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Comparative effects of dexamethasone on placental and foetal organ weights and some linear body measurements in Yankasa sheep and Sahel goats

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Abstract

Dexamethasone is a potent synthetic glucocorticoid use in veterinary and human medicine. However, it causes intra uterine growth restriction (IUGR) and decreases birth weights in some animal species and humans, although each species respond differently. This study investigated the effects of dexamethasone on placental weights and some foetal parameters in Yankasa sheep and Sahel goats with known average gestational length of 148.35 ± 1.50 days and 148.33 ± 1.58 days respectively. Ten adult Sahel goats comprising 8 does and 2 bucks and 10 Yankasa Sheep comprising of 8 ewes and 2 rams were used for this study. Pregnancies were achieved by natural mating after synchronization. Repeated dexamethasone injections were intramuscularly given at 0.25mg/kg body weight on days 1, 3 and 5 during first trimester and days 51, 53 and 55 during second trimester. Foetuses were harvested at day 78 of gestation all through Caesarean section. Foetal weights, crown-rump lengths (CRL), height at withers, heart girth, abdominal circumference, weights of adrenal glands and placental weight were evaluated. Specimens from placentas and adrenal glands were collected for histological analysis. Results showed that the mean placental weights, placental efficiency and foetal body weights were significantly ($P<0.05$) decreased in dexamethasone treated sheep and goats compared to controls. There was no significant change in foetal adrenal glands and linear body measurements between dexamethasone treatment and control groups in both species except crown-rump lengths (CRL) which was significantly ($P<0.05$) reduced in Sheep foetuses. It was concluded that dexamethasone caused significant decrease in placental weights and placenta efficiency and hence placental- maternal- foetal transport of nutrient materials in both species and also caused decrease in foetal crown-rump-lengths in sheep but not in goats. This suggests that dexamethasone has some teratogenic effects and that Sheep are more susceptible to dexamethasone treatment compared to goats.

Keywords: Dexamethasone, Foetuses, Placenta, Pregnancies, Sahel goats, Yankasa sheep

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Introduction

Dexamethasone is a synthetic glucocorticoid that is used widely in human and veterinary medicine largely for its ability to accelerate foetal lung maturation and also for the potent anti-inflammatory and immunosuppressive activities (Liggins & Howie, 1972; Andrew *et al*., 1991; Rober & Dalziel, 2006). It stimulates surfactant production by the lung (Lunghi *et al*., 2010), reduces the incidence of respiratory distress syndrome in new-born, enhances the efficacy of neonatal surfactant therapy and reduces the associated risk of intravascular haemorrhage, necrotising enterocolitis,

neonatal hyperbilirubinaemia and neonatal death (Crane *et al*., 2003). This action is critical to prepare the foetus for extra-uterine life, and this is the reason that synthetic glucocorticoid treatment is so widely used in preterm pregnancies where lung immaturity threatens neonatal viability. It is recommended that pregnant women who are at risk of preterm delivery be place on a single course of dexamethasone therapy to reduce the risks of respiratory distress syndrome (RDS), peri-natal mortality and other morbidities (Crane *et al*., 2003).

The clinical conditions for which corticosteroids are used in humans include, asthma, systemic lupus erythematosis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, nephritic syndrome, cancer, leukemia, organ transplantation, autoimmune hepatitis, hypersensitivity reactions, cardiogenic and septic shock and of course, glucocorticoid deficiency diseases such as in Addison's disease and panhypopituitarism (Ballard & Ballard, 1995; Alves *et al*., 2008).

