BF-1648
[1-7]

REVIEW ARTICLE Indian Journal of Animal Research

Efficacy of Chinese and Western Medicine on Endometritis in Dairy Cows: A Systematic Review and Meta-analysis

Peirong Chen[1], Jinni Liu[1], Bingjie Ma[1], Zhili Li[1], Qingming Qin[1], Haigang Wu[1]

10.18805/IJAR.BF-1648

ABSTRACT

Endometritis is a frequent postpartum disease of dairy cows and inflicts considerable distress on the animals and costs to the dairy industry. This study evaluated the clinical efficacy of Chinese and Western Medicine combination treatments for dairy cow endometritis to provide a reference for the prevention and treatment of these infections. This analysis provides new information for veterinary medical research. We used the keywords 'Chinese and Western Medicine, Traditional and Western Medicine, Chinese herbs, Traditional Chinese Medicine Traditional Medicine, Chinese, Zhong Yi Xue, Chinese Traditional Medicine, Chinese Medicine, Traditional, Endometritis, Metritis and Cow to assess relevant literature sources collected in CNKI, Wanfang, Vepsa, China Patent Information Network, PubMed, Web of Science and other domestic and foreign databases. We utilized Cochrane system instructions to perform a meta-analysis using RevMan 5. 3 and Stata 16.0 software. We identified 13 randomized clinical trials (RCT) involving 847 dairy cows including cows 435 treated with a combination of Chinese and Western Medicine and 412 cows treated with the Western Medicine approach. The effectiveness for the combination therapy was better than that of the control (antibiotic only) where the relative risk was 1.19 with 95% CI (1.12, 1.26) and Z =5.96, P<0.01. We found no significant heterogeneity between these studies (I^2=0<50%, P =0.50<0.1) and publication bias was absent as investigated through funnel plots and the Egger regression model (P=0.197>0.05). These results indicated that although the Chinese herbal preparations differed between studies (n=13), when coupled with Western antibiotic treatments the animals recovered faster than did the control Western antibiotic treatments. These randomized control studies indicated that the efficacy of Chinese and Western Medicine on endometritis in dairy cows is greater than that of Western Medicine treatments.

Key words: Chinese and Western Medicine, Cow, Endometritis, Meta-analysis.

Endometritis is an inflammation and infection of the uterus and is a frequent postpartum disease of dairy cows. Data from the United States, Canada and France rank its occurrence at 28 to 36% while in China estimates have ranged from 17 to 60% (Dubuc *et al*., 2010, Deguillaume *et al*., 2012; Cheong *et al*., 2012; Umar *et al*., 2021). For example, surveys of >5000 dairy cows each in northern Xinjiang and Jilin reported the prevalence at 17.6 - 25.8% and 15.88-60.26%, respectively (Zhao, 2019; Hao *et al*., 2021) while the average incidence in Baoding City was 31.7% (Li, 2020). Endometritis seriously affects the estrus and pregnancy of dairy cows in addition to stress and suffering of the animals. These infections often result in decreased milk production with accompanied prolonged conception periods and even infertility (Overton *et al*., 2008; Nyabinwa *et al*., 2020).

The leading cause of endometritis in dairy cows is uterine infection primarily by pathogenic streptococci and staphylococci, *Escherichia coli*, *Coryne bacterium pyogenes* and well as mycoplasma (Yang, 2021; Barbeau-Grégoire *et al*., 2021). Clinical treatments are primarily based on administration of antibiotics, hormones and trace elements as well as surgical stripping (Ludbey *et al*., 2022). Antibiotic treatment is widely used in dairy farming due to its simple operation, rapid effect and low cost. However, the development of antibiotic resistance by pathogens and environmental contamination by residual antibiotics are disadvantages to this type of treatment regimen. In contrast, Chinese herbal medicines are being examined for their effectiveness in treating endometritis in combination with Western medicine protocols. This combinatorial approach may overcome the disadvantages of antibiotic resistance and environmental pollution while increasing the generally slower effects of traditional Chinese medicine treatments to improve therapeutic effects (Paiano *et al*., 2022). This current study is a meta-analysis and a systematic review of published controlled clinical trials for the use of traditional Chinese and Western medicine to treat dairy cow endometritis. This study provides a reference and new information for the treatment of this disease in dairy cows.

