



UNIVERSITI PUTRA MALAYSIA

***REPRODUCTIVE PATHOPHYSIOLOGY OF NON-PREGNANT DOES
CHALLENGED WITH *Mannheimia haemolytica* SEROTYPE A2 AND ITS
OUTER MEMBRANE PROTEIN EXTRACT***

BOOREI MOHAMED ABDIRAHMAN

FPV 2021 24



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By

BOOREI MOHAMED ABDIRAHMAN

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia,
in Fulfilment of the Requirements for the Degree of
Master of Veterinary Science**

April 2021

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DEDICATION

To my parents, siblings, my wife, family and friends for their care, love, great source of motivation, inspiration, encouragement and endless support.

To my country may Allah award you peace and stability forever.



Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Veterinary Science

REPRODUCTIVE PATHOPHYSIOLOGY OF NON-PREGNANT DOES CHALLENGED WITH *Mannheimia haemolytica* SEROTYPE A2 AND ITS OUTER MEMBRANE PROTEIN EXTRACT

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April 2021

Chairman : Professor Faez Firdaus Jesse bin Abdullah, PhD
Faculty : Veterinary Medicine

Mannheimia haemolytica causes pneumonic pasteurellosis (mannheimiosis) which is a common respiratory disease in goats and sheep causing huge economic losses to farmers around the world. In Malaysia, the primary causative agent for small ruminants' pneumonic mannheimiosis is *M. haemolytica* serotype A2. The major virulence factors involved in the pathogenesis of pneumonic mannheimiosis are lipopolysaccharide (LPS) and outer membrane protein (OMP). Most of the previous studies were focused on the pathophysiology of the respiratory system in pneumonic goats due to *M. haemolytica*. It remains unclear whether *M. haemolytica* has effects on the female reproductive system. Hence, this study was intended to determine the concentration of reproductive hormones (oestrogen and progesterone), pro-inflammatory cytokines (interleukin-1 β and interleukin-6), acute phase proteins (haptoglobin and serum amyloid A) and clinical response changes in female goats after challenge with *M. haemolytica* A2 and its outer membrane protein (OMP). In this study, 12 clinically healthy non-pregnant, cross bred does were used and divided equally into three groups. Does in group 1 (control group) were challenged with 2 ml of sterile phosphate buffered saline (PBS) intranasally, and group 2 does were challenged intranasally with 2 ml of suspension containing 10⁹ colony forming unit (cfu) of *M. haemolytica* A2. Does in group 3 were challenged with 2ml of OMP intramuscularly extracted from 10⁹ cfu of *M. haemolytica* A2. Clinical responses were observed following the challenge and blood samples were collected at (0, 1, 2, 4, 6, 12 and 24 hours and at day 3, 7, 21, 35 and 56) post-inoculation for determination of (IL-1 β , IL-6, Hp, SAA, oestrogen and progesterone) with sandwich ELISA. The challenged groups showed significant differences ($p < 0.05$) in rectal temperature, respiratory rate, heart rate and rumen motility compared to the control group. The results of serum analyses revealed that the concentrations of progesterone and oestrogen were significantly decreased ($p < 0.05$), while the concentrations of pro-inflammatory cytokines (IL-1 β and IL-6) and acute phase proteins (Hp and SAA) were significantly increased ($p < 0.05$) in the challenged groups compared to the control

group. The results of histopathological lesions in the lungs, liver, lymph nodes and the reproductive organs revealed mild to moderate significant change ($p < 0.05$) in both treatment groups compared to the control group. Therefore, these findings suggest that *M. haemolytica* serotype A2 and its OMP potentially contribute to infertility in female goats and responsible for the occurrence of hormonal imbalances which in turn leads to reproductive inefficiency.



Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Perubatan Veterinar

REPRODUKTIF PATOFISIOLOGI BAGI KAMBING BETINA TIDAK BUNTING YANG DIUJI DENGAN *Mannheimia haemolytica* SEROTYPE A2 DAN EKSTRAK MEMBRAN PROTEIN LUAR

Oleh

BOOREI MOHAMED ABDIRAHMAN

April 2021

Pengerusi : Profesor Faez Firdaus Jesse bin Abdullah, PhD
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Mannheimia haemolytica yang menyebabkan *pasteurellosis pneumonik* (mannheimiosis) yang merupakan penyakit pernafasan yang biasa terjadi pada kambing dan biri-biri yang menyebabkan kerugian ekonomi yang besar kepada penternak di seluruh dunia. Di Malaysia, agen penyebab utama *Pasteurella mannheimiosis* ruminan kecil adalah *M. haemolytica* serotype A2. Faktor virulensi utama yang terlibat dalam patogenesis *Pasteurella mannheimiosis* adalah lipopolysaccharide (LPS) dan protein membran luar (OMP).

