Review Article

Oral Hypoglycaemic Agents for Diabetes in Pregnancy – An Appraisal of the Current Evidence for Oral Anti-diabetic Drug Use in Pregnancy

Francis LW Ho,[1]*MD*, Choon-Fong Liew,[1]*MBBS (Lond), MRCP (UK), FAMS (Endocrinol)*, Elaine C Cunanan,[1]*MD*, Kok-Onn Lee,[1]*MD, FRCP*

Abstract

Introduction: The use of oral hypoglycaemic drugs in pregnancy is not recommended because of reports of foetal anomalies and other adverse outcomes in animal studies and in some human cases. However, recent studies have suggested that some oral hypoglycaemic drugs may be used in pregnancy. This review will examine these studies critically. **Methods:** Literature review of articles obtained from a PubMed search of peer-reviewed journals on oral hypoglycaemic drug use in pregnancy. **Results:** In two prospective studies, one of which was a randomised controlled trial, glibenclamide was as effective and safe as insulin in gestational diabetes. In several studies, metformin did not increase foetal anomalies or malformations when used during pregnancy in women with polycystic ovary syndrome (PCOS). In one prospective study on infants born to mothers who used metformin in pregnancy, follow-up for 18 months showed no adverse effects. In several prospective and retrospective studies on women with PCOS, metformin was shown to prevent early pregnancy loss, decrease insulin resistance, reduce insulin and testosterone levels, and decrease the incidence of gestational diabetes when these women got pregnant while on metformin and continued to take it throughout their pregnancy. In a single small study, acarbose did not cause any adverse effects during pregnancy. **Conclusions:** Recent evidence shows promising findings in the safety and efficacy of some oral hypoglycaemic agents in treating pregnant diabetics. However, larger clinical studies will be needed to ensure the safety and efficacy of these drugs in pregnancy.

Ann Acad Med Singapore 2007;36:672-8

Key words: Acarbose, Gestational diabetes, Glyburide, Metformin

Introduction

Tight blood glucose control has always been emphasised in the treatment of pregnant women with diabetes to increase the likelihood of successful pregnancy outcomes. Studies have documented that uncontrolled diabetes in pregnancy increases the incidence of congenital anomalies from 2% to 3% in non-diabetic women to around 7% to 9%.[1] However, most clinicians have been limited to the use of insulin in controlling the blood sugar levels in this group of patients because it has been the only drug deemed absolutely safe for use in pregnancy.

The major concerns regarding the use of oral hypoglycaemic drugs in pregnancy have been foetal anomalies, neonatal hypoglycaemia and the development of pre-eclampsia. Studies done by Smithberg[2] and Smoak[3] on mice showed that first-generation sulphonylureas, such as tolbutamide and chlorpropamide, were associated with congenital malformations. Similarly, Denno and Sadler[4] also showed that phenformin was embryotoxic in rats, and metformin was associated with a delay in neural tube closure and reduced yolk sac protein values. There are also case reports of congenital malformations associated with the use of, or exposure to, oral hypoglycaemic agents in human pregnancy.[5,6] However, in a randomised study done by Notelovitz[7] in 1971 where he compared the use of tolbutamide, chlorpropamide, diet, and insulin in 208 subjects, there were no significant differences among the different groups in terms of perinatal mortality and congenital anomalies when glycaemic control was optimal. The author concluded that it was the poorly controlled glycaemic state that was associated with the development of foetal anomalies and not the agents used to control blood sugar levels.

