ORIGINAL ARTICLE

A Comparison between the Pregnancy Outcome of Women with Gestation Diabetes Treated with Glibenclamide and Those Treated with Insulin

J M H Lim*, Y Tayob**, P M S O'Brien***, R W Shaw****, *Department of Obstetrics and Gynaecology, University Malaya, Kuala Lumpur, **Department of Obstetrics and Gynaecology, St. Albans City Hospital, St Albans, ***Department of Obstetrics and Gynaecology, North Staffordshire Hospital, Stoke-on-Trent, ****Department of Obstetrics and Gynaecology, University Hospital of Wales, Cardiff

Summary

The pregnancy outcome of 33 women with gestational diabetes who were treated with glibenclamide and changed to insulin if glibenclamide failed, were compared with the pregnancy outcome of 21 women with gestational diabetes treated conventionally with insulin. The pregnancy outcome, with regard to the overall glycaemic control, rates of preterm labour, neonatal hypoglycaemia, fetal macrosomia, perinatal morbidity and mortality, were not statistically different between the two treatment groups. The limited number of women studied, and the non-random allocation of these women to each treatment group however, could have influenced these results. There were a few observed differences in the pregnancy outcome between the two treatment groups, which although were not statistically significant, caused some concern. In particular we noted an increased rate of fetal macrosomia in the glibenclamide treated group, which in theory could have been drug mediated.

Key Words: Gestational diabetes, Oral hypoglcaemic drugs, Fetal macrosomia

Introduction

The established drug of choice for the management of gestational diabetes when optimal glycaemic control cannot be achieved by dietary manipulation alone, is insulin. Oral hypoglycaemic drugs have not been widely used since they can cross the uteroplacental barrier, stimulate fetal insulin secretion, and consequently cause neonatal hypoglycaemia[1,2]. Furthermore, the fear of their possible teratogenic potential, and their questionable effectiveness and side effects during pregnancy, have greatly limited their routine use in pregnancy. Nevertheless, oral hypoglycaemic drugs continue to be used in certain countries, especially developing ones, where treatment with insulin is difficult[2].

In a study conducted in South Africa, Coetzee and Jackson[3] concluded that the use of oral hypoglycaemic drugs was safe, and highly successful in the management of diabetes in pregnancy, provided that care was taken to control blood glucose levels, and that delivery was properly planned. Their conclusion was based on a study of 691 diabetic pregnancies managed on a calorie restricted diet with oral hypoglycaemic drugs when necessary, and progressing to insulin therapy when oral hypoglycaemic drugs failed. Following this report, a proportion of women with gestational diabetes at the Royal Free Hospital, London, in whom dietary restriction alone was insufficient to attain satisfactory glycaemic control, were treated in a similar way using glibenclamide, and changed to insulin when glibenclamide treatment

failed. This paper reports our experience in the use of glibenclamide in gestational diabetes, and compares the outcome of these pregnancies with that of a similar group of women with gestational diabetes managed solely on insulin over the same period.

Materials and Methods

Fifty four women with gestational diabetes, whose glycaemic control was unsatisfactory on calorie restriction alone, were started on either insulin or glibenclamide. Insulin treatment was selected when a woman's preprandial or 2 hours postprandial blood glucose levels whilst on diet, exceeded 10mmol/1, or when obstetric problems, such as a poor obstetric history or polyhydramnios were present. All other women were started on glibenclamide.

Women commenced on glibenclamide were given an initial dose of 5 mg. daily, and this was increased to a maximum of 15 mg. daily where necessary. If satisfactory glycaemic control was not achieved after reaching the maximum dosage, glibenclamide was discontinued and insulin was started. Women commenced on insulin were given twice daily injections of a mixture of short acting and medium acting insulin. The dosage of insulin was adjusted as required to optimise glycaemic control.

All women were taught self monitoring of blood glucose, and they were supervised by midwives until competent. Blood glucose levels were measured using Dextrostix, and the readings were obtained either by visual comparison with a standard chart, or whenever possible, by means of a reflectance meter. Preprandial and 2 hours postprandial blood glucose levels were measured to monitor glycaemic control, and the women were followed up at weekly intervals in the joint obstetric and diabetic clinic.

