

## Results of Novidium<sup>®</sup> (Homidium chloride) Chemotherapy on the Effects of *Trypanosoma vivax* Infection on Pregnancy and Reproduction in Yankasa (YK) and West African Dwarf [WAD] Ewes

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**Abstract:** The objective of the study was to investigate the results of Novidium<sup>®</sup> (Homidium chloride) chemotherapy on the effects of *Trypanosoma vivax* infection on pregnancy and reproduction in Yankasa (YK) and West African Dwarf (WAD) ewes, infected in their first, second and third trimester of pregnancy. Three groups of ewes, made up of six pregnant YK and six pregnant WAD ewes each, were assigned at random to first, second and third trimesters of pregnancy. A fourth group of three pregnant YK and three pregnant WAD ewes formed the controls for the study. The experimental ewes in the first, second and third trimesters of pregnancy, were infected by jugular vene-puncture with 2.0 mL of blood, containing  $2 \times 10^6$  *Trypanosoma vivax* on day 23, 52 and 102 of pregnancy respectively. The control ewes were not infected. Fourteen days post infection (pi), the experimental ewes in each trimester, were divided into two groups of 3 pregnant YK and 3 pregnant WAD ewes in each group. One group was treated with Novidium<sup>®</sup> at  $1.0 \text{ mg kg}^{-1}$  body weight, while the other group remained untreated. Of the 3 YK and 3 WAD ewes in the treated and untreated groups in each trimester of pregnancy, 1 YK and 1 WAD ewe each from the second groups, were killed humanely at 21 days pi and at the end of the first and second trimester of pregnancy. The results of the study showed that the infected YK and WAD ewes were susceptible to trypanosomosis. Very low foetal weights, partial and almost complete foetal resorption, abortions and mortality were observed in the infected-untreated YK ewes. While abortions of autolyzed foetuses, abortion of a live foetus and a case of dystocia were observed in the infected-treated YK ewes. Embryonic mortality and abortions were observed in the infected untreated WAD ewes, while delivery of healthy lambs and resumption of normal oestrus was observed in the infected-treated WAD ewes. The non-infected YK and WAD control ewes had normal gestation and delivery of lambs. Chemotherapy completely ameliorated the pathogenic effects of *T. vivax* infection on pregnancy and gestation in the WAD ewes, leading to delivery of healthy lambs and resumption of normal oestrus and reproduction, in contrast to the YK ewes. The breed of ewe influenced the results of Novidium<sup>®</sup> chemotherapy on the effects of *T. vivax* infection on pregnancy and reproduction.

**Key words:** Trypanosomosis, novidium<sup>®</sup> chemotherapy, reproduction

### INTRODUCTION

Small ruminants form part of nearly all the farming systems in Nigeria. They are widely distributed in the country with varying socio-economic and cultural functions. They are an easy source of money in times of need<sup>[1,2]</sup>. Sheep contribute significantly to the national economy. Sheep kept mainly for mutton account for about 48,000 metric tons (11.0%) of the total meat supply in Nigeria per annum<sup>[3]</sup>.

Trypanosomosis is one of the most important diseases of livestock in sub-Saharan Africa. In spite of several years of research, animal trypanosomosis is still a major hindrance to animal productivity in most African countries<sup>[4]</sup>. Although the major economic impact of

trypanosomosis is on cattle production, the disease also severely affects sheep and goats throughout sub-Saharan Africa<sup>[5]</sup>. Studies on the indigenous sheep in Nigeria have shown that the reproductive efficiency of these animals is severely affected by trypanosomosis. These include abnormal oestrus<sup>[6,7]</sup>, abortions, still births and birth of weak lambs<sup>[7,8]</sup>, infertility and sterility<sup>[4,9]</sup>, low survival rates, low birth weights and premature births of lambs<sup>[10]</sup>, foetal mummification<sup>[8]</sup>. Effective animal production is dependent on the prevention and or control of detrimental diseases including trypanosomosis<sup>[11]</sup>. The livestock industry in Africa has also depended heavily on anti-trypanosomal drugs both for prevention and treatment of trypanosomosis<sup>[12]</sup>. Despite these measures, not much has been achieved in the control of trypanosomosis and its effects on animal productivity in Africa.

