SULPHONYLUREA THERAPY IN THE TREATMENT OF THE PREGNANT DIABETIC*

MORRIS NOTELOVITZ, M.B., B.CH., M.D. (RAND), M.R.C.O.G., *Principal Obstetrician and Gynaecologist and Head of the Department of Obstetrics and Gynaecology, Addington Hospital, Durban*

Treatment of the Natal Indian diabetic with insulin has proved to be unsatisfactory for three reasons: firstly, the diabetic syndrome in this racial group is characterized by a relative resistance to insulin;[1] secondly, the patients have a natural reluctance to give their own injections which makes them dependent upon friends and relatives and often leads to irregular and inconsistent treatment; and thirdly, even if they do respond to insulin, the dose required is usually excessive. The administration of a potentially dangerous drug by ill-qualified persons leaves much to be desired, particularly so in the pregnant diabetic, where a sudden alteration in the environment of the foetus could well be responsible for its intra-uterine or perinatal demise.

In an attempt to achieve some form of outpatient control, widespread use of the oral antidiabetic agents—primarily tolbutamide and chlorpropamide—was instituted. This resulted in a reduction of the previously insulin-dependent Natal Indian diabetics from 80% to 4% of the total series in 1960.[2] Included in this category were pregnant diabetics.

Reappraisal of a Previous Retrospective Study

In 1962 a retrospective study was published of 36 pregnant diabetics (most of them Natal Indians) who had been on treatment with either tolbutamide or chlorpropamide.[3] The results of this study (Table I) indicated that, whereas a control group of patients treated with insulin and/or diet had a perinatal mortality rate of 20%, the foetal loss in the sulphonylurea-treated patients was 50%.

TABLE I. RETROSPECTIVE ANALYSIS OF PERINATAL MORTALITY IN 40 PREGNANT DIABETICS TREATED WITH SULPHONYLUREAS[3]

	Durban series		*Cape Town series*		*Combined*	
	Live child	*Perinatal death*	*Live child*	*Perinatal death*	*Live*	*Dead*
Chlorpropamide	8	9	0·5*	5	8·5 (37%)	14 (63%)
Tolbutamide	9	1	4·5*	3	13·5 (77%)	4 (23%)
Insulin/diet	8	2	40	10	48·0 (80%)	12 (20%)

*The 0·5 indicates a case where tolbutamide was followed by chlorpropamide.

On further analysis it was found that the 23 chlorpropamide-treated pregnant patients accounted for a perinatal mortality of 63%. Treatment with tolbutamide was associated with a foetal loss of 23%. There was only one severe congenital abnormality following treatment with tolbutamide.

Reappraisal of this report, however, led to the conclusion that it was deficient in many respects since: (*i*) it was a retrospective study with the result that 'control' was difficult to assess in several patients, while some were known to have been unsupervised for long periods; (*ii*) patients who did not respond to 250 mg of chlorpropamide were treated with a dosage of 500 mg daily (it is significant to note that live babies were obtained in the 3 patients where 250 mg of chlorpropamide was given, and that one 20-year-old patient was well controlled on chlorpropamide during two pregnancies, both resulting in live births); (*iii*) although it was suggested that chlorpropamide in a dosage of 500 mg daily appears to be associated with a high perinatal mortality rate, it is equally fair to conclude that the patients requiring this excessive dose were not suitable for sulphonylurea treatment in the first place and that the drug, in the *correct* dosage and in *responsive* diabetics would be safe to use in pregnancy. This was borne out by a comparison of the Durban and Cape Town series (Table I). Thus, the perinatal mortality rate in the sulphonylurea-treated Natal Indian (insulin-independent) was approximately 37%, while the respective figure in the Cape Town series (mostly insulin-dependent) was almost double: 61·4%.

Prospective Random-Sample Therapeutic Study

Because of these discrepancies, plus the fact that young Natal Indian diabetics are frequently capable of good control when treated with the sulphonylureas, it was decided to embark upon a prospective random-sample study to assess the relative efficacy of tolbutamide, chlorpropamide, insulin and dietary restriction alone, in the management of the pregnant diabetic.

METHOD AND MATERIAL

Known diabetics and patients with glycosuria and/or family and obstetrical histories suggestive of diabetes were 'screened' by means of a standard 100-g glucose-tolerance test. Patients who were found to have a 'true' venous blood glucose value of 140 mg/100 ml or more 2 hours after glucose administration, were admitted to hospital where further investigations, including a full confirmatory glucose-tolerance test, were performed.