At the onset of spontaneous labour, or prior to elective delivery by either induction of labour or caesarean section, glibenclamide and subcutaneous insulin injections were discontinued. An intravenous infusion of 5% dextrose was commenced, and insulin was given to all the women by means of an insulin pump. Blood glucose levels were monitored hourly using Dextrostix, and the rate of insulin infusion was adjusted as necessary to ensure good glycaemic control until delivery.

Following delivery, all babies were examined by a paediatrician. Early feeding was encouraged, and the babies' blood glucose levels were checked at regular intervals after birth to ensure that they did not develop neonatal hypoglycaemia.

The blood glucose charts of all the women were analysed independently after delivery, and their glycaemic control during pregnancy was graded as:

1) Good : If all blood glucose levels were between 3 mmol/l and 7 mmol/l.

2) Adequate : If 90% of all blood glucose levels were good, and none were > 8 mmol/l.

3) Poor : If glycaemic control was less than adequate.

The pregnancy outcome of those women treated with glibenclamide (commencing on glibenclamide, and progressing to insulin if glibenclamide failed), was compared to the pregnancy outcome of those women who were treated conventionally with insulin.

Results

Twenty one women were commenced on insulin, and 33 women were commenced on glibenclamide. Seven of the 33 women who were commenced on glibenclamide, were changed to insulin because of unsatisfactory glycaemic control. The gestational age when their treatment was changed from glibenclamide to insulin, ranged from 30 weeks to 35 weeks. One woman who was considered to have unsatisfactory glycaemic control whilst on glibenclamide, laboured spontaneously before her treatment could be changed to insulin.

Nineteen (58%) of the 33 women who were started on glibenclamide had gestational diabetes diagnosed before 28 weeks gestation. This was statistically similar to the insulin treated group, where 9 (43%) of the 21 women had gestational diabetes diagnosed before 28 weeks gestation (Chi-square=1.11, DF=1, p>0.1).

There was no statistical difference in the overall glycaemic control between the 2 treatment groups (Chi-square=1.91, DF=2, p>0.1). Glycaemic control was good in 19 (58%), adequate in 6 (18%) and poor in 8 (24%) women in the glibenclamide treated group, whilst glycaemic control was good in 11 (53%), adequate in 7 (33%) and poor in 3 (14%) women in the insulin treated group.

Spontaneous preterm labour occurred in 4 (12%) women in the glibenclamide treated group compared to none in the insulin treated group. The preterm labour rate however, was not significantly different between the 2 treatment groups (Chi-square=2.75, DF=1, 0.1>p>0.05).

The incidence of neonatal hypoglycaemia was also not statistically different between the two treatment groups, with 1 baby from each treatment group developing mild transient neonatal hypoglycaemia shortly after delivery (Chi-square=0.11, DF=1, p>0.5).

There were no perinatal deaths in the insulin treated group, but 2 occurred in the glibenclamide treated group. One baby died of lethal cardiac anomalies, whilst the other, who was born at 37 weeks gestation, died of intraventricular haemorrhage secondary to neonatal septicaemia. The difference in the neonatal mortality rate between the treatment groups was not statistically significant (Chi-square=1.32, DF=1, p>0.1).

No perinatal morbidity occurred in the insulin treated group. However, 1 woman in the glibenclamide treated group, whose treatment was changed to insulin because of poor glycaemic control, delivered a baby with hypertrophy of the bladder neck of unknown aetiology, which resulted in bilateral hydronephrosis and subsequent renal impairment. The difference in the incidence of fetal morbidity between the 2 treatment groups was not significant (Chi-square=0.65, DF=1, p>0.5).

The distribution of birth weights in percentiles for each of the treatment groups are shown in Table I. Eight (24%) babies in the glibenclamide treated group were born with a birth weight above the 90th. percentile for gestation, compared to 1 (5%) baby in the insulin treated group. This observed increase in the number of babies born above the 90th. percentile in the glibenclamide treated group however, fell just short of statistical significance (Chi-square=3.51, DF=1, 0.1>p>0.05).

