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Full-length Research Article

Sodium Acetate Attenuates Fructose-Induced Mitochondrial Dysfunction and Cardiometabolic Disorders in Pregnant Wistar Rats

***Oyabambi A.O.[a], Agbaraolorunpo F.M.[b], Adekanye E.A.[c], Oyabambi A.A.[d] Olatunji L.A.[a]**

[a, d] *Department of Physiology, College of Health Sciences, University of Ilorin, Ilorin, Nigeria.*
[b] *Department of Physiology of College of Medicine, University of Lagos, Nigeria*
[c] *Department of Obstetrics and Gynaecology, Federal Teaching Hospital, Ido Ekiti, Ekiti State Nigeria*
[d] *Department of Industrial Chemistry, Faculty of Physical Sciences, University of Ilorin, Ilorin, Nigeria.*

Summary: Pregnancy is a known risk factor for cardiometabolic morbidity and mortality; therefore, consuming fructose-containing energy drinks during pregnancy may worsen these risks. However, the mechanisms through which acetate alleviates fructose-induced cardiometabolic disturbances in pregnancy remain unclear. This study aimed to investigate the role of sodium acetate in modulating fructose-induced cardiometabolic risks during pregnancy. Thirty-six female Wistar rats (120–150 g) were assigned to six groups (n = 6). Eighteen rats were made pregnant and eighteen remained non-pregnant. Each physiological category consisted of three groups: control (C), fructose (F), and fructose + acetate (FA). The FA group received 10% (w/v) fructose plus sodium acetate (200 mg/kg) in addition to distilled water. After three weeks of treatment, animals were anesthetized with ketamine (90 mg/kg) and xylazine (10 mg/kg). Blood samples and cardiac tissue homogenates were collected for biochemical analysis. Data were expressed as mean ± SEM, and statistical significance was accepted at $p < 0.05$. Compared with the control groups, fasting blood sugar (FBS), triglyceride–glucose (TyG) index, circulatory free fatty acids (FFA), uric acid (UA), malondialdehyde (MDA), and lactate dehydrogenase (LDH) levels were significantly elevated in fructose-treated pregnant and non-pregnant rats. Conversely, high-density lipoprotein cholesterol (HDL), pyruvate dehydrogenase (PDH), and cardiac aconitase activities were significantly reduced in both states compared with control, with reductions more pronounced in pregnant rats. Pregnancy further exacerbated fructose-induced alterations in UA, FFA, TG, HDL, and MDA. Sodium acetate supplementation effectively mitigated these cardiometabolic disturbances irrespective of gestational status. Sodium acetate restores mitochondrial oxidative capacity in pregnancy, making it a potential therapeutic agent for improving mitochondrial metabolic activity and preventing debilitating gestational cardiometabolic disorders.

Keywords: *fructose, pregnancy cardiometabolic changes, mitochondrial dysfunction, acetate, oxidative damage*

**Authors for correspondence: erumba@unical.edu.ng, Tel: +234-7065560843*

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INTRODUCTION

The prevalence of metabolic syndrome has increased in recent decades and this is not exclusive of such syndrome in pregnancy (Saklayen, 2018). Metabolic syndrome (MetS) is a cluster of risk factors, including obesity, insulin resistance, dyslipidemia, elevated blood pressure, and glucose intolerance, that increase the risk of cardiovascular disease and diabetes mellitus (Alberti *et al*., 2006). A high fructose diet has been identified to be culpable in the development of metabolic disorders, including hyperlipidemia, diabetes, non-alcoholic fatty liver disease, and obesity (Hannou *et al*., 2018; Taskinen *et al*., 2019). Sadly, the use of fructose, ranging from food additives to sweetened beverages, has increased unprecedentedly in recent years and has been suggested to contribute to the rising burden of metabolic disorders (Chan *et al*., 2021), including diabetes and cardiovascular disease (Annandale *et al*., 2021).

This is indeed worrisome as gestational diabetes mellitus (GDM) poses incredible health risks to both mothers and offspring. Gestational diabetes is characterized by impaired glucose metabolism during pregnancy, leading to adverse maternal and fetal outcomes (Sweeting *et al*., 2022). One of the key complications associated with GDM is mitochondrial dysfunction within cardiac tissues, which has been linked to oxidative stress and altered energy metabolism (Louwagie *et al*., 2021; Raji *et al*., 2021) . Given that mitochondria are the engine factory of the cells,

pertinent for the supply of energy and the defense of the body against oxidative assault (Chandel, 2021), their functional inhibition will not only compromise energy supply but also contribute to oxidative damage and cellular apoptosis in cardiac tissues (Dai *et al*., 2011; Shastry & Dunham-Snary, 2023). These changes will obviously portend a breeding ground for cardiotoxicity and cardiometabolic disorders (Shastry & Dunham-Snary, 2023).

