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Therapy of Bovine Endometritis with Prostaglandin $F_{2\alpha}$ - An Evidence Based Approach

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Peggy Haimerl
Tierärztin aus Altenburg

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Meiner Familie & Bakiri

„Manche Männer bemühen sich lebenslang, das Wesen einer Frau zu verstehen. Andere befassen sich mit weniger schwierigen Dingen z.B. der Relativitätstheorie."

(Albert Einstein)

1. INTRODUCTION

1.1 Evidence based medicine

The decision making process of veterinarians as well as farm personnel and animal scientists should be based on objective information (Holmes and Cockcroft, 2004). However, today's doctors and scientists are confronted with a large number of unstructured information every day (Smith, 1996; Eisend, 2004). Thus, it is almost impossible for them to obtain and maintain an overview of all relevant research results (Eisend, 2004). Consequently, with regard to this flood of data, relevant information has to be identified reliably (Windeler und Holle, 1997). In order to accomplish this, a critical consideration of recently published findings is necessary, which is not one of the core competences of doctors (Williams, 2007). Often several studies are available on a given question, which sometimes even show contradictory results (Eisend, 2004). Due to this challenging situation, 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 and Heuwieser, 2005).

1.1.1 Stages of evidence

In order to categorize the available publications about medical issues with respect to their quality, Bassler and Antes (2000) suggest the distinction between four stages of evidence (Table 1). Stage Ia, which represents the highest level of evidence, refers to meta-analyses of randomized, controlled studies. Evidence gained from at least one randomized, controlled study is assigned to stage Ib. Well designed, controlled studies without randomization create evidence classified as evidence-stage IIa, whereas stage IIb refers to well designed, quasi-experimental studies. 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.

Table 1: Levels of research evidence (Bassler, and Antes, 2000)

Stage of evidence	Type of evidence
I	Meta-analyses of randomized, controlled trials (Ia) Randomized, controlled trials (Ib)
II	Controlled trials without randomization (IIa) Well designed, quasi-experimental studies (IIb)
III	Well-designed, non-experimental descriptive studies (e.g. case-control studies)
IV	Opinions of respected authorities, reports of expert committees, clinical experience

1.1.2 Evidence based veterinary medicine

Evidence based medicine emerged in the 1970s in the field of human medicine. However, it is a relatively new concept in veterinary medicine (Lloret, 2009) which is still developing at a slow pace (Holmes and Cockcroft, 2004; Vandeweerd et al., 2012). One reason for this hesitant development is the considerably smaller amount of veterinary scientific literature than for human medicine. Beyond that, veterinary scientific articles seem to be of lower quality than those published in the field of human medicine (Cockcroft and Holmes, 2003a). Specifically, 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 (Holmes and Cockcroft, 2004). This hypothesis has been supported by several authors (Mair and Cohen, 2003; Arlt et al., 2010; Simoneit et al., 2011) who demonstrated that in veterinary medicine the increase of knowledge is mainly based on reviewing field reports rather than randomized, controlled clinical studies. With respect to human medicine, the Cochrane Collaboration is one of the leading organisations in the field of evidence based medicine, which by offering systematic reviews and clinical trials, helps practitioners to make medical decisions (Dicty, 2007). Ziegler et al. (2004) even assume that the Cochrane Controlled Trial Register is the most comprehensive collection of controlled clinical trials in the field of human medicine. Beyond that, Gambrill (1999) showed that there are about 60 % more randomized, controlled clinical trials available from the Cochrane Collaboration than there are from MEDLINE. Nevertheless, randomized, controlled double blind studies are said to represent the gold standard with regard to the evaluation of a certain treatment (Kastelic, 2006). In the course of literature research concerning reproductive medicine of dogs done by Dicty (2007), case studies and opinions of experts made up to 68.6 % of the scientific articles

found. According to Keene (2000), the main reason for the low number of well-designed clinical trials in veterinary medicine is the shortage of subjects.

In addition to this lack of randomized trials, the reporting of those available in conventional small-animal medicine is often incomplete (Lund et al., 1998). Nevertheless, due to the shortage of high evidence, veterinarians cannot afford to ignore uncontrolled or not randomized studies (Keene, 2000).

Besides the dearth of high evidence studies, there is remarkable variation concerning the quality of studies in veterinary science, resulting in an insufficient comparability of the various trials (Cockcroft and Holmes, 2003a).

To test this hypothesis and underlay it with recent data, my first study aimed at evaluating the quality and comparability of published veterinary literature. Due to the high prevalence of clinical endometritis in cows (up to 57.7%) (Sheldon, 2009), its immense negative impact on reproductive performance resulting in high opportunity costs for the farmers (Plaizier et al., 1998; LeBlanc et al., 2002; LeBlanc, 2008), and the fact that numerous studies have been conducted to evaluate the effect of a treatment with $PGF_{2\alpha}$ or its analogues (Burton and Lean, 1995), I decided to set the focus on the $PGF_{2\alpha}$ treatment of clinical endometritis in cows.

1.2 Endometritis

Clinical endometritis in cattle is defined as the presence of a purulent (> 50% pus) uterine discharge detectable in the vagina 21 days or more postpartum or mucopurulent (approximately 50% pus, 50% mucus) discharge detectable in the vagina after 26 days postpartum (Sheldon et al., 2006). Most recently, following a study conducted by Runciman et al. (2008), 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).

There is a wealth of information on the treatment of endometritis and this subject has been reviewed extensively by several authors (Gilbert and 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).

Hence, I 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

2) The majority of trials reveal an improvement of the reproductive performance through the application of $PGF_{2\alpha}$ to cows with endometritis.

The results of this study can be found in the following publication:

P. Haimerl, S. Arlt, and W. Heuwieser. (2012): Evidence based medicine: Quality and comparability of clinical trials investigating the efficacy of Prostaglandin $F_{2\alpha}$ for the treatment of bovine endometritis. The J. Dairy Res. 79:287-296.

Due to the wide disparity between research results concerning the endometritis treatment with $PGF_{2\alpha}$ or its analogues (Burton and Lean, 1995), my second study aimed at a quantitative evaluation of the efficacy of the $PGF_{2\alpha}$ treatment by means of meta-analysis.

The results of this study are accepted and will be published in the Journal of Dairy Science:

P. Haimerl, S. Arlt, and W. Heuwieser. (2013): Therapy of Bovine Endometritis with Prostaglandin $F_{2\alpha}$: A Meta-analysis. J. Dairy Sci. (accepted).

1.3 Meta-analyses

Meta-analyses are systematic summaries of a large collection of results from individual studies and statistically analyse those results from multiple individual studies (Glass, 1976). The principal aim of a meta-analysis is to provide an objective quantitative assessment of previously published data as well as to increase the precision of the estimate of a treatment effect by increasing the sample size and thus increasing the statistical power (Lean et al., 2009). Due to that, the results of meta-analyses are said to provide the greatest reliability when applied to the entire population (Arlt and Heuwieser, 2005, Keene, 2000). Also the Cochrane Collaboration considers the results of meta-analyses as the highest level of evidence (Maier and Möller, 2005). This way, meta-analyses help scientists in integrating and evaluating results while they also can support practitioners in decision making (Eisend, 2004). Meta-analyses are said to represent a powerful means for combining the data from several trials, and are especially useful when there is a conflict in the literature and when the sample sizes in individual trials are too small to detect a statistically significant result (L'Abbe et al., 1987; Peto, 1987). According to Lam and Kennedy (2005), meta-analyses of high quality can overcome many of the drawbacks of individual randomized controlled trials and qualitative reviews. They can reduce bias, provide adequate power to demonstrate real differences in outcomes, and resolve the results of inconsistent studies.

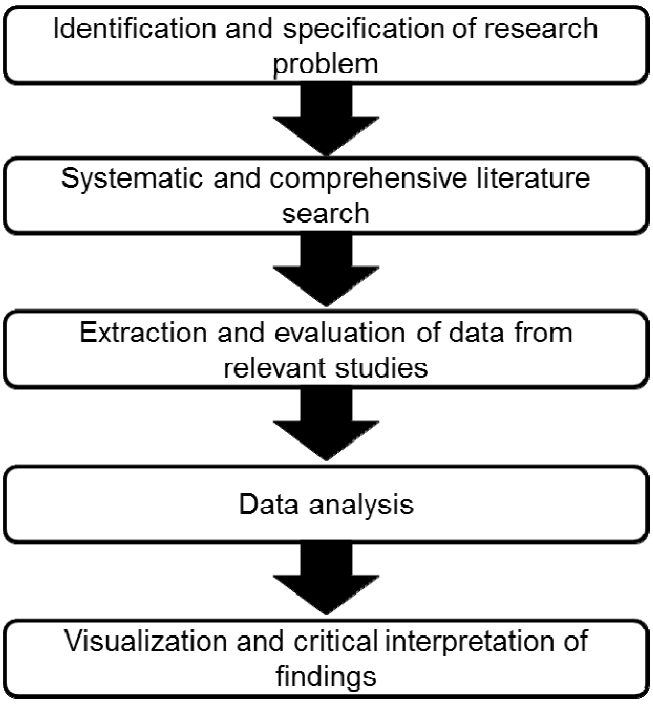
1.3.1 History of meta-analyses

The very first summarization of results that can be called meta-analysis or systematic review was conducted more than one hundred years ago by Karl Pearson, a British mathematician (Pearson, 1904). However, the term meta-analysis was introduced as an analysis of analyses only in 1976 by Glass, an American statistician and researcher working in educational psychology and the social sciences (Glass, 1976). Since that hour of birth in the seventies there has been a steady increase in the importance of meta-analyses (Eisend, 2004). Hence, the unmanageable amount of medical information was already criticized by Cochrane in 1972. He also complained about the lack of reliable summarizations of available findings being responsible for the difficulties in making decisions on the basis of current and valid information (Cochrane, 1972). Especially with regard to psychological and medical literature, there has been an immense augmentation concerning the published meta-analyses (Streiner, 2005). As stated by Barker (2005), in July 2005 there were already more than 2300 systematic reviews published in human medicine.

1.3.2 Steps in meta-analyses

According to Eisend (2004), the prototypical meta-analysis should undergo the following five steps (Table 2). As a first step, one should clearly formulate a clinical question, followed by a systematic and comprehensive search for relevant literature. In a third step, data from the included literature is extracted and evaluated according to predefined parameters. In the course of the data analysis, the extracted data are combined by using statistical techniques to obtain a pooled estimate of the treatment effect (Barker and Carter, 2005). Finally, findings should be visualized (e.g. by forest plots) and critically interpreted. In conclusion, a meta-analysis is the statistical combination of at least two studies to generate an estimate of the magnitude of the effect of the intervention under investigation (Lam and Kennedy, 2005). The results of meta-analyses are said to provide the greatest reliability when applied to the entire population (Arlt and Heuwieser, 2005).

Figure 1: Steps in meta-analysis (Eisend, 2004)



1.4 Implementation of evidence based medicine in veterinary practice

In daily practice, a veterinarian has to judge information and decide whether it can be adequately implemented for a given case. In this context, it is of top priority to base decisions on the latest and soundest scientific findings. According to Antes et al. (1999), the only way to avoid a misinterpretation of the effect of a certain therapy is a broad identification of all relevant studies concerning one particular question.

A fruitful source of information is represented by the bibliographical databases PubMed and Vet-CD (Veterinary Science Database), which is demonstrated by the fact that PubMed offers about twelve million pieces of literature acquired from 4.600 international biomedical journals (Motschall and Falck-Ytter, 2005). According to Grindlay et al. (2012), who analysed nine bibliographic databases whose subject scope included topics relevant to veterinary medicine and science, CAB Abstracts covered the highest percentage of the 121 journals considered. Nevertheless, with respect to literature research, several difficulties exist. First of all, a search for a certain piece of information often requires an amount of time that cannot be provided by a practitioner. Secondly, one precondition for the successful use of an online database is comprehensive knowledge about strategies and nomenclature concerning the search for literature (Hunt et al., 1998). Hence, in order to use such a database properly, a time-consuming familiarization with specific instruction manuals as well

as literature on literature research is necessary beforehand (Gallagher et al., 2002; Motschall et al., 2003; Türp et al., 2003; Kranke, 2004; Motschall and Falck-Ytter, 2005; Motschall et al., 2006). This, however, is, due to the shortage of time, a challenge for most veterinary practices. Finally, numerous articles found via internet are not available free of charge (Dicty, 2007). Thus, it can be assumed that literature-databases are used only rarely or even not at all by veterinarians and pet owners (Arlt, 2002).

However, the comprehensiveness of literature research alone does not ensure a truthful result regarding the effect of a certain therapy. Several other aspects, especially concerning quality assessment and the source of information have to be taken into account as well. 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 and Heuwieser, 2005). Since databases do only provide but not evaluate literature, a veterinarian who is not practiced in dealing with scientific literature is hardly able to evaluate the quality of studies and their results (Dicty, 2007). Also responsible for this drawback is the fact that in veterinary medicine some scientific journals do not make high demands on the quality of their published articles (Arlt, 2002). Nevertheless, peer reviewing is a system for improving manuscripts prior to publication and provides the framework for identifying the scientific and written quality of papers (Adler, 2012). This way, ideally, peer review is considered as a method for guaranteeing and improving scientific work (Vinther and Rosenberg, 2013).

One possible way to approach this problem is to assess the quality of a certain publication with the help of the standardized questionnaire developed by Dicty (2007). In conclusion, the utilization of comprehensive literature-databases does cause inconvenience for unskilled people. Not only due to insufficient use but also to inappropriateness of the databases itself as well as the missing quality assessment, practitioners do still show a low level of competence in using as an example MEDLINE in order to answer clinical questions (Hersh et al., 2002).

Cockcroft and Holmes (2003b) evaluated different sources of information regarding relevance, validity, labour input and usefulness in a survey (Table 2). According to the answers of physicians, systematic reviews as well as exchange of ideas with colleagues are of high relevance, whereas journal articles and the internet are not very relevant as information sources. Concerning validity, systematic reviews and journal articles are the leading sources, while exchange of ideas with colleagues offer only moderate and information found on the internet even low validity. Remarkably, journal articles and information gained on the internet involve high labour input but only low usefulness.

Table 2: Sources of information used by human doctors (Cockcroft and Holmes, 2003b)

Information source	Relevance	Validity	Work to obtain information	Usefulness
Systematic review	High	High	Low	High
Journal article	Low	High	High	Low
Internet	Low	Low	High	Low
Colleagues	High	Moderate	Low	High or moderate

To outline the current assessment and employment of evidence-based veterinary medicine (EBVM), we surveyed practitioners concerning continuing education and their skills in obtaining and evaluating scientific information.

The results of this study are accepted and will be published in the Journal "Tierärztliche Praxis":

P. Haimerl, S. Arlt, and W. Heuwieser. (2013):
Entscheidungsfindung in der tierärztlichen Praxis.
Tierärztl. Prax. (accepted).

