HIGH DOSES OF DEXAMETHASONE INDUCES EMBRYOLETHALITYAND TERATOGENIC EFFECTS ON FETAL VISCERAL IN ALBINO RATS

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Abstract: Dexamethasone a glucorticoid has been shown to impede fetal embryogenesisof the developing fetal visceral.Despite the fact that data exists on its teratogenic effect's on certain organs, there is absence ofinformation showing its teratogenic effects based on stages of development as well as exposed to variable doses. The aim of this studywas to determine the effects of differing doses of intrauterine dexamethasone on fetal visceral of albino rats. Gravidalbino rats were used in this study. When the dexamethasone was given from day 7th to day 20th, weight reduced by 41%,21% and 14% at high, medium and low dexamethasone doses respectively. When dexamethasone drug given from day 14th to 20th day; weight of the fetuses reduced by 20%,15% and 12% at high, medium and low dexamethasone doses respectively. The fetal weight reduced by 44%,36%,20% when given throughout at high, medium and low dexamethasone doses respectively Weight of the pancreas, brain, liver, placental, heart and kidney also decreased depending with the amount of dexamethasone and period of administration.Intrauterine administration of dexamethasone impaired fetal embryogenesis which is dependent on gestation period and amount of drug ingested. Dexamethasone when given had negative effects on the fetal visceral such as a kidney, liver, placental weight, brain, and pancreas. Moreover, reduced little size and reduced fetal weight.

Keywords: fetal visceral, dexamethasone, teratogenic

INTRODUCTION

Glucorticoids have copious detrimental effects to the developing organs of the developing fetuses encompassing muscles, liver, kidneys, brain, lung, placenta, spleen and heart [1]. For instance, when administered during an early pregnancy leads to placenta insufficiency by inhibiting placental VEGF expression [1]. In brain, leads to decline of the blood brain barrier permeability, reduction of fetal cerebral blood flow, hypoxia of brain, reduction in hippocampal size to learning and attention disorders [2,3]. In the kidneys, it causes diminution of nephron and glomerular of the kidney and reduction of the glomerular number resulting glomerulosclerosis and hypertension [4,5,6].

Fetal therapy by use of glucorticoids have in last four decade been in used for management of various disease during intrauterine period and newborns [1,7–9]. Dexamethasones have proved to be more effective than betamethasone during preterm birth in enhancement of fetal lung surfactant production and maturation of the fetal lung, especially to mothers who are prone to preterm deliveries pregnancy [1]. A single course of dexamethasone is given to mothers at gestation period between 24 weeks and 34 weeks with ruptured membrane and 23 weeks to 34 weeks who are at risk of preterm deliveries and between one to 7 days before delivery of multiple pregnancies [10,11].

Prenatal dexamethasone has beenreducing neonatal mortality, short term respiratory morbidity, severe neurological deficit and, necrotizing enterocolitis [4,8,10,12]. Dexamethasone its ability to cross the placenta have helped in treatment of virilizing congenital adrenal hyperplasia (CAH) which is an autosomal recessive disorder of steroidogenesis, caused by lack of 21-hydroxylase13,14. The prenatal treatment of CAH is dispensed on 5th week of intrauterine period, when genitalia are developing to stabilize androgen precursor [1,13,15]. Clinical studies on human have also shown, dexamethasone is clinically effective in treatment of third-degree heart block [4,16], also a drug of choice in treatment of Congenital cystic adenomatoid malformations [17,18]. Dexamethasone was also found to be effective in decreasing risk of periventricular leukomalacia in low birthweight (≤1.75 kg) infants [19]. Contrarywise, to its numerous clinical important, dexamethasone have also numerous adverse effects. this have been reported on studies done on animal and human studies to the fetus [20]. Dexamethasone use for instance contribute to multifarious metabolic effects like glucose intolerance, hyperglycemia which could have teratogenic

effect to the pancreas of the developing embryo or fetus [21,22]. Studies done on animal and human have proved that prenatal dexamethasone impedes the metabolism of the developing fetus resulting to low birth weight, intrauterine growth retardation, thin fetuses, increased hypothalamopituitary adrenal axis activity, reduced brain growth with delayed myelination and hypertension [2,3,23–26].

