THE PREGNANT NATAL INDIAN DIABETIC—FACTS AND FANCIES*

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The management of anaemia as reflected by a low haemoglobin concentration is governed by the definition and correction of the underlying cause. The mere fact that iron-deficiency anaemia happens to be the most common form of anaemia would never justify empirical treatment with iron. Yet the pregnant diabetic, on the basis of an elevated blood sugar, is invariably treated with insulin without regard to the cause of the disturbed carbohydrate metabolism or the need for insulin.

This and other fallacies in accepted concepts regarding the diagnosis and treatment of the pregnant diabetic form the basis of this paper, which results from the study and management of the pregnant Natal Indian diabetic over the past 4 years.

A recent editorial in The Lancet stated, 'the ease and accuracy with which the blood sugar can be measured may have led to unwarranted pre-occupation with carbohydrate in the study of the metabolic disturbance of diabetes mellitus; derangements of lipid and protein metabolism are no less conspicuous and are perhaps more closely related to the central chemical fault . . . Nevertheless, in the diagnosis and clinical control of the diabetic patient, the blood sugar is the principal guide and looks like remaining so for some time.' Thus, the successful outcome of diabetic pregnancies appears to depend upon (a) efficient methods of diagnosis and (b) effective means of controlling an elevated blood sugar.

METHODS OF DIAGNOSIS OF DISTURBED CARBOHYDRATE METABOLISM

The universally accepted approach to the diagnosis of diabetes rests upon the presence of significant symptomatology, family or obstetrical histories, or the detection of glucose in the urine. Almost every pregnant patient has her urine tested for sugar at some stage, and aglycosuria is interpreted as indicative of normal carbohydrate balance.

Crombie and others, however, have shown that absence of glycosuria does not exclude impairment of glucose tolerance, and that between 8 and 30% of non-pregnant diabetics will not be diagnosed as such if reliance is placed upon the presence of glycosuria (fasting or postprandial).

In view of the fact that renal glycosuria is said to occur in approximately 10-15% of non-diabetic pregnant women, it was thought possible that the lowered renal threshold of pregnancy would counterbalance the incidence of false negatives that occur in the non-pregnant population. To elucidate this hypothesis the incidence of glycosuria was determined in 166 positively-established pregnant Natal Indian diabetics, and no fewer than 35-5% were found to be aglycosuric at the time of the initial examination!

A simultaneous survey was conducted in 301 normal pregnant controls to assess the apparent and the 'true' incidence of diabetes, as judged by abnormal glucose tolerance in patients with and without glycosuria (Table I).

Table I. The Incidence of Diabetes in 301 Pregnant Controls

<table>
<thead>
<tr>
<th>Duration of Pregnancy</th>
<th>Patients Tested</th>
<th>Apparent Incidence of Diabetics (Glycosuric Patients Only)</th>
<th>True Incidence of Diabetes (All Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trimester</td>
<td>62</td>
<td>1-5%</td>
<td>3-2%</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>119</td>
<td>4-2%</td>
<td>9-1%</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>120</td>
<td>5-0%</td>
<td>10-0%</td>
</tr>
</tbody>
</table>

Thus, during the first trimester, only 1-5% (62 patients) had glycosuria together with an abnormal glucose-tolerance test. Yet the true incidence of diabetes—based on abnormal tolerance in patients with and without glycosuria—was more than double this figure. The same pitfall was discovered in each trimester.

These findings confirm Campbell's observations that glycosuria develops unusually late in the Natal Indian diabetic and that this is probably due to an elevated renal threshold to sugar.

The clarity of the glycosuric picture in pregnancy is further clouded by the fact that as the renal threshold for sugar falls, so glycosuria becomes less diagnostic of diabetes. Thus, of 200 normal non-pregnant outpatient controls, only 2% were found to have glycosuria, but of these 75% were diabetic. Yet, in a comparative group of 301 normal pregnant controls, 21-5% had glycosuria, but only 18-4% were diabetic.

Glycosuria in pregnant diabetics was found to be of greater diagnostic value since 45-9% of glycosurics in this group were found to have abnormal carbohydrate tolerance (Table II).