2. RESEARCH PAPERS

2.1 Evidence based medicine: Quality and comparability of clinical trials investigating the efficacy of Prostaglandin $F_{2\alpha}$ for the treatment of bovine endometritis

P. Haimerl, S. Arlt, and W. Heuwieser. 2012. The J. Dairy Res. 79:287-296.

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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

P. Haimerl,* S. Arlt,* and W. Heuwieser*[1]

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

[1]Corresponding author: Wolfgang Heuwieser, e-mail: w.heuwieser@fu-berlin.de

2.1.1 Summary

The 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. It has been postulated that there is a dearth of high level evidence research results in veterinary medicine. Also, there is a remarkable 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 utilising 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 was 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 $PGF_{2\alpha}$.

2.1.2 Keywords

Endometritis, treatment, evidence, dairy cattle

2.1.3 Introduction

The decision making process of practicing veterinarians as well as farm personnel and animal scientists should be based on objective information (Holmes and 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 and Heuwieser, 2005).

However, Holmes and 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 and 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 how to conduct high quality studies or meta-analyses (e.g. Lean, I. J., A. R. Rabiee, T. F. Duffield, and I. R. Dohoo. 2009. Invited review: Use of meta-analysis in animal health and reproduction: methods and applications. J Dairy Sci 92:3545-3565). Also, many very well conducted studies eligible for performing meta-analyses have been published during the last 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 and Heuwieser, 2005). Four stages of evidence have been suggested to categorize studies with respect to their quality (Bassler and 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. 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 remarkable variation concerning the quality of studies in veterinary science, resulting in an insufficient comparability of the various trials (Cockcroft and Holmes, 2003a).

Clinical endometritis in cattle is defined as the presence of a purulent (> 50% pus) uterine discharge detectable in the vagina 21 days or more postpartum or mucopurulent (approximately 50% pus, 50% mucus) discharge detectable in the vagina after 26 days postpartum (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 postpartum 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 and 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 estradiol.

Numerous studies have been conducted to evaluate the effect of a treatment with $PGF_{2\alpha}$ or its analogues within 40 days of calving on reproductive performance of dairy cows. It is noteworthy that there is a wide disparity between the results (Burton and Lean, 1995). Young and others (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 and others (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.

2.1.4 Material and methods

A comprehensive literature search was conducted on 04th of 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 so that only studies that focus on chronic endometritis, i.e. presence of a purulent (> 50% pus) uterine discharge detectable in the vagina 21 days or more postpartum (Sheldon et al., 2006) were included. Furthermore, we excluded studies in which the animals received concomitant treatments with other medications 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, due 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 (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, 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).

2.1.5 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 was suitable for further analysis (Table 1).

According to Sheldon's (2006) definition of chronic endometritis, diagnosis had to be conducted later than 20 days postpartum. 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 which 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. 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 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.

2.1.6 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 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 per cow; 2009: 9333 kg per cow) (Blayney, 2002; USDA, 2010) and 45.2% (1990: 4857 kg per cow; 2010: 7050 kg per 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 on 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 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 and 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 which 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). Due to a shortage of studies based on this new classification, we decided to use the definition by Sheldon (2006) (s.Ll 71-74).

Specific and repeatable exclusion criteria were defined to exclude studies that did not focus on chronic endometritis, i.e. after 21 days 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 postpartum. The self cure rate ranged from 92% in the first week to 25% in the seventh week postpartum (Falkenberg and 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 analyzed. 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 due to considerable differences. In human medicine intensive examination of appraising available literature has been conducted in the framework of evidence based medicine (EBM). However, Arlt and 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 and 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 and 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 to critically reconsider the use of $PGF_{2\alpha}$ as a standard treatment for endometritis. Further research in form of controlled, randomized and blinded trials is required to assess and quantify efficacy of this treatment.

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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 days postpartum	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	Thesis, Tierarztliche Hochschule, Hannover, Germany

		of metacresolsulfonic acid and formaldehyde ("Lotagen")	
Callahan, C.J.	1993	Treatment of postpartum 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 postpartum 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
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 .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 .1. Individual Application of the Drugs	Tierärztliche Umschau
Hüntelmann, C.	2005	Investigation on the influence of time of postpartum 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	Veterinary Record

		cloprostenol	
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)	Postpartum plasma PGF metabolite profile in cows with dystocia and/or retained placenta, and effect of fenprostalene on uterine involution and reproductive performance	The Journal of Veterinary Medical Science
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	Reproduction in Domestic Animals

		reproductive performance in cows	
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 postpartum 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

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

Criterion	Diagnosis performed (in %)			Total (%)
	After 21.d pp.[1] (n = 32)	Before or after 21.d pp. (n = 20)	No exact date of diagnosis given (n = 16)	(n = 68)
Year of publication				
≤ 1990	53.1	45.0	56.3	51.5
1991 to 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 to 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 to 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

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

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

Criterion	Diagnosis performed (in %)			Total (%)
	After 21.d pp.[1] (n = 32)	Before or after 21.d pp. (n = 20)	No exact date of diagnosis given (n = 16)	(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

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

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

Criterion	Diagnosis performed (in %)			Total (%)
	After 21.d pp.[1] (n = 32)	Before or after 21.d pp. (n = 20)	No exact date of diagnosis given (n = 16)	(n = 68)
Diagnostic methods				
External inspection[2]	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[2] + rectal palpation	21.9	30.0	12.5	22.1
Rectal palpation + vaginoscopy	21.9	30.0	12.5	22.1
External inspection[2], 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

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

[2] 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

Criterion	Results described (%)		
	As improved[1]	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

[1] According to the author's conclusion

Table 6. Reproductive performance parameters described in 68 trials studying the efficacy 4 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

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

[1] According to Bassler and Antes (2000)

[2]Level 1, i.e. randomized, controlled trials

[3]Level 2, i.e. well designed, controlled studies without randomization

[4]Level 3, i.e. well designed, descriptive non-experimental studies

2.2 Therapy of Bovine Endometritis with Prostaglandin $F_{2\alpha}$: A Meta-analysis

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Therapy of Bovine Endometritis with Prostaglandin $F_{2\alpha}$: A Meta-analysis

P. Haimerl,* S. Arlt,* and W. Heuwieser*[1]

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

[1]Corresponding author: Wolfgang Heuwieser, e-mail: w.heuwieser@fu-berlin.de

2.2.1 Abstract

The objective of the conducted meta-analysis was to assess the efficacy of the treatment of bovine endometritis with $PGF_{2\alpha}$ by statistical means. Postpartum uterine infections have a high prevalence and an immense negative impact on reproductive performance in dairy cattle. Due to a wide discordance between research results, a meta-analysis of the efficacy of the treatment of bovine endometritis with $PGF_{2\alpha}$ was conducted. A comprehensive literature search was performed utilizing online databases revealing a total of 2,307 references. In addition, five articles were retrieved by reviewing citations. After applying specific exclusion criteria and evaluating specific evidence parameters, a total of five publications, comprising six trials, were eligible for being analysed by means of meta-analysis. Data for each trial were extracted and analysed using meta-analysis software Review Manager 5.1. Estimated effect sizes of $PGF_{2\alpha}$ were calculated on calving to first service and calving to conception interval. $PGF_{2\alpha}$ treatment of cows with chronic endometritis had a negative impact on both reproductive performance parameters. Heterogeneity was substantial for calving to first service and calving to conception interval [I^2 (measure of variation beyond chance) = 100% and 87%, respectively]; therefore, random effects models were used. Sensitivity analysis as well as subgroup analysis showed that the performance of randomization was influential in modifying effect size of $PGF_{2\alpha}$ treatment. The funnel plot illustrated a publication bias towards smaller studies that reported a prolonged calving to conception interval after a $PGF_{2\alpha}$ treatment. We conclude that the investigation of this subject by means of meta-analysis did not reveal an improvement of reproductive performance of cows with endometritis after treatment with $PGF_{2\alpha}$. Furthermore, there is a shortage of comparable high quality studies investigating reproductive performance after $PGF_{2\alpha}$ treatment of cows with chronic endometritis.

2.2.2 Keywords

meta-analysis, endometritis, Prostaglandin $F_{2\alpha}$, dairy cow

2.2.3 Introduction

Postpartum uterine infections are a frequent disorder in dairy cattle with a prevalence up to 57.7% (Sheldon, 2009). In addition, they are reported to have an immense negative impact on reproductive performance resulting in high opportunity costs for the farmers (Plaizier et al., 1998; LeBlanc et al., 2002; LeBlanc, 2008).

Clinical endometritis in cattle is defined as the presence of a purulent (> 50% pus) uterine discharge detectable in the vagina 21 days or more postpartum or mucopurulent

(approximately 50% pus, 50% mucus) discharge detectable in the vagina after 26 days postpartum (Sheldon et al., 2006).

The amount of literature addressing the treatment of endometritis is huge and this subject has been reviewed by several authors (Gilbert and Schwark, 1992; Olson, 1996; Azawi, 2008; Lefebvre and Stock, 2012). Nevertheless, 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, $PGF_{2\alpha}$ and estradiol. Since self cure rate is reported to range from 92% in the first week to 25% in the seventh week postpartum (Falkenberg and Heuwieser, 2005; Hirsbrunner et al., 2006), some authors question the necessity of any treatment at all. However, limited information exists on the proportions of cows that spontaneously recover (Dubuc et al., 2011).

The effect of a treatment with $PGF_{2\alpha}$ or its analogues within 40 days after calving on reproductive performance has been investigated in several studies (Haimerl et al., 2011). Remarkably, there is a wide disparity between the results obtained (Burton and Lean, 1995). Young and others (1984), for instance, reported a significant improvement in the first service conception rates of 64 cows treated with $PGF_{2\alpha}$ compared to 64 untreated controls. Another study conducted by Macmillan et al. (1987) including 1,813 cows could not support these findings. According to a most recent study conducted by Dubuc et al. (2011), an administration of $PGF_{2\alpha}$ at both five and seven weeks postpartum did not mitigate the effects of cytological endometritis or purulent vaginal discharge on reproductive performance. Thus, the authors postulate that clinical approaches to treatment of chronic postpartum reproductive tract infection and inflammation should be reassessed.

The unmanageable amount of medical information was already criticized by Cochrane in 1972. He also complained about the lack of reliable summaries of available findings, such as meta-analyses. Such situations lead to difficulties in making decisions on the basis of current and valid information (Cochrane, 1972). Meta-analyses are systematic summaries of a large collection of results from individual studies and statistically analyse those results from multiple individual studies (Glass, 1976). According to Eisend (2004), the prototypical meta-analysis should undergo the following five steps. As a first step, one should clearly formulate a clinical question, followed by a systematic and comprehensive search for relevant literature. In a third step, data from the included literature is extracted and evaluated according to predefined parameters. In the course of the data analysis, the extracted data are combined by using statistical techniques to obtain a pooled estimate of the treatment effect (Barker and Carter, 2005). Finally, findings should be visualized (e.g. by forest plots) and critically interpreted. In conclusion, a meta-analysis is the statistical combination of at least two studies to generate an estimate of the magnitude of the effect of the intervention

under investigation (Lam and Kennedy, 2005). Due to that, the results of meta-analyses are said to provide the greatest reliability when applied to the entire population (Arlt and Heuwieser, 2005). The principal aim of a meta-analysis is to provide an objective quantitative assessment of previously published data as well as to increase the precision of the estimate of a treatment effect by increasing the sample size and thus increasing the statistical power (Lean et al., 2009). Furthermore, meta-analyses can be conducted to identify and investigate heterogeneity in the results of the included studies, based on factors such as the design and sample variables. Finally, meta-analyses can be executed for the purpose of resolving conflicts among studies and developing new directions for research (L'Abbe et al., 1987; Henry and Wilson, 1992; Wilson and Henry, 1992).

Due to the frequent occurrence of postpartum uterine infections, its economic impact as well as a wide discordance between research results concerning its therapy, a meta-analysis of the efficacy of the treatment of bovine endometritis with $PGF_{2\alpha}$ was conducted.

2.2.4 Materials and methods

A comprehensive literature search was conducted on 04th of 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 addressing the treatment of bovine endometritis with $PGF_{2\alpha}$. In addition, a systematic review of citations in the retrieved papers was carried out.

Selection by Inclusion and Exclusion Criteria

Specific exclusion criteria were defined to exclude studies that were not written in English or German or did not focus on chronic endometritis, i.e. equal to and after 21 days after parturition (Sheldon et al., 2006). In addition, studies in which the animals received concomitant treatments with other medications than $PGF_{2\alpha}$ were excluded. 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, due 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).

In order to examine quality and comparability, the remaining publications were evaluated according to various evidence parameters utilizing an evaluation form developed by Arlt et al. (2010) and recently validated by Simoneit et al. (2011). Relevant criteria of the study design such as sample size, the involvement of control groups (i.e. untreated, placebo treated, treated with another drug), blinding and randomization were considered. Inclusion criteria for being considered for the meta-analytic investigation were the presence of an untreated control group and the calculation of calving to first service interval (CFSI) or calving to conception interval (CCI) as well as the respective standard deviations.

Statistical Analysis

Data for each trial meeting those criteria were extracted and analysed using meta-analysis software Review Manager (Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011. Denmark).

Estimated effect sizes of $PGF_{2\alpha}$ were calculated on CFSI and CCI applying the effect size method (Hedges and Olkin, 1985). The effect size is the difference between the treatment and control groups for the number of days open, divided by the pooled standard deviation (Hedges and Olkin, 1985). A negative effect size indicates that a greater percentage of the treated cows have fewer days open than the untreated cows. Effect sizes were calculated for each study. In addition, an overall effect size, weighted by sample size, was calculated. Since the extracted variables were continuous, a weighted mean difference and 95% confidence interval (95% CI) was calculated for each study outcome (Hedges and Olkin, 1985). Variation in experiment level effect size was assessed with a χ^2 test for heterogeneity (Duffield et al., 2008).

Degree of heterogeneity of results among trials was quantified using the I^2 statistic (Higgins et al., 2003). The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance. Where Q is the χ^2 heterogeneity statistic and k is the number of trials, I^2 was calculated as

$$I^2 = \frac{Q - (k-1)}{Q} * 100\ \%\,.$$

Negative values of I^2 were put equal to zero; consequently, I^2 lay between 0 and 100%. A value greater than 50% may be considered substantial heterogeneity (Duffield et al., 2008).

As significant heterogeneity was found, results were reported using the random effects model and potential causes of the heterogeneity were sought. A random-effects meta-

analysis assumes that there is a normal distribution of the study effects. Sources of heterogeneity of response were explored using subgroup analysis. Subgroup analysis was pre-specified and conducted by considering aspects of study design like the way of allocation to treatment and control groups as well blinding. In this context, subgroup A and B represent the randomized and the non-randomized trials, respectively. Blinded trials were allocated to subgroup C while subgroup D comprised those not blinded. In addition, subgroups were formed according to the presence of statistically significant effects and the applied $PGF_{2\alpha}$ derivative, Dinoprost (subgroup E), Cloprostenol (subgroup F) or Tiaprost (subgroup G). Due to the fact that the randomized trials were those showing statistically significant effects, subgroups A and B additionally reflect the trials showing significant and non-significant effects, respectively.

To investigate the possible impact of large weight on the summary estimated effect obtained from the meta-analysis, a sensitivity analysis was performed considering the effect of a $PGF_{2\alpha}$ treatment on CFSI and CCI by eliminating the studies with the largest weights one by one.

Forest plots were used to visually display the estimated effect size (Z), 95% confidence intervals, and study weights. The presence of publication bias was investigated graphically using funnel plots in which the size of effect for each treatment and control group comparison was plotted against its standard error and the resulting plot observed for deficiencies in predicted funnel shape.

