Methodology

This study included RCTs that compared metformin with or without supplemental insulin versus insulin monotherapy for the treatment of GDM. Quasi-randomised and cluster-randomised trials were excluded.

Literature searches were performed in Pubmed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and China National Knowledge Infrastructure (CNKI) from inception to 27/01/2018. The search strategies for Pubmed, Embase, and CENTRAL are included in Appendices A to C. The search strategy (in Simplified Chinese) used for CNKI was adapted from the English search strategies to suit the database as appropriate. The reference lists cited by the selected studies were also screened for eligible studies.

Two reviewers performed eligibility assessment and data extraction in an independent and unblinded manner. A third reviewer was asked to participate if consensus could not be achieved between the two reviewers. Risk of bias was assessed using the assessment tool described in the Cochrane Handbook for Systematic Reviews of interventions (Spaulonci et al., 2013). Statistical analysis was carried out using Review Manager software version 5.3 (Secher et al., 2013). For dichotomous outcomes, the pooled risk ratio and 95% confidence interval were calculated. For continuous variables, the mean difference and 95% confidence interval were calculated. The pooled weighted mean differences and 95% confidence interval were calculated if the outcome measures were the same between trials. The standardised mean difference was used to combine trials that used different methods to measure the same outcome using the generic inverse variance method in Review Manager 5.3. Meta-analysis was undertaken using a fixed effects model, with a random effects model used if at least 5 studies were available for that outcome, $I^2 > 40\%$ and either $Tau^2 > 0$ or there was a low P value ($p < 0.10$) in the Chi^2 test for heterogeneity.

3. Results

3.1. Included studies

The search identified 3994 results from Pubmed, 295 results from Embase, and 262 results from CENTRAL (4551 results in total). Thirteen trials were included for meta-analysis (Moore et al., 2007; Spaulonci et al., 2013; Ainuddin et al., 2015; Ashoush et al., 2016; Hassan et al., 2012; Ijas et al., 2011; Mesdaghinia et al., 2013; Niromanesh et al., 2012; Rowan et al., 2008; Ruholamin et al., 2014; Tertti et al., 2013; Zawiejska et al., 2016; Zinnat Ara Nasreen et al.,