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

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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/w) fructose mixed with normal rat chow for minimum period of 3 weeks while the control rats were fed with the normal rat chow. They all had free access to drinking 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 sub-group was raised from 82.3±1.2 mmHg in control rats to 112.4±1.26 mmHg in the diabetic rats (P<0.0001). Diastolic blood pressure (DBP) progressively increased significantly in the diabetic rats from 63.9±3.5 mmHg in the non-pregnant sub-group to 91.9±1.8 mmHg in the 3rd trimester sub-group of the pregnant rats (P<0.0001). The DBP of the 2nd trimester subgroup of the diabetic rats was significantly raised from 61.8±4.2 mmHg in the control rats to 89.6±1.79 mmHg in the diabetic rats (P<0.0001). In addition, the mean arterial blood pressure (MAP) was significantly raised in the 1st and 2nd trimester of the diabetic rats from 70.6±3.12 mmHg in the non-pregnant diabetic rats to 96.3±3.5 mmHg and 97.13±1.15 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 pregnancy. 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-hyperinsulinemia-link.

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

Resume
La pression sanguine et le taux de changement des battements cardiaques lors de la grossesse ont été investigués chez les rats de stégue-dawley (diabétiques) nourris à du fructose. Un total de 48 rats femelles pubères ont été utilisés. Les rats expérimentaux ont été nourris avec 25% (w/w) de fructose dilué avec la ration normale de rat. Ils ont eu un accès libre à l'eau. Les systèmes pression sanguine systolique (PSS), diastolique (PSD) et la moyenne (PAM) ont été mesurés pendant une période d'au moins 3 semaines. Lorsque le groupe diabétique est comparé au groupe contrôle, la PSS (chez les groupes de 2nd trimestre) avait augmenté de 82.3±1.26 mm Hg chez les rats de contrôle à 112.4±1.26 mm Hg chez les rats diabétiques (P<0.0001). La pression sanguine diastolique (PSD) progressivement augmentait de façon significative chez les rats diabétiques de 63.9±3.5 mm Hg chez les rats non en gestation à 91.9±1.8 mm Hg chez les groupes de 3rd trimestre de la grossesse (P<0.0001). La pression sanguine moyenne (PAM) avait augmenté de 70.6±3.12 mm Hg chez les rats non en gestation à 96.3±3.5 mm Hg chez les rats de contrôle et à 97.13±1.15 mm Hg chez les rats diabétiques (P<0.0001). Il y avait une augmentation progressive en battements cardiaques, chez les deux groupes de rats diabétiques et dans le groupe contrôle, sans que cette augmentation ne soit constatée aux trimestres de grossesse. Les poids corporels des deux groupes de rats augmentèrent de façon significative, au fur et à mesure que la grossesse progressait. Ce résultat indique que l'administration d'un fructose, ouvrant la voie au long développement de l'hypertension sanguine lors de l'accouplement par le lien-insuline-résistance-hyperinsulinémie.

Intradosse
Pregnancy has been described as a state of high blood pressure [1], as well as increased risk of new-onset hypertension during pregnancy [5, 6]. Hypertension in pregnancy has been shown to influence cardiovascular and metabolic health throughout life. The relationship between essential hypertension and pregnancy has not been clearly established [2, 3]. It has been suggested that the relationship between insulin resistance and hypertension may be causal in essential hypertension, but the relationship between IR and hypertension arising de novo in pregnancy is unclear. Although the mechanisms of IR and hypertension arising de novo in pregnancy are not entirely clear, there is some evidence that IR may be involved in the pathogenesis of hypertension. If insulin-resistant women are at increased risk of hypertension during pregnancy, particularly the non-proteinuric type, and this in turn would support that hypothesis which states that insulin resistance may play a role in the pathogenesis of hypertension in pregnancy.

{snip}
Precise feeding has been shown to cause impairment of insulin binding and insulin stimulated glucose uptake [1] with a regulatory role in glucose intolerance leading to diabetes mellitus [10]. The experiments carried out in this study were designed to investigate the effect of chronic fructose feeding on blood pressure and heart rate response during pregnancy in rats. This is in order to elucidate the insulin resistance of hyperinsulinemia hypertension link and make useful inferences that may aid in preventing maternal-fetal health in both normal and diabetic pregnancy.