Fructose-induced mitochondrial dysfunction (FIMD) can be defined as the disruption of mitochondrial bioenergetics and structural integrity triggered by chronic fructose consumption, characterized by impaired oxidative phosphorylation, excess production of reactive oxygen species (ROS), and reduced ATP generation. Mechanistically, FIMD contributes to cardiovascular disease by promoting oxidative stress, lipid accumulation, endothelial dysfunction, and myocardial apoptosis, all of which accelerate the development of cardiometabolic syndrome, hypertension, and atherosclerotic changes (Hu *et al*., 2020; Regnault *et al*., 2013; Yazıcı & Sezer, 2017)

During pregnancy, the metabolic demands on the heart increase substantially, necessitating efficient mitochondrial function to support cardiac adaptation and ensure optimal fetal development. As such, cardiac mitochondrial dysfunction during gestation poses significant health risks to both the mother and her offspring (Chan *et al*., 2021). In this regard, fructose, a common dietary component, implicated in metabolic disturbances, can potentially affect cardiovascular health adversely during pregnancy (Regnault *et al*., 2013), with both oxidative stress and mitochondrial dysfunction playing prominent roles in insulin resistance development (Yazıcı & Sezer, 2017).

Acetate, a short-chain fatty acid (SCFA), exists as the sodium salt of organic acids, namely sodium acetate, sodium lactate, and sodium citrate, in the synthetic form and has been found to have therapeutic properties in modulating metabolic pathways and improving mitochondrial function in various pathological conditions (Hu *et al*., 2020). Recent studies have suggested that acetate supplementation may mitigate fructose-induced metabolic disorders by enhancing mitochondrial function in non-pregnant models (Smith *et al*., 2022). For example, in a high-fat diet-induced obese rat model, acetate treatment ameliorated hepatic and adipose dysmetabolism by modulating obestatin and restored cardiac metabolic flexibility by reducing cardiac lipid accumulation and oxidative stress, and by suppressing histone deacetylase (HDAC) activity (Joseph *et al*., 2022). Similarly, in pregnant rat models, acetate supplementation during late gestation mitigated renal dysfunction induced by excess testosterone exposure in dams (Oyabambi *et al*., 2021), and maternal acetate in rats exposed to minocycline prevented hypertension in their male offspring, accompanied by increases in the SCFA receptor GPR41 in kidney and normalization of plasma acetic acid (Hsu *et al*., 2022) . However, while these and other studies provide strong evidence that acetate can ameliorate metabolic, renal, hepatic, and some aspects of cardiovascular dysfunction, there is a paucity of studies on its specific effects on gestational cardiac mitochondrial dysfunction. Although SCFAs, including acetate, are known to influence mitochondrial function in tissues such as liver and brown adipose tissue, and correlate with receptor expression (e.g. GPR41/43) and HDAC activity in the placenta in gestational diabetes (Hsu *et al*., 2022), the question remains whether acetate supplementation during pregnancy can protect cardiac tissue (particularly mitochondrial function) in the context of maternal metabolic stress (such as fructose feeding). Thus, this study is aimed at determining the likely effect of sodium acetate on fructose-induced gestational cardiac mitochondrial dysfunction and associated metabolic disorders in female Wistar rats.

MATERIALS AND METHOD

Animals: Thirty-six, six-week-old female Wistar rats weighing between 120-150g. They were obtained from the animal house of the College of Health Sciences, University of Ilorin (Ilorin, Nigeria). The rats were acclimatized for two-weeks and fed *ad libitum* with standard rat chow and had unlimited access to tap water before being randomly assigned to six groups. Rats were maintained in the animal house under standard environmental conditions and a 12-h dark/light cycle. This study followed the guidelines established by the National Institutes of Health for the Care and Use of Laboratory Animals. This study was approved by the Faculty of Basic Medical Sciences, University of Ilorin Ethical Review Committee, and the Institutional Review Board of the University of Ilorin, with protocol identification number UERC/ASN/2018/357 approved on 09/05/2018.

Experimental design: Eighteen female Wistar rats were mated overnight with male rats and made pregnant. Pregnancy was confirmed through the presence of a post-copulatory plug and vaginal smear. The rats are designated as (P)-pregnant. Both the pregnant and non-pregnant rats had control groups (NP and P) (n=6/group), ensuring statistical relevance. They were fed and treated with fructose, acetate and normal rat chow (Fig. 1).

Collection of blood sample: After 3 weeks of exposure to fructose and high fructose drink (Oyabambi *et al*., 2021), animals were anesthetized by ketamine (90mg/kg) and xylazine (10mg/kg). Blood was collected by cardiac puncture into heparinized tube and was centrifuged at 3000 rpm for 5 min at room temperature. Plasma was stored frozen until needed for biochemical assay.

Preparation of cardiac tissue homogenates: After dissection, the heart was excised, cleared of adhering connective tissues, blotted, and weighed. After weighing, 100 mg of tissue was carefully removed, homogenized in 5ml of phosphate-buffered solution (PBS) with a glass homogenizer, and centrifuged at 10,000 rpm for 10 min at 4 °C and the supernatant was collected and stored frozen until required for biochemical assays.

