UNIVERSITI PUTRA MALAYSIA

PREPRODUCTIVE PATHOPHYSIOLOGICAL CHANGES IN NON-PREGNANT BOER DOES INOCULATED WITH Corynebacterium pseudotuberculosis VIA INTRADERMAL, INTRANASAL AND ORAL ROUTES

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By

AISHATU OTHMAN MOHAMMED

Thesis is submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Master of Veterinary Science.

December 2014

DEDICATION

This work is dedicated to my loving and caring husband, my wonderful parents, siblings and relatives.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the required for the Degree of Master of Veterinary Science

PRE PRODUCTIVE PATHOPHYSIOLOGICAL CHANGES IN NON-PREGNANT BOER DOES INOCULATED WITH *Corynebacterium* pseudotuberculosis VIA VARIOUS ROUTES.

By

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December 2014

Chairman: Faez Firdaus Jesse Abdullah, PhD.

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An experimental study was conducted in non-pregnant Boer does inoculated with *C.pseudotuberculosis via* various routes with the objectives of determining the changes in hematology, biochemical, serum electrolyte, progesterone, estrogen, interleukin-1β, and interleukin 6 as well as pathological changes in the reproductive organs and their associated lymph nodes. A total of twenty (20) healthy non-pregnant Boer does were divided into 4 groups (1, 2, 3 and 4) of 5 does per group. Group 1 was kept unexposed. Group2, 3 and 4 were inoculated with 10^7 cfu/1ml of live *Corynebacterium pseudotuberculosis* through intradermal, intranasal and oral routes respectively.

A significant decrease in red blood cell (RBC) count ($p<0.05$) in the intradermal infected with mean value of $11.3x10^9$/L, while the packed cell volume (PCV), hemoglobin concentration (HbC) mean corpuscular volume (MCV), and mean cellular hemoglobin concentration (MCHC) remained unaltered. Significant increased ($p<0.05$) in white blood cells (WBC) were observed in all the inoculated groups-2, 3 and 4 with mean value of $13.68x10^9$/L, 9.68x109/L, 8.67x109/L respectively. Significant increase ($p<0.05$) in monocyte count was observed in intranasal route with a mean of $0.754x10^9$/L. A significant reduction ($p<0.05$) in lymphocytic count was observed for the intranasal inoculated group with a mean value of $3.37x10^9$/L ($p<0.05$). Significant increase ($p<0.05$) in neutrophil was observed in intranasal and intradermal route with a mean of $8.80x10^9$/L, $6.95x10^9$/L, respectively. Creatinine levels increased ($p<0.05$) in the intranasal group with a mean of 91.33µmol/L while increased in GGT levels were observed ($p<0.05$) intradermal, intranasal and oral groups with a mean differences of 46.52U/L, 48.00U/L, 36.62U/L respectively. Lowered Calcium (Ca^{2+}) concentrations were observed in the intradermal group with a mean concentration of 2.22mmol/L and 2.23 mmol/L for the intranasal group. Albumin levels were decrease ($p<0.05$) in the

intranasal group with a mean of 28.74g/L. Plasma concentrations of progesterone were significantly ($p<0.05$) elevated in intranasal, oral and intradermal with a mean difference of 6.67pg/ml, 3.81pg/ml and 2.4pg/ml respectively. The plasma concentrations of estrogen were elevated significantly ($p<0.05$) in the oral route with a mean of 33ng/ml. However, slight rises in estrogen levels were observed in intradermal and intranasal routes in comparison with the control group.
Interleukin-1β showed a significant increase ($p<0.05$) through the intranasal, intradermal and oral routes compared to the control group with a mean statistical difference of 99pg/ml, 67pg/ml, 42pg/ml respectively while interleukin-6 levels were significantly increased in the intranasal group 85pg/ml ($p<0.05$). There were no significant differences observed in intradermal and oral groups when compared to the control group.

Histologically, inflammatory cells were observed as well as cellular necrosis, congestion in the ovary, uterine horn, cervix and vagina in intranasal and oral routes. Congestion, necrosis were observed in the ovary and uterine horn while necrosis and inflammatory cells were observed in the cervix and vagina of does inoculated through intradermal route. Lesions observed in uterus for the three groups are congestion, edema, necrosis and inflammatory cells.

The present study, therefore, highlight the effects of *C.pseudotuberculosis* on blood, progesterone, estrogen, IL-1β, IL-6 and cellular changes in the reproductive organs and associated lymph nodes which is significant in the understanding the pathophysiology of reproductive system in does infected with *C.pseudotuberculosis*.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Sarjana Sains Veterinar

PRA PERUBAHAN PATOFISIOLOGICAL PEMBIAKAN DALAM KAMBING BETINA YANG TIDAK BUNTING DIJANGKITI DENGAN *Corynebacterium pseudotuberculosis* MELALUI PEL BAGAI LALUAN.

