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Comparison of Oral and Intravenous Glucose Tolerance Tests in Third Trimester of Pregnancy

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AT THE PRESENT TIME, the type of glucose tolerance test for the assessment of abnormal carbohydrate metabolism in pregnancy remains a controversial topic. Each test has its own supporters despite the advantages and disadvantages.

The oral glucose tolerance test (OGTT) is considered to be a more physiological approach in the examination of carbohydrate metabolism. It utilizes the route normally taken by carbohydrate in the diet, and digestion and absorption promotes secretion of secretin and intestinal glucagon both of which stimulate insulin secretion.

On the other hand, the intravenous glucose tolerance test (IVGTT) bypasses this mechanism and might therefore be considered unphysiological.

Results of OGTT are on the whole more difficult to interpret and are variable in the same individual. The IVGTT however, is easier to interpret and gives good reproducibility in the same patient. Against this background of controversy, it was decided to compare the OGTT and IVGTT in the same patient in the third trimester of pregnancy, where there were indications for glucose tolerance testing.

It is known that a transient diabetic state may develop in pregnancy without antecedent abnormality. This may be associated with altered glucose tolerance curves, glycosuria and hyperglycaemia. Reversion to apparently normal metabolism status promptly follows delivery.

It has been suggested that alteration in carbohydrate metabolism in pregnancy might be due to complex synthesis and secretion of human placental lactogen (HPL), oestrogen and progesterone in the placenta (Kaplan and Grumbach, 1964). Even though the metabolic role of HPL is still uncertain, from the evidence available, it seems that it can both antagonize insulin and stimulate its secretion. HPL also promotes adipose tissue lipolysis, thus causing an increase in the level of plasma fatty acids (Grumbach et al, 1966). In women who have the relative insulin deficiency of latent diabetes, the additional stress of pregnancy will consistently impair carbohydrate tolerance and may be responsible for the first appearance of gross metabolic abnormalities of diabetes.

It is very difficult to interpret glucose tolerance in pregnancy and to determine the presence and significance of minor deviations from normal. This is because many factors may alter glucose tolerance. Pregnancy is associated with changes in gastrointestinal absorption (Hytten and Leitch, 1964) and renal function (Welsh and Sims, 1960).

There is a lack of general agreement with regard to the criteria for 'abnormal' oral glucose tolerance curve. Fasting blood sugar values have been used. However, there is a controversy with regard to the definition of upper limits of 'normal'. O'Sullivan and Mahan (1964) regard it as 90 mg./100 ml., while Malins (1968) regards it as 100 mg./100 ml. 'Peak values' and '2 hour values' of blood sugar have been used by many workers. The British Diabetic Association (Fitzgerald and Keen, 1964) defined an

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'abnormal curve' if the peak value exceeds 180 mg./100 ml. and the 2 hour value exceeds 110 mg./100 ml. (venous blood).

Recently, an 'H index' which describes the shape of an oral glucose tolerance response curve and appears to be a measure of the efficiency of homeostatic control was introduced by Billewicz et al (1973). They claimed the index could satisfactorily differentiate clinically diabetic from non-diabetic individuals and seems to provide a sensitive method of describing small changes in homeostatic control such as might occur in pregnancy.

The intravenous glucose tolerance test using 25 gm. of glucose is highly reproducible and is preferred to oral test by many investigators (Duncan, 1956, McIntyre et al, 1964). Two indices of glucose tolerance, the 'total index' and the 'increment index' have been used to evaluate the results of the tests. However, Duncan (1956) found that the 'increment index' is more reproducible and hence preferred to the 'total index' since it is not affected within two fold variation in the dose of glucose injected.

In this study, an attempt is made to compare the results of the oral and intravenous glucose tolerance tests in 16 pregnant patients in the third trimester. The criteria for 'abnormal' OGTT are based on the definition given by the World Health Organization (1965). The 'increment index' is used to evaluate the results of IVGTT. The value of less than 2.97 is regarded as evidence of impaired glucose tolerance.

