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Blood pressure and heart rate changes during pregnancy in fructose-fed Sprague-Dawley rats

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Summary
Blood pressure and heart rate changes during pregnancy were investigated in fructose-fed (diabetic) Sprague-Dawley rats. A total of 48 subcutaneous female rats were used. The experimental rats were fed with 25% (w/v) fructose mixed with normal rat chow for a minimum period of 3 weeks. While the control rats were fed with the normal rat chow. They all had free access to water. Systolic, diastolic, and mean arterial blood pressures and the heart rates were measured in both non-pregnant and pregnant control rats and their diabetic counterparts. The results indicate that systolic blood pressures significantly increased progressively during pregnancy in fructose-fed rats as compared with the non-pregnant rats (P < 0.0001) while in the control rats, except for the 2nd trimester sub-group, which had a similar value with the non-pregnant sub-group, the systolic blood pressure (SBP) also increased steadily. When the diabetic group is compared with the control group, the SBP (in the 2nd trimester subgroups) was raised from 82.35 ± 20.62 mmHg in control rats to 112.48 ± 20.62 mmHg in the diabetic rats (P < 0.0001). Diastolic blood pressure (DBP) progressively increased significantly in the diabetic rats from 63.94 ± 3.59 mmHg in the non-pregnant sub-group to 91.95 ± 13.80 mmHg in the 3rd trimester sub-group of the pregnant rats (P < 0.0001). The DBP of the 2nd trimester sub-group of the diabetic rats was significantly raised from 61.88 ± 4.20 mmHg in the control rats to 89.60 ± 7.97 mmHg in the diabetic rats (P < 0.0001). In addition, the mean arterial blood pressure (MAP) was significantly raised in the 1st and 2nd trimesters of the diabetic rats from 70.61 ± 3.12 mmHg in the non-pregnant diabetic rats to 96.23 ± 3.10 mmHg and 97.13 ± 1.55 mmHg respectively, (P < 0.0001, P < 0.0001). There was a progressive increase in the heart rates, in both control and diabetic groups, from non-pregnant sub-groups to the 3 trimesters of the pregnant rats. The body weights of the 2 groups of rats increased significantly as pregnancy progressed. These results suggest that fructose-induced diabetes could cause the development of sustained hypertension during pregnancy via the insulin-resistance-hypertension-mena-link.

Keywords: Diabetes, pregnancy, blood pressure, and heart rates

Resume
La pression artérielle et le taux de change des petits vaisseaux cardiaques lors des grossesses ont été investiguées chez les rats de striege-Dawley (diabétiques) nourri à fructose. Un total de 48 rats femelles pubères ont été utilisés. Les rats expérimentaux ont été nourris avec 25% (w/v) du fructose milage aux rats normaux pendant une période informative de 3 semaines alors que les rats de contrôle étaient aux même rat le normal. F7 avaient tous accès à l'eau potable. La sys-

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Intraductive
Pregnancy has been described as a state of insulin resistance [1]. Insulin resistance (IR) is associated with and may be causal in gestational hypertension, but the relationship between IR and hypertension arising de novo in pregnancy is unclear [2, 3, and 4]. Hypertension in pregnancy has been shown to characteristically present in the third trimester when insulin resistance is greatest and obesity has been suggested to be a risk factor for hypertension in pregnancy [5, 6]. There were reports [7, 8] of increased risk of hypertension during pregnancy in pregestational diabetic woman [9]. Hypertension in pregnancy is associated with eclampsia [10]. In fact, hypertension is considered to be an independent risk factor for pre-eclampsia [11, 12]. In fact, hypertension is considered to be a risk factor for pre-eclampsia [11, 12].
Precise feeding has been shown to cause impairment of insulin binding and insulin-mediated glucose uptake [9] with a regulatory cascade involved in glucose intolerance leading to diabetes mellitus [10]. The experiments carried out in this study were designed to investigate the effect of carotene injection on blood pressure and heart rate in pregnant rats in pregnancy rate in rats. This is in order to elucidate the insulin resistance of hyperinsulinemia hypertension link and make useful resource notes that are aimed at presenting information.I focused on both medical and diabetic pregnancy.

