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Diabetes Mellitus in Pregnancy

What are the Best Treatment Options?

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Summary

Diabetes mellitus complicates somewhere between 1 and 20% of all pregnancies worldwide. Women with all types of diabetes, including type 1 (insulin-dependent) and type 2 (non–insulin-dependent) diabetes mellitus, and gestational diabetes mellitus, as well as their infants, are at increased risk for a number of different complications. However, achieving and maintaining euglycemia throughout gestation has been demonstrated to reduce the risk of adverse outcome for both the mother and her offspring. Traditional management approaches use a combination of diet, exercise, intensive insulin regimens and multiple self monitored blood glucose determinations. There are a number of newer agents available to treat diabetes mellitus; however, their safety in pregnancy has not been thoroughly tested. Although the oral hypoglycaemic drugs are not customarily used during gestation in most of the US and Europe they have had considerable use in South Africa. Animal and human studies of the teratogenic effects of these drugs have yielded conflicting data and it is difficult to distinguish between the teratogenic effects of poor maternal metabolic control and the agents themselves. This article also addresses the current state of the knowledge regarding the drug safety of a variety of medications for conditions, including hypertension and preterm labour, commonly encountered in the management of the pregnant women with diabetes mellitus.

Diabetes mellitus complicates approximately 4% of all pregnancies in the US, which translates into more than 150 000 pregnancies per year.[1] Gestational diabetes mellitus accounts for 135 000 of these pregnancies, type 2 (non–insulin-dependent) diabetes mellitus for 12 000 and type 1 (insulin-dependent) diabetes mellitus for 7000.[1] Worldwide, estimates of the frequency of abnormal glucose tolerance during pregnancy range from <1% to nearly 20%.[2] However, the true annual incidence of diabetes mellitus in women of childbearing age is available for only a very few populations. In 1973 in the US there were 2.8 women aged 17 to 41 years with diabetes mellitus per 1000 population, while at the same time in Edinburgh, Scotland and Denmark there were 2.0 and 0.8 per 1000 population per year, respectively.[3]

Diabetes mellitus is a heterogeneous disorder of glucose intolerance. It is generally classified into the following categories: type 1 diabetes melitus; type 2 diabetes mellitus; and gestational diabetes mellitus. Type 1 diabetes mellitus most commonly develops during childhood and is, therefore, often seen in women of childbearing age. Beta cell destruction and insulin deficiency are the hallmarks of this disorder, which always requires exogenous insulin therapy. Type 2 diabetes mellitus is characterised by defects in both insulin action and secretion. Type 2 diabetes mellitus is most commonly diagnosed during the fourth and fifth decades of life and therefore is less frequently seen in women of childbearing age. Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy.[4]

Within any given population the frequencies of gestational diabetes mellitus and type 2 diabetes mellitus are similar. Black women in the US and Asian immigrants in the UK have higher rates of gestational diabetes and impaired glucose tolerance than do Caucasian women from those countries. This higher rate is also seen in south east Asian women migrating to America and Australia.[5] Excess risks for gestational diabetes mellitus have also been demonstrated for Oriental women, Hispanic women born in Puerto Rico or elsewhere outside the US, as well as women from the Indian subcontinent and the Middle East.[6] Studies appear to indicate that women from ethnic minorities have an increased risk of gestational diabetes mellitus which is independent of age and degree of obesity.[5]

1. Maternal and Perinatal Complications

Women with all types of diabetes mellitus are at greater risk for a number of pregnancy-related complications. These include preterm labour, pyelonephritis, hydramnios and hypertensive disorders. Women with pregestational diabetes mellitus are also at risk for the acute complications of diabetes mellitus because of the metabolic alterations associated with pregnancy as well as the effects of strict glycaemic control.[7] Perinatal morbidity and mortality rates are also higher in pregnancies complicated by diabetes mellitus. Neonatal morbidities affecting the offspring of women with diabetes mellitus include neonatal hypoglycaemia and other metabolic abnormalities, respiratory distress syndrome and macrosomia.[8,9] Fetal hyperglycaemia and hyperinsulinaemia are believed to cause most of the perinatal complications. Maternal hyperglycaemia leads to hypertrophy and hyperplasia of the fetal pancreatic islet cells. It is well established that perinatal mortality is directly related to the mother's level of glycaemic control.[10]

