EFFECTS OF DEXAMETHASONE EXPOSURE ON MATERNAL WEIGHT OF ALBINO RATS

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Abstract: The normal morphogenesis of maternal body weightis disrupted by the prenatal exposure to dexamethasone when used during pregnancyto treats both maternal and fetal diseases. Pregnant albino rats were used in this study. The albino rats were into control group and the experimental group. Each experimental group was further subdivided to high, medium and low group. Pregnant albino rats were given oral dexamethasone which varied from LDG 0.5 mg/kg/d, MDG.2.5 mg/kg/d, HDG 4 mg/kg/d during their first trimester, second trimester and third trimester. Control rats received food and water at ad libitum. Daily maternal weight and food intake were recordedAll the rats were sacrificed on day 20th day of gestation. High doses of dexamethasone lead to massive loss of weight especially during the first trimester.Maternal weight gainis negatively impaired by chronic and high doses of glucorticoids.

Keywords: glucorticoids, dexamethasone, maternal weight

INTRODUCTION

Dexamethasone is a fluorinated steroid that is 9-fluoropregna-1,4-diene substituted by hydroxy groups at positions 11, 17 and 21, a methyl group at position 16 and oxo groups at positions 3[1]. It acts as an adrenergic agent, an antiemetic, an antineoplastic agent, an environmental contaminant, a xenobiotic, an immunosuppressive agent and an anti-inflammatory drug[2,3]. It is highly soluble, at an 80-90% rate and has a half-life of approximately 3 hours[1].In the current SARS-CoV-2 pandemic, dexamethasone has widely been used in the treatment of COVID disease other maternal diseased treated by dexamethasone include; Crohn's diseases, multiple sclerosis, cerebral edema, inflammatory bowel diseases, allergies, Addison disease, hyperemesis gravidarum, HELLP syndrome, dermatomyosis[1,2,3,4].

Dexamethasone a glucorticoid, have also been shown to efficiently cross the placenta barrier and is consequently universally employedin the management of virilizing congenital adrenal hyperplasia in females, and enhancement of fetal maturation in utero, intraventricular hemorrhage, and necrotizing enterocolitis[4–6].In early pregnancy, steroids may be used in women for the treatment of recurrent miscarriage or fetal abnormalities such as congenital adrenal hyperplasia[4,7,8]. Prenatal dexamethasone is the drug of choice especially during mid and late trimesters of pregnancy for enhancement of lung maturity for pregnancy mothers with risk of premature delivery[9,10].

Glucorticoids have also been associated with numerous unfavorable outcomes to the countless main organs in the body involving muscles, liver, brain, lung, spleen, pancreas, brain[12,13]. Use of dexamethasone may for instancecan causemultifariousmetabolic impairments like glucose intolerance, hyperglycemia which could have indirect or direct effect to the pancreas of developing embryo or fetusexplaining the increased chronic diseases such as diabetes mellitus, hypertension[14,15].Dexamethasonehas also been shown to impedes the normal hypothalamic pituitary axis piloting to disruption of gastro-intestinal motility and adrenal axis aiding to the irritable bowel syndrome[16].In the brain, prenatal glucorticoid have been associated with damage to motor, affective and cognitive behaviors, working memory and attention deficit, anxiety and depressive disorders[17,18]. Moreover, dexamethasone it impairs spiny mouse folliculogenesis and enhances follicular atresia through induction of autophagy or combined autophagy and apoptosis[20,21]

