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# ROLE OF MANAGEMENT OF GESTATIONAL DIABETES MELLITUS, SYSTEMATIC REVIEW

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***Abstract:*** **Background: Gestational diabetes mellitus (GDM) is known as any degree of hyperglycemia with first recognition during pregnancy.Objective: The purpose of this study was to analyze the roles of different interventions for treating patients with GDM. Methodology: A systematic review was conducted by including randomized controlled trials, and retrospective cohort studies discussing the different interventions in managing gestational diabetes mellitus (GDM). A literature search was conducted using electronic databases together with a hand search of relevant journals and conference proceedings. Conclusion: The low GI diet was the only confirmed advantageous dietary intervention to be followed during pregnancy by women with GDM. According to our results, patients with GDM will not need to use insulin if they adopt a low GI diet during pregnancy and birth weight was lower but without increasing the SGA rates than the control diets.**

***Keywords:*** **gestational diabetes, managing gestational, conference proceedings.**

## 1. INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as the diabetes diagnosed during pregnancy that is not clearly overt diabetes [(1)]. According to this definition, glycemic levels meeting the thresholds of overt diabetes are considered to have pre-existing diabetes and the rest are given diagnosis of GDM [(2)]. According to diagnostic criteria [(3)], the prevalence of GDM ranges from 1.7 to 11.6% [(4,5)]. The prevalence of GDM could be as high as 18% in some regions if the criteria of the International Association of Diabetes and Pregnancy Study Groups Consensus Panel are used [(6)].

Insulin resistance increases in normal pregnancy due to progressively rising levels of feto-placental hormones such as progesterone, cortisol, growth hormone, prolactin and human placental lactogen [(7)]. The pancreas normally compensates by increasing insulin secretion, but when it fails to do so, or when insulin secretion declines due to a beta-cell function impairment [(8,9)] then GDM develops. Maternal hyperglycemia, which is typical of GDM, causes a greater transfer of glucose to the fetus, causing fetal hyperinsulinemia [(10)] and an overgrowth of insulin-sensitive (mainly adipose) tissues, with consequent excessive, unbalanced fetal growth, causing more trauma at birth, shoulder dystocia and perinatal deaths. Hyperinsulinemia can also cause numerous neonatal metabolic complications, such as hypoglycemia, hyperbilirubinemia, hypocalcemia, hypomagnesemia, polycythemia, respiratory distress syndrome, and a greater long-term risk of diabetes mellitus and obesity in the child [(11,12)] .

Recent systematic reviews [(13,14)] reinforce that the treatment of GDM is effective in reducing specific adverse maternal and newborn outcomes without evidence of short-term harm [(13)]. Dietary intervention was simultaneously evaluated with the use of insulin as needed in both systematic reviews. Although dietary therapy is considered the cornerstone treatment for GDM, data on diet intervention as the sole GDM treatment are limited and its actual role in maternal and newborn outcomes has scarcely been studied [(15)]. Moreover, in clinical practice, most of the dietary recommendations for patients with GDM have been based mainly on glucose control, through glucose monitoring data, instead of being based on data from hard maternal or newborn outcomes [(16,17)].

## 2. OBJECTIVES

Treatment of patients with gestational diabetes mellitus (GDM) it's very important to avoid the late maternal and neonatal complication, and its role in management GDM has been scarcely studied. The purpose of this study was to analyze the roles of different interventions for treating patients with GDM.

## 3. METHODOLOGY

We conducted a systematic review study by searching databases from MEDLINE, Embase, Cochrane, and Scopus to identify RCTs that reported dietary intervention and hyperglycemia in pregnancy or GDM and reported maternal and newborn outcomes, through July, 2016. In addition, we also searched all published abstracts from the American Diabetes Association (ADA) and European Association for the Study of Diabetes.

The initial search comprised the MeSH terms "management" [MeSH], "Pregnancy"[MeSH], "Diabetes, Gestational" [MeSH], or glucose intolerance and related entry terms associated with a high-sensitivity strategy for the search of RCTs available at

This systematic review, included studies that have to meet the following criteria a study had to be:

A) Randomized controlled trial of any specific form of therapeutic intervention used in the treatment of GDM.

B) Reporting at least one outcome of interest. Interventions included any form of treatment ranging from dietary intervention to drug therapy including insulin and antidiabetic agents administered on top of routine antenatal care.