Materials and methods
A total of 48 fertile female rats and 4 adult male Sprague-Dawley rats were used in this study. They were obtained from the laboratory animal center of the College of Medicine of the University of Lagos. Lagos. They weighed between 100-120g when obtained from the laboratory animal center. The females were divided into 2 naive groups of 24 rats each. These were the Control group and the Diabetic group. Each group was further subdivided into non-pregnant, 1st trimester, 2nd trimester and 3rd trimester subgroups of rats. In the departmental animal room, where the rats were kept, the temperature was between 28 and 72°F and lighting rhythm was I/8 hours of light and 12 hours of darkness. The control rats were fed with normal rat chow. The second group of rats was made diabetic [10] by breeding them with 25% (w/v) fructose mixture with normal rat chow for a minimum of 21 days. Diabetes was confirmed by measuring the fasting plasma glucose concentration in this group of rats and comparing it with that of the control group, as described in our previous report [10]. All animals had fine ascites to discoloring warts and had their weight recorded every working week.

Daily vaginal smears were performed to make sure the ovulatory cycle of the rats. To obtain the pregnant subgroup, male rats were introduced to the rats prior to the ovulation phase since this is the only phase the female rats are receptive to the male. After mating, pregnancy was confirmed on the first day of the next period of the vaginal smear of the female rats and this was regarded as Day 1 of pregnancy. All measurements were carried out (in both control pregnant and diabetic pregnant subgroups) in the 1st trimester (Day 6), 2nd trimester (Day 13) and 3rd trimester (Day 20) since the gestation period of a rat is 14 days. Each rat was weighed and anesthetized with ether. A cotton wool pad was soaked with ether and put inside a glass chamber. The selected rat was put inside this chamber and the lid was replaced. The rat was observed until it started blinking. It was then removed from the chamber and placed supine on a dissecting board for cannulation. Anesthesia was maintained by placing a funnel packed with cotton wool soaked in ether over the snout and mouth of the rat. After the internal artery was exposed by careful dissection, it was cannulated for the recording of the blood pressure [11]. A loop was placed distally and another proximally on the artery. The distal loop was firmly tied and a building clip was clamped around the artery at the centre. The proximal loop was moved next to the building clip. With a fine pair of pointed scissors, no incision was made on the artery near the distal loop. A cannula (Penrose 5/5F; 0.9 ml) (Cronin and 2000G/CH301) was filled with heparin-saline solution, injected into the lumen of the artery and pushed towards the heart. The building clip was then removed and the cannula was pulled up gently. Both femoral veins were then tied firmly over the artery with the cannula to place. The source of the cannulation was tested by a slight pull on the plunger of the attached syringe. Blood flowed into the cannula and this was flushed with the heparin-saline solution.

This cannula was then connected via a Statham strain gauge pressure transducer to a Chart 7D polygraph (Chart Instrument Ltd, Quay, ME) for measurement of blood pressure. Prior to recording, the transducer was calibrated by means of a mercury manometer. Plasma blood pressure was measured continuously. The heart rate was calculated by counting the number of blood pressure pulses per unit time, keeping the speed of guage to Brackette recording.

All results were processed as mean ± standard error of the mean. Statistical significance of performance was taken at 95% confidence level using the Student's t-2-quantile test.

Result
Blood pressure changes in control and diabetic non-pregnant and pregnant rats
In the control rats, body weights increased steadily and significantly from the non-pregnant weight of 178.3±12.7 gpm to 220±10.4±3.7 gm in the 3rd trimester of pregnancy. (P<0.001). The diabetic rats also increased in weight steadily through out pregnancy but in a greater extent than the control rats as shown in figure 1. 