Material and Methods

30 pregnant female albino rats were resourced from SAFARI animal biomedical department in Jomo Kenyatta University of Agriculture and Technology (JKUAT). The rats were weighing between 150g to 250 grams. This study

was carried out in accordance with the guiding principles in the care and use of animals. Female albino rats were housed separately in polycarbonated cages in a temperature-controlled room (22°C) with a dark/light cycle of 12:12 h. They were maintained on a standard rat pellets diet consisting 68 % starch, 4 % cellulose, 5% lipid (corn oil) and 20 % protein) and by calories: - 20 % proteins, 72 % carbohydrates, 12 % lipids, and 54mg/kg zinc, vitamins and water ad libitum for the whole of the gestation period day 1-20.The weights were taken between 8: am and 9: am and the feeding with rodent pellets given daily at 9:30 am after weighing the albino rats. and were allowed to drink water ad libitum. Dexamethasone-treated rats were givenoral dexamethasone (LDG 0.5mg, MDG1.5mg and HDG 5mg mg/kg body weight) during first trimester, second trimester and third trimester and were allowed to feed ad libitum. Control rats received no treatment and were fed with pellets and water ad libitum.

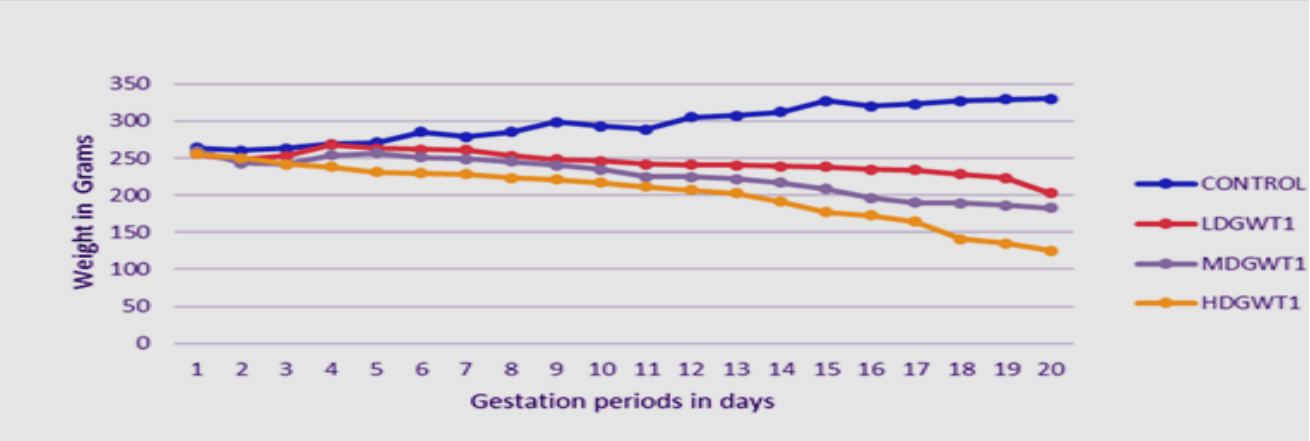
Statistical analysis

The study sought to analyze the maternal outcomes. The data was analyzed using SPSS and Excel statistical software and was expressed as mean ± standard error (SEM). The study compared how the three dose levels (Low, medium and high) and control in the three trimesters (T1, T2 and T3), affected the different parameters. These parameters were: Initial maternal weight, terminal maternal weight, weight gain, litter size, Resorbed fetuses, Placenta weight, congenital abnormalities and Dead fetuses. To determine the significance, a one-way analysis of variance with Tukey post hoc test was used and 5% significance level (α = 0.05) was assumed. The results were considered to be significant whenever the probability value (sig. value) is less than 0.05 ($p<0.05$). The results were presented below per each trimester. A Pearson correlation value of 0 indicates absence of a linear relationship between the variables. The direction of the relationship is indicated by the sign of the Pearson Correlationvalue.

RESULTS

Rats treated with dexamethasone consumed less food and weighed less than control rats. Treated rats also weighed less than pair-fed animals though their food intake was similar.

