ORIGINAL RESEARCH

Codeine-Containing Cough Syrup Produces Adverse Effects on Foetal Development in Sprague-Dawley Rats

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ABSTRACT

Background: Codeine-containing cough syrups (CCS) are consumed by people from all walks of life and almost all ages.
Objectives: The study investigated the effects of CCS on pregnancy outcomes using Sprague-Dawley rats.
Method: Twenty-five rats weighing 170 g averagely were divided into five groups: Control group received water only; Expectorant groups received doses 30 and 60 mg/kg body weight (bw) respectively (positive control); while Codeine-containing cough syrup groups (CCS) received 30 and 60 mg/kg doses /bw respectively. Cough syrups were administered to pregnant rats from gestation day 1-20 and sacrificed at day 20. Blood sample, foetus, uterus and placenta was collected for analysis.
Results: Results showed that body and uterine weights were not significantly different from control in all treatment groups. Significant reductions ($p<0.05$) were recorded in placental weight, foetal weight and crown-rump lengths except in the 60 mg/kg bw CCS group with concomitant increase in umbilical cord lengths compared to control except in the 30 mg/kg bw expectorant group. Reduced Glutathione (GSH) reduced significantly in all the treatment groups. Maternal hormonal assay showed no significant changes except for progesterone and luteinizing hormone, with significant differences in the 30 mg/kg bw CCS and expectorant groups. Histopathological findings showed presence of inflammation, necrosis, oedema, and fibrosis, with increased vascular congestions in both uterine tissue and chorion frondosum of the placenta.
Conclusion: CCS produces oxidative stress in the placenta which reaches the developing foetus thereby increasing foetal susceptibility to growth restrictions and mortality, even in the absence of obvious phenotypic malformations.

Keywords: Codeine cough syrup; Expectorant; hormonal assay; Histology, foetal parameters

INTRODUCTION

A variety of prescription drugs and even over the counter (OTC) medications can be abused. These may range from drugs used to manage simple ailments such as cold and cough, to alcohol, and other psychoactive street drugs. Prescription drugs are termed 'abused' whenever used in a manner that contradicts the physician's instructions, or when used by a third party. Such illicit

actions could lead to psychiatric distortions which may impede normal behaviour[1, 2].
Opioid analgesics are prescribed to patients for treatment of symptoms such as pain, cough, and diarrhoea, and are also widely available and accessible to the public OTC[1]. Prenatal exposure to opioid-containing medications is mostly associated with sought-after alleviation from some health challenging condition(s), which may occur during pregnancy. According to reports by the Centers for Disease Control and Prevention (CDC), there exists a higher rate of occurrence and strong correlation between the use of non-steroidal anti-inflammatory drugs (for the treatment of conditions like arthritis) and/or opioid medications with birth defects[3]. Now, the mechanism by which such developmental manifestations occur still remains uncertain and calls for more research. This is especially necessary to ascertain the extent of misuse of opioid analgesic medications within the global context.

Codeine, which is also called 3-methylmorphine, is a weak opiate popularly used to treat mild to moderate pain[4], as cough medicine and for diarrhea[5,6]. Codeine is used in various pharmaceuticals including analgesics, sedatives, hypnotics, anti-peristaltic and antitussive agents[7]. It is widely prescribed in clinical practice, with OTC preparations of codeine, freely available for consumption typically, as a component of remedies for common cold/cough[8]. According to the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria, there is a high tendency for abuse and addiction to codeine-containing cough syrups (CCS) particularly amongst the youths. This does not dispute its effectiveness in the management of certain cough but emphasizes its high potential to cause serious adverse reactions to the user[9]. The common side effects associated with the use of codeine-containing substances include nausea, constipation, fatigue, cognitive impairment, dizziness, pancreatitis[10]. Additionally, there could be cases of urinary retention, hyperactivity, abdominal cramps, respiratory distress[11], euphoria, diminished libido, apathy, skin allergy (swelling, itching, rashes), increased risk of congenital malformations and post-partum hemorrhaging[12,13]. The elevation of free radicals above the biologically generated antioxidants is a major determinant of oxidative stress. It is a key contributing factor to most pregnancy-associated disorders like preeclampsia and foetal growth restriction. Unfortunately, such adverse effects may continue to influence the overall wellbeing of the neonate even after birth[14]. Oxidative stress also mediates the extent of DNA damage in reproductive cells and prenatal psychological stress[15,16].
Generally, people abuse CCS and other opioid-containing substances either in search of therapeutic or sedative influences. The consequence of any such non-medical usage poses a threat to both economic and social stability[17]. This study aims to give more insights into the possible teratogenic effect of CCS on developing foetus; through expression of phenotypic malformations and measurement of growth parameters. It further attempts to illustrate the impact of codeine in regulating hormonal levels and oxidative stress markers during pregnancy.