[1]College of Animal Science and Veterinary Medicine, Xinyang Agriculture and Forestry University, Xinyang, 464000, People's Republic of China.

Corresponding Author: Haigang Wu, College of Animal Science and Veterinary Medicine, Xinyang Agriculture and Forestry University, Xinyang, 464000, People's Republic of China.
Email: 2009200055@xyafu.edu.cn

How to cite this article: Chen, P., Liu, J., Ma, B., Li, Z., Qin, Q. and Wu, H. (2023). Efficacy of Chinese and Western Medicine on Endometritis in Dairy Cows: A Systematic Review and Meta-analysis. Indian Journal of Animal Research. doi:10.18805/IJAR.BF-1648.

Submitted: 15-03-2023 **Accepted:** 31-05-2023 **Online:** 12-06-2023

The databases of China National Knowledge Infrastructure, Wanfang, VIP, PubMed and Web of Science were searched by computer. The search time limit was from establishing the database to May 2022. The search terms include research objects and intervention measures. We used the keywords Chinese and Western Medicine, Traditional and Western Medicine, Chinese herbs, Traditional Chinese Medicine Traditional Medicine, Chinese, Zhong Yi Xue, Chinese Traditional Medicine, Chinese Medicine, Traditional, Endometritis, Metritis and Cow to assess relevant literature sources collected in CNKI, Wanfang, Vepsa, China Patent Information Network, PubMed, Web of Science and other domestic and foreign databases. All searches combined subject words and free words and manual searches were included in the research references by experts and scholars in this field, relevant authors and veterinary drug manufacturers to collect ongoing trials and conference proceedings and obtain unpublished literature information.

Note Express 3.0 (http://www.inoteexpress.com/aegean/) was used for an initial screening of the literature search to classify and organize the material. A primary screening via title and abstract and another screening by the full text was performed to exclude documents that did not meet the inclusion criteria. A final re-screening of all documents was undertaken by two researchers that independently reviewed the selected records, extracted the data and the results were compared. Differences were resolved by a third researcher who intervened and coordinated and conducted a resolution.

The Inclusion criteria for literature are as follows:(1) The original data was published literature; (2) The type of research was either a randomized or semi-randomized controlled trial and chosen independent of data-blinding; (3) The research object must be dairy cow endometritis with clear diagnostic criteria; (4) The intervention measures were a combination of Chinese and Western medicine in the test group and Western medicine in the control group; (5) The outcome indicators possessed standardized efficacy evaluation indicators and the treatment efficiency was calculated in the study; (6) The cases consisted of two groups with straightforward numerical results for the outcomes.

The Inclusion criteria for literature are as follows (1) Reviews, comments, single case reports and diagnosis and treatment experience; (2) Repeated publications and the same trial; (3) The research object was not cattle; (4) The intervention was a combination of traditional Chinese medicine, other drugs or biological agents and the control drug was a pure traditional Chinese medicine treatment; (5) The evaluation indicators were inconsistent; (6) A control group was lacking.

The data extraction content in the literature is as follows:(1) General information: title, author, publication date and source; (2) Research characteristics: research objects, the total number of animals in the treatment and control groups, total numbers following treatment, administration methods in the treatment and control groups.

The bias risk assessment tool of the Cochrane Collaboration Network was used to assess the risk of bias of the included literature using RevMan 5.3 (http://ims.cochrane.org/revman). This software included tests of selection bias including random sequence generation, hidden grouping, allocation concealment as well as blinding (implementation bias) and blinding of participants and personnel (performance bias), blinded outcome assessment (measurement bias), blinding of outcome assessment (detection bias), incomplete data bias (loss to follow-up bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), bias and other bias. The risk level for bias indicators was divided into low risk (+): low risk of bias and unclear (?): Unclear risk of preference and high risk of bias (-).

