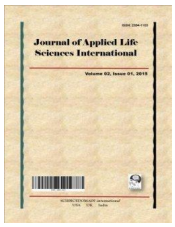

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Age-related Morphological Changes in the Foetal Adrenal of the White Fulani (*Zebu*) Cattle during the Developmental Period

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Authors' contributions

This work was carried out in collaboration between both authors. Author COI designed the study, provided the experimental animals and facilities through the department. Author SOJ wrote the literature review, protocol and carried out the measurements and statistical analysis. Author COI wrote the initial draft of the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: The aim of the study is to evaluate the gross, histology and morphometric changes of the adrenal gland during the foetal developmental period of the White Fulani *(zebu*) cattle in Nigeria, using slaughter house foetal waste.
Study Design: Experimental morphological study was carried out using slaughter house foetal specimens.
Methodology: Gross dissection, routine histology (HE) techniques and measurements of the adrenal gland were employed in this study.
Results: It showed that the topographical position of the foetal adrenals cranial to the kidneys was maintained throughout the foetal age. The weight, length, width and thickness increased with advancing gestation and the differences across the age group were significantly different at $p<0.05$. Histologically, rudiments of foetal cortical zonation were evident at 70-80 days of gestation and became more distinct with increased age. By 180 days and thereafter, the features of the adrenal zones comprising the zona glomerulosa, zona fasciculata and medulla resembled adult adrenal

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gland. The medulla in all age occupied the greater portion of the organ. The measured histometrical parameters of the capsule, cortex and medulla increased with gestational age and were significantly different at $p<0.05$. The features observed in this study suggested a strong endocrine function during the foetal growth that could support the stressful environment of the pastorally reared breed of cattle.

Keywords: Cattle; adrenal gland; foetus; morphology.

1. INTRODUCTION

The adrenal glands are complex endocrine glands regulating multiple physiological functions such as stress response, metabolism, immune functions and dynamics of the cardio-vascular system [1,2]. Insufficient normal adrenal gland function will result in disruption of carbohydrate metabolism, electrolyte levels, which may result in circulatory collapse, hypoglycaemic coma and possible death in many mammals [3].

The adrenal cortex arises from mesodermal coelomic epithelium and produces cortisol, corticosterone, sex steroids and aldosterone. The medulla originates from the neuroectoderm; pheochromoblasts derived from the neural crest migrate through the foetal adrenal cortex to form the medulla and produces norepinephrine and epinephrine [4,5]. In humans, an additional foetal zone, present during foetal life participates with placenta in the production of oestrogen during gestation and thereby playing a role in pregnancy and parturition [6]. Studies have shown that the foetal adrenals produce steroids before evidence of cortical zonation [7]. The role of foetal adrenal cortex in the initiation of parturition in sheep has also been reported and is shown by an increased corticosteroid concentration towards the end of gestation [8]. The corticosteroid stimulate the contraction of myometrium and thus initiate and control parturition [9]. The foetal adrenal gland also secrete substances responsible for maturation of foetal lungs, liver and epithelial cells of digestive tract [10].

The adrenal gland shows distinct species variations in shape, weight and size amongst domestic animals. It also varies in morphological maturation with age amongst mammals. In most mammalian species, the adrenals have been reported to assume the characteristic adult shapes in early foetal growth [11]. Their sizes appear to be influenced by several factors relating to nutrition, environment and stress. It is relatively larger in wild mammals than in related domestic forms, and larger in pregnant and lactating females than in animals that are reproductively inactive [12]. Some authors recorded increase in the weight of adrenals just before birth in sheep foetuses [13,14]. Some researchers [15] have observed a sharp increase in the adrenal weight of lamb foetuses from 136 days to birth. In foetal goat [11] showed an increase in weight, length and thickness of adrenal gland from 59 days to full term with a spurt in the combined weight after 41 days of gestation.