Table II. The Significance of Glycosuria in Pregnancy

<table>
<thead>
<tr>
<th>Group Tested</th>
<th>No. Tested</th>
<th>Incidence of Glycosuria</th>
<th>% of Glycosurics with Positive GTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pregnant</td>
<td>250</td>
<td>2%</td>
<td>75%</td>
</tr>
<tr>
<td>Pregnant controls</td>
<td>301</td>
<td>21-5%</td>
<td>18-4%</td>
</tr>
<tr>
<td>Pregnant diabetics</td>
<td>265</td>
<td>38-4%</td>
<td>45-9%</td>
</tr>
</tbody>
</table>

It is therefore apparent that the diagnostic value of glycosuria is limited and that greater reliance should be placed on postprandial blood-sugar estimations for the screening of latent or prediabetic patients. These findings confirm the recent observations of Fine.

It has been suggested that the detection of the latent or prediabetic state is not of much practical importance in the pregnant Natal Indian diabetic by virtue of the characteristic short duration of their metabolic disturbance, relative freedom from ketosis and independence from insulin. Although recognized, it is insufficiently emphasized that the severity of diabetes as judged by the duration or age of onset of the disease bears no significant relationship to the foetal mortality. On the other
hand, in the years before the recognition of overt diabetes the perinatal wastage is extremely high and may in fact vary between 10 and 50%.

In the next phase of this investigation the previous histories of normal pregnant controls (as judged by glucose-tolerance tests), of recently diagnosed diabetics, and of established diabetics were compared as to the incidence of abortions, neonatal deaths and stillbirths. The dramatic increase in the perinatal loss in the prediabetic years was thereby ascertained as depicted in Table III.

<table>
<thead>
<tr>
<th>Group</th>
<th>Abortion</th>
<th>Neonatal deaths</th>
<th>Stillbirth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>8·3%</td>
<td>1·6%</td>
<td>3·3%</td>
</tr>
<tr>
<td>Recently diagnosed diabetics</td>
<td>23·6%</td>
<td>7·8%</td>
<td>25·8%</td>
</tr>
<tr>
<td>Established diabetics</td>
<td>22·8%</td>
<td>17·1%</td>
<td>34·3%</td>
</tr>
</tbody>
</table>

Obviously the early and accurate diagnosis of abnormal carbohydrate tolerance is of paramount importance. The fact that diabetes accounts for a perinatal loss as great as Rh haemolytic disease renders it surprising that routine antenatal postpartum sugars are not employed as screening devices on all pregnant patients, particularly in population groups such as the Natal Indian where the incidence of diabetes is known to be high. The reliability and simplicity of certain diagnostic techniques—such as the use of Dextrostix—would ensure the practicability of this procedure.

METHODS OF TREATMENT

Having 'diagnosed' diabetes mellitus on the basis of an abnormal glucose-tolerance test, 'control' will, according to present-day teachings, be achieved by lowering the elevated blood-sugar concentration.

Maintenance of a normal blood-sugar concentration is dependent upon the restriction of daily caloric intake and the judicious use of specific antidiabetic agents.

Dietary Restrictions

Campbell's theory of the 'insulin-independent young diabetic' was based on the observation that certain pregnant Natal Indian diabetics remained free from ketosis without requiring insulin therapy. It was therefore rather disturbing to find that no less than 33·5% of pregnant diabetics, before 1963, had evidence of ketosis. On further investigation, however, it was noted that although the acetonuria was detected in the presence of moderate degrees of glycosuria, it was possible to produce a reduction in the frequency of acetonuria without significant impairment of diabetic control by the addition of extra carbohydrate to the diet. Thus, with this regime only 11 pregnant diabetics (8·8%) developed ketosis after 1963, the acidosis in each instance being transient in nature and not associated with foetal loss.

Consequently we now allow pregnant diabetics a normal ward diet with restrictions only on the daily consumption of refined carbohydrates and saturated fats—the latter because they may play a significant part in the aetiology of vascular disease.