MATERIALS AND METHODS

Drug

Emzolyn® cough syrups containing codeine and expectorants were purchased over-the-counter at a registered pharmacy in Lagos, Nigeria.

Drug composition

The active ingredients contained in the 100 ml CCS include diphenhydramine hydrochloride BP 14 mg, sodium citrate 57 mg, codeine phosphate BP 10.9 mg, menthol BP 1.1 mg. Excluding the codeine component, expectorant additionally contained ammonium chloride BP 135 mg.

Experimental Animals

Twenty-five Sprague-Dawley rats, weighing between 135-180 g were used for the experiment. The animals were obtained from Adetade Farm Limited, Badagry, Lagos, Nigeria. They were kept in wire mesh plastic cages in the Animal House of the Department of Anatomy under standard atmospheric condition with 12-hour light and 12-hour dark cycle. They were allowed to acclimatize for three weeks before the start of the experiment. They were allowed unrestricted access to water and rat chow. All procedures were carried out following the National Academy of Sciences' Guide for Care and Use of Laboratory Animals[18].

Mating and determination of pregnancy

Vaginal smears were taken to determine females in the proestrus phase. They were introduced to male rats overnight for mating. The next morning, the presence of sperm cells in the vaginal smear indicated successful mating and was recorded as gestation day 0.

Experimental Design

Twenty-five pregnant rats were randomly divided into five groups with five animals in each group. First group received only water, served as control. Second and third groups received 30 and 60 mg/kg body weight doses of expectorant respectively (expectorant groups designated as positive controls). Fourth and fifth groups received 30 and 60 mg/kg body weight doses of codeine-containing cough syrup respectively. Doses were determined according to the British National Formulary (BNF). The administration was per oral for 20 days using a gavage. Animals were sacrificed on the 20th day of gestation by cervical dislocation and blood was taken through cardiac puncture for hormonal assay. A vertical laparoscopy was performed, the uterine horns were excised, and the foetuses removed. The foetuses were examined for any external malformations, and parameters such as foetal weight, placental weight, crown-rump lengths and umbilical cord lengths were measured. Placental tissues and the right uterine horn were fixed in 10% formol saline for histology while the left uterine horn was stored at -20ºC for biochemical analysis.

Tissue Processing

The uterine and placental tissues were immersed in 10% formal saline for 24 hours for fixation. After fixation, the tissues were allowed to pass through ascending grades of alcohol for the purpose of dehydration. Thereafter, the tissues were passed through two changes of xylene for clearing and then passed through infiltration/impregnation where they were embedded in paraffin wax. Sections were made at 5 micrometres (ribbon section) and slides were stained with Haematoxylin and Eosin. Photomicrographs were obtained using DM 750 Leica digital photomicroscope.

Biochemical Analysis

Homogenizing Sample

The uterine tissues were washed in an ice-cold 1.15% KCl solution, blotted, and weighed. Tissue homogenization was done using 0.1M phosphate buffer (pH 7.2), each organ was placed into a mortar, followed by the addition of laboratory sand (acid-washed sand). This mixture was then blended in the mortar using a pestle. The resulting homogenate was centrifuged at 2500 rpm speed for 15 mins and thereafter the supernatant was decanted and analyzed for malondialdehyde (MDA) and antioxidant activities of Superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH).

SOD activity was determined according to the method described by Sun and Zigman[19]. MDA, the end product of lipid peroxidation was analyzed using procedures by Buege and Aust[20]. CAT and GSH activities were determined using the method described by Rukkumani and colleagues[21].

Hormonal Assays

The Estrogen enzyme immune-assay (E2 E1A) was based on the principle of competitive binding between E2 in the test

specimen and E2-HRP conjugate for a constant amount of rabbit anti-Estradiol. Test for serum progesterone level was done based on competition between the hormone conjugate and the progesterone in the sample for a limited number of binding sites on the antibody-coated plate.

Statistical Analysis

All experimental data were analyzed using one-way analysis of variance (ANOVA) and expressed as mean ± SEM. Bonferroni's multiple comparison test ranges were used to compare the group means obtained after each treatment with control measurements. A *P*-value of less than 0.05 (<0.05) was considered statistically significant.

Ethical considerations

The experimental procedures were conducted in accordance with the NIH guidelines for the care and use of laboratory animals in line with guidelines of the Health Research and Ethical Committee of the College of Medicine, University of Lagos.

RESULTS

Effect on body and uterine weights

Body weight differences were not significantly higher in the treatment groups (36.72 ± 7.10) compared to the control (27.63 ± 3.08). There was no obvious change in uterine weights across all groups (Table 1).

