

## Use of Oral Hypoglycemic Agent in Pregnancy: How far have We Reached?

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Received date: April 22, 2017; Accepted date: April 27, 2017; Published date: April 30, 2017

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### Introduction

Diabetes is prevalent medical disorder in pregnancy and its incidence is on the rise globally. Gestational diabetes constitutes 88%, and Type 2 diabetes accounts for eight per cent of all cases of diabetes in pregnancy [1]. The overall incidence of gestational diabetes varies as 4-15%.

The HAPO Study Cooperative Research Group stated that the adverse perinatal outcomes were proportional to hyperglycemia in pregnancy [2]. Hyperglycemia results in complications like fetal hyperinsulinemia, birth trauma and macrosomia. These effects were translated into the adult life which increases the risk of obesity, metabolic syndromes and Type 2 diabetes [3]. Euglycemia ensures favourable outcome in diabetic pregnancies as promoted by the American College of Obstetricians and Gynaecologists and American Diabetes Association thereby assuring maternal well-being and reduction in adverse perinatal outcomes [4,5].

The primary treatment in these patients with Type 2 diabetes and gestational diabetes is by diet modification. In case of inadequate control, the treatment is switched over to insulin [6]. But insulin therapy is cumbersome to use because of the multiple injections, its linked cost, pain at injection site, requirement for freezing, and skill required and thus resulting in poor patient compliance. Therefore, there is need for oral hypoglycemic agents as an alternative option. The ease of administration, convenience of use and storage, dosing and price are responsible for potential increase in their use.

### Oral hypoglycaemic agents

#### Sulfonylureas

Sulfonylureas are used as first line therapy in the treatment of Type 2 diabetes. Their action is by stimulation of insulin release from the functional cell mass of pancreas. They bind to receptors in pancreatic beta cells which results in closing of adenosine triphosphate channels and opening of the calcium channels. The consequent increase in cytoplasmic calcium results in releasing of insulin. They also improve insulin sensitivity in peripheral tissues.

Of all the sulfonylureas, the second generation one, glyburide does not traverse the placenta significantly. Langer et al. [6] demonstrated that glyburide was not detected in the umbilical cord even after achieving drug in therapeutic concentration in the maternal serum. This was confirmed by Elliot et al. via isolation of perfused human placental cotyledon [7]. The reason of this fact is due its high protein-binding capacity of 99.8% despite low molecular weight [8]. The reduction in fasting blood glucose levels by 36-72 mg/dl and glycosylated hemoglobin HbA1c by 1-2%. The absence of fetal

malformations and hypoglycaemia owing to its use makes it an attractive treatment option.

#### Biguanides

Metformin is a second generation biguanide. It increases insulin sensitivity and reduces insulin resistance. The biguanides don't result in neonatal hyperinsulinemia as it does not stimulate the fetal pancreas [9]. The peak plasma t<sub>1/2</sub> is 2-5 h. It is cleared by renal tubular secretion with minimal protein binding. This creates the need for adjustment of dosing during pregnancy owing increased glomerular filtration in pregnancy [10]. Studies showed that metformin crosses the placenta but had no effect on transplacental flux [9,10].

#### Other hypoglycaemic agents

Thiazolidenediones act on the peroxisome proliferator-activated receptor and thus reduces the insulin resistance. The pharmacodynamics follows the same principle as glyburide. However, these drugs cross the placenta and results in delayed growth and insulin resistance in rats as showed by Sevillano et al. [11]. Meglitinides acts via similar mechanism as sulfonylurea but through different receptor. However, because of lack of relevant data, it is not sensible to use nateglinide in diabetes in pregnancy. Alpha Glucosidase Inhibitors such as acarbose slows the absorption of carbohydrates from the intestines and thus helps in reducing the postprandial hyperglycemia as shown by Lebovitz et al. [12]. Acarbose does not cross the placenta, as it acts at the gastrointestinal tract. It is used with glyburide or metformin due to its lower efficacy [13].

#### Comparison between insulin and glyburide

To compare insulin and glyburide, the largest randomized controlled trial was conducted by Langer et al. [9]. The trial included 404 women who were administered insulin and glyburide in random fashion. The outcomes in both the groups were similar. In both the groups, more than 80% patients achieve adequate glycemic control. The hypoglycemia experienced by women was considerably less in glyburide group as compared to insulin (2% vs. 20%). The preeclampsia, caesarean rate and neonatal hypoglycemia were experienced similarly in both the groups. Kremer et al also corroborated similar findings in a cohort study.

#### Comparison between metformin and insulin

(MiG trial-Metformin in gestational diabetes trial) 13 recruited 751 patients between 28-33 weeks randomly given metformin and insulin. The two groups showed no differences in terms of lower post prandial glucose levels, neonatal hypoglycemia, birth injuries and respiratory distress syndromes. Only 46% patients required supplemental insulin.

The concentration of metformin in breast milk was low and thus safe for breast feeding [14].

## Conclusion

Currently both glyburide and metformin are classified by FDA as Category B drugs in pregnancy. The oral hypoglycemic agents are safe options in gestational diabetes mellitus. They are promising options in low resource countries. The favourable points of oral hypoglycemic agents are avoidance of multiple injections, convenience, no need of refrigeration and affordable. However, the clinicians should make their patients aware about non-availability of data regarding long-term health of the offspring's exposure to glyburide or metformin. The safeties of these drugs are only studied till prenatal period. More randomized control trials are needed to have more data on the long-term effects on neonatal function and cognitive development. Therefore, despite oral hypoglycemic agents being lucrative option, the usage is limited by paucity of good quality evidence.

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This article was originally published in a special issue, entitled:  
"Diabetes in Pregnancy", Edited by Nilanchali Singh