Few studies have described the effects of trypanosomosis on pregnancy in the YK and WAD sheep in Nigeria<sup>[8,10,13]</sup> and the effects of trypanocidal drugs chemotherapy on trypanosomal induced genital lesions<sup>[14]</sup> and semen abnormalities in cattle<sup>[11]</sup>. However there is a dearth of detailed investigation on the results of chemotherapy with a trypanocide Novidium<sup>(R)</sup> [Homidium chloride] on the effects of trypanosomosis on pregnancy in the two predominant breeds of sheep in Nigeria, the YK and WAD sheep.

The objective of this study was to investigate the result of Novidium<sup>(R)</sup> (Homidium chloride) chemotherapy on the effects of *Trypanosoma vivax* infection on pregnancy in YK and WAD ewes infected in their first, second and third trimesters of pregnancy.

### MATERIALS AND METHODS

**Animals:** Forty two healthy uniparous pregnant ewes, made up of 21 YK and 21 WAD sheep, were selected from a group of YK and WAD ewes that have earlier been synchronized by placing intravaginal progestagen sponges [Veramix<sup>R</sup>, UpJohn Ltd, West Sussex-England], containing 60.0 mg of Medroxyprogesterone, for 12 days. Forty-eight hours after sponge withdrawal, fertile rams of the same breed bred the ewes naturally. Pregnancy was confirmed in the ewes, by Radio Immuno Assay (RIA) technique for progesterone (P<sub>4</sub>) levels determination<sup>[15]</sup>. Ewes with P<sub>4</sub> levels greater than 1.5 ng mL<sup>-1</sup> at 18 days post natural breeding by rams and did not return to oestrus, 21 days after breeding, were considered pregnant.

The pregnant ewes were sprayed with an organophosphorus acaricide Rhodiocide [Rhône-Poulenc Agrochimie, Germany] to control the common ectoparasites in the environment. The acaricide was used at a dilution of 1.0 mL to 1.0 L of water to spray the ewes. They were dewormed with Flukazole [Channelle, Ireland England] per os, at a dose of 7.5 mg kg<sup>-1</sup> body weight. The drug contains 1.5% w/v Levamisole and 0.6% w/v Niclofolan. The ewes were also treated twice against common haemoparasites with long acting Terramycin [Pfizer Ikeja Lagos Nigeria] containing 216.0 mg of Oxytetracycline dihydrate per mL. The drug was administered intramuscularly at 20.0 mg kg<sup>-1</sup> body weight. Absence of trypanosomal infections in the ewes was checked using the Haematocrit-centrifuge Technique (HCT)<sup>[16]</sup>. Thereafter, the ewes were randomly assigned into three groups made up of six YK and six WAD ewes each, for first, second and third trimester of pregnancy studies. First, second and third trimesters are 0-50, 50-100 and 100-150 days of pregnancy respectively. Three

pregnant YK and 3 pregnant WAD ewes were the controls for the study.

**Infection:** *Trypanosoma vivax* (Stabilate. 150), were obtained from the Department of Veterinary Parasitology and Entomology, Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria This strain was first isolated from a bovine at Kaya village in Zaria. It was cloned and passaged twice in goats before it was cryo-preserved in 10% DMSO and kept in liquid nitrogen as stabilate 150. The stabilate was used to infect donor goat. Blood from the goat was used to infect the experimental ewes at each trimester of pregnancy. Each ewe was inoculated by jugular vene-puncture with 2.0 mL of the blood from the donor goat containing approximately 2 x 10<sup>6</sup> trypanosomes. The ewes in the first, second and third trimester, were inoculated at 23, 52 and 102 days of pregnancy, respectively. The control ewes were not inoculated.

