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Review Article

Oral Anti-diabetic Agents as an Alternative Treatment of Diabetes in Pregnancy

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Abstract: Diabetes is the commonest medical condition in pregnancy. The initial treatment of gestational and Type 2 diabetes in pregnancy is dietary and lifestyle measures. Upon failure of this, pharmacological treatment is advocated which is insulin due to its unparalleled efficacy and safety. But insulin has got some drawbacks like suboptimal patient adherence specially in developing countries. Considering this, studies are done with oral anti-diabetic agents (OAA) among which glyburide and metformin are common. The purpose of this review article is to summarize the different studies done with the OAA specially glyburide and metformin and to critically evaluate the results. Information was collected by searching pub med for related studies, abstracts and articles. Studies on glyburide show little or no transfer across the placenta while metformin cross readily. However animal studies have found no evidence to suggest that glyburide and metformin are teratogenic. In pregnancy glyburide was found to be safe and efficacious with a success rate of 80-85% and there was less incidence of maternal hypoglycemia than insulin. Some studies reported higher rate of preeclampsia, neonatal jaundice and macrosomia. Metformin was associated with reduced neonatal hypoglycemia, maternal hypoglycemia and weight gain with improved treatment satisfaction. However it was observed that failure occurred more with these two drugs in those pregnant women who were early diagnosed cases of gestational diabetes mellitus(<25 weeks), having past history of gestational diabetes mellitus, obese, elderly and with high blood sugar profile specially fasting sample. Prescription of any OAA in pregnancy should be accompanied by full information of the drug including its lack of long term safety data. With the exception of glyburide and metformin there is insufficient data to recommend treatment with any other currently available OAA during pregnancy.

Keywords: Gestational Diabetes Mellitus, Glyburide, Metformin, Pregnancy

1. Introduction

Diabetes is the commonest medical condition in pregnancy, affecting 2–15% of pregnant women [1]. Gestational diabetes mellitus (GDM) constitutes 88% and type 2 diabetes (T2DM) accounts for eight percent of all cases of diabetes in pregnancy [2]. The concerns of diabetes are mainly due to the maternal and fetal complications if the glycemic control during pregnancy is not adequate. There is a linear relationship between maternal hyperglycemia and adverse fetal outcomes. Two large randomized controlled trials in women with GDM have shown the benefit of treating mild hyperglycemia [3, 4].

The initial treatment of these pregnant women with T2DM and GDM is dietary and lifestyle measures. In the event of failure insulin is prescribed due to its unparalleled efficacy and safety. But it can be problematic for some women because of the need for daily injection, its associated costs, pain at injection sites, need for refrigeration and skillful handling. All these contribute to poor patient compliance.

This has led to the search for an alternative to insulin in the management of diabetes in pregnancy. Although oral anti-diabetic agents (OAA) were used in these patients in 1970s and 1980s, concern arose from some studies that found increased rates of perinatal mortality and neonatal hypoglycemia [5, 6]. Because of those concerns, the use of OAA in pregnancy was strongly discouraged. However more recent data on oral agents in women with gestational diabetes suggest that an important paradigm shift is occurring regarding their use in pregnancy.

The objective of this review is to examine the recent

evidences regarding the safety of oral agents in pregnancy including their transfer across the placenta, possible teratogenicity, maternal and perinatal outcome and potential developmental consequences of drug exposure.

2. Methodology

PubMed, other electronic databases and relevant guidelines were searched to identify articles that included the keywords 'pregnancy', 'diabetes' and each individual oral anti diabetic agent's name. The paper reference lists were searched manually for further information.

3. Sulfonylureas

Sulfonylurea act by increasing insulin secretion from the pancreatic β-cells. Its onset of action is around 4 hours, and its duration of action is around 10 hours. Thus, after achieving the targeted therapeutic level, they cover the basal requirement as well as postprandial glucose excursions [7]. The degree to which sulfonylurea cross the placenta differ between individual drugs because of difference in molecular weight, drug clearance and protein binding. Elliot et al. showed that first generation cross the placenta readily (21.5% for tolbutamide, 11% for chlorpropamide) and second generation cross to a much lesser extent (glipizide 6.6%, glyburide 3.9%) [8]. But a randomized controlled trial conducted by Langer et al. showed that glyburide does not cross the placenta and it is due to its high protein binding affinity (99.8%) and short elimination half-life (10h) [9]. Another study supported the lack of placental transfer of glyburide [10]. They suggested that the placenta is actively pumping glyburide back into the maternal circulation by adenosine triphosphate binding cassette transporters.