The use of dexamethasone in veterinary medicine is primarily therapeutic. It is effective in treating inflammation, acetonaemia/ketosis, hepatic lipodosis, non-specific skin disease, shock, fatty liver syndrome and stress (Andrew *et al*., 1991; Aliyu 2007; Dowling, 2010; Pierre-Louis, 2010). Although these treatments greatly improve foetal and maternal survival (Rober & Dalziel, 2006), they are not without adverse effects. Despite the widespread clinical use of dexamethasone, it has been associated with altered hypothalamo–pituitary–adrenal axis, intra uterine growth restriction (IUGR), decrease birth weight, decrease placental and foetal weights in some animal models as well as humans (Bloom *et al*., 2001; McDonald *et al*., 2003; Ain *et al*., 2005; Faria & Longui, 2006; Hewitt *et al*., 2006; Kranendonk *et al*., 2006; Baisden *et al*., 2007). The foetal and placental effects are attributable to the fact that unlike the endogenous glucocorticoids, dexamethasone is not metabolized by the placental enzyme, 11 β - hydroxysteroid dehydrogenase type-2 (11β-HSD-2) and therefore, most readily crosses the placenta and enter foetal circulation (Lindsay *et al.,* 1996; Baisden *et al*., 2007). However, different species respond to medications differently due to variations in anatomy, metabolism and inherent pharmacokinetics, hence there is paucity of information on the effects of dexamethasone on sheep and goats, particularly in the Sahelian region. This study investigated the effect of repeated maternal dexamethasone treatments of pregnant Yankasa sheep and Sahel goat on some foetal and placental parameters and organ weights with a view of assessing and comparing these parameters.

Materials and Methods

Ten apparently healthy adult Sahel goats comprising 8 does and 2 bucks and 10 Yankasa sheep comprising 8 ewes and 2 rams were used for this study. Their known mean gestational lengths were 148.35 ± 1.50 days for Yankasa sheep and 148.33 ± 1.58 days for Sahel goats respectively (Rwuaan *et al*., 1993; Waziri *et al*., 2010).

The animals were purchased from a local livestock market and private farms in Maiduguri Metropolis. The ages of the does ranged between 2 and 2½ years and the bucks ranged from 2 to 3 years, while that of the ewes were 3 to 3½ years, and the rams were 2½ to 3½ years old, based on dentition and breeding history (Dyce *et al.*, 1987). The does weighed between 23 to 25 kg and the bucks 35 kg and 38 kg. The ewes weighed between 30 to 35 kg and the rams were 39 to 42 kg. Their body condition score (BCS) of between 3.0 and 3.5 was maintained throughout the period of the experiment. Breeding history, abdominal palpation and ballottement, nature of mammary secretions, conditions of udder were used in the initial selection of the non-pregnant ones. They were managed intensively and acclimatized for six weeks at the University of Maiduguri livestock research farm before the commencement of the experiment. Their feed rations consisted of wheat offal, beans husks and hay from groundnut leaves. Mineralized salt licks and water were provided *ad libitu*m. During the stabilization period, the animals were treated with oxytetracycline LA (Introxin-200®, Interchiemie, Venray, Holland) at 20 mg/kg body weight I/M and ivermectin (paramectin®, Pharma Swede, Egypt) at 200µg/kg body weight. The males and the females were initially kept in different pens until the time of breeding.

Estrus synchronization

The animals were synchronized at the end of the acclimatization period using 250µg of cloprostenol (Estrumate®, Schering Trough Animal, Germany) 11 days apart, as previously reported (Akusu & Egbunike, 1984). The females were teased with apronned males daily and all the females that came into estrus after the second treatment were allowed to be served naturally by the male. Days of estrus were recorded and considered as day 0 of the gestation. After successful synchronization and fertile mating, the animals were randomly separated into 4 groups (2 each of ewes and does).

Accordingly, the groups were as follows: DTS (Dexamethasone treated ewe), NDS (non-dexamethasone treated ewe (Control)), DTG (Dexamethasone treated doe), and NDG (non-dexamethasone treated doe (Control).