Meta-analysis was carried out using RevMan 5.3 and STATA 16.0 (https://www.stata.com/) statistical software. The odds ratio (risk ratio, RR) was used for categorical variables and the 95% confidence interval CI) of each effect size was calculated. The X^2 test was applied to examine heterogeneity among the included studies. The fixed effect model was used for a combined analysis when statistical homogeneity was present ($P>0.1$, $I^2<50\%$). If statistical heterogeneity was found ($P<0.1$, $I^2>50\%$), the random effect model was used to analyze the source of heterogeneity. If the heterogeneity between the two groups was significant or the data sources were lacking, descriptive analysis and inverted funnel plots and Egger's test analyses were used to test for publication bias.

Literature search and screening

We initially obtained 227 articles using the search strategy and 149 were selected following duplicate exclusion. Non-clinical studies, non-controlled trials, reviews, meta-analyses and experimental animals other than cows were excluded by review of the titles and abstracts of the material resulting in 69 papers. The full texts were read and this further excluded 27 articles that did not meet the research content and 19 reports that did not match the intervention measures, experimental design, research content or outcome variables. The final results included 13 papers (Fig 1 and Table 1).

Methodological quality evaluation and analysis

The results of our final search indicated that all the included research was conducted in China and the subjects were 847 dairy cows with endometritis including 435 in the test (combination therapy) and 412 in the control (antibiotic) group. The sample size of a single study ranged from 10 to 70 cows. The risk of bias assessment for each study indicated that all 13 studies were random controlled trials and none reported random allocation concealment or specific blinding implementation methods (Fig 2). Therefore, all 13 papers reported the primary outcomes of the study. A heterogeneity inspection of the studies resulted in I^2 values of 0< 50 % and P values for the Q test at 0.50>0.1. These results indicated there was no heterogeneity among the 13 selected studies *i.e*., heterogeneity was not statistically

significant. We then selected the fixed effect to combine the effect size. The combined effect size (RR) for the 13 studies using fixed effects was 1.19 and 95% CI of (1.12, 1.26) and was statistically significant (Z=5.96, P<0.00001). Our meta-analysis indicated that the total effective levels for the combined Chinese and Western medicine treatment group versus the ciprofloxacin treatment groups were 93.10% (405/435) and 78.40% (323/412), respectively. The efficiency of the combination treatments were significantly (P<0.01) better than that of the antibiotic group.