Table 1: Effects of cough syrups on body weight differences and uterine weights in 20-day pregnant Sprague-Dawley rats

Groups	Body Weight Difference (g)	Uterine Weight (g)
Control	27.63 ± 3.08	4.20 ± 0.12
30 mg/kg EPT	48.85 ± 17.62	4.44 ± 0.74
60 mg/kg EPT	36.72 ± 7.10	4.17 ± 0.22
30 mg/kg CCS	51.60 ± 13.72	4.23 ± 0.52
60 mg/kg CCS	47.28 ± 11.31	4.06 ± 0.43

Values expressed as mean ± SEM; n-5;
EPT-Expectorant; CCS= codeine-containing cough syrup

Cough syrups on foetal parameters

In comparison to the control group, there was a significant reduction in the placentae and foetal weights across all treatment groups except in the 60 mg/kg body weight CCS group (0.57 ± 0.04 and 5.36 ± 0.19) (Table 2). In addition, a marked decrease in crown-rump lengths were observed in both expectorant and CCS groups at 30 mg/kg body weight (4.41 ± 0.18). However, all the treatment groups showed an increase in umbilical cord lengths except the 30 mg/kg expectorant group (Table 2).

Table 2: Effect of cough syrups on Foetal Parameters in Sprague-Dawley rats.

Groups	PW (g)	FW (g)	CRL (cm)	UCL (cm)
Control	0.71 ± 0.04	5.11 ±0.17	5.71 ± 0.22	1.77 ± 0.15
30 mg/kg EPT	0.54 ± 0.04[a]	3.55 ± 0.13[a]	4.04 ± 0.09[a]	2.34 ± 0.12
60 mg/kg EPT	0.55 ± 0.02[a]	4.18 ± 0.83[a]	5.04 ± 0.13	2.36 ± 0.13[a]
30 mg/kg CCS	0.44 ± 0.02[a]	4.05 ± 0.15[a]	4.41 ± 0.18[a]	2.62 ± 0.13[a]
60 mg/kg CCS	0.57 ± 0.04	5.36 ± 0.19[a,b]	5.77 ± 0.40	2.53 ± 0.15[a]

Values are expressed as mean ± SEM n=5. [a]p<0.05 significant compared to Control group. [b]p<0.05 significant compared to 30mg/kg expectorant group. PW= Placenta weight FW= Foetal weight CRL= Crown Rump Length UCL= Umbilical Cord Length, EPT= Expectorant, CCS= Codeine-containing cough syrup

Cough syrups on oxidative stress markers

There was a notable reduction in GSH across all treatment groups compared to the control group. All other oxidative stress markers analyzed, showed no significant change across all the treatment groups (Table 3).

Table 3: Effect of cough syrups on oxidative stress markers in 20-day pregnant Sprague-Dawley rats

Groups	GSH (µmol/ml)	SOD (µmol/ml/min/mgpro)	CAT (µmol/ml/min/mgpro)	MDA (µmol/ml)
Control	55.67±4.81	0.93±0.15	30.33±4.63	13.00±2.08
30 mg/kg EPT	24.25±3.63[a]	1.43±0.25	22.25±3.45	21.00±3.63
60 mg/kg EPT	18.40±3.61[a]	1.20±0.23	23.20±2.48	18.40±3.61
30 mg/kg CCS	20.20±3.80[a]	1.12±0.28	21.40±1.94	20.20±3.80
60 mg/kg CCS	23.67±4.33[a]	2.23±0.18	37.67±4.67	23.67±4.33

Values are expressed as mean ± SEM n=5. [a] $p<0.05$ significant compared to the control group. EPT= Expectorant, CCS= Codeine-containing cough syrup

Cough syrups on hormonal levels

When compared to the control group, both the 30 mg/kg expectorant and CCS treatment groups were significantly different in hormonal levels as demonstrated in the marked increase and decrease in the values of progesterone (21.5±1.3) and Luteinizing hormone (4.0±0.7) respectively. Estrogen, follicle-stimulating hormone (FSH) and prolactin on the other hand, did not record any significant change across all the treatment groups when compared to the control (Table 4).