Langer et al. in his study compared glyburide (n=201) with insulin (n=203) in 404 women with GDM [9]. In his study, 82% women in glyburide group achieved the target glycemic control which was 88% in insulin group. However insulin treated group experienced more hypoglycemia (20% vs. 4%). The glyburide and insulin-treated groups had similar rates of preeclampsia (6%) and cesarean section (23% vs. 24%). Neonatal outcomes did not differ significantly between the two groups. Furthermore, the groups had similar rates of Large for Gestational Age infants (12% vs. 13%), macrosomia (7% vs. 4%), lung complications (8% vs. 6%), hypoglycemia (9% vs. 6%), admission to a neonatal intensive care unit (6% vs. 7%) and fetal anomalies (2% vs. 2%). Also glyburide could not be detected in the cord blood of any neonate.

In another retrospective study with GDM, the pregnancy outcomes of 268 women treated with insulin were compared with 236 women treated with glyburide [11]. There was better glycemic control in glyburide group. There was no significant difference in birth weight, macrosomia, or cesarean delivery between groups. However women treated with glyburide developed preeclampsia (12% vs. 6%) more and many of their offspring received phototherapy (9% vs. 5%). This association has not been described in other studies and was not found in a prospective randomized controlled trial [9].

More than 800 women had reportedly used glyburide in pregnancy [11-14]. Among them 16-19% women failed to achieve optimal glycemic control and needed to switch to insulin. However women who failed to achieve control had high fasting glucose level (>110 mg/dl), diagnosed before 25 weeks of gestation and glucose levels were high on oral glucose tolerance test [14, 15]. Kremer et al. also showed a satisfactory glucose control in 81% study population [13]. A recent prospective comparative study from India, which compared 32 patients each in glyburide and insulin group had found no significant difference in glycemic control [16].

Another randomized controlled trial examined neonatal body composition in 99 women treated with glyburide (49) and insulin (50) [17]. Maternal glycemic control was similar in both groups except post-dinner hypoglycemia in insulin treated group. There was no difference in neonatal fat mass, BMI or ponderal index between groups. However macrosomia occurred more frequently in glyburide group (22% vs. 2.4%).

Hypoglycemia is the main side effect of glyburide treatment in non-pregnant women. In Langer's study, hypoglycemic episodes were more common in insulin-treated patients than in those taking glyburide. In another study, the continuous glucose monitoring showed that the hypoglycemic episodes in insulin-treated women with GDM was 63%, but only 28% in those treated with glyburide [18]. Thus, although some laboratory hypoglycemic episodes (using self-monitoring of blood glucose or laboratory plasma values) may be identified during pharmacological therapy, the rate of these episodes will be significantly lower in glyburide versus insulin treated women. Data are lacking regarding the use of glipizide and other sulfonylurea in pregnancy.

4. Biguanide

Among the biguanides studies were done with metformin. Metformin is an insulin sensitizer increasing muscle glucose uptake but inhibiting gluconeogenesis. It readily crosses the placenta. However regarding teratogenicity, data is available from non-randomized studies primarily from two groups of women (a) pregnant women with poly cystic ovarian syndrome (PCO) and (b) pregnant women with pre-gestational and gestational diabetes [19]. The congenital anomalies that were found in these studies were attributable to the presence of hyperglycemia during organogenesis and not to metformin. Metformin was also found not to be teratogenic in rats and rabbits at doses of up to 600 mg/kg/day, equivalent to 2–6 times the maximum recommended human dose [20].

The largest and most influential study of metformin in pregnancy is the Metformin in Gestational diabetes (MiG) study [21]. It was done in New Zealand and Australia in 2007. It recruited 751 women with GDM among which 363 women were treated with metformin and 388 with insulin. Strict glycemic targets were set and if these were not met, women treated with metformin were offered supplemental insulin. Of the 363 women in the metformin group, 168 (46.3%) required insulin, but the median doses of insulin were lower than in

women treated with insulin alone (42 vs. 50 units). The women who required supplemental insulin were overweight, with past history of GDM and had higher fasting glucose when they entered the trial. However there was no significant difference in the primary outcome, which was a composite of neonatal complications, including hypoglycemia, respiratory distress syndrome, phototherapy, birth trauma, low APGAR and prematurity. The only significantly different secondary outcome measures were maternal weight gain (metformin 0.4 kg vs. insulin 2.0 kg, $P < 0.001$) and treatment satisfaction in favor of metformin. A large group of women in this study (76.6%) in their subsequent pregnancy chose metformin over insulin (23.4%).