Prenatal developmental studies of the adrenal glands in several mammals are available including rodents [16,17], goats [11,18,19], pig [20], cattle [21], buffalo [22] and camel [23]. However morphological and morphometric information is scant on the adrenal gland of the bovine foetus, particularly on the White Fulani (Zebu) cattle breed which are under extensive pastoral rearing in the dry savanna with little vegetation. They are therefore highly exposed to adverse environmental and nutritional stressful conditions in the tropical climate.

The aim of the present study is to show the morphometric and histological changes in the foetal adrenal gland of the pastoral White Fulani (zebu) cattle and compare it with other available data on domestic animals especially the exotic breeds. The information could be useful in the clinical management of pregnant cattle.

2. MATERIALS AND METHODS

Cattle foetuses of males and females (35) ranging from 9.0-84.5 cm in crown-to-rump-length (CRL) (estimated age range of 70-260 days) were obtained from non-descript cattle sacrificed at the abattoir after Veterinary inspection for health certification. The CRL was measured in centimetres (cm) with a calibrated inelastic thread as curved line on the vertebrae column following the methods of [24]. It was measured between the most rostral parts of the

frontal bone to the rump at the ischiatic tuberosity. Thereafter the approximate gestational age of foetuses was determined following the chart and methodology provided for age determination in several domestic animals including cattle by [10]. The estimated foetal ages were grouped as follows; 70-80, 90-110, 115-145, 135-145, 150-170, 180-220, 235-260 days. The weights of foetuses and excised adrenals were taken with weighing balance (Mettler®) and presented in tables. For histological study, the right and left adrenal glands were fixed in 10% neutral buffered formalin. There were processed routinely, and paraffin sections of 6 µm were obtained. The cut sections were stained routinely with haematoxylin and eosin (HE) for routine morphology. For histometry, an ocular micrometer gauge calibrated with a stage micrometer was used to obtain values of histological parameters of the foetal adrenal gland from selected sections (40 measurements of each parameter per slide) under a light microscope with × 40 objective lens. Data were analyzed statistically using analysis of variance. Duncan's multiple range test was used to separate variant means, and significance was accepted at $p< 0.05$.

3. RESULTS

The foetal adrenal glands grossly maintained a close relationship to the cranial pole of the metanephros in all foetuses examined. The right gland was heart-shaped, while the left was irregular. The left gland was heavier, thicker and longer than the right adrenal in all gestational age group (Fig. 1). Generally the foetal adrenal weight and size (length, breath, width and thickness) increased as the gestational age progressed and were significant at $p<0.05$ (Table 1 and Table 2).

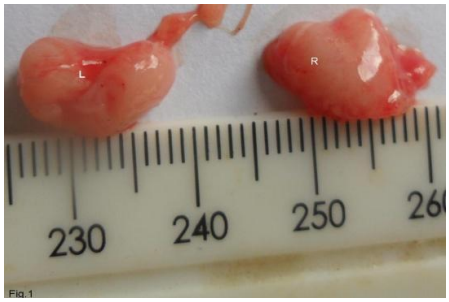


Fig. 1. Gross photograph showing the shape and size of the left and right adrenal gland in the foetal period