MATERIAL AND METHODS

Animals

Female nulliparous albino rats were obtainedfrom University of Nairobi Chiromo small animals breeding centerand kept at under humid tropical conditions 24°C on a 12:12-h light-dark cycle.The experiments with animalswere consented by JKUAT Animal Ethical Committee (AEC)and agree with to the Principle for the Care and Use of Laboratory Animals before commencement of the study.All animals were sacrificed on day 20th using carbon dioxide gas asphyxiationusing humane end points at the end of the study [27].

Prenatal Dexamethasone dispensation

All experimental groups received oral dexamethasone dissolved in normal saline using gastric gavage between 8:00 am to 9: am. The control group received only the rodent pellets and water ad libitum between 8:00am to 9: am. The dexamethasone groups received (HDG 0.65mg/kg/d, MDG 7mg/kg/d, LDG 13 mg/kg/d) during the gestation period in first trimester, second trimester and third trimester.

Harvesting of fetuses and pancreas

In all cases, the pregnant rats were sacrificed by carbon dioxide asphyxia between 09:00 and 11:00 A.M on gestational day 20, to prevent the mothers from devouring any damaged offspring. Twenty minutes after anesthesia, the abdominal wall of the mother was opened and the full extent of both uterine horns exposed. Before dissectingeach horn, fetal postureswithin the horns, and the number of aliveand dead fetuses was computedas total litter size [28].Likewise, the total number of the "devoured endometrial glands obtainedall alongthe mesometrial margin of the uterine horns that indicatinginitial uterine implantation site was calculatedand recorded. Resorption was indicated bythe unoccupied metrical glands [29]The uterine horns were excised along the antimesometrial border to reveal the fetuses, embryonic membranes and placentas. They were gently removed in totality from the uterus utilizing the blunt end of a pair of forceps. An incision along the dorsal surface of the membranes was made to unveilthe fetuses, then each fetus and its placenta were detachedand weighed and their general fetal morphology examined and recorded. [28,30]

Figure 3:2: showing gravid placenta with devoured endometrial gland

Statistical analysis

The study sought to analyze Dexamethasone Fetal 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 dexamethasone groups) and control in the three trimesters (TM1, TM2 and TM3), affected the different parameters. These parameters were: Fetal weight, fetal pancreas weight, fetal pancreas volume, fetal crump length (CRL) and fetal (biparietal diameter) BPD. 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 ($p<0.05$).

RESULTS

Table 1: Shows the TM1, TM2, TM3 intra and inter group comparisons on the mean litter sizes, endometrial glands resorptions, placenta weight and the embroylethality between the LDG, MDG, & HDG against the control

Maternal pregnancy outcome	Control	Low dexagroup (0.65mg/kg)	Medium dexagroup (2mg/kg)	High dexamethasone group (4mg/kg)
	trimester	**one**	**findings**	
Mean little size	11.77±0.27	9.07±0.52^{b}	7.6±0.70^{b*}	2.23±0.62^{c*}
Mean resorbed gland	3.67±0.93	3.87±0.48^{b}	5.4±0.85^{ab*}	7.53±0.37^{b*}
Mean placenta Weight	500±7.5	454.67±5.61^{b*}	420±12.34^{b*}	286.27±8.66^{c*}
Mean dead fetuses	1.33±0.33	3±0.58^{a}	7±2.08^{a*}	9.5±1.5^{b*}
	trimester	**two**	**findings**	
Mean little size	11.83±0.88	6.7±0.2^{ab*}	8.43±0.81^{bc*}	3.23±1.01^{d}
Mean resorbed gland	1.8±0.3	3.9±0.5^{ab*}	4.7±0.61^{b}	5.7±0.23^{b*}
Mean placenta Weight	500±7.5	454.67±5.6^{b*}	420±12.34^{b*}	286.27±8.66^{c*}
Mean dead fetuses	2.67±0.33	3±2a	6.3±0.88a	7±2.89^{b}
	trimester	**three**	**findings**	
Mean little size	10.6±0.79	9±2.31	8.13±0.13^{a}	10.83±0.66^{a*}
Mean resorbed fetuses	1.93±0.66	2.87±0.79^{ab*}	4.47±0.35^{b*}	6.17±0.60^{b*}
Mean placenta Weight	520±23.01	460.33±9.84^{ab*}	388±39.95^{b}	344.67±20.21^{b*}
Dead fetuses	2±0.58	3.33±0.88^{ab*}	5.67±0.67^{b*}	6.67±0.88^{c*}

key

*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 (P<0.05*

The comparative mean litter sizes between the dexamethasone treated groups against the control depicted inverse dose response relationship in that, as the dose increased the mean litter size reduced especially when treatment was done in trimester one and

