NEAR EAST UNIVERSITY
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META-ANALYSIS OF TWO DIFFERENT TREATMENTS FOR ENDOMETRITIS: COMPARISON OF THE RESULTS OF INTRAUTERINE AND PGF2α THERAPIES

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ABSTRACT

META-ANALYSIS OF TWO DIFFERENT TREATMENTS FOR ENDOMETRITIS: COMPARISON OF THE RESULTS OF INTRAUTERINE AND PGF2@THERAPIES

The objective for our research was to evaluate the therapeutic effectiveness for intrauterine treatment and prostaglandin treatment of endometritis through meta-analysis. For this purpose, Google Scholar and PubMed were used to find the publications (intrauterine =47 and prostagladin = 49).The start of treatment period was found to be similar between the intrauterine therapy (IUT) and prostaglandin therapy (PGF2α) among the post partum cows (33.49 and 30.18 days respectively).Period to first service (FS) was significantly different between groups of IUT andPGF2α ($P<0.002$) to the time of estrus and pregnancy (conception rate per insemination) for both groups was much same for both IUT and PGF2α in the groups (IUT=66.82±17.52 and PGF2α=71.25±13.74 days). The days open from conception to pregnancy were slightly significant between groups for IUT and PGF2@ treated cows in which PGF2α cows showed more improvement and less open days to pregnancy ($P<0.03$) with a higher recovery rate to the IUT treated cows (PGF2α=103.79±27.83 and IUT=106.84±42.41 days respectively). Endometritis treatments (IU or PGF2α) pp between the 20th and 30th day both at early and late puerperium, fertility parameters such as Day Open; InsFPR, Culled were statistically significantly low in the PGF2α group to the IU group ($P <0.05$ and $P <0.001$, respectively).

For classification of the severity of endometritis, results has shown that in the case of E1 endometritis the parameter PR (%) after IU treatment was higher (74.3%) than the PGF2α treatment (67.0%) and the difference was significantstatistically ($P <0.05$) difference between IU and PGF2α therapy in the parameters Days open, number of insemination per pregnancy and pregnancy loss in percentages (%)).

Keywords: Meta-analysis, Intrauterine therapy, Puerperium, Endometritis, Prostaglandin therapy, days open

ÖZET

ENDOMETRİTİS TEDAVİSİNDE İKİ FARKLI YÖNTEMİN META ANALİZİ: İNTRAUTERİN VE PGF2@ TERAPİLERİN SONUÇLARININ KARŞILAŞTIRILMASI

Bu çalışmanın amacı, endometritis tedavisinde intrauterin ve Prostaglandin terapilerinin terapötik etkinliğini meta-analiz yoluyla değerlendirmektir. Bu amaçla Google Scholar ve PubMed kullanılarak yayınlara (intrauterin; 47 ve prostagladin; 49 yayın) ulaşıldı. Tedavinin başlangıç periyodu, doğum sonrası ineklerde intrauterin tedavi (IUT) ve prostagladin (PGF2@) tedavisi arasında benzer bulundu (sırasıyla postpartum 33.49 ve 30.18 gün). Servis periyoduna kadar geçen süre (FS), IUT VE PGF2@ grupları arasında (P<0,002) östrus zamanı önemli oranda farklıdır. Ancak ve gebelik başına düşen tohumlama oranı her iki grup için de gruplarda hem IUT hem de PGF2@ için benzerdi (IUT=66,82±17,52 ve PGF2@=71,25±13,74 gün). Gebelik oluşması için gereken sürede IUT ve PGF2@ ile tedavi edilen gruplar arasında biraz önemliydi (PGF2@=103.79±27.83 ve IUT=106.84±42.41 gün). PGF2@ terapisinde ineklerin daha fazla gelişme gösterdiği ve gebelik oluşması için gereken sürenin daha az olduğunu (P<0.03) ve IUT ile tedavi edilen ineklere göre daha yüksek iyileşme oranı göstermiştir. Endometritis tedavileri (IU veya PGF2) pp 20.ve 30. günler arasında hem erken hem de geç puerperal dönemde, gebe kalması için geçen süre, gebelik başına tohumlama sayısı ve itlaf gibi fertilite parametreleri PGF2@ grubunda IU grubuna göre istatistiksel olarak anlamlı düzeyde düşüktü (sırasıyla P<0,05 ve P<0,001).

Endometritisin şiddetinin sınıflandırmasında, sonuçlar şunu gösterir; E1 endometritis durumunda tedavi sonrası gebelik oranı (PR) (%) parametresinin IU tedavisinin (%74,3) PGF2@ tedavisinden (%67,0) daha yüksek olduğunu ve gebe kalması için geçen süre (DayOpen), gebelik başına tohumlama sayısı (InsFRP) ve abort gibi parametrelerde IU ve PGF2@ tedavisinde gruplar arasındaki farkın istatistiksel olarak anlamlı olduğunu gösterir (p<0.05).

Anahtar Kelimeler: Meta-analiz, İntrauterin tedavi, Puerperal dönem, Endometritis, Prostaglandin tedavisi, Servis periyodu

TABLE OF CONTENTS

LIST OF IMAGES/ TABLES/ FIGURES

ABBREVATIONS

CE; Clinical Endometritis

D; Day

DIM; Day in milking

E; Endometritis, (E1+E2+E3); degree of severity of endometritis wich e3 is most severe

FIS; First Service (DAY=D)

INSFPR; Insemination for Pregnancy (Value)

NG; Not Given

NS= Non Significant

PLO; Pregnancy Loss (%)

PR; (DAY=D); Pregnancy Rate (%)

PR; Pregnancy Rate

PRFI; Pregnancy Rate To First Servıce

RB; Repeat Breeders

SCE; Subclinical Endometritis

STTH; Start the Therapy

V; Value

INTRODUCTION

META-ANALYSIS OF TWO DIFFERENT TREATMENTS FOR ENDOMETRITIS: COMPARISON OF THE RESULTS OF INTRAUTERINE AND PGF2α THERAPIES

The physiological dynamics that impact on pregnancy to parturition determine the post parturient performance of a herd conception rate. Sequel to certain known and idiopathic cause of post parturient injury to the uterus which disrupt normal physiological and anatomical architecture of the uterine lumen which leads to certain uterine diseases (Lima et al., 2013). Uterine disease had mostly been reported in herds with low reproductive performance that evidently affects profit (Lima et al, 2013, LeBlanc et al, 2002). Uterine diseases are often classified based on clinical presentation and defined based on their effects on pregnancy per AI (P/AI) or on time to pregnancy (Sheldon et al., 2006, Lima et al., 2013). Certain reproductive diseases such as metritis and endometritis would occur which depends on periods and degree of infectivity. 'Whites' is the common name referred to cattle endometritis among farmers. Uterine disease has a detrimental effect on the period of return to ovarian cycle, but it is not clear if ovarian cycle has an effect on the incidence of endometritis (Sheldon and Dobson, 2004; Dubuc et al., 2010).

Inflammation of the uterine endometrium among post parturient animals that could become complicated due to bacterial infection after 21days post calving is referred to as endometritis (Dubuc et al., 2010). The condition is prevalent from 21 days after birth and endometritis is different from metritis that starts after parturation within 20 days (puerperal metritis, clinical metritis).

