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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 pubertal 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-groups) was raised from 82.18±1.26mmHg in control rats to 112.48±1.26mmHg in the diabetic rats ($P$<0.0001). Diastolic blood pressure (DBP) progressively increased significantly in the diabetic rats from 63.94±3.95mmHg in the non-pregnant sub-group to 91.95±1.89mmHg 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 61.88± 4.20mmHg in the control rats to 89.60±1.79mmHg 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 70.61±3.12mmHg in the non-pregnant diabetic rats to 96.28±1.36mmHg and 97.13 ±1.15mmHg 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 sounguine et le taux de change des battements cardiaques lors des grossesses ont ete investiguer chez les rats de stragues-drawley (diabetiques) noums an forctose. Un total de 48 rats femelles pubertaires ont ete utilises. Les rats experimentaux ont ete noums arec 25% (W/w) du fructose milange onx rats normaux pendant urie periode mimimale de trais semarises alors que les rats de control etait noums avec le rat normal. Fls avaient tous acces a l'cau potable. La systole, diastole et la morynne de la pression arterielle du sung et le taux de batterments du coeur etaient mesures chez les rats non en gestation et les rats enceintes dwe controle et leurs partenaire diabetiques. Les resultant indiquent que la pression sanguine systolique a augmente significativement de facum progressive an cours disgressesses des rats nourris an fructose compares aux rats non enceintes ($P$ < 0.0001) alorgue chez les rats de controle a l'exception du sours groupe du second trimestre qui avait une valeur similaire avec le sours - groupe non en gestation, la pression sanguine systolique (PSS) avaient aussi augumentin refulicrement (progressivement). lorgue le groupe diabetique est conpare an groupe de controle, lu PSS (chez les soun groupes du 2nd trimestre) avait augumente de 82.18±1.26 mm Hg chez les rats de controle a 112.48±1.26 mm Hg chez les rat diabetiques ($P$ < 0.0001). La pression sanguine diastolique (PSD) progressivement augumentait de facon significative chez les rats diabetiques de 63.96±3.95 mm Hg dan le sour - groupe en non gestation a 91.95±1.89 mm Hg an sours groupe du zeme trimestre des rats enceintes ($P$ < 0.0001). La PSD du sours-groupe du ene trimestre des rat diabetiques avait augumente de 61.88±4.20 mm Hg chez les rats de controle in 89.60±1.79 mm Hg chez les rats diabetique (P < 0.0001) Em plus, la premises artenielle moyenne (PAM) avait augumente significativement chez les rats diabetiqued du jer et 2nd trimestre de 70.61±3.12 mm Hg chez les rats non diabetiques a 96.28±1.36 mm Hg et 97.13 ±1.15 mm Hg respectivement ($P$ < 0.0001) If y'avait une augumentation progressive en battements cardiaques, chez les daux groups (controle et diabetique), de sours groupe non en gestation aux trois trimestres de grossesse. le poids du corps des deux groupes de rats augumentait de facon nitoire au fur et a mesure que la gresses progressait. Ces resultats suggerent que l'alimentation an fructose pourrait causer le long developement de l'hypertension an cours des grossesses par le lien-insuline-resistance-hyperinsulinemic.

## Introduction

Pregnancy has been described as a state of insulin resistance [1]. Insulin resistance (IR) is associated with and may be causal in essential 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 gestational diabetic women. Solomon and his colleagues [2] suggested a strong association between relative glucose intolerance and increased risk of new-onset hypertension in pregnancy, particularly the non-proteinuric type and this indirectly supports that hypothesis which states that insulin resistance may play a role in the pathogenesis of hypertension in pregnancy.

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Fructose feeding has been shown to cause impairment of insulin binding and insulin mediated glucose uptake [9] with a resultant increase 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 responses during pregnancy in rats. This is in order to elucidate the insulin resistance or hyperinsulinemia-hypertension link and make useful contributions that are aimed at protecting maternal-fetal health in both normal and diabetic pregnancy.

**Materials and methods**

A total of 48 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, Idiaraba. They weighed between 100-120gm when obtained from the laboratory animal centre. The females were divided into 2 major 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 and lighting rhythm was 12hours 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 feeding them with 25% (w/w) fructose mixed 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 free access to drinking water and had their weights recorded every week.

Daily vaginal smears were performed to monitor the oestrous cycle of the rats. To obtain the pregnant subgroups, male rats were introduced to the rats just 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) since the gestation period of a rat is 21 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.

The femoral 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 bulldog clip was clamped round the artery at the centre. The proximal loop was moved near the bulldog clip. With a fine pair of pointed scissors, an incision was made on the artery near the distal loop. A cannula (Portex i/v 2FG0.d/0.63mm Greenleu 200/300/101, Kent, England) was filled with heparinised saline, inserted into the lumen of the artery and pushed towards the heart. The bulldog clip was then removed and the cannula was pushed slightly further. Both threads were then tied firmly over the artery with the cannula in place. The success 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 heparinised saline.