2.2.5 Results

In total, 4,393 publications were retrieved (Vetseek, 2369; Pubmed, 570; Medline, 565; Animal Production, 889). After excluding doublets (n = 2,086), 2,307 publications remained.

Specific exclusion criteria were defined to exclude studies that were not written in English or German (n = 905) or did not focus on chronic endometritis, i.e. equal to and after 21 days after parturition (Sheldon et al., 2006) (n = 725). In addition, studies in which the animals received concomitant treatments with other medications than $PGF_{2\alpha}$ were excluded (n = 358). Also, book chapters (n = 44), case studies (n = 36), review articles (n = 23), and abstracts (n = 1) were excluded. Furthermore, publications describing aetiological, epidemiological, microbiological or nutritional results, clinical symptoms or diagnostic procedures were rejected (n = 177). Articles not meeting the inclusion criteria, due to wrong indexation, and those not obtainable through the internet, bibliographies or inter-lending services (n = 32) were excluded as well. If multiple publications were retrieved describing the same trial, those containing the least information were regarded as doublets and excluded (n

= 6). In summary, 2,246 indexed articles had to be excluded according to the exclusion criteria, resulting in 61 remaining publications which comprised 63 individual trials. Because four articles were retrieved through search by hand, a total of 65 publications, comprising 68 trials, met the inclusion criteria. After applying the inclusion criteria (i.e. control group, calculation of median and SD of CFSI and CCI), six studies were eligible for meta-analytic investigation. However, since one of the six studies did only provide data concerning CCI, only five studies were available for the overall investigation of CFSI.

A summary of the studies used for the various analyses concerning reproductive performance after $PGF_{2\alpha}$ treatment is presented in Table 1. There were six trials in five eligible studies with 2,596 cows available to assess the impact of a $PGF_{2\alpha}$ treatment in case of chronic endometritis on CCI. Since one of those trials had not calculated CFSI, only five trials in four studies with 2,510 cows were available to assess the impact of a $PGF_{2\alpha}$ treatment on CFSI. Statistical significance was considered to be 0.05.

Over all the trials analyzed, $PGF_{2\alpha}$ treatment increased the CFSI (Z = 2.12, 95% CI = 0.59 to 15.40; P = 0.03) and the CCI (Z = 12.35, 95% CI = 16.41 to 22.61; P < 0.00001) in comparison to the control group, respectively (Table 2).

The 95% CI of individual values (based on SD) varied considerably between studies. For two trials (Feldmann et al., 2005a; Hirsbrunner et al., 2006) confidence intervals including zero could be found, indicating no effect of a $PGF_{2\alpha}$ treatment in case of chronic endometritis. Concerning overall effect sizes, noticeable confidence intervals could be found for either or both reproductive performance parameters in the subgroups A, C, E and F. In addition, all of those confidence intervals included zero.

Heterogeneity was substantial for CFSI ($\chi 2$ = 1,898.34, df = 4, P < 0.00001, I^2 = 100%) and CCI ($\chi 2$ = 37.38, df = 5, P < 0.00001, I^2 = 87%). Therefore, random effects models were used and sources of heterogeneity were explored with a subgroup analysis.

Forest plots illustrating the impact of $PGF_{2\alpha}$ on CFSI and CCI are presented in Figure 1. Confidence intervals of the single studies did not always overlap, which indicates further evidence of medium to high heterogeneity between the studies.

The results of all subgroups were heterogeneous for both CCI and CFSI (P ≤ 0.04), except subgroups B and G for CCI (P = 0.06) (Table 2). Also concerning both outcomes, significant pooled estimates for subgroups including non-randomized trials (B), non-blinded trials (D) and trials administering Tiaprost (G) could be detected. While expressed in numbers by Table 2, Figure 2 shows how the pooled data of three (CFSI) or four (CCI) randomized studies provide a smaller and non-significant effect (CFSI: Z = - 0.35, P = 0.73; CCI: Z = 0.17, P = 0.87) than do two studies which did not conduct randomization (CFSI: Z = 8.25, P < 0.00001; CCI: Z = 34.36, P < 0.00001). Comparing heterogeneity of those two subgroups, significant differences concerning CFSI (P = 0.01) as well as CCI (P = 0.04) were

detected. Comparing trials with ($P < 0.05$) and without statistically significant effects of $PGF_{2\alpha}$ treatment, the only trials providing statistical significance were those two which did not apply any method of randomization. Hence, the results found by comparing randomized and non-randomized trials equate to those found through subgroup analysis based on the question of statistical significance. Table 2 displays that only the non-blinded trials provide a significant effect for both outcomes (CFSI: $Z = 2.15$, $P = 0.03$; CCI: $Z = 16.14$, $P < 0.00001$). Heterogeneity was only significantly different for CCI ($P = 0.0003$) (Table 3). Grouping according to the $PGF_{2\alpha}$ derivative applied in the treatment group showed that solely those two studies having applied Tiaprost could find a statistically significant effect concerning both outcomes, CFSI ($Z = 8.25$, $P < 0.00001$) and CCI ($Z = 34.36$, $P < 0.00001$) (Figure 3). Also for both outcomes, except CCI associated with a Tiaprost treatment, significant differences concerning heterogeneity were found within each group which included more than one trial and therefore allowed an investigation of heterogeneity. When investigating subgroup differences, we noticed a significant difference concerning heterogeneity between the subgroups for CFSI ($P = 0.02$) (Table 2).

Sensitivity analysis, performed by stepwise excluding studies, showed that the exclusion of the two trials included in one study attributed the highest weight and showing consistently outlying results (Mejia and Lacau-Mengido, 2005) did not improve the homogeneity of either outcomes ($P = 0.29$ for CFSI; $P = 0.08$ for CCI). However, in contrast to the significant effect sizes (CFSI: $Z = 2.12$, $P = 0.03$; CCI: $Z = 12.35$, $P < 0.00001$) favoring the control group, omitting those two trials resulted in a somewhat reduced effect, (CFSI: $Z = - 0.35$, $P = 0.73$; CCI: $Z = 0.17$, $P = 0.87$), and a reduction of the variance (CFSI: 8.00 vs. - 3.58; CCI: 19.51 vs. 1.67). Concerning the CFSI, this procedure generated an effect favoring the treatment group instead of the control group (Figure 5). Since those two trials were the only ones not randomized, sensitivity analysis showed, in accordance with the results found through subgroup analysis, that the performance of randomization was influential in modifying effect size of $PGF_{2\alpha}$ treatment (Figure 2) as well as the size of variance (Tables 3 and 4). Regarding CCI, an additional exclusion of the study by LeBlanc (2003), which had the third highest weight, led to a significant reduction of heterogeneity ($P = 0.001$) (Figure 6). In addition, the effect size shifted from a previously significant effect ($Z = 12.35$, $P < 0.00001$) seen in the control group to a smaller non-significant effect ($Z = - 0.74$, $P = 0.46$) found in the treatment group. Concerning CFSI, omitting the only trial showing a positive effect of the $PGF_{2\alpha}$ treatment (LeBlanc, 2003) reduced heterogeneity significantly ($P = 0.03$) and increased the statistically significant effect size ($Z = 7.22$, $P < 0.00001$) (Figure 7).

Especially concerning CCI, the presented funnel plots (Figures 8 and 9) suggest a publication bias towards studies with higher standard error (i.e. usually smaller studies) which reported a positive effect on CCI after a $PGF_{2\alpha}$ treatment.

2.2.6 Discussion

$PGF_{2\alpha}$ has been recommended as the treatment of choice for chronic bovine endometritis by numerous authors (e.g. Lewis (1997) and Azawi (2008)), and is in some parts of the world, like Argentina, the most common intervention used in veterinary practice (Mejia and Lacau-Mengido, 2005). Despite the reported inconsistency in recent literature concerning the effect (Haimerl et al., 2011), the presented significant negative impact of $PGF_{2\alpha}$, i.e. increase of CFSI and CCI, was surprising. Yet, the presence of significant heterogeneity in response was anticipated because of the considerable variations not only in the study design but also concerning the outcomes in the existing literature as previously shown by Haimerl et al. (2012).

In addition to those findings, we revealed further variation concerning study design. One might question whether the collective analysis of six studies with three different $PGF_{2\alpha}$ derivatives of variable dosages is meaningful (Table 1). However, every study, except the one by Feldmann et al. (2005a), applied the derivative according to the respective product information. Feldmann et al. (2005a) had based their study on the thesis by Tenhagen (2001) administering 25 mg dinoprost but reported a dosage of only 5mg dinoprost. Therefore, we assume that this dose was reported erroneously. Differences between dinoprost, DL-cloprostenol and D-cloprostenol concerning their impact on uterine motility have been described (Hirsbrunner et al., 1998). Notwithstanding, the main effect i.e. luteolysis, followed by the induction of estrus and improving the immune response in cows with a responsive corpus luteum is present (Kasimanickam et al., 2005). Considering these pharmacological effects and assuming that the dosage reported by Feldmann et al. (2005a) was 25 mg, every study applied the derivative in the dosage recommended by the manufacturer. Hence, one might hypothesize that in every case the drug used was effective.

Subgroup analysis based on the chosen groups did not identify one exclusive source of heterogeneity. Instead, within every subgroup, except subgroups B, E and G concerning CCI, still significant heterogeneity, if measurable, was apparent. However, concerning CCI, in the subgroup consisting of non-randomized trials, no significant heterogeneity could be found. Both the non-randomized and randomized trials displayed significant heterogeneity when investigating CFSI. However, for both reproductive performance parameters significant differences concerning heterogeneity between the two subgroups could be found. Thus, one might hypothesize, that the heterogeneity found in both subgroups has different sources.

Weights are assigned to each trial's result according to the precision of its treatment effect estimate. Trials that have more precise estimates are more heavily weighted. Thus, one might expect that those trials having been assigned the highest weights should be those of highest quality and therefore provide the most reliable results. High quality trials use blinding and random assignment of patients (Cleophas and Zwinderman, 2007). The

precision of the estimates, however, is primarily determined by the number of probands. The two trials by Mejia and Lacau-Mengido (2005), for example, which were attributed the highest weight, did not apply any method of randomization but included a high number of cows (Trial 1, n = 678; Trial 2, n = 1,308). Nevertheless, the meta-analysis literature contains multiple examples of simple data pooling without weighting which has long been known to be even less appropriate than simple weighing by sample size (Barker and Carter, 2005).

Some authors (Lam and Kennedy, 2005; Willich, 2006) suggested that low quality studies tend to show higher treatment effects. Our results provide supporting evidence for this observation. However, it comprises too few trials to formulate valid conclusions concerning the relationship between sample size and quality. Also, there are other reviews (Kunz and Oxman, 1998) that do not support this suggestion.

According to Cleophas and Zwinderman (2007), a value of I^2 greater than fifty percent is often used as a cutoff for heterogeneity. The high I^2 values of CFSI and CCI of 100% and 87%, respectively, not only show high inconsistency between the studies but also that most of the variability across studies is due to heterogeneity rather than chance. In comparison to our data, the meta-analysis conducted by Duffield et al. (2008) on the impact of Monensin on selected plasma, serum or blood parameters in lactating dairy cattle revealed considerably lower I^2 values with the highest being 54% for cholesterol.

Significant heterogeneity suggests that the studies are not measuring a common population effect and that the differences in the study parameters are likely responsible for the varying treatment effect (Oxman et al., 1994). As mentioned by Lam and Kennedy (2005), different schools of thought exist regarding how much homogeneity is required for appropriate comparisons. They also indicate that there is some danger of over-interpreting heterogeneity. Hence, heterogeneity may occur by chance and is an important possibility when a clinical explanation is not found or when the heterogeneity is clinically irrelevant. However, it needs to be considered that a great deal of uniformity among the results of independently performed studies is not necessarily good (Riegelman, 2005). Hence, it might indicate consistency in bias rather than consistency in real effects. In contrast to that, Fourichon et al. (2000) have emphasized that an overall summary estimate may not be relevant if it is based on heterogeneous studies. Concerning the presented meta-analysis, more clinical trials should be conducted and included into an updated analysis to learn more about the sources of heterogeneity.

Subgroup and sensitivity analysis led to interesting findings concerning the summary estimate. While the investigation of all trials showed statistically significant overall effect sizes concerning CFSI and CCI, significance could not be sustained in the subgroups A (randomized trials), C (blinded trials), E (Dinoprost) and F (Cloprostenol). Concerning the randomized and the blinded trials, this effect may again be explained by the assumption

made by Willich (2006), that trials revealing a stringent study design tend to display lower treatment effects. In order to support this statement, Figure 2 illustrates how the pooled data of three (CFSI) or four (CCI) randomized studies provide a smaller and non-significant effect than do two studies which did not conduct randomization. Surprisingly, in case of CFSI, excluding non-randomized trials even resulted in a positive effect of the treatment instead of control group. Obviously, the summary result is mainly determined by the non-randomized studies.

In order to determine the precision of the effect estimates, the 95% CI of individual values (based on SD) was calculated. Concerning overall effect sizes, wide confidence intervals were found for CFSI or CCI in the subgroups A (CFSI, - 23.61, 16.46; CCI - 17.80, 21.15), C (CFSI, - 1.38, 3.38; CCI, - 15.91, 9.91), E (CFSI, - 10.53, 27.13; CCI, - 38.31, 21.84) and F (CFSI, - 31.65, 15.39; CCI, - 13.65, 33.28). These findings are surprising as they imply that trials with a sound study design did not generate a precise effect estimate. Also, in comparison to other meta-analyses, the confidence intervals calculated in our study were wider. Fourichon et al. (2000), for example investigated the effect of various diseases on reproduction in dairy cows based on the results from 70 papers. Of all the diseases considered, confidence intervals were mainly narrow, except for days open in all cows concerning the effect of retained placenta (3.0, 48.8) and cystic ovaries (- 22.8, 47.0), respectively. The meta-analysis conducted by Duffield et al. (2008) on the impact of Monensin, however, revealed large variations regarding confidence intervals, ranging from - 149.5, - 78.3 for BHBA to - 0.019, 0.037 for calcium.

However, confidence intervals for meta-analyses do not only depend on the precision of the individual study estimates, but also on the number of studies combined. Since the width of the confidence interval usually decreases as more studies are added to a meta-analysis (Borenstein et al., 2009), the limited number of trials included, especially in the single subgroups, contribute to the magnitude of the confidence intervals. This could account for the mainly narrow confidence intervals found by Fourichon (2000) since there were 70 papers included in the meta-analysis. However, meta-analytic investigations conducted by Burton and Lean (1995) revealed considerably smaller 95% CIs (- 0.44, - 0.01) concerning the CCI after a PGF treatment of cows with an abnormal puerperium, although the number of trials included was similar to our analysis (n = 7). In addition, for random-effects models, as used in this meta-analysis, precision will decrease with increasing heterogeneity and confidence intervals will widen correspondingly. Furthermore, all of those confidence intervals include zero which leads to the assumption that the mean effect size does not significantly differ from zero (Eisend, 2004). This, in turn, indicates that there is no effect after $PGF_{2\alpha}$ treatment in case of chronic endometritis.

