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REVIEW ARTICLE

Oral Hypoglycemic Agents in pregnancy: An Update

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Abstract
Introduction Traditionally, insulin has been the gold standard in the management of Type 2 diabetes in pregnancy and gestational diabetes. However, insulin therapy can be inconvenient because of the needs for multiple injections, its associated cost, pain at the injection site, need for refrigeration, and skillful handling of the syringes. This has led to the exploration of oral hypoglycemic agents as an alternative to insulin therapy.
Objectives This review examines and evaluates the evidences on the efficacy, safety, and current recommendations of oral hypoglycemic agents.
Conclusion The evidence of this study supports the use of glyburide and metformin in the management of Type 2 diabetes and gestational diabetes with no increased risk of neonatal hypoglycemia or congenital anomalies. The safety of these oral hypoglycemic agents are limited to the prenatal period and more randomized controlled trials are required to provide information on the long-term follow up on neonatal and cognitive development.

Keywords Oral hypoglycemic agents · Gestational diabetes mellitus · Type 2 diabetes

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Introduction

Diabetes is one of the common medical disorders complicating pregnancy and its incidence in women of reproductive age group is increasing globally. Gestational diabetes constitutes ~88 %, and Type 2 diabetes accounts for eight percent of all cases of diabetes in pregnancy [1]. The overall incidence of gestational diabetes is 3–6 % with a variation of 2–15 % observed, depending on the diagnostic criteria used. The incidence is three percent in South America, five percent in the United States, and fifteen percent in India [2–4].

The concerns of diabetes are mainly related to its maternal and fetal complications. Although a significant reduction in perinatal mortality has been observed in the last decade, there is little change in the perinatal morbidity [5]. Schaefer-Graf et al. [6] suggested that maternal hyperglycemia in the initial presentation is associated with the risk of fetal congenital malformations. The HAPO Study Cooperative Research Group demonstrated strongly that the adverse perinatal outcomes were related to hyperglycemia in pregnancy resulting in fetal hyperinsulinemia, macrosomia and birth trauma [7]. These effects were translated into the adult life with the risk of development of obesity, Type 2 diabetes and metabolic syndromes [8]. Achieving euglycemia optimizes the outcome in diabetic pregnancies as recommended by the American College of Obstetricians and Gynecologists and American Diabetes Association thereby promoting maternal well-being and reducing the adverse perinatal outcomes [9, 10].

The initial treatment in these patients with Type 2 diabetes and gestational diabetes is by diet modification and in the event of failure of control with diet, the treatment is shifted to insulin to achieve tight glucose control with no risk of placental transfer [11, 12]. However, insulin therapy can be inconvenient because of the need for multiple injections, its associated cost, pain at injection site, need for refrigeration, and skillful handling (a problem in low resource countries), and all these has contributed to poor patient compliance [13]. This has also led to the search for oral hypoglycemic agents as an alternative option to insulin therapy. The convenience of these oral medications pertaining to handling and storage, dosage, and cost has potential implications in low resource settings, thus increasing the likelihood of their use. There are significant concerns about recommending oral hypoglycemic agents in pregnancy because of their possible risks of transplacental passage and consequent fetal teratogenesis, hypoglycemia, hyperbilirubinemia, and polycythemia [14, 15]. The objective of this review is to summarize the evidences available in the pharmacological basis of their action, their efficacy, and safety, and to evaluate the current recommendations with the implications in clinical practice.

Pharmacodynamics of the Oral Hypoglycemic Agents

The various oral hypoglycemic agents are listed in Table 1.

Sulfonylurea

Sulfonylureas have been in use since decades in the management of Type 2 diabetes and are insulin secretogogues.

Table 1 Classification of oral hypoglycemic drugs

Sulfonyureas	First generation
	• Acetohexamide
	• Chlorpropamide
	• Tolazamide
	• Tolbutamide
	Second generation
	• Glyburide/ glibenclamide
	• Glipizide
	• Glimepiride
Biguanides	• Metformin
Thiazolidinediones	• Pioglitazone
	• Rosiglitazone
Meglitinides	• Repaglinide
	• Nateglinide
Alpha-glucosidase inhibitors	• Acarbose
	• Miglitol

They act by stimulating the release of insulin from the functional cell mass of pancreas binding to specific receptors in pancreatic beta cell plasma membrane resulting in closure of adenosine triphosphate channels. This initiates the opening of the calcium channels and leads to increase in cytoplasmic calcium thereby stimulating insulin release [16, 17]. They have been identified to enhance insulin sensitivity in peripheral tissues [18]. The pathogenesis of both gestational diabetes and Type 2 diabetes are insulin resistance and inadequate insulin secretion, and hence the beneficial role of sulfonylurea is evident. The first generation sulfonylureas are acetohexamide, chlorpropamide, tolazamide, and tolbutamide. Specifically, there are concerns regarding chlorpropamide like inducing neonatal hypoglycemia, and retrospective case control studies identified threefold increase in congenital anomalies in babies of Type 2 diabetes patients exposed to these drugs during the organogenesis period, and hence they are not recommended in pregnancy [19].