Selection of patients and method of study

Sixteen patients who were certain of their dates of the last menstrual period and were between 30 and 36 weeks' gestation were selected for the study. The mean age of the patients was 24.4 years, and the mean gravidity was 3.06. Each patient had one

Table I

Details of Patients

Case No.	Age (yrs)	Gravidity	Gestation (wks)	Height (cm)	Weight (kg) 20 wks.	Calculated Non-pregnant Weight (kg.)	Birth Weight (gm)
1	21	1	36	165	65.5	61.5	3520
2	25	6	35	161	62.6	58.6	3680
3	27	2	35	163	66.2	62.2	2800
4	26	1	36	165	57.0	53.0	5620
5	29	3	30	166	58.5	64.5	4340
6	20	3	35	155	75.7	71.7	3610
7	28	4	34	145	55.5	51.5	2980
8	25	2	34	155	76.0	72.0	3350
9	39	8	36	160	69.4	65.4	4080
10	28	3	36	171	75.0	71.0	3440
11	24	2	33	155	68.4	64.4	3150
12	22	2	33	161	55.3	51.3	3440
13	29	2	36	166	62.6	58.6	3560
14	20	3	31	166	67.2	63.2	3790
15	16	1	33	166	57.6	53.6	2830
16	42	6	32	157	77.5	73.5	2780
Mean	26.31	3.06	34.06	161	66.25	62.3	3435
S.D.±	6.68	2.01	1.91	6.41	7.43	7.44	447

Table II

Fasting Plasma Glucose Levels Day 1 (O.G.T.T.) Day 2 (I.V.G.T.T.)

Sample	Number of Cases	Mean Plasma Glucose ± S.D. (mg./100 ml.)
Day 1 (O.G.T.T.)	16	72.38 ± 6.89
Day 2 (I.V.G.T.T.)	16	64.56 ± 12.06

$t = 2.249$
Difference is significant $p < 0.05$

or more of the following indications for glucose tolerance test (see Table III). The indications were glycosuria, family history of diabetes, previous large babies (more than 10 pound), previous unexplained stillbirth, recurrent abortions and symptom of polydipsia and polyuria. OGTT was performed at the first visit and the IVGTT two or three days later.

Table III

Relationship between Results of G.T.T. and Indications for Testing

Indications for Testing	Number of Patients		
	With Indications	Abnormal O.G.T.T.	Abnormal I.V.G.T.T.
Glycosuria	8	3	4
Family history of diabetes	1	1	0
Previous large baby (10 lb.)	4	1	2
Previous stillbirth	1	1	0
Recurrent abortions	1	0	1
Symptom of polydepsia and polyuria	1	1	1

Procedure

After an overnight fast of at least 12 hours and following a 20 minute rest, 2 ml. of venous blood was taken for fasting plasma glucose. At the same time, urine sample was taken and tested for sugar, After an oral administration of 50 gm. of glucose. specimens of venous blood were collected 1 hour, 2 hour and at 2½ hours. Urine samples were also obtained at the respective times.

Having obtained informed consent, the same patients were tested three days later by the IVGTT. After an overnight fasting of approximately 12 hours and 30 minutes rest, an intravenous teflon cannula was inserted into a vein, preferably in the antecubital fossa. A two-way stopcork was attached to the cannula to facilitate frequent sampling. After obtaining two fasting blood samples for glucose examination, 50 ml. of a 50 per cent dextrose solution (25 gm. glucose) was injected intravenously in the other arm over a period of 3 to 4 minutes. Blood samples were taken at 4, 10, 20, 30, 40, 50 and 60 minutes after glucose injection. Blood samples were collected in heparinised tubes and then centrifuged.

Plasma glucose estimations using the auto-analyser

Glucose estimations were carried out on plasma samples utilizing the enzyme system, glucose-oxidase/peroxidase on an autoanalyser. This method is specific for glucose in which other reducing substances do not interfere producing unduly high values. In this method, glucose oxidase catalyses the oxidation of glucose to gluconic acid and hydrogen peroxide. The peroxidase then catalyses the transfer of oxygen to chromogenic oxygen receptor. The analyser measures the rate of consumption of oxygen which is directly proportional to the concentration of glucose in the sample.

The fasting plasma glucose level for the IVGTT was taken as the mean of the estimates of the two samples taken before glucose injection.

Criteria for abnormal Oral Glucose Tolerance Test

Recommendations given by the World Health Organization (1965) were taken as the criteria for evaluation of the results of the OGTT. This was based on the two hour value of plasma glucose as follows:-

Normal	– less than 110 mg./100 ml. (venous blood).
Probable diabetic	– 110 – 129 mg./100 ml.
Diabetic	– 130 mg./100 ml. or more.

