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Research Article

Response of Reproductive Hormones in Vaccinated and Non-Vaccinated Pneumonic Female Goats Via Experimental Infection of *Mannheimia haemolytica* Serotype A2 Under Rainy and Hot Seasons

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Abstract | Pneumonic mannheimiosis is well documented in the literature focusing on the respiratory system of small ruminants from clinical and research perspectives. However, there is still a lack of understanding of this disease's pathophysiological changes and impact on the reproductive system of affected animals. Therefore, the purpose of this study was to examine at the reproductive hormonal profile of female goats experimentally infected with *Mannheimia haemolytica* serotype A2 during rainy and hot seasons. Twenty-four healthy female, non-pregnant does were used, and divided into two equal groups, 12 does were further allocated into 3 groups (n=4), control, non-vaccinated and vaccinated in each season. After acclimatization and synchronization procedure, the vaccinated group was administered with 2 mL of alum-precipitated pasteurellosis vaccine while non-vaccinated and control groups were administered with 2 mL of phosphate-buffered saline (PBS) via the intramuscular route. At week 2, both non-vaccinated and the vaccinated groups were challenged intranasally with 2 mL of bacterial cell suspension containing 10^5 colony-forming unit (CFU) of *M. haemolytica* serotype A2. Blood samples were collected on weekly basis. The results revealed that the plasma progesterone concentration increased significantly ($p<0.05$) whereas estrogen, follicle-stimulating hormone and luteinizing hormone decreased significantly ($p<0.05$) in the non-vaccinated group compared to vaccinated and control groups in both seasons. The study outcomes shown that climate has neither significant effect on reproductive physiology nor exaggerated the effect on an experimentally infected animal. Furthermore, it is concluded that pneumonic mannheimiosis causes a negative impact on reproductive performance of the female goats where hormonal imbalances were observed which may result to pseudopregnancy or infertility in does infected with *M. haemolytica* serotype A2.

Keywords | *Mannheimia haemolytica* serotype A2, Does, Progesterone, Estrogen, Follicle-Stimulating Hormone, Luteinizing Hormone.

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INTRODUCTION

Pneumonic mannheimiosis is a respiratory problem that commonly occurs in goats, especially young ones, characterized as an acute, febrile, and fibrinopurulent bronchopneumonia and septicaemic disease of small ruminants throughout the world (Jesse et al., 2019). *Pasteurella multocida* and *Mannheimia haemolytica* has been isolated from pneumonic small ruminants (Chung et al., 2015), but the bacterium *M. haemolytica* A2 is a primary and opportunistic pathogen of small ruminants, causes mannheimiosis with high prevalence and mortality worldwide (Abdullah et al., 2014). It is a gram-negative, facultative anaerobic, non-motile, coccobacilli, fermentative, oxidase and catalase-positive bacteria (Abdullah et al., 2015). Infected animals often die within a few days after developing clinical signs and symptoms, but survivors may move to the chronic stage (Emikpe et al., 2010; Jesse et al., 2019). The disease inflicts substantial economic losses to small ruminant productivity across the world (Shahrom and Zamri-Saad, 2012; Abdullah et al., 2015) and the role of *M. haemolytica* and its relative importance is still equivocal. The disease is mainly induced by physiological stress as a result of adverse environmental and climatic conditions (Mohamed and Abdelsalam, 2008).

Among the climatic factors, temperature and relative humidity affect the pattern of disease in animals (Lamy et al., 2012). The direct effects of climate are associated to a temperature that increases morbidity and mortality rate. The indirect effects of climate are related to the changes in microbial communities that favor the transmission of diseases in small ruminants (Tubiello et al., 2008; Thornton et al., 2009; Nardone et al., 2010). Seasonal variation also plays a significant role in the reproductive hormonal profile, which delays puberty, decreases conception rate and increases abortion and compromises fertility of small ruminants (Soren, 2012; Qureshi, 2012; Dias et al., 2017). Ruminants are predisposed to pneumonia due to compromised immune defence caused by transportation stress, nutritional deficiencies, adversative environmental conditions, co-infection with a variety of respiratory viruses, mycoplasma, and pathogenic bacteria (Mohamed and Abdelsalam, 2008). Reproduction is an essential aspect of meat and milk production in modern livestock farming. High level of reproductive performance can be achieved under optimum managemental conditions (Paul et al., 2014). However, many physiological, genetic, and climate factors affect female reproductive efficiency in ruminants (Khanum et al., 2008).