Materials and methods
A total of 45 pubertal female rats and 4 adult male Sprague-Dawley rats were used in this study. They were obtained from the laboratory animal centre of the College of Medicine of the University of Lagos, Idia. They weighed between 100-120gm when obtained from the laboratory animal centre. The females were divided into 2 mature 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 these rats were kept, the temperature was between 28 and 29°C. The room was maintained by placing a funnel packed with cotton wool soaked in ether over the nostrils and mouth of the rat. Anaesthesia was induced by placing a funnel packed with ether over the nostrils and mouth of the rat. Anaesthesia 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 access to drinking water and had their weight recorded every week.

Daily vaginal smears were performed to estimate the oestrous cycle of the rat. To obtain the pregnant subgroup, male rats were introduced to the rats prior to the oestrous phase since this is the only phase the female rats are receptive to the males. After mating, pregnancy was confirmed on the next day by the presence of sperms in the vaginal smears 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) in the pregnant period of a rat in 2 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 stopped blinking. It was then removed from the chamber and placed supine on a dissecting board for cannulation. Anaesthesia was maintained by placing a funnel packed with cotton wool soaked in ether over the nostrils and mouth of the rat.

After the femoral artery was exposed by careful dissection, it was cannulated for the recording of the blood pressure. Prior to recording, the monitor was calibrated by means of a mercury manometer. Phasic blood pressure was measured continuously. The heart rate was calculated by counting the number of blood pressure pulses per unit time, knowing the speed of the pulse train on the oscillographic record.

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The 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, fell to almost 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.

** Figure 2: Weight changes in control and diabetic pregnant and non-pregnant rats

The body weight changes in both of the control and diabetic pregnant and non-pregnant groups of rats is shown in figure 2. In the control group, the body weight increased steadily through out pregnancy but to a greater extent than the control rats as shown in figure 1.
Cardiovascular changes during pregnancy in diabetic rats

**Non Pregnant**
- 1st Trimester
- 2nd Trimester
- 3rd Trimester

**CONTROL**

**DIABETIC**

**Fig. 2:** Systolic blood pressure changes in control and diabetic pregnant and non-pregnant rats.

**CONTROL**

**DIABETIC**

**Fig. 3:** Diastolic blood pressure changes in control and diabetic pregnant and non-pregnant rats.

**Fig. 4:** Mean arterial blood pressure changes in control and diabetic pregnant and non-pregnant rats.

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

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]. An increase in body weight was identified as a risk factor for the development of hypertension in pregnancy [5]. 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 weight loss caused by increased lipolysis and proteolysis. This discrepancy may be as a result of the causative factor. While the diabetes described by Guyton is caused by insulin deficiency, our result showed that the cause of the diabetes induced by fructose feeding is not due to insulin deficiency but results from impaired insulin sensitivity [5]. Kolterman and colleagues [15] had associated impairment of insulin sensitivity with increases 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 obtained 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-

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 the 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 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.

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 weight loss caused by increased lipolysis and proteolysis. This discrepancy may be as a result of the causative factor. While the diabetes described by Guyton is caused by insulin deficiency, our result showed that the cause of the diabetes induced by fructose feeding is not due to insulin deficiency but results from impaired insulin sensitivity [5]. Kolterman and colleagues [15] had associated impairment of insulin sensitivity with increases in body weight.
mester group. The high degree of insulin resistance in the 3rd trimester that was earlier reported \[lo\] might be responsible for the rise in the mean arterial blood pressure observed in the present experiment \[I\]. It had been suggested \[16\] that the anti-natriuretic effect of insulin could be a proposed mechanism by which insulin resistance and hyperinsulinemia may increase blood pressure \[\square\].

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

The result suggests 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 counterpart. This rise may be as a result of the increased stimulation of the sympathetic nervous system associated with fructose feeding and pregnancy \[\square\].

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-hyperinsulinemia link.

Acknowledgements

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References