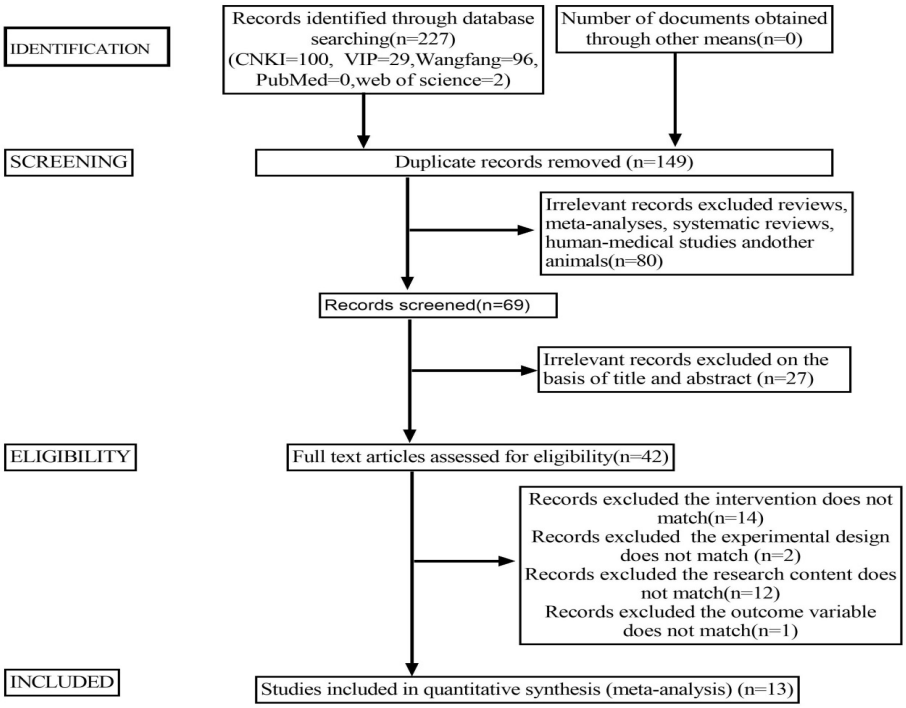

Fig 1: Literature screening process.

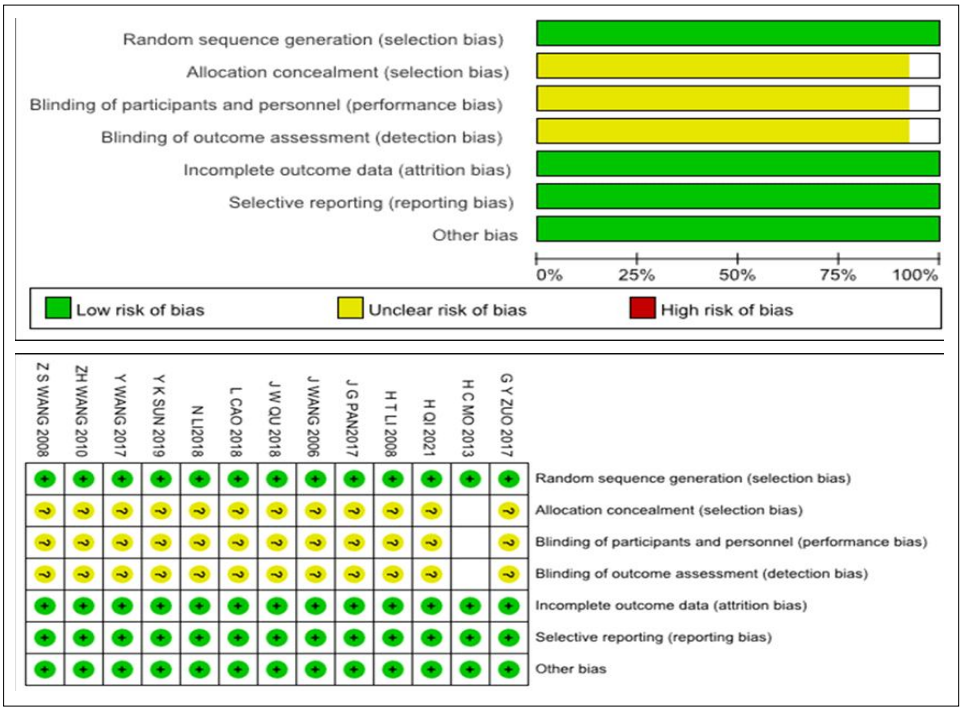

Fig 2: Bias risk assessment and publication bias assessment.

This indicated that the efficacy of combined Chinese and Western medicine in the treatment of cow endometritis was significantly better than simple Western medicine treatment. The curative effect of combined treatment was 1.19 times that of simple Western medicine treatment (Fig 3).

Dairy cow endometritis is primarily caused by bacterial infection and as such, antibiotics and anti-inflammatory drugs are therefore often used in clinical treatment. However, bacterial drug resistance and drug residue pollution have driven the search for green and safe traditional Chinese