The second generation of sulphonylurea like glyburide does not cross the placenta in significant amounts. This was demonstrated by Elliot et al. [20–22] using isolated perfused human placental cotyledon. Langer et al. [15] showed that there were no detectable glyburide levels in the umbilical cord despite the achievement of therapeutic concentrations of the drug in the maternal blood. Glyburide's inability to cross the placenta, despite its low molecular weight, is attributed to its high protein-binding capacity of 99.8 % [23]. However, another possible explanation proposed that there was pumping back of the glyburide load back into the maternal system by an unidentified placental transport system [24].

Glyburide reduced the fasting blood glucose (FBG) levels by 2–4 mmol/L (36–72 mg/dL) as well as glycosylated hemoglobin HbA1c by 1–2 % [25–27]. The efficacy of glyburide is maximal in the initial 5 years of the diagnosis; thus, patients with longer duration of type 2 diabetes may require higher dosage. This is, however, unlikely in patients with gestational diabetes as the treatment is usually confined to 8–12 weeks of duration [28]. The absence of fetal adverse effects such as malformations and hypoglycemia makes it an acceptable treatment option.

Biguanides

Metformin is the second generation biguanide that acts by increasing the insulin sensitivity and thus reducing the insulin resistance [29, 30]. It reduces the rate of hepatic glucose production, hepatic glycogenolysis, and increases the insulin-stimulated uptake of glucose in skeletal muscles [28]. The biguanides does not stimulate the fetal pancreatic cells to produce insulin and hence are not associated with neonatal hyperinsulinemia [31]. The peak plasma half-life

is 2–5 h. The mechanism of clearance of metformin is by renal tubular secretion with minimal protein binding. This reflects the need for dose adjustment in pregnancy because of the increased glomerular filtration in pregnancy [32].

Studies have identified that metformin crossed the placenta but had minimal effect on transplacental flux [22]. The transfer in human milk is minimal and hence can be used safely in lactation [33, 34].

Thiazolidenedione

Thiazolidenediones act on the peroxisome proliferator-activated receptor reducing the insulin resistance. The pharmacodynamics of these drugsare similar to glyburide. They are bound to plasma proteins (99.8 %). The drugs are metabolized in the liver [28].

Despite the similarities to biguanides, these drugs cross the placenta as demonstrated in rats resulting in delayed growth and insulin resistance [35]. A study done by Chan et al. with rosiglitazone given to pregnant women undergoing surgical termination of pregnancy between 8 and 12 weeks of pregnancy, and rosiglitazone was detected in 19 out of 31 (61 %) fetal samples [36].

One study suggested that troglitazone (the first thiazolidinedione agent) reduced the incidence of new onset diabetes in patients with gestational diabetes. However, troglitazone was withdrawn because of its hepatotoxicity [37]. The second generation thiazolidinedione (rosiglitazone and pioglitazone) was more potent, not hepatotoxic and was effective in reducing the decline of beta cell function in patients with type 2 diabetes [38, 39]. Cataldo et al. reported a case study in a woman with polycystic ovarian syndrome on rosiglitazone at the time of conception. In this case, rosiglitazone was subsequently discontinued and pregnancy was uneventful [40].

Meglitinides

Meglitinides are insulin secretogogues like sulfonylurea. Their actions were similar to sulfonylurea but via different receptor. There is no data regarding the use of nateglinide during pregnancy. Until further data is available, it is prudent not to use this drug in pregnancy. A randomized controlled trial with repaglinide and insulin demonstrated that the pre and postprandial glucose levels were the same in the treatment and the control groups and there was no difference in the fetal and neonatal outcome [15].

Alpha Glucosidase Inhibitors

Acarbose acts by slowing the absorption of carbohydrates from the intestines thereby reducing the postprandial hyperglycemia [41].