Neonatal hypoglycaemia has been a concern with the use

[1] Division of Endocrinology, Department of Medicine, National University Hospital, Singapore

Address for Correspondence: Professor K. O. Lee, Division of Endocrinology, Department of Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

Email: mdcleeko@nus.edu.sg

of oral hypoglycemic agents because Zucker and Simon[8] found tolbutamide and chlorpropamide to cause profound and prolonged hyperinsulinaemic hypoglycaemia among neonates born to women who took these drugs during pregnancy. In fact, they found the cord-serum concentrations of chlorpropamide to be similar to those in maternal serum, and the half-life of the drug in infants was similar to that in their mothers. In another paper by Kemball et al,[9] there were 4 patients with prolonged symptomatic neonatal hypoglycaemia associated with maternal sulphonylurea drug usage. All 4 infants had evidence of increased and inappropriate insulin secretion, suggesting beta-cell hyperplasia. Of the 4 hypoglycaemic infants, prolonged elimination of chlorpropamide was observed in 3 of them and chlorpropamide was detected up to 11 days after birth in these neonates.

In a cohort study by Hellmuth et al[10] consisting of 118 diabetic pregnant women on oral hypoglycaemic agents, 50 of whom were treated with metformin and 68 with a sulphonylurea, the prevalence of pre-eclampsia was found to be significantly higher in the metformin group as compared to the sulphonylurea group (32% vs 7%, P <0.001). The perinatal mortality was also noted to be significantly higher in the metformin group compared to the sulphonylurea group (11.6 vs 1.3%, P <0.02).

With all the findings in the studies mentioned, physicians have been hesitant in using oral hypoglycaemic agents in pregnant women. However, more recent evidence and studies showing the efficacy and safety of oral agents in pregnancy suggest that the use of these agents for gestational diabetes should be re-examined.

Glibenclamide (Glyburide)

Differences in placental transfer of the different sulphonylureas were first documented by Elliot et al[11] using a single human placental cotyledon perfusion model to study drug transfer between maternal and foetal circulation. Tolbutamide was found to diffuse across the placenta freely. However, there was no significant transport of glibenclamide in the maternal-to-foetal and foetal-to-maternal directions. Even increasing the glibenclamide concentration to 100 times the therapeutic level did not alter transport significantly. Glibenclamide remained undetected when cord blood was analysed using high-performance liquid chromatography. At least 99.8% of the glibenclamide was bound to protein so it was neither metabolised nor appropriated by the placenta. Glipizide, on the other hand, although a second-generation sulphonylurea like glibenclamide, was found to cross the placenta in small amounts that were significantly higher than glibenclamide. With these findings, there has been a rise in interest in the use of oral agents in pregnant diabetics, and most of the more recent studies involving sulphonylurea

use in pregnancy have been done using glibenclamide.

In a randomised, controlled trial by Langer et al,[12] a comparison was made on the use of glibenclamide and insulin in women with gestational diabetes who were unable to achieve adequate metabolic control with diet and exercise alone. Four hundred and four women were randomly assigned to take either of the two treatments. The primary end point was the achievement of good glycaemic control and the secondary end points included maternal and neonatal complications. The results showed that 82% of the glibenclamide group and 88% of the insulin group achieved good glycaemic control, but there was less maternal hypoglycaemia in the glibenclamide group (2%) as compared to the insulin group (20%). There were no significant differences between the 2 groups in the incidence of pre-eclampsia, macrosomia, neonatal hypoglycaemia, congenital anomalies, perinatal mortality, cord-serum insulin concentrations and the rate of Caesarean section. Moreover, glibenclamide was not detected in the cord serum of any infant in the glibenclamide group. This was a well-conducted randomised, controlled trial involving a large number of subjects making it a very significant study.

In a recent prospective cohort study by Kremer et al,[13] where 73 patients with gestational diabetes were treated with glibenclamide, 81% achieved satisfactory glucose control. This was similar to the proportion achieved by Langer et al.[12] However, no anomalies were identified in all of the newborn infants. Although this was not a randomised, controlled trial and the number of subjects was quite small, it supports the findings of Langer.