Sebilangan besar kajian sebelumnya difokuskan pada patofisiologi sistem pernafasan pada kambing pneumonia disebabkan oleh *M. haemolytica*. Masih tidak jelas apakah *M. haemolytica* mempunyai kesan pada sistem pembiakan betina. Oleh itu, kajian ini bertujuan untuk menentukan kepekatan hormon pembiakan (estrogen dan progesteron), sitokin pro-radang (interleukin-1 β dan interleukin-6), protein fasa akut (haptoglobin dan amiloid serum A) dan perubahan tindak balas klinikal pada kambing betina selepas ujian dengan *M. haemolytica* A2 dan protein membran luar (OMP). Dalam kajian ini, 12 haiwan yang sihat secara klinikal tidak hamil, yang dikacuk telah digunakan dan dibahagikan sama kepada tiga kumpulan. Kambing betina dalam kumpulan 1 (kumpulan kawalan) diuji dengan 2 ml garam salin biasa secara intranasal, dan kumpulan 2 diuji dengan 2 ml suspensi yang mengandungi 10⁹ unit pembentukan koloni (cfu) *M. haemolytica* A2 secara intranasal. Kambing betina dalam kumpulan 3 diuji dengan 2 ml OMP secara intramuskular yang diekstrak dari 10⁹ cfu *M. haemolytica* A2. Tindak balas klinikal diperhatikan berikutan ujian dan sampel darah direkodkan pada (0, 1, 2, 4, 6, 12 dan 24 jam dan pada hari ke 3, 7, 21, 35 dan 56) pasca inokulasi untuk penentuan (IL-1 β , IL-6, Hp, SAA, estrogen dan progesteron) dengan sandwich ELISA. Kumpulan yang diuji menunjukkan perbezaan yang signifikan (p < 0,05) dalam suhu rektum, kadar pernafasan, degupan jantung dan pergerakan rumen berbanding dengan kumpulan kawalan. Hasil analisis serum menunjukkan

bahawa kepekatan progesteron dan estrogen menurun secara signifikan ($p < 0.05$), sedangkan kepekatan sitokin pro-radang (IL-1 β dan IL-6) dan protein fasa akut (Hp dan SAA) secara signifikan meningkat ($p < 0.05$) pada kumpulan yang diuji berbanding dengan kumpulan kawalan. Hasil lesi histopatologi pada paru-paru, hati, kelenjar limfa dan organ pembiakan menunjukkan perubahan signifikan yang ringan hingga sederhana ($p < 0.05$) pada kedua-dua kumpulan rawatan berbanding dengan kumpulan kawalan. Oleh itu, penemuan ini menunjukkan bahawa *M. haemolytica* serotype A2 dan OMPnya berpotensi menyumbang kepada kemandulan pada kambing betina dan bertanggungjawab terhadap berlakunya ketidak seimbangan hormon yang seterusnya menyebabkan ketidakcekapan pembiakan.

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment 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

°C	Degree Celsius
ANOVA	One-way analysis of variance
APP	Acute Phase Proteins
APR	Acute Phase Reaction
<i>B. trehalosi</i>	<i>Bibersteinia trehalosi</i>
Bpm	Beats per Minute
BRD	Bovine Respiratory Disease
BW	Body Weight
Bwt	Body Weight
<i>C. pseudotuberculosis</i>	<i>Corynebacterium pseudotuberculosis</i>
CFU	Colony Forming Unit
CI	Confidence Interval
DVS	Department of Veterinary Services
ELISA	Enzyme Linked Immunosorbent Assay
FSH	Follicular Stimulating Hormone
GDP	Gross Domestic Product
GnRH	Gonadotropin-Releasing Hormone
H	Hour
H&E	Haematoxylin and Eosin
<i>H. somni</i>	<i>Histophilus somni</i>
H ₂ S	Hydrogen sulphide
Hp	Haptoglobin
IACUC	Institutional Animal Care and Use Committee