Trimester two (TM1, & TM2) and this was found to be statistically significant ($p < 0.05$) as compared with the control. The mean litter size was lowest in the HDG treated atTM1 with 2.23±0.62c followed by MDG at

7.6±0.70b and lastly LDG at 9.07±0.52b while that of the control was 11.77±0.27a respectively This comparative dose response relationship in the intra and inter group comparisons were further tested with ANOVA and with Tukey test on post-hoc t-tests and they were also found to be statistically significant by both P and F-values across the dexamethasone treated groups and even when the dexamethasone groups were compared with the controls (table 1).

The mean placental weight was also observed to have similar inverse dose responserelationship with the dose of treatment and the time of exposure. It was found that the lowest placental weight recorded was in the high dexamethasone treated group when treated at TM1 and lowest in the low dexamethasone group at TM3 (table 1).The number of the resorbed endometrial gland were also seen to be directly response with the dose of exposure as well as with the time of exposure in that with increasing doses of dexamethasone exposure, there was a corresponding significant increase (P<0.05) in number of endometrial glands resorptions particularly in TM1 and TM2 across all the dexamethasone treated groups as compared with the control (table 1).

On the percentage embroylethality, it was observed that the comparative mean number of dead fetuses in utero increased with dexamethasone dose and the time of exposure. When dexamethasone was administered at TM1 the mean embryo-lethality in HDG was at 9.5±1.5 followed by MDG at 7±2.08 and lastly at LDG was 3±0.58, it was statistically higher (P<0.05) when compared with the control. When dexamethasone treatment was instituted at TM2, the embryo-lethality was 7±2.89 for the HDG, MDG 6.3±0.88 was which was statistically higher (P<0.05) than the control, while and LDG embryo-lethality atTM2 was not statistically different (p>0.05). When treatment was done at TM3 the percentage embryo-lethality did not show statistical significance difference (p>0.05) with the control (table 1).

Table 2: Table below shows fetal parameters of prenatal low, medium and high dexamethasone dose levels of 20-days-old fetuses in the first, second and third trimester.

Dexamethasone groups	dexamethasone treatment periods	Fetal pancreatic weight (gms)±SEM	Fetal pancreatic volume(mm2) ±SEM	Mean fetal Crump Length(cm) ±SEM	Mean Biparietal Diameter(cm) ±SEM
control	……	**0.302+0.02**	**4.43+0.00**	**4.66+0.33**	**1.776+0.033**
LDG	**Trimester I(TM_1)**	**0.174+0.002****	**3.166+0.66****	**4.06+0.133****	**1.33+0.33**
	Trimester II (TM_2)	**0.284+0.000***	**3.93+0.88***	**4.16+0.33***	**1.50+0.577**
	Trimester III(TM_3)	**0.287+0.00***	**4.166+0.083***	**3.96+0.92***	**1.533+0.33**
MDG	**Trimester I (TM_1)**	**0.133+0.00****	**2.80+0.057****	**3.43+0.033****	**1.13+0.33****
	Trimester II (TM_2)	**0.261+0.005****	**3.13+0.18****	**3.46+0.88****	**1.36+0.33**
	Trimester III(TM_3)	**0.272+0.006****	**3.83+0.33****	**3.60+0. 577**	**1.40+0.577**
HDG	**Trimester 1(TM_1)**	**0.122+0.00****	**2.103+0.54****	**2.733+0.201****	**0.776+0.69****
	Trimester II(TM_2)	**0.206+0.00****	**2.44+0.08****	**3.2+0.57****	**1.10+0.00****
	Trimester III(TM_3)	**0.262+0.001****	**3.13+0.12****	**3.03+0.08**	**1.26+ 18**

p<0.05p<0.05 versus control.+SEM-means*

**p shows the results that have a statistically significant difference with the control and with other dexamethasone groups using Chi – square tests and using one-way ANOVA with Tukey test on post-hoc t-tests. * indicates significance (p<0.05).*

