CARBOHYDRATE TOLERANCE IN THE PREGNANT NATAL INDIAN*

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Recent studies have provided ample retrospective evidence that the perinatal wastage is extremely high in the years before the recognition of overt diabetes. Jackson[1] and others[2-5] have indicated that the foetal loss in the prediabetic period varies between 10 and 50%.

The physiological changes in carbohydrate metabolism associated with the increased demands of pregnancy are variable when compared with the non-pregnant state. Therefore, since the proof of an underlying diabetic diathesis depends on the demonstration of abnormal carbohydrate tolerance, a study was instituted to evaluate 'normal' glucose tolerance in the pregnant Natal Indian.

MATERIAL AND METHOD

The 'normal' pregnant controls who formed the basis of this study were healthy ambulatory Natal Indians who had attended the antenatal clinic of the Department of Obstetrics, King Edward VIII Hospital, Durban. They were all of the same socio-economic status. Studies of normal carbohydrate tolerance in this group were governed by the duration of pregnancy—measured in trimesters—and the absence of a history suggestive of a prediabetic state, namely, a family history of diabetes, unexplained stillbirths and neonatal deaths, glycosuria, a history of having had large babies (over 10 lb.) and a history of progressive increase in birthweight of infants. Because of the unreliability in attendance of most of our patients and the difficulties associated with follow-up studies, it was decided to base the assessment of glucose tolerance on the individual testing of different patients in each of the 3 trimesters of pregnancy.

To assess the significance of a prediabetic history, a group of patients with positive histories were subjected to similar testing. A total of 568 patients were studied. The patients had all been on an unrestricted diet for at least 3 days and had fasted for 8 - 12 hours overnight.

The 100-G Glucose-Tolerance Test

The patients were given 100 G of glucose dissolved in 200 ml. of orange-flavoured water to drink. Venous blood and urine samples were obtained in the fasting state and 2 hours after ingestion of the glucose.

Blood-Sugar Analysis

To maintain uniformity with a study of carbohydrate metabolism in the non-pregnant Natal Indian,[6] the blood-sugar levels were assayed by the same technician using the method of Herbert and Bourne.[7]

Urinalysis

Glucose oxidase paper was used to detect the presence of glucose in the urine, thereby excluding false positives from other reducing substances, and obtaining a simultaneous quantitative assessment of the degree of glycosuria.

RESULTS

Normal Glucose-Tolerance Curve during Pregnancy

The alterations in glucose tolerance during the 3 trimesters of pregnancy are reflected in Fig. 1 and are based on a graph plotted against the mean fasting and postglucose blood-sugar values obtained. It can be seen that although there is little variation in the mean fasting levels during the 3 trimesters, a definite lowering of tolerance to glucose develops with the progression of pregnancy, being most marked during the second trimester.

These differences were subjected to the 'f' test and were found to be statistically significant ($p < 0.01$).

The normal range for fasting and the 2-hour postglucose values were calculated by adding 2 standard deviations to the mean. Whereas there was little difference in the fasting values during the 3 trimesters, the 2-hour values in

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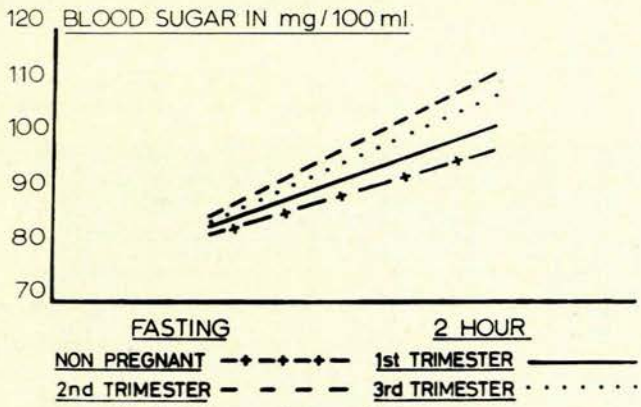

Fig. 1. Glucose tolerance during pregnancy.

the second and third trimesters were significantly higher than in the first trimester (see Tables I and II).

TABLE I. COMPARISON OF THE FASTING BLOOD-SUGAR VALUES DURING THE THREE TRIMESTERS OF PREGNANCY (IN MG./100 ML.)