The fasting level of plasma glucose of 130 mg./100 ml. or more was regarded as diabetic.

Calculation of the increment index

The result of the IVGTT is expressed as an 'increment index' described by Duncan (1956) and represent the rate of fall of blood glucose as a percentage of the value in excess of the fasting level. Amatuzio (1953) reported that if the log of the increment blood glucose is plotted against time, a straight line is obtained and the increment index can be calculated

using the formula $\frac{\log e^2}{t}$ where t is the time in minutes required for the blood glucose increment value at any point to be halved. An index of more than 2.97 is regarded as normal, 2.46 – 2.97 as suspicious of diabetes and less than 2.46 as diabetic.

RESULTS

Fasting plasma glucose

As shown in Table II, the mean fasting plasma glucose level on Day 1 when the OGTT was performed was 72.38 mg./100 ml. $\pm$ 6.89. This value is significantly higher than that obtained on Day 2 when the IVGTT was carried out, the value being 64.56 mg./100 ml. $\pm$ 12.06 ($p < 0.05$).

This finding is in agreement with that of Campbell et al (1974) who reported that although there was little day to day variation in plasma glucose, the levels were significantly elevated on the first day of the study. They suggested that this was probably due to excessive output of adrenaline on the first day due to anxiety.

None of the patients in this series had abnormal levels of fasting plasma glucose, on the basis of the criteria reported by Malins (1968).

Oral Glucose Tolerance Test

Basing the results on the recommendations given by the World Health Organization (1965), two patients (12.5%) had diabetic pattern of OGTT. Five patients (31.25%) were classified as 'probable diabetic' and nine patients (56.25%) as normal. Of the two patients who had diabetic OGTT, one had an abnormal and the other a normal IVGTT.

Table IV

Results of Oral Glucose Tolerance Test (W.H.O. Classification)

Total Number of Patients	O.G.T.T. Results		
	Normal	Suspicion of Diabetes	Diabetic
16	9 (56.25%)	5 (31.25%)	2 (12.5%)

The total number of patients showing abnormal pattern of OGTT was 7 out of 16 (43.8%). Of the 8 patients who were tested for glycosuria, 3 showed abnormal OGTT (37.5%), whilst one of the 4 patients tested because of previous large babies showed an abnormal OGTT (25%). The other 3 abnormal OGTT came from patients with family history of diabetes, previous stillbirth and symptoms of polydipsia and polyuria respectively (see Table III).

Intravenous glucose tolerance

As shown in Table V, 8 out of 16 patients (50%) had abnormal intravenous glucose tolerance. Five patients (31.3%) showed diabetic curve because their increment indices were less than 2.46. Three patients (18.7%) were regarded as 'suspicion of diabetes' since their increment indices were between the range of 2.46 to 2.97.

Table V

Results of I.V.G.T.T. (Increment Index)

Number of Patients	Increment Index		
	2.97	2.46 – 2.97	< 2.46
16	8 (50%)	3 (18.7%)	5 (31.3%)

Four out of eight patients (50%) whose main indication for the test was glycosuria had abnormal IVGTT, and 2 out of 4 patients (50%) who were tested because of having delivered large babies previously had abnormal IVGTT. The other 2 patients who had abnormal IVGTT had history of recurrent abortions and symptoms of polydipsia and polyuria respectively.

Comparison of OGTT and IVGTT

As shown in Table VI, four out of 16 patients (25%) had both abnormal OGTT and IVGTT. Three patients (18.7%) had abnormal OGTT only whilst four patients (25%) had abnormal IVGTT only. Both OGTT and IVGTT were found to be normal in 5 patients (31.3%).

Of the three patients who had abnormal OGTT only, one had diabetic pattern whilst the other two had borderline OGTT. On the other hand, of the four patients who had abnormal IVGTT only, three had gross abnormality showing diabetic pattern and only one showed borderline IVGTT. Of the 16 patients tested, two patients showed diabetic pattern of OGTT whilst there were five patients showing diabetic pattern of IVGTT.

