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Metformin in Management of Pregnant Insulin-Independent Diabetics

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Summary. Sixty pregnant "maturity-onset" (insulin-independent), established and gestational, diabetics were treated with Metformin in the second and third trimester after dietary treatment had failed. The incidence of Metformin failure was 53.8% in the established diabetics and 28.6% in the "gestational" diabetics. The 27 Metformin failures were transferred to other therapy, leaving for further analysis 33 patients who received Metformin up till delivery. Two neonatal deaths occurred in this group (1 congenital abnormality and 1 preterm infant) giving a perinatal mortality of 61/1000. This compares with a perinatal mortality of 103/1000 in the Metformin failure group and 105/1000 in a group of insulin-dependent diabetics treated during the same period. Apart from a high incidence of neonatal jaundice requiring phototherapy the infant morbidity in the Metformin group was low. The mothers of 3 infants with congenital abnormalities had received Metformin only during the last trimester of their pregnancy.

Key words: Insulin independent diabetes, pregnancy, Metformin, perinatal mortality and morbidity, congenital abnormalities.

Insulin-independent diabetes is common among young adults in the Cape-Coloured and Malay people around Cape Town [1, 2] and in Southern African Indians and is frequent among the South African Black ("Bantu") people [1, 2, 3, 4]. The "Cape Coloured" Community have arisen largely from early (17th, 18th century) Dutch Settlers and Hottentots, with smaller and later additions of Malaysian, Black (Bantu-speaking Africans of the Southern Nguni group) and Bushmen. During a period of almost 4 years, we have managed 218 pregnant insulin-independent diabetics and only 19 (8% of the total) insulin-dependent diabetics from these ethnic groups (Table 1). The experience of Notelovitz in Natal has been similar [5]. Ketoacidosis prone, "juvenile onset" diabetes is far more common in white people [6].

Until 1974 such patients were managed during pregnancy largely with insulin, often without proper dietary instruction, with generally poor control and erratic results. Since the majority were overweight it seemed more logical to use careful dietary measures and to use insulin only if the control attained was not adequate. Where diet was only partially successful Metformin was used, initially for all diet failures but later for overweight patients only.

The purpose of the study was to evaluate whether Metformin could be used safely and successfully in the control of pregnant, insulin-independent diabetics.

Subjects and Methods

Fifty-eight per cent of all the 60 patients to whom we gave Metformin were more then 20% over standard body weight (based on Kemsley's tables) [7], and had not satisfactorily responded to a standard diet of 1000 or 1400 calories alone. By "satisfactory" we mean fasting blood glucose levels below 100 mg/dl, and all 2 hour post-prandial levels below 140 mg/dl. Capillary blood was taken twice weekly by finger-prick at 0600, 1100 and 1400 hours. The specimens were collected into tubes containing fluoride and oxalate and glucose was measured in whole blood by an Auto-Analyzer using the neocuproine method. Metformin was used in a dose of 500 mg thrice daily with meals, and increased to 1000 mg t. i. d. if necessary. If control was not adequate on this regime within 2 weeks a sulphonylurea (glibenclamide 5 mg b. d.) was added or substituted. All patients had normal renal and hepatic function as assessed by routine laboratory tests.

Sixty patients received only Metformin for various periods, while continuing their diets, in the second and third trimester

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Table 1. Diabetics managed at Groote Schuur Hospital who delivered babies greater than 1000 g, from 1974 to 1978

Total	237			Perinatal mortality
Insulin-dependent	19			105/1000
Insulin-independent	218	Diet only	83	0/1000
		Diet + Metformin	33	61/1000
		Others[a]	74	101/1000
		"Untreated"	28	214/1000

[a] Patients on sulphonylurea drugs, combination of oral drugs and those transferred to insulin and includes the 27 Metformin failures

(Table 2); 39 were already known or established diabetics, of whom 21 (54%) were considered Metformin failures and received glibenclamide in addition or were transferred to insulin. The other 21 subjects were newly diagnosed during pregnancy, and will herein be called "gestational", although in some it is not known whether the glucose tolerance reverted to normal after delivery. Six of these (29%) were Metformin failures.

For comparison there were 28 comparable mild diabetics who did not present to us until the last 2 weeks of pregnancy or were even in labour (The "untreated" group, Table 1).

The criteria for diagnosis of diabetes demanded that at least two of the three blood glucose values, fasting, maximum and two hours after a 50 g glucose load, must exceed 100, 180 and 120 mg/dl respectively on two occasions.