Metformin

The use of metformin in pregnancy has been quite controversial with early reports of adverse effects in those exposed to this drug.[4,10] However, with the advent of its use in the treatment of women with polycystic ovary syndrome (PCOS), it is postulated to alleviate key pathogenetic mechanisms such as hyperinsulinaemic insulin resistance, hyperandrogenaemia, and obesity which may cause miscarriages in women with PCOS. In fact, it is believed that decreasing hyperinsulinaemic insulin resistance with metformin during pregnancy in women with the disorder would reduce the rate of early pregnancy loss.[14] Several studies have documented the beneficial effects and safety of metformin use in women with PCOS who became pregnant.

Metformin and Early Pregnancy Loss

In a retrospective study by Jakubowicz et al,[14] a comparison was made between the pregnancy outcomes of 65 women with PCOS who became pregnant while taking metformin and remained on metformin throughout their pregnancy and the pregnancy outcomes of 31 women who

also had PCOS but did not take metformin during pregnancy. The early pregnancy loss rate in the metformin group was only 8.8%, as compared to 41.9% in the control group ($P < 0.001$). In fact, the pregnancy loss rate of the metformin group was quite similar to the rate of 10% to 15% reported for clinically recognised pregnancies in normal women. They also did a subset analysis of the women in each group with a prior history of miscarriage and found that the early pregnancy loss rate was only 11.1% in the metformin group, as compared to 58.3% in the control group ($P = 0.002$). This shows that even in women with previous early pregnancy losses, metformin is still beneficial in preventing its recurrence. Although the number of subjects in this study was not very large, the percentage of reduction of early pregnancy loss with metformin was significantly high and the benefits of using metformin were consistent between those with and without a history of miscarriages as compared to those who did not use metformin at all.

Metformin and Insulin, Insulin Resistance and Testosterone Levels

Glueck et al[15] did a prospective observational study of 42 pregnancies in women with PCOS who took metformin throughout their pregnancy. In this study, they examined the effects of metformin on maternal insulin levels, insulin resistance, insulin secretion and testosterone levels. They measured and compared the different parameters at the pre-treatment and preconception baseline, at the last preconception visit on metformin, and during the first, second and third trimesters on metformin. This study demonstrated that there was a median percentage reduction of 40% in serum insulin at the last preconception visit, which did not increase in the first or second trimester ($P > 0.05$), but rose only 10% in the third trimester. There was also a 46% median percentage reduction in insulin resistance at the last preconception visit with no significant increase ($P > 0.05$) in the first, second or third trimester. Testosterone also decreased at the last preconception visit by 30% ($P = 0.01$), but rose to 74%, 61% and 95% during the first, second and third trimesters respectively. However, the median testosterone levels during the third trimester did not differ significantly from the pre-treatment levels. Therefore, by reducing the preconception insulin levels, insulin resistance, and testosterone levels, and by maintaining these insulin-sensitising effects throughout pregnancy, metformin reduces the likelihood of diabetes developing and prevents androgen excess for the foetus. These findings are consistent with metformin's known effects on improving insulin resistance in non-pregnant diabetics.

Metformin and Development of Gestational Diabetes

In a study by Glueck et al[16] comparing 33 non-diabetic women with PCOS who were on metformin during pregnancy with 39 non-diabetic women with PCOS without metformin therapy during pregnancy, gestational diabetes developed in only 3% of the women who took metformin as compared to 27% of those who did not. Based on the number of pregnancies, gestational diabetes developed in only 1 out of the 33 pregnancies (3%) in those women who took metformin as compared to 14 out of 60 (23%) pregnancies in those who did not take metformin. In addition, there were no foetal malformations nor foetal hypoglycaemia noted in the metformin group. In another study[17] by the same authors, which compared 119 pregnant women with PCOS taking metformin with 251 healthy controls without PCOS, gestational diabetes occurred in 7.6% of the metformin group as compared to 15.9% of the controls ($P = 0.027$). These results show that there is a significant reduction in the incidence of gestational diabetes with the use of metformin in pregnancy.