Although strict metabolic control and improved management protocols have dramatically reduced the incidence of most of the maternal and perinatal complications of diabetes mellitus, major malformations remain a significant cause of morbidity and mortality in infants born to mothers with diabetes mellitus. The frequency of major congenital anomalies remains significantly increased among infants of mothers with both type 1 and type 2 diabetes mellitus and can be as high as 6 to 10%.[11,12] The malformations associated with diabetes mellitus can involve multiple organ systems. However, cardiovascular and spinal cord anomalies are the most common. There is strong evidence in both human and animal studies demonstrating an association between malformations and glucose control in

early pregnancy.[13-18] In addition, clinical trials have demonstrated that strict glycaemic control prior to and during early pregnancy can reduce the rate of these malformations down to the rate seen in the background population.[19-24]

2. Management of Pregnancy Complicated by Diabetes Mellitus

Achieving and maintaining euglycaemia is the main goal of management for pregnancies complicated by gestational or pregestational diabetes mellitus.[7] The treatment approach requires a combination of diet, exercise, intensive insulin regimens and multiple blood glucose determinations.

Diet therapy is the cornerstone of diabetes mellitus management during pregnancy. The goal of dietary therapy is to achieve good metabolic control while promoting optimal fetal growth and development. All women with diabetes mellitus should be seen by a nutritionist for individualised diet counselling.

Exercise is another recognised treatment for diabetes mellitus. Although it has been shown to be very beneficial in nonpregnant individuals, data are limited regarding the risks and benefits of either periodic or regular exercise in pregnant women with pregestational diabetes mellitus. Exercise is advocated as a treatment modality for women with gestational diabetes mellitus without medical or obstetric complications.[4]

Home glucose monitoring has also become a mainstay for the outpatient management of pregnancies complicated by pregestational diabetes mellitus. Pregnancy demands an aggressive and frequent self-testing schedule; blood glucose measurements are usually obtained at least 4 to 7 times a day, both in the fasting and postprandial states. Many women with gestational diabetes mellitus also perform home blood glucose monitoring, particularly those on insulin therapy. Women with either pregestational or gestational diabetes mellitus who are unable to maintain euglycaemia (see table I for target plasma glucose levels) with diet and exercise alone are started on insulin therapy.[7,25]

2.1 Insulin

The goal of insulin therapy is to mimic the normal diurnal profile of endogenous insulin release.[7] Daily, multiple injections of insulin are usually required to simulate normal insulin release. Human insulin is recommended in pregnancy, because insulin antibodies can cross the placental barrier.[25] Insulin requirements change dramatically during pregnancy. In the first trimester, maternal insulin requirement is approximately 0.7 U/kg of bodyweight per day. This increases to 1.0 U/kg by late gestation.[26] However, wide variations in insulin requirements have been reported in women with type 1 diabetes mellitus.[27] There are several different approaches to insulin administration as outlined in table II. In addition, continuous subcutaneous insulin infusion pumps have also been shown to be effective during pregnancy.

Animal studies have suggested that insulin may be teratogenic. Landauer[29] and Zwilling[30] injected large doses of insulin into chicken eggs and found skeletal malformations in the chick embryos. Insulin has also been injected in high doses into pregnant rabbits and produced congenital malformations in the resulting offspring.[31,32] Similar experiments have also been performed on mice and rats with almost identical results.[33-35] In contrast, Ream and associates[36] did not find massive doses of insulin to be teratogenic in an *in vivo* study in rats. The teratogenic role of insulin in clinical settings is very unlikely, as maternal insulin is considered to only minimally cross the placenta and fetal pancreatic beta cells do not secrete until about 12 weeks' gestation which is beyond the period of organogenesis.