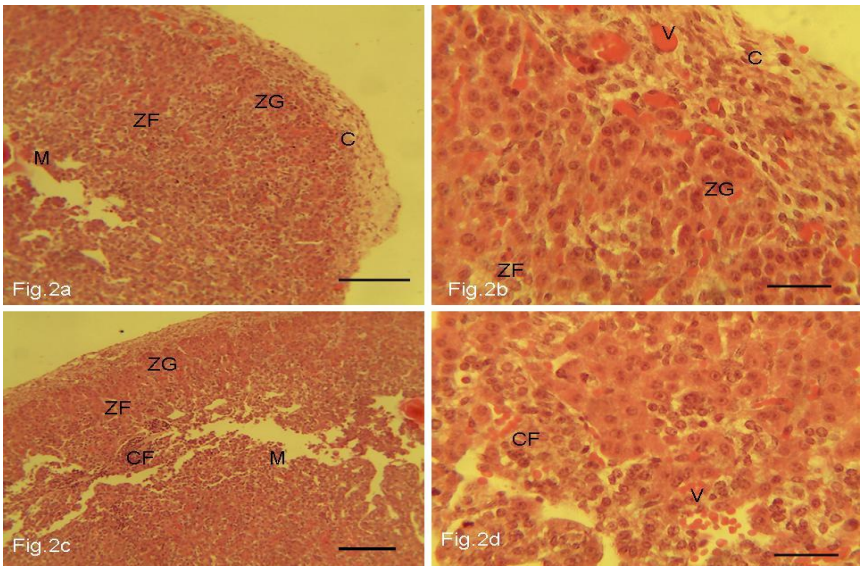


Fig. 2. (a) Photomicrograph of foetal right and left adrenal 70-80 days showing rudimentary cortex and its capsule (C), zona glomerulosa (ZF), zona fasciculata (ZF) and medulla (M).- HE, bar scale 60 µm. (b) Shows copious venous sinusoids (v), capsule (C), zona glomerulosa (ZG), zona fasciculata (ZF)- H & E. bar scale 30 µm. (c) Photomicrograph shows that the zona fasciculata (ZF) occupied much of the rudimentary cortex, medulla (M)- bar scale 60 µm. (d) Photomicrograph of the medulla showing chromaffin-like cells (CF) and copious sinusoids (V). Bar scale 30 µm

Histologically at 70-80 days, a developing capsule was present with maturing connective tissue elements. The capsule was more cellular in the inner part compared to the outer portion. These cells and collagenous tissue of the capsule continued with the loose mesenchymal connective tissue surrounding the gland. All sections examined showed evidence of rudimentary zonation of the foetal cortex without definite demarcation of the boundaries of the cortical zones. The medullary portion was apparent. The presumptive definite cortical zones observed below the capsule were zona glomerulosa and zona fasciculata without clear demarcation. However the rudimentary zona glomerulosa consisted of large polyhedral cells arranged in balls or small masses beneath the differentiating capsule (Fig. 2a).

The presumptive rudimentary foetal zona fasciculata was located deep to the zona glomerulosa and consisted of maturing rectangular cells with eosinophilic cytoplasm, they were in cords of one or 2 cells, some were arranged in vertical columns while others had no definite orientation and were all separated by copious vascular sinusoids (Fig. 2b). The zona fasculata` occupied much of the rudimentary foetal cortex (Fig. 2c). The immature adrenal medulla occupied the centre of the gland and comprised most of the adrenal mass. The cells were arranged in clusters of deeply basophilic cells with copious intervening sinusoids. Clusters of chromaffin-like cells (probably phaechromoblasts) with round to ovoid nucleus were infrequently located amongst sinusoids (Fig. 2d).

In the foetuses of 90-110 days, the differentiation of the capsule and foetal cortex into zonation was clearly established (Fig. 3a). The zona glomerulosa with their small masses of eosinophilic cells, somewhat like a follicle were more pronounced at this age. However isolated groups of cells were still observed without a definite arrangement. Blood vessels ramified in the zona gromerulosa and majority of these sinusoids branched within the zona fasciculate into narrower anastomosing sinusoids. These sinusoids widened into larger larger vessels in the medulla separated by wide cords of developing elongated chromaffin-like cells. The large cells of the zona fasciculata with their eosinophilic cytoplasm were in columns or cords of cells (Fig. 3b). These cells were generally vacuolated and the nuclei somewhat eccentrically placed. The cortico-medullary junction was well defined but a distinct zona reticularis was not observed with certainty (Fig. 3c). The medulla at this age was