The findings of the study on the maternal weight gain treads in the entire gestational period-(GD_1 to GD_{20}) following prenatal exposure to varied doses of dexamethasone shown a marked variance between the dexamethasone treated groups compared with the control. When dexamethasone was administered in trimester one (**TM_1) (line graph1)** it can be observed that there was steady decrease in maternal weights treads from gestational day one (GD_1) to Gestational Day twenty (GD_{20} among thedexamethasone treated groups (i.e LDG, MDG and HDG) when compared with the control. This steady decrease in weight loss among the dexamethasone treated groups was attributed to the devourment of fetuses that was observed when all animals were sacrificed on the final day of the experiment i.e the gestational day 20th. These teratogenic devourment and high numbers of embroylethality of the fetuses in utero was also observed to be dose dependent where the HDG recorded the highest rate of devourment (75-90%), followed by MAG (50-65%) and lastly the LDG (30-55%). These results were found to be statistically significant when compared with the control when using both ANOVA and Tukey test on post-hoc t-tests for both P and F-values(**table1)**. When the comparative treads of the maternal weight gain between the dexamethasone treated groups was compared within the groups and across the experimental groups as well as with the control, the results were also found to be all the way statistically significant ($p\leq0.005$)



Graph 1: The trimesters 1 (TM_1) comparative maternal weight trends of the dexamethasone treated groups LDG, MDG, and HDG against control group.

This treads in the mean weight gain were also seen to statistically vary ($p \leq 0.005$) across the dexamethasone treated groups when compared with the control between the initial and terminal maternal weight recorded in the entire experimental period (**table 1**).

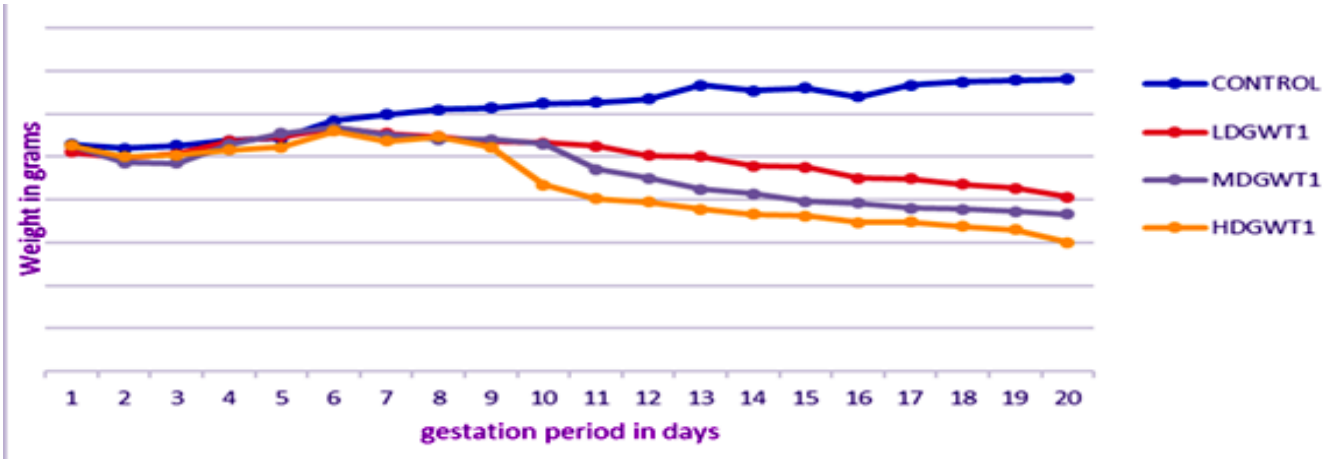
Table 1: The TM_1, TM_2 and TM_3 initial, terminal and mean weight gains or losses between the dexamethasone treated groups (i.e LDG, MDG and HDG) against the control.