Bed Rest

One of the most significant features that emerged from our study was the value of bed rest. The results of our investigation, as evidenced by the dramatic decrease in the incidence of complications, confirm the suggestion that there may be more to prolonged hospitalization than better diabetic control, better treatment of complications, and better timing of delivery (Table IV).

TABLE IV. THE VALUE OF BED REST IN THE MANAGEMENT OF THE PREGNANT DIABETIC

<table>
<thead>
<tr>
<th>Complication</th>
<th>Before 1963</th>
<th>After 1963</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketosis</td>
<td>33·3%</td>
<td>8·8%</td>
</tr>
<tr>
<td>Hydramnios</td>
<td>50·0%</td>
<td>19·3%</td>
</tr>
<tr>
<td>Toxaemia</td>
<td>33·3%</td>
<td>9·7%</td>
</tr>
<tr>
<td>Diabetic coma</td>
<td>3·3%</td>
<td>0·8%</td>
</tr>
</tbody>
</table>

Our patients are therefore hospitalized for the greater part of their pregnancies, being allowed frequent 'long-weekend passes' in order to decrease inclinations to abscond.

Oral Antidiabetic Therapy

With the introduction of oral antidiabetic agents the number of non-pregnant insulin-dependent Natal Indians was reduced from 80% to approximately 4% in 1960. A retrospective study of similar oral therapy in pregnancy, published in 1962, indicated that, whereas the sulphonylureas were free from teratogenic side-effects, the use of chlorpropamide was associated with an excessive perinatal foetal wastage. Our gynaecological department, however, held the view that this study was deficient in many respects, and we consequently embarked upon our own prospective double-blind study to evaluate the relative safety and efficacy of chlorpropamide, tolbutamide, insulin and dietary restriction in the management of the pregnant diabetic, the preliminary results of which are reflected in Table V.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Perinatal mortality before 1963</th>
<th>Perinatal mortality after 1963</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolbutamide</td>
<td>23%</td>
<td>20·0%</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>63%</td>
<td>16·6%</td>
</tr>
<tr>
<td>Insulin</td>
<td>29%</td>
<td>23·5%</td>
</tr>
<tr>
<td>Diet alone</td>
<td>—</td>
<td>5·5%</td>
</tr>
</tbody>
</table>

Why patients without supplementary therapy achieved such good results is not clear—especially as they were not selected but were, like the others, 'picked out of the bag'. The results of this study seem to indicate that the specific antidiabetic therapy of the pregnant patient should be tailored to the individual. Many will respond to dietary restriction and bed rest alone, whereas others will require additional stimulative or replacement therapy. It is equally well demonstrated that the sulphonylureas are as efficacious as insulin therapy, provided that the patients so treated have sufficient pancreatic reserve to respond to this form of therapy, and provided that correct dosage schedules are used.

In contradiction to the aforementioned publication, chlorpropamide appears to emerge as the sulphonylurea of choice. Furthermore, it has the additional advantage...
that fewer patients needed to have their treatment withdrawn because of inadequate control. There was also no suggestion that it was teratogenic.

Insulin

What, then, is the place of insulin in the treatment of the pregnant diabetic? Pregnancy per se is known to increase the insulin requirement of diabetics to an average of 66% above the prepregnancy level—frequently 200 or more units a day are required—yet in the immediate puerperium the insulin requirements are markedly reduced to levels below that of pregnancy, and even the prepregnancy dosage. Fig. 1 illustrates this feature in one of our patients. The patient’s insulin requirements increased steadily from 20 units per day when she was 20 weeks pregnant to 110 units per day at 38 weeks. Within 2 days of her elective caesarean section she was perfectly controlled without requiring insulin or any other form of specific therapy.

Furthermore it has been shown that plasma-insulin-like activity actually increases during normal pregnancy, and that many diabetics—both maturity onset and juvenile—have adequate or increased insulin-like activity. It is therefore reasonable to presume that many pregnant diabetics actually do have sufficient insulin for their metabolic needs, but that peripheral antagonism negates its efficacy. The placenta has in fact been found to be the site for the irreversible removal of insulin during pregnancy, and the pregnant rat, for example, degrades 35% more exogenous insulin per minute than non-pregnant rats.