The pathogenesis of *M. haemolytica* is well documented in the literature focusing on the respiratory system; however, the effects of the disease on the reproductive physiology of the affected animal are yet to be eluciated. Reproductive diseases are frequently associated with irregular cycling, infertility, fetal mummifications, stillbirth, and abortions among small ruminants. The existence of bacterial pathogens in the female genital tract of goats has been associated to some negative impacts on reproductive efficiency as well as life span of corpora lutea (Shallali, 2001). Previous studies show that *Pasteurella multocida* disrupts the reproductive physiology of mice (Abdullah et al., 2015) and cattle (Ibrahim et al., 2016). However, whether *M. haemolytica* infection in goats impacts reproductive physiology is undetermined. Therefore, the purpose of this study was to investigate the changes in the female reproductive hormone profile of goats infected with *M. haemolytica* serotype A2 in tropical climatic condition.

MATERIALS AND METHODS

Ethical approval

The study protocols and design, which complies with international guidelines for the use of animals in biomedical research was approved by the Institutional Animal Care and Use Committee of Universiti Putra Malaysia (UPM/IACUC/AUP-R089/2017).

Experimental animals

In this study, a total of 24 (1-year-old), non-pregnant, clinically healthy female goats weighing 20±5 kg were used. The does were housed at Animal Experimental Area, Faculty of Veterinary Medicine, Universiti Putra Malaysia. During the 14 days acclimatization, injection Ivermectin was given via subcutaneous route 1mL/50kg bodyweight to control gastrointestinal and external parasites. Estrus was synchronized by the injection of two doses of Estrumate® (synthetic prostaglandin PGF2α) at 0.2 mL/ goat (50 μg) administered via intramuscular injection, 11 days apart. The does were fed Napier grass supplemented with goat pellets (250g/goat. day), and drinking water was provided ad libitum through water nipples.

Experimental design

Twenty-four does were assigned into 2 groups for the rainy and hot seasons. In each season, twelve does were further divided into 3 groups (n=4), control, non-vaccinated and vaccinated, experiments were conducted for 8 weeks in each season. In the first stage of the experiment at week 1, animals in the vaccinated group were administered with 2 mL of alum precipitated pasteurellosis vaccine (*P. haemolytica* type A, *P. multocida* type A & D, Veterinary Research Institute, Malaysia) via intramuscular (I/M) injection. While the non-vaccinated and control groups were administered with intramuscular injection of 2 mL phosphate-buffered saline (PBS). At week 2, both non-vaccinated and the vaccinated groups were challenged intrana

Table 1: Seasonal profile of reproductive hormones of goats.

Hormones	Seasons	Plasma concentration (Mean±SD)			*P*-value
		Control	Non-vaccinated	Vaccinated	
Progesterone (ng/ml)	Rainy Season	0.19±0.07[b]	0.25±0.07[a]	0.19±0.08[b]	0.003291
	Hot Season	0.19±0.07[b]	0.25±0.07[a]	0.19±0.08[b]	0.003291
	P-value	0.27	0.77	0.42	
Estrogen (pg/ml)	Rainy Season	18.93±6.16[a]	14.74±4.57[b]	19.51±5.43[a]	0.001490
	Hot Season	19.22±6.27[a]	14.08±4.50[b]	19.34±5.19[a]	0.000447
	P-value	0.27	0.77	0.42	
Follicle Stimulating Hormone (IU/L)	Rainy Season	0.31±0.04[a]	0.21±0.04[b]	0.31±0.04[a]	<0.0001
	Hot Season	0.31±0.05[a]	0.21±0.04[b]	0.31±0.04[a]	<0.0001
	P-value	0.93	0.70	0.73	
Luteinizing Hormone (IU/L)	Rainy Season	0.28±0.05[a]	0.20±0.03[b]	0.26±0.04[a]	<0.0001
	Hot Season	0.28±0.04[a]	0.20±0.02[b]	0.27±0.04[a]	<0.0001
	P-value	0.51	0.88	0.42	

Different superscripts within row indicate significant difference ($p<0.05$).

sally with 2 mL of bacterial cell suspension containing 10^5 colony-forming unit (CFU) of *M. haemolytica* serotype A2. The experimental does were observed for clinical signs and clinical responses of mannheimiosis for 8 weeks post challenged in both seasons.

