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Evidence-based medicine: quality and comparability of clinical trials investigating the efficacy of prostaglandin $F_{2\alpha}$ for the treatment of bovine endometritis

Peggy Haimerl, Sebastian Arlt and Wolfgang Heuwieser*

Clinic for Animal Reproduction, Faculty of Veterinary Medicine, Freie Universität Berlin, Koenigsweg 65, 14163 Berlin, Germany

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The objective of this study was to evaluate the quality and comparability of published literature, and to summarize the effect of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) for the treatment of endometritis. It has been postulated that there is a dearth of high-level evidence-based research results in veterinary medicine. Also, there is a marked variation in the quality of studies in veterinary and animal science. Postpartum uterine infections occur commonly in dairy cattle and are reported to have a negative impact on reproductive performance. A comprehensive literature search was conducted utilizing online databases revealing a total of 2723 references. After applying specific exclusion criteria, a total of 68 trials were eligible for further analysis. These articles were evaluated utilizing specific parameters listed in an evaluation form such as randomization and the involvement of control groups. The analysis revealed that more than half of the trials (51·5%) were at least 20 years old. Furthermore, we found that about one third (36·8%) of all trials were controlled and randomized, while 3 of those (4·4%) were also blinded. Of those trials which calculated a calving-to-conception interval ($n = 30$), 50% of the authors claimed an improvement, which was statistically significant in 23·3% of the cases. We conclude that there is a wide discrepancy between research results investigating the efficacy of $PGF_{2\alpha}$.

Keywords: Endometritis, treatment, evidence, dairy cattle.

The decision-making process of practising veterinarians as well as farm personnel and animal scientists should be based on objective information (Holmes & Cockcroft, 2004). Therefore the implementation of evidence-based medicine becomes increasingly important. Sackett et al. (1996) defined evidence-based medicine as the conscientious, explicit and judicious use of the best external evidence currently available, for the purpose of making decisions concerning the medical care of individual patients. The term 'evidence' demonstrates the degree of certainty with which the results of a study reliably represent reality (Arlt & Heuwieser, 2005).

However, Holmes & Cockcroft (2004) have postulated that there is a dearth of methodologically performed, rigorous, large-scale clinical studies in veterinary medicine resulting in a lack of research results of high evidence. This hypothesis has been supported by several authors (Mair & Cohen, 2003; Arlt et al. 2010) who demonstrated that in veterinary medicine the increase of knowledge is mainly based on reviewing field reports rather than randomized, controlled clinical studies. Nevertheless, researchers seem to have become increasingly aware of this problem. Not only did several authors develop some kind of guidelines concerning the question of how to conduct high-quality studies or meta-analyses (e.g. Lean et al. 2009). Also, many very well-conducted studies eligible for performing meta-analyses have been published during recent years (Rabiee et al. 2005; Lean et al. 2006). Nevertheless, randomized, controlled, double-blinded studies are the gold standard with regard to the evaluation of a given treatment (Kastelic, 2006). The quality of a certain study depends on its design, its clinical relevance, the analysis of the study results, and the quality and comprehensiveness of the reporting (Arlt & Heuwieser, 2005). Four stages of evidence have been suggested to categorize studies with respect to their quality (Bassler & Antes, 2000). Stage I represents the highest level of evidence and refers to meta-analyses of randomized, controlled studies or evidence gained from at least one randomized, controlled study. Well-designed, controlled studies without randomization and well-designed, quasi-experimental studies generate evidence of stage II.

*For correspondence; e-mail: w.heuwieser@fu-berlin.de

Table 1. Research articles ($n = 68$) studying the efficacy of $PGF_{2\alpha}$ treatment of chronically endometritic cows chosen for evaluation