1. THE ENDOMETRITIS

1.1.IMPORTANCE OF THE ENDOMETRITIS

The main consequence of endometritis in a herd is decline in fertility, decrease welfare and economic loss (Mohammed et al., 2019; Galvao et al., 2009; Galvao et al, 2018; Sheldon et al., 2006; LeBlanc et al., 2008).Therefore making it a major economic consequence due to increase in calving interval, number of service per pregnancy, increase of rate of cull and lower milk production. The clinical findings that resulted in reduced reproductive performance and prolonged conception (above 21days) in cows are termed endometritis (LeBlanc et al, 2002; Gilbert et al., 2005). The prevalence is said to be from 10% to 15% among milking cows although, varies from one milking cow farm to another milking cow farm, with the total cost of 1,125 TL ($137.82) for every cow (Chaudhariet al., 2017; Sharma et al., 2018).

From delivery, 90% and more of cow uterus become contaminated by bacteria. When the condition affects mainly the superficial part of the uterus, it is called endometritis. Moreover, in some conditions, deeper infections that would affect the entire layers of the uterus can develop and this is termed called metritis (Sheldon and Dobson, 2004).

1.2. WHAT'S THE TERM ENDOMETRITIS?

This had been termed as the inflammation of the endometrium in a cow occurring after 21 days post partum without any systemic signs and a cervical diameter >7.5cm (Dubuc et al, 2010; LeBblanc,2008) or mucopurulent discharges later than 26 days of lactation (Sheldon et al, 2006; LeBlanc, 2008; Dubuc et al, 2010). It has often been defined as an injury to the epithelial lining of an intact postpartum uterus with presence of inflammatory cells (Bondurant, 1999; Dubuc et al, 2010). Clinical presentations, diagnostic criteria, period and pattern of concurrence had spurned the classification of endometritis into clinical (purulent vaginal discharges) and subclinical endometritis (Sheldon et al, 2006; Dubuc et al, 2010; Galvao et al, 2018).

1.3.RISK FACTORS

The main causes of endometritis in high yielding dairy cows are much diverse and multifactorial. Itswell known fact that the transition from parturition to lactation is backed byhigh energy demand and depletion of nutritional diet results in negative energy balance and immunosuppression which predisposes the cow to infections. The major risk factors for uterine diseases are early or first parity, male offspring, abortion, prolapsed uterus,twins, retained placenta (RP), dystocia, hyperketonemia, hypocalcemia, stillbirth, multiparty with score of the body condition (BCS) (LeBlanc et al., 2002; Dubuc et al., 2010). Few reports exist on the potential link between metritis and endometritis because most researchers consider the two subjects to be different. Certain metabolic factors which impact on energybalance such as increased Non-esterified fatty acids (NEFA), increased Beta hydroxybutyaric acid (BHBA) early postpartum and decreased dry matter intake (DMI) prepartum, have been related with an increased predisposition to endometritis (Dubuc et al., 2010). Other metabolic disorders such as abomasal displacement increase the risk of endometritis (Dubuc et al., 2010; Whiteford and Sheldon, 2005).

1.4.CLASIFICATION OF ENDOMETRITIS

Endometritis had been sub-classified intoclinical and subclinical parts are as stated below (Sheldon et al., 2006).

1.4.1. Clinical Endometritisis (CE)

Clinical endometritisis (CE) termed as mucopurulent or purulentuterine discharge observed after twenty one or twenty six days postpartum and CE had been estimated to develop in almost 20% of postpartum dairy cows with a rate of about 5% to 30% and above in some farms (McDougall et al., 2007; Galvao et al, 2018; LeBlanc et al., 2002).The classification of chronic endometritis is made differently by many authors. Some authors differentiate endometritis as mild, moderate, and severe(Knuttiet al., 2000;

Mateus et al., 2002).The classification of 1st, 2nd and 3rd degrees of endometritis is mostly used (Aslanet al., 1995; Tenhagenand Heuwieser, 2000; Drillichet al., 2005).

1.4.1.1.First Degree Endometritis (Catarrhal Endometritis; E1):

The discharge can only be determined with vaginoscopy. With rectal palpation, no changes in the uterus or cervix can be detected. The oestrus cycle is regular.

1.4.1.2.Second Degree Endometritis (Mucoprulent Endometritis; E2):

The mucopurulent discharge can be observed from the outside. Purulent parts can be seen in the discharge. During rectal palpation, the uterus is often thickened.

1.4.1.3.Third Degree Endometritis (Prulent Endometritis; E3):

The discharge is purulent and always present. The amount can vary during the day. The oestrus cycle is mostly irregular (Aslan et al, 1995; Tenhagen et al, 1999; Drillich et al, 2005).

1.4.2. Subclinical Endometritis

Subclinical endometritis had been termed as the presence of 18% and above of immune cells in uterine samples taken between 21days to 33 days postpartum or about 10% and above white blood cells in samples taken at days34–47 (Sheldon et al., 2006). Cows with subclinical endometritis do not show uterine exuding; despite, the gravity of the infection is still considered sufficient to impair reproductive performance and has been reported one of the most prevalent of all uterine diseases; its reported to affect about 30% of lactating dairy cows with the incidence ranging from 11% to 70% and above in some farms (Gilbert et al., 2005; Hammon et al., 2006; Barlund et al., 2008; Galvão et al., 2018).

1.5.DIAGNOSTIC OPTIONS FOR ENDOMETRITIS

Diagnosis is usually analyzed on the history of calving and observed signs following rectal and vaginal exam. Other standard methods involve use of a scaling system to categorize color, nature and odor of the vaginal exudates which can dictate the severity of the infection and if treatment may be necessary.

Diagnosis for endometritis using these methods:

1= Transrectal uterine palpation=TRUP (inflated uterine horn or horns, asymmetry, thickness in the endometrium, palpable uterine lumen and / or palpable fluid TRUP is subjective and imprecise (Ramoun et al., 2019).

2= Biopsy of the endometrial wall and bacteriology culture of the uterus (reliable but not representative) (Fig 1) (Van et al., 2018).

3= Vaginoscopy: fast and easy method to identify pleurisy in vaginal exudates;

The nature of the discharge is important;

Clinical endometritis;

- Translucent secretion is normal
- Pleurisy(above50% pus) and mucoprulent (ratio 50% pus and 50% mucus)
- Repulsive smelling exudates are indicative of disease
- More options of investigating uterine exudates:
    - The gloved hand
    - Use of the Metricheck device

Subclinical endometritis in cow is established by finding;

>18% neutrophils in uterine cytology 21–33 days post partum

Or>10% neutrophils at 34–47 days, in the absence of clinical endometritis (Sheldon and Owens, 2018).

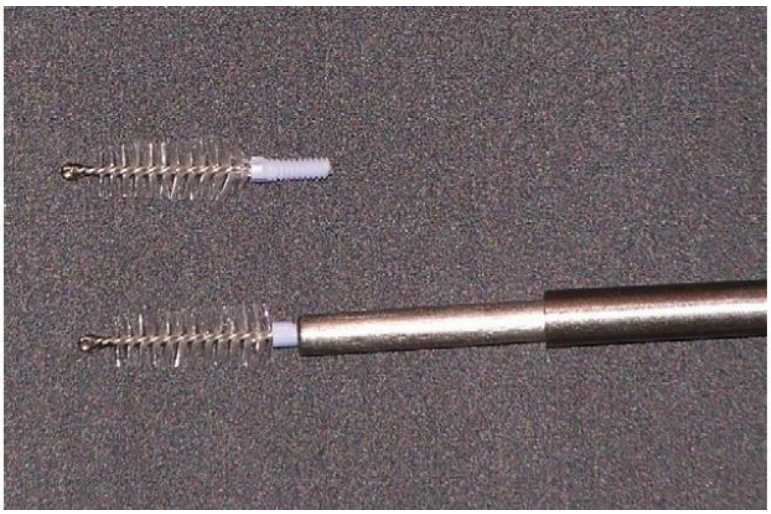

Fig 2: 1cm Cytobrush handle plastic with die and thread then threaded into the stainless steel stylet (Barlund et al., 2008)

Uterine and cervical diameter measurement can be included in the scaling system. Endometrial biopsy however is the method of achieving a definitive diagnosis, though it is scarcely conducted.