In the first study, although there was a significant difference in the rates of gestational diabetes between users and non-users of metformin in women with PCOS, the sample sizes were generally small. The subjects in the second study were not evenly matched in terms of numbers between the study group and the controls, but the interesting point is the comparison of the incidence of gestational diabetes between PCOS women taking metformin and healthy control subjects without PCOS. Even though it is expected that women with PCOS will generally have a higher incidence of gestational diabetes because of the inherent insulin resistance when compared to healthy subjects, this study demonstrated a significantly lower rate of gestational diabetes in those with PCOS who took metformin when compared to the healthy controls.

Metformin and Pre-eclampsia

In contrast to the earlier findings of Hellmuth et al[10] which showed a high prevalence of pre-eclampsia in pregnant women taking metformin, Glueck et al[18] showed that there was no significant difference in the rates of pre-eclampsia between those taking metformin (5.2%) and the controls (3.6%) ($P = 0.5$) when they compared 97 pregnancies of women with PCOS taking metformin with 252 pregnancies of healthy women. Even when they did a subgroup analysis comparing only pregnancies of primigravidas in both groups, the incidence rate of pre-eclampsia was the same for both at 4.4% each. In a further study[17] by the same authors, 122 PCOS pregnancies taking metformin were compared to 252 pregnancies of healthy women without PCOS. The incidence of pre-eclampsia did not differ between the metformin group and the control group (4.1% vs 3.6%, $P = 0.8$).

Metformin and Foetal Outcomes

Even in 1979, Coetzee et al[19] from South Africa had already reported in a study of 33 metformin-treated pregnant women that infant morbidity was low and mortality rates were not higher in the metformin-treated patients compared to insulin-treated patients (61/1000 vs 105/1000). The same authors also showed in another study[20] involving 171 pregnant women with established type 2 diabetes mellitus that the overall perinatal mortality was definitely lower in the metformin-treated group compared to the untreated group (42/1000 vs 364/1000).

In 2 recent studies, one involving 126 infants and the other 100 infants, Glueck et al[17,18] demonstrated that the use of metformin in pregnant women with PCOS did not increase the risk of developing major birth defects as compared to the USA national rate reported by the Centres for Disease Control and Prevention (CDC) (1.6% vs 1.9%), and therefore concluded that there was no evidence that metformin is teratogenic. The prematurity rate of infants was not significantly different from controls (20% vs 18%)[17] and the birth weight percentiles were also similar between the neonates of metformin-treated PCOS patients and community controls.[18] Moreover, they had neither second or third trimester foetal losses nor neonatal hypoglycaemia.[18] Jakubowicz et al[14] also demonstrated in their study that of the 62 metformin-treated pregnant women with PCOS who had live births, all of the delivered neonates were normal with appropriate size for gestational age, except for 1 infant born with achondrodysplasia, which is an inherited disorder unlikely to be related to metformin therapy.

Metformin and Infant Development

To further document metformin's safety for use in pregnancy, Glueck et al[17] prospectively assessed the growth and motor-social development during the first 18 months of life of 126 neonates born to 109 women with PCOS who conceived while taking metformin and continued taking it through their pregnancy. The lengths and weights of the metformin exposed infants were compared with gender-specific CDC infant data. The investigators found that there were no systematic differences in growth between the metformin-exposed infants and the CDC infants over 18 months. There were also no motor-social developmental delays noted in the drug-exposed infants. The importance of this study lies in the fact that it shows no harmful effects of metformin on infants even beyond the neonatal period.

Acarbose

The use of acarbose in pregnancy seems to be a good option because it primarily acts in the gut by delaying carbohydrate absorption and is not absorbed, thereby having no systemic effects. However, this drug has not yet been studied well in pregnancy. In a small study by Zarate et al,[21] 6 pregnant women with moderately elevated levels of fasting and postprandial blood glucose were treated with acarbose, after which, the fasting and postprandial glucose levels normalised. The pregnancies were uneventful and the newborn babies were normal. Although this study shows promising results, it is still a very early and small study on acarbose use in pregnancy, and therefore, no plausible and definitive conclusions can be drawn from it in terms of the safety and efficacy of acarbose use in gestational diabetes.

