



UNIVERSITI PUTRA MALAYSIA

***PATHOPHYSIOLOGY AND REPRODUCTIVE HORMONES
DISTURBANCES OF NON-PREGNANT DOES POST-CHALLENGED
WITH *Mannheimia haemolytica* SEROTYPE A2 AND ITS
LIPOPOLYSACCHARIDE ENDOTOXIN***

KAMARULRIZAL BIN MAT ISA

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By

KAMARULRIZAL BIN MAT ISA

**Thesis Submitted to the School of Graduate Studies, University Putra
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Master of Veterinary Science**

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DEDICATION

This thesis is dedicated to my beloved family, research colleagues, and friends.
May Allah bless you all...



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

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February 2021

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

Pneumonic manheimiosis is a common respiratory disease occurring in goats and sheep with worldwide prevalence. It causes enormous economic losses to small ruminant farmers due to high morbidity and mortality rates, especially in young animals, and decreased productivity among flock survivors. In Malaysia, pneumonic manheimiosis in goats is predominantly caused by *Mannheimia haemolytica* serotype A2, a Gram-negative bacterium belonging to the genus *Mannheimia* and the family *Pasteurellaceae*. During disease pathogenesis, the bacteria produce Lipopolysaccharide (LPS) endotoxin, one of the major virulence factors responsible for the pathophysiological effects of pneumonic manheimiosis. Previous investigations have revealed that LPS endotoxin from certain Gram-negative bacteria such as *Escherichia coli* and *Pasteurella multocida* could adversely affect the reproductive system of female animals. However, it is unknown whether LPS endotoxin of *M. haemolytica* serotype A2 may also induce similar insidious effects, as most earlier studies focused primarily on the respiratory system. Moreover, there is limited information regarding the pathology of the reproductive organs and the response of reproductive hormones in female goats infected with pneumonic manheimiosis. Therefore, this study was designed to investigate the effects of *M. haemolytica* serotype A2 and its LPS endotoxin on clinical responses, reproductive hormones (progesterone and oestrogen), pro-inflammatory cytokines (interleukin-1 β and interleukin-6), acute-phase proteins (haptoglobin and serum amyloid A) and histopathology of reproductive organs, vital organs, and its associated lymph nodes in female goats' model. A total of 12 clinically healthy adults, non-pregnant crossbred does, aged between 12 to 18 months, weighing approximately 25 \pm 2kg, were used in this study. They were randomly divided into three equal experimental groups (Group 1, Group 2, and Group 3) and kept in three separate pens. Does in Group 1 served as a negative control group and were given

intranasally with 2 ml of sterile phosphate-buffered saline (PBS). Does in Group 2 were challenged intranasally with 2 ml of bacterial cell suspension containing 10^9 colony-forming unit (CFU) per ml of *M. haemolytica* serotype A2, while does in Group 3 were challenged intravenously with 2 ml of LPS endotoxin extracted from 10^9 CFU/ml of *M. haemolytica* serotype A2. Following the challenges, all does were closely monitored, and clinical responses were recorded daily for 60 days. Blood samples were collected serially at predetermined intervals for serological analysis using commercial ELISA kits. On the 60th day post-challenged, all does were euthanised by slaughter for macroscopic and microscopic post-mortem examinations. The results revealed that does in both challenged groups (Group 2 and Group 3) showed significant alterations ($p < 0.05$) in clinical responses at several time points compared to the control group. The clinical responses observed were pyrexia, tachycardia, tachypnoea, mild crackle lung sound, mild coughing, serous to mucoid nasal discharges, and mild to moderate rumen hypomotility. Analysis of serum samples demonstrated significant increases ($p < 0.05$) in the mean concentrations of reproductive hormones (progesterone and oestrogen), pro-inflammatory cytokines (IL-1 β and IL-6), and acute-phase proteins (Hp and SAA) in both challenged groups at several time points compared to the control group. Histopathological results revealed that both challenged groups displayed significant macroscopic lesions in the lungs and microscopic lesions ($p < 0.05$) were observed in the ovaries, fallopian tubes, uterine horns, uterine body, lungs, liver, and its associated lymph nodes. The severity of cellular alterations ranged from normal to moderate for haemorrhage and congestion; degeneration and necrosis; inflammatory cell infiltration, and oedema. In conclusion, this study reports for the first time that pneumonic manheimiosis caused by *M. haemolytica* serotype A2 is capable of inducing pathological changes in the reproductive organs and interfering with the production of reproductive hormones in non-pregnant does, where its LPS endotoxin responsible for the etiopathogenesis. These novel discoveries suggest that pneumonic manheimiosis may potentially interfere with reproductive efficiency and predispose infected does to infertility.