Oleh

AISHATU OTHMAN MOHAMMED

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Satu uji kaji telah dijalankan pada kambing betina yang tidak bunting dengan menjangkiti kambing-kambing tersebut dengan *C.pseudotuberculosis* melalui suntikan intradermal, intranasal dan laluan oral dengan objektif untuk menentukan hematologi, biokimia, elektrolit serum, profil hormon pembiakan (progesteron dan estrogen), interleukin-1β, interleukin 6 dan perubahan patologi dalam organ-organ pembiakan dan nodus limfa yang berkaitan. Sebanyak dua puluh (20) kambing betina yang tidak bunting dan sihat telah dibahagikan kepada 4 kumpulan (1,2,3 dan 4), 5-ekor dalam setiap kumpulan. Kambing dalam kumpulan 1 tidak dijangkiti. Kumpulan 2, 3 dan 4 telah dijangkiti dengan 10^7 cfu/ml *Corynebacterium pseudotuberculosis* melalui suntikan intradermal, intranasal dan laluan oral.

Penurunan ketara dalam kiraan sel-sel darah merah (RBC) ($p < 0.05$) dalam kambing yang dijangkiti melalui suntikan intradermal dapat dilihat, dengan nilai purata $11.3x10^9$/ L, manakala isi padu sel padat (PCV), kepekatan hemoglobin (HBC), min isi padu korpusel (MCV), dan purata kepekatan hemoglobin sel (MCHC) kekal tidak berubah. Peningkatan ketara ($p < 0.05$) dalam sel-sel darah putih (WBC) diperhatikan dalam semua kumpulan yang dijangkiti-2, 3 dan 4 dengan nilai min $13.68x10^9$/ L, $9.68x10^9$/L, $8.67x10^9$/L. Sedikit penurunan ($p<0.05$) dalam kiraan limfosit diperhatikan untuk kumpulan dijangkiti secara intranasal dengan nilai min $3.37x10^9$/L ($p<0.05$). Tahap kreatinin meningkat ($p<0.05$) dalam kumpulan intranasal dengan min 91.33µmol/L manakala peningkatan dalam tahap GGT diperhatikan ($p<0.05$) dalam semua kumpulan di jangkit sama ada secara suntikan intradermal, intranasal dan oral dengan perbezaan min 46.52U/ L, 48.00U/ L, 36.62U/ L. Tidak ada ($p < 0.05$) perubahan ketara dalam AST, T.Protein, APT dan elektrolit serum dalam semua kumpulan tetapi penurunan kepekatan kalsium (Ca2 +) diperhatikan dalam kumpulan suntikan intradermal dengan kepekatan min 2.22mmol/L dan 2.23 mmol/L bagi kumpulan intranasal. Tahap albumin meningkat ($p<0.05$) dalam kumpulan

intranasal dengan min 28.74g/ L manakala tiada perubahan yang diperhatikan dalam tahap kepekatan kalium (K +) dan natrium (Na +) bagi ketiga-tiga kumpulan. Kepekatan plasma progesteron meningkat secara ketara ($p<0.05$) pada kumpulan intranasal, oral dan suntikan intradermal dengan perbezaan min 6.67pg / ml, 3.81pg/ml dan 2.4pg/ml. Kepekatan plasma estrogen telah meningkat dengan ketara ($p <0.05$) dalam laluan oral dengan min 33ng/ml. Walau bagaimanapun, sedikit peningkatan dalam tahap estrogen diperhatikan dalam suntikan intradermal dan intranasal berbanding dengan kumpulan kawalan.

Interleukin-1β menunjukkan peningkatan yang signifikan ($p<0.05$) melalui intranasal, suntikan intradermal dan laluan oral berbanding dengan kumpulan kawalan dengan perbezaan statistik min 98pg/ml, 67pg/ ml, 42pg/ml manakala peningkatan ketara pada tahap interleukin-6 diperhatikan dalam kumpulan intranasal 85pg/ ml ($p<0.05$). Tiada perbezaan yang ketara diperhatikan dalam kumpulan suntikan intradermal dan oral berbanding kumpulan kawalan.

Melalui histologi, penyusupan sel polimorfonukleus dapat diperhatikan selain nekrosis sel, kesesakan sel darah di ovari, tanduk rahim, pangkal rahim dan faraj dalam kumpulan intranasal dan oral. Kesesakan sel darah, nekrosis dalam tanduk ovari dan rahim manakala nekrosis dan penyusupan sel neutrofil dalam serviks dan faraj pada kumpulan dijangkiti melalui suntikan intradermal. Uterus dalam ketiga-tiga kumpulan menunjukkan kesesakan sel darah, edema, nekrosis dan penyusupan neutrofil.