The 95% CI of individual values varied considerably between studies, which is further evidence for considerable heterogeneity. Since I^2 reflects the extent of overlap of confidence intervals, which is not dependent on the actual location or spread of the true effects (Borenstein et al., 2009), the high values for I^2 are consistent with the limited overlapping of the single confidence intervals. Beyond that, for two trials (Feldmann et al., 2005a; Hirsbrunner et al., 2006) confidence intervals including zero could be found.

Grouping according to the $PGF_{2\alpha}$ derivative showed that only those two studies having applied Tiaprost could find a statistically significant effect concerning both outcomes. This was not astonishing, however, because this subgroup exclusively consisted of the two trials executed by Mejia and Lacau-Mengido (2005), which were those two not randomized and solely showing significant effect estimates. Therefore, it remains unclear if the statistical significance of the effect estimate is due to the derivative applied or the differences in study design.

Another essential objective of a meta-analysis is to search for potential bias, that may be introduced by deficient literature search or selection (Barker and Carter, 2005). As shown by several authors (Egger and Smith, 1998; Montori et al., 2000; Song et al., 2000), one of the most frequently occurring events is missing studies with “negative” outcomes, which is due to a number reasons. “Negative” trials, or those that fail to show superiority of the experimental treatment, tend to be left unpublished (publication bias) or published more slowly (pipeline bias), and are less often retrieved by the searching process (retrieval bias). Another problem is that “positive” trials are more likely to be published more than once, not always in a readily identifiable way. Publication bias can have an important impact on the outcomes of meta-analyses (Scifres et al., 2009). Measuring the effects of publication bias quantitatively can be difficult. Nevertheless, various approaches exist. The most widely applied method for detecting publication bias in a meta-analysis is the funnel plot, in which the effect size for individual trials is plotted against a measure of the precision of the treatment effect estimate, such as the size of the trial (Egger et al., 1997). In the present meta-analysis, the measure of precision was the standard error. When a funnel plot is used to study an unbiased sample of trials, the observed effect sizes should range symmetrically around the true effect size, which will be most accurately estimated by the largest trials, thus giving a symmetrical, funnel-shaped plot (Barker and Carter, 2005). In the conducted meta-analysis, however, neither concerning CFSI nor CCI such a funnel shape was detected. Especially with regard to CCI, a strong asymmetry was found towards studies with higher standard error, reporting a positive effect on CCI after a $PGF_{2\alpha}$ treatment. Such an asymmetry is often caused by small trials not providing much evidence of efficacy and therefore not being published or retrieved, leading to larger estimates of treatment effect being observed in smaller trials (Barker and Carter, 2005). However, there are difficulties in

assessing the shape of a funnel plot when the number of trials included is small (Tang and Liu, 2000; Sterne and Egger, 2001).

In addition, small trials tend to overestimate treatment effects because of methodological differences (either design flaws or more rigorous implementation of treatment), causing a false appearance of publication bias when none actually exists (Schulz et al., 1995; Stuck et al., 1998). This “small-study effect” (Kjaergard et al., 2001) leads to the paradox that increasing success in locating small, unpublished trials may actually bias a meta-analysis toward overestimation of treatment effect (Barker and Carter, 2005). Several authors (Sterne et al., 2000; Sutton et al., 2000) have estimated that approximately 25 to 50% of meta-analyses may be affected by publication bias and that treatment effects were overestimated by up to 47% as a result.

Beyond that, the shape of the funnel plot is extremely sensitive to the method used to express treatment effect and precision. Thus, applying the fixed-effects method in the present meta-analysis might have led to different results. However, a fixed-effects analysis only is appropriate when the trials are so similar in design and execution that one can assume they address the same research hypothesis, using the same methods and treatments in the same population, and when the formal test of homogeneity demonstrates a lack of heterogeneity between the trial results (Barker and Carter, 2005). Thus, due to the considerable heterogeneity found, random-effects analysis was conducted assuming that the true effect size varies from study to study and the summary effect is our estimate of the mean of the distribution of effect sizes (Borenstein et al., 2009). With reference to heterogeneity, Terrin et al. (2003) and Tang and Liu (2000) recently demonstrated that an asymmetrical funnel plot is only related to publication bias if the trials included are homogeneous. Hence, the results found concerning publication bias have to be considered carefully.

The last step in performing a meta-analysis is to assess its robustness with the help of a sensitivity analysis, i.e. checking the stability of the results in relation to the different ways the analysis could reasonably be performed (Olkin, 1999). Thus, sensitivity analysis strengthens the estimation and interpretation of effects obtained from several studies (Fourichon et al., 2000) and meta-analysis derived conclusions that are robust to multiple sensitivity analyses gain credibility in application to general practice (Barker and Carter, 2005). There are several ways to perform sensitivity analyses (Barker and Carter, 2005). By excluding the two non-randomized trails due to the highest weights (Mejia and Lacau-Mengido, 2005), we simultaneously investigated the possible impact of large weight and low quality studies on the summary estimated effect obtained from the meta-analysis. This approach led to a considerable reduction of effect estimates, accompanied by the loss of statistical significance. Remarkably, omitting those two trials resulted in an effect on CFSI

seen in treatment instead of the control group. These results clearly illustrate that the inclusion criteria applied are an important factor in determining the summary result. According to Cleophas and Zwinderman (2007), this observation leads to the conclusion that the present meta-analysis lacks robustness, and to the necessity of more clinical trials to obtain more reliable results.

Meta-analysis methods have been developed to calculate the summary estimates of several studies in order to integrate the available information from different source studies and to examine the potential origin of heterogeneity of the results. However, the findings of a meta-analysis must be considered with caution since these methods have been developed to summarize the results of randomized, controlled trials. And thus, extending its use to observational studies must account for the variability of study designs and of populations employed (Fourichon et al., 2000). Therefore, one might favor the strict exclusion of non-randomized trials. However, as pointed out by Khan et al. (1996), it may be worthwhile not to completely reject the studies with lower methodology since they can be used for assessing sensitivity. In addition, there have not been many meta-analyses carried out in the field of veterinary medicine, for several reasons (Holmes, 2004; Arlt et al., 2005). One of which is a shortage of randomized, controlled studies in veterinary medicine (Arlt and Heuwieser, 2005). Therefore, if an adequate number of randomized, controlled trials are missing, trials of lower evidence levels should be integrated to enhance the power of the meta-analysis.

In conclusion, our meta-analysis did not reveal an improvement of reproductive performance of cows with endometritis after treatment with $PGF_{2\alpha}$. Therefore, we encourage reconsidering PGF as a routine treatment of cows with chronic endometritis. This is particularly important as a blanket treatment of $PGF_{2\alpha}$ could be perceived by the general public as unjustified hormone use. Furthermore, we conclude that there is a shortage of comparable and high quality studies investigating reproductive performance after $PGF_{2\alpha}$ treatment of cows with chronic endometritis. Additional confirmatory trials are necessary to shed more light on the contradictory results published, to assess the practical value of the treatment and to identify the sources of heterogeneity. The latter may reveal important aspects concerning study quality and applicability of the results in livestock research.

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Table 1. Summary of studies used for meta-analysis of reproductive performance after therapy of chronic endometritis with $PGF_{2\alpha}$, considering different subgroups

Study	Total cows, n	Dose of $PGF_{2\alpha}$ (mg per cow)	Date of first treatment	Date of second treatment	Measured outcomes	Included in subgroup[7]						
						A	B	C	D	E	F	G
Steffan et al. (1984)	153	25.0	37.d pp.	14 days after 1st treatment	CCI[1], CR[2], SC[3]	Y[8]	N[9]	N	Y	Y	N	N
Mejia and Lacau-Mengido (2005) – Trial 1	678	0.75	30.-50.d pp.	20d after 1st treatment (if necessary)	CCI, CFSI[4], PR[5], SC, FSCR[6]	N	Y	N	Y	N	N	Y
Mejia and Lacau-Mengido (2005) – Trial 2	1,308	0.75	30.-50.d pp.	20d after 1st treatment (if necessary)	CCI, SC, CFSI, PR,	N	Y	N	Y	N	N	Y
LeBlanc (2003)	316	0.5	20.-33.d pp.	14d after 1st treatment (if necessary)	CCI, SC, CFSI, PR, FSCR	Y	N	N	Y	N	Y	N
Hirsbrunner et al. (2006)	Not given	0.15	21.-35.d pp	14 days after 1st treatment	CCI, SC, CFSI,	Y	N	Y	N	N	Y	N
Feldmann et al. (2005)	178	5.0	≥21.d pp	14d after 1st treatment (if necessary)	CCI, SC, CFSI, PR, FSCR	Y	N	N	Y	Y	N	N

[1] calving to conception interval

[2] cure rate

[3] services per conception

[4] calving to first service interval

[5] pregnancy rate

[6] first service conception rate

[7] A = randomized trials / trials showing a statistically significant effect; B = non-randomized trials / trials showing no statistically significant effect; C = blinded trials; D = non-blinded trials; E, trials administering Dinoprost; F = trials administering Cloprostenol; G = trials administering Tiaprost

[8] Yes

[9] No

Table 2. Summary of effect sizes (Z), 95% confidence intervals (95% CI), mean differences (MD), between-studies variance (Tau^2), ratio of true heterogeneity to total observed variation (I^2), Chi^2 and expected variation (df), and *P*-values for each outcome and subgroup

Group analyzed[1]	Z	*P*-value (of Z)	95% CI	MD	Tau^2	I^2 (%)	Chi^2	df	*P*-value (of df)
Calving to first service interval									
All trials	2.12	0.03	0.59, 15.40	8.00	60.88	100	1,898.34	4	< 0.00001
A	- 0.35	0.73	- 23.61, 16.46	- 3.58	284.77	97	72.18	2	< 0.00001
B	8.25	< 0.00001	17.87, 29.00	23.44	16.10	100	477.32	1	< 0.00001
C	1.46	0.14	- 1.38, 3.38	4.00	N. a.	N. a.	N. a.	N. a.[2]	N. a.
D	2.15	0.03	0.79, 17.32	9.05	60.02	100	1,857.68	3	< 0.00001
E	0.86	0.39	- 10.53, 27.13	8.3	N. a.	N. a.	N. a.	N. a.	N. a.
F	- 0.68	0.50	- 31.65, 15.39	- 8.13	283.61	98	65.56	1	< 0.00001
G	8.25	< 0.00001	17.87, 29.00	8.25	16.10	100	477.32	1	< 0.00001
Calving to conception interval									
All trials	12.35	< 0.00001	16.41, 22.61	19.51	7.02	87	37.83	5	< 0.00001
A	0.17	0.87	- 17.80, 21.15	1.67	333.96	89	27.85	3	< 0.00001
B	34.36	< 0.00001	20.96, 23.50	22.23	0.63	73	3.66	1	0.06
C	- 0.46	0.65	- 15.91, 9.91	- 3.00	N. a.	N. a.	N. a.	N. a.	N. a.
D	16.14	< 0.00001	18.59, 23.73	21.16	4.23	83	23.62	4	< 0.0001
E	- 0.54	0.59	- 38.31, 21.84	- 8.24	362.94	77	4.35	1	0.04
F	0.82	0.41	- 13.65, 33.28	9.81	264.11	92	12.06	1	0.0005
G	34.36	< 0.00001	20.96, 23.50	22.23	0.63	73	3.66	1	0.06

[1] A = randomized trials / trials showing a statistically significant effect; B = non-randomized trials / trials showing no statistically significant effect; C = blinded trials; D = non-blinded trials; E, trials administering Dinoprost; F = trials administering Cloprostenol; G = trials administering Tiaprost

[2] Test for heterogeneity was not applicable since only one study having applied Dinoprost offered data concerning calving to first service interval

Table 3. Differences between the three subgroups concerning Chi^2, the expected variation (df) and its *P*-value, and ratio of true heterogeneity to total observed variation (I^2) regarding calving to first service interval based on the six included trials

	Chi^2	df	*P*-Value (of df)	I^2 (%)
Randomization (A vs. B)	6.48	1	0.01	84.6
Blinding (C vs. D)	1.01	1	0.32	0.9
Agent (E vs. F vs. G)	8.37	2	0.02	76.1

Table 4. Differences between the three subgroups concerning Chi^2, the expected variation (df) and its *P*-value, and ratio of true heterogeneity to total observed variation (I^2) regarding calving to conception interval based on the six included trials

	Chi^2	df	*P*-Value (of df)	I^2 (%)
Randomization (A vs. B)	4.26	1	0.04	76.5
Blinding (C vs. D)	12.95	1	0.0003	92.3
Agent (E vs. F vs. G)	5.00	2	0.08	60.0

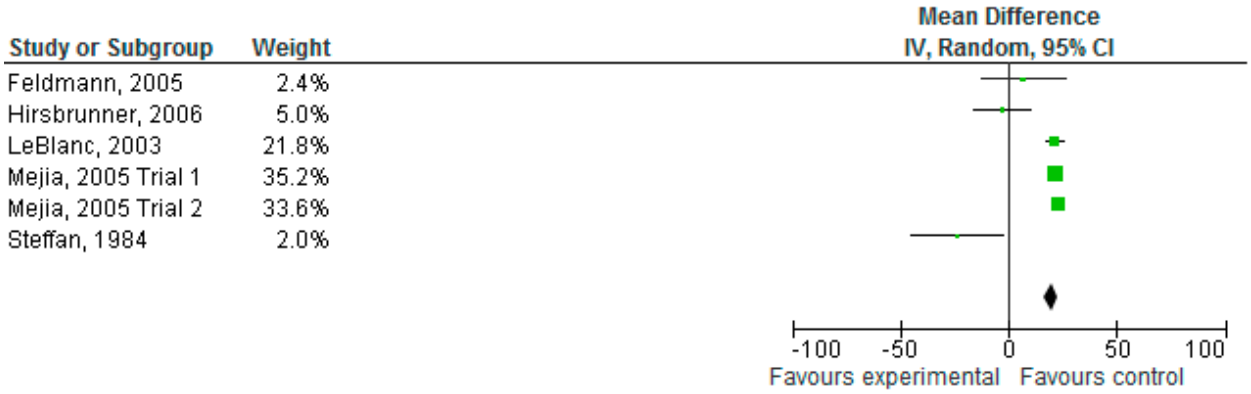

Figure 1. Forest plot of the effect of $PGF_{2\alpha}$ on calving to first service interval (top) and calving to conception interval (bottom) in dairy cows suffering from chronic endometritis. Each square represents the mean effect size for that study. The upper and lower limit of the line connected to the square represents the upper and lower 95% confidence interval (CI) for the effect size. The size of the square reflects the relative weighting of the study to the overall effect size estimate with larger squares representing greater weight. The diamond at the bottom represents the 95% CI for the overall estimate.

The solid vertical line represents a mean difference of zero or no effect. Squares located on the left side of this line represent studies showing an effect in the group treated with $PGF_{2\alpha}$, whereas squares located on the right side of this line indicate an effect found in the control group. Study or subgroup refers to the first author and year of the publication.