Dexamethasone treatment

The animals in the treated group were given dexamethasone (Dexaphan®, Pharma Pharmaceuticals, Swede-Egypt) intramuscularly at 0.25mg/kg body weight on days 1, 3 and 5 during first trimester and day 51, 53 and 55 during second trimester. Animals in the control group were left untreated. The animals were keenly observed for possible clinical changes throughout the period of the study. Their initial body weights, rectal temperatures, pulse rates and respiratory rates were measured and recorded. This was continued at two weeks interval during the course of the experiment. Pregnancies were later confirmed by failure to return to estrus and by ultrasonograhic examination using Draminski Ultrasound Pregnancy Detector (UPD-PD032013EX-1.2, Draminsky Agricultural Engineering Co. Inc., Owocowa-Olsztyn, Poland).

The pregnant animals from both the control and treatment groups were selected at day 78 of gestation and the foetuses harvested through caesarian section (CS). The foetuses were located and gently removed and were towel dried and weighed, and sex and uterine location were recorded. Foetal weights were determined using a sensitive table weighing scale (Camry Premium Scale, Home Premium, China, Model: WS101/SP-20). The foetuses were also immediately examined for possible developmental changes. Indices such as foetal weight, crown-rump length, height at withers, heart girth, abdominal circumference, weights of adrenal glands as well as the placental weights were evaluated. The parameters considered for the developmental horizons were based on earlier studies (Sivachelvan *et al.,* 1996; Waziri *et al*., 2012). The placentas and adrenal glands were similarly removed and weighed using digital weighing scales and some specimens of the placentas and the adrenal glands were collected for histological analysis as described by Drury *et al.* (1967). The sections were stained with Haemotoxylin and Eosin (H&E) for histological examination using light microscope (Multiple Headed Microscope; DESC-LN-0100-MG001, Vamed Engineering, UK). Microphotographs were taken using Canon IXUS camera, pixel: 16.5 (China). Post operatively, antibiotics (pen-strep treatment 200,000iu: 200mg, 1ml/25 kg), analgesic (dichlofenac sodium 75mg/animal) injections and intravenous infusion solution (5% dextrose) therapy were administered to each animal.

Statistical analysis

Data collected were expressed as mean **±** SD The significant differences between the dexamethasone treated and non-dexamethasone treated groups were compared using student's t – test. Significant differences were considered at $p < 0.05$. Statistical software package, GraphPad InStat® version 3.0 (2003) was used for the analyses.

Results

Twenty six (26) foetuses, comprising of 14 males and 12 females, were obtained from the pregnant ewes and does as follows: 6 foetuses each from 4 ewes of the treatment and control groups respectively with 50 % twinning rate in either group; 7 foetuses each from 4 does of the treatment and control groups respectively with 25 % twinning rate in either group.

The mean values of foetal body weights, placental weights, placental efficiency, crown-rump length, height at withers, heart girth, abdominal circumference and foetal adrenal glands weight at mid-gestation are presented in table 1. The mean placental weight, placental efficiency and foetal body weight significantly ($P<0.05$) decreased in both dexamethasone treated ewes and does compared to their controls. Linear body measurements (abdominal circumference, height at withers and heart girth) were not significantly ($P>0.05$) altered by dexamethasone treatment in both animal species except the values of crown-rump lengths (CRL) which were significantly ($P<0.05$) reduced in sheep foetuses. The mean weights of foetal adrenal glands were not significantly affected in both dexamethasone treated sheep and goat foetuses compared to their control groups. Histologically, there was no observable differences in the placentas of both dexamethasone treated and control groups in both sheep and goats (Plates I-II). With regard to adrenal glands, the results indicated that although histologically zona glomerusa, zona fasciculate and zona reticularis as well as adrenal medulla showed normal rudimentary growth pattern in dexamethasone treated groups as in control groups of the same gestational age, zona glomerulosa and zona fasciculata predominate over zona reticularis in dexamethasone treated groups compared to their controls in both animals (Plates III-IV).