Author	Year of publication	Title	Journal/Source
Anderson, D.B.	1985	Chronic endometritis – a field study	Proceedings for 1983–84 of British Cattle Veterinary Association
Anderson, D.B.	1988	The role of prostaglandin therapy in the early post-partum cow	Proceedings for 1986–87 British Cattle Veterinary Association
Baars, J.C.	1980	Prostaglandin (Prosolvin) treatment of uterine disorders in the dairy cow	Proceeding of XI International Congress on Diseases of Cattle
Bach, S.	1985	Prostaglandin F2 alpha (Enzaprost) for treating infertile cows	Archiv für Experimentelle Veterinärmedizin
Barvi, S.A.	1994	Comparative efficacy of cloprostenol and estradiol for the treatment of endometritis in crossbred dairy cows	Pakistan Veterinary Journal
Bentele, W.	1980	Efficacy of tiaprost for the treatment of bovine endometritis	Tierärztliche Umschau
Bentele, W.	1980	Treatment of pyometra and lochiometra in cattle with the prostaglandin F2 analogue tiaprost	Tierärztliche Umschau
Böhme, H.	1986	Effectiveness of various treatments in the late puerperium	Tierhygiene-Information
Bonnett, BN	1988	Prostaglandin therapy and its relationship to histology, culture results and subsequent reproductive performance in dairy cows biopsied at 26 and 40 d post partum	Proceedings of 11th International Congress on Animal Reproduction and Artificial Insemination,
Bruns, G.U.	1997	Comparative study of the treatment of bovine endometritis with the prostaglandin analogue cloprostenol or a combination of metacresolsulfonic acid and formaldehyde ('Lotagen')	Thesis, Tierarztliche Hochschule, Hannover, Germany
Callahan, C.J.	1993	Treatment of post-partum metritis in dairy cows caused by Actinomyces pyogenes	Bovine Practitioner
Chauhan, F. S.	1983	Treatment of chronic endometritis with prostaglandin $F_{2\alpha}$ and antibiotic in cows and buffaloes	Indian Veterinary Journal
Copeland, D.D.	1978	Therapeutic and feedlot abortion application of prostaglandins	Bovine Practitioner
Coulson, A.	1978	Treatment of metritis in cattle with prostaglandin $F_{2\alpha}$	Veterinary Record
Drillich, M.	2002	Effects of the intensity of a post-partum examination on reproductive performance in high yielding dairy cows	Deutsche Tierärztliche Wochenschrift
Drillich, M.	2005	Treatment of chronic endometritis in dairy cows with cephapirin, tiaprost or a combination of both	Tierärztliche Praxis
Drillich, M.	2005	Treatment of chronic endometritis in dairy cows with an intrauterine application of enzymes: a field trial	Theriogenology
Duncanson, G.R.	1980	A four year study on a hundred and twenty cow dairy unit with a high rate of retained placenta and subsequent endometritis	Proceeding of XI. International Congress On Diseases of Cattle
Etherington, W.G.	1985	Interrelationships between post-partum events, hormonal therapy, reproductive abnormalities and reproductive performance in dairy cows: a path analysis	Canadian Journal of Comparative Medicine
Falkenberg, U.	2005	Influence of time of initiation of a prostaglandin $F_{2\alpha}$ protocol in dairy cows with puerperal endometritis	Deutsche Tierärztliche Wochenschrift
Feldmann, M.	2005	[Treatment of chronic bovine endometritis and factors for treatment success]	Deutsche Tierärztliche Wochenschrift
Fivaz, B.H.	1978	Bovine post-partum metritis and the reconception period	Rhodesian Veterinary Journal
Guay, P.	1980	Metritis following parturition: serum progesterone and 17 beta-oestradiol levels. The significance of the corpus luteum and the advisability of using a luteolytic agent as a treatment	Canadian Veterinary Journal
Günzler, von O.	1979	Treatment of pyometra in cows with Estrumate (cloprostenol)	Tierärztliche Umschau
Heuwieser, W.	2000	Effect of three programmes for the treatment of endometritis on the reproductive performance of a dairy herd	Veterinary Record
Hirsbrunner, G.	2006	Effects of a single administration of prostaglandin $F_{2\alpha}$, or a combination of prostaglandin $F_{2\alpha}$ and prostaglandin E2, or placebo on fertility variables in dairy cows 3–5 weeks post partum, a randomized, double-blind clinical trial	Reproductive Biology and Endocrinology

Table 1. (*Cont.*)

