OBSTETRICS

Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis

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OBJECTIVE: The objective of this review was to provide pooled estimates of randomized controlled trials comparing the effects of oral hypoglycemic agents with insulin in achieving glycemic control and to study the maternal and perinatal outcomes in gestational diabetes mellitus.

STUDY DESIGN: A protocol for the study was developed. All metaanalyses were performed using Stats Direct statistical software (Stats Direct Ltd, Cheshire, UK).

RESULTS: Six studies comprising 1388 subjects were analyzed. No significant differences were found in maternal fasting (weighted mean difference [WMD], 1.31; 95% confidence interval [CI], 0.81–3.43) or postprandial (WMD, 0.80; 95% CI, –3.26 to 4.87) glycemic control. Use of oral hypoglycemic agents (OHAs) was not associated with risk of neonatal hypoglycemia (odds ratio [OR], 1.59; 95% CI, 0.70–3.62), increased birthweight (WMD, 56.11; 95% CI, −42.62 to 154.84), incidence of caesarean section (OR, 0.91; 95% CI, −0.68 to 1.22), or incidence of large-for-gestational-age babies (OR, 1.01; 95% CI, 0.61–1.68).

CONCLUSION: Our study demonstrates that there are no differences in glycemic control or pregnancy outcomes when OHAs were compared with insulin.

Key words: gestational diabetes mellitus, insulin, oral hypoglycemic agents

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Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[1] The incidence of GDM depends on diagnostic criteria and varies widely between racial groups. The overall incidence of 3-6% has steadily increased over time,[2,3] ranging from 2.2% in South America to 15% in the subcontinent of India.[4] GDM is associated with increased risks of obstetric morbidity, fetal macrosomia, and perinatal death.

Subcutaneous insulin therapy has been the mainstay of treatment of women with gestational diabetes not controlled by diet modification. Oral hypoglycemic agents (OHAs) have traditionally been avoided in women with diabetes in pregnancy because of the potential risks of neonatal hypoglycemia and teratogenicity associated with placental transfer to the fetus.

There are conflicting studies regarding transfer of glyburide across placenta. The in vitro studies have shown minimal transfer.[5] A recent in vivo study has shown transfer at term but mentions that glyburide appears safe to fetus at maternal doses up to 20 mg/d and that the glyburide concentration-response relationship remains uncertain.[6] Metformin does cross the placenta but acts as an insulin sensitizer, not insulin secretagogue, and is less likely to cause severe neonatal hypoglycemia.[7]

From animal and human data, it was found that glyburide and metformin confer a low risk of teratogenicity[8] and do not have an impact on infant growth and motor development.[9]

Conventionally, treatment for gestational diabetes has been offered in the form of dietary manipulation with supplementary insulin if adequate glycemic levels are not achieved. However, the use of OHAs may provide the flexibility of treatment and high efficacy for both patients and an increasingly overburdened clinical service. Understanding the risks and benefits of the use of insulin and oral hypoglycemic agents for both maternal and neonatal outcome is essential for the care of women with gestational diabetes. The number of reported randomized controlled trials (RCTs) comparing OHAs with insulin is increasing, although most were underpowered and other studies were observational in nature. Therefore, the aim of this systematic review was to provide pooled estimates of RCTs comparing the effects of oral hypoglycemic agents with insulin in achieving glycemic control and to study the maternal and perinatal outcomes in gestational diabetes mellitus.

Materials and Methods

Identification of relevant trials

We attempted to identify all relevant published and nonpublished randomized controlled clinical trials comparing oral hypoglycemic agents and insulin in