Table 4: Effect of cough syrup on hormonal levels in 20-day pregnant Sprague Dawley rats

Group	Progesterone (ng/ml)	Estrogen (pg/ml)	LH (pg/ml)	FSH (mIU/ml)	Prolactin (mIU/ml)
Control	10.0±1.7	13.0±1.7	59.0±3.5	10.7±0.9	0.3±0.3
30 mg/kg EPT	21.5±1.3[a]	28.8±6.0	4.0±0.7[a]	14.3±3.2	2.0±0.4
60 mg/kg EPT	18.7±1.7	14.6±1.3	50.8±12.5	13.4±1.9	1.4±0.6
30 mg/kg CCS	20.2±1.7[a]	18.0±2.8	14.9±3.7[a]	9.6±3.3	2.4±1.4
60 mg/kg CCS	16.1±2.5	13.5±1.2	29.8±12.5	8.3±1.9	2.6±1.7

Values are expressed as mean ± SEM n=5. [a] $p<0.05$ significant compared to the control group. EPT= Expectorant, CCS= Codeine-containing cough syrup

Histoarchitectural analysis

Histological representations of the control uterine and placenta tissues showed normal appearance of the histoarchitecture depicted by the normal mucus-secreting glands, intact epithelial lining, blood vessels, and floating and anchoring chorionic villi (Plates A and F). This is unlike some of the features seen in the treatment groups such as eroded epithelial lining, fibrotic and/or oedematous areas, and dilated or congested blood vessels (Plates B, C, D, E, G, H, I, J)

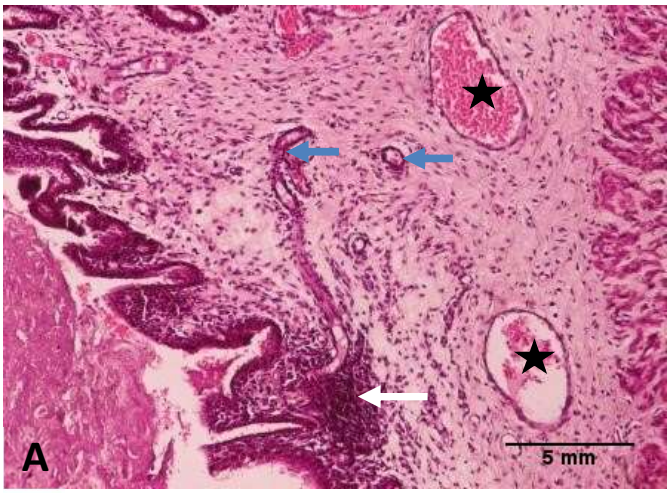

Plate A: Photomicrograph showing H&E-stained uterine section of control group (X100) - endometrial layer with normal mucus-secreting glands (blue arrows), large blood vessels (asterisks) and cellular proliferation (white arrow) within the stratum functionalis

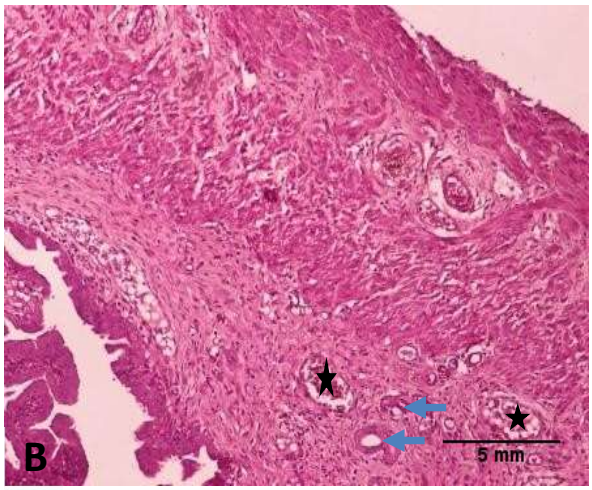

Plate B: Photomicrograph showing H&E-stained uterine section from 30 mg/kg body weight expectorant group (X100) demonstrating endometrial layer with normal mucus-secreting glands (blue arrows) and large blood vessels (asterisks), similar to the control group.

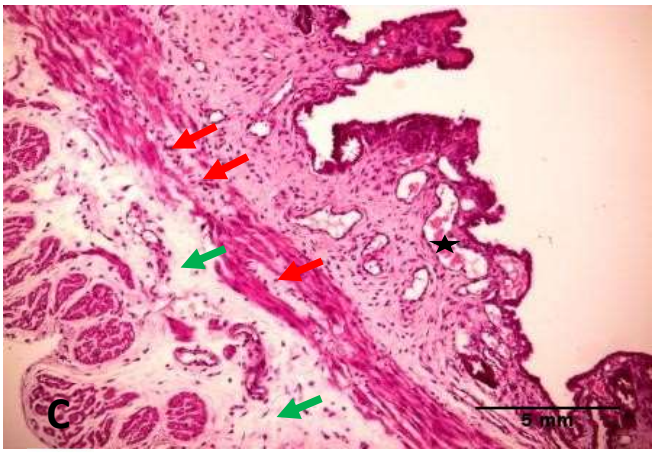

Plate C: Photomicrograph showing H&E-stained uterine section of 60 mg/kg body weight expectorant group (X100) demonstrating endometrium layer with a blood vessel (asterisks), loss of tissue mass (red arrows) in the myometrium and increased intercellular spaces due to mild edema within same myometrium layer (green arrows). This appears mildly deteriorated compared to the control group which has a compact myometrium.