Author	Year of publication	Title	Journal/Source
Huggenberger, G.	1982	Comparison of prostaglandin analogues (cloprostenol and tiaprost) with Lugol's iodine solution for treating chronic endometritis in cows	Thesis, Ludwig-Maximilians-Universitat München, Germany
Humke, R.	1982 (Exp. 1)	The treatment of genital catarrhs of cattle with a prostaglandin analog and antibiotics 0·1. Individual application of the drugs	Tierärztliche Umschau
Humke, R.	1982 (Exp. 2)	The treatment of genital catarrhs of cattle with a prostaglandin analog and antibiotics 0·1. Individual application of the drugs	Tierärztliche Umschau
Hüntelmann, C.	2005	Investigation on the influence of time of post-partum examination and the initiation of a $PGF_{2\alpha}$ treatment of chronic endometritis in dairy cows	Thesis, Freie Universitat Berlin, Berlin, Germany
Jackson, P.S.	1977 (Exp. 1)	Treatment of chronic post-partum endometritis in cattle with cloprostenol	Veterinary Record
Jackson, P.S.	1977 (Exp. 2)	Treatment of chronic post-partum endometritis in cattle with cloprostenol	Veterinary Record
Jacob, T.C.	1993	Prostaglandin therapy for bovine endometritis	Journal of Veterinary and Animal Sciences
Jacob, T.C.	1995	Oestrus induction using $PGF_{2\alpha}$ in crossbred cows with post-partum clinical endometritis	Indian Journal of Animal Reproduction
Janowski, T.	2001	Combined GnRH and $PGF_{2\alpha}$ application in cows with endometritis puerperalis treated with antibiotics	Reproduction in Domestic Animals
Kaufmann, T.B.	2010	Systemic antibiotic treatment of clinical endometritis in dairy cows with ceftiofur or two doses of cloprostenol in a 14-d interval	Animal Reproduction Science
Knutti, B.	2000	Reproductive efficiency of cows with endometritis after treatment with intrauterine infusions or prostaglandin injections, or no treatment	Journal of Veterinary Medicine
Laven, R.A.	2003	Understanding the dynamics of bovine endometritis: comparison of the response to injectable luprostiol and topical cephapirin	Cattle Practice
Le Blanc, S.J.	2003	Field study of the diagnosis and treatment of clinical endometritis in dairy cattle	Journal of Dairy Science
Leidl, von W.	1983	Treatment of endometritis in cattle	Praktischer Tierarzt
Lusky, K	1984	Use of the cloprostenol preparation 'Oestrophan' for treating reproductive disorders in cattle	Monatshefte für Veterinärmedizin
Mansfeld, R.	1999	Two different programs to improve reproductive efficiency in dairy herds with special regard to the treatment of endometritis	Reproduction in Domestic Animals
Markusfels, O.	1984	The influence of post parturient metritis, corpus luteum enucleation and cloprostenol on conception rates in dairy cows	Refuah Veterinarith
Mejia, M.E.	2004 (Exp. 1)	Endometritis treatment with a $PGF_{2\alpha}$ analog does not improve reproductive performance in a large dairy herd in Argentina	Theriogenology
Mejia, M.E.	2004 (Exp. 2)	Endometritis treatment with a $PGF_{2\alpha}$ analog does not improve reproductive performance in a large dairy herd in Argentina	Theriogenology
Michiel, G.	1995	Efficacy of three injectable solutions of the prostaglandin analogue luprostiol for treating recently calved cows and cases of anoestrus or endometritis	Thesis, Justus-Liebig-Universitat, Giessen, Germany
Murray, R.D.	1990	Bovine endometritis: comparative efficacy of alfaprostol and intrauterine therapies, and other factors influencing clinical success	Veterinary Record
Nakao, T.	1997 (Exp. 3)	Post-partum plasma PGF metabolite profile in cows with dystocia and/or retained placenta, and effect of fenprostalene on uterine involution and reproductive performance	Journal of Veterinary Medical Science

Table 1. (*Cont.*)