Rosiglitazone

Rosiglitazone has not been recommended for use in pregnant women because it has been shown that treatment with the drug during mid to late gestation was associated with foetal death and growth retardation in animal models. It is classified as Category C by the Food and Drug Authority (FDA) for use in pregnancy, which means the risk of adverse outcomes cannot be ruled out. However, there have been 2 reported cases of rosiglitazone exposure during pregnancy. The first patient[22] was a diabetic and hypertensive woman who took 4 mg/day of rosiglitazone for the first 7 weeks of gestation when she was not aware that she was pregnant. Her treatment was changed to insulin when the pregnancy was confirmed and she gave birth to a normal healthy infant at the 36th week of gestation. The second patient[23] was a multigravid, diabetic woman who had been managed on diet and exercise alone, and had not received any drug therapy until the 13th week of her sixth pregnancy. She was started on rosiglitazone 4 mg/day from the 13th to the 17th week of gestation, during which she was discovered to be pregnant. Rosiglitazone was stopped and insulin was initiated. She delivered a healthy baby boy without any malformations on the 37th week of gestation. Although these 2 reports did not show any adverse effect from the brief exposure to rosiglitazone, it would be difficult to make any conclusions regarding the safety of its use in pregnancy at the moment.

A study on the placental transfer of rosiglitazone in the first trimester of pregnancy was recently reported by Chan et al.[24] In this study, rosiglitazone was given to 31 pregnant women between the 8th to 12th week of gestation who were undergoing surgical termination of their pregnancy. Rosiglitazone was detected in 19 foetal samples (61.3%). This shows that there is a high risk of placental transfer and foetal exposure to the drug.

Conclusions

There is now a changing trend in the acceptability of using oral hypoglycaemic agents in non-insulin dependent

pregnant diabetics. Recent evidence (Table 1) has shown that there are some oral hypoglycaemic drugs which may be safe and, therefore, useful, especially for those who are only mildly to moderately hyperglycaemic and who do not desire multiple daily insulin injections. In some countries where the use of insulin may not always be possible, the option of using oral hypoglycaemic agents may be particularly attractive.

Among the sulphonylureas, only glibenclamide has been shown not to cross the placenta.[11] Moreover, the best and strongest evidence available so far in terms of safety and efficacy is that of glibenclamide as shown in a randomised controlled study involving a large number of subjects (n = 404) and a direct head-to-head comparison with the gold standard use of insulin in the treatment of gestational diabetes.[12] However, it would be reassuring to have more of such randomised controlled studies comparing glibenclamide and insulin to confirm these findings.