2.2 Hypoglycaemia

Some investigators have suggested that it is hypoglycaemia rather than insulin that is terato-

Table I. Target plasma glucose levels in pregnancy

Fasting	60-90 mg/dl
1h postprandial	<140 mg/dl
2h postprandial	<120 mg/dl
Nocturnal	60-120 mg/dl

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genic. In animal models, it has been shown that even brief periods of maternal hypoglycaemia can cause fetal malformations. Smoak and Sadler[37] found that even a 2 hour exposure to a hypoglycaemic milieu during days 8 and 9 of gestation in post implantation mouse embryos resulted in maldevelopment. These findings are consistent with other investigators using animal models.[38,39] In contrast, data from clinical studies, although less extensive, do not corroborate the experimental findings.

Some of the first reports on the effects of hypoglycaemia on human fetuses can be found in the psychiatric literature in reference to insulin coma therapy during pregnancy. Impastato and coworkers[40] reported on 19 women who received insulin coma therapy during early gestation. Two women delivered children who were later reported to have developmental delays, but no structural anomalies were seen in any of the offspring.

Findings are also inconclusive when the data specific to diabetes mellitus in pregnancy are reviewed. Rowland and colleagues[41] reported a 4-fold increase in heart disease in infants of mothers with diabetes mellitus when the pregnancy was complicated by hypoglycaemia. In contrast, a number of clinical trials have demonstrated no increase in the incidence of congenital anomalies despite severe and frequent maternal hypoglycaemia. The Diabetes-in-Early Pregnancy Study[26] did not find an association between maternal hypoglycaemia and congenital malformations, nor did the series reported by Pedersen[42] and Kitzmiller and colleagues.[20] Furthermore, because frequent hypoglycaemic episodes occur in humans rather commonly with tight glucose control and because stringent metabolic control is associated with a decrease in the malformation rate, hypoglycaemia is not felt to be a major contributor to the genesis of congenital anomalies in humans.

2.3 Oral Hypoglycaemic Agents

The incidence of birth defects among offspring of mothers with type 2 diabetes mellitus is 2- to 3-fold higher than that observed in the offspring of women without diabetes mellitus.[43,44] Cardiovascular defects are 20.6 times more common in these infants than in infants of nondiabetic women.[44] Causes for these malformations are not known but may be related to altered maternal metabolic state

and/or drug therapy taken by pregnant women with diabetes mellitus.

Oral hypoglycaemic agents have been implicated as teratogens in humans and animals. Results of studies in rats and mice have suggested that the sulphonylureas tolbutamide and chlorpropamide are teratogenic, although these early studies failed to show conclusively that the compound themselves and not altered maternal metabolism were the primary teratogen.[45-48] A study by Smoak[49] demonstrated that exposure to a combination of hypoglycaemia and chlorpropamide did not increase the incidence of malformations in cultured mouse embryos above that resulting from chlorpropamide exposure alone. Thus chlorpropamide itself appears to be embryotoxic.

Currently, oral hypoglycaemic agents are not recommended for use during pregnancy because of the possibility of fetal teratogenesis and prolonged neonatal hypoglycaemia.[50-57] The sulphonylureas work by stimulating pancreatic beta cells to produce and release insulin. First generation sulphonylureas have been shown to cross the placenta but there is conflicting evidence regarding the newer agents. Using an *in vitro* isolated perfused placental cotyledon model, Eliott and colleagues[58] demonstrated that glibenclamide (glyburide), one of the second-generation oral agents, crosses the human placental only minimally. Contrasting results, however, have been reported by Sivan and colleagues,[59] who examined placental transport of glibenclamide using an *in vivo* model. They injected pregnant rats with labelled glibenclamide, diazepam and albumin. Diazepam was chosen as a control since it shares similar protein binding, partition coefficients and molecular weight with glibenclamide and readily crosses the placental barrier. Albumin does not cross the placenta and was chosen as a second control. Radioactivity was measured in both maternal blood and in the whole fetal extracts. They found that glibenclamide concentration in fetal tissue consistently reflected its concentration in maternal blood when measured at consecutive intervals after intravenous injection in the mother. These data suggest that glibenclamide does, in fact, cross the placenta and would therefore, be expected to stimulate fetal pancreatic insulin release. Because the adverse fetal consequences of maternal diabetes mellitus are believed to be related to fetal hyperinsulinaemia, any agent that increases fetal insulin production would not be recommended for use during pregnancy.

