

# Are Oral Hypoglycemic Agents Contraindicated in Pregnancy!

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### Summary:

*The incidence of gestational diabetes is increasing. There has been a traditional reluctance to recommend oral antidiabetic drugs for the management of hyperglycaemia in gestational diabetes mellitus. The medical management of gestational diabetes is still evolving, and recent randomized controlled trials have given a glimpse of hope for woman who likes to avoid insulin and prefer oral agents.. As insulin therapy is considered the gold standard of pharmacotherapy for gestational diabetes, it becomes a usual recommendation to use it in pregnancy. The current short acting insulin analogs lispro and aspart are safe, but*

*there are only limited data to support the use of long acting insulin analogs. There are randomized controlled trials which have demonstrated efficacy of the oral agents glyburide and metformin. Whilst short-term data have not demonstrated adverse effects of glyburide and metformin on the fetus, and they are increasingly being used in pregnancy, there remain long-term concerns regarding their potential for harm. This controversy related article gives an overview of the rationale for use of oral antidiabetic agents in the treatment of gestational diabetes.*

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### Discussion:

In a policy statement by the American Diabetes Association and the American College of Obstetricians and Gynecologists in 2004 revealed "Oral glucose lowering agents have generally not been recommended during pregnancy"<sup>1</sup>. Conventionally, treatment has been offered in the form of dietary management with insulin added if diet alone does not achieve acceptable glycaemic levels. The statement is based on first-generation sulfonylureas (tolbutamide and chlorpropamide) which can easily cross the placenta leading to almost similar cord and maternal serum concentrations<sup>2</sup>. Early experience with these drugs included numerous cases of profound and prolonged neonatal hypoglycemia.<sup>3</sup> Retrospective studies of series of women with type 2 diabetes mellitus suggested an association between first-trimester sulfonylurea therapy and major congenital malformations<sup>4,5</sup>

Most centers followed the American lead of O'Sullivan from the early 1970s in which dietary management was combined with a single dose of intermediate acting insulin. The consensus about this management was

challenged by the classic randomised controlled trial of Persson and colleagues in 1985. The outcomes in relation to birthweight, frequency of foetal macrosomia, newborn skinfold thicknesses and common neonatal complications, respiratory distress, hypoglycaemia, hyperbilirubinaemia and polycythaemia were not significantly different between the groups. With so much controversy, why oral therapy still needed? Insulin therapy is associated with: I. the fear of injections (particularly when multiple). II. the issue of compliance. III. the risks of hypoglycemia. IV. The increase in appetite and weight. So the next question arises is what to do? The solution is: 1. We need oral drugs which do not cross the placenta and 2. Oral drugs which cross the placenta without causing fetal hypoglycemia, hyperinsulinemia. and teratogenic effects.

The case of Glyburide (Glibenclamide) then came into play. Using an isolated perfused human placental model, Elliott et al. demonstrated minimal placental transfer of glyburide, but greater transport of glipizide and particularly chlorpropamide and tolbutamide<sup>6,7</sup>. Then a comparison of glyburide and insulin in women with gestational diabetes mellitus was done<sup>8</sup>. The results of

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which showed there were no significant differences in mean neonatal glucose concentrations, macrosomia, neonatal intensive care unit (NICU) admission, or fetal anomalies (Table I).

**Table-I**

*Comparison of insulin versus Insulin in Langer study*

	Glyburide group	Insulingroup
1. Fetal anomaly	2%	2%
2. Large for gestational age	12%	13%
3. Lung complications	8%	6%
4. Hypoglycemia	9%	6%
5. Admission in Neonatal ICU	6%	7%

Further reports of five small retrospective reports of glyburide use for GDM have been published since 2000.<sup>9,10,11,12,13</sup> Summary of those studies showed similar results of glyburide treatment, compared with insulin. In 2005 Langer reanalyzed the results of his trial. The rate of macrosomia was 16 vs. 5% ( $P$  0.01), respectively, in the high and low

glyburide dose groups.<sup>14</sup>

The metformin use in pregnancy was also scrutinized critically as metformin was shown to be able to significantly cross the placenta, with fetal concentrations in the range of half of maternal concentrations<sup>15</sup>. However, it does not stimulate insulin secretion or release, and does not cause hypoglycemia, enhances insulin action. Several trials did not report any major congenital malformations in infants born to mothers who received metformin throughout pregnancy, whether those mothers were diabetics<sup>16,17</sup> or non diabetics<sup>18</sup>. Several studies in South Africa more than 20 years ago<sup>19,20</sup> and in New Zealand in 2006<sup>21</sup> reported no adverse pregnancy outcomes. The largest trial of metformin against insulin, popularly known as MiG study is completed and the results of which are published.<sup>22</sup> It would therefore seem that there is a place for the use of metformin in the management of gestational diabetes. Metformin reduces pregnancy-associated weight gain compared with the alternatives. There was no excess of neonatal hypoglycaemia in the metformin group or of respiratory distress syndrome, birth trauma, or low Apgar scores. A MEDLINE search (1966-March 2007) showed oral antidiabetic agents in

pregnancy and lactation is on way of paradigm shift<sup>23</sup>. It showed neither glyburide nor metformin has caused developmental toxicity in humans. Glyburide has been used for the treatment of gestational diabetes, and metformin has been used in women with PCOS who eventually became pregnant. Such data on the use of OHAs in pregnancy are shifting the paradigm that once stated that they should never be used in pregnancy. This shift may be welcome to women with gestational diabetes who are inconvenienced by injections and to those in areas where insulin may not be readily available or is cost prohibitive. But there are notable limitations to the current literature. First, there are possible publication biases. Though published and unpublished studies show no differences between groups-this is due to small groups included in the studies. Large group studies are needed to delineate the real picture.

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