	1st trimester	*2nd trimester*	*3rd trimester*
Mean	84·53	85·95	84·73
SD	13·01	11·70	14·18
Normal range (mean + 2SD)	84·53 - 110·55	85·95 - 109·35	84·73 - 114·09

TABLE II. COMPARISON OF POSTGLUCOSE BLOOD-SUGAR LEVEL DURING THREE TRIMESTERS OF PREGNANCY (IN MG./100 ML.)

	1st trimester	*2nd trimester*	*3rd trimester*
Mean	104·89	113·79	108·57
SD	18·47	19·92	22·40
Variance	301·41	350·00	479·68
Range	104·89 - 141·83	113·79 - 153·63	108·57 - 153·37

'f' test for significance $p < 0{\cdot}01$.

Non-pregnant Compared with Pregnant Glucose Tolerance

When the mean non-pregnant glucose-tolerance curve is compared with that occurring during pregnancy, it is found that both the fasting and the 2-hour blood-sugar values are lower than those obtained during pregnancy. Thus the mean fasting and postglucose levels in the non-pregnant state are 83·57 and 99·73 mg./100 ml. respectively, as compared with 84·53 and 104·89 mg./100 ml.; 85·95 mg./100 ml. and 113·79 mg./100 ml.; and 84·73 mg./100 ml. and 108·57 mg./100 ml. for the first, second and third trimesters respectively (see Fig. 1). These values, when subjected to the 'f' test for statistical analysis, were found to be significant ($p < 0{\cdot}01$).

Fasting Blood-Sugar Values

Having established the upper limit of the fasting blood-sugar value during the third trimester of pregnancy at 115 mg./100 ml., the fasting values of established pregnant diabetics were studied in order to assess the significance of this single determination in the diagnosis of diabetes. Thus, of the 152 patients who were analysed, only 48 or 31·5% had fasting blood-sugar levels of 115 mg./100 ml. or more.

Glycosuria

The frequency of glycosuria was determined in pregnant controls without prediabetic histories and in those with significant histories. In the first trimester of pregnancy (Table III) the incidence of glycosuria in the control group

TABLE III. INCIDENCE OF GLYCOSURIA IN PREGNANT NATAL INDIANS 2 HOURS AFTER 100 G OF GLUCOSE

Duration of pregnancy	*Without prediabetic history*	*With prediabetic history*
1st trimester	6·4% (4/62)	16·3% (7/43)
2nd trimester	28·5% (34/119)	41·1% (42/102)
3rd trimester	22·5% (27/120)	44·1% (53/120)

without prediabetic histories was 6·4% (4/62), compared with 16·3% (7/43) in those patients with such histories. The comparative results for the second trimester of pregnancy were 28·5% (34/119) and 41·1% (42/102) respectively, while similar differences were observed in the third trimester—22·5% (27/120) compared with 44·1% (53/120) respectively.

The differences in the frequency of glycosuria between the two control groups were statistically significant for each trimester. The over-all incidence of glycosuria in those patients without positive histories was 21·5% and in those with suggestive histories 38·4% (Table IV).

TABLE IV. SIGNIFICANCE OF GLYCOSURIA DURING PREGNANCY

Type of patient	*No. tested*	*No. with glycosuria*	*Incidence of glycosuria*	*Number of glycosurics with positive GTT*	*% of glycosurics with positive GTT*
No prediabetic history	301	65	21·5%	12	18·4
Prediabetic history	265	102	38·4%	46	45·9

To assess the significance of glycosuria in pregnancy, the postprandial blood-sugar values were analysed in both glycosuric and aglycosuric subjects (Table IV). Only 18·4% of the glycosurics in the control group had abnormal carbohydrate tolerance, whereas 45·9% of those patients with a prediabetic background had elevated blood-sugar levels.

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 V).