Author	Year of publication	Title	Journal/Source
Narayana, K.	1986	The clinical efficacy of low-dose cloprostenol, a prostaglandin $F_{2\alpha}$ analogue, in infertile conditions in cattle and buffaloes	Indian Veterinary Journal
Ohtani, S.	1997	Effect of intrauterine infusion of polyvinyl-pyrrolidone iodine and intramuscular injection of prostaglandin $F_{2\alpha}$ on reproductive performance in cows	Reproduction in Domestic Animals
Otel, V.	1985	Practical results in regulating the puerperal period of cows	Tierärztliche Umschau
Pepper, R.T.	1985	Survey of the treatment of bovine endometritis	Proceedings for 1983–84 British Cattle Veterinary Association
Pepper, R.T.	1987 (Exp. 1)	Preliminary results of treatment and endocrinology of chronic endometritis in the dairy cow	Veterinary Record
Piccinelli, F.	1989	Treatment of uterine diseases in cows with prostaglandins	Praktischer Tierarzt
Rao, Y.	2001	Evaluation of $PGF_{2\alpha}$ analog treatment with and without antibacterials in endometritis in crossbred cattle	Indian Veterinary Journal
Roy, G.P.	1990	Trials of Dinofertin in different types of reproductive disorders	Indian Veterinary Journal
Sarkar, P.	2006	Effect of administration of garlic extract and $PGF_{2\alpha}$ on hormonal changes and recovery in endometritis cows	Asian-Australasian Journal of Animal Sciences
Sheldon, I.M.	1997	Comparison of three treatments for bovine endometritis	Cattle Practice
Sood, P.	2003	Impact of uterine microbial panorama on the therapeutic efficacy of single injection of $PGF_{2\alpha}$ in cows with clinical endometritis	Indian Journal of Animal Sciences
Sprowson, G.W.	1981	Therapeutic use of prostaglandin $F_{2\alpha}$ during the post-partum period in dairy cows [cloprostenol]	Zimbabwe Veterinary Journal
Steffan, J.	1984	Treatment of metritis with antibiotics or prostaglandin $F_{2\alpha}$ and influence of ovarian cyclicity in dairy cows	American Journal of Veterinary Research
Tenhagen, B.A.	2003	Influence of stage of lactation and milk production on conception rates after timed artificial insemination following Ovsynch	Theriogenology
Thiel, K.C.	1998	Treatment of bovine endometritis, of differing degrees of severity, with cloprostenol or povidone-iodine solution, with reference to plasma progesterone and the uterine microflora at the time of treatment	Thesis, Tierarztliche Hochschule, Hannover., Germany
Tischer, M.	1998	Treatment of chronic endometritis among cows of a dairy herd: combination of intrauterine antiseptic therapy with a prostaglandin analogue (tiaprost)	Thesis, Freie Universitat, Berlin, Germany
Tsousis, G.	2005	Strategien der Endometritisbehandlung und Auswirkung auf die klinische Heilung und die Fruchtbarkeit von Milchkühen im Rahmen der Integrierten Tierärztlichen Bestandsbetreuung	Thesis, Tierärztliche Hochschule Hannover, Germany
Wenkoff, M.S.	1978	Therapeutic evaluation of the use of prostaglandin analog ICI80996 in cattle	Canadian Veterinary Journal
Wonchee Solorzano, Z.	2002	Evaluation of different treatments used in the early post partum in dairy cows with metritis	Tecnica Pecuaria en Mexico
Zuber, H.	1980	Practical experiences with the prostaglandin analogue Estrumate for the treatment of endometritis in cattle	Deutsche Tierärztliche Wochenschrift

Evidence being categorized as stage III is obtained through well-designed, descriptive studies that are not experimental. Finally, the lowest stage of evidence (stage IV) covers opinions of experts, results presented at scientific meetings as well as clinical experience of accredited authorities. In order to improve the quality of publications, scientists developed checklists containing important aspects for conducting trials. For instance, the CONSORT and the PRISMA statements aim to improve the reporting of randomized clinical trials, as well as systematic reviews and meta-analyses. The REFLECT statement is a modification of the CONSORT statement for veterinary science as livestock and food safety. Besides the lack of high-evidence studies, there is a marked variation in the quality of studies in veterinary science, resulting in insufficient comparability of the various trials (Cockcroft & Holmes, 2003).

Clinical endometritis in cattle is defined as the presence of a purulent (>50% pus) uterine discharge detectable in the

Table 2. Relevant criteria of 68 trials studying the efficacy of $PGF_{2\alpha}$ treatment of chronically endometritic cows

	Diagnosis performed (in%)			
Criterion	After 21 d p.p.[†] ($n=32$)	Before or after 21 d p.p. ($n=20$)	No exact date of diagnosis given ($n=16$)	Total (%) ($n=68$)
Year of publication				
⩽1990	53·1	45·0	56·3	51·5
1991–2000	18·8	20·0	25·0	20·6
>2000	28·1	35·0	18·8	27·9
Definition of endometritis given	84·4	75·0	62·5	76·5
Number of total endometritis cases				
⩽50	9·4	15·0	31·3	16·2
51–150	15·6	45·0	25·0	26·5
>150	71·9	40·0	43·8	55·9
>200	43·8	35·0	25·0	36·8
Not specified	3·1	0·0	0·0	1·5
Endometritic animals exclusively treated with $PGF_{2\alpha}$				
⩽50	12·5	35·0	37·5	25·0
51–150	48·0	32·4	37·5	48·5
>150	28·1	10·0	25·0	22·1
>200	21·9	10·0	6·3	14·7
Not specified	9·4	0·0	0·0	4·4

[†] According to Sheldon et al. (2006)

vagina 21 d or more post partum, or mucopurulent (approximately 50% pus, 50% mucus) discharge detectable in the vagina after 26 d post partum, (Sheldon et al. 2006). Most recently, following a study conducted by Runciman et al. (2008) which aimed to evaluate the role of vaginoscopy in predicting a reduction in reproductive performance parameters associated with a positive discharge detected by vaginoscopy, cytological endometritis diagnosed with a cytobrush and purulent vaginal discharges diagnosed by Metricheck device have been described as distinct manifestations of uterine inflammation (Dubuc et al. 2010b). The prevalence of post-partum uterine infections (up to 57·7%) (Sheldon, 2009) and the resulting opportunity costs (decreased fertility, increased culling) underline the importance of this disease (Plaizier et al. 1998; LeBlanc et al. 2002a; LeBlanc, 2008).