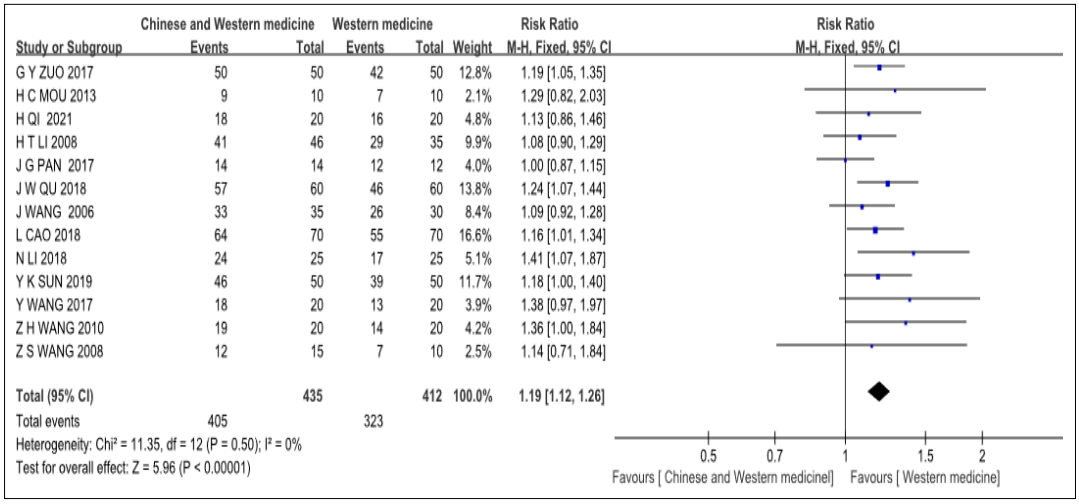

Fig 3: Meta analysis forest map of Chinese and Western Medicine on Endometritis in cow.

Table 1: Basic characteristics of literature.

Author	Year of publication	Number of treatment groups	Effective rate treatment of group	Number of control groups	Effective rate of control group	Medication in the treatment group	Medication in the control group
Sun, Y.K.	2019	50	92.01%	50	78.17%	Traditional Chinese Medicine + Enrofloxacin	Enrofloxacin
Qu, J.W.	2018	60	95%	60	76.67%	Traditional Chinese Medicine + Enrofloxacin.	Enrofloxacin
Zuo, G.Y.	2018	50	100%	50	84.00%	Traditional Chinese Medicine + Gentamicin	Gentamicin
Cao, L.	2018	70	91.43%	70	78.57%	Traditional Chinese Medicine + Enrofloxacin	Enrofloxacin
Li, N.	2018	25	96%	25	68.00%	Traditional Chinese Medicine + Gentamicin	Gentamicin
Pan, J.G.	2017	14	100%	12	100.00%	Traditional Chinese Medicine + Oxytetracycline	Ofloxacin, Florfenicol, Doxycycline
Wang, J.	2006	35	94.30%	30	86.70%	Traditional Chinese Medicine + Gentamicin	Gentamicin
Wang, Z.H.	2010	20	95%	20	70.00%	Traditional Chinese Medicine + Compound Antibiotics	Compound antibiotics
Wang, Z.S.	2008	15	80%	10	70.00%	Traditional Chinese Medicine + Enrofloxacin Lactate	Enrofloxacin lactate
Wang, Y.	2017	20	90%	20	65.00%	Traditional Chinese Medicine + Oxytetracycline	Oxytetracycline
Mo, H.C.	2013	10	90%	10	70.00%	Traditional Chinese Medicine + Compound Neostigmine	Compound Neostigmine
Qi, H.	2021	20	90%	20	80.00%	Traditional Chinese Medicine + Ceftiofur	Ceftiofur
Li, H.T.	2008	46	91.3%	35	82.9%	Traditional Chinese Medicine + Ciprofloxacin	Oxytetracycline

