Non-insulin pharmacological therapy in pregnancy

Sarita Bajaj

Abstract

During pregnancy, when glycaemic levels remain uncontrolled, despite lifestyle modification, pharmacotherapy is advised, usually insulin which has been the gold standard for treatment. Recent studies however suggest that certain oral anti diabetic agents (OADs) may be safe and acceptable alternatives. There may be potential advantages for the use of metformin over insulin in GDM with respect to maternal weight gain and neonatal outcomes. However, as metformin crosses the placenta, its use during pregnancy raises concerns regarding potential adverse effects on the mother and foetus. Glibenclamide, a second generation sulfonylurea, more effective in glycaemic control in women with GDM has a lower treatment failure rate than metformin but there is lack of long term follow up data. Even though generally well tolerated, some studies report higher rates of preeclampsia, macrosomia, neonatal jaundice, neonatal hypoglycaemia and longer stay in neonatal care unit.

Keywords: Gestational diabetes mellitus (GDM), Oral antidiabetic agents (OADs), Efficacy and safety of OADs.

Introduction

Amongst women of reproductive age, the incidence of diabetes is rising globally. As a result, glucose intolerance in pregnancy and the prevalence of overt diabetes in pregnancy has also risen.[1] If glycaemic control during pregnancy is not adequate, there is an increased incidence of adverse outcomes for both mother and infant.[2] Adequate glycaemic control can be achieved with medications; but insulin is the mainstay of management of hyperglycaemia in pregnancy, when lifestyle measures do not suffice. However, insulin therapy may require multiple daily injections and the associated cost may hinder continuous treatment for some patients, which reduces patient adherence. OADs are being researched as an alternative to insulin therapy considering their ease of use and lower cost. This has resulted in increased use of OADs in pregnancy. This is applicable especially for metformin and glibenclamide. Understanding the use and safety of OADs during pregnancy for the mother and for development of the offspring, is essential for the caregiver.

Department of Medicine, MLN Medical College, Allahabad, India.
Correspondence: Email: drsarita.bajaj@gmail.com

Non- Insulin Therapy in Pregnancy

Effective treatment of GDM reduces foetal mortality to the same level as that in non-diabetic pregnant women. Lifestyle change is an essential part GDM management and may suffice for many women. Pharmacotherapy is essential, if MNT fails to achieve glycaemic targets. Insulin is started within 1 to 2 weeks, if the majority (at least 4/7 per week) of fasting values exceed 90 mg/dl. If the FPG concentration on the OGTT is >120mg/dl, then the patient is started on insulin immediately along with meal plan.[2] In resource challenged societies like India, the cost of treatment of GDM with insulin is many folds higher as compared with Metformin, a significant consideration in developing countries.[3]

Metformin

Category B drug in pregnancy. Currently - not accepted as first line pharmacotherapy for GDM. Metformin has however shown benefits of reduction in both neonatal and maternal hypoglycaemia as well as weight gain with higher treatment satisfaction. It may be more suitable for women with mild GDM. In short term use, neonatal outcomes do not deteriorate with the use of metformin as compared to insulin. Long term impacts of metformin use are also encouraging.[4,5] A follow up study of neonates whose mothers received metformin displayed normal weight, social and motor skills at six months; there were no reported differences in weight, height, social, or motor skills between the neonatal groups at 18 months.[6] Obesity is a high risk for future metabolic disorders, lesser the weight gain, lesser the incidence of complications. Metformin prevents hepatic gluconeogenesis, glucose absorption and stimulates glucose uptake in peripheral tissues. It also has complex actions on endothelial function and reactive oxygen species production, helps reduce endothelial activation and maternal inflammatory response of insulin resistance.[7,8] In the MiG Study, use of metformin (alone or with supplemental insulin) in GDM was not associated with increased perinatal complications as compared with insulin. Approximately 92% of women continued metformin to term whereas 46% needed supplemental insulin. There were no significant differences in primary composite outcome between the two groups and no serious adverse events were reported with metformin. Women preferred metformin to insulin. Incidence of neonatal hypoglycaemia in the insulin group was higher than in the metformin group. Reducing neonatal hypoglycaemia with metformin treatment could avoid potentially harmful central nervous system effects.[9,10]

Table: Pragmatic use of Metformin in mild GDM*, based on biopsychosocial health model.

Domain	Clinical situations
Contraindications General	◆ All contraindications to Metformin use in non-pregnant individuals
Pregnancy specific c	◆ Ketonuria
	◆ Any evidence of maternal distress
	◆ Any evidence of foetal distress
Indications Biological	As monotherapy
	◆ GDM not responding to medical nutrition therapy
	◆ GDM detected during late third trimester
	◆ Poor compliance with the treatment plan when the treatment plan includes insulin.
	◆ Lack of skills for self-management with insulin therapy and monitoring.
	As combination therapy, with insulin.
	◆ Uncontrolled hyperglycaemia, not responding to optimized insulin regimes.
	◆ Unwanted weight gain with insulin therapy
Psychological	◆ If the suggestion of insulin causes extreme psychological stress.
	◆ When suggestion of insulin causes patient to reduce nutritional intake in order to maintain glycaemia
Social	◆ If the suggestion of insulin causes extreme family/social stress
	Financial burden
	◆ In health-care settings where insulin is not available or accessible
	◆ In health-care settings where regular glycaemic monitoring is not feasible
Precautions	◆ Regular foetal surveillance
	◆ Regular maternal surveillance
	◆ Obstetric monitoring
	"◆ Medical monitoring

*An abnormal result on an oral glucose-tolerance test but a fasting glucose level below 95 mg/dl (Ref.: Landon et al.)