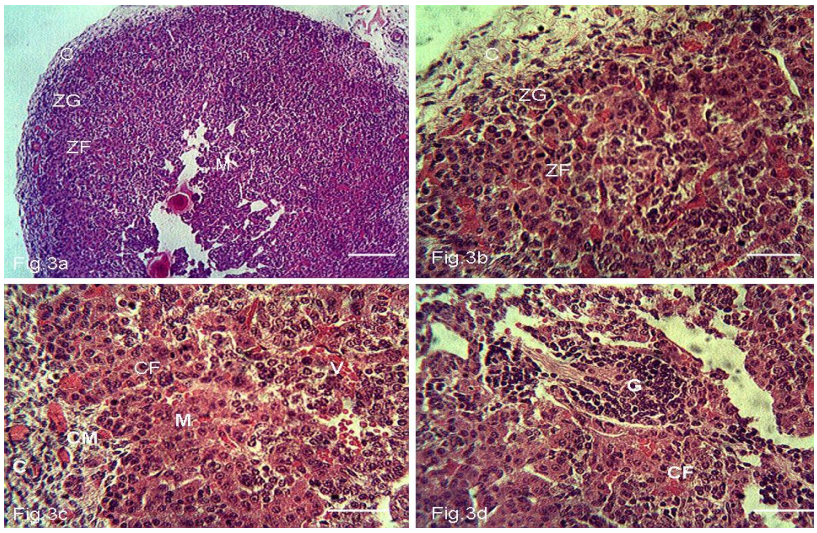


Fig. 3. Photomicrographs of adrenal gland of 90-110 cattle foetus. (a): Shows further differentiation of capsule (C), zona glomerulosa (ZF) , zona fasciculata (ZF) and medulla (M)- bar scale 60 µm. (b): Shows columns or cords of cells in the zona fasciculata (ZF) and increased blood sinuses (V) with zona glomerulosa (ZG) and encasing capsule (C)- bar scale 30 µm- HE. (c): Shows definite cortic-medullary boundary (CM), medulla (M) and venous sinuses amongst chromaffin-like structures in the medulla.—Bar scale 30 µm. (d): Ganglion cells (C) were apparent in the medulla. (CF) represent the cortico-medullary junction- scale bar 30 µm

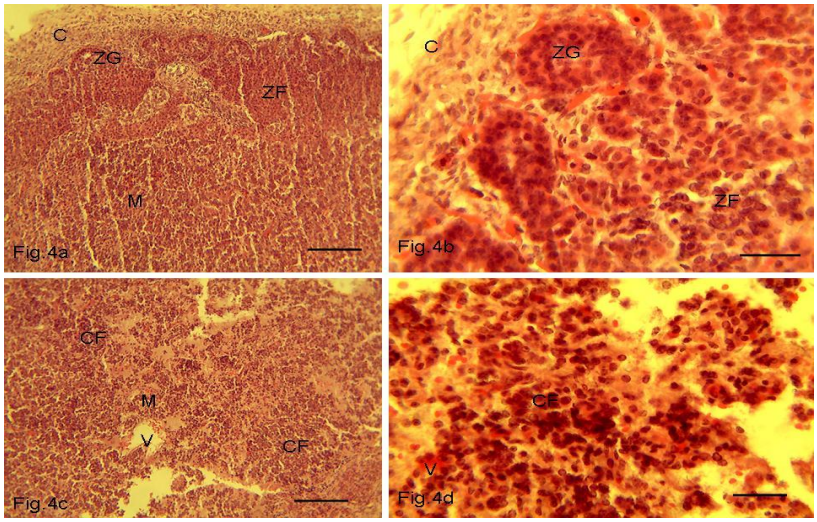
differentiated into an outer region of basophilic cells and inner region with eosinophilic (paler) cells. These cells were generally round to polygonal, arranged in groups or columns. Some sinusoids of variable size were found between the cell groups and ganglion-like structures. Few sympathetic ganglion-like cells were apparent (Fig. 3d). The overall size of the medulla increased.