Only those patients whose duration of pregnancy would allow at least 6 consecutive weeks of treatment were admitted to the therapeutic trial. The patients who qualified for the series had their treatment selected on a random-sample basis, with the exception of established diabetics already on specific therapy. The 'treatments' available were either tolbutamide (Rastinon—maximum dose 1·5 g daily), chlorpropamide (Diabinese—maximum dose 250 mg daily), insulin and dietary restriction alone. Patients who failed to respond to a given form of therapy were treated with an alternative method—usually insulin.

A total of 207 pregnant diabetics were treated in the series. Of these 77 were Bantu (Zulu). The remainder were all Natal Indian females of similar socio-economic status, differing only in their religious affiliation. As indicated in Table II the patients were equally distributed as regards age and parity. In the final analysis, 58 patients completed treatment on chlorpropamide, 46 received tolbutamide and 47 were treated with insulin for the greater part of their pregnancy, while 56 were treated on dietary restriction alone (Table II). The over-all supervision,

*Paper presented at the 6th World Congress of Gynaecology and Obstetrics, New York, April 1970.

TABLE II. DISTRIBUTION OF TREATMENT: MEAN AGE AND PARITY

Treatment	No. of patients	Mean age (years)	Mean parity
Chlorpropamide	58	30·9	4·2
Tolbutamide	46	29·7	3·6
Insulin	47	31·8	4·8
Diet	56	32·7	4·2

general management and obstetrical treatment was identical in all other respects.

RESULTS

The efficacy of specific antidiabetic treatment during pregnancy is best assessed according to two criteria, namely the ability of a particular preparation to 'control' the metabolic disturbance, and the perinatal mortality rate.

Control of the Diabetes

Diabetic 'control' may be judged by a variety of criteria but for comparison in the present series 'good control' was based on postprandial blood-sugar levels consistently below 150 mg/100 ml; 'fair control' if the level was below 200 mg/100 ml; and 'poor control' if values were above 200 mg/100 ml.

Table III reflects the degree of control obtained. Thus, 80% of patients treated with chlorpropamide were classified as being 'well controlled', as compared with 82·5% of patients on tolbutamide and only 36·4% of patients on insulin. However, the latter group is 'loaded' with patients who did not respond to other forms of therapy and were subsequently treated with insulin for the greater part of the pregnancy.

TABLE III. COMPARATIVE RESULTS OF TREATMENT—DIABETIC CONTROL*

Treatment	Good <150 %	Fair <200 %	Poor >200 %
Chlorpropamide	80·0	12·5	7·5
Tolbutamide	82·5	12·5	5·0
Insulin	36·4	36·4	27·2
Diet alone	83·0	12·7	4·3

*Postprandial blood-sugar level in mg/100 ml.

Although the patient's therapy was chosen on a random-sample basis, fewer patients were 'poorly controlled' on dietary restriction alone (4·3%) when compared with patients on specific therapy—7·5%, 5·0% and 27·2% for chlorpropamide, tolbutamide and insulin respectively.

Secondary Failure

Patients were regarded as having failed to respond to treatment if their postprandial blood-sugar values were constantly above 200 mg/100 ml; if they developed diabetic ketoacidosis, or if they became symptomatic having been asymptomatic previously.

According to these criteria 10·7% of the patients originally on treatment with chlorpropamide had their treatment revised as compared with 20·7% of patients treated with tolbutamide, 11·1% on dietary restriction alone and 10·6% on insulin. Patients in the last group required the addition of phenformin to achieve 'control'. One patient was admitted in diabetic coma for which she received insulin, but subsequently became stabilized on dietary restriction alone.

Perinatal Mortality

The perinatal mortality is summarized in Table IV. Patients treated by dietary restriction alone, for some unaccountable reason, yielded the best results as only 7 out of the 56 pregnancies resulted in foetal loss due to stillbirth or neonatal death, a perinatal mortality rate of 12·5%. The respective perinatal mortality rates for chlorpropamide, tolbutamide and insulin were 13·7%, 15·2% and 17·02%.

TABLE IV. PERINATAL MORTALITY

Treatment	Stillbirth (No.)	Neonatal death (No.)	Total %
Chlorpropamide	7	1	13·7
Tolbutamide	4	3	15·2
Insulin	3	5	17·02
Diet	4	3	12·5

Unfortunately, the safety or efficacy of drug therapy during pregnancy is frequently judged according to its effect on the perinatal mortality and morbidity, without adequate regard to the *reason for its prescription* or the *presence of other obstetrical complications*. Further analysis of the results in the present series (Table V) has shown that of the 30 perinatal deaths, no fewer than 18 were associated with some major obstetrical abnormality such as severe pre-eclamptic toxaemia, prolapsed placenta praevia, abruptio placenta, extreme prematurity, and postmaturity. In one instance perinatal death resulted following repeated attacks of maternal hyperpyrexia due to a recurrent urinary tract infection.