Biochemical assays

FBS and TyG index: Fasting blood sugar was done using a hand-held OneTouch Ultra glucometer strip (LifeScan Inc., Milpitas, CA 95035, U.S.A) after 12 hours of overnight fast. The TyG index was given as a product of fasting blood sugar (FBS) and triglyceride (TG) i.e TyG index = ln [Fasting triglyceride-(mg/dl) × fasting glucose (mg/dl)]/2 (Oyabambi *et al*., 2024)

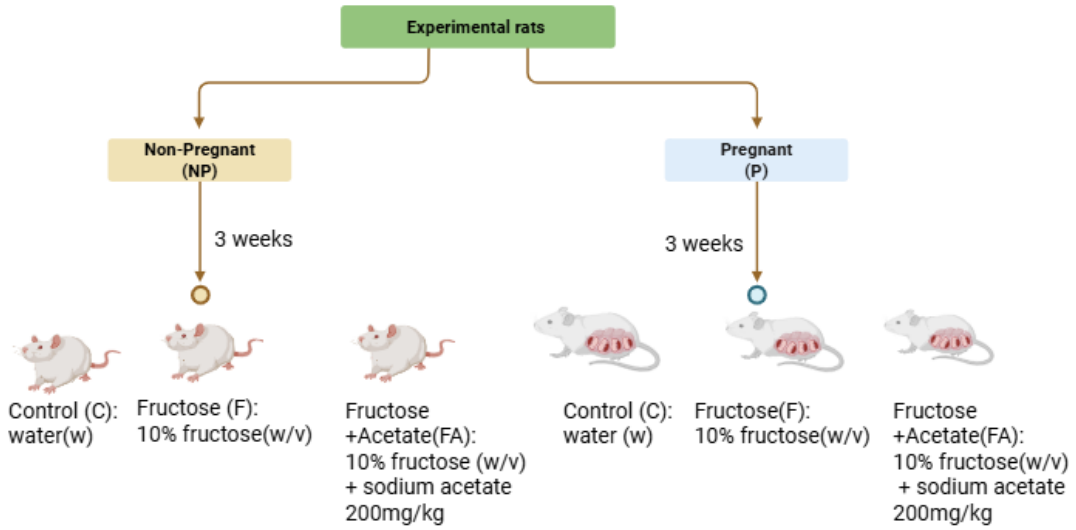

Figure 1:
Grouping of experimental rats

Serum Uric acid was measured in the laboratory by an automated technique based on the measurement of Jaffe chromogen and by the URICASE/POD (Boehringer Mannheim, Mannheim, Germany) method implemented in an autoanalyzer. The assay kit was obtained from Fortress Diagnostics (Co Atrim UK; product code: BXC0602). The contents of the kit were a buffer, an enzyme reagent, and a standard. After preparing the reagent, 20 µl of the standard was added to each sample, 800 µl of the buffer was added, the mixture was mixed and incubated for 1 minute, and the initial absorbance was read. Two hundred microlitres (200 µl) of the enzyme reagent was then added to each well containing the sample, and the absorbance was read after exactly 5 minutes. Uric acid concentration was determined as follows: [(Abs sample/Abs standard) * standard conc.].

Pyruvate dehydrogenase and lactase dehydrogenase were measured by standardized enzymatic colorimetric method using assay kit obtained from Fortress diagnostics (Antrim, United Kingdom).

Cardiac Aconitase: Aconitase was determined by automated enzymatic methods (kits from Boehringer Mannheim, 38242 Meylan, France) adapted to a Cobas Mira apparatus (Roche, Basel, Switzerland) with a sensitivity index of 10 mmol/L for the determinant.

Fasting triglyceride (TG), High-density lipoprotein-cholesterol (HDL) and **Plasma malonaldehyde (MDA)**, were measured by non-enzymatic colorimetric assay obtained from Oxford Biomedical Research Inc. (USA) and uric acid (UA) was determined using kits from Randox Laboratory Ltd. (Co. Antrim, UK).

Statistical Analysis
Data were presented as Mean ± SEM. Comparisons of data obtained from the rat groups were performed with two-way ANOVA and Tukey's Post Hoc test. Analysis and Data Visualisation were carried out in RStudio.

RESULTS

FBS response to fructose drink with and without sodium acetate treatment in non-pregnant and pregnant rats: FBS was significantly higher in the fructose-treated non-pregnant and pregnant rats compared to control rats. However, the combined treatment of the rats with fructose-water and acetate significantly lowered FBS compared to the fructose-alone rats in both the non-pregnant and pregnant rat groups (Figure 2).

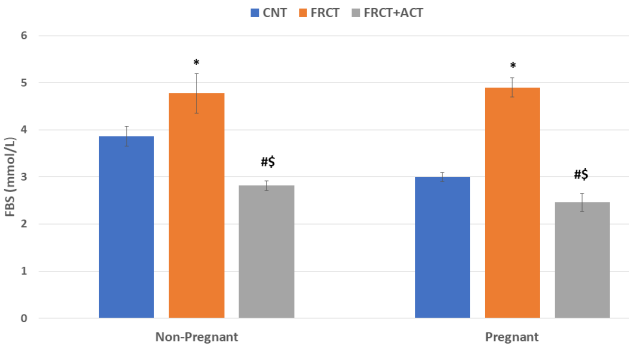

Figure 1:
FBS (mg/dl) in control (CNT), fructose (FRCT) & fructose + acetate (FRCT + ACT) in treated non-pregnant vs pregnant(P) rats; *$^{*}P<0.001$, $^{\$}P<0.001$ vs control , $^{\#}P < 0.001$ vs. fructose. No significant effect of pregnancy on FBS. FBS: Fasting blood sugar*

TG, FFA and HDL responses to fructose drink with and without acetate treatment in non-pregnant and pregnant rats respectively: TG (Figure 3) and FFA (Figure 4) were significantly elevated by fructose drink but were attenuated significantly by sodium acetate in similar rats exposed to fructose drinks, in both the non-pregnant and pregnant states. However, the elevated TG and FFA were both observed to be significantly more pronounced in the pregnant rats group compared to the non-pregnant rat group, and this did not in any way alter the effectiveness of acetate in restoring these levels to values comparable to those of control rats for FFA and TG.