At about 115-125 days, there was further maturation of the cortical and medullary parenchyma with the different zones clearly distinguished from the foetal cortex appearance. However cells that appeared to be migratory sympathochromaffin cells were observed in the zona glomerulosa. The medulla with outer basophilic and inner eosinophilic staining clumps of chromaffin-like cells apparently increased in size and number of cells. The cortico-medullary junction could be differentiated at this age (Figs. 4a, b, c, d). There were no remarkable differences in the histology of the adrenal in the 135-145 days and the previous age. However the medulla increased exponentially in size. By 150-170 days further maturation showed the greatest change in the thickness of the capsule, cortex and the medulla and their cellular and connective tissue components (Fig. 5a). The capsule now consisted of two layers; an outer fibrous and inner cellular layer with some aggregations of adipose tissue (Fig. 5b). The zonation of the cortex was maintained with increased vacuolation of the cytoplasm of the cells of the zona fasciculata (Fig. 5c). Irregular blood sinusoids matured further and increased in the medulla. Some cortical cells were also noticed amongst the medullary cells without forming strands (Fig. 5d). In the adrenals of 180-220 days and 235-260 days, there were similar appearance in the histology and maturation of the capsular, cortical; and medullar tissue resembling adult adrenal structure. Remarkably copious aggregates of glomus-like cells with few irregular blood sinusoids were common in the zona glomerulosa. The zona fasculata showed a definite arrangement of polyhedral cells into columns. The outer medulla showed numerous dark-staining chromaffin cells arranged in clumps with interposed large vascular networks of blood sinusoids (Figs. 6a, b, c, d).

Histometrically, the measured parameters that included thickness of the capsule, cortex and medulla increased with gestational age and were significant at $p< 0.05$ (Table 3). A spurt in the growth of these parameters was noticed between 180-220 days and 235-260 days of gestation.

4. DISCUSSION

The study has provided a base-line morphometric and histological features of harvestable foetal adrenal gland of white Fulani (zebu) cattle which are under stressful management in the tropical environment.



Figs. 4a, b, c, d. Photomicrographs of adrenal gland of foetuses of 115-125 days showing (a): further maturation of the adrenal zones with clear maturation of the zones and medulla that included capsule(C), ZG (zona glomerulosa), ZF (zona fasciculata), medulla (M) and venous sinuses and chromaffin-like cells (CF). HE. Bar scale: 60 µm, 30 µm, 60 µm & 30 µm respectively