Thirty-three patients received Metformin alone up to delivery and form the basis for further analysis. Of these 33 patients, 17 (52%) were more than 20% overweight and 9 (27%) were 10–20% overweight. The mean weight was 124.2% (range 96–166%). Eighteen of the 33 Metformin treated patients were established diabetics, 10 of whom were already taking oral antidiabetic drugs, which had been discontinued when diet was started.

Patients were admitted to the ward after referral to the special Obstetric-Diabetic antenatal clinic and again at 32 weeks gestational age. In between they were seen weekly or fortnightly at the clinic, where blood and urine glucose estimations were made. Delivery was planned any time from 37 weeks onwards depending on the level of surfactant present in the liquor. The level of surfactant-like activity was determined by the bubble test (Foam stability test) [8, 9].

All infants were admitted to a special care nursery where they were carefully assessed and were clinically scored for gestational age according to the criteria of Dubowitz et al. [10]. Dextrostix (Ames) estimations of blood glucose were done on the neonates at least hourly or as indicated. Total serum bilirubin and packed cell volume estimations were done when indicated.

The p values were calculated using Student's t test.

Results

Established Diabetics (Treated with Metformin to Term)

The mean maternal age in the established diabetic group was 32.7 years. There were 18 deliveries of infants weighing 1000 g or more. Eighteen children were born alive and had a mean birth weight of 3048 g (range 1970–4350 g) and a mean gestational age of 37.6 weeks (range 34.8–40.0 weeks). The average time patients were under our care was 13.8 weeks, but ranged from 1–26 weeks. The average total dose of Metformin was 94 g, but ranged from 7.5 g to 378 g. The latter patient had already been on Metformin throughout her pregnancy before she was referred to us. Fourteen patients remained on 1500 mg per day; in 4 the dose was increased to 3 g.

There was one neonatal death from multiple congenital abnormalities (hare-lip, cleft palate and heart defect). The mother had received no treatment in the first trimester and only Metformin (500 mg three times per day) for the last 3 weeks of her pregnancy.

"Gestational Diabetics" (Treated with Metformin to Term)

In the "gestational diabetic" group the mean maternal age was 35.6 years. There were 15 deliveries, of which 14 infants were discharged alive and well. The mean birth weight was 3001 g (range 2000–5100 g) and the mean gestational age 37.4 weeks (range 30–40 weeks).

The average length of care under the diabetic team was 8 weeks but ranged from 2–25 weeks. The mean total dose of Metformin was 37.3 g and ranged from 6 g to 147 g. Apart from 2 patients all these patients were taking 1500 mg per day.

There was one neonatal death. The mother had premature rupture of the membranes and delivered a pre-term infant weighing 2000 g. The infant died of immaturity and hyaline membrane disease. The mother had been treated for diabetes for only 2 weeks and had received Metformin 500 mg 8 hourly for 8 days (total dose 12 g).

Whole Group (Treated with Metformin to Term)

Mean blood glucose was decreased by Metformin therapy (mean ± SD, 128.0 ± 16.3 mg/dl vs. 109.3 ± 13.4 mg/dl, $p < 0.01$).

There were no stillbirths and 2 neonatal deaths, giving a perinatal mortality for all patients receiving Metformin of 61/1000 (Table 1).

Neonatal morbidity was evaluated carefully (Table 3). The mean 5 minute apgar score was 9.7. (This is a composite indication of neonatal well-being; the highest obtainable score is 10). The most common problems were jaundice requiring phototherapy (10 patients) and polycythaemia (a packed cell colume of 70% or greater, 3 patients). Hypoglycaemia was not a problem and in the 3 neonates who did have a "Dextrostix" reading below 45 mg/dl

Table 2. Patients treated with Metformin

		Established diabetics	"Gestational diabetics"
Started on metformin	60	39	21
Metformin failures	27	21 (54%)	6 (27%)
Metformin until confinement	33		
Mean body weight	124% of standard		
Mean age	35 years		
Mean (± SD) blood glucose before Metformin	128±16.3 mg/100 ml		
Mean (± SD) blood glucose after Metformin	109±13.9 mg/100 ml		

Mean birthweight of infants: 3026 grams

Table 3. Clinical features of infants of diabetic mothers

	Metformin group (n = 33) %	All diabetic mothers (n = 237) %	General obstetric population[a] (n = 11,832) %
Large for gestational age	18	20	10
Small for gestational age	3	2	10
Jaundice	30	19	9
Polycythaemia	9	6	–
Necrotising enterocolitis	3 (1 case)	1	–
Major congenital abnormalities	9	5	3.5[b]

[a] Combined figures for 1976 of 3 hospitals within the Groote Schuur Hospital group each having neonatal specialist care and supplying data to a central computer

[b] Includes all recognisable congenital abnormalities

there were no symptoms of hypoglycaemia and the condition was easily treated with intravenous glucose.