Following infection, the ewes were monitored daily for parasitaemia by the haematocrit centrifuge technique<sup>[16]</sup> and rectal temperatures using a centigrade clinical thermometer. Packed Cell Volume [PCV] and Total Plasma protein (TP) values were determined according to Coles<sup>[17]</sup> twice weekly. Body weights were determined weekly using a top loading scale and recorded in kilograms. Foetuses from the ewes were weighed and recorded in grams. The weights of the foetuses were also expressed as percentages [%] of their dam's weight (percentage foetal weight) at the time of abortion, lambing or when the dams were killed humanely.

Sera samples were collected from the pregnant ewes post infection, twice weekly. The solid phase RIA technique for progesterone levels determination<sup>[15]</sup> was used to assay the sera samples, to monitor pregnancy, embryonic death and return to oestrus in the ewes. Decline in P<sub>4</sub> levels in the infected pregnant ewes to values less than 0.1 ng mL<sup>-1</sup> pi indicated embryonic mortality. Subsequent increase in P<sub>4</sub> levels to values greater than 1.5 ng mL<sup>-1</sup> followed by decline to values less than 0.1 ng mL<sup>-1</sup> indicated an oestrous cycle.

**Treatment:** Fourteen days pi, the YK and WAD ewes in the first and second trimester groups were divided into two equal groups made up of 3 YK and 3 WAD ewes per group. One group was treated with Novidium<sup>(R)</sup> (Homidium Chloride May and Baker Ltd. Dagenham England) intramuscularly at 1.0 mg Kg<sup>-1</sup> bodyweight, while the other group remained untreated. Relapsed infections were treated again at the same dose and route.

In the third trimester 50% of the infected YK and WAD ewes aborted or died without aborting, before 14

days pi. The remaining YK and WAD that have not aborted by 14 days pi were divided into two groups. One group was made up of 1 YK and 1 WAD, while the other group was made up of 2 YK and 2 WAD. The latter group was treated with Novidium<sup>(R)</sup> as above, while the other group remained untreated.

Following chemotherapy Of the 3 YK and 3 WAD in the treated and untreated groups in the first and second trimesters, 1 YK and 1 WAD each from the treated and untreated groups, were killed humanely at 21 days pi and at the end of the first and second trimesters of pregnancy. Thorough post mortem examinations were carried out on the ewes and their foetuses. The remaining ewes were allowed to carry their pregnancies as long as possible. None of the treated and untreated YK and WAD ewes in the third trimester were killed, the ewes were allowed to carry their pregnancies as long as possible. Ewes that died from the infection were examined at post mortem as mentioned earlier.

**STATISTICAL ANALYSIS**

Statistical analysis of the percentage foetal weights of the fetuses from the treated and untreated YK and WAD ewes was carried out using SAS proc GLM procedure<sup>[18]</sup>.

**RESULTS**

**Clinical signs:** The infected YK and WAD ewes developed parasitaemia within 3-4 and 3-9 days pi respectively. The infection was mild, severe and very severe in the YK infected in the first, second and third

trimesters of pregnancy respectively. It was mild, severe and variable in the WAD infected in the first, second and third trimesters respectively. High peaks of parasitaemia and pyrexia that fluctuated until treatment or death of ewes were observed. Loss of body weights was observed in the infected YK ewes in all the three trimesters of pregnancy (Table 1). Loss in body weights in the WAD was only observed in the second and third trimesters of pregnancy. The infected WAD ewes in the first trimester gained weight despite the infection (Table 2).

Following chemotherapy, trypanosomes were cleared from peripheral blood circulation of the infected-treated YK and WAD ewes within four days post chemotherapy. Consequently, the observed clinical signs and pyrexia similarly subsided in the treated ewes within six days. Thereafter, clinical parameters such as body weights showed recovery towards pre-infection values post chemotherapy (Table 1 and 2). Exception was the body weights of the infected-treated YK ewes in the third trimester (Table 1).The abortions observed in the infected WAD stopped following chemotherapy.