TABLE V. MAIN CAUSE OF PERINATAL MORTALITY

Treatment	Obstetrical factor	Poor diabetic control	Undetermined
Chlorpropamide	5	1	2
Tolbutamide	3	3	1
Insulin	5	2	1
Diet	5	0	2
Total	18	6	6

Poor metabolic control—which is clearly not a failure of drug therapy *per se* but due rather to poor patient selection or inadequate therapy—had an adverse effect on the perinatal mortality and accounted for 6 perinatal deaths. A major contributory factor could not be found in only 6 cases.

Congenital Abnormality

Only 2 of the infants born in the series had obvious congenital abnormalities at birth. One was born with choanal atresia, the mother having been on tolbutamide during the first trimester, while the second baby had a congenital heart lesion (Fallot's tetrad) which was incompatible with life. Treatment in the latter instance was with insulin, which had been commenced when the patient was 30 weeks pregnant.

It should be noted, however, that of the 104 patients

who completed the series on the oral hypoglycaemic agents, only 26 fell pregnant while on treatment or started treatment during the first trimester.

Apgar Rating and Therapy

The various methods of therapy were compared to assess the effect (if any) of treatment on the Apgar rating at birth (Table VI). Although the numbers are small, the

TABLE VI. IMMEDIATE EFFECT OF THERAPY ON APGAR RATING AT BIRTH

	Apgar score		
Treatment	*8 - 10* %	*5 - 7* %	*<5* %
Chlorpropamide	84·4	12·5	3·1
Tolbutamide	83·4	16·6	0·0
Insulin	71·0	6·4	22·6
Diet	94·0	3·0	3·0

results indicate that the oral hypoglycaemic drugs have no significant effect on the infant at birth. The poor results obtained with insulin were most probably due to the fact that many of the patients were metabolically unstable at the time of delivery due to poor diabetic control.

Unfortunately, routine blood-sugar estimations of the infants were not always obtained in the immediate postpartum period, and the incidence of neonatal hypoglycaemia could therefore not be accurately assessed. Symptomatic hypoglycaemia, however, did not present as a clinical problem and was not found to be any more common in the infants of the sulphonylurea-treated as compared with the insulin- or dietary-treated mothers.

DISCUSSION

The use of the sulphonylureas during pregnancy has had limited support because of their alleged teratogenic effect on the foetus, the inability to control the metabolic disturbance, and the adverse effect on perinatal survival.[3-5]

Diabetes, Sulphonylureas and Teratogenesis

The frequency of congenital malformation in the newborn of diabetic mothers varies between 2 and 5%, and is therefore greater than the 0·7 - 1·7% incidence quoted for the general population.[6] More recently, Pederson *et al.*[7] have confirmed that the frequency of foetal malformation is approximately 3 times greater in diabetic than in non-diabetic controls. When the newborn of diabetics are followed up for months or years the recognition of malformation increases and incidences of 9 - 12·5% have been reported.[8,9] Therefore, although some authors[10,11] have denied an increase in congenital malformation, there is nevertheless sufficient evidence to associate disturbed carbohydrate metabolism *per se* with a greater likelihood of development of congenital abnormalities.

Teratogenic effects have also been observed under experimental conditions with virtually all antidiabetic medication in clinical use. As early as 1931, Lichtenstein *et al.*[12] noted multiple malformations in the offspring of rats when insulin was used, while carbutamide given to pregnant rats in doses of 200 mg daily, resulted in a 40 - 60% abortion and a 15·39% foetal abnormality rate. Tolbutamide and chlorpropamide produced the same proportion of abortions but a much lower incidence of teratogenesis—between 2 and 4%.[13]

Species specificity, the large doses of antidiabetic drugs administered and the impossibility of producing a diabetic state in animals identical with that in humans, precludes satisfactory conclusions which could be applicable to the clinical usage of the drugs concerned. This is borne out in a survey of the literature which has indicated that the use of sulphonylureas during pregnancy is *not* associated with a greater incidence of congenital abnormalities,[14-17] and that insulin may, in fact, be more teratogenic than the oral antidiabetic drugs.[11]

Only two of the patients in the present series delivered abnormal infants: one following treatment with insulin and the other with tolbutamide.

