Advances in Medical Sciences 59 (2014) 95–101

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original Research Article

The use of glyburide in the management of gestational diabetes mellitus: A meta-analysis

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ARTICLE INFO

Article history:
Received 27 December 2012
Accepted 11 September 2013
Available online 22 March 2014

Keywords:
Gestational diabetes mellitus
Glyburide
Insulin
Meta-analysis

ABSTRACT

Purpose: Glyburide has been used for managing gestational diabetes mellitus (GDM) in a number of countries. It is rather inexpensive. However, its efficacy and safety remain controversial. With this meta-analysis, we evaluated glyburide in comparison with insulin.
Material/methods: With a systematic literature search strategy, a total of 93 randomized controlled trials (RCTs) with insulin and glyburide comparison were identified. Based on the revised Consolidated Standards of Reporting Trials (CONSORT) checklist, five of them met the inclusion criteria and were included in this meta-analysis.
Results: Six hundred and seventy four subjects were included in these five RCTs. When compared with insulin, glyburide had an increased relative risk (RR) for neonatal hypoglycemia (RR: 1.98; 95% confidence interval [CI]: 1.17, 3.36). Estimation of standard mean differences (SMD) showed that both fetal birth weight and incidence of macrosomia were higher in subjects receiving glyburide than in those receiving insulin (SMD: 0.21; 95% CI: 0.06, 0.36; RR: 2.22; 95% CI: 1.07, 4.61 respectively). There were no significant differences in maternal glucose control, glycated hemoglobin, the rate of Cesarean section, large-for-gestational age, neonatal hypocalcemia, length of stay for neonatal ICU admissions, preterm birth, or congenital anomalies.
Conclusions: Our study suggested that in women with GDM, glyburide is as effective as insulin, but the risks of neonatal hypoglycemia, high fetal birth weight, and macrosomia were higher.

1. Introduction

Gestational diabetes mellitus (GDM) is one of the most common medical problems during pregnancy, occurring in up to 5–14% of pregnant women [1,2]. Hyperglycemia is associated with adverse outcomes in women with GDM, which include increased risks of macrosomia, neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia, idiopathic respiratory distress syndrome, stillbirth, and neonatal death. Nearly 80% of women with GDM reach good glycemic control with diet alone, other women require insulin or oral hypoglycemic agent (OHA) [3].

In the guidelines of the American Diabetes Association [4], it is recommended that additional agents should be added if blood glucose was not well controlled with diet alone for 2 weeks. In such cases, subcutaneous insulin has been the treatment of choice, because it does not pass through placenta to the fetus. However, insulin is inconvenient and expensive [5]. GDM and type 2 diabetes share common features of insulin resistance, making OHA a choice for patients with GDM. Several authoritative randomized clinical trials [6] and reviews [7–9] show that OHAs are as effective as insulin in terms of controlling hyperglycemia in patients with GDM, with similar maternal and neonatal outcomes, including studies on glyburide [6], metformin [10–12], and acarbose [13]. In these studies, there were no significant differences in maternal and neonatal outcomes. Glyburide is rather inexpensive oral drug. It may be an option for those who cannot afford expensive treatment, especially in developing countries such as China and India.

Glyburide, which is a second-generation oral sulfonylurea, stimulates insulin secretion from pancreatic beta-islet cells, and thus, causes cellular membrane depolarization. It has been shown that glyburide is more effective than the first generation agents and has a better safety profile. The study by Elliott et al. [14] shows

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http://dx.doi.org/10.1016/j.advms.2014.03.001
1896-1126/

that glyburide is undetectable in the cord serum of infants. In addition, the transfer rate of glyburide is only 0.26% from mother to fetus or from fetus to mother, 2 h after dosing. The adverse event rate is minimal for placental transfer of glyburide to the fetus, even with five-times therapeutic dosage, and does not reach significance even with 100 times therapeutic dosage. Extensive plasma protein binding (99%) and a short elimination half-life are thought to be the major determinants that limit placental transfer of glyburide [15,16]. Other researchers [17] suggested that glyburide is actively excreted by transporter systems other than P-glycoprotein. The authors proposed that a small portion of glyburide is transported by P-glycoprotein, and most of the fetal load is pumped back to the mother by a yet-unidentified placental transport system. It was also shown [18] that with equivalent dosage, the plasma concentrations of glyburide are approximately 50% lower in pregnant women than those in non-pregnant subjects. Hebert et al. [18] reported that the average ratio of umbilical cord/maternal plasma glyburide concentration at the time of delivery was 0.7. They also showed [18] that glyburide transfer occurred at term, and glyburide appeared safe to the fetus with a maternal dosage up to 20 mg/d. However, the glyburide concentration-response relationship remained uncertain. The data from both animal and human studies suggested that glyburide confers a low risk of teratogenicity [19] and does not have an impact on infant growth or motor development [20]. Recent study by Melamed et al. [21] raised concern about the safety of glyburide. The results were controversial for its transplacental transfer, there were no adequate data regarding its safety during the first trimester, and there was an increased incidence of neonatal morbidity, it remains unclear if glyburide can be used safely in women with GDM. The limited placental transfer of glyburide was attributed to its high protein binding, rapid clearance rate, and the role of placental efflux transporters. However, there are also many other maternal, placental, and fetal factors that may alter the transplacental passage of drugs used in pregnancy [22]. As such, further investigation is needed to evaluate its safety during pregnancy.