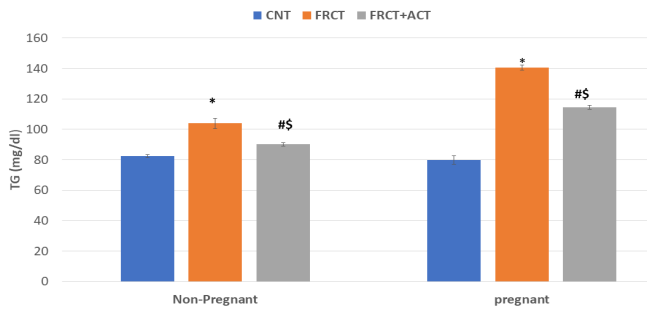

Figure 2:
TG (mg/dl) in control (CNT), fructose (FRCT) & fructose + acetate (FRCT + ACT) in treated non-pregnant vs pregnant(P) rats; *P<0.001, $P<0.001 vs control, #P<0.001 vs fructose. A significant effect of pregnancy was observed (p<0.001) on plasma TG. TG: Triglyceride

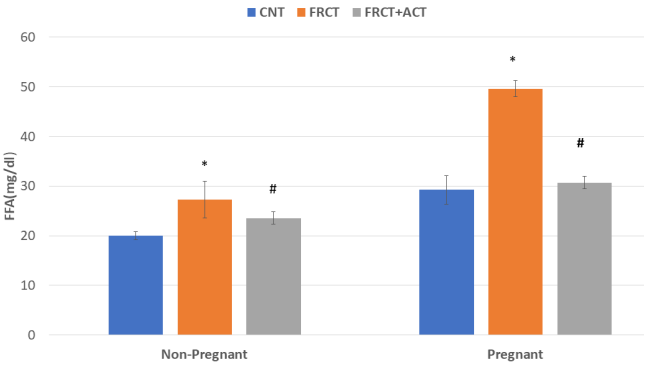

Figure 3:
FFA (mg/dl) in control (CNT), fructose (FRCT) & fructose + acetate (FRCT + ACT) in treated non-pregnant vs pregnant(P) rats; *P<0.001 vs control, #P<0.01 vs fructose. significant effect of pregnancy observed (p<0.001) on plasma FFA. FFA: Free fatty acid

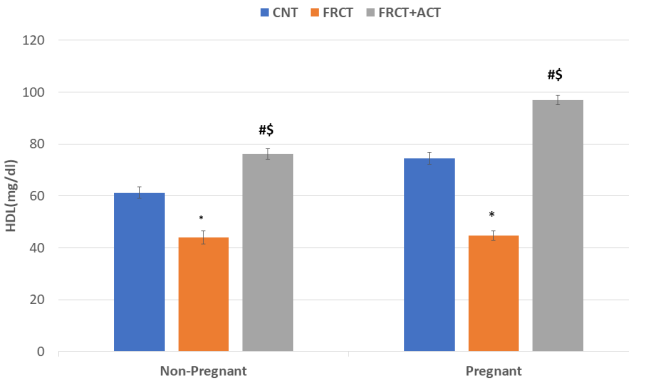

Figure 4:
HDL (mg/dl) in control (CNT), fructose (FRCT) & fructose + acetate (FRCT + ACT) in treated non-pregnant vs pregnant(P) rats. *P<0.001, $P<0.01 vs control, #P<0.01 vs fructose. significant effect of pregnancy observed (p<0.001) on plasma HDL. HDL: High-Density Lipoprotein

Meanwhile, HDL was significantly suppressed in both non-pregnant and pregnant fructose-drinking rats compared with control rats. However, these levels were significantly increased in the acetate-treated rats exposed to fructose water in both groups. Again, the effect of acetate in this regard was more pronounced in the pregnant state and the basal level of HDL was also higher for control rats that were pregnant compared to the non-pregnant rats (Figure 5).

UA and TyG index responses to fructose drink with and without acetate treatment in non-pregnant and pregnant rats respectively: Baseline uric acid (UA) was significantly higher in the control of pregnant rats compared to the control of non-pregnant rats, and this difference was remarkably accentuated by fructose-drink to twice its control level in the non-pregnant rats, and a third of its control level in the pregnant rats (Figure 6). However, acetate treatment was observed to significantly reverse this trend in rats exposed to fructose drink but treated with acetate in both rat groups. But most importantly, the attenuating effect of acetate on fructose-induced uric UA elevation was significant and comparable in non-pregnancy and pregnancy states.