Table 1: Effects of dexamethasone on foetal, organs and placental weights, and some linear body measurements in Yankasa Sheep and Sahel goat at mid gestation

Parameters	Groups*	Sheep	Goat
Foetal weight (g)	NDT	780.72±9.52	622.80±0.9
	DTT	596.9±0.70[a]	439.60±0.5[a]
Placental weight (g)	NDT	310.30±0.80	346.41±0.22
	DTT	298.55±0.40[a]	290.20±0.6[a]
Placental efficiency	NDT	2.52±0.26	1.79±0.08
	DTT	2.0±0.10[a]	1.51±0.50[a]
CRL (cm)	NDT	20.63±0.18	18.66±0.28
	DTT	19.50±0.20[a]	18.65±0.32
Height at withers (cm)	NDT	17.50±0.20	15.12±0.07
	DTT	17,60±0.20	15.10±0.10
Heart girth (cm)	NDT	14.25±0.15	14.13±0.04
	DTT	14.20±0.17	14.15±0.01
ADC (cm)	NDT	16.31±0.50	15.50±0.08
	DTT	16.30±0.51	15.40±0.08
Adrenal glands (mg)	NDT	360.0±0.1	322.20±0.20
	DTT	359.4±0.5	321.0±0.80

NDT=Non dexamethasone treated (control); DTT = Dexamethasone treated

[a] = significant decrease compare to respective control

*N = 6 for each sheep group; 7 for each goat group

CRL=Crown Rump Length

ADC=Abdominal Circumference

Discussion

The study showed that dexamethasone treatment significantly (P<0.05) decrease foetal body and placental weights as well as placental efficiency in sheep and goats. This implies that prenatal dexamethasone treatment has negative effects on placenta and foetal weights in these species. The observed decrease in placenta weights in sheep and goats in this study are similar to other reports where decreased placental weights were observed in rats and humans following dexamethasone treatment during pregnancy (McDonald *et al*., 2003; Ain *et al*., 2005; Hewitt *et al*., 2006). In other studies, dexamethasone exposure during late pregnancy has been shown to significantly reduce placental weights in rats, sheep, mice and non-human primates (McDonald *et al*., 2003; Hewitt *et al*., 2006; Fowden *et al.,* 2008). In humans, it was reported that dexamethasone administration induced intra uterine foetal growth restriction and decreased placental mass by approximately 50 % (Koppe *et al*., 1977; Ain *et al*., 2005).

The possible cause of the observed decreased foetal weights in the present study, may be due to defects in placental morphology (Bloom *et al.,* 2001), even though histologically, there was no observable differences in the placenta of both dexamethasone treated and control groups.

Bloom *et al.* (2001) stated that most of the actions of glucocorticoids on foetal growth are mediated by changes in the placenta morphology and functions. The size of foetus is proportional to the placental size. When the size of the placenta is restricted, as in compromised placental function, the foetus is also often growth restricted (Price *et al.,* 1992). A poorly developed or inefficiently functional placenta is therefore associated with a reduction in birth weight.

Foetuses are normally protected from the higher maternal concentrations of glucocorticoids by the placental enzyme, 11 β-hydroxysteroid dehydrogenase type-2 (11β-HSD-2). This enzyme acts as a barrier to prevent inappropriate action at glucocorticoid-responsive tissues during foetal development (Wyrwoll *et al.,* 2009). Dexamethasone easily crosses placenta (Lindsay *et al.,* 1996; Baisden *et al*., 2007) and is a poor substrate for 11β-HSD-2 (Mandl *et al*., 2006). As it is poorly metabolized by 11β-HSD-2, therefore, it most readily crosses the placenta, but the extent to which it actually crosses