Oleh itu, kajian ini menyerlahkan kesan *C.pseudotuberculosis* pada progesteron, estrogen, IL-1β, IL-6, darah dan perubahan sel dalam organ-organ pembiakan berserta nodus limfa yang berkaitan, yang mana penting dalam memahami patofisiologi sistem pembiakan dalam kambing yang dijangkiti *C.pseudotuberculosis*.

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It is relatively impossible for me to give the catalogues of all the names of my friends who made my stay memorable at Universiti Putra Malaysia. I will always live to remember Dr. Salamatu Mohammed Tukur, Amirah, Adza Rina and all those who contributed positively, a big thank you.

I certify that a Thesis examination committee has met on August 2014 to conduct the final examination of Aishatu Othman Mohammed on her thesis entitled Pre productive Pathophysiological Changes in non-pregnant Boer does inoculated with *Corynebacterium pseudotuberculosis* via various routes. In accordance with the Universities and University College Act 1971 and the constitution of the Universiti Putra Malaysia [P.U. (A) 106] 15 March 1998. The committee recommends that the student be awarded the Master of Veterinary Science.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Veterinary Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

%	Percentage
µmol/L	Micromoles per liter
Alb	Albumin
AST	Aspartate transaminase
ALP	Alkaline phosphatase
AGPT	Agar gel precipitation test
Ca	Calcium
Cl	Chloride
CK	Creatinine Kinase
CLA	Caseous lymphadenitis
CFU	Colony forming unit
C.pseudotuberculosis	*Corynebacterium pseudotuberculosis*
DPX	Distyrene Plasticizer Xylene
E3	Estrogen
EDTA	Ethylene diaminetetraacetic acid
ELISA	Enzyme link immunosorbent assay
Fig	Figure
GGT	Gamma-glutamyl transpeptidase
g/L	Gram per liter
Hb	Haemoglobin
K	Potassium
IL	Interleukin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
ML	Milliters
Mmol/L	Millimolar per liter
N	Number of animals
ng	Nanogram
Na	Sodium
OD	Optical density
PBS	Phosphate buffered saline
PCV	Pack cell volume
PCR	Polymerase chain reaction
P4	Progesterone
PLD	Phospholipase D
Pg	Pictogram
RBC	Red blood count
RIA	Radioimmunoassay
TPU	Taman pertanian Universiti
T.bil	Total bilirubin
UPM	Universiti Putra Malaysia
U/L	Units per liter
WBC	White blood cells

CHAPTER ONE

INTRODUCTION

1.1 GENERAL BACKGROUND

Corynebacterium pseudotuberculosis is an intracellular gram-positive, facultative anaerobic small curved rod bacterium (Jesse *et al*., 2011). *C. pseudotuberculosis* is generally regarded as an important animal pathogen and the etiological agent of the disease that is commonly called caseous lymphadenitis (CLA) in sheep and goats, and can also infect several other hosts, including human (Dorella, *et a*l., 2006; Baird, *et al*., 2007; Guimaraes*et al.*, 2011a). The disease is distributed worldwide and has a major economic impact in most sheep and goats raising areas (Baird and Fontaine, 2007; Seyffert, *et al*., 2010; Guimaraes, *et al*., 2011a). The disease is also of zoonotic importance as it may on rare occasions cause regional lymphadenitis in humans, particularly in farm workers and meat inspectors (Peel, *et al*., 1997).

Transmission of CLA can be through oral, intradermal and the peritoneal routes (Goldberger *et al*., 1981; Stoops *et al*., 1984; Collet *et al*., 1994; AdzaRina*et al*., 2013).The ability of the organism to survive for a long time in the environment coupled with its resistance to commonly available antibiotics are key features contributing to its increase in transmission within a herd (Williamson, 2001; Baird and Fontaine, 2007; Seyffert*et al*., 2010; Abdullah *et al*., 2013). Another challenge is the difficulty in identifying sub-clinically infected animals (AL-Gaabary*et al*., 2009).CLA in sheep and goats is usually associated with the development of large external abscesses in the subcutaneous tissues, lymph nodes and visceral organs such as liver, spleen and kidneys (Aloso*et al.*, 1993; Arsenault *et al*., 2003).

Treatment of CLA with antibiotic is inefficient/ ineffective becauseit thick capsule (abscess) prevent adequate penetration to reach a minimum effective dose within the lesion (Piontkowski and Shievvers, 1998; Standfort*et al*., 1998; Williamson, 2001). The best way for preventing and controlling this disease is by vaccination, culling of infected animals respectively (Luis *et al*., 2007).