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

**PATOFISIOLOGI DAN GANGGUAN HORMON-HORMON REPRODUKTIF
PADA KAMBING BETINA TIDAK BUNTING PASCA-DICABAR DENGAN
Mannheimia haemolytica SEROTYPE A2 DAN ENDOTOKSIN
LIPOPOLISAKARIDA**

Oleh

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Februari 2021

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Fakulti: Perubatan Veterinar

Mannheimiosis pneumonik merupakan penyakit pernafasan yang biasa terjadi pada kambing dan bebiri dengan kelaziman di seluruh dunia. Penyakit ini menyebabkan kerugian ekonomi yang sangat besar kepada para peternak ruminan kecil kerana kadar morbidity dan kematian yang tinggi, terutamanya pada ternakan muda, dan penurunan produktiviti di kalangan haiwan yang terselamat. Di Malaysia, penyakit mannheimiosis pneumonik pada kambing dan bebiri sebahagian besarnya disebabkan oleh *Mannheimia haemolytica* serotaip A2, bakteria Gram-negatif yang tergolong dalam genus *Mannheimia* dan famili *Pasteurellaceae*. Semasa patogenesis penyakit, bakteria tersebut akan menghasilkan endotoksin lipopolisakarida (LPS), iaitu satu faktor virulen utama yang bertanggungjawab terhadap kesan patofisiologi penyakit mannheimiosis pneumonik. Kajian terdahulu menunjukkan bahawa endotoksin LPS daripada beberapa bakteria Gram-negatif seperti *Escherichia coli* and *Pasteurella multocida* boleh memberi kesan buruk kepada sistem pembiakan haiwan betina. Walaubagaimanapun, tidak diketahui sama ada endotoksin LPS daripada *M. haemolytica* serotype A2, juga boleh menyebabkan kesan berbahaya yang serupa, kerana kebanyakan kajian awal tertumpu terutamanya pada system pernafasan. Lebih-lebih lagi, terdapat sedikit maklumat mengenai patologi organ-organ pembiakan dan tindak balas hormon-hormon pembiakan pada kambing betina yang dijangkiti mannheimiosis pneumonik. Oleh itu kajian ini dirancang untuk mengkaji kesan *M. haemolytica* serotype A2 dan endotoksin LPS terhadap tindak balas klinikal, hormon pembiakan (progesteron dan oestrogen), sitokin pro-radang (interleukin-1 β dan interleukin-6), protein fasa akut (haptoglobin dan serum amyloid A) dan histopatologi organ pembiakan, organ vital dan kelenjar nodus limfa yang berkaitan pada model kambing betina. Sejumlah 12 ekor kambing betina dewasa kacukan yang sihat secara klinikal, tidak bunting, berumur antara 12 hingga 18 bulan, dan berat badan kira-kira