Six children (18%) had birth weights above the 10th percentile for our population. One child was below the 10th percentile and was also polycythaemic, developed hypoglycaemia, necrotising enterocolitis and jaundice and possibly had a ventricular septal defect of the heart. The mother was a gestational diabetic and received Metformin for the last 5 weeks of her pregnancy. She was also hypertensive taking Methyldopa and Clonidine. This child was discharged alive.

There were 3 children (9%) with congenital abnormalities (2 involving heart defects and 1 sacral agenesis), but the mothers of these infants had not taken Metformin during the first 28 weeks of pregnancy.

Side-effects in the mothers were minimal. Of 60 patients who were tried on Metformin first only 2 discontinued the drug because of nausea and vomiting; none complained of diarrhoea.

All Diabetic Pregnancies

Retrospective analysis of our whole series of 237 pregnant diabetic patients (Table 1) showed that 12 patients had received Metformin in the first trimester, but none was associated with a known congenital abnormality. The prevalence of known major congenital abnormalities in all infants of all our diabetic mothers was 5.3%.

The perinatal mortality (6%) among our patients seems acceptable as we deal mainly with a low socio-economic group who often do not attend antenatal clinics till late in their pregnancy and then irregularly.

In comparison the perinatal mortality among our 84 "diet only" patients was zero and 2 infants of 19 insulin-dependent mothers died. Among the 27 "Metformin failures" the perinatal mortality rate was 103/1000. Among the group of 28 "untreated" mothers the mortality was 214/1000 (Table 1).

Discussion

Animal work has indicated that biguanides are safe to use during pregnancy, and that Metformin does not cross the placenta [11]. Metformin has been little used during human pregnancies, but Stowers and Sutherland [12] and Pedersen and Pedersen [13] have found it to be safe and satisfactory in small numbers of patients (5 and 11 respectively), though the former authors reported that it did appear in

amniotic fluid. We have never consciously used any oral drug during the first 14 weeks of pregnancy, but looking at our retrospective data on 12 patients who received Metformin while unaware that they were pregnant there was no evidence of teratogenesis.

We chose this substance rather than a sulphonylurea because of the tendency towards weight gain with the latter group and we chose Metformin rather than Phenformin because of its lesser association with lactic acidosis.

Metformin did not seem to contribute to the 2 neonatal deaths in any way. As in other reported series the neonatal morbidity was high (45%). Soler and Malins [14] reported a neonatal morbidity of 50% in insulin-dependent diabetics in Birmingham, England, and Gabbe et al., [15] from Los Angeles, stated that approximately two thirds of the infants of insulin-dependent diabetics experienced some morbidity.

The 18% of 'large for gestational age' infants might be related to obesity, since 20% of obese mothers had infants above the 90th percentile for weight against 12% of normal weight mothers.

The incidence of jaundice requiring phototherapy in this group of infants was 30% while for infants of all diabetic mothers seen during the same period it was 19%. This difference is not statistically significant at the 5% level. In 4 of 10 infants with jaundice, labour had been induced with oxytocin. The mean gestational age of these infants was 37.6 weeks (range 35.2–39.3). The incidence of jaundice requiring phototherapy in our general neonatal population is approximately 4%. Polycythaemia occurred in 9% of the neonates and was frequently associated with jaundice. Gabbe et al. [15] included jaundice and polycythaemia in their group with infant morbidity, but did not give the exact numbers. Soler [16] reports a 19% incidence of severe neonatal jaundice in infants of diabetics and states that it was the single most common neonatal problem.

One instance of necrotising enterocolitis occurred and Gabbe et al. [15] reported 2 cases contributing to the neonatal deaths in their series. We have had altogether 2 cases in 246 live born infants of diabetic mothers (1 infant died) and as this is a fairly rare complication it is possible that there is an association with diabetes.

Symptomatic hypoglycaemia was not found and, in the 9% of infants who had "Dextrostix" readings below 45 mg per dl, intravenous glucose rapidly corrected the blood glucose level. As Metformin does not cause hypoglycaemia, this was expected. This may also reflect the good control of maternal glycaemia, since poor control of maternal blood glucose probably results in fetal hyperinsulinism, which in turn causes neonatal hypoglycaemia.

Congenital abnormalities were seen in 3 infants (9%), but considering the types of abnormalities, it seems impossible that Metformin given in the third trimester could have been responsible.