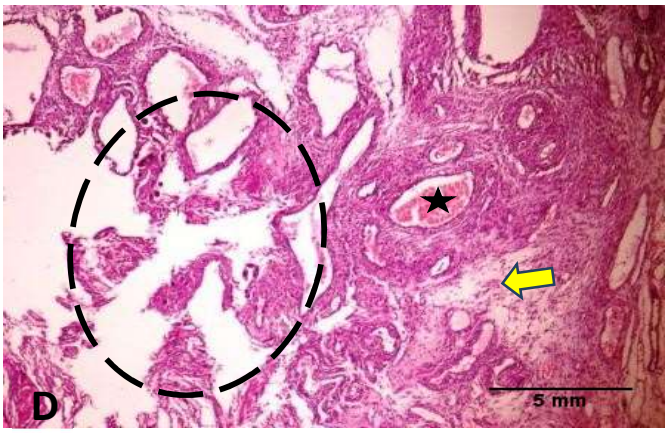

Plate D: Photomicrograph showing H&E-stained uterine section of 30 mg/kg body weight CCS group (X100) demonstrating endometrium with blood vessel (asterisks), epithelial lining appears scattered with obvious tissue erosion (circled portion). Loss of stromal parenchymal cells within the stroma basalis of the endometrium due to edema (yellow arrow); features depicting increased deterioration of epithelium when compared to both the 30 and 60 mg/kg

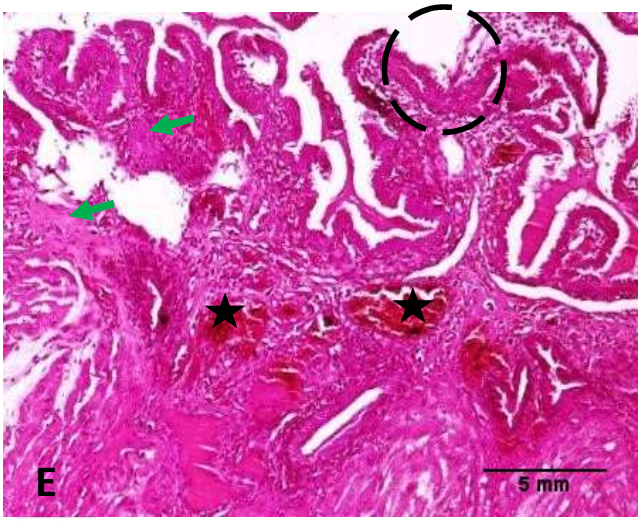

Plate E: Photomicrograph showing H&E stained uterine section of 60 mg/kg body weight CCS group (X100) demonstrating endometrium having eroded epithelial lining (circled portion), congested blood vessels (asterisks), and edematous regions (green arrows). This appears aggravated especially the aspect of vascular congestion when compared to the control and other treatment groups.

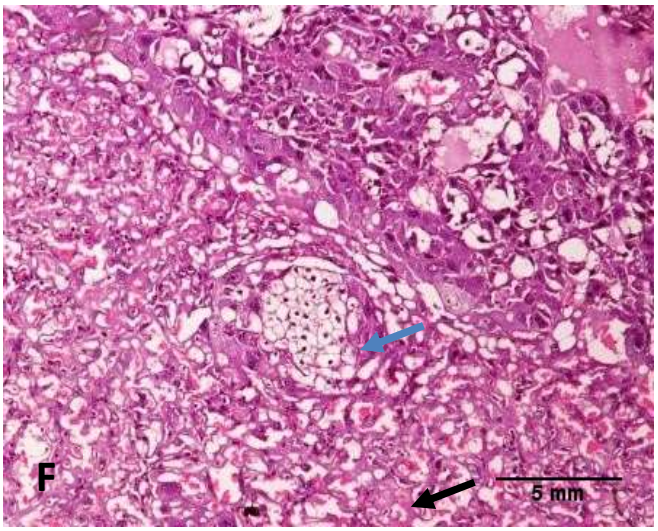

Plate F: Photomicrograph showing H&E stained placental section of control group (X100) demonstrating normal floating and anchoring chorionic villi with a layer of syncytiotrophoblast (blue arrow), normal maternal blood cells are seen within the intervillous spaces (black arrow).