First trimester

Fetal Pancreas Volume (FPV) in the control group (0.43±0.015) was found to be significantly higher than that in the low dose group (0.3±0.000), medium (0.3±0.00) and high dose (0.3±0.00), F (3, 8) = 72.43, p = < 0.0001 however the fetal pancreas volume in low dose, the medium dose and high dose was not statistically different from each other.

According to the post hoc test results Fetal Crump Length (FCRL) (4.47±0.03) was found to be significantly higher than that in the low dose group (4.07±0.133), medium (3.43±0.03) and high dose (2.73±0.09), F (3, 8) = 82.81 as indicated by the p value, p = < 0.0001 which was less than 0.05.low dose, medium dose and high dose group were statistically different from each other.

Fetal Biparietal Diameter (FBPD) in the control group (1.43±0.03) was found to be significantly higher than that in the low dose group (1.33±0.03), medium (1.10±0.06) and high dose (0.997), F (3, 8) = 10.28, p = 0.004. The weight in low dose and the medium dose was not statistically different but was found to be lower in the high dose group.

Trimester two

As indicated by the post hoc test results Fetal weight in the control group (6.87±0.03) was found to be significantly higher than that in the low dose group (5.11±0.16), medium (4.32±0.07) and high dose (3.48±0.14), F (3, 8) = 172.1 as showed by the p value, p = < 0.0001. Which is less than 0.05.

Fetal Pancreas Volume in the control group (0.43±0.02) was found to be significantly higher than that in the low dose group (0.3±0.000), medium (0.3±0.02) and high dose (0.3±0.00), F (3, 8) = 72.43, p = < 0.0001 The weight in low dose, the medium dose and high dose was not statistically different from each other.

According to the post hoc test results Fetal CRL (4.47±0.03) was found to be significantly higher than that in the low dose group (4.13±0.09), medium (3.47±0.09) and high dose (3.03±0.09), F (3, 8) = 68.29, p = < 0.0001. The weight in low dose and the control dose was not statistically different but was found to be lower in the high dose group.

Fetal BPD in the control group (1.63±0.15) was found to be significantly higher than that in the low dose group (1.5±0.06), medium (1.34±0.03) and high dose (1.20±0.058), F (3, 8) = 4.76, as indicted by the p Value p = 0.04 which was less than 0.05. However, the low dose, medium dose and high dose group were not statistically different from each other.

Trimester Three

As showed by the post hoc test results Fetal weight in the control group (6.83±0.03) was found to be significantly higher than that in the low dose group (5.27±0.11), medium (4.42±0.05) and high dose (3.99±0.074), F (3, 8) = 290.8, this was indicated by the p Value p = < 0. 0001.which was less than 0.05

Fetal Weight in the control group (0.017±0.0002) was found to be insignificantly higher than that in the low dose group (0.017±0.0000), medium (0.017±0.000) and high dose (0.023±0.003), F (3, 8) = 3.1, as indicated by the p value p = 0.92. which is greater than 0.05 The weight in low dose the medium dose and high dose group was not statistically different from each other.

Fetal Pancreas Volume in the control group (0.43±0.015) was found to be significantly higher than that in the low dose group (0.3±0.000), medium (0.3±0.000) and high dose (0.3±0.000), F (3, 8) = 72.43, p = < 0.0001 The weight in low dose, the medium dose and high dose was not statistically different from each other.

According to the post hoc test results Fetal CRL (4.47±0.03) was found to be significantly higher than that in the low dose group (4.23±0.09), medium (3.6±0.06) and high dose (3.2±0.06), F (3, 8) = 86.55 as showed by the p-value p = < 0.0001 which is less than 0.05, however, the weight in low dose and the control dose group was not statistically different from each other.

Fetal BPD in the control group (1.73±0.03) was found to be significantly higher than that in the low dose group (1.53±0.03) and medium (1.4±0.06b) F (3, 8) = 18.36, as showed by the p value p = 0.001 which was less than 0.05. However, the high dose (1.35±0.029) was not statistically different from the control group.