medicine alternatives. Still, conventional Chinese medicine treatments have problems such as extended treatment times and elevated dosages. Therefore, adopting combination treatment methods is a way to improve therapeutic effects. The principles of Chinese veterinary medicine indicate that cow endometritis is caused by internal resistance of damp heat and uterine blood addiction. The treatment incorporates the herbs *Coptidis* spp. (Ranunculaceae), *Forsythia* spp (Oleaceae) and *Angelica* spp. (Apiaceae) to clear away heat and detoxify, promote blood circulation and remove blood stasis. Danshen (*Salvia bowleyana*), motherwort (*Leonurus cardiac*), safflower (*Carthamus tinctorius*) and dandelion (*Taraxacum officinale*) are typical added ingredients. In particular, berberine, organic acids and flavonoids found in *Coptidis* and *Forsythia* have been proven effective against *Staphylococcus aureus*, *E. coli*, *Streptococcus* spp. and suppurative bacteria such as *Bacillus.* Motherwort and safflower alkaloids can enhance uterine smooth muscle contractility while *Salvia miltiorrhiza*, safflower and dandelion promote circulation and remove blood stasis. *Angelica* polysaccharides have also been implicated as immune regulators. *In vitro* bacteriostatic tests of Chinese and Western drugs against bacteria that cause endometritis are most effective when used in combination. For instance, the combination rhubarb, motherwort and ciprofloxacin (EDM) possessed superior anti-bacterial activity versus components used individually (Liu, 2008, He, 2008). These types of combination drugs can also decrease contamination in the environment and in dairy products (Wang, 2006). Another compound preparation Gongyanqing demonstrated a preventative effect on young (100%) and adult (91.30%) dairy cows that was significantly better than enrofloxacin alone (Guo, 2002). In addition, the compound preparation could increase T lymphocyte and neutrophil effectiveness during infection while enhancing overall antioxidant capacity (Liu, W. 2008). Combination drugs have also been developed to promote estrus and embryo implantation in cattle and thereby increase the conception rate. Therefore, traditional Chinese and Western medicine combinations can synergize through antibacterial anti-inflammatory activities and immune regulation to promote circulation and remove blood stasis while enhancing pregnancy during treatment of dairy cow endometritis (Li, 2008). These 13 randomized control studies indicated that combination therapies promoted a curative effect in treating bovine endometritis that was significantly better than that of Western therapy alone.

Publication bias analysis

An examination of publication bias was conducted and this data generated a symmetrical funnel plot. Egger's test results also indicated that P=0.197 (P>0.05) and the selected studies displayed had no obvious publication bias. This indicated that these 13 studies were positive, accurate and reliable tests for the hypothesis that the combined therapies was better for treatment of cow endometritis that the use of the Western approach on its own (Fig 4).

Limitations of this meta-analysis

Meta-analysis is a re-analysis based on published literature and the quality of the included literature greatly influences the reliability of the outcome (Raboisson *et al*., 2014). Chinese and English databases were searched and the results were primarily from the Chinese literature in domestic general professional journals. A few of these 13 random controlled trials (RCT) were small while none of the studies described the hiding of the allocation scheme and the specific implementation of the blind method. Therefore, selection and measurement bias may have occurred. The components of traditional Chinese medicines used for these studies differed as did the specific curative effects. However, the treatment principles of their prescriptions were all determined under the guidance of Chinese veterinarians and therefore were similar in prescribing effect. Other high-quality RCTs are needed to support and verify the combined results presented here.

CONCLUSION

This meta-analysis of 13 randomized studies demonstrates a curative effect of the combination of Chinese and Western

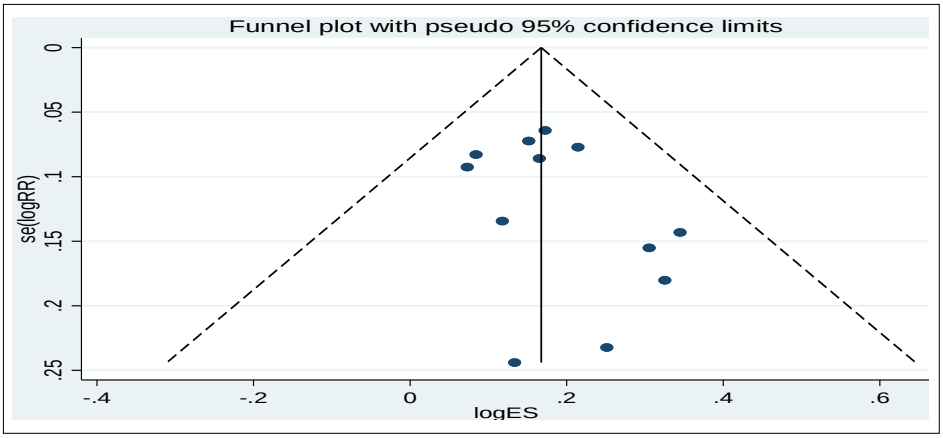

Fig 4: Test results of publication bias.

medicine in the treatment of cow endometritis that was significantly better (1.19) than that of Western therapy alone. This systematic review provides a decision-making reference for the clinical treatment of dairy cow endometritis.