25±2kg digunakan dalam kajian ini. Mereka dibahagi secara rawak dan sama rata kepada tiga kumpulan eksperimen (Kumpulan 1, Kumpulan 2, dan Kumpulan 3) dan disimpan di dalam tiga petak kandang berasingan. Kambing betina dalam Kumpulan 1 berfungsi sebagai kumpulan kawalan negatif dan diberikan 2 ml garam buffer fosfat steril (PBS) secara intranasal. Kambing betina dalam Kumpulan 2 dicabar secara intranasal dengan 2 ml suspensi sel bakteria yang mengandungi 10⁹ unit pembentuk koloni (CFU) per ml *M. haemolytica* serotaip A2, sementara kambing betina dalam Kumpulan 3 pula dicabar secara intravena dengan 2 ml endotoksin LPS yang diekstrak dari 10⁹ CFU/ml *M. haemolytica* serotaip A2. Selepas cabaran, semua kambing betina dipantau dengan teliti dan tindak balas klinikal dicatat setiap hari untuk selama 60 hari. Sampel darah diambil secara bersiri pada selang waktu yang ditentukan untuk analisis serologi menggunakan kit-kit ELISA komersial. Pada hari ke-60 setelah dicabar, semua kambing betina dimatikan secara penyembelihan untuk pemeriksaan post-mortem makroskopik dan mikroskopik. Keputusan kajian menunjukkan bahawa kedua-dua kumpulan yang dicabar (Kumpulan 2 dan Kumpulan 3) menunjukkan perubahan yang signifikan ($p < 0.05$) dalam tindak balas klinikal pada beberapa titik waktu berbanding dengan kumpulan kawalan. Ini termasuklah pyrexia, takikardia, tachypnoea, bunyi paru-paru ringan, batuk ringan, discaj hidung serous ke mukoid dan hipomotiliti rumen ringan hingga sederhana. Analisis serum darah menunjukkan peningkatan yang ketara ($p < 0.05$) dalam kepekatan purata hormon pembiakan (progesteron dan oestrogen) serta sitokin pro-radang (IL-1 β dan IL-6) dan protein fasa akut (Hp dan SAA) di kedua-dua kumpulan yang dicabar pada beberapa titik waktu berbanding dengan kumpulan kawalan. Keputusan histopatologi menunjukkan kedua-dua kumpulan yang dicabar mempamerkan lesi-lesi makroskopik pada paru-paru dan lesi mikroskopik yang ketara ($p < 0.05$) pada ovari, tiub fallopi, tanduk rahim, badan rahim, paru-paru, hati dan kelenjar nodus limfa yang berkaitan. Keterukan perubahan selular bermula dari normal hingga sederhana untuk pendarahan dan kongesi; degenerasi dan nekrosis; penyusupan sel keradangan, dan edema. Kesimpulannya, kajian ini melaporkan buat pertama kalinya bahawa mannheimiosis pneumonik yang disebabkan oleh *M. haemolytica* serotype A2 mampu menyebabkan perubahan patologi pada organ pembiakan dan mengganggu pengeluaran hormon pembiakan pada kambing betina tidak bunting, di mana endotoksin LPSnya bertanggungjawab untuk etiopatogenesis. Penemuan novel ini menunjukkan bahawa mannheimiosis pneumonik mungkin berpotensi menjejaskan kecekapan pembiakan dan mendedahkan kambing betina yang terjangkit kepada ketidaksuburan.

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Kamarulrizal, 2021

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LIST OF ABBREVIATIONS

| | |
|-------|---------------------------------------------|
| °C | Degree Celsius |
| β | Beta |
| % | Percentage |
| ANOVA | Analysis of variance |
| APPs | Acute-phase proteins |
| APR | Acute-phase response |
| CFU | Colony forming unit |
| DNA | Deoxyribonucleic acid |
| DVS | Department of Veterinary Services |
| ELISA | Enzyme Linked Immunosorbent Assay |
| FSH | Follicle-stimulating hormone |
| GnRH | Gonadotrophin-releasing hormone |
| H&E | Haematoxylin and Eosin |
| Hp | Haptoglobin |
| IACUC | Institutional Animal Care and Use Committee |
| IL-1β | Interleukin 1β |
| IL-6 | Interleukin 6 |
| kg | Kilogram |
| LH | Luteinizing hormone |
| LKT | Leukotoxin |
| LPS | Lipopolysaccharide |
| ml | Millilitre |
| mM | Millimolar |
| MT | Metric tonne |

| | |
|------|----------------------------------------|
| ng | Nanogram |
| NZ\$ | New Zealand Dollar |
| OD | Optical Density |
| OMPs | Outer membrane proteins |
| PBS | Phosphate Buffered Saline |
| PCR | Polymerase chain reaction |
| pg | Picogram |
| PGE2 | Prostaglandin E2 |
| RNA | Ribonucleic acid |
| rpm | Revolutions per minute |
| SAA | Serum amyloid A |
| SEM | Standard error mean |
| SPSS | Statistical package for social science |
| SSL | Self-sufficiency level |
| UPM | Universiti Putra Malaysia |