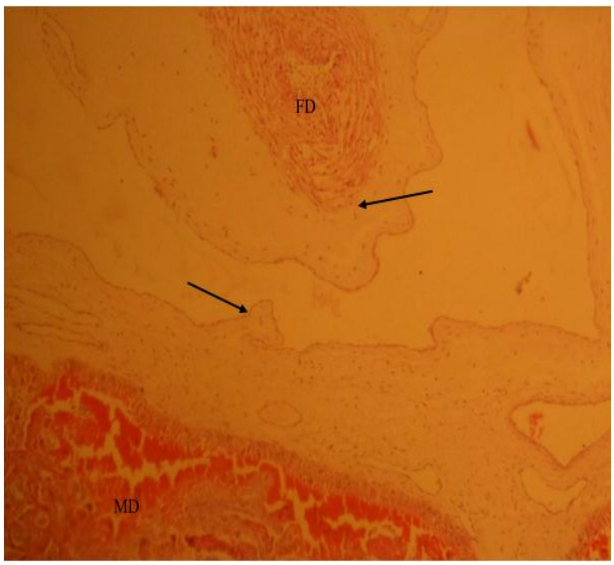

Plate I: Photomicrograph of a cross section of placenta from dexamethasone treated Yankasa ewe during second trimester (day 78). Note the short rudimentary chorionic villi (arrows), fibrinoid deposits (FD) and maternal deciduas (MD) H & E X 100

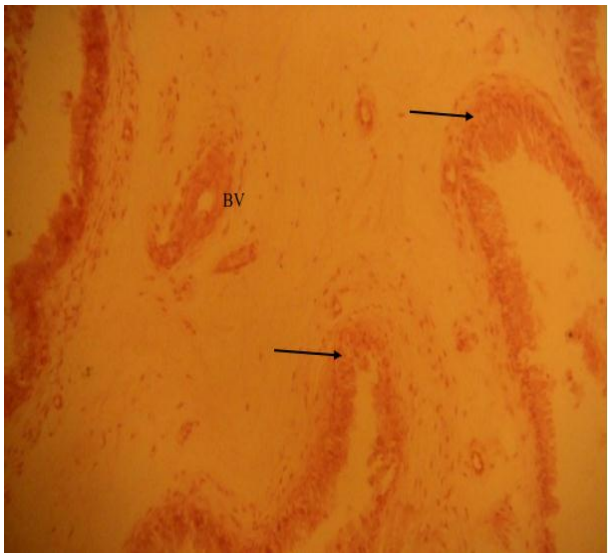

Plate II: Photomicrograph of a cross section of placenta from dexamethasone treated Sahel Doe during second trimester (day 78). Note the prominent chorionic villi (arrows) and the blood vessels (BV) H & E X 100

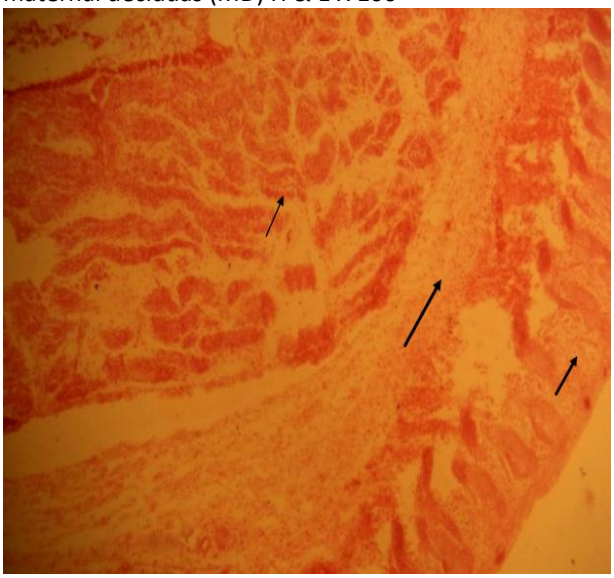

Plate III: Photomicrograph of cross section of adrenal gland of Sahel goat foetus at day 78 from a dam treated with dexamethasone. Note predominant zona glomerulosa (thin arrow) and zona fasciculata (long arrow) and zona reticularis (thick arrow) H & E x100