There is a wealth of information on the treatment of endometritis and this subject has been reviewed extensively by several authors (Gilbert & Schwark, 1992; Olson, 1996; Azawi, 2008). However, the treatment of endometritis is still an issue of considerable controversy (Arlt et al. 2009; Dubuc et al. 2011). This may be due to the wide variety of therapies available for endometritis, including systemic or local antibiotics, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and oestradiol.

Numerous studies have been conducted to evaluate the effect of a treatment with $PGF_{2\alpha}$ or its analogues within 40 d of calving on reproductive performance of dairy cows. It is noteworthy that there is a wide disparity between the results (Burton & Lean, 1995). Young et al. (1984), for instance, reported a significant improvement in the first service conception rates of cows given $PGF_{2\alpha}$, whereas a study conducted by Macmillan et al. (1987) and including 1813 cows could not support these findings.

To shed some light on this issue, the overall objective of this study was to evaluate the quality and comparability of published literature and to summarize the effect of $PGF_{2\alpha}$ for the treatment of endometritis. Specifically we set out to test two hypotheses: (1) studies published are diverse in respect to relevant quality criteria such as control groups, blinding, randomization, and sample size and (2) the majority of trials reveal an improvement of the reproductive performance through the application of $PGF_{2\alpha}$ to cows with endometritis.

Materials and Methods

A comprehensive literature search was conducted on 4 August 2010 utilizing the search engine Vetseek (http://www.vetseek.info), databases Pubmed (http://www.pubmed.gov), Medline (http://www.medline.de), and Animal Production (http://www.ovid.com/site/catalog/DataBase/22.jsp) to identify literature related to the treatment of endometritis with prostaglandin in dairy cattle. The subject headings 'endometritis AND cattle', 'endometritis AND cattle AND prostaglandin' were used to include all articles written in English or German addressing the treatment of bovine endometritis with $PGF_{2\alpha}$. In addition, a systematic review of citations in the retrieved papers was carried out. We defined specific exclusion criteria to only include studies that focus on chronic endometritis, i.e. presence of a purulent (>50% pus) uterine discharge detectable in the vagina 21 d or more post partum (Sheldon et al. 2006). Furthermore, we excluded studies in which the animals received concomitant treatments with medications other than $PGF_{2\alpha}$. Also, book chapters, case studies, review articles and abstracts were excluded. Furthermore, publications describing aetiological, epidemiological, microbiological or nutritional results, clinical symptoms or diagnostic procedures were rejected. Articles not meeting the inclusion criteria, owing to wrong indexation, and those not obtainable through the internet, bibliographies or inter-lending services were excluded as well. If multiple publications were retrieved describing the same trial, those containing the least information were regarded as doublets and excluded. Retrieval and management of references was performed with Endnote (Version X3 for Windows, Thomson Reuters, New York, NY, USA).

The remaining publications were evaluated according to various evidence parameters utilizing an evaluation form developed by Arlt (2010) and recently validated by Simoneit et al. (2011). Relevant criteria of the study design such as sample size, the involvement of control groups, either untreated, placebo-treated or treated with a drug other than $PGF_{2\alpha}$, blinding and randomization were considered. Furthermore, type and definition of endometritis, diagnostic methods, the drug and dosage applied, route of application,

Table 3. Relevant criteria of 68 trials studying the efficacy of $PGF_{2\alpha}$ treatment of chronically endometritic cows

	Diagnosis performed (in%)			
Criterion	After 21.d p.p.† (*n* = 32)	Before or after 21.d p.p. (*n* = 20)	No exact date of diagnosis given (*n* = 16)	Total (%) (*n* = 68)
Control group	75·0	70·0	63·0	70·6
Untreated	18·8	25·0	25·0	22·1
Placebo	6·3	5·0	6·3	5·9
Reference group	65·6	60·0	50·0	60·3
Blinding				
Yes	9·4	0·0	6·3	5·9
No	81·3	100·0	93·8	89·7
Not specified	9·4	0·0	0·0	4·4
Randomization				
Yes	40·6	45·0	37·5	41·2
Computerized	9·4	20·0	6·3	11·8
By ear tag number	18·8	5·0	6·3	10·3
Alternate allocation	6·3	5·0	6·3	5·9
Not specified	6·3	15·0	25·0	13·2
No	50,0	50·0	37·5	47·1
Not specified	9·4	5·0	25·0	11·8
Randomization + control group	37·5	40·0	37·5	38·2
Computerized	9·4	20·0	6·3	11·8
By ear tag number	15·6	0·0	0·0	7·4
Alternate allocation	6·3	5·0	6·3	5·9
Not specified	6·3	15·0	18·8	13·2
Randomization, control group + blinding	6·3	0·0	6·3	4·4

† According to Sheldon et al. (2006)

number of treatments, treatment time relative to calving, and reproductive performance parameters, i.e. calving to first service interval, calving to conception interval and conception rate, were documented in a spreadsheet. Descriptive statistics were compiled using SPSS for Windows (Version 18.0; SPSS Inc., Munich, Germany).