When a cow phase approach to diagnosis to postpartum endometritis is done, clinical examination could start after approximately28 days in milk (DIM) with vaginoscopy. endometritis can be indicated by the presence of foul uterine discharge or cervical diameter greater than 7.5 cm after 20 DIM or after 26 DIM with mucopurulent discharge. Two straightforward and clinical findings are the presence of mucopurulent or purulent discharge from the cervix or cervical diameter greater than 7.5 cm recognized in cows are at high risk of a significant extended time to conception with high relevance (LeBlanc et al., 2002).

1.6.ENDOMETRITIS AND THERAPY

The nature and clinical presentation had served as the bases of therapeutic administration of various treatment methods. There are various treatments for endometritis which had been reported, their acceptance which is based upon both personal preference and published data, while majority ofstudies have related and compared the clinical results of cowsto various treatments (Sheldon et al., 1998)which due to ethical considerations, there have been little studies in which evaluation have been done with untreated or placebo-treated controls (Sheldon et al., 1998). Preventive measures for endometritis had been advocated to be from peripaturient period which includes the administering of selenium and vitamin E at peri-parturient care of cows had seem to be of high importance (Purohit et al., 2015).

The therapies mentioned for the treatment of endometritis have been quite large. Each purpose of therapy is to achieve optimal uterine defense and repair mechanism, lower pathogenic bacteria load while inhibiting inflammatory reactions which could inhibit fertility (Purohit et al, 2015). Different research had presented use of different intrauterine and systemic antibiotic administration (Sheldon et al., 1998; McDougall, 2001; LeBlanc et al, 2002; Ahmadi et al, 2019; Kasimanickam et al., 2004; Knutti et al., 2000) and use of hormonal therapy such as prostaglandin F2 alpha (α) or its analog which effects uterine clearance of lochia and pathogenic contaminants (Lima et al., 2013; LeBlanc et al., 2002; Heuwiser et al 2000; Galvao et al., 2009). Certain other alternative chemoattractant agents are had been reported to be effective other than antibiotics due to its varying after treatment complication such as residual and resistance result, other agents such as Lugol's iodine infusion, hyper immune serum, E. *Coli* polysaccharides, Eucalyptus, 50% dextrose, hydrogen peroxide, polyvinyipirrolidone (PVP)-iodine, Lotagen (Nakao et al., 1988; Dolezel et al., 2010; Ahmadi et al., 2014; Tischer et al., 1998; Singh et al., 2000) and no treatment alternatives (self cure) had been published.

1.7.TREATMENT/ THERAPY

Higher treatment with mild incidence of endometritis had been reported. A treatment indicated includes use of antibiotics, intrauterine antiseptics and hormones (Galvao et al, 2018; Purohit et al, 2015).

1.7.1. ANTIBIOTICS

Important issues could be observed an antibiotic for the management of endometritis. Criteria such as;

- Specific efficiency in an infected uterine cavity
- Appropriate effectiveness against the causing bacteria
- Does not inhibit the uterine defense system
- Achieve required therapeutic level and period of activity in the infected uterine environment
- None or low milk withdrawal time
- Cost efficiency
- No harmful effect to fertility

Broadly, a broadspectrum antibiotic which is effective against gram-negative anaerobes and *Actinobaccillus pyogenes* should be much chosen. Most recommended antibiotics are oxytetracycline and cephalosporin due to its specificity to the conditions listed. Reports on oxytetracyclines resistance had been made including certain medications induce irritation to the endometrium thus cephalosporin should mostly be considered effective antibiotic choice of treatment. Aminoglycosides ,penicillin and Sulphonamides (Singh et al., 2018), nitrofurazones had reduced effect due to uterine environment and infecting organism present. Metranidazole and chloramphenicol are banned from being used in food-producing animals. Parenteral administration of antibiotics that have very short therapeutic index and broad effect is much advised.

1.7.2. HORMONES

1.7.2.1. Oestrogens

Use of oestrogen treatment for the management of endometritis is still controversial due to the understanding that the uterus is more resistant to infection during oestrus. It is not allowed to be used in cattle in the EU (Stephen et at., 2019).

1.7.2.2. Prostaglandins

PGF2α or analogues can be administered parenterally (Haimeri et al., 2018; Mıshra et al., 2018). PGF2α can be considered the choice treatment possibly when a corpus luteum is observed. The treatment with prostaglandins prevents the inhibitory actions of progesterone in the uterus creating oestrus, thereby enhance uterine defense actions. PGF2α might have an additional benefit of ecbolic effect that aid in clearance of the uterine contents. PGF2α has none milk withdrawal period which makes it an ideal for dairy cattle treatment. PGF2α are mainly used in chronic situations.

Furthermore, for PGF2α would be much efficient when a functional corpus luteum is present and older than 5 days. The main known protocol is the administration of two prostaglandin injections within 10 to14 day's interval and the meta-analysis has shown it has the same cure rate as parenteral ceftiofur (3^{rd} generation cephalosporin) and treated cows had lesser days open to the non treated cows. In other studies, PGF2α is applied three (3) times at 7 days intervals (Lefebvre et al., 2012, Kasimanickam et al., 2006).it is reported that presence of clinical or subclinical endometritis at the start of Presynch–Ovsynch estrous synchronization program does not harm the first service conception rate in cows (Kasimanickam et al. 2006).

1.7.2.3. ANTISEPTICS

Use of antiseptics such as Chlorhexidine and metakresol sulphonic acid (Lotagen) given intrauterine had been reported to be a efficient alternative to the use antibiotic, although few studies had been carried done to affirm these reports and the detrimental advert effects of these treatments on fertility of the cows are reported (Stojanov et al ., 2018).

1.7.2.4. Fluid Therapy

Fluid therapy is essential with non-steroidal anti-inflammatory drugs (Sheldon and Owen, 2018).

1.7.2.5. Reflexotherapy- electropunture (still experimental);

This is a new trial involving use of alternative medicine in the treatment of infertility which has had improvement in reducing the period of recovery from endometritis in dairy cattle (Kapralov et al., 2018).Some practitioners use uterine douching with normal saline or Lugol's iodine for treatment. African cattle herders (Fulani's) prefer use of herbal medicine (*Nigella sativa*, *Quercus infectoria*, neem plant) for treating endometritis (Kadam et al., 2019).

1.8.EVALUATİON ON PGF2α AND INTRAUTERINE THERAPY

This meta-analysis seeks to clarify better of the treatment methods employed in the management of endometritis in the cow.

Meta-analysis is reported to provide one of the highest evidence in scientific research (Haimerl et al, 2018). Meta-analyses is a systemic summaries of a collections of data accessed in varying research which are then applied analysis statistically of those findings from different data studies thus defining outcomes (Glass, 1976; Haimerl et al, 2013). It is used to refer to statistical analysis of large collections of analyzed results for the purpose of integrating the findings, which would be described as "an analysis of analysis" (Glass, 1976). Presence of large volume of methodologically conducted research in veterinary studies results in weak referential evidence of scientific results (Haimerl et al, 2012). Evaluation of field reports had been a classical ways of advancing knowledge in veterinary science rather than from single controlled reports. The evidenced based reports is said to be the best format for information for which clinical decisions could be made (Lefebvre et al, 2012). Eisend, 2004 proposed that a typical meta-analysis should have five (5) important stages, which are;

A. A clear statement of a clinical question,
B. A comprehensively systemic research for important literatures should carry out.
C. Numerical data from selected literature are taken and analyzed inline with certain tenet parameters.
D. The numerical data are analyzed by using appropriate statistical methods to access a summed estimated reports of the treatment (Barker and Carter, 2005).
E. Lastly, results are then critically analyzed and interpreted (Haimerl et al, 2013).