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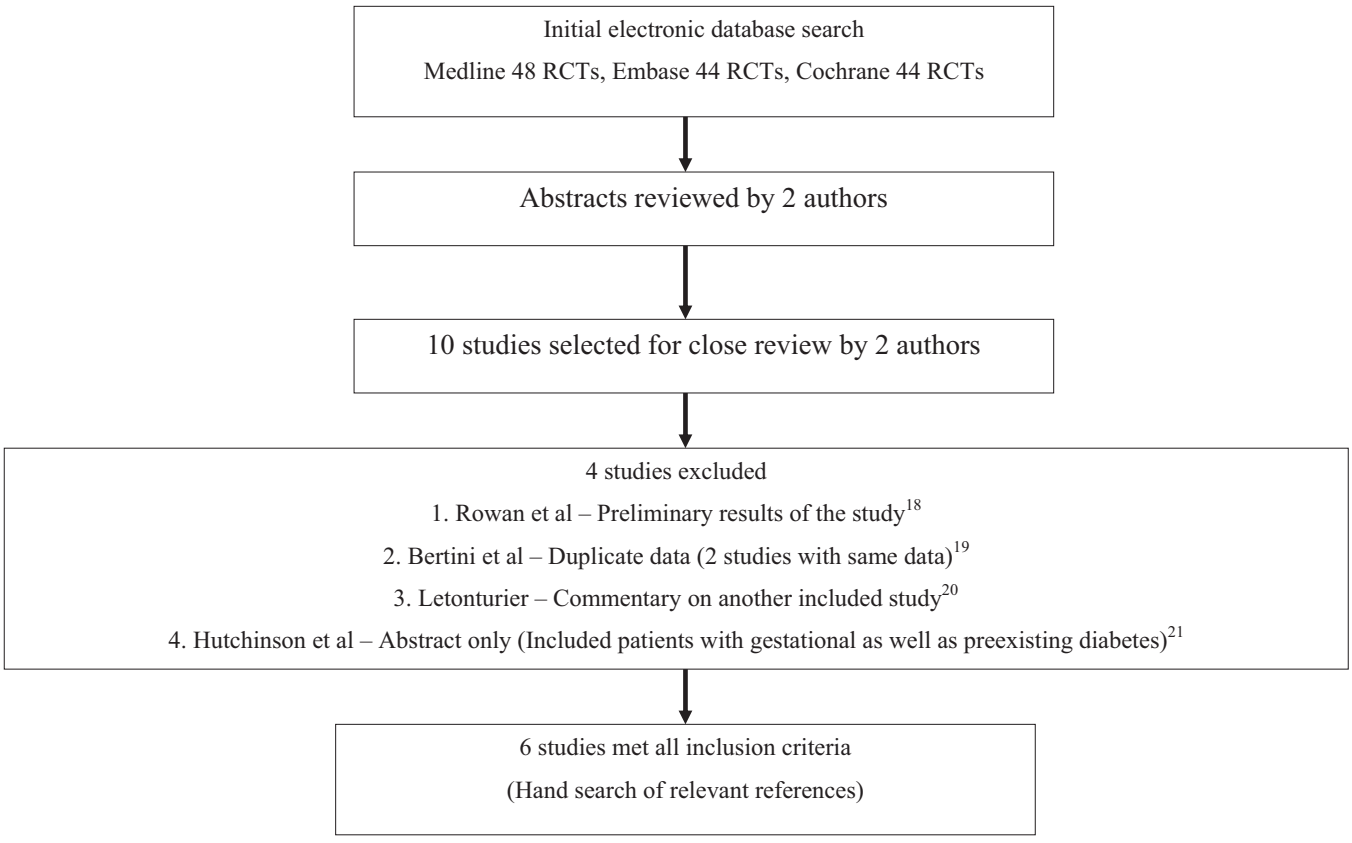
FIGURE 1
Search strategy



RCT, randomized controlled trial.

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the management of gestational diabetes. We performed extensive search on Medline, Embase, and Cochrane without language restriction and using a combination of MeSH and text words for all RCTs comparing oral hypoglycemic agents and insulin in the management of gestational diabetes. For our literature search, we secured the expertise of librarians from our hospital and also the Royal College of Obstetricians and Gynecologists (RCOG). Furthermore, we set up a literature search alert for the local National Health Service library for any new articles relevant to our search. In addition, letters, editorials, references in journal articles, and text books were reviewed.

Methods

A protocol with explicitly defined objectives, criteria for study selection, approaches to assessment of study quality, maternal and perinatal outcomes, and statistical methods was developed. We followed the guidelines for metaanalysis and systematic reviews of health care interventions outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement,[10] which is an evolution of the quality of reporting of metaanalysis guideline.[11] Local research ethics committee approval was not required because of the nature of this review.

Inclusion and exclusion criteria

To be included in the metaanalysis, studies had to fulfill the following inclusion criteria published in the revised Consolidated Standards of Reporting Trials (CONSORT) statement checklist.[12]

1. Population was patients with gestational diabetes.
2. Study design was RCTs.
3. Interventions we compared were insulin vs oral hypoglycemic agents (metformin or glyburide).
4. Outcomes: studies that measured o1ne or more of the following: maternal glycemic control, neonatal hypoglycemia, birthweight, macrosomia, birth injuries, neonatal intensive care unit (NICU) admissions, small for gestational age (SGA) and preterm births, intrauterine fetal deaths (IUFD), congenital anomalies, maternal hypoglycemia or ketoacidosis, hypertensive complications, incidence of cesarean section, side effects of treatment, and maternal satisfaction/quality of life.

Quality assessment and data extraction

All abstracts were evaluated independently by 2 reviewers (J.S.D. and T.F.), and disagreements were resolved by discussion. Final eligibility of studies was decided by consensus. The full articles of studies that met the inclusion criteria were examined independently by 2 au-