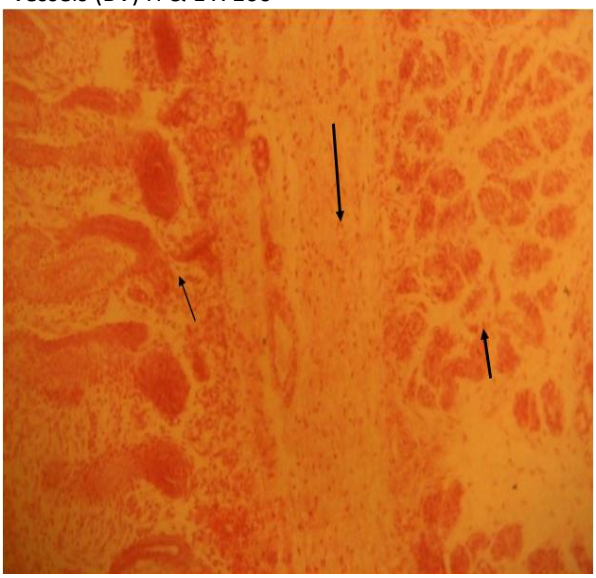

Plate IV: Photomicrograph of cross section of adrenal gland of Yankasa sheep foetus at day 78 from a dam treated with dexamethasone. Note the zona glomerulosa (thin arrow) and zona fasciculata (long arrow) and zona reticularis (thick arrow) H & E x100

the placenta into the foetal circulation and accesses foetal tissues may vary among species (Dodic *et al*., 2002). The placenta and foetal tissues in more susceptible species would have a greater proportion of glucocorticoid exposure following maternal dexamethasone treatment. This may explain the differences in the extent of responses to dexamethasone treatments in Yankasa sheep and Sahel goats in this study.

The mechanism responsible for decrease in the crown-rump lengths (CRL) in sheep foetuses in this study is not clear. However, the decrease indicate that the growth pattern may be asymmetrical such that other linear body measurements

(abdominal circumference, height at withers and heart girth) were not significantly affected like the crown-rump lengths. Asymmetric growth usually occurs during pregnancy and is usually caused by inadequate availability of substrates for foetal metabolism (Brodsky & Christou, 2004; Forbes & Westwood 2008). This type of growth pattern is usually associated with decreased cell size or mass and foetal weight with less effect on total cell number and other foetal body measurements (Gluckman & Hansan, 2004). In the present study, the disorder may be caused by selective effect of limited foetal metabolic substrate availability, resulting from decreased utero-placental exchange or perfusion associated with decrease placental weight (Thorens & Mueckler, 2010) or altered gene expression (Angiolini *et al*., 2006; Vallet & Freking 2007; Cleal & Lewis, 2008) imposed by dexamethasone. The mechanism seems to have some elements of interspecies variation as the Yankasa sheep were more prone than those of goats.

The insignificant difference in mean foetal adrenal gland weights of dexamethasone treated sheep and goat foetuses compared to their controls contradict the reports of Ogueh *et al.* (2000) and Novy & Walsh (1983). Novy & Walsh (1983) observed significant decreased in adrenal weights of rhesus macaques foetuses following maternal dexamethasone treatment. Ogueh *et al.* (2000), on the other hand, asserted that corticosteroid therapy causes adrenal suppression and alter glucose tolerance in humans.

The predomination of zona glomerulosa and zona fasciculata over zona reticularis in dexamethasone treated groups compared to controls in both species suggests some adverse effects of dexamethasone on adrenal glands histology in these species (Stewart, 2008; Wooding & Burton (2008).

In conclusion, dexamethasone caused significant decrease in placental weights and placenta efficiency, hence placental-maternal-foetal transport of nutrient materials in Yankasa sheep and Sahel goats. This translated into decrease foetal weights in both species. This confirms previous findings that antenatal dexamethasone administration retards placental and foetal growth. The decrease foetal linear body measurements observed in foetuses from dexamethasone treated Sheep, and not in goats, suggests some teratogenic effects of dexamethasone in sheep which may imply that Yankasa sheep is more sensitive or susceptible to the influence of dexamethasone compared to Sahel goats.

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