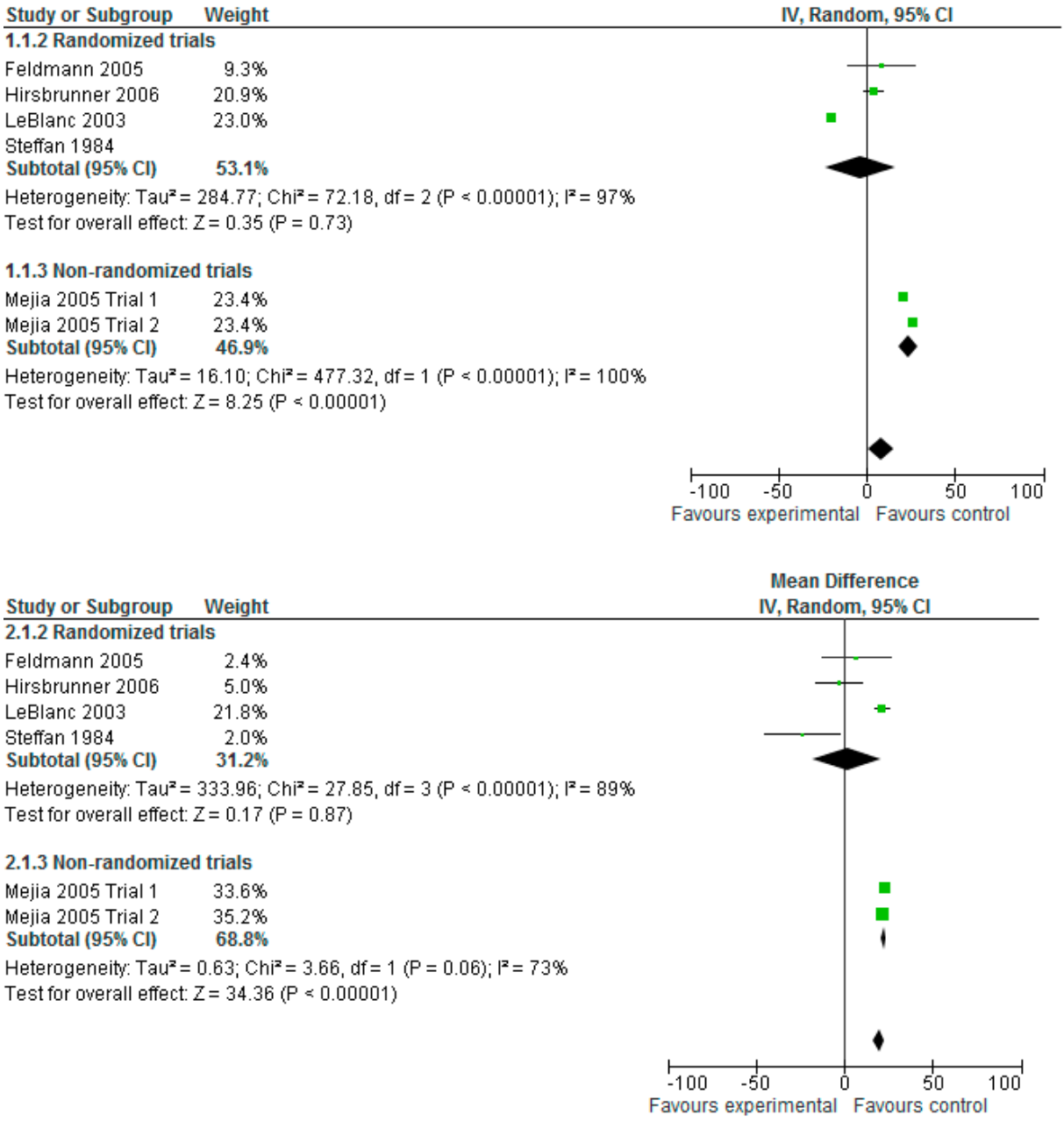

Figure 2. Forest plot of the effect of $PGF_{2\alpha}$ on calving to first service interval (top) and calving to conception interval (bottom) in dairy cows suffering from chronic endometritis. Subgroups were created according to the way of allocation to treatment and control groups.

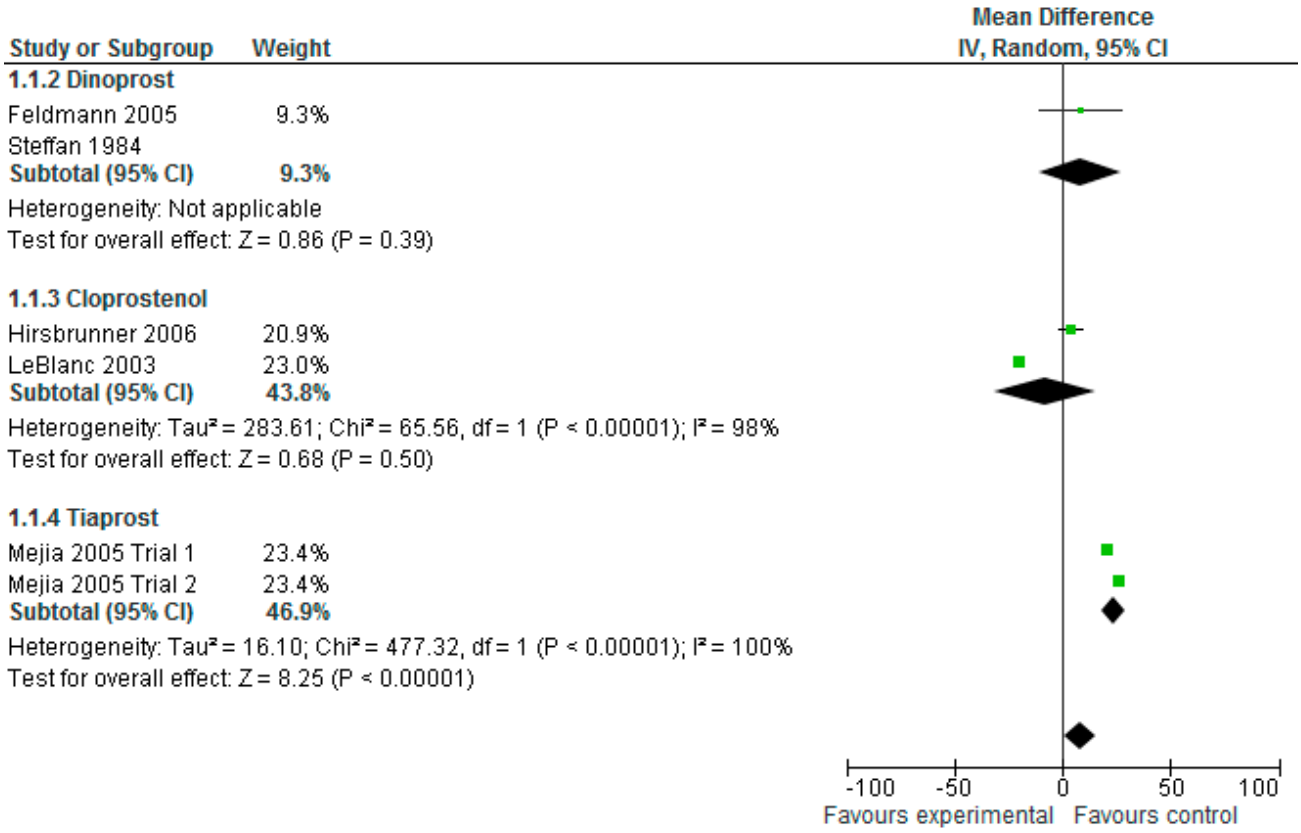

Figure 3. Forest plot of the effect of $PGF_{2\alpha}$ on calving to first service interval in dairy cows suffering from chronic endometritis. Subgroups were created according to the $PGF_{2\alpha}$ derivative applied.

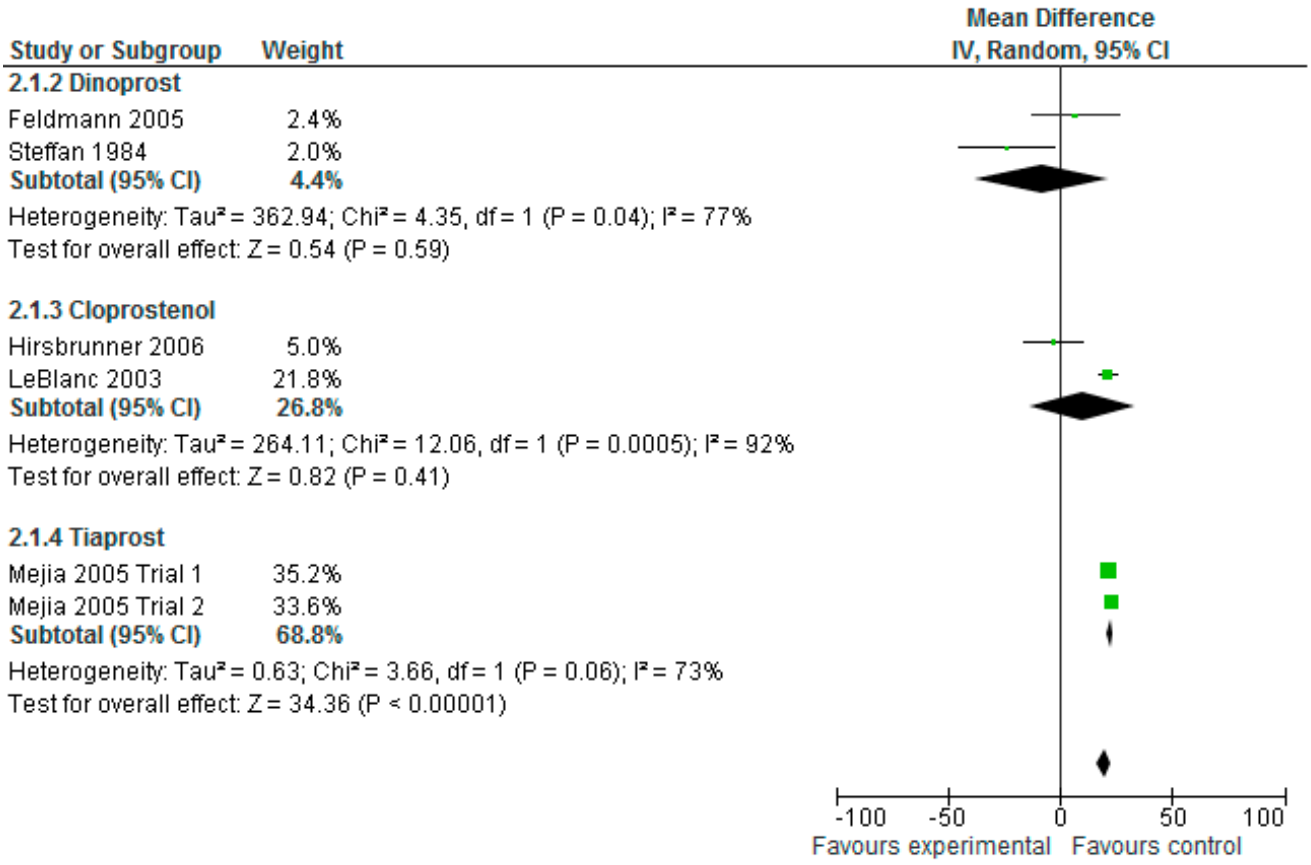

Figure 4. Forest plot of the effect of $PGF_{2\alpha}$ on calving to conception interval in dairy cows suffering from chronic endometritis. Subgroups were created according to the $PGF_{2\alpha}$ derivative applied.

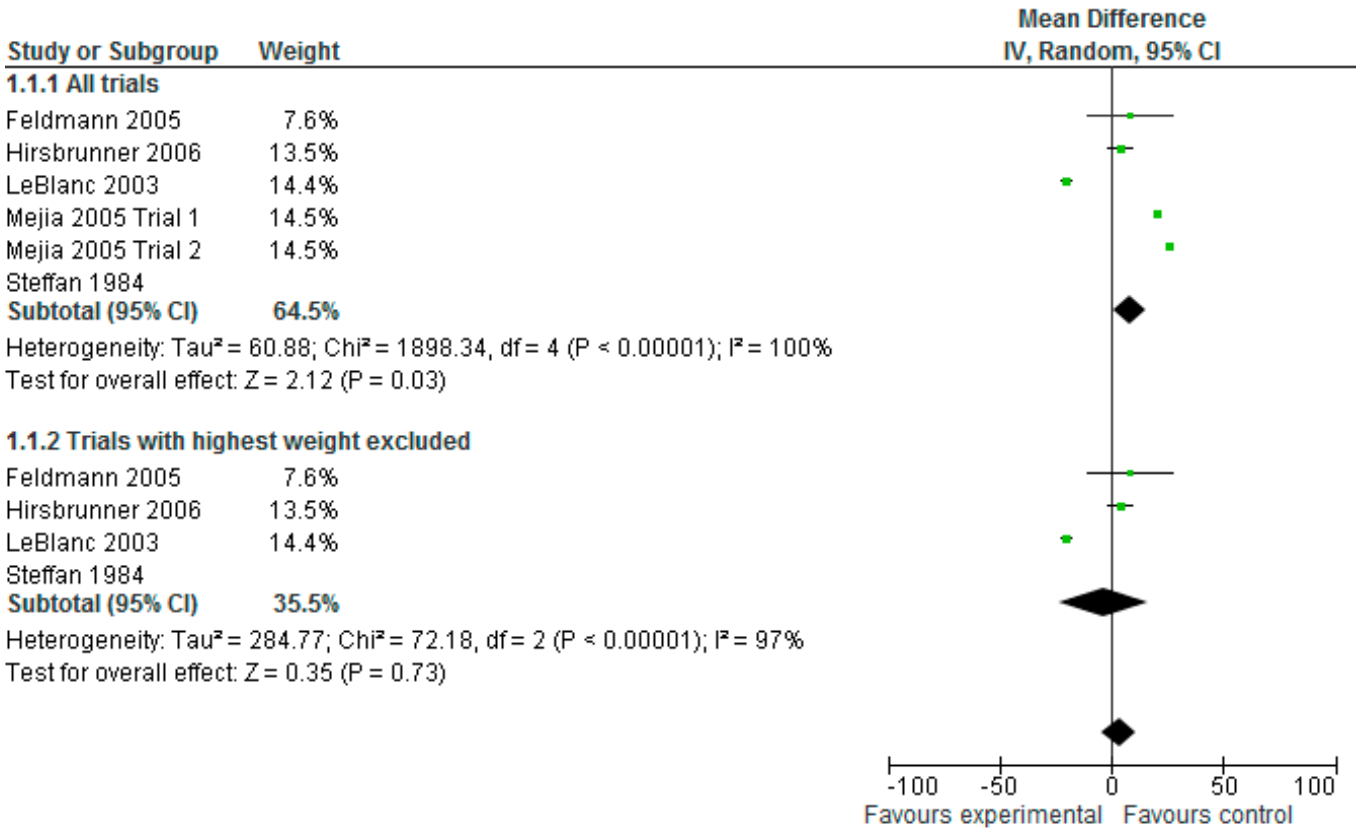

Figure 5. Forest plot of the effect of $PGF_{2\alpha}$ on calving to first service interval in dairy cows suffering from chronic endometritis. Results of sensitivity analysis after the two trials with the highest weight (Mejia and Lacau-Mengido, 2005) had been excluded.