IL-1 α	Interleukin -1 Alpha
IL-1 β	Interleukin-1 beta
IL-6	Interleukin-6
IU	International Unit
kDa	Kilo Daltons
kg	kilogram
L	Litre
LH	Luteinizing Hormone
LKT	Leukotoxin
LPS	Lipopolysaccharide
<i>M. glucosida</i>	<i>Mannheimia glucosida</i>
<i>M. haemolytica</i>	<i>Mannheimia haemolytica</i>
<i>M. ruminalis</i>	<i>Mannheimia ruminalis</i>
mg	Milligram
mL	Millilitre
NaCl	Sodium Chloride
Neu5Ac	N-acetylneuraminic acid
ng	Nanogram
OD	optical density
OMP	Outer Membrane Protein
OMP A	Outer Membrane Protein A
<i>P. multocida</i>	<i>Pasteurella. multocida</i>
PBS	Phosphate Buffered Saline
PCR	Polymerase Chain Reaction

Pg	Picogram
PGF _{2α}	Prostaglandin F2alpha
PLD	Phospholipase D
PolySia	Polysialic acid
rpm	Revolutions per minute
SAA	Serum Amyloid A
SCM	Sub-clinical Mastitis
TNF-α	Tumour necrosis factor-alpha
B	beta
Mg	Microgram
μl	Microliter

CHAPTER 1

INTRODUCTION

1.1 Background of the study

The small ruminant sector of Malaysia is very small compared to the poultry and swine sectors as its primarily owned by smallholder farmers (Jesse et al., 2018). The current report from the Department of Veterinary Services (DVS) states the population of small ruminants to be 320,203 goats and 121,173 sheep in 2020 (DVS, 2020). The main breeds of goats in Malaysia include British Alpine, Jamnapari, Saanen, Shami, Kambing Katjang, Boer and Toggenburg (Mohsin et al., 2019; Muayad et al., 2019). The small ruminant industry in Malaysia is usually owned by smallholders raised under a semi-intensive system where individual flocks (5-50 animals) are housed in elevated houses at night and limited daytime grazing and feed supplements are allowed.

The local demand for mutton and goats' milk in Malaysia remains very high, while the small ruminant production is becoming an attractive enterprise, contributing significantly to the gross domestic products (GDP) and subsistence of farmers in the country (Melissa et al., 2016). Nonetheless, many issues challenge the productivity of small ruminants in the country, among these, the disease is a significant factor. The significant economic diseases of small ruminants in Malaysia include pneumonic pasteurellosis, contagious ecthyma, and caseous lymphadenitis (Abdullah et al., 2013a; Jesse et al., 2020).

Pneumonic pasteurellosis (pneumonic mannheimiosis) is a disease of small ruminants leading to a significant reduction in growth performance caused by *Mannheimia haemolytica* which is an opportunistic bacterium (Ponnusamy et al., 2017). *M. haemolytica* is a small gram negative bacterium with a shape of rods or coccobacilli, non-spore-forming, non-motile, facultatively anaerobic, fermentative and oxidase-positive, that generally inhabits in the domestic and wild animals' upper respiratory and digestive tract mucous membrane as a commensal; it is surrounded by a polysaccharide capsule on which serotyping is based on and produces β -haemolysis (Wilson & Ho, 2013).

M. haemolytica has a variety of potential immunogens. Capsular polysaccharide, LPS, OMPs, fimbriae, iron-regulated proteins and a secreted leukotoxin (LKT) are the most potential ones to activate immunity (Confer, 1993). These factors enable *M. haemolytica* to cytolysse alveolar phagocytic cells and replicate in the lung that further increase bacterial proliferation and involvement of the direct or indirect effect in lung injury (Jeyaseelan et al., 2002). *M. haemolytica* A2 has been reported as the most common isolate from sheep and goat pneumonic pasteurellosis in Malaysia and worldwide (Shahudin et al., 2018; Avalos-Gómez et al., 2020).

Pneumonia in small ruminants is the main cause of economic losses to producers worldwide. The financial consequences of pneumonia represent 8% of the total production charges, which includes poor food conversion rate, increased production costs, medical expenses, and decreased food availability for humans (Rico et al., 2017). Besides, the disease has an occurrence of acute febrile course with extreme fibrinous or fibrinopurulent bronchopneumonia, fibrinous pleurisy, and septicaemia (Abdullah et al., 2015). It's worth mentioning that young animals are more susceptible to the infection than adults, and experience more severe infection where sudden death can occur with or without any apparent clinical signs (Chung et al., 2015a). Pneumonia is usually caused by inhalation of contaminated droplets from the affected animals, those are the clinical cases or recovered carriers where infection remains in these animals (Tadesse et al., 2017). *M. haemolytica* is carried in the nasopharynx of healthy animals (Rowe et al., 2001), and it is vulnerable to the environmental effect as the mediated contagion is unclear to be a necessary factor in transmitting the disease.