Blood samples

Weekly blood samples were drawn aseptically in heparinized tubes from the jugular vein, and immediately centrifugated at 3000 rpm/min for 15 minutes to collect plasma and stored at -20°C until analyzed.

Inoculum preparation of *Mannheimia haemolytica* serotype (A2)

The wild type *M. haemolytica* utilized in this investigation was obtained from earlier mannheimiosis outbreaks and validated by gram staining and biochemical testing. Bacteria were cultivated on blood agar (enriched with 5% horse blood) at 37°C for 24 hours. A newly grown bacterial colony clusters were assorted with normal saline to attain required concentration of 10^5 CFU/mL was determined by using McFarland Nephelometer Barium Sulphate Standards (McFarland, 1907).

Hormonal assay

Commercial Radioimmunoassay test kits (Beckman Coulter, Immunotech®) were used to quantify plasma concentrations of progesterone (IM1188), estrogen (A21854), follicle-stimulating hormone (IM2125) and luteinizing hormone (IM1381) according to manufacturer instructions.

Statistical analysis

The Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA) were used to analyze all the data obtained from this study. One-way analysis of variance (ANOVA) at a significance level of 0.05 was applied.

RESULTS

Environmental data

The mean temperature and rainfall data obtained in this study were insignificantly different ($p>0.05$) during the rainy and hot seasons. However, the average humidity level was significantly ($p<0.05$) higher in the rainy compared to the hot season (Figure 1).

Reproductive hormones

Between seasons, progesterone, estrogen, follicle-stimulating hormone, and luteinizing hormone levels recorded in all groups were similar ($p>0.05$). Whereas, within each season, significantly increased ($p<0.05$) concentration of progesterone were observed in non-vaccinated as compared to the vaccinated and control groups. Simultaneously, a significantly decreased ($p<0.05$) concentration of estrogen, follicle-stimulating hormone, and luteinizing hormone were observed in the non-vaccinated group as compared to the vaccinated and control groups (Table 1).

A significant increase ($p<0.05$) in the mean concentration of progesterone (P4) was observed during the post-infection period (week 3-4) in the non-vaccinated group, but, at the same time, the concentrations were decreased to basal levels in control and vaccinated groups. However, there was a slight decrease of progesterone concentration in the non-vaccinated group at week 6 while, from week 7 till to the end of the experimental period the concentration was increased systematically (Figure 2). For estrogen (E2) profile in different treatment groups of experimental goats showed a significant decreased ($p<0.05$) concentration in the non-vaccinated group during post-infection compared to control and vaccinated groups throughout the experimental period (Figure 3). Hormonal concentration in different experimental groups revealed a significant decreased (p<0.05) concentration of follicle-stimulating hormone (FSH) post-infection in the non-vaccinated group throughout the experimental period (Figure 4). Plasma mean concentrations of luteinizing hormone (LH) in different experimental groups showed consistently decreased significant (p<0.05) concentration in the non-vaccinated group throughout the experimental period (Figure 5).

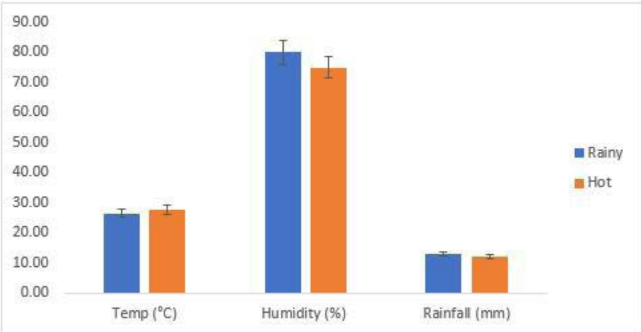

Figure 1: Climate factors recorded in different seasons; humidity level was significantly (p<0.05) higher in the rainy season as compared to the hot season