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Kalra and Gupta have proposed a pragmatic, individualized approach to use of metformin in mild GDM, based on the biopsychosocial model of health (Table).[3] The use of metformin during pregnancy decreases the rates of early pregnancy loss and preterm labour and prevents foetal growth restriction. With the use of metformin during pregnancy, no teratogenic effects, intrauterine deaths or developmental delays have been reported. Despite its crossing the placenta, apparently there are no serious safety concerns with metformin.[11] Women on metformin for PCOS can continue the drug up to end of 1st trimester.

Glibenclamide

Glibenclamide is a second generation sulfonylurea (SU) which acts by increasing the release of insulin from the beta cells of the pancreas. Unlike other SUs it does not cross the placental barrier, probably due to high degree of protein binding hence foetal exposure is minimal. It is comparable with insulin in glycaemic control and neonatal outcomes. A large retrospective study and a recent meta-analysis of RCTs indicate higher rates of macrosomia and neonatal hypoglycaemia for women treated with glibenclamide versus insulin.[12] A large glibenclamide versus insulin RCT with adequate power to detect neonatal and pubertal outcomes is needed. As glibenclamide crosses the placenta, additional studies are needed to evaluate the effect of exposure of the foetal pancreas to insulin secretagogues and the long-term effects on weight and cardio-metabolic status during childhood and adolescence.[13]

Acarbose

Acarbose reduces intestinal carbohydrate absorption mainly by blocking the cleavage of oligosaccharides and disaccharides to smallest units and reduces postprandial hyperglycaemia. It may have potential benefits in pregnancy due to < 2% absorption into the maternal circulation.[14] No harmful effects have been suggested by animal studies, but there is dearth of observational data in human pregnancy. No RCT is available with respect to use of acarbose in pregnancy. The use of α-glucosidase inhibitors in pregnancy is not recommended at present.

Present scenario of OADs in Diabetes Management

During pregnancy, the use of OADs is not recommended by the American Diabetes Association (ADA) or US Food and Drug administration (FDA).[15,16] UK National Institute for Health and Care Excellence (NICE) guidelines consider metformin and glibenclamide safe in pregnancy and lactation.[17] Regarding the use of OADs (glibenclamide and metformin) in pregnancy, the Endocrine Society suggests that glibenclamide may be considered as a suitable

alternative to insulin therapy for management of hyperglycaemia in women with GDM who fail to achieve target blood glucose values after a 1- week trial of MNT and exercise. The exception is for those women with a diagnosis of GDM before 25 weeks of gestation and for those women with FPG > 110 mg/dl, where insulin therapy is preferred.[2] Recommendation for the use of metformin is in those women with gestational diabetes, who do not have adequate glycaemic control despite MNT, and who refuse or cannot use insulin or Glibenclamide, and are not in the 1st trimester. Even though metformin crosses the placenta freely, followup of MiG study (Metformin in Gestational Diabetes) had shown favourable effects on children in metformin group compared to those in the insulin group.[18] Such data for Glibenclamide is not available. International Federation of Gynaecology and Obstetrics (FIGO) 2015 recommendations for pharmacological therapy of GDM state that insulin, glibenclamide, and metformin are safe and effective therapies for GDM during 2nd and 3rd trimester, and may be initiated as first-line treatment after failing to achieve glucose control with lifestyle modification. Among OADs, metformin may be a better choice than glibenclamide.[19]

Conclusions

Scant data is available on the exposure of the foetus to OADs during pregnancy, infancy and breastfeeding with lack of RCTs evaluating the use of OADs in women with GDM. Because insulin is not transferred across placenta nor into breast milk it remains the optimal anti hyperglycaemic agent during pregnancy and lactation. Both glibenclamide and metformin are not yet FDA approved for use in pregnancy. However, results of RCTs comparing insulin with OADs (Glibenclamide and metformin) after 1st trimester in women with GDM has shown no notably significant differences in foetal and maternal health outcomes during pregnancy and short term outcomes in offspring. Therefore, patients of GDM who refuses to take insulin or who have a mild elevatation in blood glucose values, especially beyond 25 weeks of gestation may be prescribed OADs. OADs can be used as adjuvant to insulin in severe hyperglycaemia requiring large doses of insulin for control and as monotherapy in mild degrees of hyperglycaemia. OADs are not the drug of choice but do have a case based role in GDM management used in a rational manner. Prescription of any OAD in pregnancy needs to be accompanied by a comprehensive explanation and deliberation of possible limitations and side effects, and documentation of the reason for considering OADs. The woman should be well informed about lack of long term safety data of use of OADs in pregnancy.

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