Funding

The study was supported by the Key Science and Technology Program of Henan Province (232102110074), the Foundation of Henan Education Committee (22A230018), Scientific and technological Innovation team of Poultry Germplasm Resources Application and healthy breeding in Dabie Mountain of Xinyang Agriculture and Forestry University (XYKJTD-013).

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

Barbeau-Grégoire, N., Boyer, A., Rousseau, M., Gauthier, M.L., Dubuc, J. (2021). Validation of on-farm bacteriological systems for endometritis diagnosis in postpartum dairy cows. Animals (Basel). 11(9): 2695. Published 2021 Sep 15. doi: 10.3390/ani11092695.

Cao, L., Sun, P., Wen, H.M. (2018). Traditional Chinese medicine prescription combined with antibiotics in the treatment of chronic endometritis in dairy cows. Shandong Animal Husbandry and Veterinarian. 39(1): 11-12.

Cheong, S.H., Nydam, D.V., Galvão, K.N., Crosier, B.M., Ricci, A., Caixeta, L.S., Sper, R.B., Fraga, M., Gilbert, R.O. (2012). Use of reagent test strips for diagnosis of endometritis in dairy cows. Theriogenology. 77(5): 858-64. doi: 10.1016/j.theriogenology.2011.09.009.

Deguillaume, L., Geffré, A., Desquilbet, L., Dizien, A., Thoumire, S., Vornière, C., Constant, F., Fournier, R., Chastant-Maillard, S. (2012). Effect of endocervical inflammation on days to conception in dairy cows. J. Dairy Sci. 95(4): 1776-83. doi: 10.3168/jds.2011-4602. PMID: 22459826.

Dubuc, J., Duffield, T.F., Leslie, K.E., Walton, J.S., LeBlanc, S.J. (2010). Definitions and diagnosis of postpartum endometritis in dairy cows. J. Dairy Sci. 93(11): 5225-33. doi: 10.3168/jds.2010-3428. PMID: 20965337.

Guo, S.N. (2002). Studies on the New Kind Compound Medicine Gongyanqing for Prevention and Treatment of Cow Endometritis. Northeast Agricultural University. Harbin, China.

Hao, J.F., Li, G.Q., Zhang, Y.H. (2021). Epidemiological Investigation of Endometritis in Dairy Cows in Jilin Area from 2017 to 2019. Chinese Journal of Veterinary Medicine. 57(4): 50-53.

He, C.Y. (2008). Studies on New Form of Veterinary Drugs for Dairy Cow with Endometritis [D]. Heilongjiang Bayi Agricultural Reclamation University. Daqing, China.

Li, H.T. (2008). Development and Trials on Compound of “Beneficial Pregnancyliquid”. Shihezi University, Shihezi, China.

Li, N. (2018). Traditional Chinese medicine prescription combined with antibiotics in the treatment of chronic endometritis in dairy cows. China Animal Husbandry and Veterinary Abstracts. 34(3): 251-254.

Li, R. (2020). Investigation on Incidence and Drug Sensitivity Test of Dairy Cow Endometritis in Banding Area. Hebei Agricultural University, Baoding, China.

Liu, W. (2008). Effects of New Chinese and Western Medicine Compound Emulsion on Clinical Pharmacodynamics and Immunoligic Function for Dairy Cow with Endometritis. Heilongjiang Bayi Agricultural Reclamation University, Daqing, China.

