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Glucose Tolerance During Pregnancy In Fructose-Fed Rats

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SUMMARY

The effect of chronic fructose-feeding on glucose tolerance during pregnancy was investigated. 48 pubertal female rats were used. The experimental rats were fed with 25% fructose mixed with normal rat chow for a minimum period of 3 weeks and the control rats were fed with the normal rat chow. They all had free access to drinking water. At the end of the feeding period of 3 weeks, the animals were fasted and 24 hours later, 30% glucose solution given at a dose 0.3ml per 100g body weight was administered orally and blood samples obtain from the femoral artery. Plasma glucose estimation was done as described by Schmidt and Trinder (1969). Fasting and 2 hr plasma glucose levels remained significantly higher in the fructose-fed rats ($p < 0.01$) throughout the duration of pregnancy. Fasting glucose levels in the control rats was $77.42 \pm 2.39 \text{mg\%}$ while that of the fructose-fed rats was $91.25 \pm 3.58 \text{mg\%}$. In the fructose-fed group, an average increase of 36% was observed in the 2 hr plasma glucose level over the fasting glucose level while an increase of 25.21% was observed in the control rats. A prolonged glucose tolerance was obtained in the fructose-fed rats.

INTRODUCTION

Diabetes mellitus may be caused by insufficient production of insulin or insulin resistance¹. There are also situation in which an abnormal elevation of plasma glucose level secondary to some clinical factors (such as acromegaly, Cushing's disease etc.) has been observed. Diabetes mellitus will lead to glycosuria, polyuria and polydipsia. Glycosuria was first reported in an uncomplicated pregnancy by Burt². Since then, glucose homeostasis during pregnancy has been intensely studied. Diabetes mellitus is one of the manifestations of the disturbance in glucose homeostasis during pregnancy³.

Several works have been done to elucidate the pathogenesis of diabetes mellitus during pregnancy especially that caused by insulin resistance. Balon *et al.*⁴ and Kaufmann *et al.*³ had demonstrated disturbance in glucose homeostasis caused by insulin resistance during pregnancy. Insulin resistance has been linked to contrainular activity of pregnancy hormones which may cause, in susceptible women, impaired glucose tolerance (gestational diabetes) or may cause in diabetic women a worsening of metabolic control^{5,6}.

Increased dietary fructose has been shown to produce insulin resistance^{4,7}. Fructose feeding has been shown to modify multiple aspect of carbohydrate metabolism; it was shown to cause a decrease in glucose oxidation at hepatic tissue⁸ at adipose tissue⁹ and at striated muscle¹⁰.

The number and total volume of islet of Langerhans was found to increase during pregnancy¹¹. In spite of these findings, pregnancy was still described as a diabetogenic state and this was verified using the oral glucose tolerance test.

MATERIALS AND METHODS

48 pubertal female of the Sprague-Dawley strain were used in the study. The rats were divided into two groups of control and fructose-fed rats. The fructose-fed rats were fed with normal rat chow mixed with fructose (ratio 3:10 i.e 25% fructose feed for three weeks before the commencement of the experiment, while the control rates were fed with the normal rat chow. Both groups of rats had free access to water.

Estrous cycle of the animals were monitored. Male rate of proven fertility was introduced into the cage of the female rate that was expected to get into the estrous phase within 12 hours to allowing for mating. Day 1 of pregnancy was taken as the day sperms were seen in the vaginal smear of the rat. Measurements were carried out in the first trimester (Day 6), second trimester (Day 13) and third trimester (Day 20).

The rates were anaesthetized by inhalation of anaesthetic ether. A 30% glucose solution was given at a dose of 0.3ml per 100g body weight 12 by means of oro-gastric cannula over a period of 1 minute. Plasma glucose estimation was as described by Schmidt and Trinder¹³. D + glucose from Griffin and George, England was used in preparing standard glucose solutions and standard curve was plotted. From the standard curve, glucose concentration in each plasm sample was obtained by extrapolating it's absorbance to the glucose concentration axis. All results were analysed using Student's "unpaired" t-test. The level of significance was taken, as $P < 0.05$.

RESULTS

The results obtained from the control group (fig. 1) showed two major changes: maximum plasma glucose concentration was attained 60 minutes after glucose loading and plasma glucose concentration fell to almost normal levels after 120 minutes in both pregnant and non-pregnant rats.

For fructose-fed (diabetic) rats the elevated plasma glucose levels (Fig. II) were sustained during pregnancy especially in third trimester.

DISCUSSION

The result of the present study is similar to that obtained by Vannini⁵ and Reaven¹⁴. The plasma glucose concentration in human subjects used by these workers however, returned to fasting level earlier than it did in the rats used in the present study. The delay in returning the elevated plasma glucose level to baseline values suggest any of the following that the rate of insulin production may fall during pregnancy, that the rate of delivery of insulin to target tissues may fall or that the action of insulin may be impaired during pregnancy. However, it was earlier suggested by Godsky *et al.*¹⁵ that there is an increase in insulin secretion as well as total volume of islets of Langerhans during pregnancy in rats. Therefore the delay observed may be due to a fall in insulin action during pregnancy. This agrees with the views of Vannini⁵. Prolonged glucose tolerance curve was linked to constrainsular activity of pregnancy hormones. Estrogen and progesterone were implicated, they are believed to be involved in degradation of insulin with insulinase, alteration of cortisol dynamics and production of prolactin and placental lactogen. All these changes affect insulin receptors and make them resistant to insulin action which in turn is responsible for the impaired glucose tolerance or gestational diabetes in the control pregnant rats (see Fig 1).

Plasma glucose levels in the three trimesters were significantly higher in the fructose-fed rats than those of the control rats. The elevated plasma glucose levels failed to return to the baseline value in the three trimesters after 2 hours unlike they did in the pregnant control rats. The result is similar to that obtained by Martinez *et al.*⁷ using dog model but contradicts that obtained by Kaufmann *et al.*³. This difference may be due to the rat model used, Kaufmann and his colleagues used 'BB' wister rats which is an insulin dependent diabetic rat. The result of the present study shows that fructose-fed rats are not insulin dependent, the hyperglycaemia observed may be due to insulin resistance rather than insulin deficiency. The present study shows a correlation between the level of hyperglycaemia and gestational period in both control and fructose-fed rats. This is similar to the result obtained using human subjects¹⁶. This suggests that the degree of insulin resistance increases with gestational period.

The impaired insulin action in the fructose-fed rats may be due to decreased receptor affinity or reduction in the number receptors, abnormal cell function that determines the

response to a given concentration of insulin-receptors complexes^{17,18}. It may also be due to a decrease in glucose oxidation in hepatic tissues⁸ or in striated muscle⁹ and adipose tissue¹⁰. Thus the overall effect of fructose feeding is a potentiated insulin resistant state as confirmed by the level of significance between the results obtained from the pregnant control and fructose-fed rats.

In conclusion, chronic fructose-feeding have been shown to aggravate the impaired glucose tolerance during pregnancy in the rats. This finding adds to the ever growing evidence that insulin resistance impairs glucose tolerance and plays a major role in the development of diabetes during pregnancy.

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Fig. 1: Graph showing the plasma glucose concentration at 0 minutes (fasting) and 30, 60, 90 and 120 minutes after oral administration of 30% glucose solution in the control group.

Fig. II: Graph showing the plasma glucose concentration at 0 minutes (fasting) and 30, 60, 90 and 90 minutes after oral administration of 30% glucose solution in the fructose-fed group.

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