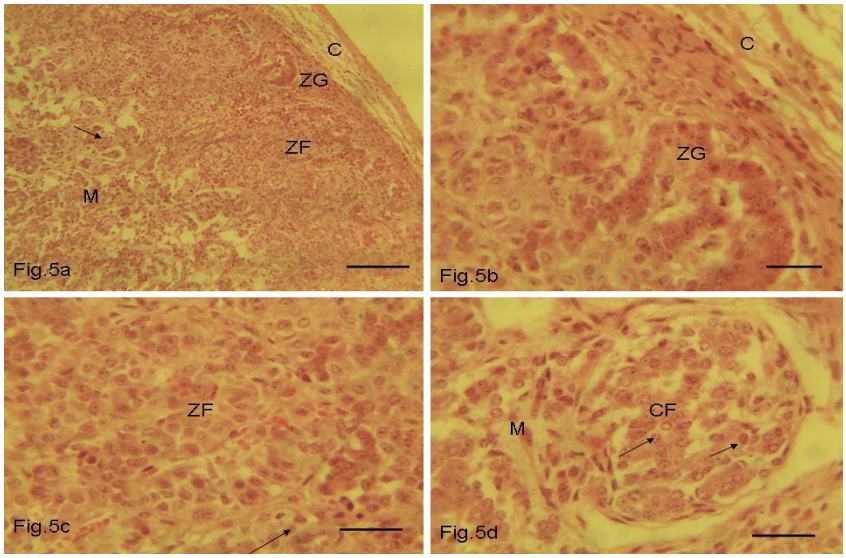
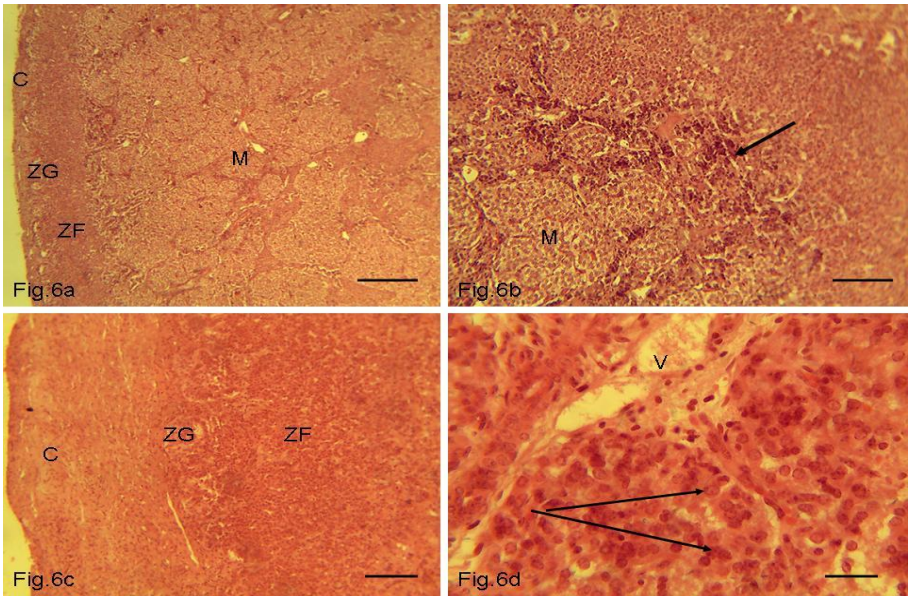


Fig. 5. Photomicrographs of adrenal gland of foetuses of 150-170 days showing. (a): Increased in further maturation and increased thickness of capsule, cortex and medulla and cellular components; capsule (C), ZG (zona glomerulosa), ZF (zona fasciculata) and medulla (M). (b): Shows the cellular components of the capsule(C) and zona glomerulosa (ZG). (c): shows the cortex with increased vacuolation of cells of the zona fasciculata (ZF). (d): cortical cells were present amongst medullary components, medulla (M) and chromaffin-like cells (CF). Bar scale-30 µm, HE



Figs. 6a,b,c,d. Photomicrograph of adrenals of 180-220 days & 235-260 days showing further maturation of the histological components resembling adult features: capsule (C), zona glomerulosa (ZG), zona fasciculata (ZF), medulla (M), venous sinuses (V) and arrows indicate ganglion clusters. Bar scale -40 µm, 40 µm, 40 µm, 30 µm respectively. HE

Grossly the adrenal glands were observed at the cranial extremity of the kidneys. The right and left differed in shape and size during development, similar to results in previous reports in some

domestic animals [18,25,26]. The adrenal weight and size (length, breath and thickness) increased as the gestational age progressed. This present morphometrical findings relating to adrenal weight and size in relation to gestational age is similar to the studies on foetal adrenal gland of goat [11,26] and in buffalo [24]. The minor differences observed may be due to species differences, nutritional availability and some environmental and climatic differences. It has been suggested that the adrenal weight increased in the foetal age is due to development of the foetal zone of the adrenal cortex and that the development of the adrenal cortical foetal zone is a direct result of increase in the width and length of the adrenal gland [27]. The present study observed definite foetal cortical zone in the developing adrenal which will mature further in adult adrenal gland, similar to the findings of [28] in buffalo foetuses of 70-80 cm CRL.

