Indian J Med Res 145, May 2017, pp 588-591
DOI: 10.4103/ijmr.IJMR_1572_16

Quick Response Code:

Commentary

Metformin in gestational diabetes mellitus

The primary goal of therapy for gestational diabetes mellitus (GDM) is to achieve euglycaemia and thus decrease adverse perinatal outcomes. The proportion of patients who require pharmacotherapy to achieve this end result is dependent on diagnostic criteria used. However, with current low diagnostic thresholds, the proportion requiring pharmacotherapy is lesser than in the past where insulin has been the gold standard treatment for GDM when dietary and lifestyle measures have failed. Theoretically, insulin sensitizers should have been the ideal agent in the treatment of GDM, but foetal concerns have outweighed practical utility till the recent past. Oral hypoglycaemic agents are cost-effective, patient-friendly, potentially compliance-enhancing and also more physiological, given that insulin resistance is likely to be the main pathogenetic mechanism in GDM[1]. Metformin has been in use since decades for patients of type II DM and also for many years now in insulin-resistant polycystic ovarian syndrome (PCOS) patients[2]. However, its use in pregnancy has been limited.

The metformin in gestational (MiG) diabetes trial[3] was a landmark study being one of the largest randomized controlled trials in women with GDM which prospectively assessed a composite of neonatal complications as the primary outcome and secondary outcome of neonatal anthropometry at birth. It was concluded that metformin alone, or with supplemental insulin, was not associated with increased perinatal complications. This trial has been the basis of many subsequent studies to assess the safety and efficacy of metformin use in GDM.

Several outcome variables have been used as secondary outcome measures in the majority of studies addressing therapeutic options for diabetes in pregnancy. These variables are associated with short-term metabolic complications such as hyperbilirubinaemia, hypoglycaemia, respiratory complications and polycythemia in neonates and maternal and foetal consequences of a macrosomic foetus[4]. However, in addition to evaluating these short-term problems, study of factors that are likely to have a longer impact on infancy and childhood also needs to be done. Hence, other outcome criteria should be identified to assess the appropriateness of pharmacological therapy.

The success rate of a drug in achieving targeted glucose levels also depends on disease severity as reflected by plasma glucose values. The rate of success for achieving glycaemic control in metformin-treated patients ranged from 54 to 79 per cent[5]. Thus, though the safety and efficacy of metformin appears to be well documented the most effective or ideal oral hypoglycaemic agent is yet to be identified.

Two meta-analyses[6,7] comparing the use of metformin and glyburide in GDM concluded that metformin was a better hypoglycaemic agent in pregnancy as glyburide was associated with significant increase in the risk of macrosomia and large for gestational age (LGA) births. This could be the result of increased insulin production in the foetus as a response to transplacental transfer of glyburide. Increased neonatal hypoglycaemia was also reported with glyburide, but it was significant only in one of them. Results remained non-significant for preterm births and caesarean section rate[7].

One meta-analysis[8] reported better results for maternal outcomes in terms of weight gain and pregnancy-induced hypertension, in the metformin group compared to insulin group. The improvements in insulin resistance, inflammation or endothelial function, in metformin group could be the basis for its effect on reduced incidence of pregnancy-induced hypertension. However, this did not result in any significant differences in the caesarean section or pre-eclampsia rates between the two groups. There is a

possibility that this reduction of inflammatory response also contributes to lowering of preterm birth rates, though there are conflicting reports on this matter[9]. In a subgroup of women in the MiG trial[10], maternal plasma triglyceride levels increased more in those treated with metformin compared with insulin. There is a lack of clarity whether ethnicity-related dietary changes or differences in metformin response alter glucose control. Metformin does not stimulate secretion of insulin and, therefore, does not directly cause maternal hypoglycaemia, a side effect that remains a concern with both glyburide and insulin.

Metformin, being an insulin-sensitizing drug, would be expected to reduce neonatal birth weight when given to obese women during pregnancy. This, in turn, would result in a reduction in future life risk of obesity and metabolic syndrome in the offspring. A Cochrane review[11] has outlined additional potential benefits of metformin on mother and child in normally glucose-tolerant obese pregnant women. In contrast, EMPOWaR (Effect of metformin on maternal and fetal outcomes in obese pregnant women)[12], a multicentre, randomized, double-blind, placebo-controlled trial, concluded that metformin did not have a role in reducing the birth weight of offspring of obese pregnant women, possibly indicating that this was mediated through a pathway other than insulin resistance.