This cannula was then connected via a Statham strain gauge pressure transducer to a Grass 7D polygraph (Grass Instruments Ltd., Quincy, MG) for measurement of blood pressure. Prior to recording, the transducer 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 paper or from base recording.

All results are presented as mean ± standard error of the mean. Statistical test of significance was performed at 95% confidence level using the Student's unpaired t-test.

**Results**

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

In the control group, body weights increased steadily and significantly from the non-pregnant weight of 128.33±2.79gm to 220.00±4.65gm in the 3rd trimester of pregnancy ($P<0.0001$). The diabetic rats also increased in weight steadily through out pregnancy but to a greater extent than the control rats as shown in figure 1.

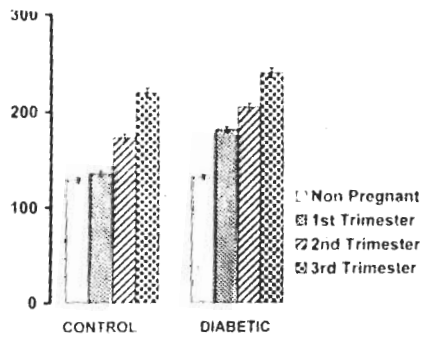


**Fig. 1: Weight changes in control and diabetic pregnant and non-pregnant rats**

*** - *3rd trimester subgroups, diabetic rats versus control rats,($P < 0.0001$)*

** - *2nd trimester subgroups, diabetic rats versus control rats, $P < 0.0001$*

* - *1st trimester subgroups, diabetic versus control rats, $P < 0.0001.0$*

*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.

Changes in the diastolic blood pressure are presented in figure 3. In the control group, the diastolic blood pressure followed a similar pattern as the systolic blood pressure. In the diabetic group, there was a significant rise ($P<0.0001$) in the diastolic blood pressure in the non-pregnant subgroup from 63.94±3.95mmHg to 90.15±1.37mmHg in the 1st trimester subgroup. However there was little change during pregnancy in the diabetic rats as shown in figure 3.

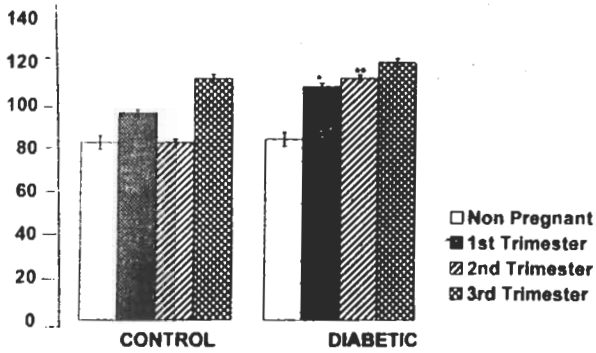


**Fig. 2**: Systolic blood pressure changes in control and diabetic pregnant and non-pregnant rats.
** - *2nd trimester subgroups, diabetic versus control rats, P < 0.0001*
* - *1st trimester subgroups, diabetic versus control rats, P <0.013.*

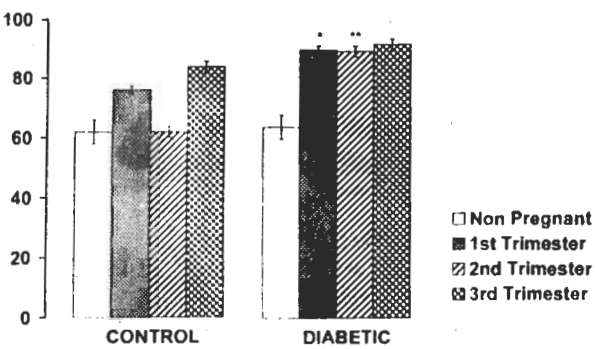


**Fig. 3**: Diastolic blood pressure changes in control and diabetic pregnant and non-pregnant rats
** - *2nd trimester subgroups, diabetic rats versus control rats, P < 0.0001*
* - *1st trimester subgroups, diabetic versus control rats, P < 0.016*

The mean arterial blood pressure (MAP) changes are shown in figure 4. The MAP increased significantly ($P < 0.0001$) from the non-pregnant state to 1st trimester of pregnancy in both groups of control and diabetic rats. However, in the control rats, the MAP of the 2nd trimester subgroup fell significantly to non-pregnant level ($P < 0.0024$) only to rise in the 3rd trimester. The high MAP in the diabetic rats during the 1st trimester of pregnancy was maintained in the 2nd trimester and further raised in the 3rd trimester.