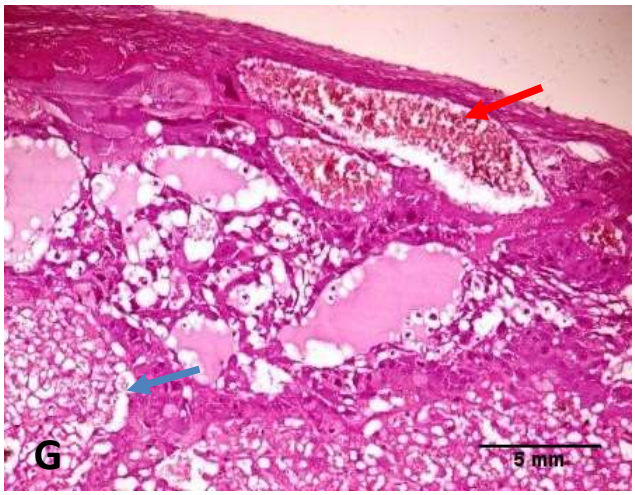

Plate G: Photomicrograph showing H&E stained placental section of 30 mg/kg body weight expectorant group (X100) demonstrating normal floating and anchoring chorionic villi with a layer of syncytiotrophoblast (blue arrow). The chorionic frondosum layer shows severe vessel dilatation and vascular congestion (red arrow) when compared to the control group.

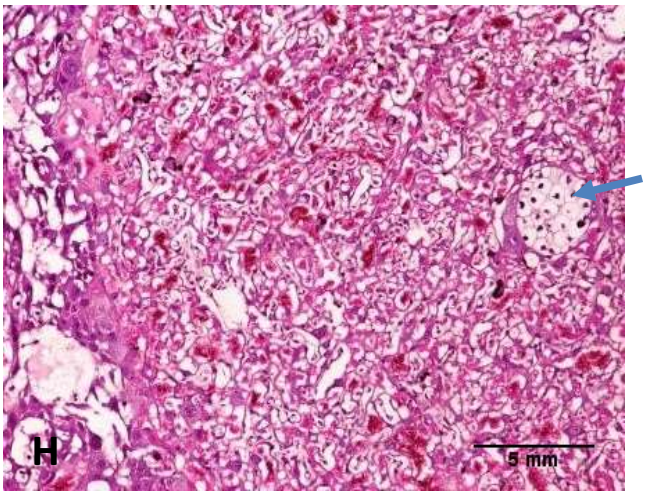

Plate H: Photomicrograph showing H&E stained placental section of 60 mg/kg body weight expectorant group (X100) demonstrationg chorionic frondosum layer which shows mild anchoring chorionic villi with a layer of syncytiotrophoblast (blue arrow).

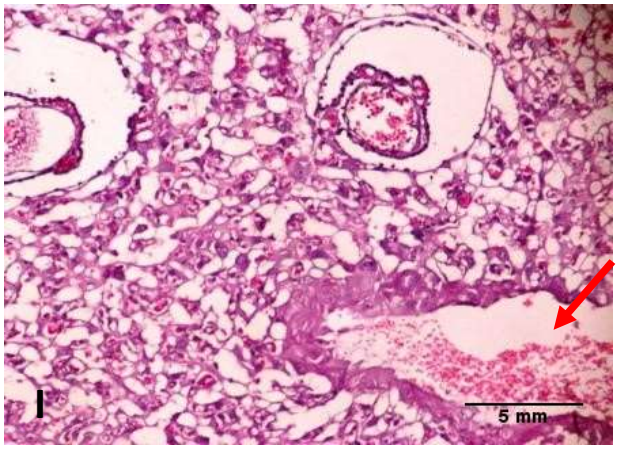

Plate I: Photomicrograph showing H&E stained placental section of 30 mg/kg body weight CCS group (X100) demonstrating chorionic frondosum layer with mild vessel dilatation and vascular congestion (red arrow), similar to that seen in the 30 mg/kg expectorant group.

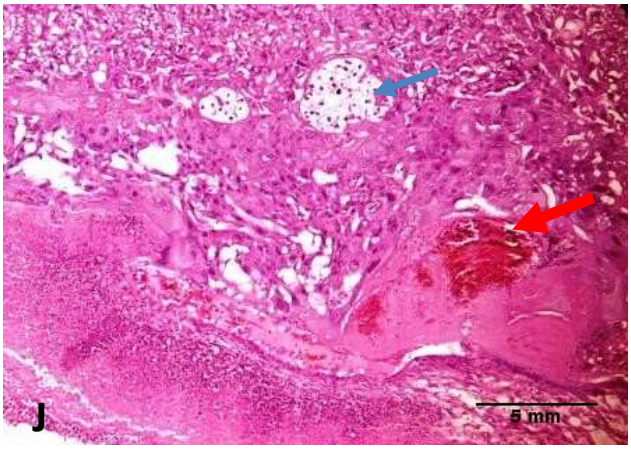

Plate J: Photomicrograph showing H&E stained placental section of 60 mg/kg body weight CCS group (X100) demonstrating poor chorionic frondosum layer which appears fibrotic and well-vascularized and also shows vascular congestion (red arrow), normal floating and anchoring chorionic villi with a layer of syncytiotrophoblast are seen (blue arrow); vascular congestion appears heightened compared to the expectorant groups.