Similarly, TyG index witnessed a slight but significant rise in fructose-treated rats exposed to fructose drink, with no disparities in the pattern of response in pregnant and non-pregnant rat groups. Again, treatment with acetate attenuated the effect of fructose on TyG index, restoring TyG index to levels comparable to those observed for control rats of non-pregnant and pregnant rat groups respectively (Figure 7).

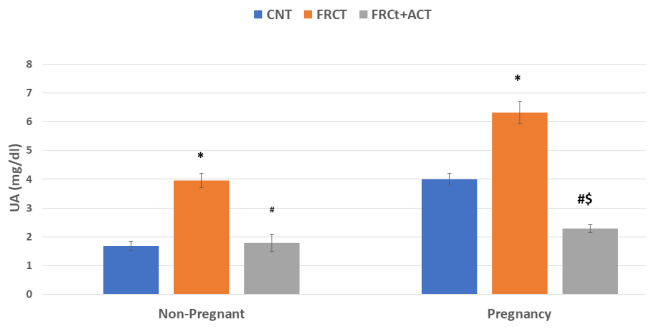

Figure 5:
UA (mg/dl in control (CNT), fructose (FRCT) & fructose + acetate (FRCT + ACT) in treated non-pregnant vs pregnant(P) rats; *P<0.001, $P<0.05 vs control, #P<0.001 vs fructose. Significant effect of pregnancy was observed (p<0.001) on plasma UA. UA:Uric acid

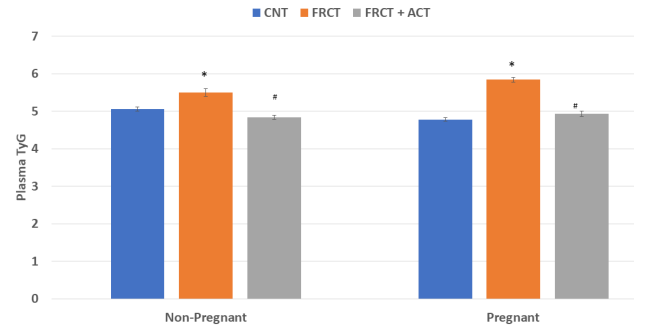

Figure 6:
TyG index in control (CNT), fructose (FRCT) & fructose + acetate (FRCT + ACT) in treated non-pregnant vs pregnant(P) rats. *P<0.001 vs control, #P<0.001 vs fructose. No significant effect of pregnancy was observed on circulatory TyG. TyG: Triglyceride-Glucose Index

PDH and LDH responses to fructose drink with and without acetate treatment in non-pregnant and pregnant rats, respectively: While PDH level (Figure 8) was observed to be lower compared to control in response to fructose drink, LDH (Figure 9) was elevated under a similar experimental condition in both non-pregnant and pregnant

rats, with no significant contribution of pregnancy to the levels of these observed changes. Meanwhile, acetate treatment altered these anticipated responses to fructose drinks, raising PDH levels higher while conversely suppressing LDH to a level comparable to twice the those seen in the fructose-drinking non-pregnant and pregnant rats. Again, the modulating effect of acetate on fructose-induced change in circulatory PDH and LDH was independent of pregnancy.

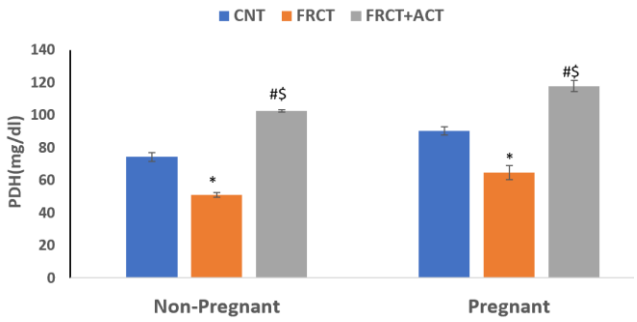

Figure 7:
PDH (mg/dl in *control (CNT),* fructose (FRCT) *&* fructose + acetate (FRCT + ACT) *in* treated non-pregnant vs pregnant(P) rats. *P<0.001, $P<0.001 vs control ,#P<0.001 vs fructose. No significant effect of pregnancy. PDH: Pyruvate Dehydrogenase

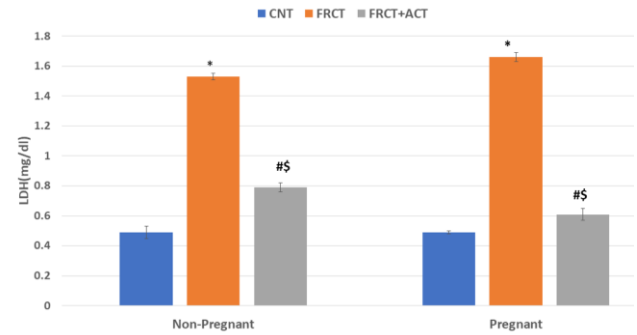

Figure 8:
LDH (mg/dl) in *control (CNT),* fructose (FRCT) *&* fructose + acetate (FRCT + ACT) *in* treated non-pregnant vs pregnant(P) rats. *P<0.001 , $P<0.001, $P<0.05 vs control, #P<0.001 vs fructose . No significant effect of pregnancy. LDH: Lactate Dehydrogenase