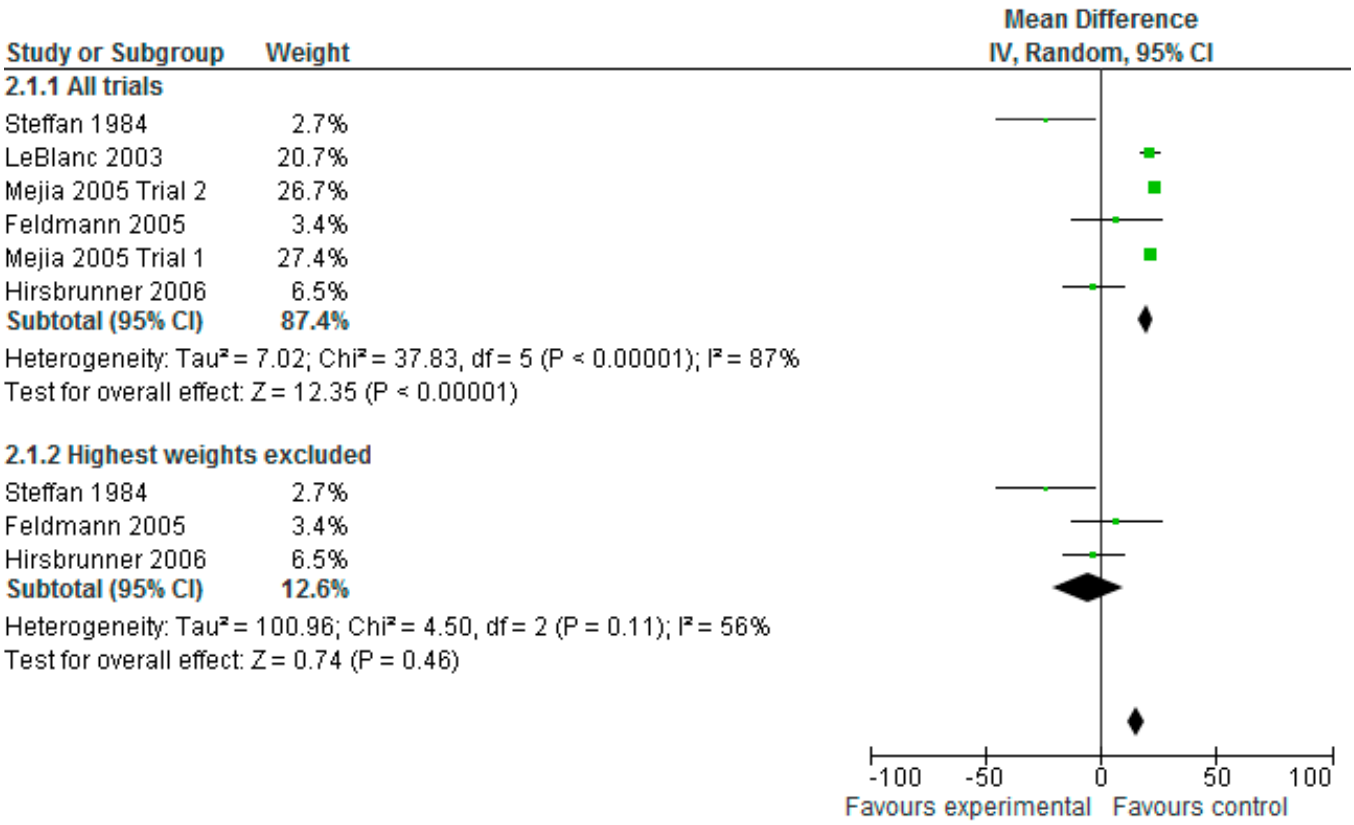

Figure 6. Forest plot of the effect of $PGF_{2\alpha}$ on calving to conception interval in dairy cows suffering from chronic endometritis. Results of sensitivity analysis after the three trials with the highest weight (LeBlanc, 2003; Mejia and Lacau-Mengido, 2005) had been excluded.

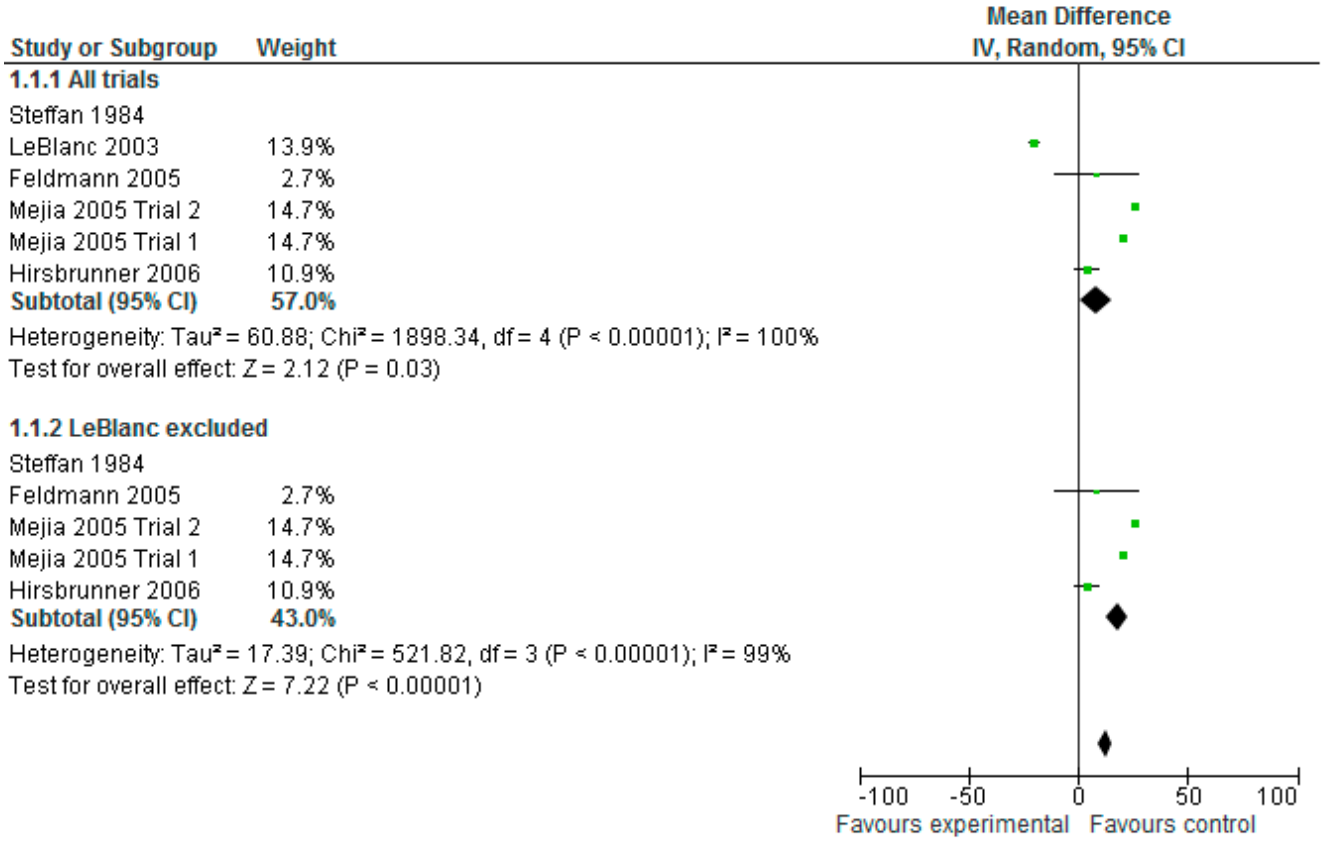

Figure 7. Forest plot of the effect of $PGF_{2\alpha}$ on calving to first service interval in dairy cows suffering from chronic endometritis. Results of sensitivity analysis after the only trial showing an effect in the treatment group (LeBlanc, 2003) had been excluded.

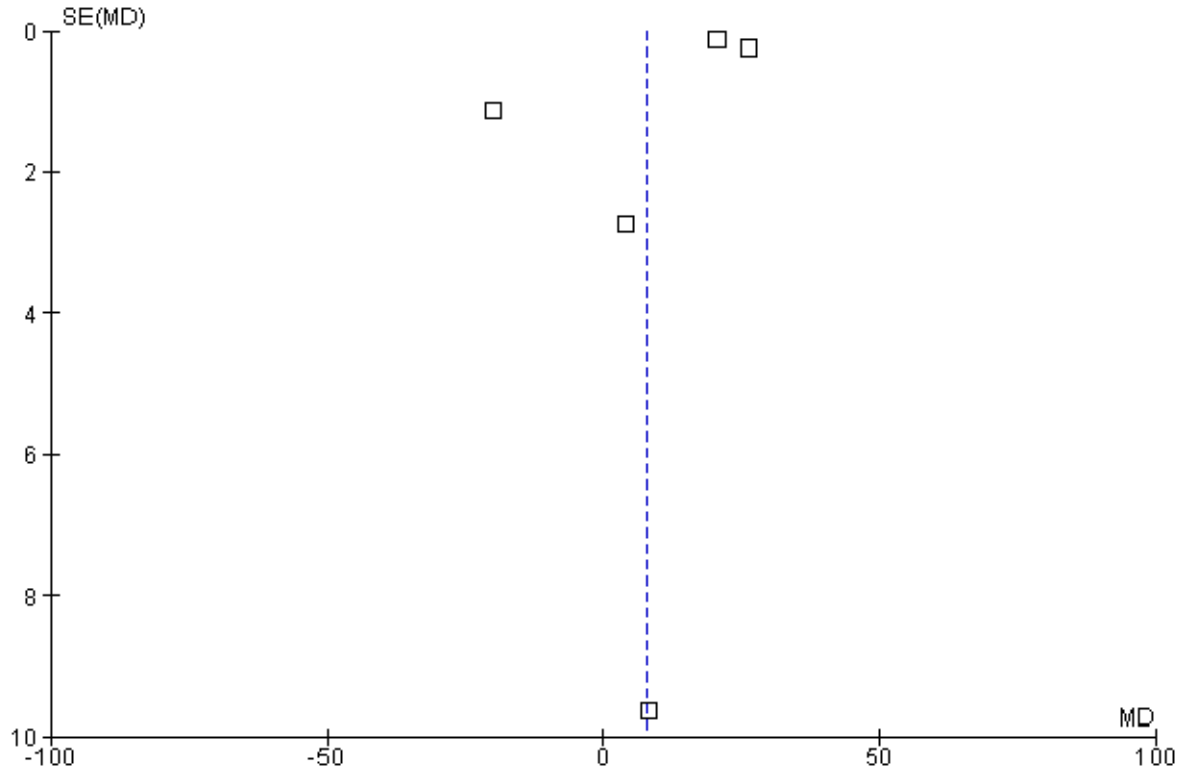

Figure 8. Funnel plot of $PGF_{2\alpha}$ effect on calving to first service interval for assessing publication bias. MD = mean difference; SE of MD = Standard error of the standardized mean difference. The vertical line represents the mean effect size. Publication bias may be present if there are an unequal number of studies (particularly smaller weight studies) on one side of the horizontal line.

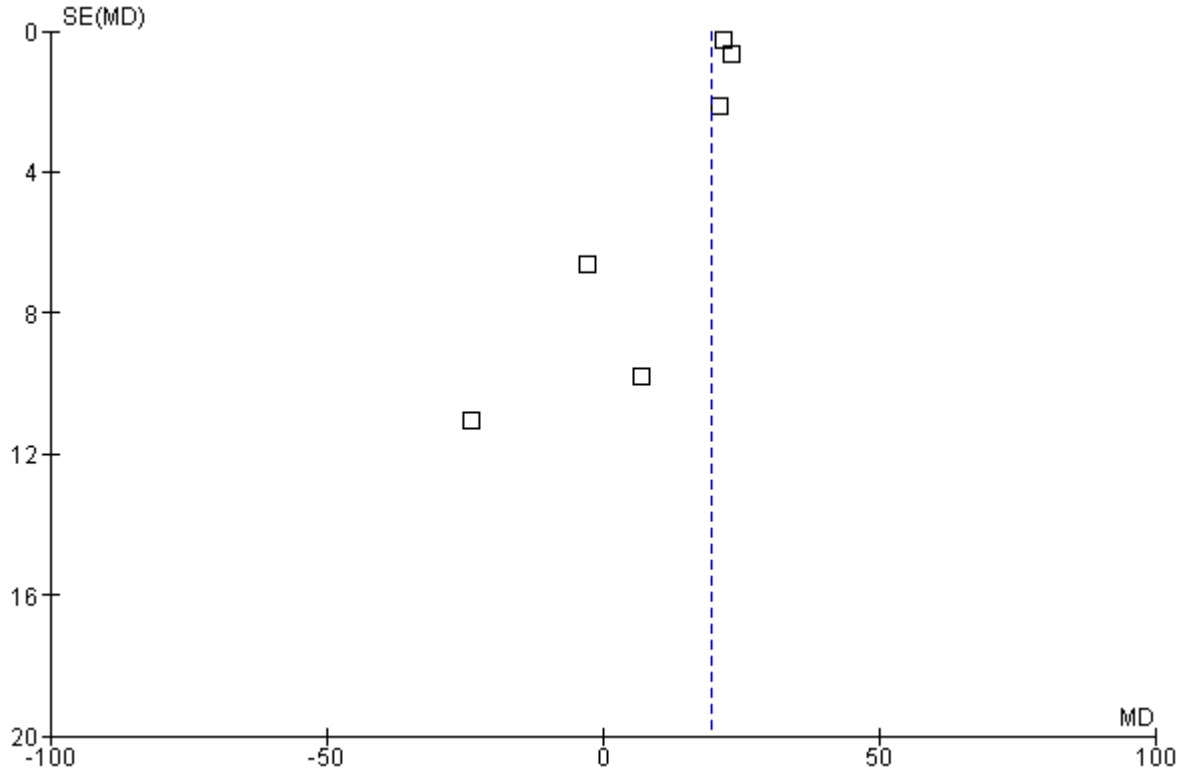

Figure 9. Funnel plot of $PGF_{2\alpha}$ effect on calving to conception interval for assessing publication bias. MD = mean difference; SE of MD = Standard error of the standardized mean difference. The vertical line represents the mean effect size. Publication bias may be present if there are an unequal number of studies (particularly smaller weight studies) on one side of the horizontal line.

2.3 Entscheidungsfindung in der tierärztlichen Praxis

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Entscheidungsfindung in der tierärztlichen Praxis

P. Haimerl[1]; S. Arlt[1]; W. Heuwieser[1]

[1]Tierklinik für Fortpflanzung der Freien Universität Berlin

Korrespondenzadresse: Prof. Dr. W. Heuwieser, Tierklinik für Fortpflanzung, Fachbereich Veterinärmedizin, Freie Universität Berlin, Königsweg 65, 14163 Berlin, Deutschland, Email: w.heuwieser@fu-berlin.de

2.3.1 Zusammenfassung

Gegenstand und Ziel: Im veterinärmedizinischen Alltag sollten diagnostische sowie therapeutische Entscheidungen auf neueste Erkenntnisse von hoher Evidenz gestützt sein. Um einen Überblick über die momentane Einschätzung und Anwendung der Konzepte der Evidenzbasierten Veterinärmedizin (EBVM) zu erhalten, wurden im Rahmen von Fortbildungsveranstaltungen klinisch tätige Tierärzte/innen hinsichtlich ihres Informationsbeschaffungs-, -bewertungs- und Fortbildungsverhaltens befragt.