Outcome of pregnancy

Seven patients (44%) had induction of labour for various indications. One patient however, had an elective Caesarean section. Of the 15 patients who were in labour, 7 (47%) had spontaneous vaginal deliveries. Eight of the patients required assistance in the forms of instrumental delivery (4 patients) or emergency Caesarean section (4 patients). The main indication for assisted delivery was 'foetal distress'. One patient who needed emergency Caesarean section for 'foetal distress' delivered a

Table VI

Relationship between O.G.T.T. and I.V.G.T.T.

Total Number of Patients	Abnormal O.G.T.T. and I.V.G.T.T.			
	Both Abnormal	Abnormal O.G.T.T. only	Abnormal I.V.G.T.T. only	Both Normal
16	4 (25%)	3 (18.7%)	3 (25%)	5 (31.3%)

congenitally malformed infant having thoraco-lumbar' meningmyelocele. This infant ultimately died on the seventh day. Both the OGTT and IVGTT of this patient was normal.

There was no stillbirth and all the other 15 infants were healthy at the time of discharge. Four infants (25%) had one minute Apgar score of between 0 – 6.

Birthweight

The mean birthweight of 16 infants 3435 gm. (Table I). Even though there were four patients who previously delivered infants weighing more than 10 pounds, in this series there was only one patient who delivered a macrosomic infant (birth weight 4340 gm.). However, both the OGTT and IVGTT of this patient were normal.

DISCUSSION

The assessment of abnormalities of carbohydrate metabolism in the non-pregnant state is fraught with difficulties because of the many factors which control its homeostasis. The situation is made more complex in pregnancy by the increasing levels of hormones which are considered to be diabetogenic, for example oestrogen, cortisol and Human placenta lactogen (HPL).

Most authorities would accept that patients with fasting glycosuria, family history of diabetes, obesity above 85th percentile, previous history of large for dates baby, unexplained stillbirth, recurrent abortions, unexplained neonatal death and hydramnios should be subjected to glucose tolerance test.

The significance of glycosuria in pregnancy is controversial. The presence of glycosuria in urine depends on blood sugar, glomerular filtration rate and tubular reabsorption of glucose, and there is evidence that each of these factors is altered in pregnancy. Sutherland et al (1970) claimed that there was no correlation between random glycosuria with chemical (gestational) diabetes. However, they found 15 percent incidence of abnormal IVGTTs in 62 pregnant patients with second fasting morning glycosuria. In this study, there is lack of standardization with regard to glycosuria. Some of the patients had second fasting glycosuria, whilst others had random glycosuria on two or more occasions and a few had random glycosuria with additional indications for the test. Sutherland et al (1970) felt that fewer women with glycosuria in pregnancy need to be tested unless there in second fasting morning glycosuria where the risk is about 8 per 1,000 ante-natal women. In this study, 4 out of 8 patients (50%) who had glycosuria were found to have abnormal intravenous glucose tolerance.

There are four patients who delivered large babies previously (birth weight more than 4100 gm.). One of them delivered a 'large baby' in the present study (birth weight 4340 gm.). Two out of 4 patients (50%) had abnormal IVGTT. Even though several factors such as genetic predisposition, parenteral size, gestational maturity up to 41 weeks and multiparity could influence the birth weight, the association of diabetes with high birth weight has been reported by many workers, Knitzer (1952) found diabetic glucose tolerance in 31 percent of the patients who delivered 10 pound infants 2½ years previously. Mickal et al reported diabetic glucose tolerance in 60 percent of those women followed for 12 years after delivery of an infant weighing 4500 gm. or more.

It is generally accepted that the fasting blood sugar levels in pregnancy are lower than in non-pregnant state. The difference is probably of the order of 10 mg./100 ml. (Bleicher, O'Sullivan and Frienkel, 1964; Tyson, 1969). The levels of fasting blood sugar quoted in late pregnancy range from 66 mg./100 ml. to 71 mg./100 ml. Lind (1973) in his study reported fasting blood sugar levels of 68.8 mg./100 ml. in late pregnancy. The mean fasting blood sygar levels taken on Day 1 and Day 2 in this series were 72.38 mg./100 ml. and 64.56 mg./100 ml. respectively.

The generally accepted fasting blood sugar values for normal and diabetic patients as reported by Malins (1968) are as follows:-

Normal	:	60 – 100 mg./100 ml.
Suspicion of diabetes	:	100 – 130 mg./100 ml.
Frank diabetes	:	above 130 mg./100 ml.