In humans, there have been scattered case-reports of congenital malformations associated with oral hypoglycaemic agents. Piacquadio and colleagues[60] compared pregnancy outcome in 20 pregnant women with type 2 diabetes mellitus exposed to oral hypoglycaemic drugs during embryogenesis to pregnancy outcome in 40 pregnant women with type 2 diabetes mellitus who were not exposed to oral hypoglycaemic drugs during pregnancy (control group). 50% of the infants born to women in the exposed group had congenital malformations, compared with only 15% of infants born to women in the control group. Five infants (25%) in the exposed group had ear malformations, anomalies not commonly described in diabetic embryopathy. Hyperbilirubinemia, polycythemia and hyperviscosity requiring partial exchange transfusions were also more common complications among babies in the exposed versus the control groups. Three babies in the exposed group, but none in the comparison group, had severe prolonged neonatal hypoglycaemia. One criticism of this study was its failure to consider the altered metabolic state of the diabetic mothers in the production of malformations.

It is difficult to distinguish between the possible teratogenic effects of poor maternal metabolic control and fetal exposure to oral hypoglycaemic agents during early pregnancy. Therefore, Towner and colleagues[61] undertook a study to determine the relative impact of maternal glycaemic control and modality of maternal anti-diabetic therapy during early pregnancy on the risk of malformations in infants. From their prospectively collected data, they identified 332 consecutive infants born to women with type 2 diabetes mellitus who did not participate in a preconceptional diabetes care

programme. Overall, 16.9% (56/332) infants were born with congenital anomalies. Stepwise logistical regression was used to identify the maternal characteristics that were independently associated with the risk of major and minor congenital malformations in these infants. Regression analysis revealed 2 maternal characteristics that were independently associated with major malformations: maternal glycohaemoglobin level at initial presentation for care and maternal age at onset of diabetes. The risk of major malformations was unrelated to the mode of antidiabetic therapy during early pregnancy. No relationship was found between maternal glycaemia or treatment modality and rates of minor congenital anomalies. These data indicated that the risk for major congenital anomalies in women with type 2 diabetes mellitus appears to be related to maternal glycemic control rather than the mode of antidiabetic therapy during early pregnancy.

Less is known about the risk of teratogenesis associated with other classes of oral hypoglycaemic agents, e.g. the biguanides which include phenformin and metformin. Both phenformin and metformin have been used clinically to treat patients with type 2 diabetes mellitus but since phenformin has a propensity for producing lactic acidosis, metformin has become the biguanide of choice. To address the issue regarding the safety of the biguanides in pregnancy, Denno and Sadler[62] exposed neurulating mouse embryos in culture to phenformin and metformin and examined them for embryotoxicity. In addition, dose response curves were established and included concentrations in the pharmacological range. Metformin produced no alterations in embryonic growth and no major malformations. Approximately 10% of all embryos exposed to metformin regardless of dose, exhibited open cranial neuropores after 24 hours of culture. However, this anomaly appeared to represent a delay in closure as opposed to an overt defect, since no embryos exposed to the highest concentration of the drug and cultured for 48 hours showed open neural tubes.

In contrast, phenformin produced dose dependent changes in incidence of malformations, protein content, and embryo lethality. Malformations included neural tube closure defects, craniofacial hypoplasia and reduction in the size of the first and second visceral arches. Since the reduction in protein content was small and not dose related, this effect of phenformin may have little clinical significance. Phenformin at doses >0.1 mg/ml produced embryo lethality and all embryos were killed at a dose of 0.4 mg/ml.