2. WHY THE USE OF META ANALYSIS?

The principal purpose and intents of a meta-analysis are to make available a clear observational and quantifiable analysis for initial reports so as to enhance the expertness of a treatment effect by increase of the sample size thereby enhancing its numeric value (Lean et al., 2009). In addendum, meta-analyses can be carried out to note and verify variations in the outcomes of concluded studies due to factors such as the sample design and variable samples. In summation, meta-analyses might be done for the reasons for solving differences between studies and creating new ways for such investigations (Wilson and Henry, 1992). Meta-analysis is the statistical evaluation of a minimum of two or more studies to create an estimate of the degree of a therapy on the actions or reactions under study (Lam and Kennedy, 2005, Haimerl et al, 2013).

Main objective of this research is to summarize therapeutic methods and purpose of employing local intrauterine therapy or intramuscular use of prostaglandin hormone or its analog in the treatment of endometritis in the postpartum cows. Clinical results of trials that estimated different agents, its doses, routes of therapy and periods of non-antibiotic therapy in relation to days post partum have given conflicting results. Due to the volume of published literatures on the effect, impact, treatment and management of endometritis in the bovine, the varying inconclusive reports on therapy of the investigations on the best method of therapy either intramuscular therapy of Prostagladin F2α (Haimerl et al., 2012, Haimerl et al., 2013) or local intrauterine therapies, a meta-analysis was conducted comparing the prostaglandin therapy and intrauterine methods of treatment. The magnitude of low fertility affecting reproduction remains to be quantified (Fourichon et al, 2000).Therapy of endometritis should be evaluated against its potential therapeutic benefits and residue consequences and the degree of the severity of the condition (Purohit et al., 2015).Evaluation of the uterine health in a herd and economic impact of postpartum infection is a major concern for the herd health management. Studies had proven equivocally that postpartum diseases are not a separate entity from the whole herd management programs and reproductive performance from conception to calving. Postpartum uterine infections are common occurrence in dairy cattle which had

been reported to have a delegatory impact on reproductive performance (Dubuc et al, 2010; Heimerl et al, 2012; Gundling et al., 2012; Purohit et al, 2015) and the development of puerperal disorders were often than not an offshoot of multi-factorial (Galvao et al., 2018) mostly influences from the cows periparturient period (Purohit et al., 2015). Certain conditions such as nutrition, environmental conditions (temperature, humidity, rainfall, seasons, and housing system), negative energy balance, partum hygiene, twin birth and management practices all play role in the overall outcome of a dam post partum wellbeing and performance. Dubuc et al, (2010) and Galvao et al, (2018) reported low fertility are due to negative impact of uterine infection on the uterus and ovaries and hormones secretions.

3. ENDOMETRITIS LITERATURE REVIEW

Therapeutic regiments in the management of reproductive performance disorders in animals especially in dairy cows are of high opportunity cost, demanding huge economic input for the dairy industry (Galvao et al, 2009; Knutti et al., 2000). Physiologically, healthy reproductive tract is essential for a positive reproductive performance especially in postpartal cows. The normal clean uterus gets infected by the microorganisms in the environment atdelivery or immediately postpartal phase (Lima, 2018) which could be predispose due to placentaretention, calving beddings or pen, twining, dystocia and weak immunity (Fourichon et al., 2000) the truth is that usually reproductive tract is invaded by microorganisms to a variable extent at delivery depending on the animal's immune system and the hygiene condition of the environment which could overwhelm the dams immune system (Sheldon et al., 2019). The contaminants ranges from varying number of microorganisms and main bacteria reported to be involved in endometritis infection in cow is *Trueperella (Arcanobacterıum pyogenes*) (Brick et al., 2012). Moreso, varying anaerobes which are gram-negative could be involved such as *Escherichia coli* had been implicated (Brick et al, 2012; Neelam and Kumar, 2019). The presence of these opportunistic organisms could affect time to estrus and cyclic activity, prolong conception rate and stop fertilization and lead to early death of embryo from produced toxins in the uterus by the bacteria. It is said to lead to increased incidence of ovarian cysts (Lıu et al., 2018).Post-reproductive insults are of the most critical conditions affecting reproductive performance in the cow characterized by increased artificial insemination number (AI) per conception, increased culling rate, extended calving to conception time and increased early embryonic death (EEM) (Sheldon and Dobson et al, 2004; Gilbert et al, 2005) and therapy to endometritis conditions are still controversial (Dubuc et al, 2011; Machado et al, 2015; Haimerl et al, 2018). Despite of varying treatment methods reported from research, this controversy exists probably due to high physiological self-cure rates (Dubuc et al., 2011; Giuliodori et al., 2017) and several treatment options that, in part, showed unsatisfactory treatment outcomes (Madoz et al., 2014).

Endometritis in dairy cows has been defined as endometrial inflammation occurring 21 d or more after parturition without indicating any systemic signs of illness (Sheldon et al., 2006). Histological, endometritis is termed as a disruption of the endometrial epithelium with inflammatory cells (Bondurant, 1999; Dubuc et al., 2010).

Clinical endometritis in cattle is define as the presence of a pleurisy (greater 50% pus) or mucopurulent (ratio of 50% pus and 50% mucus) vaginal discharge detectable more than 20 or 26 day at postpartum (Sheldon et al., 2006).Due to no cytological evidence of endometritis in some herds with abnormal vaginal exudates, the term "purulent vaginal discharge" was been introduced (Dubuc et al., 2010).

Sub-clinical endometritis that is seen with high ratio of neutrophils in uterine samples has an important effect on fertility of dairy cows (Kasimanickam et al., 2004; Gilbert et al., 2005; Rutigliano et al., 2008). Cow diagnosed with retained placenta and metritis at early postpartum has two times the odd of succumbing to subclinicalendometritis infection after 30 day in milk (Rutigliano et al., 2008).As reported by Kasimanickam et al. (2004), endometritis is an inflammation of the endometrium characterized by delayed uterine involution and poor reproductive outcome which is classified into two (2) categories: clinical endometritis (CE) and subclinical endometritis (SE). More detailed clarification was prescribed by Leblanc et al, 2002 whom defined CE as the presence of purulent or mucopurulent uterine discharge detectable externally or in the anterior vagina and or with a cervical diameter greater than 7.5 cm and a uterine horn diameter of 8 cm or more after 30 days postpartum. According to Kasimanickam et al., 2004 and Leblanc et al., 2002, SE can be defined as the presence of fluid detected ultrasonography in the uterine lumen at 31 days postpartum or later, with a cervical diameter of between 5 and 7 cm and a uterine diameter of between 5 and 8 cm (Zobel et al., 2013).