CHAPTER 1

INTRODUCTION

1.1 Background of the study

In many parts of the world, goat farming is a vital livestock industry that provides a wide variety of products for human needs. These include meat, milk, fur, leather, and other related products of animal origin, which generate a source of income for farmers (Casey and Webb, 2010; Patel and Pandey, 2013). Since the beginning of domestication around 10,000 years ago (Zeder et al., 2000), the global population of goats has increased not only in low-income countries but also in middle or high-income countries as well (Morand-Fehr et al., 2004). Goats have become valuable livestock throughout the world in various aspects of everyday life, including social, economic, cultural, and religious, which contribute to the sustainability of life (Pollot and Wilson, 2009).

Over the last two decades, goat farming in Malaysia has started to grow and transform from a traditional rearing system into an intensive farming system on a commercial scale. Growth in the human population has triggered the establishment of new goat farms to meet the demand for meat and milk (Shahudin et al., 2018). According to livestock statistics data from the Department of Veterinary Services (DVS) of Malaysia, the total population of goats and sheep in Malaysia in 2019 was 434,248 heads, which can supply around 4,200.6 metric tonnes (MT) of mutton per year. However, the self-sufficiency level (SSL) was only 11.83%, as the total consumption of mutton in Malaysia was 35,498.8 MT in that year. As a result, the government had to import massive quantities of mutton as well as live animals from foreign countries to meet the increasing domestic demand (Department of Veterinary Services, 2020).

Despite the growth of small ruminant industry players, the number of sheep and goats in Malaysia is still lacking (Loh, 2004). Fatalities due to infectious diseases are among the major factors that hinder the growth of small ruminant populations in this country, as well as others (Jesse et al., 2019a). One of those diseases is pneumonia; the most common respiratory disease occurring in sheep and goats with a worldwide prevalence (Ackermann and Brogden, 2000). It causes enormous economic losses to the goat farmers due to high morbidity and mortality rate, increased treatment and prevention costs, delayed marketing, and decreased productivity among survivors of the flock. (Hawari *et al.*, 2008; Hussain *et al.*, 2017). Small ruminants of all ages are at risk of getting an infection, but younger animals are more susceptible (Chung et al., 2015). The incidence rate of pneumonia ranges from 10% to 40%, with a mortality rate of more than 20%, which is usually greater in lambs and kids (Rico et al., 2017). Pneumonia is an aetiologically complex disease that develops when the host is

subjected to multiple predisposing factors such as stressful conditions (e.g., bad weather, transportation, poor housing, and malnutrition) and coinfections (e.g., viral, bacterial, and parasite). These result in disruption of the host's defence mechanisms, which allows the commensal organisms, including *Mannheimia haemolytica* and *Pasteurella multocida*, to proliferate and gain access to the lung, and eventually lead to infection (Zamri-Saad and Mera, 2001; Singh *et al.*, 2011; Abdullah *et al.*, 2014; Chung *et al.*, 2015).

In Malaysia, pneumonia in sheep and goats is predominantly caused by *M. haemolytica* serotype A2, and the disease is considered endemic (Saharee and Fatimah, 1993; Affendy *et al.*, 2000; Sabri *et al.*, 2000, Abdullah *et al.*, 2014). It is a small rod or coccobacilli, Gram-negative, non-motile, non-spore-forming, and facultative anaerobic bacteria that belong to the genus *Mannheimia* and the family *Pasteurellaceae* (Donachie, 2000). In healthy ruminants, the organism lives as normal flora in the upper respiratory tract without causing any pathological effect on the respiratory system (Singh *et al.*, 2019). However, they become opportunistic secondary invaders when the pulmonary defence mechanisms are compromised and transformed into a pathogenic entity, inducing injuries and damages to the respiratory system (Jayaweera *et al.*, 2014).