Results

In total, 4393 publications were retrieved (Vetseek, 2369; Pubmed, 570; Medline, 565; Animal Production, 889). After excluding doublets (*n* = 1670), 2723 publications remained. According to the exclusion criteria, 2662 indexed articles had to be excluded resulting in 61 remaining publications which comprised 63 individual trials. Because 4 articles were retrieved through search by hand, a total of 65 publications, comprising 68 trials, met the inclusion criteria and were suitable for further analysis (Table 1).

According to Sheldon's (2006) definition of chronic endometritis, diagnosis had to be conducted later than 20 d post partum. However, several studies complied only partly with this time period (*n* = 20), whereas others did not provide an exact time of diagnosis at all (*n* = 16). To account for this variation, we decided to subdivide the studies according to their date of diagnosis.

More than half of all 68 trials (51·5%) were older than 20 years (Table 2). Trials that did not give a specific definition of endometritis made up 23·5% of all trials analysed. We found a sample size smaller than 50 in 16·2% of all trials and about one-third of the studies (36·8%) had included more than 200 animals. Overall, 70·6% of all trials included a control group (Table 3). Of those, 60·3% had a positive (a drug other than $PGF_{2\alpha}$), 22·1% an untreated, and 5·9% a placebo-treated control group. In 41·2% of all trials, the authors stated that allocation to treatment and control group had been conducted in a random manner. In 11·8% of all studies randomization was computerized, whereas 16·2% allocated the cows enrolled in an alternating order or with the help of ear-tag numbers, and 13·2% did not offer any details concerning the mode of randomization. Our investigation revealed that 38·2% of all trials were controlled and randomized. In this context, control groups were either untreated, placebo-treated or treated with a drug other than $PGF_{2\alpha}$. Trials were considered as randomized if the animals had reportedly been allocated to the various groups in random manner, i.e. by chance. Only 3 of those articles (4·4%) were also blinded.

Among the 68 trials, a wide variety of methods to diagnose the disease in question could be identified (Table 4). However, 13·2% did not specify the particular method used.

Table 4. Relevant diagnostic and therapeutic criteria of 68 trials studying the efficacy of $PGF_{2\alpha}$ treatment of chronically endometritic cows

	Diagnosis performed (in%)			
Criterion	After 21 d p.p.[†] ($n=32$)	Before or after 21 d p.p. ($n=20$)	No exact date of diagnosis given ($n=16$)	Total (%) ($n=68$)
Diagnostic methods				
External inspection[‡]	3·1	5·0	0·0	2·9
Rectal palpation	34·4	0·0	0·0	16·2
Vaginoscopy	3·1	0·0	0·0	1·5
External inspection[‡] + rectal Palpation	21·9	30·0	12·5	22·1
Rectal palpation + vaginoscopy	21·9	30·0	12·5	22·1
External inspection[‡], rectal palpation + vaginoscopy	6·3	20·0	6·3	10·3
Other	0·0	0·0	12·5	2·9
Imprecise information	3·1	10·0	18·8	8·8
Not specified	6·3	5·9	5·0	13·2
Multiple treatment(s)				
Yes	34·4	10·0	6·3	20·6
No	15·6	30·0	37·5	25·0
If necessary/partly	34·4	35·0	12·5	29·4
Not specified	18·8	25·0	37·5	25·0
Route of administration				
Intramuscular	59·4	75·0	62·5	64·7
Subcutaneous	3·1	0·0	0·0	1·5
Diverse routes used	9·4	5·0	37·5	5·9
Not specified	18·8	28·1	20·0	27·9
Definition of reproductive performance parameters given	25·0	25·0	0·0	19·1

[†] According to Sheldon et al. (2006)
[‡] External inspection of the vulvar region

Table 5. Reproductive performance parameters described in 68 trials studying the efficacy of $PGF_{2\alpha}$ treatment of chronically endometritic cows

	Results described (%)		
Criterion	As improved[†]	As significantly improved ($P<0·05$)	As not improved
Calving to first service interval ($n=22$)	36·4	22·7	4·5
Calving to conception interval ($n=30$)	50·0	23·3	20·0
Conception rate ($n=48$)	35·4	12·5	8·3

[†] According to the authors' conclusion

Concerning reproductive performance parameters, 19·1% of the studies provided a concise definition. By taking a closer look at the single parameters, it becomes obvious that the conclusions of the authors concerning an improvement are only partly proved as statistically significant (Table 5).