3.1. THERAPUETIC INCEDENCES

The essential purpose of instituting therapy of uterine infections is to ensure early clearance of uterine contaminants, shorter involution time with boost of the uterine immunity and return of normal reproductive efficiency within a possible shorter period (Smith et al, 2002, Galvao et al 2009;Kacar and Kaya, 2014). The appropriate treatment regime requires an understanding of the clinical presentation of the disease signs with its severity and diagnostic technique. There are many ways to prevent and control postpartum endometritis which had been evaluated to date including intrauterine infusions of antibiotics and or antiseptics, systemic administration of either antibiotics, enzymes and hormonal therapy which includes estrogens, prostaglandins (PGF2α), gonadropine releasing hormone (GnRH) (Purohit et al,2015). Haimerl et al, 2018 reported on the equivocal use of PGF2α for the treatment of endometritis.Guang-min Yu et al, 2016reported improvement in uterine health with PGF2α when used in post-parturient cows. Although, the prevalence and effect of this disease is well established and investigated. Dilemma of whether and how to treat endometritis is still controversial and non-conclusive (Sheldon et al.,1998;McDougall,2001; LeBlanc et al, 2002; Ahmadi et al, 2019; Kasimanickam et al., 2004;Knutti et al., 2000). Earlier period of treatment had been done with mainly antibiotics, but much recently due to certain restrictions to the use of antibiotics such as residual effects, resistance, abuse and control laws (USA) other alternative treatment methods had been sort by many researchers (McDougall et al, 2001; Mari et al, 2012; Gümen et al, 2012; Polat et al, 2015; Melia et al, 2020). There are varying reports on the treatment of this condition in the dairy cow which data had shown this treatment could differ from clinical and subclinical endometritis treatment (Smith et al, 2002, Kacar and Kaya, 2014). (Haimerl et al, 2012, Haimerl et al, 2013, Haimerl et al, 2018) working on meta-analysis reported that there are no adequate evidential proof on the efficacy of PGF2α for endometritis treatment in the cow while Giuliodori et al, 2017 reported PGF2α is ineffective in CE treatment and Galvão et al., (2009) found that an improvement to fertility when PGF2α was used to treat SE which was inferred to corpus luteum presence on the ovaries. Antibiotic infusion method to treat the effects of uterine diseases on fertility through intrauterine (i.u.) treatment was

investigated to be positive with different antibiotics (Galvao et al, 2009; Runciman et al, 2008; McDougall et al, 2013). Galvao et al (2009) suggested use of intrauterine treatment with antibiotics for SE. Kacar and Kaya, 2014 or new one reported on the preference of intrauterine treatment on therapy for CE and SE due to intrauterine tends to maintain a high concentration of therapeutics (drugs) in the endometrium while Heuwieser et al, 2000 reported that systematic use of PGF2α is a preferred method to intrauterine treatment of endometritis.

It had been demonstrated that of several reports on the effect of intrauterine treatment indicate a P/AI of 29.8% pregnancy and cumulative of overall 30.5% using hypertonic dextrose (50% dextrose) treatment (Brick et al, 2012) and first service conception rates and an overall conception rate at 180 days of 27.4% (Galvao et al, 2009) while other report on dextrose is said to be detrimental to uterine health with no effect. Intrauterine dextrose infusion did not have an effect on calving-to-conception interval (FSCR) and early embryonic mortality (EEM) at first service (Machado et al, 2015).

4. MATERIALS AND METHODS

4.1. MATERIALS OF LITERATURE AND GROUPS

A thorough literature search was conducted from February, 2020, utilizing the search engines: science direct (https://www.sciencedirect.com/science/article),the databases Pubmed (http://www.pubmed.gov), Turkish Journal of Veterinary and Animal Sciences (http://journals.tubitak.gov.tr/veterinary) and researchgate(https://www.researchgate.net/publication) which were used to identify literatures related to the treatment of endometritis with prostaglandin in dairy cows (systemic administration) and intrauterine endometritis treatment were searched also separately which encompasses varying experimental treatment designs involving; antibiotics, dextrose, antiseptics, enzymes. The search terms "endometritis treatment in cattle" and "endometritis treatment in cattle and use of prostaglandin" and ''endometritis treatment in cattle through intrauterine treatment'' were involved to include all publications involving treatment of bovine endometritis with PGF2α and intrauterine treatment.

Fifty (50) literatures were selected for intrauterine treatment methods and fifty (50) publications were selected for systemic treatment with prostaglandin injections.

In this work these different therapies were compared.

For this meta-analysis research the following literatures were used:

For intrauterine therapy (different medications were not distinguished from one another) the publications from these authors were used Table 1):

Table 1: Authors and year of publications for intrauterine therapy

	NAMES OF AUTHOR	YEAR OF PUBLICATION FOR INTRAUTERINE THERAPY
1	Mutiga et al.,	1978
2	Farca et al.,	1997
3	Nakao et al.,	1998
4	Sheldon et al;	1998
5	Tischer et al.,	1998
6	Knutti et al;	1999
7	Heuwiser et al.	2000
8	Singh et al.,	2000
9A	Ozturkler et al.,	2001
10	Janowski et al, a	2001
11	Janowski et al, b	2001
12	McDougall et al.,	2001
13	LeBlanc et al.	2002
14	Kim et al;	2003
15	Kasimanickam et al;	2004
16	Shams-Esfandabadi,	2004
17	Drillich et al;	2005
18	Sarkar et al;	2006
19	Runcıman et al;	2008
20	Polat et al.,	2009
21	Bademkiran et al.,	2009
22	Galvao et al.,	2009
23	Warriach et al.,	2009
24	Dolezel et al.,	2010
25	Khillare et al;	2010

26	Gabriel et al.,	2011
27	Gumen et al;	2011
28	Brick et al.	2012
29	Djuricic et al.,	2012a
30	Djuricic et al.,	2012b
31	Djuricic et al.,	2012c
32	Mari et al;	2012
33	Janowski et al.,	2013
34	Zobel et al.,	2013a
35	Zobel et al.,	2013
36	Ahmed et al.,	2014
37	Ahmadi et al;	2014
38	D. Đuričić et al.,	2014
39	Kaveh et al;	2014
40	Sahoo et al.,	2014
41	Mido et al.,	2015
42	Denis-Robichaud, J., & Dubuc, J.	2015
43	Machado et al;	2015
44	Maquivar et al.,	2015
45	Tison et al;	2016
46	Makki et al.,	2017
47	Parikh et al.,	2017
48	Ahmadi et al.,	2019
49	Kavitha K et al.,	2019
50	Lehimcioğlu et al;	2019

PGF2-α therapy the following literatures were used (Table 2):

Table 2: Author and year of publication for ProstaglandinF2α therapy

	NAMES OF AUTHOR	YEAR OF PUBLICATION FOR PGF2α
1	Gustafsson et al.,	1976
2	Young et al.,	1986
3	McClary et al.,	1989
4	White et al.,	1990
5	Archbald et al.,	1990
6	Morton et al.,	1992
7	Sheldon et al.,	1998
8	Tischer et al.,	1998
9	Schofield et al.,	1999
10	Heuwiser et al	2000
11	Knutti et al.,	2000
12	Janowski et al.,	2001
13	Tenhagen et al.,	2001
14	LeBlanc et al.;	2002
15	Kasimanickam et al.,	2004
16	Ahmadi et al.,	2005
17	M. Drillich et al.,	2005
18	M.E. Mejía et al.,	2005
19	Gaby Hirsbrunner et al.,	2006
20	Hendricks et al.	2006
21	Mohammad et al.,	2006
22	Sarkar et al.,	2006
23	Akoz et al.,	2008
24	Akhtar et al.,	2009
25	Galvao et al.,	2009

26	Polat et al.,	2009
27	Kaufmann et al., a	2010
28	Kaufmann et al., b	2010
29	J. Dubuc et al.,	2011
30	Gabriel et al.,	2011
31	Mushtaq H et al.,	2011
32	Salasel B. and Mokhtari.,	2011
33	Zidane et al.,	2011
34	Kaya et al., a	2012
35	Kaya et al., b	2012
36	Kaya et al.,	2012
37	Salemi et al.,	2012
38	Zobel et al.,	2013
39	Ravikumar et al.,	2013
40	Lima et al.,	2013
41	Ahmadi et al.,	2014
42	Bartolome et al.,	2014
43	Guang-Min Yu et al.,	2016
44	Majeed et al.,	2016
45	Jeremejeva et al.,	2016
46	Cut NilaThasmi et al.,	2017
47	Giuliodori et al.,	2017
48	Makki et al.,	2017
49	Ahmadi et al.,	2019
50	Kavitha K et al.,	2019

4.2. METHOD

4.2.1. Grouping Methods

For this meta-analysis, only intrauterine therapy (IU) and PGF2α therapy were compared. The different medications for IU (such as antiseptic solutions, antibiotics, ozone or glycols) and for PGF2α (such as injections, sprays, tablets or bolus) were not taken into account.