Since the sulphonylureas cross the placental barrier, continued observation of the offspring in order to study their pancreatic function and/or late emergence of congenital abnormality is necessary before one can categorically state that the sulphonylureas (as with any other drug in pregnancy) are safe to use in pregnancy. However, one should never lose sight of the fact when evaluating or selecting treatment for the pregnant diabetic, that the teratogenic agent is often the diabetic state itself.

Sulphonylureas and Diabetic Control

Dolger *et al.*[18] treated 52 diabetic pregnancies with tolbutamide and achieved excellent control of the hyperglycaemia in the majority of patients. Although increased dosages were required during the last few months of gestation, only 4 patients needed insulin. Good diabetic control was also achieved by Douglas and Richards[15] in their 34 chlorpropamide-treated pregnant diabetics.

Satisfactory control was obtained in over 80% of the pregnant Natal Indian diabetics treated with either tolbutamide or chlorpropamide. A disturbing feature, however, was the relatively high incidence of 'secondary' failure. Thus, 10·7% and 20·7% of the patients on chlorpropamide and tolbutamide respectively had to have their treatment altered to achieve satisfactory control of the diabetes. These results may have been influenced by the failure of the patients to adhere to their diet or to take their medication, while some were undoubtedly unsuitable for oral therapy. None of the sulphonylurea failures could be attributed to the development of 'late' side-effects.

When treating non-pregnant subjects who have failed to respond to sulphonylurea therapy, the dose of the drug is increased to the recommended maximum or substituted with another sulphonylurea or combined with a diguanide. However, these measures were not adopted in the present series since the object was to assess the relative safety and efficacy of tolbutamide and chlorpropamide when used alone and in the usual dosage. It is felt that patients requiring a dose greater than the usual recommended amount are not responsive to sulphonylureas and should not receive oral hypoglycaemic therapy. It was failure to adhere to this criterion which probably led to the poor results obtained previously by Jackson *et al.*[3]

In the present series, chlorpropamide was shown to be

more effective than tolbutamide during pregnancy, as 'good' diabetic control was achieved as frequently, and fewer patients needed to have this form of treatment withdrawn because of failure to respond.

Retrospective analysis has indicated that the poor control of patients on treatment with insulin might have been improved if larger doses of insulin had been used. The mean daily dose of insulin received by the patients in this group was 92·9 IU (range 20 - 200 IU); in addition no fewer than 62·1% of the patients required more than 80 units of insulin per day to achieve metabolic control, i.e. twice that needed by a pancreatectomized individual. The clinical observation of insulin resistance among these patients has recently been confirmed in a preliminary study of their insulin-secretory patterns.[19] Thus it is reasonable to presume that many pregnant diabetics actually do have sufficient insulin for their metabolic needs, but that peripheral antagonism negates its efficacy.

Therefore, the widely accepted concept that pregnant diabetics should *always* be treated with insulin[6] is unsound and is reflected in the results obtained in our series. We feel that the specific antidiabetic therapy of the pregnant diabetic should be individually chosen. Excellent diabetic 'control' can frequently be achieved by dietary restriction and bed rest alone; others will respond to the sulphonylureas—tolbutamide and chlorpropamide—provided that the patients so treated have sufficient pancreatic reserve to respond to this form of treatment and that correct dosage schedules are used. Only those patients who fail to respond to these methods or who develop ketoacidosis need to be treated with insulin.

Sulphonylureas and Perinatal Mortality

The retrospective study published by Jackson *et al.*[3] indicated that whereas the sulphonylureas were not associated with the production of serious congenital abnormalities, chlorpropamide, in a dosage of 500 mg daily, appeared to be associated with a high perinatal mortality (63%). These results are contrary to those found in the literature, for most authors have obtained satisfactory diabetic control and perinatal salvage rates when treating *selected* cases with oral hypoglycaemics. A recent review[20] of the literature showed that only 7·4 and 12·5% of diabetic patients receiving treatment with tolbutamide and chlorpropamide, respectively, suffered a perinatal loss.

Analysis of our recent series has likewise confirmed the impression that both the sulphonylureas—tolbutamide and chlorpropamide—are safe to use during pregnancy and that adequate diabetic control can be satisfactorily achieved without affecting the perinatal salvage rate adversely. Thus, over 80% of an *unselected* group of pregnant diabetics were delivered of live infants having been on treatment for all or the greater part of their pregnancies with either of the oral hypoglycaemic agents (Table IV). Of equal importance is the observation that of the 15 perinatal deaths associated with sulphonylurea therapy, no fewer than 8 were directly attributable to some obstetric factor, while 4 were due to poor metabolic control of the diabetes—clearly not a fault of the drug treatment *per se*. The Apgar rating of the children born to mothers on sulphonylurea treatment was not significantly altered, thus excluding the possibility of a 'harmful' action of the sulphonylurea manifesting in the early neonatal period. The reported occurrence of severe neonatal hypoglycaemia in the infants of mothers treated with chlorpropamide,[21] was not a noticeable feature of this study. It must, however, be noted that blood-sugar estimations were only done on those infants exhibiting clinical evidence of hypoglycaemia or some other abnormality. The only neonatal death associated with chlorpropamide therapy was due to the erroneous premature induction of labour at 35 weeks' gestation, in an otherwise well-controlled 'uncomplicated' diabetic.