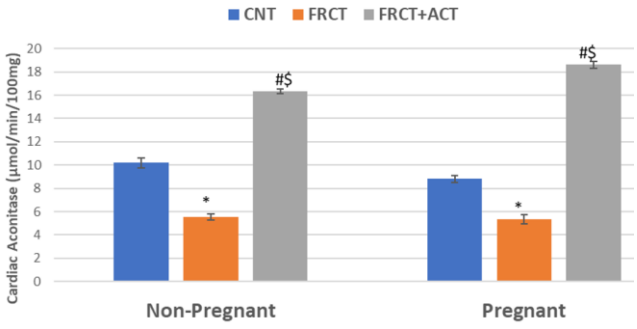

Figure 9:
Cardiac aconitase (umol/min/100mg) in control (CNT), fructose (FRCT) & fructose + acetate (FRCT + ACT) in treated non-pregnant vs pregnant(P) rats; *P<0.001, $P<0.001 vs control (C), #P<0.001 vs fructose. No significant effect of pregnancy.

Cardiac aconitase and MDA responses to fructose drink with and without acetate treatment in non-pregnant and pregnant rats, respectively: Cardiac aconitase (Figure 10) was observed to be significantly lower to almost half the control levels in response to fructose drink in a way similar to PDH response to fructose drink in non-pregnant and pregnant rats, and this effect was not moderated by pregnancy. However, acetate treatment under these conditions significantly increased cardiac aconitase levels to over twice those seen in the fructose-induced cardiac aconitase suppression, and further above the control levels. In contrast, fructose drinking elevated circulating MDA (Figure 11), with about twofold and threefold increases in non-pregnant and pregnant rats, respectively. Again, this fructose-induced change in circulatory MDA was mitigated by a reversal to nearly half of the fructose-induced elevation, and this was similar in pregnant and non-pregnant rats. However, acetate could not return MDA to a level comparable to the control levels, irrespective of the pregnancy status.

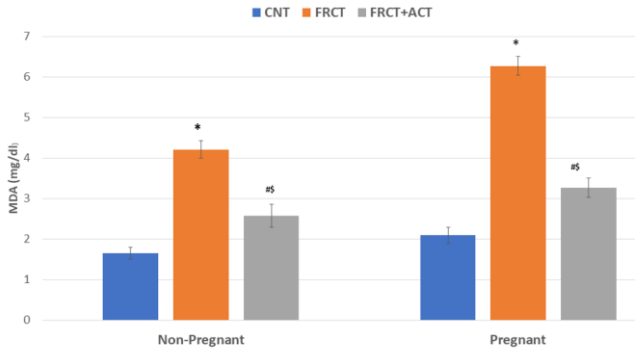

Figure 10:
MDA (mgl/dl) in control (CNT), fructose (FRCT) & fructose+ acetate (FRCT + ACT) in treated non-pregnant vs pregnant(P) rats; *P<0.001, $P<0.001 vs control, #P<0.001 vs fructose. significant effect of pregnancy observed (p<0.001) on plasma MDA. MDA: Malondialdehyde

DISCUSSION

Pregnancy is associated with cardiometabolic changes that plausibly affect both the mother and the fetus (Ramlakhan *et al*., 2020). Our study revealed that fructose intake in pregnant rats resulted in mitochondrial dysfunction, lipid abnormalities, impaired insulin signaling, oxidative stress, and reduced cardiac energy production—effects that were prevented by sodium acetate supplementation. This observation is particularly relevant given that fructose-containing beverages, including many trending energy drinks, are increasingly popular among urban residents and are readily accessible options for pregnant women seeking to meet the heightened energy demands of pregnancy (Haddad-Tóvolli & Claret, 2023)

As observed in the present study, fructose intake significantly increased fasting blood glucose in both pregnant and non-pregnant rats; however, this effect was mitigated in rats that received sodium acetate supplementation alongside the fructose drink. Notably, the impact of fructose on fasting blood glucose was comparable in both physiological states, underscoring that the effect is independent of pregnancy and can occur in the absence of gestation. Consistent with our findings, Tappy and Lê (2010)reported that fructose consumption induces metabolic disturbances, including elevated fasting glucose, irrespective of reproductive status, while Softic *et al*. (2016)

further demonstrated that fructose promotes features of metabolic syndrome through mechanisms unrelated to pregnancy.

Elevated fasting blood glucose (FBS) is a hallmark of impaired glucose uptake by peripheral tissues, often resulting from resistance to insulin signaling. Excessive consumption of high-calorie foods or refined sugars—leading to increased fat deposition, reduced cholesterol clearance by HDL, and elevated circulating FFAs—is a known precursor to impaired cellular glucose uptake. Pregnancy itself is characterized by reduced glucose uptake, largely driven by disruptions in lipid metabolism mediated by human chorionic somatomammotropin (HCS) (Haddad-Tóvolli & Claret, 2023; Hadden & McLaughlin, 2009). In our study, fructose intake markedly elevated FFAs and triglycerides (TGs) in both non-pregnant and pregnant rats, with the effect being more pronounced during pregnancy. Conversely, fructose consumption significantly reduced HDL levels in both physiological states, with pregnancy exerting no modifying influence on this response.