Maternal pregnancy outcome	Control	Low dexamethasone group (0.5mg/kg)	Medium dexamethasone group (2mg/kg)	High dexamethasone group (4mg/kg)	F	P-value
The trimester one findings (TM_1)						
Mean initial maternal weight	259.33±4.67 a	254±.58a	258±2.52a	264.7±4.91a	1.48	0.29
Mean terminal maternal weight	330.3±15.06 a	225.33±11.35b	218.33±3.67b	163.67±2.96 b	20.97	0.000*
Mean weight gain	71±1.58a	-28.67±1.81b	-39.67±1.17bc	-101±5.86c	26.79	0.000*
The trimester two findings (TM_2)						
Mean initial maternal weight	210.67±4.06 a	211±3a	252.33±24.29ab	275±6.92a	6.13	0.02*
Mean terminal maternal weight	302.67±3.38 a	182.33±12.6b	196.3±30.75b	191.67±10.4 8b	10.45	0.004*
Mean weight gain	92±1.73a	-28.67±15.03b	-56. ±9.87bc	-83±8.35c	60.4	0.000*
The trimester three (TM_3) findings						
Mean initial maternal weight	235.67±9.60 a	217.33±13.33a	224.67±10.65a	216.3±9.28a	0.68	0.59
Mean terminal maternal weight	312.67±13.1 7a	255.67±14.43b	247±9.81b	230±9.30b	9.11	0.006*
Mean weight gain	73.67±5.90a	38.33±4.63b	22.33±2.40bc	13.67±0.88c	44.72	0.000*

The means, followed by the same letter in a row are not statistically different at ($P<0.05$) using one-way ANOVA with Tukey test on post-hoc t-tests. * Indicates significance values ($p<0.05$).

The trimester two (TM_2) maternal weight gain when dexamethasone was administered from (GD_7 to GD_{20})

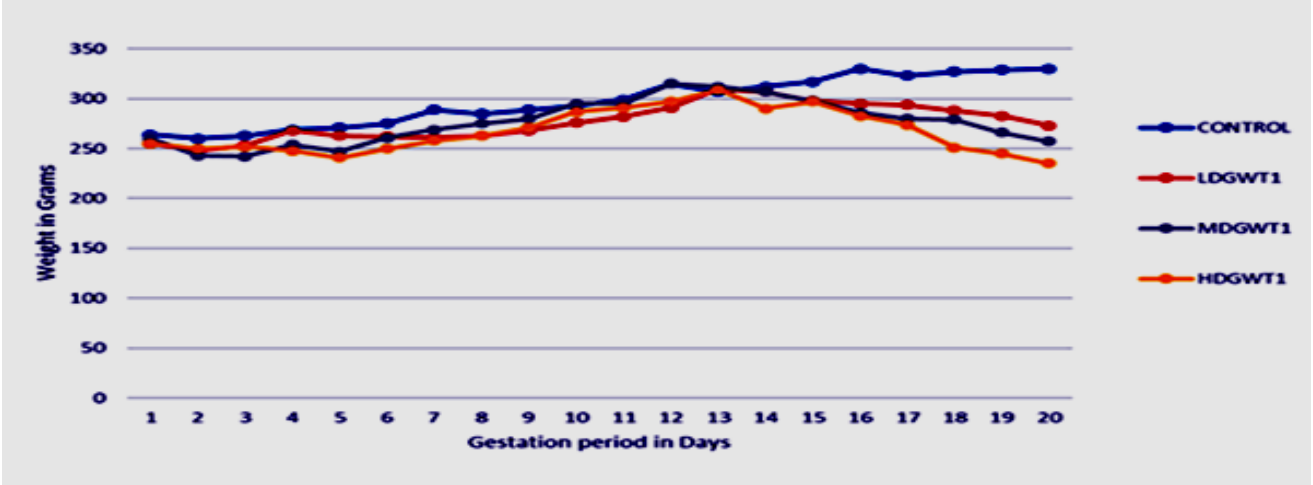
When dexamethasone was administered at trimester two **(TM_2)**it was observed that there was a steady weight gain in all dexamethasone treated groups from gestational day one (GD_1) to gestational day seven (GD_7) (**graph 1**). This was followed with marked massive weight drop in all dexamethasone groups from GD8 to GD20 (**graph1)**; When the mean weight gain or weight losses were compared within and across the groups between the dexamethasone treated groups with the control, they were all found to be statistically significant {LDG p=0.047; MDG p=0.001; HDG p=0.001}.