Metformin has been documented in several trials to be safe for use in pregnancy, and in fact, even beneficial in terms of decreasing the incidence of early pregnancy loss and the development of gestational diabetes, reducing insulin levels and insulin resistance, and preventing androgen excess in women with PCOS.[14-18] However, these studies had all been done on non-diabetic patients with PCOS and not on pregnant diabetics. Moreover, none of these studies had been randomised controlled trials and most of them involved relatively small number of subjects.
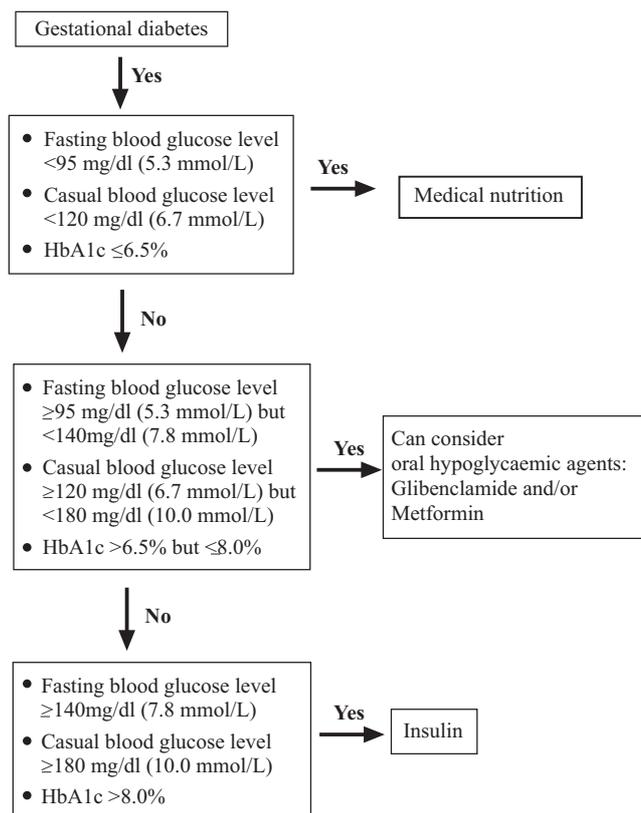
The efficacy of metformin in gestational diabetes is presumably attributed to its insulin sensitising effects, thereby improving glucose control. However, there is no direct evidence yet from good studies documenting the efficacy and safety of its use in patients with gestational diabetes. A large prospective, randomised controlled trial called "metformin in gestational diabetes (MiG)" comparing the use of metformin and insulin in gestational diabetes is currently ongoing in New Zealand and Australia.[25] This study will provide us with a significant basis to decide whether or not we should use metformin in gestational diabetes.

Both glibenclamide and metformin are currently classified by the FDA as Category B drugs for use in pregnancy, which means that there is no evidence of risk in humans.[26,27] With the present safety profile of the 2 drugs, Langer[28-31] proposed the following treatment plan for gestational diabetes: medical nutrition for patients with a fasting blood glucose level of <95 mg/dl (5.3 mmol/L), or a random blood glucose level of <120 mg/dl (6.7 mmol/L), or HbA1c of <7%; oral hypoglycaemic agent therapy (glibenclamide and/or metformin) for a fasting blood glucose level of >95 mg/dl (5.3 mmol/L), or a random blood glucose level of <140 mg/dl (7.8 mmol/L), or HbA1c of ≥8%; and insulin therapy for a fasting blood glucose level of >140 mg/dl (7.8 mmol/L), or a random blood glucose level of >180 mg/dl (10 mmol/L), or HbA1c of >12%. However, the ranges of the blood sugar levels and HbA1c values that determine the

Table 1. Selected Studies Using Oral Hypoglycaemic Agents in Pregnancy

Drugs	Authors	Year	No. of subjects	Study design	Outcomes
Glibenclamide (Glyburide)	Langer et al[12]	2000	404	Randomised Controlled Trial	Glyburide's efficacy was comparable to insulin in the control of blood sugar levels. There were no significant differences in the neonatal outcomes between the 2 groups.
	Kremer et al[13]	2004	73	Prospective Cohort Study	No congenital anomalies were found in the neonates of those treated with glyburide.
Metformin	Jakubowicz et al[14]	2002	96	Retrospective Study	Reduced the rate of early pregnancy loss in women with PCOS.
	Glueck et al[16]	2002	70	Prospective and Restrospective	Reduced the development of gestational diabetes in women with PCOS with no foetal malformations in the neonates of the treated subjects.
	Glueck et al[15]	2004	42	Prospective Observational Study	Reduced preconception insulin levels, insulin resistance, and testosterone levels while maintaining insulin-sensitising effects throughout pregnancy.
	Glueck et al[18]	2004	349	Prospective Case Series	No significant difference in pre-eclampsia rates between treatment and control groups.
	Glueck et al[17]	2004	126	Prospective Case Series	No systematic differences in growth between the drug-exposed and non-exposed infants. There were also no motor-social developmental delays noted in the infants of treated subjects.
Acarbose	Zarate et al[21]	2000	6	Prospective Case Series	Blood sugar levels were adequately controlled. The pregnancies were uneventful and the newborn babies were normal.