Material und Methoden: Die Befragung klinisch tätiger Tierärzte wurde zwischen Mai 2010 und November 2011 im Rahmen fünf verschiedener Fortbildungsveranstaltungen durchgeführt. Der Fragebogen enthielt insgesamt 32 Fragen, welche sich auf Person/Tätigkeit (n = 4), erworbene Qualifikationen (n = 3), das Fortbildungsverhalten (n = 5) sowie die Anwendung der EBVM (n = 20) bezogen. Zusätzlich zur Auswertung der Angaben aller Befragten wurden die Angaben von Kleintier-, Großtier- und Gemischtpraktikern miteinander verglichen.

Ergebnisse: Insgesamt wurden 293 Fragebögen ausgefüllt. Mehr als die Hälfte aller Klein- (58,3%) bzw. Großtierpraktiker (54,9%) gaben an, ihre Englischkenntnisse reichten aus, um englischsprachige Fachvorträgen oder Publikationen ohne Mühe erfassen zu können. 10,4% aller Befragten gab an, keine veterinärmedizinischen Zeitschriften regelmäßig zu lesen, während 20,8% der klinisch tätigen Tierärzte angaben, regelmäßig englischsprachige Fachliteratur zu lesen. Der überwiegende Anteil der Tierärzte fragte im Problemfall ihren Chef oder Kollegen um Rat. Diese beiden Informationsquellen werden als qualitativ hoch oder sehr hoch eingeschätzt. Beinahe alle Teilnehmer (92,6%) gaben an, die Lösung für auftretende fachliche Probleme in einem Fachbuch zu suchen, dem ebenfalls eine hohe bzw. sehr hohe Qualität einräumt wird. 68,6% der Befragten schätzen ihre Fähigkeit, geeignete Literatur zu finden, als sehr hoch oder hoch ein. Eine hohe Fähigkeit, die gefundene Literatur hinsichtlich ihrer Qualität (Evidenz) kritisch beurteilen zu können, schrieben sich jedoch lediglich 52,1% der Befragten zu.

Schlussfolgerung und klinische Relevanz: Die Mehrheit der klinisch tätigen Tierärzte ist nur begrenzt in der Lage, Informationen hinsichtlich ihrer Evidenz einzuschätzen. Daher sollte ein Ziel sein, es Tierärzten bereits im Studium sowie in ihrer postgraduellen Ausbildung näher zu bringen, sich mit medizinischen Informationen kritisch auseinanderzusetzen und klinische Entscheidungen basierend auf soliden Daten zu treffen.

2.3.2 Summary

Objective: In daily practice, a veterinarian has to judge information and decide whether it can be adequately implemented for a given case. In this context, it is of top priority to base

decisions on the latest and soundest scientific findings. In Germany, every practitioner has to take part in 20 to 40 hours of continuing education. To outline the current assessment and employment of evidence-based veterinary medicine (EBVM), we surveyed practitioners concerning continuing education and their skills in obtaining and evaluating scientific information.

Materials and Methods: A survey amongst veterinary practitioners was conducted throughout five conferences between Mai 2010 and November 2011. The questionnaire contained 32 questions concerning demographic data and profession (n = 4), qualification (n = 3), continuing education (n = 5) and skills concerning EBVM (n = 20). Besides evaluating the statements of all participants, veterinarians were classified based on the type of practice and their statements compared.

Results: In total, 293 questionnaires were returned. The majority of small animal practitioners (58.3%) and those working with food animals (54.9%) declared being capable of comprehending scientific talks or papers in English without difficulty. 10.4% of all practitioners negated reading veterinary journals on a regular basis, while 20.8% stated to regularly read English veterinary journals. The majority of the practitioners sought advice from their employer or a colleague. They attribute a high or very high quality to both information sources. Almost every participant (92.6%) stated to consult medical books, and 88.6% certify this information source a high or very high quality. 68.6% of the practitioners evaluated their skills in finding suitable literature as high or very high. However, only about half (52.1%) of all participants attributed themselves a high ability to evaluate the quality of the found literature.

Conclusions and clinical relevance: Most practitioners are hardly able to assess the evidence of scientific information. Therefore, courses that introduce EBVM should be taught in veterinary education and post graduate education to train critical appraisal of information and to support decision-making based on valid, clinically relevant data.

2.3.3 Einleitung

Im veterinärmedizinischen Alltag ist es Aufgabe eines Tierarztes, Fachinformation vor ihrer Anwendung am Tier, im Sinne eines individuellen, Fall-spezifischen Vorgehens, hinsichtlich Eignung und Qualität zu beurteilen (3, 9). Dabei sollten diagnostische und therapeutische Entscheidungen stets auf neueste und wissenschaftlich solide Erkenntnisse von hoher Evidenz gestützt sein (11). Unter evidenzbasierter Medizin (EBM) wird der gewissenhafte, bewusste und vernünftige Gebrauch der gegenwärtig besten externen, wissenschaftlichen Evidenz für Entscheidungen in der medizinischen Versorgung individueller Patienten verstanden (16). Dabei beschreibt der Begriff Evidenz den Grad an

Sicherheit, mit der durch Studien erlangte Ergebnisse die Realität widerspiegeln (3) und damit in einer anderen Population (z.B. in der Praxis) reproduzierbar sind. Da Erkenntnisse hoher Evidenz in der Regel durch Studien gewonnen und in Fachzeitschriften veröffentlicht werden, stellen Publikationen ein wichtiges Bindeglied zwischen Forschung und Praxis dar (1). Neben Forschungsergebnissen können auch traditionell geprägtes veterinärmedizinisches Wissen, persönliche Erfahrungen oder auf Plausibilität beruhende Erwägungen zu einer korrekten medizinischen Entscheidung führen. Somit sollten, im Sinne einer bestmöglichen Betreuung des einzelnen Patienten, wissenschaftlich hochwertige Erkenntnisse stets mit persönlicher Fachkompetenz kombiniert werden (2).

In Deutschland ist nach § 6 Abs. 2 der Musterberufsordnung der Bundestierärztekammer jeder berufstätige Tierarzt verpflichtet, abhängig von einer eventuellen Spezialisierung, jährlich 20 bis 40 durch die Akademie für Tierärztliche Fortbildung zugelassene Fortbildungsstunden zu absolvieren.

Zusammen mit dem fortwährenden, logarithmischen Wachstum des veterinärmedizinischen Wissens selbst (5) nimmt auch im Rahmen des raschen technologischen Fortschritts die im Internet zugängliche Masse an Informationen ständig zu (10, 15). Im tierärztlichen Alltag ist es aufgrund dieser Informationsflut essentiell, die jeweils relevante Information verlässlich zu identifizieren (19). Um dies zu erreichen, ist eine kritische Betrachtung der jüngst veröffentlichten Forschungsergebnisse nötig. Dies zählt allerdings nicht zu den Hauptkompetenzen von Medizinern (18). Auch in der veterinärmedizinischen Lehre wird die Fähigkeit zur kritischen Bewertung von Informationen kaum unterrichtet und trainiert (4). Daher ist es dem einzelnen klinisch tätigen Tierarzt kaum möglich, zu einer speziellen klinischen Frage hilfreiche und zuverlässige Information in angemessener Zeit zu finden (2, 7).

Ziel der Untersuchung war es, einen Überblick über die Informationsbeschaffung und das subjektive Empfinden über deren Evidenzgrad durch die Tierärzteschaft zu erhalten. Im Rahmen verschiedener Fortbildungsveranstaltungen wurden klinisch tätige Tierärzte/innen im Zeitraum Mai 2010 bis November 2011 hinsichtlich ihres Verhaltens bei Informationsbeschaffung, -bewertung und Fortbildung befragt. Insbesondere sollte ermittelt werden, welche Informationsquellen für die Bewältigung der Fragestellungen im Praxisalltag genutzt werden und wie die Qualität dieser bewertet wird.

2.3.4 Material und Methoden

Zur Erhebung der Daten wurde eine empirische Untersuchung mittels eines Fragebogens durchgeführt. Um ein möglichst breites Spektrum an Tätigkeits- bzw. Interessensgebieten abzudecken, wurde die Befragung im Rahmen fünf verschiedener

Fortbildungsveranstaltungen durchgeführt. Dabei handelte es sich zum einen um zwei im Mai 2010 durch die pharmazeutische Industrie durchgeführte Veranstaltungen für Nutztierärzte. Veranstaltungsorte waren Schleswig-Holstein (100 Teilnehmer) und Brandenburg (80 Teilnehmer). Zum anderen fand eine Befragung im Rahmen des 8. Berlin-Brandenburgischer Rindertages (255 Teilnehmer), welcher vom 7.-9. Oktober 2010 durchgeführt wurde, statt. Außerdem wurden die Teilnehmer sowohl des 56. (21.-24. Oktober 2010, Düsseldorf) als auch des 57. (10.-13. Novermber 2011, Berlin) DGK-DVG-Jahreskongresses zum Thema „Entscheidungsfindung in der tierärztlichen Praxis“ befragt. Die Zahl der Kongressteilnehmer betrug hier jeweils 950 bzw. 1800.

Die Fragebögen waren den Tagungsmappen beigefügt worden, welche jedem Teilnehmer zu Kongressbeginn ausgehändigt wurde, oder als Tischvorlage ausgelegt. Außerdem wurden die Kongressteilnehmer durch diverse Redner auf die Durchführung der Befragung hingewiesen und um Teilnahme gebeten.

Um die Verständlichkeit zu prüfen, wurde vor dem Einsatz des Fragebogens ein Pretest mit den Mitarbeitern der Tierklinik für Fortpflanzung durchgeführt (n = 12).
Der selbstentwickelte Fragebogen (s. Anhang) enthielt insgesamt 32 Fragen. Davon bezogen sich 4 Fragen auf Person bzw. Tätigkeit und 3 auf die Qualifikation. 5 Fragen zielten auf das Fortbildungsverhalten ab, während 20 Fragen, die zum Teil mithilfe einer 5-stufigen Likert-Skala bewertet werden sollten (n = 19), eine Beleuchtung der Einschätzung und Anwendung der Konzepte der EBVM bezwecken sollten.

Die Auswertung der Daten erfolgte mit dem Statistikprogramm SPSS® (19.0 für Windows Version 19.0.0). Die Ergebnisse wurden deskriptiv als Häufigkeiten und Häufigkeitsverteilungen ausgewertet. Dabei wurden zum einen die Angaben aller Befragten ausgewertet sowie die Angehörigen verschiedener Tätigkeitsfelder, Kleintier-, Großtier- und Gemischtpraxis, miteinander verglichen. Um die befragten Tierärzte hinsichtlich eines gruppenspezifischen Antwortverhaltens zu untersuchen, wurden Kreuztabellen angefertigt. Anschließend wurden die vorhandenen Daten mithilfe des Chi-Quadrat-Tests auf signifikante Abhängigkeiten getestet. Dabei wurde als Signifikanzniveau der Wert $\alpha = 0,05$ gewählt. Abhängig von der Anzahl der befragten klinisch tätigen Tierärzte, die zu bestimmten Fragen keine Angabe machten, variiert die angeführte Grundgesamtheit (n).

2.3.5 Ergebnisse

Insgesamt wurden 293 Fragebögen größtenteils vollständig ausgefüllt. Dies entspricht einer Gesamtrücklaufquote von 9,2%. Davon entstammten 139 Stück Veranstaltungen für Nutztierärzte (Schleswig-Holstein, 2010: 34 Bögen, Rücklaufquote: 34,0%; Brandenburg, 2010: 52 Bögen, Rücklaufquote: 65,0%; 8. Berlin-Brandenburgischer

Rindertag, 2010: 53 Bögen, Rücklaufquote: 20,8%) und 154 Bögen einem DGK-DVG-Jahreskongress (56. DGK-DVG-Jahreskongress, Düsseldorf, 2010: 42 Bögen, Rücklaufquote: 4,4%; 57. DGK-DVG-Jahreskongress, Berlin, 2011: 112 Bögen, Rücklaufquote: 6,2%). 5 Teilnehmer arbeiteten an Universitäten oder im Bereich Lebensmittelsicherheit. Diese konnten somit nicht in eine der gewählten Gruppen eingeordnet werden und wurden bei der weiteren Betrachtung der einzelnen Tätigkeitsgruppen nicht berücksichtigt.

Person / Tätigkeit

Das Durchschnittsalter aller Befragten betrug 40,7 Jahre. Etwa die Hälfte (51,0%) aller Großtierpraktiker war jünger als 35 Jahre, während dies auf 32,2% der Kleintierpraktiker zutraf (Tab. 1). 61,1% aller Befragten waren weiblich, was auf 71,9% der Kleintierärzte und 47,7% der in der Gemischtpraxis tätigen Tierärzte zutraf. Hinsichtlich des Geschlechts bestanden zwischen Gemischt- und Kleintierpraktikern signifikante Unterschiede ($p < 0,001$). Es gaben genauso viele Teilnehmer an, selbstständig tätig wie als Assistenzarzt/ärztin angestellt zu sein (jeweils 45,5%). Die Mehrheit der selbstständig Tätigen (52,8%) arbeitete in der Gemischtpraxis, während der Großteil der Assistenztierärzte (54,9%) Großtierpraktiker waren. Bezüglich der Position (selbstständig oder als Assistenztierarzt tätig) ließen sich sowohl zwischen Klein- und Großtierpraktikern ($p = 0,003$) als auch zwischen Großtierpraktikern und den in der Gemischtpraxis Tätigen Unterschiede ($p = 0,002$) identifizieren.