## 4. RESULTS

When an appropriate diet, alone or associated with physical exercise, does not suffice to control blood glucose levels in pregnant women, subcutaneous insulin therapy has been considered the standard for management of GDM [24,25,26]. However, insulin has several disadvantages including multiple daily injections, the risk of hypoglycemia and maternal weight gain [27]. It requires modification based on the patient's body mass index, glucose levels and lifestyle[28]. Therefore, detailed guidance for dose change of insulin is necessary to ensure the safe self-administration of insulin. Meanwhile, substantial costs of health education on the safe use of insulin as well as the cost of the drug itself are followed. Naturally, safe and effective oral therapy would be more acceptable even highly desired for women with GDM [29,30].

The use of oral anti-diabetic drugs in pregnancies is not recommended by the American Dental Association (ADA),[20] whereas UK National Institute for Health and Care Excellence (NICE) guidelines consider metformin and glyburide safe in pregnancy and lactation[21]. No OAA is approved by the US Food and Drug administration (FDA) for treatment of diabetes in pregnancy [22]. The Endocrine society has come out a very clear guidelines regarding use of OAAs (glyburide and metformin) in pregnancy[19].They suggest that glyburide is suitable alternative to insulin therapy for glycemic control in women with gestational diabetes who fail to achieve sufficient glycemic control after a 1-week trial of MNT and exercise, except for those women with a diagnosis of gestational diabetes before 25-weeks gestation and for those women with fasting plasma glucose > 110 mg/dl (6.1 mmol/L), in which case insulin therapy is preferred. Regarding metformin, the suggestion for use is in those women with gestational diabetes, who do not have satisfactory glycemic control despite MNT, and who refuse or cannot use insulin or glyburide, and are not in the first trimester. The support behind glyburide as first alternative rather than metformin is controversial [23].

In the meta-analysis, 3 studies measured fasting and postprandial blood sugar and 2 detected the HbA1c% to check the efficiency of metformin. The results are the same as the previous reviews [26,31] that metformin is comparable with insulin in glycemic control. Metformin reduces hyperglycemia by suppressing hepatic glucose output (hepatic gluconeogenesis), increasing insulin sensitivity and enhancing peripheral glucose uptake [32]. These effects are potentially useful during pregnancy when glucose control deteriorates with changes to insulin resistance [28]. In addition, we found that the average postprandial glycemic levels at first week after randomization were significantly lower in the metformin group. This finding indicates that metformin group reached glucose targets sooner. The reason might be that it takes time for the participants to master the usage and dose-computation of insulin.

In this meta-analysis, the incidence of requiring additional insulin to achieve euglycemia was especially high in the study of Rowan [33] (46.3%). Various racial groups and glycemic targets might contribute to the differences among studies.We found that women requiring supplemental insulin had higher fasting glycemic concentrations in OGTT. This indicates that metformin might be especially suitable for mild GDM patients and provides information for the further development of GDM management.

Our search identified retrospective cohort study [18] of the 10,682 women diagnosed with GDM. 8609 (80.6%) were treated with subcutaneous insulin injections and 2073 (19.4%) received glyburide for glycemic control. The median GA at diagnosis of GDM was 27.1 weeks (intra-quartile range, IQR: 23.7–29.3 weeks) for women treated with subcutaneous insulin; it was 27.0 weeks (IQR: 24.0–29.0 weeks) for the glyburide group. Maternal characteristics associated with a higher frequency of glyburide use included nulliparity, African American or Asian, and prepregnancy BMI < 26.0 kg/m$^2$ ($p < 0.001$ for all; **Table I**). Women who received the diagnosis of GDM between 20 and 32 weeks were more likely to be treated with glyburide (21.3%) than those diagnosed prior to 20 weeks (19.7%) or after 33 weeks gestation (17.1%, $p = 0.001$). The use of glyburide was more frequent in women who did not attend college and in women whose primary language was not English (**Table I**). Further, in this cohort, we observed 225 women who were started on glyburide for treatment of GDM on initial visit, and 84 (37%) were switched from glyburide to insulin by the last CDAPP visit. [18]

**Table I: Maternal characteristics associated with women with GDM who were treated with either subcutaneous insulin or glyburide. (18)**