Table 3: Table below shows correlation analysis effects of prenatal low, medium and high dexamethasone dose levels of 20-days-old fetuses in the first, second and third trimester.

FETAL PARAMETERS		Fetal Weight	Fetal Pancreas Weight	Fetal pancreas Volume	Fetal CRL	Fetal BPD
Fetal Weight	r	1				
	P					
Fetal pancreas Weight	r	-.162	1			
	P	.346				
Fetalpancreas Volume	r	.843**	-.119	1		
	P	.000	.490			
Fetal CRL	r	.889**	-.265	.660**	1	
	P	.000	.118	.000		
Fetal BPD	r	.819**	-.169	.572**	.753**	1
	P	.000	.325	.000	.000	

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

Table 4: Table below shows the effect of control, low, medium and high dexamethasone dose levels of various organ weights of 20-days-old fetuses during the first, second and third trimester.

FETAL ORGANS(wt.) (gms)	Control	LDG (low dexaGroup 0.65mg/kgbwt)	MDG(medim dexaGroup 2mg/kgbwt)	HDG (high dexaGroup 4mg/kgbwt)	F	P-value
fetal wt TM1	6.14±0.03	4.81±0.11b	3.89±0.22c	3.33±0.12d	146.46	0.000*
TM2	6.14±0.03	5.21±0.16b	4.82±0.07c	3.58±0.14d	172.1	0.000*
TM3	6.14±0.03	5.37±0.11b	5.22±0.05c	4.99±0.074d	290.8	0.000*
Brain (wt.) TM1	185.7±0.100a	143.67±2.85b	125±2.52c	115.67±2.40c	99.7	<0.001*
TM 2	185.7±0.100a	167.0±1.154b	145±2.52c	127±1.53d	261.7	<0.001*
TM 3	185.6±0.001a	175.3±3.67b	157.3±0.33c	134.7±1.86d	117.5	<0.001*
LIVER (wt.) TM1	290.00±0.001a	224±0.001b	210±3.21c	144.33±2.19d	944.8	<0.001*
TM2	290±0.001a	236.8±4.22b	216±0.001c	205.1±5.1c	130.9	<0.001*
TM3	290±0.001a	235.7±1.67b	229.33±3.33b	213.33±3.33c	117.7	<0.001*
HEART (wt.) TM1	22.7±0.001a	13±0.58b	11.53±0.33b	9.67±0.433c	213.7	<0.001*
TM 2	22.7±0.001a	18.53±0.33b	16.87±0.33c	16.4±0.33c	99.22	<0.001*
TM3	22.7±0.001a	20.53±0.33b	18.53±0.33c	17.03±0.33d	72.7	<0.001*
KIDNEY (wt.)	22.8±0.001a	16.57±0.33b	14.57±0.33c	12.47±0.33d	238.6	<0.001*

TM1						
TM 2	22.8±0.001a	18.57±0.88b	15.57±0.33c	12.13±0.33d	82.1	<0.001*
TM 3	22.8±0.001a	20.23±0.33b	18.23±0.33b	14.8±1.00c	43.5	<0.001*
PANCR (wt.) TM1	0.303±0.001a	0.177±0.002b	0.138±0.003b	0.127±0.002c	1258.95	<0.001*
TM 2	0.303±0.001a	0.29±0.003b	0.29±0.003b	0.21±0.003c	203.7	<0.001*
TM3	0.303±0.001a	0.300±0.001b	0.300±0.001b	0.214±0.003c	477	<0.001*
PLACE (wt.) TM1	520±0.001a	424.33±3.33b	362.33±3.18c	311±1.53d	1372.9	<0.001*
TM2	520±0.001a	461.3±3.33b	415.3±3.33c	382±4.16d	362	<0.001*
TM 3	520±0.001a	470±5.77b	446.3±3.18c	426.3±3.18d	121.8	<0.001*