DISCUSSION

The active metabolite contained in the substance codeine, is morphine. This morphine can cross the blood-placenta barrier during foetal development. It also can be transferred into the neonatal system via breast milk of codeine consuming nursing mothers, thereby exposing the new-born to life-threatening complications[22,23]. Therefore, it may be safe to categorize codeine-containing substances as potential teratogens. This study aimed to investigate the effects of the abuse of codeine-containing cough syrups on pregnancy and pregnancy outcomes in adult female Sprague-Dawley rats. It sought to give novel insights into the effect of such drug abuse on the developing foetus including; phenotypic changes, level of oxidative stress, histoarchitectural alterations, and the subsequent impact on reproductive hormones.

There is a heightened tendency for weight increase in opiate addicts. This occurs as a result of glycaemic dysregulation which causes a preference for sugary foods in such individuals.[24] However, codeine is a weak opiate that has seldom been associated to exhibit such weight gain properties. Nonetheless, there are indications that the use of codeine can cause organ-specific weight increase as opposed to general body weight in other mammals[25]. Some studies have indicated weight loss and delayed postnatal development in foetuses exposed to codeine[26] while others have recorded weight loss due to anorexic behaviour following opiate withdrawal[27].

It has been earlier reported that foetal parameters can be used as predictive markers to developmentally incurred health threatening conditions in adulthood.[28] The results from this study showed significant weight loss in all treatment groups (aside the 60 mg/kg CCS group) when compared to the control group. There was also a significant reduction in the crown-rump length (CRL) in the 30 mg/kg treatment groups. Although the CRL decrease was insignificant in the 60 mg/kg expectorant group, however such decreases in foetal weight and CRL are indicative of restricted growth and consequently may result in increased mortality rate in these groups[29,30]. Meanwhile, other parameters measured when compared to the control group showed low placental weights (PW) and increased

umbilical cord length (UCL) in the treated groups. Both the placenta and the umbilical cord are crucial for healthy development, as they provide the medium through which the foetus receives nutrients. A lengthy umbilical cord is associated with increased movement that heightens the risk of torsion, thereby posing a threat to the sufficient supply of nutrients to the foetus and/or strangulation[31,32]. These possible ill outcomes of a long umbilical cord may lead to foetal under-nutrition and mortality. This may explain the likely cause of death of four pups in the groups that received the low and high doses of CCS. In addition, PW is susceptible to any change in environmental conditions during gestation. It can be used as an indicator for both maternal and foetal wellbeing[33]. There are studies that have demonstrated that a low placental weight depicts maternal complications due to changes in biological compositions[34,35].

Oxidative stress is an established marker of toxicity on several biological tissues. Under oxidative conditions, lipids are the most involved category of biomolecules[36]. There are studies that have stated the MDA marker as the most studied product of lipid peroxidation and has also described it as a major biomarker to determine the level of oxidative stress in an organism[36,37]. However, in this study, there was no significant change in MDA, CAT, and SOD across all groups in the day-20 pregnant dams. Nevertheless, there was a marked decrease in the GSH levels across all treatment groups when compared to the control group. GSH is an abundant water-soluble endogenous antioxidant. It is a reduced peptide with the primary role of scavenging excessive ROS production. As opposed to other antioxidants, GSH exists in high concentrations within biological tissues[38]. The significant decrease in the GSH level observed in all treated groups is similar to that recorded from another study using dextromethorphan on testicular cells. It elucidates the overwhelming properties of a major reactive by-product of oxidation; hydrogen peroxide. The mechanisms involved in the removal of hydrogen peroxide from the uterine cells in the case of the present study, may have become compromised, leading to the antioxidative response of GSH[39,40]. The GSH activation may have been shortly sufficient to compensate for the oxidative stressed state, accounting for the insignificance seen in the other biomarkers. The weak nature of the codeine concentration in the cough syrups could have been suppressed by GSH scavenging activities alone. Although earlier studies with the administration of codeine showed a marked decrease in the levels of all antioxidants analyzed above[25,41] it is possible that direct analysis of foetal oxidative markers like the phenotypic parameters shown above may have yielded significance.