Line graph 2: The TM_2 comparative maternal weights gain trends between the dexamethasone treated group (LDG), (MDG), and (HDG) against control

The trimester three (TM_3) maternal weight gain when dexamethasone was administered from (GD_{14} to GD_{20})

When dexamethasone was administered **in trimester 3 (TM_3)** there was a steady weight gain in all the dexamethasone treated groups LDG, MDG and HDG in the first and in the second trimester (**TM_2**) i.e., from GD_1 to GD_{14} (***line graph 3***). This was followed by a marked and sudden weight drop in weight losses among all Dexamethasone groups from GD15to GD20, following introduction of dexamethasone treatment. The animals continued with massive weight loss up to GD_{20}. The comparative means weight loss between the dexamethasone treated groups against the controls were found to be statistically significant {LDG p=0.016; MDG p=0.021; HDG p=0.001} when compared with the control (**table 1**).



Line Graph: **Showing thetrimester 3 (TM_3) comparative mean maternal weight gain treads between the dexamethasone treated groups LDG, MDG, and HDG against control group**

The intra and intergroup liner Correlational analysis of the maternal and fetal pregnancy outcomes

When the linear correlation analysis was done within and across the dexamethasone treated groups on the maternal weight and fetal pregnancy outcomes to establish the correlation significance levels, the strength and direction of the linear relationship on the maternal weight and fetal pregnancy outcome parameters namely: litter size, resorbed fetuses, placenta weight, and dead fetuses shown a strong linear relationship between all this variables when dexamethasone was administered at trimester one and two (TM_1& TM_2) variables across and within groups. A value between 0.3 and 0.5 (**table 2**) indicates a moderate linear relationship while a value below 0.3 indicated a weak relationship as previously described by a study by Kothari (2014) stated that an absolute correlation value of 0.5 and above indicated weak relationship. on the other hand, a Pearson correlation value of **0** as indicated in the table 4.5 below indicates absence of a linear relationship between the stated variables. The direction of the relationship is indicated by the sign of the Pearson Correlation value(r). Finally, the significance of the relationship was achieved through p-values of ($P \leq 0.005$). where all relationships in table 4.5 below that were less than 0.05 at 95% confidence level did indicates that the linear relationship between variables of maternal and fetal outcomes were statistically significant and vice versa.

Table 1: Showing the liner correlation by Pearson and P values of the maternal weight in comparison with mean litter sizes, endometrial glands resorptions, placenta weight, and the percentage embroylethality for the dexamethasone treated groups (LDG, MDG and HDG) against control in the TM_1, TM_2 and TM_3

		Mean weight gain	Mean initial maternal weight	Mean terminal maternal weight	Mean little size	Mean resorbed fetuses	Mean placental weight	Mean dead fetuses
Mean weight gain	r	1						
	P							
Mean initial maternal weight	r	.125	1					
	P	.467						
Mean terminal maternal weight	r	.177	.243	1				
	P	.303	.153					
Mean little size	r	.603**	.118	-.011	1			
	P	.000	.493	.951				
Mean resorbed fetuses	r	-.722**	-.033	-.020	-.403*	1		
	P	.000	.848	.908	.015			
Mean placental weight	r	.715**	.139	-.077	.457**	-.773**	1	
	P	.000	.418	.655	.005	.000		
Mean dead fetuses	r	-.639**	-.211	.192	-.470**	.731**	-.843**	1
	P	.000	.225	.270	.004	.000	.000	

NB: r is the Pearson's correlation coefficient, P is the p-value, * and ** indicate significance i.e. $p<0.05$