The fact that results from this study indicate that phenformin is embryotoxic at concentrations equal to serum concentrations obtained in patients treated with the agent clinically, suggests that metformin is the safer drug for use during pregnancy. However, metformin is not without adverse effects since it produced a delay in neural tube closure and also reduced yolk sac protein values at 2 different concentrations. While delayed closure of the neural tube may not have resulted in gross morphological abnormalities, it was not possible to assess subtler alterations that might result from such a delay.

Although the oral hypoglycaemic drugs are not customarily used in pregnancy throughout most of the US and Europe, both metformin and sulphonylureas have had considerable clinical use in South Africa.[50,63-66] Coetzee and Jackson[50,63-66] have utilised these agents for glycemic control both in cases of type 2 diabetes mellitus preceding pregnancy and in gestational diabetes mellitus, if diet therapy failed. It is recommended that women managed with oral agents should be hospitalised for 3 to 4 days before the delivery. The oral agents should be discontinued at this time and replaced by a continuous intravenous infusion of insulin 24 hours before delivery.[67]

In 1984, Coetzee and Jackson[63] reported on the pregnancy outcomes of 171 women with established type 2 diabetes mellitus treated with oral hypoglycaemic agents. 78 women received the drugs during the first trimester of pregnancy and 93 did not. Pregnancy outcomes were compared between these 2 groups. Only 2 major congenital

anomalies and 4 spontaneous abortions were observed in the group who received drug therapy. Coetzee and Jackson[63] concluded that modern oral hypoglycaemic drugs are well tolerated during pregnancy provided that excellent control of blood glucose levels is achieved. This conclusion is supported by a recent case report of a successful pregnancy in a woman with gestational diabetes mellitus treated with the combined use of a sulphonylurea and insulin.[67] In addition, Coetzee and Jackson[64] treated more than 150 women with gestational diabetes with metformin and glibenclamide between 1974 and 1983. They found no cases of serious neonatal hypoglycaemia and a very acceptable rate of perinatal morbidity. More intensive investigation regarding the feasibility of oral agents in pregnancies complicated by type 2 diabetes mellitus and gestational diabetes mellitus is needed.

2.4 Dietary Therapy and Artificial Sweeteners

Although sugar substitutes are not a necessary component of the diabetic diet, they can be useful in facilitating compliance with nutritional recommendations during pregnancy. There are several sugar substitutes or non-nutritive sweeteners currently available for widespread use. These include saccharin, aspartame and acesulfame.[68] Of the 3, aspartame is by far the most popular and has been approved for use in a wide variety of food products. Aspartame is a dipeptide of L-aspartic acid and L-phenylalanine methyl ester. It is metabolised to aspartate, phenylalanine and methanol in the small intestine. Aspartame, which is approximately 200 times sweeter than sugar, is considered safe for use during pregnancy by the US Food and Drug Administration (FDA). Studies have demonstrated that, while aspartic acid does not readily cross the placenta, phenylalanine does, and fetal concentrations have been reported to be 1.3 times higher than maternal concentrations. However, maternal phenylalanine concentrations have been reported to be consistently below toxic concentrations even at twice the acceptable daily intake of this sweetener.[69,70]

Saccharin is the oldest artificial sweetener available but consumption of this product has declined dramatically since the introduction of aspartame. Saccharin is approximately 300 times sweeter than sugar. Saccharin has been shown to cross the placenta, although there is no evidence that it is harmful to the fetus.[68] Saccharin is not metabolised by the body and is excreted unchanged by the kidneys. Acesulfame-K is a potassium salt of a cyclic sulfonamide and is 200 times sweeter than sucrose. Like the other sweeteners, testing has not demonstrated its use to be harmful during pregnancy.[68]

2.5 Newer Therapies for Diabetes Mellitus

There are a number of newer agents available to treat diabetes mellitus, however, the safety of these agents in pregnancy has not yet been tested. Data are lacking regarding the use of troglitazone, the first of a new class of oral anti-hyperglycaemic drug[71] which works more by changing insulin receptor dynamics than by stimulating insulin release. Troglitazone lowers blood glucose levels by improving target cell response to insulin in both muscle and adipose tissue and also inhibits gluconeogenesis. It has a unique mechanism of action in that it is dependent on the presence of insulin for activity. Troglitazone is classified as a Category B drug in the US (meaning that either animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).[72] It was not demonstrated to be teratogenic in rats or rabbits given up to 2000 mg/kg or 1000 mg/kg, respectively, during organogenesis.[71]