**Foetuses:** Low foetal weights were observed in the foetuses from the infected-untreated YK ewes. The percentage foetal weights of the foetuses from the infected-untreated YK ewes in the first and second trimester were significantly lower ( $p \leq 0.05$ ) than those of the foetuses, from the infected-treated ewes (Table 1). However in the third trimester the percentage foetal weight of the foetuses from the infected-untreated and infected treated YK ewes were not significantly ( $p \geq 0.05$ ) different (Table 1). In the WAD ewes, low foetal weights were observed in the second and third trimester.

Table 1: Influence of Novidium chemotherapy on Foetal weights and gestation of *T. vivax* infected 1st, 2nd and 3rd trimester Yankasa ewes

Animals groups and observations	Trimester of pregnancy when infected/treated						Control ewes uninfected none
	1st Trimester		2nd Trimester		3rd Trimester		
	Untreated	Treated	Untreated	Treated	Untreated	Treated	
Nature of infection	mild	none	severe	none	V. Severe	none	none
Highest% change in body weight.	-8.31	-6.2	-23.0	-13.2	-35.5	-27.8	+12.8
Foetal weights. (Mean ±SD)	0.8±0.5	1.3±0.3	103.0±44.9	328.4±0.9	877.5±62.9	1035.0±0.7	2067.0±208.2
% Foetal weight (Mean ±SD)	2.8±1.1*10 <sup>-3</sup>	5.3±2.4 <sup>b</sup> x10 <sup>-3</sup>	0.5±0.2 <sup>a</sup>	1.5±1.1 <sup>b</sup>	4.3±1.0 <sup>a</sup>	5.0±1.1 <sup>a</sup>	8.8±0.30
Foetal resorption	Yes	None	Yes	None	None	None	None
Low foetal weight.	Yes	None	Yes	None	None	None	None
Abortions	None	None	Yes	None	Yes	Yes	None
Dystocia	None	None	None	None	None	Yes	None
Death of foetuses in-utero	None	Yes	None	Yes	None	None	None
Expulsion of Autolysed fetuses	None	Yes	None	Yes	None	None	None
Peri-orbital oedema and haemorrhage	None	None	Yes	None	None	None	Hone
Normal lambing	None	None	None	None	None	No	Yes

% Foetal weight is weight of foetus expressed as percentage of dam's weight  
 % Foetal weights in a trimester with different letters in superscript are significantly different ( $p = 0.05$ )  
 (-) Loss in body weight (+) Increase in body weight

Table 2: Influence of Novidium chemotherapy on Foetal weights and Gestation of *T. vivax* infected 1st, 2nd and 3rd trimester West African Dwarf ewes

Animals groups and observations	Trimester of pregnancy when infected/treated						control ewes uninfected none
	1st Trimester		2nd Trimester		3rd Trimester		
	Untreated mild	Treated none	Untreated severe	Treated none	Untreated V. Severe	Treated none	
Highest % change in body weight.	+23.3	+10.8	-30.4	+21.4	-15.2	+14.0	+26.8
Foetal weights (Mean ±SD)	1.52±1.1	1.6±1.2	30.0±21.2	68.2±56.2	651.7±68.3	1283.3±160.7	1800±100.0
% Foetal weight (Mean ±SD)	7.2±5.1 <sup>a</sup> x10 <sup>3</sup>	7.0±5.0 <sup>a</sup> x10 <sup>3</sup>	0.19±0.13 <sup>a</sup>	0.5±0.49 <sup>b</sup>	4.6±0.5 <sup>a</sup>	6.6±0.6 <sup>b</sup>	7.63±0.06
Embryonic death	Yes	None	Yes	None	None	None	None
Low Foetal weight	None	None	Yes	None	Yes	None	None
Abortions	None	None	Yes	None	Yes	None	None
Dystocia	None	None	None	None	None	None	None
Death of Foetuses in- utero	None	None	None	None	None	None	None
Abortion of Autolysed fetuses	None	None	None	None	None	None	None
Peri-orbital oedema and haemorrhage	None	None	None	None	None	None	None
Normal lambing	None	None	None	Yes	None	Yes	Yes