Table 1. Gross morphometry showing Crown – Rump – Length (cm), estimated foetal age (days,) and mean foetal weight (g) and mean combined adrenal weight of foetuses of cattle

CRL(cm)	Estimated foetal age (days)	Mean foetal weight (g)	Combined mean adrenal weights (g)
9.5 – 12.5	70 – 80	112.4 ± 0.2^{a}	0.098 ± 0.01^{a}
15.0 – 20.5	90 – 100	116.6 ± 0.6^{b}	0.123 ± 0.03^{b}
22.5 – 28.0	115 – 125	170.8 ± 1.3^{c}	0.196 ± 0.01^{c}
32.5 – 37.3	135 – 145	1107.6 ± 8.2^{d}	0.213 ± 0.04^{d}
40.5 – 47.5	150 – 170	1503.6 ± 13.4^{e}	0.276 ± 0.01^{d}
52.3 – 65.0	180 – 220	2400.7 ± 15.2^{f}	0.342 ± 0.09^{e}
70.5 – 84.5	235 – 260	3500.4 ± 10.4^{g}	0.463 ± 0.03^{f}

Note: a, b, c, d, e, f, g: means in the same column with same superscript are not significantly different from each other. Those with different superscript are significantly different (P < 0.05)

Table 2. Gross morphometry of the Left (L) and Right (R) adrenal gland of the cattlefoetuses that included length (long axis) (L), Breath (short axis) (B) and Thickness (T)

Estimated foetal age (days)	Measured parameters relating to size (cm)					
	LL(cm)	LR(cm)	BL(cm)	BR(cm)	TL(cm)	TL (cm)
70 – 80	$0.7 \pm .01^{a}$	$0.6 \pm .01^{a}$	$0.3 \pm .09^{a}$	$0.3 \pm .01^{a}$	-	-
90 – 100	$0.8 \pm .03^{b}$	$0.8 \pm .02^{b}$	$0.4 \pm .05_{b}$	$0.3 \pm .04^{a}$	$0.1 \pm .02^{a}$	$0.1 \pm .02^{a}$
115 – 145	0.8 ± 0.3^{b}	$0.8 \pm .01^{b}$	$0.5 \pm .02^{c}$	$0.4 \pm .02^{b}$	$0.3 \pm .01^{b}$	$0.3 \pm .05^{b}$
135 – 145	$1.2 \pm .04^{c}$	$0.9 \pm .04^{c}$	$0.5 \pm .01^{d}$	$0.5 \pm .03^{c}$	$0.3 \pm .04^{b}$	$0.3 \pm .04^{b}$
150 – 170	$1.3 \pm .04^{d}$	$1.1 \pm .09^{d}$	$0.7 \pm .02^{e}$	$0.6 \pm .07^{d}$	$0.5 \pm .01^{c}$	$0.4 \pm .01^{c}$
180 – 220	$1.4 \pm .01^{e}$	$1.4 \pm .01^{e}$	$0.9 \pm .01^{e}$	$0.8 \pm .01^{e}$	$0.7 \pm .03^{d}$	$0.6 \pm .01^{d}$
235 – 260	2.5 ± 0.3^{f}	2.1 ± 0.2^{f}	$1.1 \pm .09^{f}$	$0.9 \pm .03^{f}$	$0.9 \pm .03^{e}$	$0.8 \pm .02^{e}$

Note: Means in a column with different superscript are significantly different at P<0.05

Table 3. Morphometry showing mean values of histometric measurement (μm) of the thickness of the capsule, cortex and medulla of cattle foetuses with their estimated foetal CRL and Age