Interestingly, rats that received sodium acetate supplementation along with the fructose drink maintained significantly lower FFA and TG levels compared with rats given fructose alone, alongside a markedly increased HDL concentration. The acetate-mediated modulation of FFA and HDL was even more pronounced during pregnancy, providing clear evidence of its potential nutritional and therapeutic value in addressing metabolic disturbances in gestation. This finding aligns with the report by Oyabambi *et al*. (2021),who demonstrated that sodium acetate ameliorated systemic and renal oxidative stress in high-fructose, insulin-resistant pregnant Wistar rats—further reinforcing acetate's protective role in pregnancy-associated dyslipidemia and cardiometabolic dysfunction.Therefore, it is reasonable to suggest that excessive caloric intake from fructose promotes dyslipidemic changes in pregnancy, characterized by elevated FFA and TG and a reciprocal reduction in HDL. These alterations serve as early harbingers of impaired glucose uptake and disrupted insulin signaling. Encouragingly, acetate supplementation appears to act as a protective modulator, showing promise in mitigating gestational diabetes associated with high-calorie diets.

Insulin resistance driven by increased adiposity and dyslipidemia disrupts energy balance and promotes purine breakdown, resulting in elevated uric acid levels (Lu *et al*., 2023). A fructose-rich diet exacerbates this process by inducing metabolic syndrome, obesity, and gout through accelerated purine turnover and uric acid generation (Russo *et al*., 2021). Elevated uric acid levels during pregnancy are recognized cardiometabolic risk factors requiring close monitoring (Riis *et al*., 2022), as they promote inflammatory responses and oxidative stress-mediated tissue injury (Glantzounis *et al*., 2005; M. Zhang *et al*., 2023).In the present study, baseline uric acid levels were significantly higher in pregnant rats than in non-pregnant rats. Exposure to fructose drinks led to a significant rise in uric acid levels in both groups, with pregnancy further exacerbating this elevation. However, acetate supplementation under the same fructose-rich conditions significantly prevented these increases, restoring uric acid levels to values comparable to controls. This observation is consistent with findings by Hsu *et al*. (2022), who reported that maternal acetate supplementation reversed adverse cardiometabolic programming, including hypertension, in offspring. Their work suggests that acetate not only regulates maternal glucose-lipid homeostasis but may also confer long-term cardiovascular protection.

Insulin resistance, driven by increased adiposity and dyslipidemia, disrupts energy balance and promotes purine breakdown, resulting in elevated uric acid levels. A fructose-rich diet exacerbates this process by inducing metabolic syndrome, obesity, and gout through accelerated purine turnover and uric acid generation. Elevated uric acid level during pregnancy is considered as cardiometabolic risk that requires monitoring, as they promote inflammatory responses and oxidative stress injuries. Most importantly in this current study, baseline uric acid levels were significantly higher in pregnant rats compared to non-pregnant rats. Exposure to fructose drinks led to a significant surge in uric acid levels in both non-pregnant and pregnant rats, with a significantly exacerbated level engendered by pregnancy. However, supplementation with acetate under the same fructose drink conditions resulted in the significant blockade of these rises to levels comparable to controls. This observation is consistent with, who showed that maternal acetate supplementation reversed adverse cardiometabolic programming, including hypertension, in offspring, suggesting that acetate not only regulates maternal glucose–lipid balance but also has long-term protective implications for cardiovascular health.

Another crucial marker of insulin resistance significantly altered by fructose drink in this study was the Triglyceride-Glucose index (TyG). TyG index was significantly higher in rats exposed to fructose drink, regardless of their gestational status, but remained unchanged with acetate supplementation under the same conditions. This finding reinforces the previously reported observation of disrupted insulin signaling caused by fructose-induced dyslipidemia in this study. Insulin resistance, characterized by increased TyG index, hyperuricemia, and dyslipidemia, creates a fertile ground for cardiometabolic complications, including pregnancy-induced hypertension, preeclampsia and peripartum cardiomyopathy. Again, given that acetate supplementation mitigated these drivers of insulin resistance, it is not impossible that it may address similar cardiometabolic issues in pregnancy. found that acetate improved β-cell metabolism and mitochondrial respiration under oxidative stress conditions, providing a mechanistic explanation for the improved insulin signaling and glucose homeostasis observed in our study. The pharmacological potential of acetate in this regard is supported by an experimental study showing that acetate supplementation prevented minocycline-induced hypertension in pregnancy.