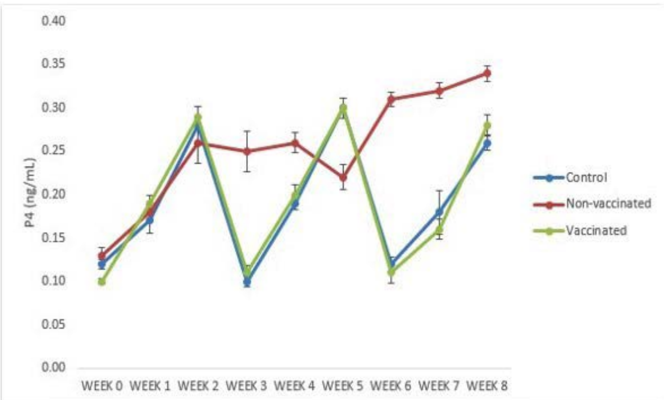

Figure 2: Mean plasma concentration of progesterone in *M. haemolytica* A2 infected female goats

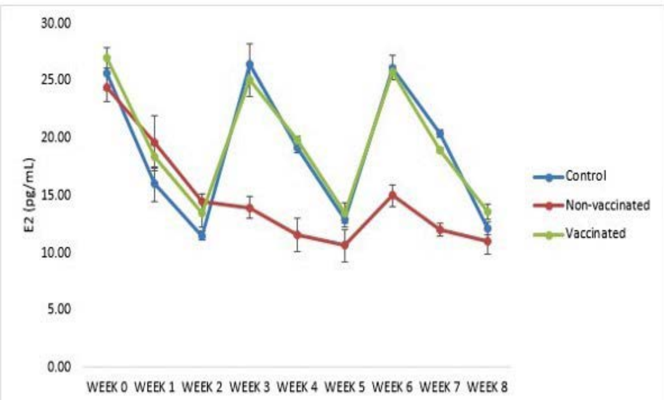

Figure 3: Mean plasma concentration of estrogen in *M. haemolytica* A2 infected female goats

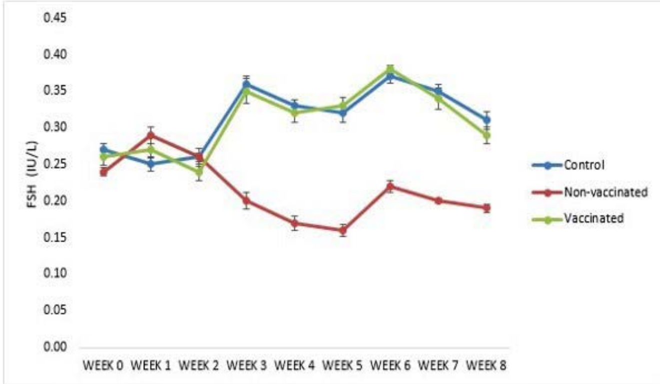

Figure 4: Mean plasma concentration of follicle stimulating hormone in *M. haemolytica* A2 infected female goats

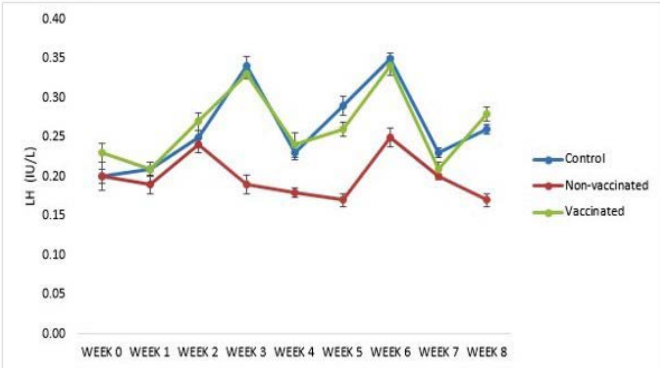

Figure 5: Mean plasma concentration of luteinizing hormone in *M. haemolytica* A2 infected female goats

DISCUSSION

The finding of this study revealed that the climatic factor did not significantly affect the hormonal parameters of the reproductive system in goats under the tropical condition of Malaysia. However, experimentally induced infection with *M. haemolytica* serotype A2 caused a significant (P<0.05) effect on the hormonal profile of non-vaccinated female goats compared to that in the vaccinated and control groups.