Goetzl and Wilkins [5] found that glyburide was significantly less costly than insulin for the treatment of GDM. The average annual cost per patient was $165.84 USD. Glyburide is an inexpensive and convenient drug, and it has been used as an alternate for insulin in patients with GDM in some countries [5,23,24]. Some studies compared the efficacy and safety of glyburide and insulin in treating patients with GDM [7,25]. Both of these studies supported the existance of a trend toward infant obesity and neonatal hypoglycemia for glyburide use, but the observed differences were not statistically significant. In our present meta-analysis, we compared the efficacy and safety of glyburide and insulin, in treating patients with GDM, with hope to clarify the above mentioned controversies.

2. Material and methods

2.1. Inclusion and exclusion criteria

According to the revised Consolidated Standards of Reporting Trials (CONSORT) statement checklist [26], studies meeting the inclusion criteria were included in this meta-analysis. The studies included patients with GDM who were not well controlled with diet alone and were thus given insulin or glyburide. Only randomized controlled trials (RCT) were included in our study. The primary endpoints were: maternal fasting plasma glucose, 2-h postprandial plasma glucose, maternal glycated hemoglobin, the rate of Cesarean section, neonatal hypoglycemia, birth weight, large-for-gestational age (LGA), macrosomia, and neonatal intensive care unit (NICU) admissions. Secondary endpoints included preterm birth, intrauterine fetal death (IUFD), congenital anomaly, maternal hypoglycemia or ketoacidosis, preeclampsia and incidence of side effects, neonatal hypocalcemia, hyperbilirubinemia, polycythemia, and intrauterine death.

2.2. Search strategies

All relevant published and unpublished RCTs comparing glyburide and insulin in the management of GDM were identified. Two investigators independently searched Cochrane Central Register of Controlled Trials (CENTRAL, issue 2, 2011), PubMed (1978–2011), Embase (1978–2011), Chinese BioMedical Literature on disk (CBMdisc) (1970–2011), and China National Knowledge Internet (CNKI) (1979–2011). The following keywords and MeSH headings were used in the search: glibenclamide or glyburide and insulin and gestational diabetes mellitus. References to the retrieved articles were screened manually.

Additional searches were undertaken using ClinicalTrials.gov [27], which is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. A literature search alert was set up with the local National Health Service library. Letters, editorials, references in journal articles, and textbooks were also reviewed.

2.3. Quality assessment and data collection

All abstracts and articles were independently evaluated by two reviewers (Ya-chang Zeng and Yue Chen), and a consensus on final eligibility was agreed. Data were extracted independently for methodology and outcome measures according to predetermined criteria.

Quality assessments of observational studies were based on recommendations of the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [28], which included evaluation of random sequence generation, blinding treatment, participants and personnel, outcome assessments, completeness of outcome data, objective reporting, and potential bias.

2.4. Data analysis

All statistical analyses were performed using Stata software (version 11.0, Stata, Texas, USA). The analyses were performed using a fixed-effects model or random-effects model. Relative risk (RR) was calculated for dichotomous outcomes, and standardized mean differences (SMD) were calculated for continuous outcomes. Variance was expressed in terms of 95% confidence intervals (CI).

Heterogeneity between trials was assessed by using the I^2 test ($I^2 > 75\%$ was regarded as great heterogeneity) and Cochran Q test for continuous variables ($p < 0.05$ was regarded as heterogeneity across studies). Homogeneity across studies was also assessed by qualitative visual interpretation using Forest and L'Abbes plots.

3. Results

As shown in Fig. 1, a total of 93 articles were screened, five articles [6,29–32] fulfilled all the inclusion criteria and were included in this meta-analysis. The characteristics and quality assessments of the studies are presented in Table 1. Overall quality and individual study assessments were provided in Fig. 2. The subjects receiving insulin and those receiving glyburide were matched for age, BMI, gestational week, fasting and 2-h postprandial blood glucoses, and hemoglobin A1c levels at the time of joining the study. A total of 674 subjects were included in