PCOS: polycystic ovary syndrome

```
┌─────────────────────┐
│ Gestational diabetes │
└─────────────────────┘
          │ Yes
          ▼
```

- Fasting blood glucose level <95 mg/dl (5.3 mmol/L)
- Casual blood glucose level <120 mg/dl (6.7 mmol/L)
- HbA1c ≤6.5%

→ **Yes** → Medical nutrition

          │ No
          ▼

- Fasting blood glucose level ≥95 mg/dl (5.3 mmol/L) but <140mg/dl (7.8 mmol/L)
- Casual blood glucose level ≥120 mg/dl (6.7 mmol/L) but <180 mg/dl (10.0 mmol/L)
- HbA1c >6.5% but ≤8.0%

→ **Yes** → Can consider oral hypoglycaemic agents: Glibenclamide and/or Metformin

          │ No
          ▼

- Fasting blood glucose level ≥140mg/dl (7.8 mmol/L)
- Casual blood glucose level ≥180 mg/dl (10.0 mmol/L)
- HbA1c >8.0%

→ **Yes** → Insulin

HbA1c: glycosylated haemoglobin A1c

Fig. 1. Treatment plan for gestational diabetes.

specific treatment option in this treatment plan are not very clear and well-defined, and the threshold for the HbA1c value to start insulin treatment is quite high (HbA1c >12%). Therefore, we suggest the treatment plan for gestational diabetes to be as illustrated in Figure 1.

Acarbose shows promise in its use for gestational diabetes because this drug is not absorbed in the gut significantly and, therefore, has no systemic effects. However, with just one small study, it is still too early to determine how effective and safe this drug is for treating gestational diabetes. As with the other oral hypoglycaemic agents, large randomised controlled trials with head-to-head comparisons with other oral agents and insulin will help determine the use of acarbose for gestational diabetes. This drug is also currently classified as Category B by the FDA for use in pregnancy.

Oral hypoglycaemic agents, which have been previously regarded as unsafe for pregnancy, are being re-evaluated for their use in non-insulin dependent pregnant diabetics. Most of the evidence available so far suggests that some of these drugs, when used in their normal non-pregnancy doses, may be safe and beneficial for women with gestational diabetes. However, further well-conducted, large-scale clinical studies will be needed to confirm the safety and

efficacy of these drugs for use in pregnant diabetics and to gather widespread acceptability in the medical community. At present, we still advocate caution in the use of oral hypoglycaemic agents in pregnancy, and one should always consider the benefits and risks of giving these drugs.