None of the patients in this study had an abnormal fasting level of blood glucose, even though the IVGTT showed 50 percent incidence of impaired glucose tolerance. The insignificant relationship between fasting blood glucose and increment index, suggests that fasting blood sugar is of no predictive value as far as the handling of glucose is concerned following a glucose load. This supports the suggestion made by Wright et al (1968) that the finding of a normal fasting blood sugar does not exclude diabetes and that a glucose tolerance should be done if there are other reasons for suspecting the diagnosis.

From this small series, it is interesting to note that four patients (25%) showed abnormality in both the OGTT and IVGTT, whilst five patients (31.3%) showed both normal OGTT and IVGTT. In these nine patients, the decision is clear. However, the problem lies in the other seven patients in whom three (18.7%) showed abnormality in OGTT only, and four (25%) showed abnormality in IVGTT only. Three out of four patients showing abnormal IVGTT and one out of three patients showing abnormal OGTT had a severe degree of abnormality. This may suggest that IVGTT is more useful in detecting abnormal carbohydrate tolerance in pregnancy.

In comparing the validity of the OGTT and IVGTT during pregnancy, Benjamin and Casper (1966) concluded that the OGTT is more reliable than the IVGTT. On performing both tests in 144 patients in the third trimester, they found that the OGTT when 'normal' in pregnancy was 88 percent valid, and when 'abnormal' was 89.4 percent valid. The corresponding figures for the validity of the IVGTT were 53 percent and 95.7 percent respectively (the validity is based on comparison of the results of GTTs during pregnancy with those of the stressed GTTs done six weeks after delivery). Hence, when 'normal' the difference was striking, the intravenous test showing 47 percent incidence of false negative results as contrasted with an incidence of 12 percent false negative results with the oral tests. Supporters of OGTT also claimed that the intravenous tests have several disadvantages such as the need for frequent sampling, the accuracy in timing the sampling and also the occasional occurrence of venous thrombosis.

On the other hand, supporters of the IVGTT like Lunbaek (1962) claimed that OGTT is a clumsy tool, takes several hours to perform and it depends upon the state of the digestive tract and renal function which are usually altered during a pregnancy. Thus, the results are difficult to interpret. Duncan (1956), McIntyre et al (1964) and Fisher et al (1974) have shown that the IVGTT is reproducible and hence a reliable method of detecting minor degree of impairment of glucose tolerance in pregnancy.

Several factors are known to affect the glucose tolerance during pregnancy. Fisher et al (1974) showed that the glucose tolerance decreases with advancing stage of gestation. Sharp et al (1964) showed that the carbohydrate tolerance during pregnancy declines with advancing age of the patients. Several workers have reported a high rate of abnormal glucose tolerance in obese pregnant patients (Ogilvie, 1935; Beaudain, 1953). Pyke (1956) and Fitzgerald et al (1961) demonstrated an increasing incidence of diabetes with increasing parity.

There seems to be a great deal of disagreement as to the significance of abnormal glucose tolerance during pregnancy. Gross (1962) claimed that the difficulties experienced by a pregnant diabetic such as recurrent abortions, increased incidence of stillbirths and neonatal deaths are also experienced by individuals who have impaired carbohydrate tolerance during pregnancy. On the other hand, O'Sullivan (1961) and other workers have reported high incidence of abnormal OGTT in normal pregnant patients.

As regard to treatment of pregnant patients with abnormal glucose tolerance, there is no general agreement towards instituting diet or small doses of insulin depending on the degree of abnormality. However, O'Sullivan et al (1966) have shown that when these patients are treated, they tend to produce average sized infants and the perinatal mortality was significantly reduced.

The significance of abnormal glucose tolerance during pregnancy in predicting the future possibility of developing diabetes mellitus has also been studied by O'Sullivan et al (1971). In a follow-up of 603 patients with indication of glucose tolerance testing and who were found to have abnormal tests in pregnancy, one-third had developed diabetes mellitus 15 years later. It is interesting to follow-up the eleven patients in this series who either showed abnormal OGTT, IVGTT or both in 15 years from now. Perhaps one could then comment on the validity of each type of glucose tolerance test.

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