TABLE V. INCIDENCE OF ABNORMAL CARBOHYDRATE TOLERANCE IN PREGNANT NATAL INDIANS—GLYCOSURIC SURVEY COMPARED WITH POSITIVE 2-HOUR BLOOD-SUGAR LEVELS

Duration of pregnancy	*Patients tested*	*Glycosurics with +ve GTT*	*% Abnormals*	*Aglycosurics with +ve GTT*	*Total % abnormal*
Patients without 'prediabetic' history					
1st trimester	62	1	1·5	1	3·2
2nd trimester	119	5	4·2	6	9·1
3rd trimester	120	6	5·0	6	10·0
Patients with 'prediabetic' history					
1st trimester	43	5	11·5	5	23·3
2nd trimester	102	15	14·7	4	18·6
3rd trimester	120	26	21·6	8	28·3

Thus during the first trimester only 1·5% (1/62 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. The same pitfall was found in each trimester; the 'apparent' incidence of 4·2% in the second trimester was found to be 9·1%, while the suspected 5·0% incidence in the third trimester doubled to 10·0%.

A similar trend was observed in patients with a prediabetic history, except that the degree of abnormality was very much greater—in the first trimester 11·5% were

thought to be diabetic, the corrected figure doubling to 23·3% ; while the 14·7% incidence in the second trimester rose to 18·6%. The incidence recorded in the third trimester was 21·6% instead of 28·3%.

DISCUSSION

Normal Carbohydrate Metabolism in Pregnancy

Until recently, there was comparatively little information in the literature on the changes in carbohydrate metabolism during pregnancy, as most of the previous conclusions had been drawn from studies on glycosuria.[8] It has even been suggested that glycosuria be used as a test for pregnancy.[9]

Höst[10] compared the results of oral glucose-tolerance tests in normal men and non-pregnant and pregnant women, and found that, whereas the curve in late pregnancy was lower than that in the non-pregnant state, the blood-sugar levels in the earlier months of pregnancy were definitely higher. Similarly, Hurwitz and Jensen,[11] in a study of 25 healthy pregnant women, found that the 2-hour reading of their glucose-tolerance test was abnormal in a large percentage of cases, and that this finding increased as pregnancy advanced.

However, Cobley and Lancaster,[8] in an extensive review of the literature (1911 - 1955), concluded that there was comparatively little change in glucose tolerance during pregnancy. This was confirmed by their own study of 158 normal women, on whom glucose-tolerance tests were performed at monthly intervals throughout their gestation. Jackson[12] performed 509 standard tolerance tests on 42 women at the 36th week of pregnancy, and on 142 others on the 6th postpartum day, and found that glucose tolerance was not lowered. He concluded that 'any lowering of carbohydrate tolerance in late pregnancy or the puerperium is probably abnormal' and should not be regarded as a physiological variant. There are 4 factors which are probably responsible for the divergence of opinion on carbohydrate metabolism in pregnancy.

'Loading' dose. Jackson[12] believes that many false positives are obtained during pregnancy because too large a dose (100 G) is used. He compared 50-G tolerance tests in normal pregnant women with tests based on 1·75 G/kg. ideal body-weight (usually 100 G), and found that the difference between the mean 2-hour level of the 50-G test and that of the ideal-body-weight test was highly significant statistically (97 ± 20 compared with 118 ± 27 mg./100 ml.). Furthermore, when considering individual tests, he found that only 1·4% of normal pregnant patients had abnormal curves when the 50-G dosage was used, compared with 17·7% following the ideal-body-weight method.

'Lag-type' response during pregnancy. Although 81% of the patients reported by Hurwitz and Jensen[11] had abnormal 2-hour readings, normal fasting and 3-hour blood-sugar levels were recorded in all but one patient. This delayed or 'lag' curve has been reported by many other authors,[8,12-16] and is known to increase directly with the period of gestation. It is thought to be due to a decreased peripheral utilization of glucose ; augmentation of contra-insulin factors such as the pituitary, adrenal and lipotropic fractions ; the slower release of insulin from an overtaxed pancreas ; and increased degradation of insulin by the placenta.[16]

The suggestion has therefore been made that the glucose-tolerance test in pregnancy should be carried out over a period of 3 hours.

Duration of pregnancy. It has often been stated that impairment of tolerance tends to progress with the duration of pregnancy.[13,17,18] Jackson[19] believes that, whereas impairment of the tolerance typically increases in later pregnancy in diabetes and prediabetes, the same is not true with the advance of normal pregnancy. His findings have indicated that, if anything, the mean curve of glucose tolerance in the first trimester is higher than in later pregnancy.