Therefore, the widely accepted concept that pregnant diabetics should always be treated with insulin is unsound. Greater efforts must be made to determine the individual’s basic, inherent fault, and treatment should then be prescribed accordingly.

A GLIMPSE INTO THE FUTURE

What really matters is whether the pregnant diabetic—as judged by serum insulin assays—does or does not have endogenous insulin sufficient for her metabolic needs. Those with absolute insulin deficiencies obviously require replacement therapy, whereas those with adequate amounts of serum insulin require further investigation to establish the underlying cause of their metabolic disorder.

Fig. 2 depicts some of the factors which are known to exert a diabetogenic effect during pregnancy. Of these, only adrenocortical function has been investigated in the pregnant Natal Indian diabetic, and we have shown that the pregnant diabetic (as a group) has a significantly greater 17-ketosteroid and 17-glucocorticoid excretion rate than the non-diabetic pregnant controls. We believe that the importance of these findings is enhanced by our further discovery that the daily oestriol excretion pattern in the pregnant Natal Indian diabetic is significantly lower than that in control non-diabetics, for the biological inactivation of the normally increased cortisol in pregnancy is dependent upon an oestrogen-induced protein—transcortin.

Therefore the theoretical treatment of patients who fall into this category should be oestrogen substitution therapy and/or suppression of excess adrenocortical function, rather than treatment of the symptomatic end-result, the elevated blood sugar.

CONCLUSION

The experience gained in the management of the pregnant Natal Indian diabetic has thus served to highlight some of the ‘facts and fancies’ regarding the investigation and treatment of the pregnant diabetic. Whereas treatment of the metabolic end-result—the elevated blood sugar—has produced a dramatic improvement in the perinatal mortality rate, further improvement can only result from establishing and treating the cause of the hyperglycaemia.

It is advocated that the diagnostic value of glycosuria during pregnancy be treated with caution and that routine postprandial blood-sugar estimation be employed instead. The absence of symptomatology and/or the need for insulin should not be regarded as evidence of a mild metabolic disturbance, since the perinatal mortality rate in these patients is often extremely high.

Excellent diabetic ‘control’ can frequently be achieved by dietary restriction and bed rest alone, and therefore treatment of the pregnant diabetic should always be adjusted to the individual. The sulphonylureas—tolbutamide and chlorpropamide—are safe to use in pregnancy provided that the patients so treated have sufficient pancreatic reserve to respond to this form of treatment and that correct dosage schedules are used.
SUMMARY
A survey of 301 cases of pregnant Indian diabetics is presented. It was found that glycosuria during pregnancy must not be accepted at face value. Absence of symptomatology and/or the need for insulin is not an indication of a mild disease. The role of the oral antidiabetic preparations is discussed.

I wish to thank Dr. H. R. J. Wannenburg, Medical Superintendent of King Edward VIII Hospital, for allowing access to the case records; Prof. D. Crichton, Head of the Department of Obstetrics and Gynaecology of the University of Natal, for his advice; Dr. J. McKechnie who participated in and initiated the therapeutic trial; Mrs. A. Ellis for technical assistance; and the members of the Obstetric Unit at King Edward VIII Hospital, for their help during the past 4 years.

I should like to express my appreciation to Messrs. Pfizer Laboratories Ltd. for their financial support, without whose assistance this investigation could not have been carried out.

THE HAEMOGLOBIN STATUS OF THE CAUCASIAN POPULATION OF DURBAN AND EAST LONDON*


The 'Regulations for the Control of Blood Transfusion Services' in the Republic of South Africa require females with a haemoglobin concentration below 12·5 G/100 ml., and males with a haemoglobin concentration below 13·5 G/100 ml., to be rejected as blood donors. This survey was stimulated by our impression that in Durban and East London an unnaturally high proportion of Caucasian females were being rejected as blood donors, and by the conclusions of the WHO Study Group on Iron-Deficiency Anaemia that anaemia constitutes a public health problem of considerable importance in many countries.

MATERIAL AND METHODS
The cyanmethaemoglobin method was employed for the haemoglobin estimations, using a cyanmethaemoglobin standard supplied by Diagnostic Reagents (Ltd.), and the PCVs were determined with a Hawksley microhaematocrit centrifuge.