Liu, Z.Y. (2008). Study on Compound Effervescent Tablets of Traditional Chinese and Western Medicine in the Treatment of Endometritis in Dairy Cows. Inner Mongolia University, Hohhot, China.

Ludbey, P.A., Sahibzada, S., Annandale, C.H. (2022). A pilot study on bacterial isolates associated with purulent vaginal discharge in dairy cows in the south-west region of Western Australia. Aust Vet J. 100(5): 205-212. doi:10.1111/avj.13152.

Mo, H.C. (2013). Study on the efficacy of different formulations in the treatment of postpartum endometritis in dairy cows. Modern Agricultural Science and Technology. (8): 251-252.

Nyabinwa, P., Kashongwe, O.B., Hirwa, C.D., Bebe, B.O. (2020). Influence of endometritis on milk yield of zero-grazed dairy cows on smallholder farms in Rwanda. Vet Anim Sci. 7; 10:100149. doi: 10.1016/j.vas.2020.100149. PMID: 33089007; PMCID: PMC7567037.

Overton, M., Fetrow, J. (2008). Economics of postpartum uterine health. Dairy Cattle Reproduction Council Annual Meeting and Convention. 39-43.

Paiano, R.B., Baruselli, P.S. (2022). The use of herbal treatments as alternatives to control uterine diseases in dairy cows. Trop Anim Health Prod. 54(2): 148. Published 2022 Mar 30. doi: 10.1007/s11250-022-03153-3.

Pan, J.G. (2017). Diagnosis and clinical treatment of bovine endometritis. Gansu Animal Husbandry and Veterinarian. 47(12): 117-118.

Qi, H. (2021). Etiological Analysis and Integrated Control of Cow Endometritis in a Large-scale Dairy Farm. Northwest University of Agriculture and Forestry Science and Technology, Yangling, China.

Qu, J.W. (2018). Observation on the efficacy of traditional Chinese medicine combined with antibiotics in the treatment of chronic endometritis in dairy cows. Animal Husbandry Veterinary Science. 6-12.

Raboisson, D., Mounié, M., Maigné, E. (2014).Diseases, reproductive performance and changes in milk production associated with subclinical ketosis in dairy cows: A meta-analysis and review. J. Dairy Sci. 97(12): 7547-7563. doi:10.3168/jds.2014-8237.

Sun, Y.K., Ma, G.N., Yang, C.W. (2019). Clinical effect of beneficial pregnancy liquid with lactic acid ciprofloxacin to endometritis of dairy cows. Chinese Journal of Animal Medicine. 11: 11-12.

Umar, T., Yin, B., Umer, S. (2021). MicroRNA: Could It Play a Role in Bovine Endometritis. Inflammation. 44(5): 1683-1695.

Wang, J. (2006). Study on New Drug for Endometritis in Cows. Henan Agricultural University. Zhengzhou, China.

Wang, Y. (2017). Pathogen isolation and identification of endometritis in dairy cows and comparison of different treatment trials. Chinese Herbivore Science. 37(4): 41-42.

Wang, Z.H. (2010). The Study on Occurring Regularitv and Diagnose and Treatment Technology of Cow Endometritis in the Southern of Henan. Henan Agricultural University. Zhengzhou, China.

Wang, Z.S. (2008). Preliminary Study on the Therapeutic Effect of Chinese and Western Compound Medicine on Endometritis in Dairy Cows. Ningxia University. Yinchuan, China.

Yang, J. (2021). Isolation and identification of pathogenic bacterias of endometritis in dairy cows and the molecular characteristics of trueperella pyogenes. Chinese Academy of Agricultural Sciences. DOI: 10.27630/d.cnki.gznky.2021.000284.

Zhao, X. (2019). Isolation, Identification and Control of Pathogenic Bacteria of Endometritis in Some Large-scale Ranching Cows in Xinjiang. Shihezi University. Shihezi, China.

Zuo, G.Y., Du, W.H. (2018). Observation on the efficacy of traditional Chinese medicine combined with antibiotics in the treatment of chronic endometritis in dairy cows. Animal Husbandry Veterinary Science. (5): 2.