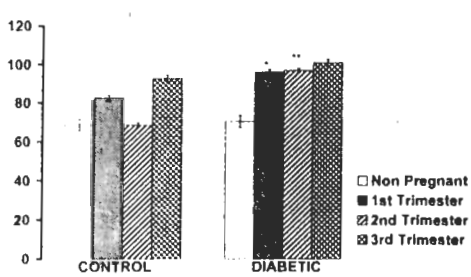


**Fig. 4**: Mean arterial blood pressure changes in control and diabetic pregnant and non-pregnant rats.
** - *2nd trimester subgroups, diabetic versus control rats, P < 0.0001.*
* - *1st trimester subgroups, diabetic versus control rats, P < 0.011.*

*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 with the respective control sub groups. On the other hand, the heart rates of the diabetic 2nd and 3rd trimester subgroups were significantly higher than the control counterparts.

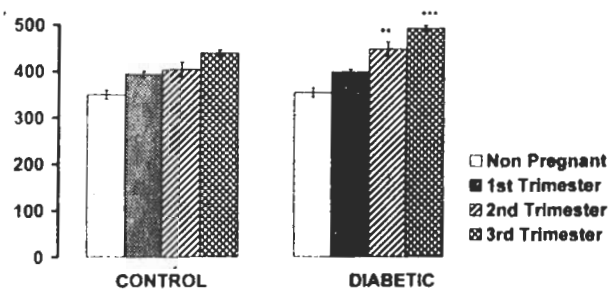


**Fig. 5**: Heart rate changes in control and diabetic pregnant and non-pregnant rats.
*** - *3rd trimester subgroups, diabetic rats versus control rats, P < 0.003*
** - *2nd trimester subgroups, diabetic versus control rats, P < 0.049.*

## 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 timester 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 [5]. The weight, related increase in blood pressure could be due to systemic haemodynamics changes such as an increase in cardiac output [12], increase in heart rate [13].

The increase in weight observed in the diabetic rats, 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 as 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 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-

mester 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 [1]. 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 [17].

*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 [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-hyperinsulinemia link.

## Acknowledgements

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## References

1. Ryan EA, O'sivillan MJ and Skyler JS. Insulin action during pregnancy: Studies with euglycemic insulin clamp technique. Diabetes 1985; 34: 380-389.
2. Solomon GC, Graves SW, Greene MF and Seeley EW. Glucose intolerance as a predictor of hypertension in pregnancy. Hypertension 1994; 23(pt 1): 717-721.
3. Ferrannini E, Buzzigoli G and Bonadonna R. Insulin resistance in essential hypertension. N. Eng. J. Med. 1987; 317: 350-357.
4. Beathy OC, Harper R, Sheridan B and Atkinson AB. Insulin resistance in the offspring of hypertensive parents. Br. Med. J. 1993; 307: 92-96.
5. Eskanzi B, Fenster L and Sydney S. A multivariate analysis of risk factors for pre-eclampsia. JAMA 1991; 266: 237-241.
6. Hall JE. Renal and cardiovascular mechanisms of hypertension in obesity. Hypertension 1994; 23: 381-394.
7. Goldman M, Kitzmiller JL, Abrams B, Cowan RM and Laros RK. Obstetric complication with GDM: Effects of maternal weight. Diabetes 1978; 40: 79-82.
8. Suhonen L and Terramo K. Hypertension and pre-eclampsia in women with gestational glucose intolerance. Acta. Obstet. Gynaecol. Scand. 1993; 72: 269-272.
9. Beck-Nielson H, Pederson O and Sorensen NS. Effect of diet on cellular insulin binding and insulin sensitivity in young healthy subjects. Diabetologia 1978; 15: 259-296.
10. Olatunji-Bello II and Nwachukwu D. Glucose tolerance during pregancy in fructose-fed rats. J. Med. Med. Sci. 1999; 1(2): in press
11. Sofola OA, Dina TA, Egbe PE and Owolabi OA. Dietary salt loading enhances baroreflex sensitivity in sprague-dawley rats. Nig. J. Physiol. Sci. 1991; 7 (2) : 95 - 99
12. Rocchini AP. Cardiovascular changes in obesity-induced hypertension. Hypertension 1992; 19(Suppl.1): I-56-I-60.
13. Hall JE. Hyperinsulinemia: a link between obesity and hypertension? Kidney Int. 1993; 43: 1402-1417.
14. Guyton AC. Textbook of Medical Physiology. 8th ed. Pp864-867.
15. Koltermann OG, Insel J and Olefsky JM. Mechanism of insulin resistance in human obesity. J. Clin. Invest. 1980; 65: 1272-1284.
16. Johnson MD, Zhang HY and Kotchen TA. Sucrose does not raise blood pressure in rats maintained on a low salt intake. Hypertension 1993; 21: 779-785.
17. Ferrari P and Weidmann P. Insulin, insulin sensitivity and hypertension. J. Hypertens. 1990; 8: 491-500.

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