Source of Blood Samples
All 4 series consisted of Caucasians who had never donated blood before.

Series 1. This series comprised 1,023 males and 600 females enrolled as blood donors between July 1966 and April 1967. This sample is not necessarily representative of the Caucasian community of Durban, as blood donors are to a large extent drawn from the so-called 'working-classes'. In addition, all the subjects were volunteers, and the act of volunteering may of itself have resulted in their selection. The haemoglobin concentration was determined in every instance, and the PCV in 129 males and 157 females.

Series 2. The opportunity of determining the haemoglobin status of a section from the upper socio-economic group was fortuitously presented to us when an appeal was made to the Jewish community for individuals who had never donated blood, in order to meet the purpose of sending dried plasma to Israel during the recent upheaval in the Middle East. A total of 427 subjects, consisting of 207 males and 220 females, were examined. The haemoglobin concentration was determined in every instance, but PCVs were not determined.

Series 3. This series consisted of 70 males and 50 females from East London, selected in exactly the same way as subjects in series 1. The haemoglobin concentration and PCV of every individual were determined.

Series 4. This series consisted of 89 males and 80 females from the Bluff and Woodlands suburbs of Durban; both these suburbs are essentially 'working-class' areas. The haemoglobin concentration and PCV of every individual were determined.

RESULTS
Males
The mean haemoglobin concentration varied from 14·72 to 15·18 G/100 ml. in the different series (Table I), showing good agreement with the results reported from the United Kingdom as analysed by Walsh et al., but significantly lower than Australian values. The incidence of

<table>
<thead>
<tr>
<th>Series</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hb. G/100 ml.</td>
<td>MCHC %</td>
</tr>
<tr>
<td>Series 1</td>
<td>14·97</td>
<td>33·8</td>
</tr>
<tr>
<td>Series 2</td>
<td>15·18</td>
<td>13·46</td>
</tr>
<tr>
<td>Series 3</td>
<td>14·96</td>
<td>33·63</td>
</tr>
<tr>
<td>Series 4</td>
<td>14·72</td>
<td>34·17</td>
</tr>
</tbody>
</table>

Textbooks
<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wintrobe (USA)³</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td>Whitby &amp; Britton (UK)⁴</td>
<td>15·6</td>
<td>34</td>
</tr>
<tr>
<td>MRC Survey (UK)⁵</td>
<td>15·1</td>
<td>13·83</td>
</tr>
<tr>
<td>Walsh et al. (Australia)⁶</td>
<td>15·71</td>
<td>13·89</td>
</tr>
</tbody>
</table>

The haemoglobin status of a section from the upper socio-economic group was fortuitously presented to us when an appeal was made to the Jewish community for individuals who had never donated blood, in order to

*Date received: 21 December 1967.
†Thame, Oxon, England.

REFERENCES

†The source of blood samples was Fortuitous.

∧The cyanmethaemoglobin method was employed for the haemoglobin estimations, using a cyanmethaemoglobin standard supplied by Diagnostic Reagents (Ltd.), and the PCVs were determined with a Hawksley microhaematocrit centrifuge.

©The haemoglobin concentration was determined in every instance, but PCVs were not determined.

1. The sample is not necessarily representative of the Caucasian community of Durban, as blood donors are to a large extent drawn from the so-called 'working-classes'. In addition, all the subjects were volunteers, and the act of volunteering may of itself have resulted in their selection. The haemoglobin concentration was determined in every instance, and the PCV in 129 males and 157 females.

2. The opportunity of determining the haemoglobin status of a section from the upper socio-economic group was fortuitously presented to us when an appeal was made to the Jewish community for individuals who had never donated blood, to do so for the purpose of sending dried plasma to Israel during the recent upheaval in the Middle East. A total of 427 subjects, consisting of 207 males and 220 females, were examined. The haemoglobin concentration was determined in every instance, but PCVs were not determined.

3. This series consisted of 70 males and 50 females from East London, selected in exactly the same way as subjects in series 1. The haemoglobin concentration and PCV of every individual were determined.

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