From the table 4 above, the fetal weight reduced by 44%,36%,20% when given throughout at high, medium and low dexamethasone doses respectively. When the dexamethasone was given from day 7th to day 20th, weight reduced by 41%,21% and 14% at high, medium and low dexamethasone doses respectively. Moreover, when dexamethasone drug was given from day 14th to 20th day; weight of the fetuses reduced by 20%,15% and 12% at high, medium and low dexamethasone doses respectively. During the first trimester, fetal weight in the control group (6.57±0.03) was found to be significantly higher than that in the low dose group (4.21±0.11), medium (3.39±0.22) and high dose (2.73±0.12), F (3, 8) = 146.46, p = < 0.0001. The weight in low dose and the medium dose was statistically different and was found to be lower in the high dose group. As showed by the post hoc test results Fetal weight in third trimester in the control group (6.83±0.03) was found to be significantly higher than that in the low dose group (5.27±0.11), medium (4.42±0.05) and high dose (3.99±0.074), F (3, 8) = 290.8, this was indicated by the p Value p = < 0.0001.which was less than 0.05 .

From the table 4 above brain weight in the first trimester, the brain weight in the control group (M=178.93, SE = 3.33) was found to be significantly different from that in the low dose group (M=143.67, SE = 2.85), the medium dose group (M=125.00, SE = 2.52) and the high dose group (M=115.67, SE = 2.40), F (3, 8) = 99.7, p=<0.001. The results also indicated that there was no significant difference between medium dose group and high dose group. During the second trimester, the brain weight in the control group (M=185.70, SE = 0.100) was found to be significantly different from that in the low dose group (M=167.0, SE = 1.15), the medium dose group (M=145, SE = 2.52) and the high dose group (M=127.00, SE = 1.53), F (3, 8) = 261.7, p=<0.001.In the third triminster,the brain weight in the control group (M=185.70, SE = 0.100) was found to be significantly different from that in the low dose group (M=175.3, SE = 3.67), the medium dose group (M=157.3, SE = 0.33) and the high dose group (M=134.7, SE = 1.86), F (3, 8) = 117.5, p=<0.001..

Liver weight in first trimester, in the control group (M=290.00, SE = 0.001) was found to be significantly different from that in the low dose group (M=224.00, SE = 0.001), the medium dose group (M=210.0, SE = 3.21) and the high dose group (M=144.33, SE = 2.19), F (3, 8) = 944.8, p=<0.001.while in second trimester, liver weight in the second trimester control group (M=290.00, SE = 0.001) was found to be significantly different from that in the low dose group (M=236.814, SE = 4.22), the medium dose group (M=216, SE = 0.001) and the high dose group (M=205.1, SE = 5.1), F (3, 8) = 130.9, p=<0.001.And during the third triminster,liver weight in the control group (M=277.0, SE = 0.001) was found to be significantly different from that in the low dose group (M=235.7, SE = 1.67), the medium dose group (M=229.33, SE = 0.001) and the high dose group (M=213.33, SE = 3.33), F (3, 8) = 117.7, p=<0.001.

During the first triminster,fetal heart weight in the control group (M=22.70, SE = 0.001) was found to be significantly different from that in the low dose group (M=13.00, SE = 0.58), the medium dose group (M=11.53, SE = 0.33) and the high dose group (M=9.67, SE = 0.433), F (3, 8) = 213.7, p=<0.001. The results also indicated that there was no significant difference between low dose group and medium dose group while in second trimester fetal heart weight in the control group (M=22.70, SE = 0.001) was found to be significantly different from that in the low dose group (M=18.53, SE = 0.33), the medium dose group (M=16.87, SE = 0.33) and the high dose group (M=16.4, SE = 0.33), F (3, 8) = 99.22, p=<0.001.and during the third trimester fetal heart weight in the control group (M=22.70, SE = 0.001) was found to be significantly different from that in the low dose group (M=20.53, SE = 0.33), the medium dose group (M=18.53, SE = 0.33) and the high dose group (M=17.03, SE = 0.33), F (3, 8) = 72.7, p=<0.001.