Under study and relevant variables of the evaluation criteria were reviewed based on certain criteria that are;

- Date for start of treatment,
- First service interval,
- Percentage average pregnancy per artificial insemination (P/AI),
- Percentage cumulative pregnancy,
- Percentage pregnancy loss,
- Number of insemination and number of culled animal.

The groups were classified and compared with one another as follows:

1 = The cows that are puerperium in the early (D 20-30) and late (D> 30) (compare: IU to PGF2α)

2 = General comparison of intrauterine versus PGF2α therapy (all data)

3 = Comparison with regard to the severity (E1, E2, E3) of the endometritis

In summation, a thorough systematic review of cited research papers in the retrieved documents was done. The resultant reproductive performance was based on these parameters.

4.2.2. Models for Exclusion and Selection of Articles

Certain exclusion criteria were referred to exclude studies that were not consonance with the subject of endometritis treatment with certain relevant parameters of review

available or indicated. Publications which were not focus on treatment of endometritis; which, occur on the 21 day or after 21 days after parturition (Sheldon et al., 2006). Secondly, studies in which the animals received combined treatments with other medications other than PGF2α were included and studies that PGF2α combined with intrauterine treatment were excluded and intrauterine treatment with systemic treatment would be excluded. Furthermore, publications with discussions of etiological, epidemiological, microbiological, or nutritional, clinical symptoms, or diagnostic procedures would be excluded (Haimerl et al, 2018). Articles not meeting the inclusion criteria due to not obtainable through the internet, bibliographies services were excluded. When similar publication was obtained which has same trial, the work with the fewer details would be excluded. The remaining publications would be evaluated according to varying evidential parameters as reported earlier. Relevant criteria for analysis were calculation of calving to first service interval (CFSI) and calving to conception interval (CCI).

4.2.3. Statistical Analysis

The SPSS®14.01 (SPSS Inc., Chicago, Illinois, USA) package program was used for analysis of the statistics. The Shapiro-Wilk Test was carried out to evaluate if the distribution of the groups were homogenous. The values were represented as mean ± standard error of mean (SEM).

$P \leq 0.05$ was considered significant statistically.

If the distribution of the groups is homogeneous, then the paired simple t-test was used. Otherwise Mann-Whitney U test was used.

5. RESULTS

There were a population of 9832 cattle involved in the experiments in which the non antibiotics treatment were 62.29% (n=38 publications) while the antibiotics was 37.7%.Ozone spray, povidone iodine, 50% dextrose was 28.94%, 15.78%, 13.15% of the non antibiotics medications, respectively which all involved a single treatment within 21-38 days. Cephapirin (metricure device) was the most used intrauterine therapy (47.82%) for the antibiotics treatments, while oxytetracycline, gentamicine, penicilin and enrofloxacine were 21.73%, 14.28%, 4.34%, and 4.34% respectively. Most antibiotics treatment involved two treatments of two (2) weeks intervals of one treatment at first day then second at the second week (14th days) with most requiring aid to achieve therapy. The economic input is of importance when considering treatment for this conditions and a consideration of residuals effect in deciding therapy in also fundamental in a farm management. For PGF2α mostly synthetic PGF2α were used in the evaluation studies (Dinoprost, cloprostenol).The start of therapy is within 21 days and more. The numbers of cows involved in this study were 7446.

Table 3: Effects of two different endometritis treatments (IU or PGF2) pp between the 20th and 30th day

	IU		PG		
Fertility Parameter	**N**	**S±X (min-max)**	**N**	**S±X (min-max)**	**P**
StTh (D)	37	25,51±3,52 (20-30)	37	24,10±3,53 (20-30)	P>0.05
FirstS (D)	30	78.72±18.4	34	79.11±19.37	P>0.05
PA/I (Value)	35	49.63±18.48	36	47.66±13.48	P>0.05
PR (%)	33	69.28 ±15.0	32	70.40±15.1	P>0.05
DayOpen	28	115.18±28.8	31	104.37±20.94	**P<0.05**
InsFPR (Value)	22	2.18±0.56	32	1.80±0.63	**P<0.01**
Culled (%)	16	10.17±7.89	26	6.18±7.53	**P<0.01**
PLo (%)	24	25.50±12,921		24,67±14,09	P>0.05

StTh=Start the Therapy (Day=D); Pregnancy Rate (%) (PR); FiS= First Service (Day=D)_Pregnancylos (%) =PLo; InsFPR=Insemination for Pregnancy (Value)

In the early puerperium phase between the 20th and 30th day, the parameters StTh, FirstS, PA / I, PR and PLo in the groups IU and PG was not statistically different (P> 0.05). But fertility parameters such as Day Open; InsFPR, Culled were statistically lower in the PG group to in the IU group (P <0.05 and P <0.001, respectively; Table 3).

Table 4: Effects of two different endometritis treatments (IU or PGF2) after the 30th day postpartum

	IU		PG		
Fertility Parameter	**N**	**S±X (min-max)**	**N**	**S±X (min-max)**	**P**
StTh (D)	24	58,58±17,95 (34-80)	20	52,06±11,74 (34-75)	P>0.05
FirstS (D)	14	94.40±26.15 (54-125)	14	77.47±13.18 (48-95)	P>0.05
PA/I (Value)	23	45.12±14.8 (20-71)	18	53.67±22.12 (23-90)	P>0.05
Pregnancy (%)	19	58.65±15.90 (30-85)	17	69.17±13.55 (42-94)	P>0.05
DayOpen	21	130.70±39.82	11	101.82±20.0	**P<0.01**
InsFPR (Value)	14	2.50±0.52 (1,80-3)	15	1.80±0.45 (1-2,37)	P>0.05
Culled (%)	7	14.14±8.70 (4-30)	9	3.54±3.40 (1,20-12)	**P<0.001**
PLo (%)	12	33,26±14,93	14	28,16±13,90	P>0.05
StTh=Start the Therapy (Day=D); Pregnancy Rate (%) (PR); FiS= First Service (Day=D)_Pregnancylos (%) =PLo; InsFPR=Insemination for Pregnancy (Value)					

In the late puerperium only DayOpen and the culled rate is in advantage to the PGF2α therapy was significantly different. The other parameters were not significantly different for the two therapies (Table 4)

Table 5: Comparison of intrauterine therapy with PGF2 therapy for endometritis (no classification, total)

	IU		PG		
Fertility Parameter	**N**	**S±X (min-max)**	**N**	**S±X (min-max)**	**P**
StTh (D)	61	41,14±23,79 (20,0-100)	57	33,91±15,36 (20,0-75,0)	P>0.05
FirstS (D)	44	81,82±24,05 (28,0-125,0)	48	78,63±17,66 (44,0-132,0)	P>0.05
PA/I (Value)	58	47,84±17,13 (20,0-95,0)	54	49,67±16,89 (22,0-90)	P>0.05
Pregnacy(%)	52	65,39±16,03 (30,0-97,0)	49	69,97±14,46 (23,0-96,0)	P>0.05
DayOpen	49	121,83±34,50 (55,0-280,0)	42	103,70±20,50 (60,0-164,0)	**P<0.01**
InsFPR (Value)	36	2,30±0,56 (1,0-4,0)	47	1,80±0,58 (1,0-4,0)	**P<0.001**
Culled (%)	23	11,38±8,16 (1,50-30,0)	35	5,50±4,76 (1,20-34,0)	**P<0.01**
PLo (%)	36	28,09±13,91 (7,0-52,0)	39	25,93±13,95 (6,0-77,0)	P>0.05
StTh=Start the Therapy (Day=D); Pregnancy Rate (%) (PR); FiS= First Service (Day=D)_Pregnancylos (%) =PLo; InsFPR=Insemination for Pregnancy (Value)					

Without classification into early and late puerperium, if the endometritis were added together, the results show that there is a significant difference between the IU and PGF2-α therapy in the parameters DayOpen,InsFRP and PLo (%). DayOpen was found to be shorter (P <0.001), InsFPR value significantly lower (P <0.001) and the potential value of the culled rate (%) lower (P <0.01) after PGF2α therapy (Table 5).