| | **Insulin injections (%), (*n* = 8609)** | **Glyburide (%), (*n* = 2073)** | ***p* value** |
|---|---|---|---|
| Parity | | | |
| Nulliparas (*n* = 2037) | 77.5 | 22.5 | $p < 0.001$ |
| Multiparas (*n* = 8167) | 81.5 | 18.5 | |
| Age | | | |
| Maternal age < 19 (*n* = 104) | 82.7 | 17.3 | $p < 0.001$ |
| Maternal age 20–34 (*n* = 5676) | 79.1 | 20.9 | |
| Maternal age >35 (*n* = 4484) | 82.5 | 17.5 | |
| Race/Ethnicity | | | |
| White (*n* = 2278) | 81.9 | 18.1 | $p < 0.001$ |
| African American (*n* = 385) | 77.7 | 22.3 | |
| Latina/Hispanic (*n* = 5450) | 81.1 | 18.9 | |
| Asian (*n* = 1616) | 75.1 | 24.9 | |
| Other (*n* = 488) | 83.2 | 16.8 | |
| Body mass index (kg/m$^2$) | | | |
| <19.8 (*n* = 48) | 75 | 25 | $p < 0.001$ |
| 19.8–26.0 (*n* = 1774) | 77.3 | 22.7 | |
| 26.1–29.0 (*n* = 2719) | 79.3 | 20.7 | |
| >29.0 (*n* = 5475) | 82.2 | 17.8 | |
| Gestational age at GDM diagnosis | | | |
| < 20 weeks (*n* = 1004) | 80.3 | 19.7 | $p = 0.001$ |
| 20–32 weeks (*n* = 3985) | 78.7 | 21.3 | |
| ≥33 weeks (*n* = 147) | 82.9 | 17.1 | |

Diet is the cornerstone treatment of patients with gestational diabetes mellitus (GDM), thus here we involved our study in demonstrating roles of diet in managing GDM acording to evidance based trailes.

**Low GI Diet helps in managing GDM:**

The low GI diet was the only confirmed advantageous dietary intervention to be followed during pregnancy by women with GDM. Low GI diet analyses included four studies [34,35,36,37] and 257 patients, aged 32.9 years, in whom the diagnosis of GDM was established at 26.8 weeks (24.1–30.1). Regarding diet characteristics, mean energy intake was similar in the

intervention (1,675 kcal/day, range 1,477–1,834) and control (1,694 kcal/day, range 1,485–1,932) groups. The GI score in the low GI dietary intervention ranged from 47 to 49 (mean 48.9), whereas in the control group the range was 47 to 58 (mean 53.5). Dietary GI in all trials was calculated based on food composition tables and published GI values using the glucose = 100 scale. The daily total fiber intake was 27.5 g/day (25.6–30) in the intervention and 23.6 g/day (22.9–25) in the control groups.

Data from low GI trials allowed us to evaluate the maternal weight gain in the last visit of the study, frequency of cesarean section, insulin use, SGA and macrosomia, and newborn weight. Patients in the low GI diet group used insulin less frequently (RR 0.767 [95% CI 0.597, 0.986]; *P*= 0.039), and the newborn weight (MWD −161.9 g [95% CI −246.4, −77.4]; *P* = 0.000) was lower than those in the control group. However, there was no significant change in maternal weight gain (MWD −0.412 kg [−1.842, 1.017]; *P* = 0.428) or cesarean section rates (RR 1.045 [0.736, 1.483]; *P* = 0.286) or an increase in the number SGA newborns (RR 1.588 [0.603, 4.182]; *P* = 0.349) or with macrosomia (RR 0.479 [0.147, 1.561]; *P* = 0.222) [34,35,36,37]. The less frequent use of insulin means that 13 out of 100 patients with GDM will not need to use insulin if they adopt a low GI diet during pregnancy.

**Total Energy Restriction Diet for GDM:**

Total energy restriction diet analyses included two RCTs [38,39] with 425 patients aged 30.6 years (30.4–30.7) in whom GDM diagnosis was established at between 24 and 30 weeks of pregnancy. Energy restriction intervention was a calorie-restricted diet of 35 kcal/ideal body weight (kg)/day in one of the studies [38]. In the other [39], a moderate restriction diet representing 70% of recommended dietary intake for women with GDM was adopted. This means a reduction of ∼30% total of energy intake.

In the total energy restriction category, data for cesarean rates, frequency of macrosomia, and neonatal hypoglycemia were available. Incomplete data about other newborn outcomes and maternal weight prevented us from further analyses. Total energy restriction intervention did not increase the number of cesarean sections (RR 1.091 [95% CI 0.769, 1.496]; *P* = 0.588), frequency of macrosomia (1.002 [0.649, 1.547]; *P* = 0.992), or neonatal hypoglycemia (1.014 [0.718, 1.434]; *P* = 0.936).

## 5. CONCLUSION

The low GI diet was the only confirmed advantageous dietary intervention to be followed during pregnancy by women with GDM. According to our results, patients with GDM will not need to use insulin if they adopt a low GI diet during pregnancy and birth weight was lower but without increasing the SGA rates than the control diets. Beneficial effect on birth weight was already observed in non-GDM pregnant patients after a low GI diet. and metformin is comparable with insulin in glycemic control. Metformin reduces hyperglycemia by suppressing hepatic glucose output (hepatic gluconeogenesis), increasing insulin sensitivity and enhancing peripheral glucose uptake.

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