% Foetal weight is weight of foetus expressed as percentage of dam's weight

% Foetal weights in a trimester with different letters in superscript are significantly different (p<0.05)

(-) Loss in body weight (+) Increase in body weight

The percentage foetal weights of the fetuses from the infected-untreated WAD ewes in the second and third trimester were significantly lower (p<0.05) than those of the fetuses from the infected-treated WAD ewes (Table 2). However in the first trimester low foetal weights were not observed in the fetuses from the infected untreated WAD ewes. The percentage foetal weight of the fetuses from the infected-untreated and infected-treated WAD ewes was not significantly (p≥ 0.05) different (Table 2).

Partial foetal resorption and almost complete foetal resorption were observed in fetuses from infected-untreated YK ewes in the first and second trimesters of pregnancy respectively (Table 1). Severe peri-orbital oedema was observed in a foetus from one infected-untreated YK ewe in the second trimester (Table 1). These anomalies were not observed in fetuses from the infected-treated YK ewes and also in the fetuses from the infected-untreated and infected-treated WAD ewes (Table 1 and 2).

**Pregnancy and reproduction:** In the infected untreated YK ewes, the infected-untreated YK in the first trimester, left to carry the pregnancy to term died without aborting, 41 days post infection at 64 days of pregnancy. Similarly infected-untreated YK ewe in the second trimester, left to carry the pregnancy to term died, 11 days post infection at 63 days of pregnancy. The foetus recovered from the ewe was pin-eye in size, almost completely resorbed, it weighed 0.531 mg and had a percentage foetal weight of 0.0003%. In the third trimester the infected-untreated YK ewe left to carry the pregnancy to term, aborted a live foetus, 32 days post infection at 138 days pregnancy, the foetus weighed 0.91 kg.

In the infected-treated YK ewes, the infected-treated YK ewe in the first trimester left to carry the pregnancy to term had four relapsed infections. Even though the relapsed infections were treated with Novidium<sup>(R)</sup> at the same dose and route, the ewe aborted an autolysed foetus, 87 days post-infection at 110 days of pregnancy. Similarly, the infected-treated YK ewe in the second trimester left carry the pregnancy to term had three relapsed infections between 21-43 days post chemotherapy. Despite repeated chemotherapy following the relapses, the ewe aborted a dead autolysed foetus, 54 days post infection at 106 days of pregnancy. This ewe resumed estrous after a prolonged anaestrous of six months, became pregnant after natural breeding by a ram, but aborted the foetus. In the third trimester, one of the infected-treated YK ewes left to carry their pregnancies to term, aborted a live foetus, 35 days post infection at 141 days of pregnancy, the other infected-treated YK ewe had dystocia, 40 days post infection at 146 days of pregnancy. The foetus weighed 1.140 kg.

In the infected-untreated WAD ewes, the infected-untreated WAD ewe in the first trimester left to carry the pregnancy to term had early embryonic mortality. Following the embryonic mortality, the ewe self-cured from the infection and also resumed oestrus with oestrous cycle lengths of 18, 24, 14, 18 and 18 days. The ewe was bred naturally by a ram, became pregnant and lambled to a healthy lamb at term. The infected-untreated WAD ewe in the second trimester, left to carry the pregnancy died from the infection, possibly due to abortion related complications. The ewe died, 41 days post infection at 93 days of pregnancy. In the third trimester, the infected-untreated WAD in the third trimester left to carry the

pregnancy to term aborted a weak foetus, 39 days post infection at 145 days of pregnancy

In the infected-treated WAD ewes, the infected-treated WAD in the first trimester left to carry the pregnancy to term had early embryonic mortality before chemotherapy. This ewe resumed oestrous following the embryonic mortality and chemotherapy, with oestrous cycle lengths of 19,22,22,18 and 18. The ewe became pregnant after natural breeding by a ram and lambd to a healthy lamb at term. The infected-treated WAD ewe in the second trimester left to carry the pregnancy to term delivered a healthy lamb at term. The two infected-treated WAD ewes in the third trimester carried their pregnancies to term and delivered healthy lambs.