Inclusion of prediabetics. Prediabetes is extremely common during normal pregnancy and the possibility of including such patients among 'normal' controls would inevitably elevate the mean curve.[19]

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It may be concluded from the literature that the fasting blood-sugar level in pregnancy tends to be lower than normal. The results of the present study have indicated that, whereas the mean fasting blood-sugar level is, if anything, slightly raised during pregnancy, the normal range (calculated by the mean + 2 standard deviations) is lower than in the non-pregnant state. Gross[16] and others[20-23] have shown that the fasting blood-sugar level is a very poor guide in detecting diabetes as, apart from producing an abnormal metabolic strain,[16] many mild to moderately severe diabetics have fasting blood-sugar values well within normal limits.[16,20,22,23] The same is true in the Natal Indian, low fasting blood-sugar levels being extremely common in undisclosed or recently diagnosed diabetics.[21]

The range of normal values for fasting blood-sugar levels in venous blood depends upon the method of analysis employed, and may vary from 60 - 100 mg./100 ml. (Somogyi-Nelson) to 80 - 120 mg./100 ml. (Folin-Wu). In the present series, this value was found to range between 80 and 115 mg./100 ml. (Herbert and Bourne). Based on these results, it was found that only 31·5% of established pregnant diabetics had values exceeding the norm, thus confirming the conclusions quoted above.

Nevertheless it has been said that the fasting blood-sugar level should never be omitted as 'there is no more final test for the diagnosis of diabetes than an elevated fasting blood sugar'.[22] Further, whenever the maximum fasting blood-sugar level is exceeded, the rest of the curve is almost always of the diabetic type.[19,20]

While conceding the latter point, this study has served to illustrate that the fasting blood sugar *per se* is a poor guide for the detection of diabetes, and it is my opinion that more good will be derived by abandoning this investigation in favour of routine single 2-hour postprandial or postglucose blood-sugar analyses.

Glucose tolerance and the duration of pregnancy. Alterations in glucose tolerance were observed during the 3 trimesters—thus the mean 2-hour postglucose levels were 104·55 mg./100 ml. for the first trimester, 113·79 mg./100 ml. for the second trimester and 108·57 mg./100 ml. for the third trimester. Although the difference between the mean is slight, statistical analysis proved it to be significant at the 1% level. The same is true when the upper limits of the 'normal range' are considered, as the value for

the first trimester is 141·83 mg./100 ml., compared with 153·63 mg./100 ml. for the second and third trimesters. On clinical grounds, however, the trend towards the lowering of glucose tolerance during the middle and last trimesters of pregnancy does not seem to justify the alteration of criteria for the diagnosis of diabetes, and although slight allowance should be made for the physiological variations found in late pregnancy, impairment of tolerance over and above the quoted norms should be regarded as a sign of latent or overt diabetes.

The 'loading' dose and normal tolerance. It was decided to employ the '100-G' oral glucose-tolerance test in this study for 2 reasons: to maintain uniformity with the evaluation of carbohydrate tolerance in the non-pregnant Natal Indian female,[6] and to correlate the findings with the results obtained in a prospective therapeutic trial, since patients in the latter study had been subjected to similar loading doses.

Although Jackson[12] found a statistically significant difference between the mean 2-hour blood-sugar levels when the 50-G and the ideal-body-weight tests were compared, only 8% of the 'normal' controls in the present series had postprandial blood-sugar levels above 140 mg./100 ml.—a figure which approximates the incidence of diabetes in the Natal Indian population—while only 2% were above 150 mg./100 ml. Since the vast majority of the 'tested population' responded in a 'normal' fashion to a loading dose of 100 G of glucose, it is reasonable to conclude that values above the quoted figures of normality are indicative of an abnormal response.