In this study, the mean progesterone plasma concentration in the non-vaccinated group showed an increased concentration from week 3 to week 8 post-challenge. The outcomes of present study are similar with previous studies, where an increased in progesterone concentration was observed post-challenge with *Pasteurella multocida* type B:2 and its lipopolysaccharides (Abdullah et al., 2015) and with intraperitoneal infection of *Corynebacterium pseudotuberculosis* in female mice (Khuder et al., 2012). Similarly, increased progesterone concentration has been reported in goats challenged with *C. pseudotuberculosis* via the intra-

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nasal route (Othman et al., 2014). Conversely, decreased in the progesterone concentration has also been reported in buffalo heifers infected with *Pasteurella multocida,* outer membrane proteins and its immunogen lipopolysaccharides (Jesse et al., 2017), in experimental goats with intradermal *C. pseudotuberculosis* in acute (Khuder et al., 2012), and chronic infection (Jesse et al., 2015). The major role of progesterone is to maintain pregnancy, cyclic function, estrous expression and in hypophyseal-gonadal interrelationship (Khuder et al., 2012), and it is also essential in uterine growth, blastocyst implantation as well as fetal development during pregnancy by nullifying of the uterine tones (Frandson et al., 2009). The results of our study in line with previous studies revealed that *M. haemolytic* infection produced a significant negative impact on the reproductive cycle indicated by pseudo-pregnancy and anestrus.

The difference in the progesterone concentration in this study and previous studies (Frandson et al., 2009; Khuder et al., 2012; Othman et al., 2014; Abdullah et al., 2015, Jesse et al., 2015; Jesse et al., 2017) might be due to time of inoculation, difference in cycling pattern and phase of cycle between goat, buffalo and mice, dosage of bacterial inoculation, and route and virulence of bacteria. Furthermore, it must be noted that in the present study, female goats were challenged with *M. haemolytica* serotype A2 at week 2, which is the diestrus phase of the estrus cycle and it is the time when progesterone level remains high (Davila et al., 2017). Progesterone produced in the luteal phase is responsible for the maintenance of pregnancy and the integrity of uterine endometrium and inhibits gonadotropin release by the anterior pituitary (Sato et al., 2016), and may be responsible for the observed discrepancies in the hormonal profile of infected non-vaccinated female goats in the present study. Progesterone concentrations may fluctuate by endotoxin exposure in large follicles (Magata et al., 2014). Endotoxin has an affinity to bind with hormone-producing cells in pituitary glands and ovaries, which may stimulate the infiltration of inflammatory cells into the particular organs. Meanwhile, the bacteria's endotoxin may have direct influence on the cells and cause a septicaemia (Ali et al., 2015). The increase in the concentration of progesterone may have resulted from destructive lesions in endocrine tissues caused by the bacteria or its components, and this is also known to stimulate the production of Interleukin-1β and I Interleukin-6 as reported by previous studies (Abdullah et al., 2015; Khuder, 2015; Jesse et al., 2016; Othman et al., 2016; Ibrahim et al., 2016).

In present study, results showed decrease in mean plasma concentration of estrogen in non-vaccinated group from week 4 to week 8 as compared to vaccinated and control groups. The results of our study are in concordance with previous studies, where a significant decrease in estrogen concentration post-challenge with *P. multocida* type B:2 in buffalo heifers through oral, subcutaneous and intravenous route in different treatment groups (Jesse et al., 2017) and in cows experimentally infected with *Staph. aureus* has been reported (Lavon et al., 2011). Whereas, the results of the present study are in discrepancy with various previous findings, who have reported significantly increased estrogen concentration in goats experimentally inoculated with *C. pseudotuberculosis* via oral, intranasal and intradermal routes (Othman et al., 2014), and in mice interperitoneally inoculated with *C. pseudotuberculosis* (Khuder et al., 2012). However, it has been reported that the rise in serum estrogen concentration in goats infected with *C. pseudotuberculosis* is the consequence of cellular damage of ovaries and the pituitary gland of infected goats (Jesse et al., 2015). Furthermore, the alteration in reproductive tissue might interrupt the activities of the hypophyseal-pituitary-gonadal axis in goats (Khuder et al., 2012). On the other hand, the estrogen hormone has a significant role in tissue maintenance and reproductive physiology in animals and acts on specific target tissues like reproductive organs, pituitary or hypothalamic glands, gonads, and mammary tissue (Jesse et al., 2015). Thus, the above studies revealed that a bacterial infection that results in hormonal imbalance causes infertility in farm animals (Sheldon et al., 2009).