Similar observations were made when assessing reproductive performance parameters examined in randomized and controlled trials as well as randomized, controlled, and blinded trials (Table 6).

Considering high-level evidence studies for which a conception rate was calculated ($n=16$), 7, 7 and 2 articles respectively revealed a positive, none or a negative effect (Table 7). Of those 7 articles revealing a positive effect, only 3 showed statistical significance. Twenty-two of thirty articles which were attributed to a moderate or high evidence level did not demonstrate a statistically significant effect of a $PGF_{2\alpha}$ treatment. Six low-quality papers concluded a positive effect without statistical validation.

Discussion

The checklists introduced may also be useful for critical appraisal of published reviews, but they are not explicitly designed as quality assessment instruments to determine the quality of articles (Simoneit et al. 2011). Hence, for our study, we applied the evaluation form designed by Arlt et al. (2010).

One might question whether studies older than 20 years should be included in such systematic literature assessment since the dairy industry has changed considerably

Table 6. Reproductive performance parameters described in 68 trials studying the efficacy of $PGF_{2\alpha}$ treatment of chronically endometritic cows

Reproductive performance parameter	Randomized, controlled trials (%) ($n=25$)	Randomized, controlled, blinded trials (%) ($n=3$)
Calving to first service interval	40·0	33·3
Increase	8·0	33·3
Statistically significant	0·0	0·0
Decrease	16·0	0·0
Statistically significant	8·0	0·0
Calving to conception interval	52·0	33·3
Increase	4·0	0·0
Statistically significant	0·0	0·0
Decrease	24·0	33·3
Statistically significant	12·0	0·0
Conception rate	72·0	33·3
Increase	28·0	0·0
Statistically significant	12·0	0·0
Decrease	8·0	0·0
Statistically significant	0·0	0·0

Table 7. Effects on conception rate after $PGF_{2\alpha}$ treatment described in trials studying the efficacy of $PGF_{2\alpha}$ treatment of chronically endometritic cows

		Level of evidence[†]		
Effect of $PGF_{2\alpha}$ treatment	Total	Low[‡]	Moderate[§]	High[¶]
Positive, statistically significant	6	0	3	3
Positive, authors' assessment	15	6	5	4
None	9	0	2	7
Negative	7	1	4	2
Total	37	7	14	16

[†] According to Bassler and Antes (2000)
[‡] Level 1, i.e. randomized, controlled trials
[§] Level 2, i.e. well designed, controlled studies without randomization
[¶] Level 3, i.e. well designed, descriptive non-experimental studies

particularly in respect to housing, feeding, and management (LeBlanc et al. 2006). In the last two decades milk yield has increased by 39·2% (1990: 6705 kg/cow; 2009: 9333 kg/cow) (Blayney, 2002; USDA, 2010) and 45·2% (1990: 4857 kg/cow; 2010: 7050 kg/cow) (BMELV, 1992; ADR, 2010) in the United States and Germany, respectively. Thus, it can be questioned whether trials conducted more than 20 years ago support adequate evidence for specific recommendations in livestock health care today. On the other side, these studies provided observational evidence for the efficacy of $PGF_{2\alpha}$ and were a relevant component of the development of the current best-practice standard.

The majority of the trials evaluated had insufficient detail of study design. In 16·2% of the trials the total sample size was smaller than 50, and only 36·8% had included more than 200 animals. More important than the absolute number of animals included, is the question whether the sample size of each group was large enough to test the proposed research hypothesis. None of the authors, however, mentioned a calculation of sample size for the study. Therefore, a final evaluation of the adequacy of the sample size is not possible.

Our investigation revealed that only about one-third of all trials was controlled and randomized. The mean sample size of those trials was 165·3 ± 99. Untreated or placebo-treated control groups were included in only 28% of all trials. An overall shortage of randomized, controlled trials in veterinary medicine was also described by Kastelic (2006). This deficiency might be due to the high costs involved and ethical issues related to leaving diseased animals untreated.

A computer-generated random allocation of animals to treatment groups was implemented in only about a fourth of the randomized trials. The other trials allocated their animals according to ear-tag numbers or in an alternating order or did not offer any details concerning the mode of randomization at all.

According to Lund et al. (1994), a truly random allocation scheme (assured by computer or random number table) implies a predetermined probability for every potential study subject for assignment to a treatment group. In contrast, systematic assignments, e.g. based on days of the week, are not recommended because they are vulnerable to manipulation. Allocation to study groups based on ear-tag numbers, however, can be considered as random because those numbers are assigned at birth and thus long before the study and without any fore knowledge of it.