In first trimester fetal kidney weight in the control group (M=22.8, SE = 0.001) was found to be significantly different from that in the low dose group (M=16.57, SE = 0.33), the medium dose group (M=14.57, SE = 0.33) and the high dose group (M=12.47, SE = 0.33), F (3, 8) = 238.6, p=<0.001 while in second trimester fetal kidney weight in the control group (M=22.8, SE = 0.001) was found to be significantly different from that in the low dose group (M=18.57, SE = 0.88), the medium dose group (M=15.57, SE = 0.33) and the high dose group (M=12.13, SE = 0.33), F (3, 8) = 203.7, p=<0.00 and in the third trimester fetal kidney weight in the control group (M=23.5, SE = 0.001) was found to be significantly different from that in the low dose group (M=20.23, SE = 0.33), the medium dose group (M=18.23, SE = 0.33) and the high dose group (M=14.8, SE = 1.00), F (3, 8) = 43.5, p=<0.001

Fetal Pancreas weight in the first trimester ;control group (M=0.304, SE = 0.003) was found to be significantly higher than that in the low dose group (M=0.177, SE = 0.002), the medium dose group (M=0.138, SE = 0.003) and the high dose group (M=1258.95, SE = 0.002), F (3, 8) = 1258.95, p=<0.001, while in second trimester Fetal Pancreas weight in the control group (M=0.303, SE = 0.001) was found to be significantly higher than that in the low dose group (M=0.29, SE = 0.003), the medium dose group (M=0.29, SE = 0.003) and the high dose group (M=0.21, SE = 0.003), F (3, 8) = 203.7, p=<0.001 and in the third trimester, Fetal Pancreas weight in the control group (M=0.303, SE = 0.001) was found to be and significantly higher than that in the low dose group (M=0.300, SE = 0.001), the medium dose group (M=0.300, SE = 0.001) and the high dose group (M=0.214, SE = 0.003), F (3, 8) = 477, p=<0.001. Antennal dexamethasone leads to hyperglycemia, glucose intolerance and hyperinsulinemia1,22,44.

During the first triminster, the placental weight in the control group (M=520.0, SE = 0.001) was found to be significantly different from that in the low dose group (M=424.33, SE=3.33), the medium dose group (M = 362.33, SE=3.18) and the high dose group (M = 311, SE= 1.53), F (3, 8) = 1372.9, p=<0.001.

While in the second trimester, placenta weight in the control group (M=520.0, SE = 0.001) was found to be significantly different from that in the low dose group (M=461.3, SE=3.33), the medium dose group (M = 425.33, SE=3.33) and the high dose group (M = 382, SE= 4.16), F (3, 8) = 362, p=<0.001.

And in third trimester, the placenta weight in the control group (M=520.0, SE = 0.001) was found to be significantly different from that in the low dose group (M=470.0, SE=5.77), the medium dose group (M = 446.3, SE=3.18) and the high dose group (M = 426.3, SE= 3.18), F (3, 8) = 121.8, p=<0.001.

DISCUSSION

In this study, the effects of antenatal exposure to wide range of glucorticoids level were observed to have negative manifestation to the fetal outcome. The major impairments were observed in the first and second trimester and in low and high dexamethasone doses. From this study, when dexamethasone is given throughout the gestation period at high doses leads to major detrimental effects to both fetus and the mother wellbeing, this is controversial to what had been described before [31].

Fetal pregnancy outcomes had inverse dose response relationship in that with the increasing dexamethasone doses there was significant reduction ($p<0.05$) mean (fetal weight, biparietal diameter, crown lump length) in LDG, MDG and HDG as compared with the control (table 1). This in accord with the fact that as the pregnancy progresses towards parturition, the effect of 11β hydroxysteroid dehydrogenase type 2 enzyme declines exposing the fetus to maternal glucorticoids leading to poor development of fetus [9,41]

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, 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 1 and 3 respectively). Maternal glucorticoids to fetus are protected by a barrier in consist majorly of 11β hydroxysteroid dehydrogenase type 2 enzyme that converts exogenous and endogenous glucorticoids into their inactive 11 keto metabolite [7,13,22]. Another factor that contributes to protect the fetus from excess glucorticoids is p glycoprotein 1(p-gp1)which is a multidrug resistant protein1 .as the pregnancy progresses towards parturition the effect of 11β hydroxysteroid dehydrogenase type 2 enzyme declines exposing the fetus to maternal glucorticoids thus explain the reason for poor development of fetus at last gestation period [1,9,45–47]. Research done on pregnant ewe administered with intramuscular dexamethasone on 40th and 41th day of gestation period showed decline in number of binucleate cell (BNCs), increased Bax p53 and impaired placenta apoptic markers, sex-specific impairment of in placental development affecting the fetal growth which may lead to intrauterine growth retardation [7,9,46].additionally, dexamethasone may malfunction embryogenesis through impairment of placental nutrient of exchange materials like, glucose and amino acid transporter [1].Likewise, study done on rats and humans 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 [41].