Several researches have been conducted that explain how disease affects conception and pregnancy maintenance. Briefly, the inflammation mediators such as cytokines, interleukins, and prostaglandin F2α are induced by diseases and are linked to decreased fertility (Moore et al., 1991). For example, diseases such as mastitis, where before breeding, can disrupt hormonal balance and delay ovulation (Lavon et al., 2010). Mastitis can affect corpus luteum structure formation and regression, progesterone secretion, endometrial mechanisms, and embryo development after insemination (McDougall et al., 2005). Moreover, the disease called Caseous Lymphadenitis (CLA) also interferes the female and male reproductive physiology causing a negative impact on small ruminant's reproductive performance (Khuder, 2015).

In our study, the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations decreased significantly in the non-vaccinated group post-challenged with *M. haemolytica* serotype A2, compared to vaccinated and control groups. The results showed an agreement with a prior study reported by Jesse et al. (2017). They described that *P. multocida* B:2 infection interrupts the GnRH production by the hypothalamus and leads to a decreased in the production of FSH and LH concentrations by tissue changes in the pituitary gland in buffalo heifers. Similarly, Faccio et al. (2013) found a decreased in FSH and LH concentrations in female rats infected with *Trypanoso-*

ma evansi. Researchers using bacterial pathogens such as *Brucella mellitensis* and *Corynebacterium pseudotuberculosis* observed changes in reproductive hormonal levels in the female mice and goats challenged with the stated bacteria (Othman et al., 2014; Othman et al., 2016; Jesse et al., 2016). The different phases of the reproductive cycle achieved by the interaction between hormones released by the hypothalamus, anterior pituitary gland, and ovary (Ünlühizarci et al., 2001), inequities at any stage of oestrus cycle result in anoestrus (Terzano et al., 2012). In the present study, *M. haemolytica* serotype A2 was found to inhibit the hypothalamic secretions of GnRH, which in turn decreases the anterior pituitary's production of FSH and LH concentration. Decreased plasma concentration of FSH and LH concentrations perhaps was a result of the irreversible (necrosis) or reversible (degeneration) damage induced by *P. multocida* (Jesse et al., 2017). Although the pathogenesis of *Pasteurella* and *Trypanosoma* differs, the nature of reproductive dysfunction in the two diseases may be similar. The rise and decline in the concentration of these hormones may have resulted from tissue cell damages caused by the bacteria or its components (Chen et al., 2000; Othman et al., 2014; Mahmmod et al., 2015).

CONCLUSION

For the first time based on the findings of present research, it is determined that *M. haemolytica* serotype A2 has an association with reproductive hormonal imbalances in pneumonic female goats. This disease might induce pathophysiological changes to the hormone-producing cells, leading to pseudo-pregnancy and infertility, which may affect the reproductive potentials of infected animals. The results suggested that climate has neither a significant effect on reproductive physiology nor exaggerated the effects on infected animals with *M. haemolytica* serotype A2.

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CONFLICT OF INTEREST

The researchers have no potential conflict of interest.

NOVELTY STATEMENT

The Pneumonic mannheimiosis causes a negative impact on reproductive performance of the female goats where hormonal imbalances were observed which may result to pseudopregnancy or infertility in does infected with M. haemolytica serotype A2.

AUTHORS CONTRIBUTION

FFAJ conceived and framed the main idea of this study. The first draft was made by AM and FFAJ. The first draft was read and corrected by AM, FFAJ, ABH and ELTC. The second draft and finalized by AM, FFAJ, MAML, BP and KRB.

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