The use of oral hypoglycaemic agents in gestational diabetes

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Introduction
Tight glycaemic control has been a cornerstone in the prevention of maternal and neonatal complications associated with gestational diabetes. For decades, insulin has been the only drug considered to be absolutely safe in pregnancy. The use of oral hypoglycaemic agents (OHAs) in gestational diabetes was thought to be associated with congenital anomalies, pre-eclampsia, and neonatal hypoglycaemia.1–5 Previous studies on animal models showed that the use of OHAs was associated with congenital malformation, neural tube defects, and reduction in yolk sac protein values.1–3 A small number of case reports on human subjects reported congenital malformations associated with the use of, or exposure to, oral agents during pregnancy.4 Based on these facts, physicians were hesitant to use oral agents in pregnant women. Nevertheless, recent work on oral agents and pregnancy has revealed that some oral agents are safe, with comparable efficacy to insulin when used in patients with gestational diabetes. Compared with insulin, oral agents are simple to use and are less expensive, hence compliance is improved. Oral agents are ideal in Africa, where proper use and manipulation of insulin is problematic, resulting in poor glycaemic control. The oral agents glibenclamide and metformin are widely available in Africa and yet are being underutilised; this article reviews the use of metformin and glibenclamide in the management of gestational diabetes in Africa.

Glibenclamide
Studies have shown that glibenclamide is a safe oral agent for use in pregnancy since it rarely crosses the placenta.6 A randomised study by Notelevitz in 1971 compared the use of tolbutamide, chlorpropamide, diet, and insulin in 208 subjects and found no significant difference in terms of congenital anomalies and perinatal mortality with optimal glycaemic control.7 Furthermore, a large randomised controlled trial by Langer et al. comparing the use of glibenclamide (known in North America as ‘glyburide’) and insulin in women with gestational diabetes who failed to achieve glycaemic control with diet or insulin showed no significant differences between the two groups in the incidence of pre-eclampsia, neonatal hypoglycaemia, congenital anomalies, macrosomia, perinatal mortality, cord-serum insulin concentrations, and rates of Caesarean section.8 A total of 404 women were randomly selected to take either of the treatments and the results showed that 82% of the glibenclamide group and 88% of the insulin group achieved good glycaemic control, with less maternal hypoglycaemia in the glibenclamide group as compared with the insulin group (2% and 20% respectively).9 Additionally, a number of non-randomised or retrospective studies have indicated that glibenclamide is effective in achieving glycaemic control in the majority of patients.9 Failure to achieve glycaemic control with glibenclamide was linked to higher glucose level upon diagnosis of gestational diabetes and early dietary failure.10 With regard to the safety of glibenclamide to the foetus, Elliot et al. documented the differences in transfer of sulfonylureas through the placenta. While tolbutamide diffused freely, with glibenclamide there was no significant transport in the maternal to foetal and foetal to maternal directions.11 Even with increased concentration of glibenclamide above the therapeutic level, there were undetectable levels of the drug when analysed using high-performance liquid chromatography.12 Similarly, glibenclamide was not detected in the cord serum of any infants in the study by Langer et al.8 With the established information from the published data, we can recommend the use of glibenclamide to women with gestational diabetes who are reluctant to use insulin. However, more studies should be done to improve and supplement the established safety and efficacy data for the use of glibenclamide in pregnancy.

Metformin
Metformin inhibits hepatic gluconeogenesis and glucose absorption and stimulates glucose uptake in the peripheral tissues.13–15 It also has an effect in reducing weight gain.15 Many studies regarding metformin have been carried out in patients with polycystic ovary syndrome (PCOS). Jakubowicz et al. compared the pregnancy outcomes of 65 women with PCOS who became pregnant while taking metformin throughout pregnancy to 35 women who had PCOS and did not take metformin during pregnancy. The early pregnancy loss rate was low in the metformin group (8%) compared with the control group (42%).16 In a similar fashion, Glueck et al. compared 33 non-diabetic women with PCOS who were on metformin during pregnancy with 39 non-diabetic women with PCOS without metformin therapy during pregnancy. The study noted a 27% incidence of gestational diabetes in the control group compared with 3% in the women who took metformin. Furthermore, there was no foetal malformation or foetal hypoglycaemia in the metformin group.17 A larger controlled, randomised trial (the Metformin in Gestational Diabetes (MiG) study), compared 751 patients in two treatment arms.18 One arm received metformin only, and the other had a supplement of insulin when the maximum metformin dosage of 2500 mg daily failed to achieve optimal glucose.

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levels. The primary outcome was measured by neonatal hypoglycaemia, respiratory distress, need for phototherapy, birth trauma, Apgar score less than 7, or prematurity. There was no difference in the primary outcome between the two treatment arms (32% in metformin versus 32% in the insulin arm). In addition, fewer congenital anomalies were reported in the metformin group (II) as compared with the insulin group (18). Furthermore, more women using metformin indicated that their treatment was acceptable compared with those on insulin. A 10-year retrospective analysis of pregnant women with type 2 diabetes in South Africa found that metformin alone was not associated with increased perinatal mortality. Even in combination with glibenclamide, no increase in perinatal mortality was noted. When compared with insulin, metformin-treated pregnant women had low infant morbidity and mortality rates. A study in India concluded that metformin was safe either as an adjunct to insulin treatment or even as a monotherapy.

Glibenclamide has been shown not to cross the placenta and metformin has been documented in several trials to be safe for use in pregnancy. Given the available data, glibenclamide and metformin appear to be the best oral hypoglycaemic agents to use during pregnancy, and the current authors advocate the routine use of these agents in the management of gestational diabetes, especially in poorly resourced countries.

**References**