Kaplan[24] considers the 100-G oral glucose-tolerance test to be unsatisfactory during pregnancy in that too many subjects yield abnormal results. Yet, Fajans and Conn have recently proved the value of producing an abnormal stress for the detection of prediabetes by priming their patients with cortisone. It can be argued that the larger dose of 100 G of glucose fulfils a comparable situation. Because the pre- or latent diabetic is particularly liable to an excessive perinatal loss,[1-5] and since the treatment of these patients has been shown to improve the infant survival rate, it is surely wiser to err on the side of having to deal with a few extra false positives, than to investigate the cause of an unexplained stillbirth.

Glucose tolerance in the pregnant and non-pregnant Natal Indian. A comparison of the normal range of glucose tolerance in the pregnant and non-pregnant Natal Indian female shows a similar pattern during the first trimester only—thus the fasting and postglucose values of the non-pregnant patients is 83·57 - 117·05 mg./100 ml. and 99·73 - 137·93 mg./100 ml. respectively, while the comparable values for the pregnant controls is 84·53 - 110·55 mg./100 ml. and 104·89 - 141·83 mg./100 ml. Whereas the range of the fasting blood-sugar levels during the second and third trimesters closely approximates the above results (85·95 - 109·35 mg./100 ml. and 84·73 - 114·09 mg./100 ml. respectively), the postprandial range is significantly higher during the second and third trimester (113·79 - 153·63 mg./100 ml. and 108·57 - 153·37 mg./100 ml.). These results are contrary to the observations of Cobley and Lancaster,[8] and Jackson,[12] that pregnancy induces little, if any, change in glucose tolerance.

The practical significance is however limited, for clinical experience has demonstrated variations in the reproducibility of oral glucose tolerance of up to 20 mg./100 ml. Furthermore, evidence is available which suggests that abnormal glucose tolerance may well be a comparatively late manifestation of diabetes, while it is common experience to deliver women with mild disturbances in carbohydrate metabolism, of grossly affected 'diabetic' babies. Nevertheless, an upper limit of normality has to be established, and it is suggested that pregnant patients with postprandial blood-sugar levels between 130 and 150 mg./100 ml. (Herbert and Bourne) be kept under close surveillance, while those with values exceeding 150 mg./100 ml. should be regarded as abnormal and in need of suitable treatment.

Relatively few studies comparing glucose tolerance in pregnant and non-pregnant diabetic subjects have been published. As indicated in Table VI, certain authors[25,26] require higher 2-hour postglucose levels for the diagnosis of diabetes in the pregnant patient. Values above 140 mg./100 ml. were regarded as abnormal in the prospective therapeutic study[28] referred to previously, as the results of the present investigation were not available for guidance. It is interesting to note, however, that of the 227 diabetics on the trial only 28 had values between 140 and 150 mg./100 ml., and, of these, 3 pregnancies resulted in stillbirth, while one produced a live 12 lb. 9 oz. infant.

TABLE VI. COMPARISON OF UPPER LIMITS OF GLUCOSE TOLERANCE IN NON-PREGNANT AND PREGNANT SUBJECTS

Author	*Blood-sugar levels measured in mg./100 ml.*	*Fasting*	*1 hour*	*2 hour*
O'Sullivan & Mahan[25]	Pregnant	90	165	145
	Non-pregnant	110	170	120
White[26]	Pregnant	—	180	140
	Non-pregnant	—	150	110
Jackson[19]	Pregnant	86	127	97
	Non-pregnant	89	125	94
Barnes[27]	Pregnant	100	160	100
	Non-pregnant	100	160	140
Present series	Pregnant	115	—	150
	Non-pregnant	120	—	140

A significant number of people with suggestive prediabetic histories have abnormal glucose tolerance. This effect appears to be exaggerated by the advent of pregnancy, for between 18·6 and 28·3% of normal pregnant Natal Indians with such histories were found to have abnormal carbohydrate tolerance (Table V). This figure is similar to that quoted by Fajans and Conn,[29] as 25% of their non-pregnant subjects with prediabetic histories had abnormal cortisone-stressed glucose-tolerance tests. Pregnancy would therefore appear to be the ideal time to screen the younger population group for diabetes and this supports my contention that every gravid patient should have a postprandial blood-sugar assessment during each of the 3 trimesters. Even if the glucose-tolerance test reverts to normal in the puerperium, such patients should be regarded as suspect and retested annually.