Metformin has been shown to pass freely across the placenta, and hence it is important to assess the potential effects of metformin treatment on growth of the foetus. The beneficial outcomes in pregnant women with pre-pregnancy PCOS with metformin use even during the first trimester almost rule out the possibility of potential harm in terms of any teratogenic effect though there are no adequate well-controlled studies, regarding the teratogenicity of metformin hydrochloride tablets in pregnancy[13]. Also, the data from animal studies[13] found that metformin was not teratogenic (pregnancy category B) at doses up to 600 mg/kg/day, which represents an exposure of about two to six times the recommended maximum human daily dose of 2000 mg/day. The two-year follow up of offspring in MiG (MIG TOFU)[14] reassures no harmful effect in the offspring. The MiTy kids trial[15], which is a two-year follow up study, currently underway in Canada, may provide more insight into the effect of metformin on early childhood adiposity and insulin resistance. However, these studies may be questioned by the fact that the earliest effects of diabetes in pregnancy on childhood obesity often do not manifest until after 6-9 yr of age. Hence, longer follow up studies will be required to determine the impact of *in utero* metformin exposure on the development of obesity and metabolic syndrome in these children.

Studies to observe transfer of metformin to infants during lactation report that mean exposure to the infants is <1 per cent of weight-normalized maternal dose[16]. No hypoglycaemia or any other delayed adverse effect has been observed on weight, height, motor-social development or rates of illness in an infant at the age of three and six months[17]. However, caution in its use has been advised when lactating premature infants and infants having renal function impairment subsequent to sepsis or other causes[18].

It appears that the focus of foetal/neonatal evaluation needs to shift from the conventionally used birth weight and anthropometric data to additional evaluation of body fat composition. Further assessments are required to determine whether metformin reduces visceral/ectopic fat. This may be a more useful exercise in the evaluation of long-term outcomes of a particular form of pharmacotherapy over another.

The study by Singh *et al*[19] in this issue is a prospective interventional study, though non-randomized, framed in line with the objectives of the MiG trial. However, the number of GDM patients receiving metformin was too small to interpret the efficacy and side effects in a non-homogeneous population. The percentage of caesarean deliveries in the metformin-treated women would probably be more accurately delineated when the non-diabetes-related, solely obstetric indications of caesarean deliveries like previous two caesareans, placenta praevia and malpresentation are excluded. The higher occurrence of cholestasis of pregnancy in the metformin-treated group is an interesting new finding. The significance of this association merits further evaluation. Is this a part of routine hepatic effect of metformin or does it reflect a problem of intrahepatic cholestasis of pregnancy[20]. Clarity on this issue may emerge from studies having larger number and different populations. Furthermore, the higher occurrence (10 of 64) of LGA foetuses as against fewer (3 of 64) uncontrolled sugar levels with metformin requires an explanation. Does it indicate that despite achieving euglycaemia with metformin there is only minimal effect on foetal growth factors which are being mediated through some other, possibly genetic, mechanism? On this issue, the correlation

of outcomes with maternal body mass index may be relevant. The figures of 14.1 per cent SGA and 15.6 per cent LGA foetuses born to euglycemic GDM mothers are unusual, and no potentially acceptable hypothesis for these findings has been proposed. However, the relevance of these numbers may be questionable in light of the small number of patients on metformin. It would be interesting to determine whether these findings are replicated in other ethnic groups or large-sized cohorts. It is suggested to categorize women into obese and non-obese groups for future studies, thus understanding the role and confounding effect of metformin in non-diabetic obese women.

Most guidelines currently recommend the use of metformin and glibenclamide in resource-limited areas where insulin administration may be problematic; however, it is still recommended as a second line to insulin. The World Health Organization[21], Australian Obstetrics and Gynecological Society[22], International Diabetes Federation (2009)[23] and Canadian Diabetes Association guidelines[24] currently recommend the use of metformin in settings where insulin administration has logistic or compliance issues. The National Institute for Health and Clinical Excellence suggests metformin as the first-line drug in GDM[25]. However, the German Diabetes Association and German Association of Gynecology and Obstetrics guidelines (2014)[26] do not recommend the use of any oral hypoglycaemic agents during pregnancy. The Indian associations may start endorsing oral hypoglycaemic agents both in light of recommendations by other international agencies and also because of good acceptability and favourable outcomes in Indian population.

Future research should attempt to fill the gaps in the knowledge of metformin and GDM. It would be of great interest to know the correlation between metformin, foetal growth restriction and body fat composition in children by conducting long-term studies. The short duration of metformin use in pregnancy probably does not affect parameters such as lipid profile in the mother. However, its consequences in the next generation remain to be elucidated. Moreover, it is possible that the change, if any, is linked to the inherent genetic code of the individual together with some epigenetic changes. What may also need subsequent elucidation is whether GDM does have an identifiable genetic component (likely to) and if so, then the pharmacogenetics of metformin may be worth evaluating. This may eventually identify those individuals who are likely to attain maximum benefit from its use. It will also be worthwhile to conduct follow up studies of women who used metformin in GDM to document whether it alters the subsequent development of type II DM, its impact on choice of lifestyle change and subsequent weight gain.

The use of metformin in GDM is likely to continue and may also become more frequent. These data should be compiled - preferably in a registry - and subsequently analyzed to assess long-term outcomes in both women and their children.

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Received September 26, 2016

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