We speculate that the allocation of animals in studies that claimed to be randomized but did not provide any information about the method (13·2%) should a priori be considered as not randomized but as haphazard. However, missing data, especially regarding older studies, could be due to incomplete reporting. Therefore, studies with missing data should not a priori be judged as low quality.

Randomized, controlled clinical trials provide the highest validity of results obtained (Schulz et al. 1995). However, this specific study design is not applicable to every question (Antes, 1998; Smith & Pell, 2003). For example, it might be unethical to include an untreated control group if that would inevitably imply serious distress, suffering or even death for the animals involved (Sayre et al. 2010). The process of randomization helps to assure that treatment groups are comparable with respect to known and unknown factors that could influence the primary outcome variable of the study (Lund et al. 1994). Our finding that only 38·2% of the trials were controlled and randomized clearly limits the strength of evidence of $PGF_{2\alpha}$ as treatment of bovine endometritis.

Conclusions or treatments inferred from uncontrolled and unrandomized trials are in general less likely to be true than those based on randomized controlled trials. In our analysis, we found a considerable percentage (25·0%) of uncontrolled studies that described reproductive performance

parameters. Drawing inference and implementing treatment decisions based on such results, however, should be considered carefully. A wide variety of diagnostic methods were applied in the 68 trials evaluated. It has been demonstrated that different methods to diagnose endometritis differ in their sensitivity (Drillich et al. 2002; LeBlanc et al. 2002b).

The classification of cytological endometritis and purulent vaginal discharge has been most recently described (Runciman et al. 2008; Dubuc et al. 2010a). Owing to a shortage of studies based on this new classification, we decided to use the definition by Sheldon (2006).

Specific and repeatable exclusion criteria were defined to exclude studies that did not focus on chronic endometritis, i. e. after 21 d after parturition (Sheldon et al. 2006). Several studies, however, complied only partly with this time period and had also enrolled cows earlier, whereas others did not provide an exact time of diagnosis at all. Therefore we decided to classify studies according to their time of diagnosis. This classification was important because several authors observed a significant self-cure rate in cows with chronic endometritis during the first weeks post partum. The self-cure rate ranged from 92% in the first week to 25% in the seventh week post partum (Falkenberg & Heuwieser, 2005; Hirsbrunner et al. 2006). A considerable inconsistency existed also regarding the calculation of the pregnancy outcome. Some authors assessed overall conception rates, whereas others calculated a first service conception rate or a pregnancy rate. Overall, only 19·1% of all studies provided a concise definition of reproductive performance parameters used. In addition, a specific definition of endometritis was not given in 23·5% of all trials analysed. This lack of homogeneity to some extend limits comparability of study results.

Our results demonstrate that an impressive percentage of studies addressing the efficacy of $PGF_{2\alpha}$ are severely flawed in the study design, and that comparability between publications is limited owing to considerable differences. In human medicine intensive examination of the appraising of available literature has been conducted in the framework of evidence-based medicine (EBM). However, Arlt & Heuwieser (2010) point out the need for further appraisal of scientific publications in veterinary medicine.

One objective of the study was to summarize the effect of $PGF_{2\alpha}$ for the treatment of endometritis. Of those trials assessing reproductive performance parameters (calving to first service interval, calving to conception interval, conception rate), statistically significant effects on reproductive performance were reported only in a small fraction of trials. Twenty-two of 37 studies that evaluated conception rate were attributed to a moderate or high evidence level and did not show any statistically significant effect of $PGF_{2\alpha}$ treatment (Table 7). A positive effect was revealed by 21 articles. Of those, only 6 reported a statistical significance. However, it is stressed by different authors that different factors, such as the time of diagnosis (LeBlanc et al. 2002b), the severity of endometritis, or the additional occurrence of other puerperal disorders (Burton & Lean, 1995) may influence the efficacy of a $PGF_{2\alpha}$ treatment. Based on our results, we propose a tendency of low-quality papers concluding a positive effect without statistical validation ($n = 6$). However, it is important to emphasize that low-quality trials do not necessarily show larger effects of a certain intervention (Kunz & Oxman, 1998). We conclude that the evidence for the efficacy of $PGF_{2\alpha}$ for the treatment of chronic bovine endometritis is limited. In combination with most recent results (Dubuc et al. 2010b), we suggest that the use of $PGF_{2\alpha}$ as a standard treatment for endometritis should be critically reconsidered. Further research in the form of controlled, randomized and blinded trials is required to assess and quantify the efficacy of this treatment.

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