When one considers the fact that diabetes accounts for a perinatal loss as great as Rh-haemolytic disease, it is rather surprising that routine antenatal postprandial blood-sugar values 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 and that of haemolytic disease to be low.

Glycosuria during Pregnancy

The presence of glycosuria depends on the concentration of glucose in the afferent glomerular arteriole, the glomerular filtration rate and the tubular reabsorption[26] of filtered glucose. Recent studies by Sims and Krantz[30] and Welsh[31] have shown that, whereas the glomerular filtration rate increases from 103 ml./min. in non-pregnant, to 150 ml./min. in pregnant patients, there is virtually no difference between normal pregnant patients and those with glycosuria—154 ± 4·5 ml./min. and 151 ± 7·5 ml./min. respectively. The tubular reabsorption of glucose in pregnant glycosurics, however, is considerably lower than that in pregnant controls and in non-pregnant normal females—310 ± 20 mg./min. as compared with 378 ± 20 mg./min. and 366 ± 16 mg./min.

It would therefore appear that both an increase in the glomerular filtration rate and a decreased tubular reabsorption of glucose are responsible for the presence of glycosuria, with the latter factor playing the dominant role.

Renal glycosuria occurs in approximately 10 - 15% of non-diabetic pregnant women,[29] the reason probably being the increased cortisone levels found in the later months of pregnancy, since cortisone and ACTH are known to decrease tubular reabsorption of glucose and increase the glomerular filtration rate.[32,33] The increased renal plasma flow in pregnancy may also be responsible for changes in the renal threshold of glucose.

The results of the present study have confirmed the increased tendency of glycosuria to occur during pregnancy—in the non-pregnant control group the incidence of glycosuria was only 2%, whereas 21·5% of pregnant patients (under identical circumstances) had evidence of sugar in the urine. This difference, together with the more frequent occurrence of glycosuria with the duration of pregnancy, is probably due to a combination of the factors mentioned previously.

The presence of glycosuria in the normal pregnant patient is, however, not as significant as that found in prediabetic or even normal non-pregnant females. Only 18·4% of glycosurics in 'normal' pregnant patients were found to have abnormal glucose-tolerance tests, as opposed to 45·9 and 75% in prediabetic pregnant patients and in normal non-pregnant females.

Consequently it is of particular importance that pregnant patients should be screened for diabetes on the basis of postprandial blood-sugar values, rather than glycosuria. Many prediabetics and latent and even overt diabetics have high renal thresholds resulting in aglycosuria in the presence of raised blood-sugar levels. Thus venous blood-glucose levels of 200, 228, 226, and 328 mg./100 ml. were recorded in some of our patients without evidence of sugar in the urine.

The scope of this investigation did not permit the evaluation of renal thresholds and glomerular filtration rates in the pregnant Natal Indian.

The tendency to abnormal glucose tolerance in patients with prediabetic histories is well documented, and the same is probably true for glycosuria. The difference in over-all frequency of glycosuria in the present study—21·5% in normal controls and 38·4% in prediabetics—is statistically significant ($p < 0.05$). A possible cause of this feature in the Natal Indian prediabetic might be hyperactive adrenocortical function.[28]

CONCLUSIONS AND SUMMARY

Standard 100-G oral glucose-tolerance tests were performed during the 3 trimesters of pregnancy in 568 normal pregnant non-diabetic Natal Indians, 267 of whom had significant prediabetic histories.

Glucose tolerance was found to change with the progression of pregnancy and, whereas no appreciable difference in tolerance could be demonstrated between non-pregnant patients and those in the first trimester of pregnancy, a definite lowering of tolerance occurred in the second and third trimesters. Therefore pregnant subjects with postprandial blood-sugar levels between 130 and 150 mg./100 ml. should be kept under surveillance, while those with values in excess of 150 mg./100 ml. should be regarded as diabetic and put onto specific treatment.

The incidence of glycosuria was found to increase with the duration of pregnancy, the difference being exaggerated in patients with prediabetic histories. The demonstration of sugar in the urine of pregnant subjects was found to yield fallacious results, as only 18·4% of such patients in the control group had abnormal glucose-tolerance tests, while many aglycosuric subjects were found to have 'diabetic' curves. The detection and diagnosis of diabetes mellitus should not depend on urinalysis.