SUMMARY

A study was undertaken to determine the safety and efficacy of sulphonylurea therapy in the treatment of the pregnant diabetic. A total of 207 patients were treated, of whom 58 completed treatment on chlorpropamide, 46 received tolbutamide and 47 received insulin, while 56 were treated on dietary restriction alone. Analysis of the results showed that good metabolic control was achieved by the majority of patients on oral hypoglycaemic therapy and that these preparations were not associated with an increased perinatal mortality or incidence of congenital abnormality. Poor metabolic control and perinatal loss were found to be more closely related to the diabetes *per se*, and the presence of associated obstetrical complications. The sulphonylureas are safe to use during pregnancy provided that patients responsive to this form of treatment are chosen and that correct dosage schedules are employed. The sulphonylureas are of particular value in patients who are illiterate or unreliable and in whom self-administered insulin therapy may be otherwise dangerous.

I wish to thank Dr H. R. J. Wannenberg, Medical Superintendent of King Edward VIII Hospital, for allowing access to the case records; Prof. D. Crichton and Dr J. McKechnie who participated in and helped to initiate the therapeutic trial; Mrs A. Ellis for technical assistance; and the members of the Obstetric Unit at King Edward VIII Hospital for their help. I should also like to thank Pfizer Laboratories Ltd for financial support.

REFERENCES

1. Campbell, G. D. (1960): Brit. Med. J., **1**, 537.
2. *Idem* (1963): S. Afr. Med. J., **37**, 1195.
3. Jackson, W. P. U., Campbell, G. D., Notelovitz, M. and Blumsohn, D. (1962): Diabetes, **11**, suppl., 98.
4. Peel, J. *in* Stallworthy, J. A. and Bourne, G. L., eds. (1966): *Recent Advances in Obstetrics and Gynaecology*, 11th ed., p. 194. London: J. & A. Churchill.
5. Moss, J. M. (1966): Sth. Med. J. (Bgham, Ala.), **59**, 565.
6. Kyle, G. C. (1963): Ann. Intern. Med., **59**, suppl. 3, 51.
7. Pederson, L. M., Tygstrup, I. and Pederson, J. (1964): Lancet, **1**, 1124.
8. White, P. (1960): Diabetes, **9**, 345.
9. Paley, R. G. and Higgins, F. E. *in* Oberdisse, K. and Jahnke, K., eds. (1959): *Diabetes Mellitus: III Kongress der Int. Diabetes. Fed.*, p. 575. Stuttgart: George Thieme.
10. Cardell, B. S. (1953): J. Obstet. Gynaec. Brit. Emp., **60**, 834.
11. Oakley, W. (1953): Brit. Med. J., **1**, 1413.
12. Lichtenstein, H., Guest, G. M. and Warrant, J. (1931): Proc. Soc. Exp. Biol. (N.Y.), **78**, 398.
13. Tuchman-Duplessis, H. and Mercier-Parat, L. (1959): J. Physiol. Path. gén., **51**, 65.
14. Stern, J. and Lavienville, M. (1963): Presse méd., **71**, 1547.
15. Douglas, C. P. and Richards, R. (1967): Diabetes, **16**, 60.
16. Nusimovich, B., Baldi, E. and Mir, P. (1964): *Fifth Congress of the International Diabetes Federation*, p. 89. Amsterdam: Excerpta Medica Foundation.
17. Malins, J. M., Cooke, A. M., Pyke, D. A. and Fitzgerald, M. G. (1964): Brit. Med. J., **2**, 187.
18. Dolger, H., Brookman, J. J. and Nechemias, C. M. (1962): Diabetes, **11**, suppl., 97.
19. Notelovitz, M. and Vinik, A. I.: Unpublished data.
20. Notelovitz, M. (1968): 'The pregnant Natal Indian diabetic with chapters on carbohydrate metabolism', M.D. thesis, University of the Witwatersrand, Johannesburg.
21. Farquhar, J. W. (1968): S. Afr. Med. J., **42**, 237.