Pneumonia due to *M. haemolytica* (also called pneumonic manheimiosis) is an acute infectious disease, causing inflammation to the alveoli and bronchioles of the lung (El-Deeb and Tharwat, 2015). It is characterised by an acute febrile course with severe fibrinous or fibrinopurulent bronchopneumonia, fibrinous pleurisy, and septicaemia in infected animals (Mohamed and Abdelsalam, 2008). The severity of pneumonic manheimiosis depends on the rate and extent of bacterial proliferation as well as the virulence of the organism. Among several recognised virulence factors, lipopolysaccharide (LPS), also known as endotoxin, has been identified as one of the potent virulence factors involved in the pathogenesis of pneumonic manheimiosis (Mohamed and Abdelsalam, 2008). Besides causing direct pulmonary parenchyma injury, LPS endotoxin is also highly immunostimulatory and plays an important role in activating innate immune cells, particularly macrophages and neutrophils (Mohamed and Abdelsalam, 2008; Jesse *et al.*, 2017). Activation of these immune cells will result in the release of pro-inflammatory cytokines such as interleukin 1 β (IL-1 β) and interleukin 6 (IL-6) (Ackermann and Brogden, 2000; Singh *et al.*, 2011), which in turn stimulates the production of positive acute-phase proteins (APPs) such as Haptoglobin (Hp) and Serum Amyloid A (SAA) (Salvesen *et al.*, 2016).

Apart from direct damage to the respiratory system, the LPS endotoxin of Gram-negative bacteria is also capable of causing insidious effects on the reproductive system. Several lines of research evidence suggest that LPS endotoxin from certain Gram-negative bacteria such as *Pasteurella multocida* and *Escherichia coli* may interfere with the normal functions of the female reproductive system. LPS-induced histopathological injury to the hypothalamic-pituitary-gonadal axis (HPG axis) and reproductive organs, mainly the oviducts and uterus, will result

in reproductive hormonal imbalances, irregular oestrous cycles, delayed ovulation, impaired fertilisation, implantation failure, embryonic death, and abortion (Williams et al., 2008; Agrawal et al., 2011; Bidne et al., 2018; Jesse et al., 2020). Such reproductive problems may impede the development of the small ruminant industry and result in significant financial losses to goat and sheep farmers (Ali et al., 2019).

1.2 Problem statement

Previous investigations have shown that LPS endotoxin from certain Gram-negative bacteria can adversely affect the reproductive system of female animals. However, it is unknown whether LPS endotoxin of *M. haemolytica* serotype A2, which is the leading causative bacteria of pneumonic manheimiosis in small ruminants, may also induce similar insidious effects, as most earlier studies focused primarily on the respiratory system. Furthermore, there is a paucity of information on the pathology of the reproductive organs and the responses of reproductive hormones in female goats infected with pneumonic manheimiosis.

1.3 Objectives

This study is designed to obtain new information and answer the gap of knowledge with the following objectives:

1. To study changes in clinical signs and responses in non-pregnant does post-challenged with *M. haemolytica* serotype A2 and its LPS endotoxin.
2. To measure the levels of reproductive hormones (progesterone and oestrogen) in non-pregnant does post-challenged with *M. haemolytica* serotype A2 and its LPS endotoxin.
3. To measure the concentrations of pro-inflammatory cytokines (IL-1 β and IL-6) and acute-phase proteins (Hp and SAA) in non-pregnant does post-challenged with *M. haemolytica* serotype A2 and its LPS endotoxin.
4. To evaluate the severity of tissue changes in the reproductive organs, vital organs, and its associated lymph nodes in non-pregnant does post-challenged with *M. haemolytica* serotype A2 and its LPS endotoxin.

1.4 Hypotheses

The hypotheses of this study are outlined as follows:

1. Experimental does post-challenged with *M. haemolytica* serotype A2 and its LPS endotoxin will show changes in clinical signs and responses.
2. Experimental does post-challenged with *M. haemolytica* serotype A2 and its LPS endotoxin will show alterations in serum levels of progesterone and oestrogen hormones.
3. Experimental does post-challenged with *M. haemolytica* serotype A2 and its LPS endotoxin will show alterations in serum concentrations of IL-1 β , IL-6, Hp, and SAA.
4. Experimental does post-challenged with *M. haemolytica* serotype A2 and its LPS endotoxin will demonstrate histopathological changes in the tissues of reproductive organs, vital organs, and its associated lymph nodes.

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