For post mortem lesions, the most noticeable gross lesions are the marbling of the lung, presence of excess straw-coloured fluid in the thoracic cavity and appearance of frothy exudates in the trachea, bronchi and damaged lung surface (Jesse et al., 2019a). Bilateral pulmonary lesions are common with cranioventral distribution, and the most affected areas are below the horizontal line commonly by the trachea bifurcation, apical and the cardiac lobes. Infections involving large parts of the diaphragmatic lobe in severe cases may be more common (Mohamed & Abdelsalam, 2008). Additionally, the bacterial LPS and LKT play a significant role in the migration of neutrophils into the lungs, resulting in severe pulmonary inflammation and tissue damage in pneumonic animals (Cozens et al., 2019).

Little information is available on the changes of reproductive hormones (Oestrogen and Progesterone), pro-inflammatory cytokines interleukin-1 β (IL-1 β) and interleukin-6 (IL-6) concentration and acute phase proteins (APP) haptoglobin (Hp) and serum amyloid A (SAA) in non-pregnant does challenged with *M. haemolytica* and its immunogen OMP. In addition, there is no report on the pathological changes in the reproductive system in non-pregnant does challenged with *M. haemolytica* and its immunogen OMP. This study was designed to determine the changes in progesterone, oestrogen, IL-1 β , IL-1 β , Hp and SAA concentrations as well as pathological changes in the reproductive organs, experimentally infected by *M. haemolytica* and its immunogen OMP.

1.2 Problem statement

Pneumonia due to *M. haemolytica* serotype A2 infection is one of the most common respiratory problems occurring in small ruminants in Malaysia and the disease was considered endemic (Saharee & Fatimah, 1993). It may cause huge economic losses to the farmers as the infected animals might die within few days and if survived, their productivity will be decreased while the cost for the treatment and prevention programs increases (Mohamed & Abdelsalam, 2008).

The reproductive physiology of does refers to the normal reproductive activity that begins when the females reach puberty, which occurs at 5 months of age, where the hypothalamic-pituitary-gonadal axis plays a key role in regulation, with the hypothalamus modulating pituitary gonadotropins secretion or inhibitory factors (Dávila et al., 2017). Whereas a disorder in these physiological processes is referred to as reproductive pathophysiology.

The pathophysiology of the respiratory system due to *M. haemolytica* was focused on in previous studies (Abdullah et al., 2015). It remains to be studied whether *M. haemolytica* have effects on the reproductive system as it was often overlooked by the farmers and veterinarians. To the knowledge of the author, there is a gap to be filled out to determine these effects and little information is known on the reproductive physiology and pathological changes in female goats inoculated with *M. haemolytica* A2 and its OMP.

1.3 Hypothesis

It is hypothesised that there will be host cell response in does following experimental infection with *M. haemolytica* serotype A2 and its immunogen OMP extract as well as reproductive involvement.

1. Does inoculated with *M. haemolytica* serotype A2 will show more severe clinico-pathological changes compared to does inoculated with bacterial immunogen OMP extract.
2. There will be changes in clinical responses, reproductive hormones (progesterone and oestrogen), APP and pro-inflammatory cytokines concentrations in the experimental animals infected with *M. haemolytica* serotype A:2 and its immunogen OMP extract.

1.4 Objectives

The main objective of this study was to add knowledge in *M. haemolytica* infection towards understanding the pathophysiology of the reproductive system in goats (female) after inoculation with *M. haemolytica* and its outer membrane protein (OMP) extract. The specific objectives of this study were as follows:

1. To determine changes in clinical response and to detect the concentration of progesterone and oestrogen hormones in does after inoculation with *M. haemolytica* serotype A2 and its OMP extract.
2. To determine the concentration of pro-inflammatory cytokines (IL-1 β and IL-6) and acute phase proteins Hp and SAA in does after inoculation with *M. haemolytica* serotype A2 and its OMP extract.

3. To evaluate the severity of tissue changes of reproductive organs, its associated lymph nodes and pituitary gland in does after inoculation with *M. haemolytica* serotype A2 and its OMP extract.



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