REFERENCES

1. Yogev Y, Langer O. The use of anti-hyperglycaemic and hypoglycaemic agents in pregnancy. Fetal Matern Med Rev 2004;15:133-43.
2. Smithberg M, Runner MN. Teratogenic effects of hypoglycemic treatments in inbred strains of mice. Am J Anat 1963;113:479-89.
3. Smoak IW. Embryopathic effects of the oral hypoglycemic agent chlorpropamide in cultured mouse embryos. Am J Obstet Gynecol 1993;169:409-14.
4. Denno KM, Sadler TW. Effects of the biguanide class of oral hypoglycemic agents on mouse embryogenesis. Teratology 1994;49:260-66.
5. Campbell GD. Chlorpropamide and foetal damage. BMJ 1963;1:59-60.
6. Larsson Y, Sterky G. Possible teratogenic effect of tolbutamide in a pregnant prediabetic. Lancet 1960;2:1424-6.
7. Notelovitz M. Sulphonylurea therapy in the treatment of the pregnant diabetic. S Afr Med J 1971;45:226-9.
8. Zucker P, Simon G. Prolonged symptomatic neonatal hypoglycemia associated with maternal chlorpropamide therapy. Pediatrics 1968;42:824-5.
9. Kemball ML, McIver C, Milner RD, Nourse CH, Schiff D, Tiernan JR. Neonatal hypoglycaemia in infants of diabetic mothers given sulphonylurea drugs in pregnancy. Arch Dis Child 1970;45:696-701.
10. Hellmuth E, Damm P, Molsted-Pedersen L. Oral hypoglycaemic agents in 118 diabetic pregnancies. Diabet Med 2000;17:507-11.
11. Elliot BD, Langer O, Schenker S, Johnson RF. Insignificant transfer of glyburide occurs across the human placenta. Am J Obstet Gynecol 1991;165:807-12.
12. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med 2000;343:1134-8.
13. Kremer CJ, Duff P. Glyburide for the treatment of gestational diabetes. Am J Obstet Gynecol 2004;190:1438-9.
14. Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. J Clin Endocrinol Metab 2002;87:524-9.
15. Glueck CJ, Goldenberg N, Wang P, Loftspring M, Sherman A. Metformin during pregnancy reduces insulin, insulin resistance, insulin secretion, weight, testosterone and development of gestational diabetes: prospective longitudinal assessment of women with polycystic ovary syndrome from preconception throughout pregnancy. Hum Reprod 2004;19:510-21.
16. 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.
17. Glueck CJ, Goldenberg N, Pranikoff J, Loftspring M, Sieve L, Wang P. Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy. Hum Reprod 2004;19:1323-30.
18. Glueck CJ, Bornovali S, Pranikoff J, Goldenberg N, Dharashivkar S, Wang P. Metformin, pre-eclampsia, and pregnancy outcomes in women with polycystic ovary syndrome. Diabet Med 2004;21:829-36.

19. Coetzee EJ, Jackson WP. Metformin in management of pregnant insulin-independent diabetics. Diabetologia 1979;16:241-5.

20. Coetzee EJ, Jackson WP. Pregnancy in established non-insulin-dependent diabetics. A five-and-a-half year study at Groote Schuur Hospital. S Afr Med J 1980;58:795-802.

21. Zarate A, Ochoa R, Hernandez M, Basurto L. Effectiveness of acarbose in the control of glucose tolerance worsening in pregnancy. Ginecol Obstet Mex 2000;68:42-5.

22. Yaris F, Yaris E, Kadioglu M, Ulku C, Kesim M, Kalyoncu NI. Normal pregnancy outcome following inadvertent exposure to rosiglitazone, gliclazide, and atorvastatin in a diabetic and hypertensive woman. Reprod Toxicol 2004;18:619-21.

23. Kalyoncu NI, Yaris F, Ulku C, Kadioglu M, Kesim M, Unsal M, et al. A case of rosiglitazone exposure in the second trimester of pregnancy. Reprod Toxicol 2005;19:563-4.

24. Chan LY, Yeung JH, Lau TK. Placental transfer of rosiglitazone in the first trimester of human pregnancy. Fertil Steril 2005;83: 955-8.

25. Simmons D, Walters BN, Rowan JA, McIntyre HD. Metformin therapy and diabetes in pregnancy. Med J Aust 2004;180:462-4.

26. Drug Facts and Comparisons 2003. St. Louis, Mo: Facts & Comparisons Ltd, 2003.

27. Physicians Desk Reference 2003. Montvale, NJ: Thompson, 2003.

28. Langer O. Gestational diabetes and oral hypoglycemic agents. OBG Management 2003;15:62-76.

29. Langer O. When diet fails: insulin and oral hypoglycemic agents as alternatives for the management of gestational diabetes mellitus. J Matern Fetal Neonatal Med 2002;11:218-25.

30. Langer O. Insulin and other treatment alternatives in gestational diabetes mellitus. Prenatal Neonatal Med 1998;3:542-9.

31. Langer O. Oral hypoglycemic agents in pregnancy: their time has come. J Matern Fetal Neonatal Med 2002;12:376-83.