Another crucial marker of insulin resistance significantly altered by fructose consumption in this study was the triglyceride–glucose (TyG) index (Guo *et al*., 2024). The TyG index was markedly elevated in rats exposed to fructose, irrespective of gestational status, but remained unchanged in those that received acetate supplementation under the same conditions. This observation reinforces earlier findings in this study highlighting disrupted insulin signaling driven by fructose-induced dyslipidemia. Insulin resistance, reflected by an increased TyG index, hyperuricemia (Han *et al*., 2023), and dyslipidemia, creates

a fertile ground for cardiometabolic complications, including pregnancy-induced hypertension (Mustaphi *et al*., 1996), preeclampsia (Colmenares-Mejia *et al*., 2023; Lüscher *et al*., 2022) and peripartum cardiomyopathy (Sagy *et al*., 2017). Given that acetate supplementation mitigated these key drivers of insulin resistance, it is plausible that acetate may also address related cardiometabolic disorders in pregnancy. This proposition is supported by findings from Hu *et al*. (2020), who reported that acetate improved β-cell metabolism and mitochondrial respiration under oxidative stress, offering a mechanistic basis for the improved insulin signaling and glucose homeostasis observed in our study. The pharmacological potential of acetate is further reinforced by evidence showing that acetate supplementation prevented minocycline-induced hypertension in pregnancy (Hsu *et al*., 2022)

Furthermore, this study provides evidence of mitochondrial energy system disruption, as indicated by fructose-induced suppression of circulatory pyruvate dehydrogenase (PDH) and cardiac aconitase, accompanied by reciprocal elevations in circulatory lactate dehydrogenase (LDH) and malondialdehyde (MDA) in rats exposed to fructose water. This mitochondrial oxidative dysfunction appeared largely independent of pregnancy status, except for MDA, which was further accentuated by gestation. As observed, acetate supplementation effectively prevented these alterations under the same experimental conditions.

Taken together, the combined suppression of PDH and cardiac aconitase, alongside the elevation of LDH and MDA, indicates impaired energy production and heightened oxidative stress (Hurd *et al*., 2012), ultimately predisposing fructose-exposed rats to cellular damage and apoptosis. Such disruption of mitochondrial energy metabolism further triggers dysregulation of lipid and carbohydrate pathways, thereby creating a vicious cycle that promotes insulin resistance and dyslipidemia. This mechanism is biologically plausible given that PDH is a key enzyme responsible for converting pyruvate into acetyl-CoA, the entry substrate for the citric acid cycle (CAC). Suppression of PDH activity limits this conversion, diverting pyruvate toward lactate production via increased LDH activity.

The resulting reduction in acetyl-CoA availability compromises the CAC, leading to diminished ATP production and increased oxidative stress. Similarly, aconitase catalyzes the conversion of citrate to isocitrate; its inhibition further impairs CAC progression and exacerbates oxidative injury. These observations point to a potential pathway through which acetate mitigates fructose-induced cardiometabolic damage. This interpretation aligns with previous studies implicating mitochondrial dysfunction in hypertension (Dikalov & Ungvari, 2013), preeclampsia (Jahan *et al*., 2023), gestational diabetes (Sobrevia *et al*., 2020), and acute fatty liver disease (Ramanathan & Ibdah, 2022), where mitochondrial bioenergetic failure and oxidative stress are central contributors (Jahan *et al*., 2023; Marín *et al*., 2020). Additionally, mitochondrial impairment in adipose tissue has been shown to drive metabolic imbalance, thereby acting as a catalyst for cardiovascular disease (AlZaim *et al*., 2022).

Our study demonstrates that sodium acetate—a short-chain fatty acid naturally present in fruits, vegetables, and fermented foods—offers significant protection against cardiometabolic risk in pregnant mothers by enhancing mitochondrial bioenergetics, with potential benefits for both maternal and fetal health. Specifically, acetate's ability to regulate blood glucose levels may support improved insulin signalling, glucose utilisation, and mitochondrial integrity (Hu *et al*., 2020; Joseph *et al*., 2022; Oyabambi *et al*., 2021). These actions contribute to better lipid metabolism, lower plasma uric acid, and an improved TyG index. Collectively, these benefits suggest that acetate may help preserve cardiovascular health by counteracting the mitochondrial dysfunction and metabolic disturbances induced by high-fructose diets or beverages during pregnancy.

Overall, fructose consumption induced comparable metabolic disturbances and mitochondrial dysfunctions in both non-pregnant and pregnant rats, with the exception of more severe dyslipidemia, hyperuricemia, and oxidative cellular injury observed in the pregnant group. However, acetate supplementation effectively mitigated these harmful changes at both cellular and mitochondrial levels in pregnant and non-pregnant rats alike. These findings suggest that sodium acetate supplementation may serve as a promising intervention for preventing or attenuating fructose-induced mitochondrial oxidative dysfunction and bioenergetic impairment. Furthermore, this study highlights the potential role of acetate in preventing or managing debilitating cardiometabolic disorders linked to mitochondrial dysfunction—including pregnancy-induced hypertension, preeclampsia, and gestational diabetes

Authors contribution

AOO, EAA, and AAO conceived and designed the research. AOO, EAA and AAO and conducted the experiments. AOO, FMA and AAO contributed to the new reagents and analytical kits. AOO, FMA, EAA, LAO, and AAO analyzed and interpreted the data. AOO, FMA, EAA, LAO, and drafted the manuscript. All authors read and approved the manuscript, and all data were generated in-house and that no paper mill was used.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Availability of data and materials

All authors agreed that the data generated or analysed during this study are included in this published article as its supplementary information files

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