Fasting blood-sugar values were found to be a poor guide in detecting diabetes, as only 31·5% of established pregnant diabetics had values exceeding the normal range of 80 - 115 mg./100 ml. It is proposed that this investigation be abandoned in favour of single postglucose blood-sugar analysis.

As the treatment of prediabetic patients is known to improve the perinatal survival rate, it is suggested that all gravid patients be screened as a routine by single 2-hour postglucose or postprandial blood-sugar estimations during each of the 3 trimesters of pregnancy. Patients whose glucose tolerance reverts to normal in the puerperium should be regarded as suspect and retested annually.

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REFERENCES

1. Jackson, W. P. U. and Woolf, N. (1958): Diabetes, **7**, 446.
2. Miller, H. C., Hurwitz, D. and Kuder, K. (1944): J. Amer. Med. Assoc., **124**, 271.
3. Gilbert, J. A. L. and Dunlop, D. M. (1949): Brit. Med. J., **1**, 48.
4. Hagbard, L. (1958): Acta obstet. gynec. scand., **37**, 497.
5. Pomeranze, J., Stone, M. L. and King, E. J. (1959): Obstet. and Gynec., **13**, 1818.
6. Notelovitz, M. (1969): S. Afr. Med. J., **43**, 259.
7. Herbert, F. K. and Bourne, M. C. (1930): Biochem. J., **24**, 299.
8. Cobley, J. F. C. and Lancaster, H. O. (1955): Med. J. Aust., **1**, 171.
9. Kleitsman, R. J. (1929): Zbl. Gynäk., **53**, 104.
10. Höst, H. F. (1925): Lancet, **1**, 1022.
11. Hurwitz, D. and Jensen, D. (1946): New Engl. J. Med., **234**, 327.
12. Jackson, W. P. U. (1952): Brit. Med. J., **2**, 690.
13. Hagen, A. (1961): Diabetes, **10**, 438.
14. Wilkerson, H. L. C. (1957): *Ibid.*, **6**, 329.
15. Basil-Jones, B. J. (1949): Med. J. Aust., **2**, 558.
16. Gross, M. (1962): Clin. Obstet. Gynec., **5**, 482.
17. Pedowitz, P. and Shevlin, E. L. (1957): Obstet. and Gynec., **9**, 524.
18. Wilkerson, H. L. C. (1959): Ann. N.Y. Acad. Sci., **82**, 219.
19. Jackson, W. P. U. (1964): *On Diabetes Mellitus*, p. 129. Springfield, Ill.: Charles C. Thomas.
20. Fajans, S. S. *in* Williams, R. H., ed. (1960): *Diabetes*, p. 389. New York: Paul Hoeber.
21. Campbell, G. D. (1963): S. Afr. Med. J., **37**, 1195.
22. Mosenthal, H. O. and Barry, E. (1950): Ann. Intern. Med., **33**, 1175.
23. Stewart, W. K. and Robertson, P. C. (1963): Lancet, **2**, 184.
24. Kaplan, N. M. (1961): Arch. Intern. Med., **107**, 212.
25. O'Sullivan, J. B. and Mahan, C. M. (1964): Diabetes, **13**, 278.
26. White, P. (1965): Med. Clin. N. Amer., **49**, 1015.
27. Barnes, P. H. (1961): Canad. Med. Assoc. J., **85**, 681.
28. Notelovitz, M. (1967): M.D. thesis, University of the Witwatersrand.
29. Fajans, S. S. and Conn, J. W. (1958): Ann. N.Y. Acad. Sci., **82**, 208.
30. Sims, E. A. H. and Krantz, K. E. (1958): J. Clin. Invest., **37**, 1764.
31. Welsh, G. W. (1960): Diabetes, **9**, 363.
32. Kass, E. H., Ingfar, S. H. and Finland, M. (1950): Proc. Soc. Exp. Biol. (N.Y.), **73**, 669.
33. Dunstan, H. P., Corcoran, A. C., Taylor, R. D. and Page, I. H. (1950): Arch. Intern. Med., **81**, 627.