Discussion

The results of our study show that women with gestational diabetes managed with glibenclamide can have a pregnancy outcome similar to those managed solely on insulin, provided that glycaemic control is good, and that treatment is changed to insulin if glycaemic control is poor. In addition, it appears that if glibenclamide is stopped in the period prior to delivery, and treatment is changed to intravenous insulin, the risk of neonatal hypoglycaemia can be reduced to levels comparable to that of women managed solely on insulin. However, the limited numbers, and the non-random allocation of the women to the 2 treatment groups in this study, confound the interpretation of the results, and could have influenced the outcome. With this in mind, there are a few observed differences in the pregnancy outcome between the two treatment groups which, although not of statistical significance, are of concern and should perhaps be considered before advocating glibenclamide therapy.

First we considered the two cases of perinatal mortality, which both occurred in the glibenclamide treated group. Although on first inspection this seems alarming, on closer scrutiny it is very unlikely that these deaths could have resulted from the use of

Table I
Distribution of birth weights in percentiles of the two treatment groups

Birth weight (percentiles)	Glibenclamide group n = 33	Insulin group n =21
< 10th	0	1
10th to < 50th	9	10
50th to 90th	16	9
> 90th	8	1

glibenclamide. The drug was not commenced until after the period of organogenesis in the baby who died of a lethal cardiac anomaly, and the cause of the intraventricular haemorrhage which led to the death of the second baby was neonatal septicaemia.

Secondly we considered the case of the baby in the glibenclamide treated group who developed bilateral hydronephrosis and renal impairment, secondary to bladder neck hypertrophy of unknown aetiology. It remains uncertain whether this could have resulted from the use of glibenclamide. Similarly, it is unclear whether the observed higher incidence of spontaneous preterm labour in the glibenclamide treated group when compared to the insulin treated group, could have been related to the drug.

Finally we considered the observed increase in incidence of macrosomic babies which occurred in the glibenclamide treated group. Any baby whose birth weight exceeds the 90th. percentile for its gestation may be considered macrosomic[4]. Nutrient oversupply before 28 weeks gestation, may modulate fetal weight gain thereafter by stimulating pancreatic beta cell ontogeny and insulin secretion[5]. Women who develop gestational diabetes before 28 weeks gestation, are therefore more likely to have macrosomic babies even if subsequent glycaemic control is good. Poor glycaemic control following the diagnosis of gestational diabetes, further contributes to fetal macrosomia by providing the fetus with excessive nutrients.

Since both treatment groups were statistically similar with respect to the overall glycaemic control, and to the proportion of women who had gestational diabetes diagnosed before 28 weeks gestation, it is surprising to find a disproportionately large number of macrosomic babies in the glibenclamide treated group when compared to the insulin treated group. Although this difference in the incidence of fetal macrosomia fell just short of statistical significance, the higher incidence of fetal macrosomia observed in the glibenclamide treated group is worrying, since in theory it could have been drug mediated.

Glibenclamide, a sulphonylurea, acts primarily by stimulating the beta islet cells of the pancreas to produce insulin. Since glibenclamide crosses the placenta, it could cause fetal hyperinsulinaemia, which is known to result in neonatal hypoglycaemia, when drug exposure extends to delivery[1,2]. However, the possible effects of prolonged drug induced fetal hyperinsulinaemia on fetal growth, has not to our knowledge been previously described.

Susa *et al*[6] implanted osmotic mini-pumps containing insulin into monkey fetuses and demonstrated a 34% increase in fetal body weight, associated with enlargement of the heart, liver and spleen, after 3 weeks of pharmacological hyperinsulinaemia. When less extreme fetal hyperinsulinaemia was induced, a 23% increase in body weight and enlargement of the heart occurred, with large deposits of adipose tissue being the predominant component of the weight gain. Despite high levels of serum insulin used in some cases, the fetuses remained euglycaemic. Based on a similar model, glibenclamide induced fetal hyperinsulinaemia could stimulate fetal growth, thereby causing fetal macrosomia.

The adverse effects of fetal hyperinsulinaemia resulting from poor maternal glycaemic control, are well recognised[7]. Perhaps the possible adverse effects of drug induced fetal hyperinsulinaemia should also be considered when using sulphonylureas to manage women with gestational diabetes. Before advocating glibenclamide as an alternative treatment for gestational diabetes, larger prospective, randomised and controlled studies are needed to fully evaluate the usefulness and safety of sulphonylureas in pregnancy, and in particular to determine whether they do increase the risk of preterm labour and fetal macrosomia.

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