Another retrospective study compared the use of metformin with glyburide and insulin in 105 women with gestational diabetes and 55 women with T2DM [22]. There was a higher incidence of preeclampsia in metformin-treated women [32% vs. 7% (glyburide) vs. 10% (insulin), $P < 0.001$] and a higher incidence of perinatal mortality (11.6%) compared with women not treated with metformin (1.3%, $P < 0.02$). The age and BMI of the metformin-treated women (32 years, 31.2 kg/m2) were significantly higher than the other groups (glyburide group 28 years, 22.8 kg/m2, insulin group 29 years, 24.8 kg/m2), which may be the risk factors for these adverse pregnancy outcomes. Other studies showed that the incidence of preeclampsia was either unchanged or reduced in women taking metformin throughout pregnancy [23-25]. Metformin improves endothelial dysfunction, hemostasis and oxidative stress. In this way it may decrease the incidence of preeclampsia.

In a study of 100 women treated with metformin and 100 treated with insulin, there was less maternal weight gain in the metformin group, while neonates had less prematurity, neonatal jaundice and admission to the neonatal unit ($P < 0.01$) [26]. Similarly several other studies comparing metformin with insulin showed that maternal weight gain is lower in metformin treated group; neonates were also smaller, glycemic control was similar in both group and neonatal hypoglycemia was reduced in metformin group [27, 28]. Two further studies comparing the use of metformin with insulin also found no difference in maternal and neonatal variables like caesarean delivery, birth weight, APGAR scores at 5 min, respiratory distress syndrome, hyperbilirubinemia, neonatal hypoglycemia and NICU admission [28, 29].

Studies comparing the effect of metformin and glyburide showed that more women taking metformin were switched to treatment with insulin (34.7 vs. 16.2%) [30, 31]. Women who switched to insulin were relatively older, had higher baseline BMI, more marked hyperglycemia and earlier diagnosed cases of GDM. There was more cesarean deliveries in metformin group (15% vs. 3%) but no difference in preeclampsia. There was no difference in neonatal hypoglycemia or macrosomia rates but mean birth weight was 200 gm greater in glyburide group. In another study comparing metformin with glyburide showed that there was less weight gain in metformin group than glyburide group [31]. There were no differences in glycemic control, birth weight, macrosomia or neonatal hypoglycemia. A further report by the same group described the use of metformin and glyburide in 104 and 96 women, respectively, again finding no differences in adverse neonatal outcomes [32]. Birth weight was about 200 gm lighter in the metformin group, while neonatal blood glucose levels were significantly higher.

Metformin in women with type 2 diabetes in pregnancy (MiTy) trial is currently going on in 25 centers in Canada (Clinical Trials Registry No; NCT 01353391) [33]. It is randomizing 500 women with T2DM in pregnancy to receive metformin or placebo in addition to their usual regimen of insulin. The primary outcome is a composite fetal outcome. This study will clarify whether adding metformin to insulin in women with T2DM will be beneficial to the mothers and infants.

To see the long term effects, neonates of the mothers who were diagnosed cases of PCO and received metformin preconceptionally and also throughout pregnancy were followed up up-to 18 months [23]. There were no differences in height, weight, motor, or social skills between these neonatal groups. In first follow-up of the MiG study, infants of women with GDM who had been randomized to receive either metformin or insulin during pregnancy have been examined at 2 years of age [34]. A healthier fat distribution was found in the arms of the infants whose mother received metformin in pregnancy. However the earliest effects of diabetes in pregnancy on childhood obesity often do not become manifest until after 6-9 years of age [35, 36]. Hence, longer follow-up studies will be required to determine the impact of in utero metformin exposure on the development of obesity and the metabolic syndrome in offspring.