As acarbose acts at the gastrointestinal tract, there is no blood stream transfer to the placenta [42]. It is less effective than glyburide in reducing the glycemic levels and hence its use is restricted in combinations with glyburide or metformin [42].

Efficacy and Safety of Oral Hypoglycemic Agents

Insulin and Glyburide

Four randomized controlled trials compared the effects of insulin and glyburide and evaluated the maternal outcomes such as preeclampsia, cesarean delivery, weight gain, glycemic control and hypoglycemia. The neonatal outcomes included neonatal hypoglycemia, macrosomia, congenital anomalies [15, 42–44]. Among them the largest trial was by Langer et al. that included 404 women who were randomly assigned to insulin and glyburide. The outcome was comparable as 82 % of glyburide group and 88 %of insulin group achieved good glycemic control. In addition, the glyburide group experienced less maternal hypoglycemia (2 %) compared to insulin group (20 %). There was no difference in other maternal outcomes like preeclampsia, rate of cesarean delivery and neonatal hypoglycemia. This trial proved glyburide as a safe and effective alternative therapy. A prospective cohort study by Kremer included seventy-three participants on glyburide. The results demonstrated a satisfactory glucose control in 81 %of participants and corroborated the evidence of the study by Langer et al. [45]. However, a study by Ogunyemi et al. reported the higher mean FBG levels ($p = 0.02$) and 2 h postprandial level in women on glyburide compare with insulin [46]. It was addressed that glyburide failed to achieve euglycemia in 6–20 % of the subjects. The factors associated with glyburide failure were identified in the study conducted by Kahn et al. [47] which included maternal age of more than equal to 34 years and diagnosis of gestation diabetes before 25 weeks of gestation.

The studies did not show significant difference in the average FBG, 2-hours post prandial glucose levels (PPG) and the proportion of women undergoing cesarean section between the glyburide and insulin groups. However, it was identified that the limited power of the studies with small sample size could have attributed to the inability to detect statistical difference in the outcomes [45].

Insulin, Glyburide, and Acarbose

In the randomized controlled trial by Bertini et al. [48] where the subjects were assigned to insulin, glyburide and acarbose showed no significant statistical difference in the FBG, PPG, and incidence of preeclampsia between these

groups. However, there was a higher proportion of small-for-gestational age infant in insulin group than the other groups. In a small study of six pregnant women by Zarate et al., it was observed that the elevated FBG and PPG were stabilized after starting with acarbose, and pregnancy outcome was uneventful with no fetal and neonatal complications [49].

Metformin and Insulin

(MiG trial–Metformin in gestational diabetes trial), a large randomized controlled trial included 751 participants between 28 and 33 weeks of gestation who were randomly assigned to metformin and insulin. It was noted that only 46.3 % of the metformin group required supplemental insulin to maintain euglycemia. A large number of women (76.6 %) opted for metformin over insulin (27.2 %), ($p < 0.001$ %) in their subsequent pregnancies. The results also demonstrated lower PPG levels in women on metformin, and there was no statistically significant difference between the two groups in terms of adverse neonatal outcomes like hypoglycemia, birth trauma, respiratory distress syndrome, and preterm birth [50]. As metformin crossed the placenta, the potential effects of metformin on growth of the children were studied in The Offspring Follow-Up (TOFU) study. TOFU study compared the body composition in terms of fat distribution of the children (born of the women who participated in the MiG trial) at 2 years of age. The results demonstrated that exposure to metformin in utero has led to more fat being stored in subcutaneous sites (subcapsular and biceps skinfolds), which suggested that there was less ectopic or visceral fat in these children. There was no difference in total body fats when compared with children whose mothers were treated with insulin alone during pregnancy. However, to infer that less ectopic fat was a result of a more insulin-sensitive pattern of growth requires further evaluation [51].

Jakubowicz et al. in his retrospective study assessed pregnancy outcomes in 65 pregnant women with polycystic ovarian syndrome with and without metformin. The early pregnancy loss was 8.8 % in group on metformin compared with 41.9 % in group without metformin [52–54]. Glueck et al. compared the development of gestational diabetes in women with polycystic ovarian syndrome on metformin and without metformin therapy. This study showed the development of gestational diabetes was (3 %) in metformin group compared with (23 %) those not within metformin group, thereby indicating a significant reduction [55]. Coetzee et al. [56] reported that metformin was associated with decreased infant morbidity and mortality compared with patients treated with insulin. Hale et al. observed that the concentration of metformin in breast milk was low, and the mean exposure to the drug was 0.28 %—much below the 10 % level—which is of concern for breastfeeding. Therefore, it was concluded that the use of metformin is safe for breast feeding [57].