CRL(cm)	Estimated foetal age (days)	Thickness of the adrenal zones		
		Capsule (μm)	Cortex (μm)	Medulla (μm)
9.5 – 12.5	70 – 80	42.1 ± 2.5^{a}	420.3 ± 10.2^{a}	367.5 ± 11.6^{a}
15.0 – 20.5	90 – 100	44.1 ± 4.7^{a}	542.3 ± 9.6^{b}	954.6 ± 22.8^{b}
22.5 – 28.0	115 – 125	51.6 ± 6.1^{b}	735.2 ± 7.6^{c}	1020 ± 28.4^{c}
32.5 – 37.3	135 – 145	59.5 ± 5.9^{c}	525.5 ± 16.6^{b}	1050 ± 33.1^{d}
40.5 – 47.5	150 – 170	65.1 ± 3.8^{d}	540.7 ± 18.1^{b}	1064 ± 29.2^{d}
52.3 – 65.0	180 – 220	69.4 ± 6.1^{e}	$630.\ 7 \pm 9.2^{d}$	1575 ± 28.4^{e}
70.5 – 84.5	235 – 260	74.5 ± 6.4^{f}	840.1 ± 10.3^{e}	1675.5 ± 36.2^{f}

Note: a, b, c, d, e, f: means in the same column with same superscript are not significantly different from each other. Those with different superscript are significantly different (P < 0.05)

In the present study, the foetal cortical cells became established early in gestation and the glomerular and fascicular zones became clearly distinguishable at about 115-125 days of gestation (CRL 22.5—28.0 cm). It has been reported that the foetal adrenal gland of cattle exhibited a clear zona glomerulosa (ZG) and fasciculata (ZF) at 130 days of gestation [21]. This is close to the present report in cattle. The minor differences in timing of zonation may be due to species differences, nutritional and climatic influences during gestation. It was also reported that the ZG developed in the period of rapid growth between the 6oth and 120th day of gestation in sheep [15]. Some researchers [8,29], detected the presence of a well-defined ZG at the 50th day of gestation in sheep. Zonation of the adrenal gland of the camel was distinct from about 80 days of gestation (CRL 11.5 CM). In the cortex, a definitive zone and foetal zone were not clearly distinguished from each other; this was probably because embryos or earlier foetuses were not used in this study. The foetal zones probably has regressed in the foetal age group used or is nonexistent in cattle foetuses or were completely not present in the foetuses used in this study and requires further investigation by additional techniques. The foetal zone is a transient zone and usually the third cortical layer and occupies about 80-90% of the cortical volume. It regresses as development progresses. The foetal zone has been reported to persist throughout the foetal age in the camel [23] and in the sheep [8]. It is replaced in the adult sheep by the zona reticularis. The foetal zone is present in humans before the third month of gestation and also very distinct in species such as monkey, cat leopard, tiger, lion, elephant seal, sloth and the armadillo [29,30].

In this study, the medulla remained thicker than the cortex throughout the foetal life. This has also been observed in the equine foetal adrenal gland and several other developing adrenal of domestic animals [15,23,24]. The result showed migratory sympatho-chromaffin cells in thyroids of 115-125 of gestation. It is possible these cells were missed-out in the earlier foetal adrenals. Migratory ovine sympatho-chromaffinoblasts have been reported in the adrenal cortex at 35 days gestation (CRL 2.4 cm) in sheep [31]. The present finding of chromaffin-like cells in foetus is supported by the observation of chromaffin cells in cattle foetuses of 60 days [21]. In the species in which the newborn is reasonably mature, it appears that the migration of medullary cells has begun by the end of first third of gestation. It has been shown in sheep that migration and differentiation of medullary cells is well established at about gestational age of 53 days [31] and is similar to what has been described in primates, man and in the pig [32]. The ultimate fate of these primitive cells is to differentiate to phaechromoblasts and phaechromocyte in the medulla. These cells will eventually give rise to the noradrenaline and adrenaline-secreting central medullary cells.

5. CONCLUSIONS

The morphologic features of the foetal adrenal gland towards the end of gestation suggest that it may be engaging in full secretion of most corticosteroids and sex hormones from the cortex, and adrenaline and noradrenaline from the medulla.

ETHICAL APPROVAL

The samples were foetal wastes obtained from government licensed slaughter house and the experiment was approved by the Department.

COMPETING INTERESTS

Authors have declared that there is no competing interest.

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