Prospective cohort studies of metformin in PCO patients have shown some benefits [37, 38]. There was significant reductions in miscarriage and fetal loss particularly when the women continued metformin throughout pregnancy. In one study, the spontaneous miscarriage rate was reduced from 62% to 26% after the same women began metformin treatment ($P < 0.0001$) [37]. A further important finding of these studies was an up to tenfold reduction in incidence of GDM in metformin-treated women [24, 25].

5. Thiazolidinediones

Thiazolidinediones are insulin sensitizers. Several studies have shown that, similar to metformin, thiazolidinediones improve insulin resistance and hyperandrogenism and are being used to treat PCO [39]. Although they do not appear to be teratogenic but they readily cross the placenta and their use has been associated with fetal death and growth retardation, secondary to placental dysfunction. There are only limited data in human pregnancy and so their use in pregnancy is not recommended.

6. Acarbose

It reduces intestinal carbohydrate absorption by inhibiting the cleavage of disaccharides and oligosaccharides to

monosaccharides in the small intestine. The drug itself is not absorbed in the body. Animal studies have suggested no harmful effects, but at present the use of acarbose is not currently recommended because of the lack of human pregnancy safety data [40]. There are theoretical concerns that the reduced carbohydrate absorption may alter bowel flora causing prostaglandin E secretion, with the potential to induce labor.

7. Current Position of Oral Anti-diabetic Agents in Pregnancy

Glyburide has not been approved for use in pregnancy by the American Diabetes Association or American College of Obstetrics and Gynecology (ACOG) [41, 42]. However in a survey of ACOG Fellows [43], 13% stated that they use glyburide as first-line therapy for the treatment of gestational diabetes, which was very uncommon 5 years back [44].

UK National Institute for Health and Care Excellence (NICE) guidelines consider metformin and glyburide safe in pregnancy and lactation [45]. In the clinical practice guideline (2015) of Malaysian Medical council metformin is recommended for the management of GDM in selected cases [46]. Since the original study in 2000 many experts and authoritative organizations in the United States (e.g., the Fifth International Workshop on Gestational Diabetes and the North American Diabetes in Pregnancy Study Group) have endorsed the use of glyburide as an alternative pharmacological therapy to insulin during pregnancy [47-49].

No OAA is approved by the US Food and Drug administration (FDA) for treatment of diabetes in pregnancy [50]. However the North American Endocrine society has come out a very clear guidelines regarding use of OAA in pregnancy [51]. They suggest that glyburide is suitable alternative to insulin therapy for glycemic control in women with GDM who fail to achieve sufficient glycemic control after a 1-week trial of Medical Nutrition Therapy (MNT) and exercise, except for those women with a diagnosis of GDM 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 GDM, 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. Scottish Intercollegiate Guidelines Network (2013) has stated that metformin or glyburide may be considered as initial pharmacological glucose-lowering treatment in women with GDM [52].

8. Discussion

The aim of diabetes management in pregnancy is to achieve normoglycemia and meeting this goal is more important than the means by which it is achieved. OAAs are not the drug of choice in women with GDM. However, they do have an important place in GDM management, provided they are used in a rational manner. Among the OAA metformin and glyburide, have now reasonable amount of data to support their use in pregnancy or at least to start a debate for their usefulness and safety.

The pathogenesis of both GDM and T2DM are insulin resistance and inadequate insulin secretion, so the beneficial role of glyburide is evident. Several retrospective and randomized studies using glyburide have shown 80–85% success rate [7]. Moreover, glyburide is comparable to insulin in glycemic control and pregnancy outcome. However the association between glyburide dose, GDM severity, and selected maternal and neonatal factors were analyzed [53]. It was found that the dose of glyburide increased with the severity of GDM. The success rate (i.e., achievement of glycemic control) decreased as disease severity increased. Evidence has shown that glyburide may be a reasonable alternative to insulin for some women with gestational diabetes, especially those who have fasting glucose concentrations less than 110 mg/dl and are in the third trimester [44].

Several other experimental and observational studies have demonstrated that glyburide can effectively lower blood glucose in women with GDM, possibly with a lower treatment failure rate than metformin. While many studies have shown differences in fetal and maternal outcomes between glyburide and insulin, they are limited in their power to demonstrate differences. One commentary suggested that, had the number of participants been doubled in the Langer trial with similar results, the observed differences in glycemic control between groups may have been significant [54]. By contrast, other studies have reported higher rates of preeclampsia, neonatal jaundice requiring phototherapy, longer stay in the neonatal care unit, macrosomia and neonatal hypoglycemia in women who were treated with glyburide. There are no reports of the long-term effects of glyburide on offspring exposed to the drug in utero [33]. The efficacy of glyburide is maximal in the initial 5 years of the diagnosis; thus, patients with longer duration of T2DM may require higher dosage. This is, however, unlikely in patients with GDM as the treatment is usually confined to 8–12 weeks of duration [55].