![Figure 1: Weight changes in control and diabetic pregnant and non-pregnant rats](image-url)

** - 1st trimester subgroups, diabetic rats versus control rats (P<0.001)
** - The trimester subgroups, diabetic rats versus control rats (P<0.001)
** - Non-trimester fasting, diabetic rats versus control rats (P<0.001)

Blood pressure changes in the control and diabetic non-pregnant and pregnant rats
The systolic blood pressure of both the control and diabetic groups of rats is shown in figure 2. In the control group, the systolic blood pressure increased in the 1st trimester, did not remain at the pre-gestational level in the 2nd trimester and then increased again in the 3rd trimester. In the diabetic group, systolic blood pressure increased progressively with gestational period with the highest systolic blood pressure recorded in the 3rd trimester. Changes in the diastolic blood pressure are presented in figure 3. In the control group, the diastolic blood pressure followed a similar pattern to the systolic blood pressure. In the diabetic group, there was a significant rise (P<0.001) in the diastolic blood pressure in the non-pregnant subgroup from 63±14.9 mmHg to 93±13.2 mmHg in the 1st trimester subgroup. However, there was little change during pregnancy in the diabetic rats as shown in figure 3.
Heart rate changes in the control and diabetic pregnant and non-pregnant rats (See Figure 5)

The heart rate increases significantly from non-pregnant values and with each stage of pregnancy in both the control and diabetic rats. However, there was little or no change in the heart rate of the diabetic non-pregnant rat and 1st trimester subgroup when compared to their respective control subgroups. On the other hand, the heart rates of the diabetic 2nd and 3rd trimester subgroups were significantly higher than the control counterparts.

Fig. 5: Heart rate changes in control and diabetic pregnant and non-pregnant rats.

** Non-pregnant subgroup, diabetic versus control rat, P < 0.003
** 2nd trimester subgroup, diabetic versus control rat, P < 0.001
** 3rd trimester subgroup, diabetic versus control rat, P < 0.049

Discussion

Body weight changes in control and diabetic non-pregnant and pregnant rats

The body weight of the control rats correlated with the blood pressure in non-pregnant, 1st trimester and 3rd trimester subgroups. This is similar to the result obtained in humans by Solomon and his colleagues [2]. Increase in body weight was identified as a risk factor for the development of hypertension in pregnancy [3]. The weight-related increase in blood pressure could be due to systemic hemodynamics changes such as an increase in cardiac output [12], increase in heart rate [13].

The increase in weight observed in the diabetic rat, contradicts the view of Guyton [14] who associated diabetes with decrease in body weight resulting from increased wasting away of tissues caused by increased lipolysis and proteolysis. This discrepancy may be a result of the causative factor. While the diabetes described by Guyton is caused by insulin deficiency, our result shows that the cause of the diabetes induced by fructose feeding is not due to insulin deficiency but results from impaired insulin sensitivity [10]. Kolterman and colleagues [15] had associated impairment of insulin sensitivity with insulin resistance in body weight.

Blood pressure changes in the control and diabetic non-pregnant and pregnant rats

The result obtained from our control group show that the mean arterial blood pressure fell in the second trimester to non-pregnant levels, then increased to a very high level in the 3rd trimester. The high blood pressure obtained in the 3rd trimester is similar to that observed from pregnant women [5]. For the diabetic group, there was a steady rise in the mean arterial pressure from non-pregnant subgroup to the 3rd tri-
mater group. The high degree of insulin resistance in the 3rd trimester that was earlier reported [10] might be responsible for the rise in the mean arterial blood pressure observed in the present experiment [12]. It had been suggested [16] that the anti-antinuretic effect of insulin could be a propitious mechanism by which insulin resistance and hypertension may increase blood pressure [17].

Heart rate changes in the control and diabetic pregnant and non-pregnant rats

The results suggest that fructose feeding had little or no effect on heart rate in the control non-pregnant and 1st trimester sub-groups. However, effect of fructose feeding on the heart rate is enhanced in the 3rd trimester sub-group as compared with the control counterparts. This rise may be as a result of the increased stimulation of the sympathetic nervous system associated with fructose feeding and pregnancy [17].

Conclusion

Our results add to the growing evidence that insulin resistance is involved in the development of new-onset hypertension in pregnancy, particularly transient hypertension. We suggest that fructose-induced diabetes can cause the development of sustained hypertension during pregnancy via the insulin-resistance-hypertension link.

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