DISCUSSION

The findings of this study on the mean maternal weight gain throughout the entire gestation period were seen to depict an inverse dose response relationship in that with the increasing dexamethasone doses there was significant reduction ($P<0.03$) in mean maternal weight gain (table 1) which led to acute reduction in food consumption during

the treatment period, which increased after the last dexamethasone dose. The reduction in food intake was accompanied by a significant reduction in weight gain and loss visceral adiposity. This is inmarked contrast to the previously observed effects of dexamethasonein male mice which were giventhree doses of 11 mg/kg dexamethasone over the course of5days and fed with high fat diet for 8weeks[22].The increased weight gain observed in the dexamethasone-treated mice was attributed to the fact that glucocorticoids exert orexigenic and antthermogenic effects as well as stimulate the accumulation of bothbody fat and visceral fat which are concurring withthe engrained effect of stress-related weight gain[23,24,25].

The reduction in mean maternal weight gain and fetal pregnancy outcomes distinctly reveals that the maternal and fetal pregnancy outcome parameters are an important indicator to the kind of perturbations caused in the development of the fetal organs. This study established that there is a very strong correlation (0.3-0.5) between the maternal and fetal pregnancy outcomes. This is in agreement with a study done on rats and humans which reported that glucorticoids leads to decline in progesterone hormone upsurge, prostaglandin synthetase activity and prostaglandin F2α generation in early pregnancy, leading to the abortions, resorption of fetuses and dead fetus[26,27]. Moreover, in this study it was established that any increase in the dexamethasone, had a subsequent significant ($P<0.05$) reduction in all fetal growth parameters including the mean little size, mean resorbed gland, mean placenta weight, mean crown-rump and the mean percentage embroylethality. This was observed to have a dose response relationship in that these parameters decreased with the increasing dexamethasone treated groups (LDG, MDG and HDG) (table 4.2 and 4.3 respectively). This is also in agreement with findings of a study that reported that glucorticoids inhibits hypothalamic corticotropin-releasing-hormone resulting in reduction in body weight set point [28]

This could be attributed by the lessened food intake which was associated with; reduced appetite for food and water intake, loss of muscles and adipose tissue. This is in agreement with findings of the studies by Malkawi et al who reported that glucorticoids distorts the obese (Ob) gene and leptin hormone that is concerned with the synthesis of adipose tissues leading to reduced body weight by decreasing food consumption[29,30]. Moreover, glucorticoids inhibits hypothalamic corticotropin-releasing-hormone resulting in reduction in body weight set point[31].

Others contributors to massive weight loss include protein synthesis inhibition leading to loss of muscle bulkiness and decreased energy, and fatty acid synthesis impairment[32]. The mechanism of dexamethasone impediment to the general fetal development inutero is assumed to be associated with decline in progesterone hormone upsurge prostaglandin synthetase activity and prostaglandin F2α generation in early pregnancy leading to the abortion's, resorption of fetuses and dead fetus[33,34].

Glucocorticoids have been shown to induce lipolysis by impeding lipoproteins lipase and modifying the action of lipase hormone andhindering the uptake of free fatty acid by adipose tissue[35,36,38,39]. Cortisol have also been reported toaffect lipid metabolism negativelyin the presence of high-caloric diet[36].

CONCLUSION

In conclusion the study has showed that dexamethasone is teratogenic to the developing fetal pancreas as it causes significant reduction in pancreatic total volume. Exposure of pancreas and other organs to high and medium doses of dexamethasone at first and second trimester lead to advanced presents the best "window of opportunity" for expression of dexamethasone teratogenesis's in albino rats. These adverse effects in fetuses born to mothers ingesting dexamethasone during pregnancy period predispose to adult diabetes and hypertensions. These teratogenic outcomes were also observed to be dose and time dependent with the most critical teratogenic dose being high and medium dexamethasone dose when exposed at first and second window period. Such an effect of dexamethasone on pancreas in children born to mothers may predispose to pancreatic disorders in postnatal period.

Conflict of interest statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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