Metformin though it crosses the placenta but it has not shown any teratogenic effect. Moreover there appears to be a reduction in miscarriage and onset of GDM in PCO patients While many of the studies of the use of metformin in GDM are limited by small numbers, they are similarly encouraging, showing at least equivalent neonatal outcomes for metformin compared with insulin, while reporting reductions in maternal hypoglycemia and weight gain and improved treatment satisfaction. Metformin does not stimulate the fetal pancreatic cells to produce insulin and hence are not associated with neonatal hyperinsulinemia and subsequently neonatal hypoglycemia. Women with high BMI, prior history of GDM and high baseline glucose have a high chance of missing their glycemic targets with metformin alone. So these types of patients may be considered for starting of insulin along with metformin [33]. It seems reasonable to continue metformin if a woman becomes pregnant while taking the drug as it is likely

that any potential harm is outweighed by the risk of worsening glycemic control.

Most women with diabetes in pregnancy require increasing doses of insulin for good glycemic control; some women with exceptionally high insulin resistance require very large doses of insulin for optimal control. It has been hypothesized that metformin may help to sensitize these women to insulin, thus allowing for lower amounts of insulin to be used [56]. The safety of this approach will be demonstrated more definitely after the publication of MiTY [33] study results.

With both drugs, many women do not achieve adequate glycemic control and require insulin. It is important to minimize the time of hyperglycemia and so doses should be rapidly escalated to the maximally tolerated doses, while being mindful of the risk of side effects.

When making a decision between metformin and glyburide, the benefits of less maternal weight gain, lower birth weight and treatment satisfaction favor the use of metformin over glyburide. Although a greater proportion appears to require supplementary insulin, the addition of insulin to metformin is more straightforward than the switch from glyburide. Although both metformin and glyburide appear safe, but the concept that glyburide does not cross the placenta has been challenged. Hebert et al. described a maternal to fetal ratio for glyburide of 0.7 [57]. They attributed these diverging results to the use of a method with a detection limit of 0.25 ng/mL, while that of the method of Langer et al was 10 ng/mL [9]. So if indeed glyburide does cross the placenta in significant quantities, the potential to stimulate fetal insulin production is of concern.

Women with high levels of hyperglycemia, which in the treating physician's opinion are unlikely to respond to MNT alone, may be started immediately on pharmacological treatment. The choice in such cases is usually insulin [51]. Women with significant obstetric morbidity (e.g., macrosomia, intrauterine growth retardation, hydramnion), expected deterioration of glycemia (e.g., planned antenatal corticosteroid therapy), and abnormal laboratory reports (e.g., ketonuria, increased fetal abdominal circumference on ultrasound) may also be started on insulin along with MNT [58].

Insulin therapy involves daily injections, which may lead to suboptimal adherence by many women. In many developing countries, women cannot afford insulin therapy. However, it is evident that if the women are given the choice of insulin versus tablets, they will invariably prefer taking drugs orally than taking minimum three daily injections.

9. Conclusion

Data on the use of OAA in pregnancy are changing the previous concept that OAA should never be used in pregnancy. This is always welcome to women with GDM who are inconvenienced by injections and to those in areas where insulin may not be readily available or is cost prohibitive. With the growing rates of diabetes, especially in the developing world, such a shift may be greatly appreciated. Prescription of any OAA in pregnancy should be accompanied by explanation and discussion of potential limitations and side effects of the drug and documentation of the reason why OAAs are being considered. However, regardless of the mode of therapy, whole patient care (glucose monitoring, education, diet adherence and so forth) will determine overall success in managing this disease and the potential to maximize the quality of perinatal outcome. With the exception of glyburide and metformin there is insufficient data to recommend treatment with any other currently available OAA during pregnancy. The existing body of research should encourage us to rely on evidence-based knowledge and not emotion-based misinformation when considering this medication for use with diabetic pregnant women.

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