Clinical Practices of Oral Hypoglycemic Agents in Pregnancy

Baris Akincia et al. investigated the practice patterns of clinicians (family physicians, internists, and obstetricians) in Turkey with respect to diabetes in pregnancy. The results suggest that there is considerable variation in the clinical practice patterns. Internists were more likely to use insulin analogs. A significant number of physicians stated that they used oral hypoglycemic agents, and a considerable number of family physicians have used the drugs which have not been proven to be safe in pregnancy [58]. Hence, the conclusion was made that there was room for improvement in the knowledge and practices related to the use of oral hypoglycemic agents in pregnancy. It was also suggested that an education program to enhance the clinical aptitude of physicians, particularly family physicians, in the medical management of gestational diabetes was of critical importance.

This could be facilitated by continuing medical education and training programs to update clinician's knowledge on the rationale of usage of oral hypoglycemic agents in pregnancy in conjunction with local protocols.

Current Developments

After the discovery of insulin, attempts were made to create oral insulin. The success of oral insulin depends on its ability to resist the enzymatic degradation, during its transit in the gastrointestinal system [59]. The advances in this area have resulted in understanding the techniques of effectively delivering oral insulin and the development of oral insulin. Several systems that provide protection to insulin during the transit in the gastrointestinal system have been developed. These systems include matrices that use medium chain fatty acids designed to release insulin in the duodenum, a hepatic-directed vesicle (HDV) containing liposomes encapsulating insulin, which delivers it directly into the liver cells; an absorption enhancer; and solubilizer that enhances the drug absorption in the small intestine; and low molecular weight chemical entities that act as carriers for the drug [60]. ORMD-0801 is an oral insulin that has completed its phase I trials, and the results are encouraging as it has proven to be safe, well tolerated, and insures consistent reduction in glucose and C-peptide [61]. The other alternative routes of insulin delivery being developed are buccal and inhaled, whereby insulin is delivered directly into the mouth via a metered dose spray (RapidMist device) [59].

Summary of the Studies

Currently both glyburide and metformin are classified by the FDA as Category B drugs for use in pregnancy. Glyburide does not cross placenta and has strong evidence of its efficacy which is well established in the large randomized trial by Langer et al. This conclusion by Langer et al. regarding glyburide is upheld in various randomized controlled trial and observational studies. However, one needs to keep in mind that glyburide still fails in about 20 % of women. The other oral hypoglycemic agent demonstrated to be effective is metformin especially in polycystic ovarian syndrome where it is beneficial in reducing the pregnancy loss, reducing the development of gestational diabetes, and improving the insulin sensitivity. The benefits of using metformin in pregnancy is well demonstrated in the randomized controlled trial by Rowen et al. 2008 with metformin in gestational diabetes trial (MiG trial). It is also concluded that metformin is not associated with increased perinatal complications as compared with insulin, and that the women preferred metformin to insulin treatment. The follow up of these exposed children of age 2 years studied in the MiG–TOFU trial reveals that metformin-exposed infants had more subcutaneous fat and less visceral fat, which may probably result in increased insulin sensitivity pattern of growth in future. Acarbose appears promising because of its pharmacodynamic profile in the absence of systemic effects. Although this drug has also been categorized as FDA category B drug, there is a need for further randomized trials comparing acarbose with other oral hypoglycemic agents and insulin before validating its effectiveness. Further studies are mandatory to recommend the use of thiazolidinediones and meglitinides in pregnancy.

Conclusions

The overall evidence suggests that oral hypoglycemic agents are a safe alternative in the presence of mild-to-moderate hyperglycemia. They can be an effective alternative in developing countries where resources and availability of the insulin is of concern. As the incidences of type 2 diabetes and gestational diabetes increase, it becomes important to have alternatives to women who are not adequately controlled with diet and exercise and are unable to be compliant with standard insulin therapy. The advantages of oral hypoglycemic agents are simple to administer, convenient, pain free, and cost effective. The current evidence from the data as discussed in this review supports the use of glyburide and metformin in the management of Type 2 diabetes and gestational diabetes. There is still a room for improvement in the knowledge and practices of prescribing these agents among the health providers. The providers should communicate to the women that there are no data available on the long-term health of the offspring's exposure to glyburide or metformin, as the safety aspects of these oral hypoglycemic drugs are limited to the prenatal period. We therefore need more randomized control trials to provide more information on the long-term follow up on neonatal function and cognitive development.

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