Generally, opioids exert a reducing action on reproductive hormones including estrogen, testosterone, and LH. This further causes delayed sexual response amongst other health complications.[42,43] The hormonal assay showed no significant change in the prolactin level across all groups. Although morphine has been demonstrated to induce hyperprolactinemia in pregnant and/or lactating mothers,[44] it is also capable of regulating sufficient prolactin secretion in adult rodents which were exposed to the substance during puberty[45]. This often occurs when this drug is either taken directly in its raw form[44,46] or when combined with other abusive substances like nicotine via cigarette smoking[47]. However, this was not the methodological approach of the present study. Other contributing factors that may have influenced the level of prolactin are FSH and estrogen; where the later has been associated with hyperprolactinemia[48,49]. The results from the present study showed a corresponding insignificant change in FSH, estrogen, and prolactin at day 20 of gestation. This further indicates that estrogen did not facilitate the stimulating properties of codeine-containing syrups in this study. However, there was a significant increase in the progesterone levels in both the expectorant and CCS groups at the 30

mg/kg body weight when compared to control. This was found to correlate with the corresponding decrease in LH within same groups. Such is somewhat expected due to the suppressive properties exerted by progesterone on LH, and the cessation of ovulation[50].

Histological appearance of uterine tissue showed a normal endometrial layer containing mucus-secreting glands, blood vessels, and stromal cells in the control and 30 mg/kg expectorant groups. However, slight cellular proliferation was seen in the control group. Meanwhile, the 60 mg/kg body weight expectorant group and the 30 mg/kg body weight CCS group, showed fluid-like infiltration into the myometrial and endometrial layers respectively. This deteriorating state was aggravated by the slight loss of cellular mass in the 60 mg/kg expectorant group, and highly eroded epithelial lining in the 30 mg/kg CCS group. The eroded epithelial lining also occurred in the 60 mg/kg group, which presented with congested blood vessels and expanded intercellular spaces due to oedema. These results correspond with those of Dehghan and colleagues[51], who reported vascular congestions and apoptotic lesions after morphine administration. Another study also stated changes from the normal histological structure of the uterus after administration with Nalbuphine, an opioid analgesic, in rats[52]. The congested blood vessels and loss of cell mass reported in this present study is suggestive of oxidative stress and correlates with our earlier result on GSH.

The histoarchitecture of the placenta of animals given expectorants at 30 and 60 mg/kg doses per body weight as compared to the control group, showed a chorionic frondosum layer with severe vessel dilatation and vascular congestion and necrosis in the decidual basalis layer. While the animals that received the low dose (30 mg/kg) codeine-contained cough syrup also showed the chorionic frondosum layer of the placenta with vascular congestion and mild vessel dilatation. The decidual basalis layer was moderately inflamed, there was severe infiltration of inflammatory cells. The group with high dose (60 mg/kg) codeine-contained cough syrup had a poorly formed chorionic frondosum layer that appeared fibrotic. Though it had a normal floating, and anchoring chorionic villi, the blood vessels were also congested. Earlier studies have demonstrated the presence of opioid-containing substances in the placenta, which resulted in delayed villous maturation and subsequently foetal mortality[53,54].

Our present study illustrates the negative impact of exposure to codeine-containing cough syrup to the female reproductive organ (demonstrated in uterine structural changes). It further shows the possible penetration into the foetal system via the placenta. This is expressed in the results obtained after measurement of the foetal parameters; which significantly deviated from those of the control group. The groups that received expectorants were slightly impacted when compared to the other treated groups. This demonstrates codeine-containing cough syrup as a developmental toxicant. Experiment by Awodele and colleagues[55], showed that codeine-containing cough syrups had no effects on the physical appearance of the foetuses. This emphasizes the absence of phenotypic congenital malformations to exposed pups in the present study. There have also been epidemiological studies that made conclusions on the similar absence of malformations. However, there is much certainty of perinatal and postnatal complications[12,56]. The difference in the pharmacokinetics of codeine to morphine in adults when compared to developing foetus poses as a key determinant for reduced oxidative response in the dams. This also explains the insignificant change in weight of 20-day rats, unlike the reduction stated in the foetus born to those of the treated groups. Future studies could focus on ascertaining the oxidative stress levels of the foetus to achieve a more comprehensive report.

CONCLUSION

This study demonstrates that abuse of both codeine containing and non-codeine containing cough syrups during pregnancy may obstruct the normal developmental process. Such exposure could further cause a limitation to the available nutrients needed by the foetus. These adverse effects on the developing foetus may not present as any obvious phenotypic alteration. It may also not directly influence any notable deterioration to the mothers. Still, caution is required during the administration of all opioid containing pharmacological agents to not just pregnant women but generally to females of childbearing age.

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