Although gastro-intestinal side-effects to Metformin are recognised to be fairly frequent, only 3% of patients were changed to other regimens because of nausea and vomiting and no subject developed diarrhoea.

The diet-only group is not strictly comparable to the group on Metformin, since diet alone in the latter group had failed properly to control the blood glucose. In this study mean blood glucose levels were improved significantly by the use of Metformin. We do not know whether the use of Metformin has affected the outcome because we started with the belief that blood glucose levels should be properly controlled during pregnancy in order to obtain best results. We have therefore no strict control group in which diet alone was continued despite unsatisfactory blood glucose levels.

At least in our part of the world we have long known that completely untreated mild diabetics or even "pre-diabetics" have a perinatal loss of 20–40% [17] as exemplified here by our "untreated" group, among which the perinatal mortality rate was 214/1000.

In view of the above findings we consider that a logical plan of treatment in the obese insulin-independent patient is the use of diet in the first place and where this fails or is incompletely successful the addition of Metformin, before going on to further treatment, can be tried.

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References

1. Jackson, W. P. U.: Diabetes and related variables among the five main racial groups in South Africa. Postgrad Med. J. **48**, 391–398 (1972)
2. Michael, C., Edelstein, I., Whisson, A., MacCullum, M., O'Reilly, I., Hardcastle, A., Toyer, M. G., Jackson, W. P. U.: Prevalence of diabetes, glycosuria and related variables among a Cape coloured population. S. Afr. Med. J. **45**, 795–801 (1971)
3. Campbell, G. D.: Insulin-independent young diabetics in Natal. Br. Med. J. **1960 II**, 537–538
4. Campbell, G. D.: Diabetes in Asians and Africans in and around Durban. S. Afr. Med. J. **37**, 1195–1208 (1963)

5. Notelovitz, M.: The pregnant Bantu diabetic. S. Afr. Med. J. **44**, 1171–1175 (1970)
6. Jackson, W. P. U.: Diabetes mellitus in different countries and different races, prevalence and major features. Acta Diabetol. Lat. **7**, 361–401 (1970)
7. Kemsley, W. F. F.: Body weight at different age and heights. Ann. Eugen. (Lond.) **16**, 316–334 (1952)
8. Gunston, K. D., Davey, D. A.: The bubble test as a measure of amniotic fluid surfactant and as predictor of hyaline membrane disease. S. Afr. Med. J. **54**, 495–497 (1978)
9. Statland, B. E., Sher, G., Freer, D. E., Kraybill, E. N., Smith, H. Y., Hisley, J. C.: Evaluation of a modified foam stability (FS–50) test. An assay performed on amniotic fluid to predict fetal pulmonary maturity. Am. J. Clin. Pathol. **69**, 514–519 (1978)
10. Dubowitz, L. M. S., Dubowitz, V., Goldberg, C.: Clinical assessment of gestational age in the newborn infant. J. Pediatr. **77**, 1–10 (1970)
11. Cohen, Y., Costerousse, O.: Etude expérimentale du metabolisme du dimenthylbiguanide marqué an carbon 14. 4° Congr. Fed. Intern. Diab., Genève 1961. Med. Hyg. 145–148 (1961)
12. Stowers, J. M., Sutherland, H. W.: The use of sulphonylureas biguanides and insulin in pregnancy. In: Sutherland, H. W., Stowers, J. M. (ed.) Carbohydrate metabolism in pregnancy and the newborn incorporating the proceedings of the international colloquium at Aberdeen, Scotland, July 1973, pp. 205–220. Edinburgh, London, New York: Churchill Livingstone 1975
13. Pedersen, J., Molsted-Pedersen, L.: Oral "antidiabetic" compounds in pregnancy. In: Early diabetes in early life. Davalos, R. C., Cole, H. S. (ed.) pp. 487–494. New York, San Francisco, London: Academic Press Inc. 1975
14. Soler, N. G., Malins, J. M.: Strict control of diabetes during pregnancy in relation to perinatal mortality and morbidity. Diabetes **26** (Suppl. 1), 418 (abstract 260) (1977)
15. Gabbe, S. G., Mestman, J. H., Freeman, R. K., Goebelsmann, U. T., Lowersohn, R. I., Nochimson, D., Centrulo, C., Quilligan, E. J.: Mangement and outcome of pregnancy in diabetes mellitis, Classes B to R. Am. J. Obstet. Gynecol. **129**, 723–732 (1977)
16. Soler, N. J.: Induction and neonatal jaundice in infants of diabetic. Br. Med. J. **1978 I**, 783–784
17. Jackson, W. P. U.: Studies in pre-diabetes. Br. Med. J. **1952 II**, 690–700

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