In June of 1996, the US FDA approved the insulin analogue lispro which is a rapid-acting insulin that has a more rapid onset and shorter duration of action than human regular insulin.[73] Reproduc-

tion studies have been performed in pregnant rats and rabbits given parenteral doses of insulin lispro up to and exceeding 4 times the average human dose. The results have revealed no evidence of harm to the offspring of these animals.[73] There are, however, no adequate and well controlled studies in pregnant women to unequivocally demonstrate its safety. It is classified as a Category B drug.

Acarbose is an oral glucosidase inhibitor indicated for the management of type 2 diabetes mellitus.[74] Acarbose competitively inhibits glucosidase enzymes in the brush border of the small intestine. In addition, acarbose inhibits pancreatic amylase and other enzyme systems which effectively reduces the rate of complex carbohydrate digestion and the subsequent absorption of glucose, thereby, lowering postprandial glucose excursions in patients with diabetes mellitus. As with the previous agents, reproduction studies in animals have revealed no evidence of impaired fertility or harm to the offspring.[74] However, no adequate and well controlled studies have been performed in clinical trials.

3. Management of Hypertension in Pregnant Women with Diabetes Mellitus

Hypertension associated with gestation is generally classified into 4 categories which include chronic hypertension, preeclampsia-eclampsia, pre-eclampsia superimposed upon chronic hypertension and transient hypertension.[75] Pregnant women with hypertensive disorders of pregnancy are at increased risk of developing placental abruption, disseminated intravascular coagulation, cerebral haemorrhage, hepatic failure and acute renal failure. In addition, the fetuses of these women are also at higher risk of intrauterine growth retardation and death.[76]

Bedrest is considered to be the cornerstone of therapy for the pregnant diabetic woman with chronic hypertension. An antihypertensive agent is added if systolic blood pressure is consistently >150mm Hg and/or diastolic pressure is >100mm Hg.[76] The goal of therapy is to keep the systolic pressure <130mm Hg and diastolic pressure >85mm Hg or lower if tolerated.[77] Methyldopa is generally considered the first-line drug and agent of choice for the treatment of hypertension during pregnancy.[7] Methyldopa is generally prescribed at a dosage of 250mg 3 to 4 times per day. Second line agents included hydralazine and β-blockers.[76] Other drugs considered to be useful and relatively safe during pregnancy include diltiazem (a calcium antagonist), clonidine and prazosin.[77] β-blockers may intensify insulin-induced hypoglycaemia and are therefore generally avoided. Although ACE inhibitors have been shown to slow the progression from incipient to overt nephropathy in nonpregnant individuals with diabetes mellitus they are contraindicated in pregnancy because of their potential teratogenic effects.[78]

4. Diabetes Mellitus–Related Medications and Breastfeeding

Numerous factors are known to influence the transfer of drugs and chemicals into breast milk. These factors include the degree of protein binding since only free drug can pass from the maternal plasma into milk, volume of distribution in the mother and the difference in pH between maternal plasma and breast milk.[79] Typically drugs found in breast milk are at low concentrations, which may or may not have clinical effects on the infant. Although insulin does not cross into the breast milk, it is not known whether insulin lispro is excreted in significant amounts in human milk.

Less is known regarding the oral hypoglycaemic agents. Acarbose is poorly absorbed from the gastrointestinal tract and theoretically is the best choice of oral agents for glucose control in lactating women. Troglitazone is another potentially good choice since its >99% protein binding and large volume of distribution in the maternal compartment should ensure that relatively little drug crosses into breast milk. The older sulphonylureas (chlorpropamide and tolbutamide) have been shown to be excreted into breast milk and a similar excretion pattern would be expected for the newer sulphonylureas.[72] Although both glipizide and glibenclamide are highly protein-bound, they have

small volumes of distribution suggesting that there might be a higher potential for passage into milk.[79] Metformin is probably the least desirable of the oral hypoglycaemic agents because of its nonprotein binding capacity.[79] The effect on the nursing infant from exposure to these oral agents via the breast milk is largely unknown.