Disturbances in blood parameters and serum electrolytes has been observed in mice challenged with *C.pseudotuberculosis* and its exotoxin phospholipase D (PLD) (Abdinasir*et al*., 2012). Progesterone and estrogen concentration were significantly higher in mice inoculated with *C.pseudotuberculosis* and its exotoxin phospholipase D (PLD) (Zaid *et al*., 2013). A significant reduction in progesterone level and progesterone estrogen ration in cows and buffalo infected with *Brucellamelitensis* compared to the control group have been reported by Jabbar*et al*., (2012).Progesterone production by granulosa cells is increased in vitro by IL-1β in cattle and inhibits estradiol-17β production(Barak *et al*., 1992; Barratta*et al*., 1996).

The FSH- stimulation of estrogen and progesterone released may be associated with upregulation of IL-6(Salmassi, *et al*.,2001). Experimentally challenged female mice with *C.pseudotuberculosis* and its exotoxin (PLD) via intraperitoneal route showed histopathological changes such as severe congestion, profound thrombus formation and necrosis of ovaries and uterus, while testis and epididymis showed similar lesions (Zaid *et al*., 2012).

There has been reports that the disease causes decrease in reproduction, wasting, poor wool growth, decreased milk and meat production, premature culling, carcass condemnation and rarely death in sheep, goats and other species (Williamson 2001; Paton *et al*., 2003; Arsenault *et al.*, 2003; Peterhans*et al.*, 2004). The disease is globally distributed and sustained by latent infections(Pato*et al*., 1994; Arsenault *et al.*, 2003; Ivanović*et al*., 2007). currently, the disease has been reported in many parts of Asia (OIE 2009), including Malaysia (Komala*et al*., 2008).Ruminant production in Malaysia ischanging steadily from subsistence to intensive operations (Jesse *et al.*, 2013a). The ruminant's population in Malaysia is predominantly made up of cattle, buffaloes, goats and sheep. Therefore, the ruminant industry is the foremost in the production of food such as milk, meat and the by- products such as hide for the leather industry in Malaysia.

Infertility caused by the organism (*C.pseudotuberculosis*) in non-pregnant Boer does is the main constraint in farm production for econonmic and public health reasons, as it results in wastage from culling and meat condemnation while infected animals are capable of rapidly transmitting the disease within the flock. Hence, infertility due to *C.pseudotuberculosis* is the main focus of this study in a bid to highlight the mechanismsinvolved in the disruption of the reproductive system via known different routes of infection. Reproductive hormonal (progesterone and estrogen) changes investigated in this study would be very useful as an indicative marker of infertility response to CLA.Understanding of alterations in biochemical and haematological parameters consequent to *C.pseudotuberculosis* inoculation/infection is vital to the prompt diagnosis and scoring the health status of the animal.

There is currently dearth of information on the effects of *C.pseudotuberculosis* on pre reproductive pathophysiological changes through the various routes of infection. Therefore, this study would obtain additional data on the effects of CLA onreproduction in non-pregnant Boer does.

The objectives of this study are:

1. To study the changes in blood parameters (haematological, biochemical and serum electrolyte) of non-pregnant Boer does following infection with *C.pseudotuberculosis* via different routes of inoculation.

2. To determine the plasma progesterone and estrogen concentration in non-pregnant Boer does infected with *C.pseudotuberculosis* via different routes of inoculation.

3. To investigate the inflammatory cytokines (IL-1β and IL-6) responses in the serum of non-regnant does infected with *C.pseudotuberculosis* via different routes of inoculaton.

4. To observe the histopathological alterations in the reproductive organs and associated lymph nodes of the affected animals experimentally infected with *C.pseudotuberculosis* via different routes of inoculation.

The hypotheses of this study are outlined below:

1. There might bechanges in the blood parameters in non-pregnant Boer does inoculated via different routes with *C.pseudotuberculosis*.

2. Infection of non-pregnant Boer does with *Corynebacterium pseudotuberculosis*via different routes of inoculation may alter the concentration of progesterone and estrogen concentration.

3. There might be changes in the concentration of inflammatory cytokine associated with *C.pseudotuberculosis* infections through different routes of inoculation in non-pregnant Boer does.

4. There will be cellular changes in the reproductive organs and associated lymph nodes of non-pregnant Boer does inoculated with *C.pseudotuberculosis* via different route of inoculation.

Therefore, this study will provide a better understanding on the pathogenesis of infertility during CLA infection in non-pregnant Boer does.

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