Prenatal administration of dexamethasone impaired fetal visceral such as a kidneys, liver, placental weight, brain, pancreas, little size and fetal weight (table 2). These prejudicial effects were consequently observed to be dependent on the gestation period and amount of the dexamethasone administered. For instance, from the table 3 and4 above, the fetal weight reduced by 44%,36%,20% when given throughout at high, medium and low dexamethasone doses respectively. When the dexamethasone was given from day 7th to day 20th, weight reduced by 41%,21% and 14% at high, medium and low dexamethasone doses respectively. In addition,when dexamethasone drug was given from day 14th to 20th day; weight of the fetuses reduced by 20%,15% and 12% at high, medium and low dexamethasone doses respectively. From this finding it shows that the reduction of weight in albino rats is a direct effect of the dexamethasone on fetal growth pathways which also indirectly inhibit food intake [32–35]. Additionally, Intrauterine glucorticoids have been noted to impair development of the intestines especially small intestine resulting to immobility of the gut [36.] Feng et al found that prenatal dexamethasone exposure on day 16 to 18 of embryogenesis led to reduced fetal body weight and intrauterine growth retardation thus explaining the direct effect growth restriction [37].

The perturbations upon dexamethasone use in the current study were found to have deleterious impact to the developing fetal pancreas with significant reduction in mean fetal pancreas weights, as well as the histo-stereological parameters such as; total pancreas volumes reduction, in all dexamethasone groups (table 1-3). Antennal dexamethasone leads to hyperglycemia, glucose intolerance and hyperinsulinemia [1,22,44].Our present resultsdemonstrating significant decrease of fetal placental with increase with dexamethasone dosages. This is attributed to the fact that prenataldexamethasone impairs placental embryogenesis, growth and proliferation, vasculogenesis and angiogenesis as well as glucose transport, by altering VEGF (vascular endothelial growth factor), VEGFR1 and VEGFR2 when administered during early pregnancies, leading to placenta insufficiency [1,41,45]

.Dexamethasone effects caused reduced brain growth with delayed myelination and hypertension [2,3,23–26].Additional effects on the restrict growth of the brain include ;decline of the blood brain barrier permeability, reduction of fetal cerebral blood flow,increased hypothalamopituitary adrenal axis activity, hypoxia of brain, reduction in hippocampal size to learning and attention disorders [2,3].Studies in animal studies shows that prenatal dexamethasone decreases ALP, GGT, total bilirubin, AST and ALT values low-dose dexamethasone and high-dose dexamethasone groups compared to the control group [38]. Other teratogenic effects of prenatal dexamethasone in the liver include; immunosuppression, growth retardation, fatty liver elevated liver triglycerides and induced programming liver steatosis due to altered leptin expression [38,391,22,40].

According to our results there was decrease in fetal kidneys when dexamethasone was administered during first trimester and second trimesters in both high and medium doses especially compared to control (table3). Research conducted in rats demonstrated that, prenatal dexamethasone resulted gross suppression, alteration of cell proliferation and reduction in nephron number seen in the adult offspring of dexamethasone exposed mothers[6,35,].

The consequences of thatare a reduction in glomerular number, glomerulosclerosis which may predispose to adult hypertension [43]. Further studies showed, ewes exposed to daily steroids during development also had significant hypertension at 2 months of age [6]. Prenatal dexamethasone led retarded heart growth resulting to cardiomegaly also decreased cardiomyocyte number contributed to left ventricular hypertrophy and cardiac malfunction [1,41,42]. The above explains the hypertension in adults.

CONCLUSION

Maternal administration of synthetic GCs can alter fetal growth but this phenotype is strongly dependent on the dosing and timing of exposure during gestation.

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