Many of the antihypertensive agents, for example captopril, enalapril, atenolol, clonidine, diltiazem, hydralazine, methyldopa, metoprolol, minoxidil, nifedipine, prazosin and most of the diuretics are compatible with breastfeeding, although the diuretics may diminish milk production.[79]

5. Drugs That Must Be Used Cautiously

Studies have indicated that the incidence of prematurity in diabetic pregnancies is 3 times higher than pregnancies in nondiabetics. This increased rate has been attributed in part to a higher rate of iatrogenic preterm delivery.[72] In a recent study by Miodovnik and colleagues,[80] it was reported that the rate of spontaneous preterm labour was 31.1% in patients with type 1 diabetes mellitus, a rate that is 3 to 4 times more than that reported in the general obstetric population. Women with diabetes mellitus who have glycemic control during the second trimester of pregnancy were found to be particularly at high risk for preterm delivery.

Magnesium sulfate therapy is considered the drug of choice in diabetic patients with premature labour, since this drug has no effect on diabetic control. However, this therapy requires the patient to be hospitalised. In contrast, β-sympathomimetic tocolytic agents can be administered orally but have been reported to induce hyperglycaemia and ketoacidosis. β-sympathomimetic drugs cross the placenta freely and in the past have been associated severe cardiovascular complications in the fetus. These include stillbirth, heart failure, disturbances of rate and rhythm, myocardial ischaemia or infarction, hydrops and neonatal death. The mechanism of fetal toxicity appears to be an increased myocardial concentration of intracellular calcium leading to over-excitation and cell necrosis.[81] However, a prospective trial by Karlsson and colleagues[82] demonstrated no significant increase in neonatal morbidity including cardiovascular effects among infants whose mothers had received β-sympathomimitics. In addition Meinen and coworkers[83] reported no pathological myocardial effects when fenoterol was administered in therapeutic doses to pregnant rabbits. Lastly despite the effects of these agents on glucose control, some investigators[72,80] have reported the successful use in women with diabetes mellitus in carefully controlled clinical situations. Treatment with β-sympathomimetic tocolytic agents in women with diabetes mellitus requires great caution, intensive monitoring of glucose levels and treatment with an infusion of intravenous insulin as needed.

Premature delivery may be necessary because of maternal or fetal complications before fetal lung maturation has occurred. Under these circumstances pharmacological acceleration of fetal lung maturation should be considered. Fetal respiratory distress syndrome has been shown to be reduced with the use of corticosteroids. Recommendations of the US National Institutes of Health Consensus Conference on Antenatal Steroids[84] include administration of glucocorticoids when the fetus is younger than 34 weeks or has evidence of immature lungs and there is no specific maternal contraindication. Although maternal diabetes mellitus does not preclude glucocorticoid use, glucocorticoids may cause severe hyperglycaemia and even ketoacidosis. This does not mean that glucocorticoids should not be used but rather that they should be used with caution. Periods of increased maternal glucose levels can be managed by additional insulin therapy. Thyrotropin-releasing hormone has been shown in some studies to further enhance lung maturation and this agent may have a unique role to play in diabetic patients since it does not cause hyperglycaemia.

6. Conclusion

In summary, the issue of drug safety in pregnant women with diabetes mellitus is very similar to that for all pregnant women. Although the oral

hypoglycaemic drugs are not customarily used in pregnancy throughout most of the US and Europe, both metformin and sulphonylureas have had considerable clinical use in South Africa. However, insulin therapy has not been implicated as a teratogen in human pregnancies. To date studies would indicate that the increased incidence of congenital malformations in these pregnancies is more related to the altered maternal metabolic milieu than the drug therapy provided to these women.

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