### DISCUSSION

All the infected YK and WAD ewes in the three trimester groups developed clinical trypanosomosis. The trimester of pregnancy and breed of ewe influenced the severity of the infection. YK ewes in the third trimester were most susceptible. Similar observations have been reported in trypano-susceptible Zebu cattle<sup>[19]</sup>.

Abortions were observed in both the infected-untreated YK and WAD ewes in the second and third trimesters of pregnancy. Most of the abortions in the infected-untreated YK and WAD ewes occurred in the third trimester within 14 days post infection. The abortions of many ewes within a short period of infection as observed in the infected-untreated YK and WAD ewes in the third trimester have been reported in trypano-susceptible Zebu cattle<sup>[20]</sup>. These abortions occurred during the acute phase of the infection when parasitaemia and pyrexia were both high in the infected ewes. These showed that foetuses from *T.vivax* infected YK and WAD ewes, were most susceptible in the third trimester of pregnancy and during the acute phase of infection.

Stress induced by pyrexia has been reported to activate the production of cortico steroids from the foetal adrenal gland<sup>[21]</sup>. These corticosteroids stimulate the production of prostaglandin F<sub>2</sub> alpha (PGF<sub>2</sub>α) and oestrogen from the placenta. The PGF<sub>2</sub>α initiates abortion by reducing myometrial activity threshold, through reduction in concentration of progesterone, while oestrogen causes uterine contraction and expulsion of the foetus<sup>[22,25]</sup>. Direct invasion of the embryo as a result of intra-uterine infections of trypanosomes have been reported<sup>[19,20,14,24,25]</sup>. These contributed to the pathogenesis of the abortions observed in the YK and WAD ewes in this study.

It was observed in this study that following chemotherapy; abortions were completely ameliorated in the infected-treated WAD ewes leading to delivery of

healthy lambs, whereas abortions were only delayed in the infected-treated YK ewes. The relapsed infections accompanied with high parasitaemia and pyrexia as observed in the infected-treated YK ewes despite repeated chemotherapy might have triggered the processes of abortion in the infected-treated YK ewes.

### CONCLUSIONS

In this study it was observed that chemotherapy ameliorated the effects of *T. vivax* infection on body weights of the infected-treated YK ewes and their foetuses in the first and second trimester (Table 1) and in the infected-treated WAD ewes and foetuses in all the three trimesters (Table 2). However these observed positive effects of chemotherapy on body weight in the infected-treated YK ewes and fetuses, did not translate to successful gestation and lambing in the YK ewes, hence the observed abortions despite chemotherapy in the treated YK ewes. In contrast the positive effects of chemotherapy on body weights of dam and fetuses in the infected-treated WAD ewes translated to successful gestation and delivery of healthy lambs that survived. This suggests very strongly that the breed of the ewe influenced the results of chemotherapy on pregnancy, gestation and delivery in *T. vivax* infected pregnant YK and WAD ewes. This present results with previous reports<sup>[26]</sup> in which the breed of ewe influenced the results of Novidium<sup>(®)</sup> chemotherapy on clinical data of *T. vivax* infected first, second and third trimester YK and WAD ewes.

The present study has shown that the beneficial effects of chemotherapy on clinical data in WAD ewes, as observed in a previous study (Bawa et al., 2005<sup>b</sup>) and body weight of dams and fetuses of WAD ewes, as observed in the present study will translate to successful gestation, lambing and resumption of normal oestrus and reproduction in infected-treated WAD ewes, in contrast to YK ewes.

Trypanosomosis still poses a serious threat to ovine reproduction, which may be of enormous economic importance in endemic areas such as Sub-Saharan Africa. It is suggested from this study that the beneficial effects of trypanotolerance as demonstrated in WAD ewes in a previous study<sup>[28]</sup> coupled with chemotherapy could be exploited to enhance ovine reproduction in trypanosomosis endemic areas of Africa. Further studies on animal trypanosomosis, trypanotolerance and chemotherapy are recommended.

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