Table 6: Severity of Endometritis and the results of the classification of the Severity

Groups	PR (%)	PRFS (%)	Day Open	InsFPR	Culled (%)
E1 (Low degree endometritis) (N= 48 Publications)					
IntUter	74.3±12,7	53,8	102,4±23,5	1,9±0,3	17,7±4,5
PGF2	67.0±20,9	47,5	117,9±32,6	2,0±0,2	12,6±2,2
P	**P<0.05**	P>0.05	**P<0.05**	P>0.05	P>0.05
E2 (Moderate endometritis) (N=42 Publications)					
IntUter	52,8±24,3	50,4±11,3	138,12±27,8	2,2±0,2	25,7±5,8
PGF2	61,7±32,6	56,4±17,2	114,28±12,44	1,7±0,4	19,6±7,9
P	P<0.05	P>0.05	**P<0.01**	**P<0.05**	**P<0.01**
E3 (severe endometritis) (N=36 Publications)					
IntUter	33,5± 7,6	20,0±6,8	130,35±9,3	2,5±0,5	30,7±9,7
PGF2	37,8±3,2	29,0±2,0	125,57±11,0	2,0±0,3	23,9±4,9
P	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05

D:Day; V: Value PR: Pregnancy Rate; PRFI (Pregnancy Rate to First Service=Submission rate); InsFPR=Insemination for Pregnancy (Value)

The classification of the severity of endometritis (Table 6) has shown that in the case of E1 endometritis the parameter PR (%) after IU treatment was higher (74,3%) than the

PGF2α treatment (67.0%) and the difference was significant statistically (P <0.05). In contrast, DayOpen

Were higher for the PGF2α treatment than the IU treatment (P <0.05). In the case of E2 endometritis, the PR percentage values in the PGF2α treatment were higher (61.7%) than the IU values. The calculated results showed that the Day Open, InsFPR and Culled Rate values were statistically significant lower (P <0.01 and 0.05; Table 4). In the E3, there was no significant difference between UI and PGF2α.

6. DISCUSSIONS

This present study were undertaken to find out the impact of different treatment route methods for endometritis in the cow to proffer a most current therapeutic method of treatment by meta-analysis while providing comparable information to available articles (Wilson and Henry, 1992;Lam and Kennedy, 2005; Haimerl et al, 2013). This present study evaluated fifty (50) different articles for both intrauterine and PGF2α treatment which eventually 47 articles were elegible for intrauterine treatment and 49 articles were eligible for PGF2α treatment. Various reports regarding the management and treatment of endometritis had remained inconclusive when treatments were carried out with intrauterine medications and /or intramuscular injection of PGF2α (Gilbert and Schwark, 1992; Haimerl et al, 2013). Most research study had focused on PGF2α and its effect in treatment of uterine diseases or PGF2α and antibiotics (Haimerl et al, 2013;Haimerl et al, 2018).We hypothesized that investigating the route of treatment could give a hint to the efficient therapeutic route not just the therapy itself. Local application of therapy tends to maintain a high concentration of therapeutics (drugs) in the endometrium (site) while systemic use of PGF2α has a hormonal and general modulating effect on the reproductive tract (Galvao et al., 2009).

The criteria for measurement of therapeutic effects on reproductive performance were based on clearance of vaginal discharges, observed standing estrus, number of services, days open and days to conception or culled cows (Nakao et al., 1988; Fourichon et al., 2000). Therefore, effect of therapy on reproductive performance could be estimated or measured based on different criteria which are; 1.early or delayed event occurrence such as period from start of therapy to cure and period to observed estrus or first and last service to conception date as measured between the IUT therapy and PGF2α treated animals.2.possible changes in the possibility of an event occurring or reaching expected state as preplanned expected estrus or heat time for the cows, first service time, conception within a time frame or pregnancy within a given day postpartum between the IUT therapy and PGF2α therapy cows.3.repitation of an event to reach an expected outcome such as number of service per conception or number conceived at first service

(FS) and number of insemination per conception (InsFS) between the IUT and PGF2α treated cows.

In this work no significant difference was found between the IUT and PGF2α therapy in all endometritis without classification. An advantage for PGF2α therapy could only be recorded in the Culled (%) and Day Open period parameters. In various publications the results have shown that various IU therapies (EucaComp; Lotagen) were successful (Pregnancy rate 62.9% versus 56.9%) in endometritis therapy (Walter et al., 2005). In contrast to these results, some authors have found better PGF2α therapy results (Drillich et al., 2005).Kaya, (2008) did not find any difference between the various IU and PGF2α therapies. In general, the meta-analysis findings also showed that there was no difference between the two therapies, only with small exceptions. There were more indication of reproductive outcome with the use of PGF2α for the management of endometritis on general evaluation of these parameters which agree with the findings from other articles (LeBlanc et al., 2002;Kasimanickam et al, 2005).Haimerl et al (2018) on meta-analysis of PGF2α on endometritis therapy, reported an improvement in pregnancy rate with PGF2α due to presence of ovarian corpus luteum or in cow in luteal phase of estrus cycle (LeBlanc et al., 2002;Kasimanickam et al, 2005)while other articles showed non reproductive improvement when comparing PGF2α (LeBlanc et al, 2018; Dubuc et al, 2011).Although, few studies prove that routine postpartum administration of PGF2α lower period to conception (Etherington et al., 1988; Risco et al., 1994; LeBlanc et al., 2002). For as much as work had been done on endometritis treatment, there are yet none conclusive results on its therapy which is still a controversy among veterinary practitioners in spite of series of work done to mitigate the condition by evaluating various treatment measures (Brezlaff et al, 1987; Gilbert and Schwark., 1992; LeBlanc et al., 2002;Lehimcioğlu et al., 2019;).There is fewer evidence for prove of the benefit of any intrauterine antimicrobial on reproductive performance in cows with endometritis (Steffan et al., 1984; Lehimcioğlu et al., 2019). Some reports have concluded that PGF2α is much as effective as or preferable to IUT infusion of antimicrobials or other local agents for the treatment of endometritis (LeBlanc et al., 2002; Lehimcioğlu et al., 2019). Although, there remains a lack of sufficient propelling

evidence on this findings and IUT administration of antibiotics to dairy cows remains the norm among practitioners (LeBlanc et al., 2002).In this meta-analysis it was found that, statistically speaking, PGF2α therapy achieved better results on day >30 than IU therapy and repeated administration of PGF2α to cows in these herd reports had no effect on the prevalence of clinical endometritis at 22-30 days post partum (Hendricks et al., 2006). These results indicate that the PGF2α applications can achieve better results in the endometritis that developed after the 30th day (LeBlanc et al., 2002).

