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 hypoglycemia.[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.[4,5] 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 Notelovizt 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 diabeteswho 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).[8] 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.[11] 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.[12–14] It also has an effect in reducting 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 diabetesin the control group compared with 3% in the women who took metformin. Furthermore, there was no foetal malformation nor foetal hypoglycemia 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 (11) as compared with the insulin group (18). Furthermore, more women using metformin indicated that their treatment was acceptable compared with those on insulin.[18] 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.[19] 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.[19] Hale et al. reported low concentrations of metformin in breast milk, with the mean infant exposure to the drug being 0.3% of the weight-normalised maternal dose, far below the 10% level of concern for breastfeeding.[20] A study in India concluded that metformin was safe either as an adjunct to insulin treatment or even as a monotherapy.[21]

Langer has suggested that OHAs (glibenclamide or metformin) may be appropriate for gestational diabetespatients with a fasting blood glucose (FBG) of 5.3–7.8 mmol/L or haemoglobin (HbA1c) levels of 7.0–8.0%. Below these levels, dietary treatments alone may be appropriate, and above these levels, insulin can be considered.[22]

Other oral agents

Apart from glibenclamide, other sulfonylureas such as tolbutamide and chlorpropamide cross the placenta, and thus pose a significant threat to the foetus.[23,24] No data are available regarding the safety and efficacy of pioglitazone, glipizide, and glimepiride.

Acarbose has been documented to be relatively safe in diabetic pregnancy. It acts primarily in the gut by delaying carbohydrate absorption, is not absorbed, and therefore has no systemic effect. A study by Bertini et al compared neonatal outcome in gestational diabetespatients treated with insulin, glibenclamide, and acarbose, and showed no statistical difference in fasting or postprandial plasma glucose (PPG) levels, and PPG levels or average newborn weight in the three groups.[25]

Rosiglitazone is not recommended in pregnancy due to adverse outcomes on the foetus in the mid and last trimester. A study by Chan et al. detected rosiglitazone in 19 foetal serum samples out of 31 pregnant women given the drug between the 8th and 12th weeks before surgical termination of pregnancy.[26]

Conclusion

Recent evidence has shown that glibenclamide and metformin are safe and useful in gestational diabetes patients who do not desire daily insulin injections. These oral agents are gaining acceptability by the medical community for use in gestational diabetes. They are particularly attractive in developing countries where the use of insulin may not always be possible. Being cheap and relatively easy to use, these agents may be considered as first-line treatment for gestational diabetes, reserving insulin as a second-line treatment in those cases where oral agents fail to achieve optimal glycaemic control. 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

1. Smithberg M, Runner MN. Teratogenic effects of hypoglycemic treatments in inbred strains of mice. *Am J Anat* 1963; 113: 479–89.
2. Smoak IW. Embryopathic effects of the oral hypoglycemic agent chlorpropamide in cultured mouse embryos. *Am J Obstet Gynecol* 1993; 169: 409–14.
3. Denno KM, Sadler TW. Effects of the biguanide class of oral hypoglycemic agents on mouse embryogenesis. *Teratology* 1994; 49: 260–6.
4. Campbell GD. Chlorpropamide and foetal damage. *Brit Med J* 1963; 1: 59–60.
5. Larsson Y, Sterky G. Possible teratogenic effect of tolbutamide in pregnant prediabetic patients. *Lancet* 1960; 2: 1424–6.
6. Coustan RD. Pharmacological management of gestational diabetes – an overview. *Diabetes Care* 2007; 30: S206–S208.
7. Notelovitz M. Sulphonylurea therapy in the treatment of the pregnant diabetic. *S Afr Med J* 1971; 45: 226–9.
8. Langer O, Conway DL, Berkus MD, et al. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 2000; 343: 1134–8.
9. Moore TR. Glyburide for the treatment of gestational diabetes. *Diabetes Care* 2007; 30 (Suppl.2): S209–S213.
10. Coetzee EJ, Jackson WPU. Oral hypoglycaemics in the first trimester and foetal outcome. *S Afr Med J* 1984; 65: 635–7.
11. Elliot BD, Langer O, Schenker S, et al. Insignificant transfer of glyburide occurs across the human placenta. *Am J Obstet Gynecol* 1991; 165: 807–12.
12. Cusi K, Consoli A, DeFronzo RA. Metabolic effects of metformin on glucose and lactate metabolism in non-insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1996; 81: 4059–67.
13. Hundal RS, Krssak M, Dufour S, et al. Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes* 2000; 49: 2063–9.
14. Natali A, Ferrannini E. Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review. *Diabetologia* 2006; 49: 434–41.
15. Lee A, Morley JE. Metformin decreases food consumption and induces weight loss in subjects with obesity and type II non-insulin-dependent diabetes. *Obesity Res* 1998; 6: 47–53.
16. Jakubowicz DJ, Iuorno MJ, Jakubowicz S, et al. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2002; 87: 524–9.
17. Glueck CJ, Wang P, Kobayashi S, Phillips H, Sieve-Smith L. Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. *Fertil Steril* 2002; 77: 520–5.
18. Rowan A, Hague W, Gao W, et al (for the MiG Trial Investigators). Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008; 358: 2003–15.
19. Ekpebegh CO, Coetzee EJ, van der Merwe L, et al. A 10 year retrospective analysis of pregnancy outcome in pre-gestational type 2 diabetes: comparison of insulin and oral glucose-lowering agents. *Diabetic Med* 2007; 24: 253–8.
20. Hale TW, Kristensen JH, Hackett LP, et al. Transfer of metformin into human milk. *Diabetologia* 2002; 45: 1509–14.
21. Ramachandran A, Snehalatha C, Vijayalakshmi S, et al. Use of metformin in pregnancies with diabetes: a case series from India. *J Assoc Phys India* 2004; 53: 157–8.
22. Langer O. Gestational diabetes and oral hypoglycemic agents. *Obstet Manage* 2003; 15: 62–76.
23. Zucker P, Simon G. Prolonged symptomatic neonatal hypoglycemia associated with maternal chlorpropamide therapy. *Pediatrics* 1968; 42: 824–5.
24. Kemball ML, McIver C, Milner RD, et al. Neonatal hypoglycaemia in infants of diabetic mothers given sulphonylurea drugs in pregnancy. *Arch Dis Child* 1970; 45: 696–701.
25. Bertini AM, Silva JC, Taborda W, et al. Perinatal outcomes and the use of oral hypoglycemic agents. *J Perinat Med* 2005; 33: 519–23.
26. Chan LY, Yeung JH, Lau TK. Placental transfer of rosiglitazone in the first trimester of human pregnancy. *Fertil Steril* 2005; 83: 955–8.