In many publications (Hendricks et al, 2006; Purohit et al, 2015 ;) it was mentioned that a better response to the PGF2α application can be achieved in the presence of a corpus luteum. Nevertheless, better fertility results could be achieved after the IU therapy with the E1 endometritis (PR 74.3% and Day Open 102 days) compared to PGF2α therapy (PR 67% and day Open 117 days).These results show that the severity of the endometritis can also influence the success of the therapy.

Lehimcioğluet al., (2019) work on intrauterine therapy of subclinical cases of repeat breeder cows showed no significant improvement nor difference among the two different treatment groups on carvacrol and lugol's iodine and control group (71.15%, 69.23% and 68.62%, respectively) which is comparable to local intrauterine antibiotic use reported on conception rate and pregnancy by other authors (Shams-Esfandabadi et al., 2004; Ahmadi et al., 2007; Sharma et al., 2018; Dubuc et al, 2011).

On this current study report on days to reproductive parameters such as period to begin therapy comparing IUT and PGF2α between 20^{th} to 30^{th} day and 30 days and above days showed overall no statistically significant difference regarding therapy which agrees with Dubuc et at (2011) report on PGF2α treatment at 35 d and 49 DIM did not influence uterine health and contradicts the reproductive performance findings from LeBlanc et al., 2002 work which reported higher conception and pregnancy rate when therapy were initiated later in the post partum period between 27 to 33 days compared to early therapy of 20^{th} to 26^{th} days therapy, similarly, these reports has PGF2α (104.37±20.94 days) with shorter days to therapy to IUT (115.18± 28.8 days) which is

similar with this report finding and Dubuc et al,(2011) reported benefits of PGF2α are likely due to a response of synchronization of estrus due to most of these articles did not consider uterine health state as a determinant or a result of treatment. From 30th day above which agrees that there is evidence of better responsiveness to therapy or resumption of ovarian cycle at later days post partum and possible self cure of the condition (Gilbert and Schwark, 1992; Dubuc et al, 2011; LeBlanc et al., 2002; Giuliodori et al., 2017).From this study, the proportion of cows with later treatment days was more at 30th day above although not significant as much and between IUT and PGF2α treated cows were more showed better response to treatment with PGF2α than with IUT treated cows but IUT had a shorter days to response cure at 30th days above. This poses an important question on determining exert endometritis diagnosis and treatment period (Dubuc et al., 2011; Brick et al., 2012).

The results for the combined endometritis (no classification) therapy is significance with a shorter days to conception and number of culled cows for PGF2α treated cows ($P<0.05$) which reports were similar to Nakao et al., 1988 and other researcher had similar positive report on the use of PGF2α for mitigating the effects of endometritis on the uterine health (Steffan et al., 1984;Galvao et al., 2009;Dubuc et al., 2011) although, not overall performance of treatment with PGF2α was not supported by the evidence.

Evaluating the analysis of intrauterine therapy and PGF2α therapy on severity of the infection, we observe a gradual decrease in severity as we move down the table (from E1 to E3) with an increase in treated cows indicating a high possibility of subclinical infection in a herd which could be undiagnosed with some self-recovery incidences (Gilbert et al., 2005; Cheong et al., 2011; Sheldon et al., 2018) and intrauterine treatment having higher parameter PR (%) after IU treatment was higher (74.3%) to the PGF2α treatment (67.0%) and the difference was significant statistically ($P <0.05$) on mild endometritis which agree with other reports as Galvao et al., 2009 found no benefit of 3 injections at separate interval of PGF2α treatment of subclinical endometritis. Other studies also failed to find any benefit after a single injection of PGF2α (LeBlanc et al., 2002;), after 2 interval injections of PGF2α in cows with purulent vaginal discharge

(PVD) (Dubuc et al., 2011, Stephen et al., 2019) which treatment were started between 20^{th} to 33^{rd} day post partum. This findings tails with this present report on this effects and agrees with the findings of other researchers that PGF2α treatment of cases of endometritis might be best instituted at later perperium than at early stage of the infection. Giuliodori et al., 2017 results on the treatment of cases on purulent vaginal discharge at 20^{th} to 26^{th} day postpartum with PGF2α was not effective in alleviating the condition or cure was prolonged with the treated cows having prolonged days open and delay conception or cases of early embryonic mortality (EEM). In contrast, Shams-Esfendabadi et al., 2004 reported higher clearance of clinical signs but low outcome on pregnancy when intrauterine antibiotics were (oxytretracycline 49.2% and penicilin 47.7%) used for endometritis treatment. Apart from this study no other data had reported with any valuable statistical proof on evidence regarding these separations of severity of endometritis treatment protocols.

If the comparison between the therapy groups is analyzed according to the endometritis severity grade then the calculations show that for the E1 endometritis the IU therapy have higher PR ($P < 0.01$) and lower Open Day results ($P < 0.05$).In contrast to that, the E2 endometritis had better fertility results after PGF2α treatment than IUT treatments. As for E3 endometritis, the literature meta-analysis has shown that there are no significant differences between the two treatment groups. Heuwieser et al (2000) also found that the PGF2α treatment had a positive effect on the Open Day, but the other fertility parameters could not be significantly improved after the PGF2α applications. Even Kaya (2008) in her research could not find any significant difference between the IUT and PGF2α therapies, neither generally considering all endometritis together or under the classification (E1, E2, E3) of endometritis. It was also concluded from her that the degrees of endometritis give different responses to different therapies.

7. CONCLUSION

In addition, the effects of therapy (IUT andPGF2α) on reproductive performance as well reported in the chosen literature which reveals much difference in the research method and in the quantitative evaluation of those effects. Meta-analysis methods had been coined to evaluate the summary reports of varying studies in order to evaluate the available data from relevant source studies and therefore examine the potential sources of differences of the findings. The results of a meta-analysis must be considered with caution (Haimerl et al., 2018; Fourichon et al., 2000) and therefore, extends its importance to observational studies that must account for the variability of study designs and of populations employed.

This present study had not been much reported significant differences statistically with intrauterine therapy and PGF2α therapy on overall evaluation of the reproductive parameters. PGF2a therapy had shorter days to first service (FS), lesser number of inseminations on pregnancy, and low culled rate to intrauterine therapy but overall pregnancy rate, return to estrus cycle are much similar between the two types of therapy. The days to start of therapy were more favorable for intrauterine therapy at early puerperium treatment to PGF2α which reveals better treatment outcome at later days of treatment which present a concern on when should endometritis therapy could be initiated and if there are reason to permit self cure to therapy in the management of endometritis since evidence reveals a more decrease in infectivity at later post partum especially in resumed cyclic cows with corpus lutum.

The degree of infectivity determines therapy and response to kind of therapy involving intrauterine and PGF2a. There is higher hazard to pregnancy with low cases of endometritis (E1) involving intrauterine therapy compared with moderate and severe cases of endometritis treatment with PGF2a but several reports are still to provide sufficient reports to support this claims regarding these therapy.

The presented report supports the results of the previous meta-analysis. The numbers of published articles and their strength of evidence are still limited regarding PGF2α and

IUT therapy. This report's conducted trials, furthermore, reveals a different therapy evaluation on the holistic therapy methods, including evaluation of period of treatment and severity of the treatment cases regarding the treatment methods. Reproductive performance after IUT treatment and PGF2α treatment of endometritic cows did not improve. Therefore, these results do require further study and more updated study on the evaluation of IUT therapy and PGF2α therapy for the treatment of endometritis.

Therefore, we do not recommend a treatment of bovine endometritis with PGF2α as a single treatment option to improve reproductive performance rather a safe and preventive measures should be the best practice in managing endometritis occurrence. These two therapies may be more precisely combined with endometritis induction, grade, or post-treatment into the uterine atrium.

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