Qualifikation

Hinsichtlich der Qualifikation verfügten die Befragten durchschnittlich über 13,0 Jahre Praxiserfahrung (Tab. 2). Während der Großteil der Kleintier- (40,9%) sowie der Großtierpraktiker (46,0%) zwischen 5 und 15 Jahren Praxiserfahrung aufweisen konnte, waren 43,5% der in der Gemischtpraxis tätigen Tierärzte bereits mehr als 15 Jahre in der Praxis tätig. 43,9% der Befragten gaben an, über keine weitere Qualifikation, wie Promotion, eine Fachtierarzt- oder Zusatzbezeichnung, zu verfügen. Unter Berücksichtigung der einzelnen Tätigkeitsgruppen waren es 33,3% der Kleintier-, 49,0% der Großtier- und 53,3% der Gemischtpraktiker, die keine der genannten weiterführenden Qualifikationen erlangt hatten. Insgesamt führten 6,5% der Befragten an, ihre Englischkenntnisse seien mangelhaft. Dabei lagen die befragten Kleintierärzte mit 1,6% deutlich unter und die Gemischtpraktiker mit 11,1% klar über diesen Wert. Mehr als die Hälfte aller Klein- (58,3%) bzw. Großtierpraktiker (54,9%) gaben an, ihre Englischkenntnisse reichten aus, um englischsprachige Fachvorträge oder Publikationen ohne Mühe erfassen zu können. Dies traf für etwa ein Viertel (26,9%) der in der Gemischtpraxis Tätigen zu. Bei der Untersuchung

des gruppenspezifischen Antwortverhaltens zeigten sich zwischen allen 3 Tätigkeitsgruppen statistisch signifikante Unterschiede (Klein- und Großtierpraktiker: p = 0,003; Kleintier- und Gemischtpraktiker: p = 0,000; Großtier- und Gemischtpraktiker, p = 0,049)

Fortbildungsverhalten

Beinahe alle Befragten (98,9%) gaben an, regelmäßig Fortbildungsveranstaltungen zu besuchen, wobei der Großteil (41,5%) 20-40 ATF-Stunden pro Jahr absolvierte (Tab. 3). Die meisten ATF-Stunden wurden von den Kleintierpraktikern absolviert. Dabei konnten zwischen Klein- und Großtierpraktikern sowie zwischen Kleintier- und Gemischtpraktikern deutliche Unterschiede festgestellt werden (p < 0,001). Auch zwischen Groß- und Gemischtpraktikern ließen sich statistisch signifikante Unterschiede bezüglich der geleisteten ATF-Stunden identifizieren (p = 0,022). 10,4% aller Befragten gaben an, keine veterinärmedizinischen Zeitschriften regelmäßig zu lesen. Dies galt für 13,5% der befragten Kleintierpraktiker sowie für 7,3% der in der Gemischtpraxis Tätigen. 86,9% aller Befragten lesen regelmäßig deutschsprachige veterinärmedizinische Zeitschriften. Etwa jeder fünfte Teilnehmer (20,8%) gab an, zusätzlich oder ausschließlich regelmäßig veterinärmedizinische Zeitschriften in englischer Sprache zu lesen. Bezüglich der Frage, wie viel Zeit sie durchschnittlich in das Suchen und Durcharbeiten von medizinischen Informationen investierten, kreuzte die Mehrzahl der Befragten (50,2%) 2-5 Stunden pro Woche an. Bei mehr als einem Drittel (37,0%) betraf dies in etwa 1 Stunde pro Woche oder weniger.

Beschaffung von Information und Einschätzung über deren Evidenzgrad

Fragen bezüglich genutzter Informationsquellen sowie deren Qualitätseinschätzung sollten mithilfe einer 5-stufigen Likert-Skala beantwortet werden (Tab. 4). 77,4% der Befragten gaben an, ihren Chef um Rat zu fragen („trifft voll und ganz zu“ bzw. „trifft zu“), falls sie bei einem Fall nicht weiterwüssten. Bezüglich eines Kollegen als Informationsquelle traf dies auf 83,1% zu. Dabei schätzen 84,7% der Befragten die Qualität dieser beiden Informationsquellen als hoch oder sehr hoch ein. Die Universität als Anlaufstelle bei spezifischen Problemen wird beinahe von der Hälfte aller Befragten (48,4%) genutzt („trifft voll und ganz zu“ bzw. „trifft zu“) und gleichzeitig von 78,6% als qualitativ hoch- oder sehr hochwertig bezeichnet. Insgesamt 66,2% der befragten Tierärzte gaben an, dass sie eine veterinärmedizinische Fachzeitschrift zu Rate ziehen, wenn sie bei einem Fall nicht weiter wissen („trifft voll und ganz zu“ bzw. „trifft zu“). Dabei sprachen 18,2% der Befragten deutschsprachigen und 25,7% englischsprachigen Fachzeitschriften eine maximale Qualität zu. Beinahe alle Teilnehmer (92,6%) gaben an, die Lösung für auftretende fachliche Probleme in einem Fachbuch zu suchen („trifft voll und ganz zu“ bzw. „trifft zu“). Dies spiegelt sich auch darin wieder, dass 88,6% der Befragten dem Fachbuch eine hohe bzw. sehr hohe Qualität einräumten. Bezüglich der Anwendung von Literaturdatenbanken verneinten 34,9% der Befragten, bei Bedarf diese Art der Informationsbeschaffung zu nutzen. Hinsichtlich der

Nutzung von Suchmaschinen traf das auf 23,6% der Befragten zu. Die Qualität des Internets wurde von dem Großteil (52,0%) der Befragten als mäßig eingeschätzt. 52,1% der teilnehmenden Tierärzte gaben an, themenverwandte Fortbildungsveranstaltungen zu besuchen, während deren Qualität als Informationsquelle von 64,2% als hoch und von 24,7% sogar als sehr hoch bezeichnet wird. Hinsichtlich der zugesprochenen Qualität bestanden signifikante Unterschiede zwischen den Antworten der Kleintier- und der Großtierpraktiker ($p = 0,027$). So schätzten Kleintierpraktiker Fortbildungsveranstaltungen generell als qualitativ hochwertiger ein. 68,6% der Befragten schätzen ihre Fähigkeit, geeignete Literatur zu finden, als sehr hoch oder hoch ein, wobei die Tierärzte aus der Kleintierpraxis im Vergleich zu denen aus der Gemischtpraxis ihr eigenes Können diesbezüglich signifikant besser beurteilten ($p = 0,004$). Eine hohe Fähigkeit, die gefundene Literatur hinsichtlich ihrer Qualität (Evidenz) beurteilen zu können, schrieben sich 52,1% der Befragten zu. Bezüglich neuer Methoden für Therapie oder Diagnostik will die Mehrheit (58,4%) vor einer Anwendung dieser in der eigenen Praxis warten bis breite Erfahrungswerte vorliegen (Abb. 1). Ein deutlich geringerer Prozentsatz (28,8%) ist bereit, eine neue Methode bei der ersten sich bietenden Gelegenheit anzuwenden. In diesem Zusammenhang bestanden statistisch signifikante Unterschiede sowohl zwischen Klein- und Großtierpraktikern als auch zwischen den Tierärzten, die in der Kleintierpraxis arbeiteten, und denjenigen, die in der Gemischtpraxis tätig waren ($p < 0,0001$). Dabei verzichteten Großtierpraktiker genauso wie in der Gemischtpraxis Tätige im Gegensatz zu den Kleintierpraktikern eher darauf, eine neue Methode anzuwenden, wenn bereits eine wirksame Methode existierte.

2.3.6 Diskussion

Im Rahmen der Auswertung von Umfrageergebnisse gilt es auch immer, den angewandten Fragebogen hinsichtlich Verständlichkeit und Aussagekraft kritisch zu betrachten. Um beides zu gewährleisten, wurde im Vorfeld ein Pretest an klinisch tätigen Tierärzten (Mitarbeitern der Tierklinik für Fortpflanzung) durchgeführt ($n = 12$). Aufgrund der Antworten konnte gefolgert werden, dass die Fragen verstanden wurden. Auch kann die Anwendung einer so genannten Likert-Skala diskutiert werden, da die Befragten durch eine Solchen dazu tendieren, Extremaussagen zu vermeiden. Jedoch werden Likert Skalen häufig verwendet, da der Befragte den Level der Übereinstimmung bzw. Ablehnung spezifizieren kann, was die Genauigkeit der Ergebnisse wiederum steigert.

Die Ergebnisse dieser Umfrage erlauben interessante Einblicke in das Fortbildungsverhalten der Tierärzte/innen in Deutschland und die Anwendung der Grundlagen der EBVM. Jedoch kann diese Umfrage nur sehr eingeschränkt als repräsentativ

angesehen werden, da die Fragebögen im Rahmen von Fortbildungen und Kongressen ausgeteilt wurden. Insofern erfolgte die Stichprobenauswahl an Hand einer einfachen Verfügbarkeit und bedingt eine Vorselektion der Umfrageteilnehmer (convenience sample). Somit kann vermutet werden, dass unter den Teilnehmern Personen überrepräsentiert sind, die sich gern und viel fortbilden.

Besonders auffällig sind die niedrigen Rücklaufquoten der Befragungen im Rahmen der DGK-DVG-Jahreskongresse. Grund hierfür ist möglicherweise der Umstand, dass die Bögen in den Tagungsmappe enthalten waren. Da sich im Rahmen solch groß angelegter Veranstaltungen dort ebenfalls zahlreiches Werbematerial der Industrie befindet, ist die Umfrage möglicherweise vielen Kongressteilnehmern entgangen. Im Gegensatz zu den Fortbildungsveranstaltungen für Großtierpraktiker, war es uns durch die zeitgleiche Durchführung verschiedener Work Shops bzw. Seminare bei den Kleintierkongressen zudem nicht möglich, jeden Teilnehmer durch explizite Hinweise der Redner auf die Befragung zu erreichen.

Beinahe die Hälfte der Befragten (47,4%) sagte aus, dass sie auf Grund ihrer Sprachkenntnisse englische Fachvorträge oder Publikationen ohne Mühe verstehen können. Die Kongressbeiträge waren bei allen Veranstaltungen in Zusammenhang mit der vorliegenden Umfrage fast ausnahmslos in deutscher Sprache. Daher kann eine Vorselektion der Teilnehmer durch die Kongresssprache weitgehend ausgeschlossen werden. Allerdings gaben nur 20,8% der Befragten an, regelmäßig englischsprachige veterinärmedizinische Fachzeitschriften zu lesen. Dies kann insofern ein Problem darstellen, als dass vermutlich viele praxisrelevante Informationen zunächst auf Englisch publiziert werden und erst verspätet in der deutschen Literatur aufgegriffen werden.

Bemerkenswert ist, dass beinahe jeder der befragten klinisch tätigen Tierärzte im Falle eines veterinärmedizinischen Problems Fachbücher zu Rate zieht und dessen Qualität auch vom überwiegenden Anteil als hoch oder sehr hoch eingeschätzt wird. Tatsache ist allerdings, dass die Information in Fachbüchern aufgrund des langen Weges bis zur Veröffentlichung nicht selten als veraltet anzusehen ist (17). Außerdem existieren kaum festgelegte Qualitätsanforderungen oder -kontrollen, z.B. in Form eines Gutachtersystems, sodass Fachbücher im schlechtesten Fall lediglich die Meinung einzelner Experten repräsentieren. Nach Bassler und Antes (1) repräsentiert eine solche Expertenmeinung den niedrigsten Grad an Evidenz.

Ebenfalls auf der untersten Evidenzstufe einzuordnen ist der Rat eines tatsächlichen oder vermeintlichen Experten (Hochschulangehöriger, Chef, Kollege). Nichts desto trotz wird v.a. der Rat des Chefs oder eines Kollegen im Falle eines medizinischen Problems von einem beträchtlichen Anteil der Befragten eingeholt und als qualitativ hoch bzw. sehr hochwertig beurteilt. Auch Cockcroft et al. (6) sprachen dem Ideenaustausch mit Kollegen

eine hohe Relevanz, jedoch nur eine moderate Validität zu. Dem in einer Fachzeitschrift publizierten Artikel als Quelle medizinischer Information sprachen sie dahingegen eine hohe Validität, jedoch nur eine geringe Relevanz zu. Diese Aussagen decken sich mit den Ergebnissen unserer Studie, die zeigen, dass nicht einmal zwei Drittel der Befragten Fachzeitschriften zu Rate ziehen.

Literaturdatenbanken und Suchmaschinen, stellen durchaus wertvolle und ertragreiche Informationsquellen dar (14), werden im Bedarfsfall jedoch nicht einmal von jedem zweiten praktizierenden Tierarzt genutzt. Dies liegt vermutlich daran, dass eine Literatursuche mithilfe der genannten Medien nicht nur zeitintensiv ist, sondern auch eine gewisse Erfahrung bezüglich Suchstrategien sowie den zu verwendenden Schlagwortkombinationen voraussetzt (12). Eine entsprechende Einarbeitung ist dem Tierarzt aufgrund des Zeitmangels in der täglichen Praxis kaum möglich. Zudem sind zahlreiche der im Internet gefundenen Artikel von Fachzeitschriften gebührenpflichtig (8). Interessanterweise gelingt es dem Großteil der Befragten aber trotz des existenten Zeitmangels 2-5 Stunden pro Woche in das Suchen und Durcharbeiten medizinischer Informationen zu investieren. Zusätzlich besteht das Problem der fehlenden Kompetenz hinsichtlich einer Qualitätsbewertung. Die Qualität einer Studie wird durch ihr Design, ihre klinische Relevanz, die Analyse der Studienergebnisse sowie die Vollständigkeit der Berichterstattung bestimmt (3). Da Datenbanken und Suchmaschinen Literatur lediglich zur Verfügung stellen, diese jedoch nicht bewerten, ist ein Veterinärmediziner, der im Umgang mit wissenschaftlicher Literatur ungeübt ist, kaum in der Lage, die Qualität einzelner Studien und ihrer Ergebnisse einzuschätzen (8). Vorangegangene Studien haben gezeigt, dass die Qualität klinischer Studien sehr unterschiedlich sein kann, auch wenn diese in Zeitschriften mit Peer-Review-Verfahren publiziert wurden (13). Im Rahmen der durchgeführten Umfrage wurde gefragt, wie die Teilnehmer ihre Fähigkeiten zur Qualitätsbewertung von Literatur einschätzten. Dabei wurde nicht auf spezifische Qualitätskriterien wie Vorhandensein einer Kontrollgruppe oder objektive Berichterstattung eingegangen. Möglicherweise hätte eine gezieltere Befragung spezifischer die Stärken und Schwächen der einzelnen Teilnehmer bezüglich der Bewertung medizinischer Informationen aufgezeigt. Entsprechend sollten die Fähigkeiten, praktizierender Tierärzte, Schwachstellen in Fachartikeln zu finden, in Folgestudien eingehend untersucht werden. Im Studium werden diese Fähigkeiten kaum vermittelt (10, 15) und auch im Berufsleben gibt es hierfür nur vereinzelt Fortbildungsangebote. Daher muss befürchtet werden, dass ein entsprechendes Problembewusstsein hinsichtlich möglicher Schwachstellen in der Literatur wenig ausgeprägt ist.

Schlussfolgernd kann festgehalten werden, dass sich die Umfrageteilnehmer entsprechend der Musterberufsordnung der Bundestierärztekammer fortbilden. Es ist jedoch

auch festzustellen, dass die Anwendung der Konzepte der EBM, und insbesondere die Fähigkeit zur Einschätzung der Qualität diverser Informationsquellen durch den praktischen Tierarzt, momentan noch enorme Mängel aufweisen. Es besteht der dringende Bedarf, die Grundlagen der EBM sowohl in die Ausbildung der Studenten als auch in die postgraduelle Ausbildung zu integrieren.

2.3.7 Literatur

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Tab. 1 Demographische Angaben unter Berücksichtigung des Tätigkeitsfeldes

Table 1 Demographic data considering several disciplines

	Gesamt[2] (n=293)		**Kleintierpraktiker (n=128)**		**Großtierpraktiker[1] (n=51)**		**Gemischtpraktiker (n=109)**	
Aussage	Absolut	%	Absolut	%	Absolut	%	Absolut	%
Geschlecht								
männlich	114	38,9	36	28,1	19	37,3	57	52,3
weiblich	179	61,1	92	71,9	32	62,7	52	47,7
Alter								
≤ 35 Jahre	108	39,1	39	32,2	25	51,0	40	39,6
36-50 Jahre	116	42,0	64	52,9	19	38,8	32	31,7
> 50 Jahre	52	18,8	18	14,9	5	10,2	29	28,7
Position								
selbstständig	133	45,5	64	50,0	12	23,5	57	52,8
Assistent	133	45,5	55	43,0	28	54,9	48	44,4
Sonstiges	26	9,0	9	7,0	11	21,6	3	2,8

[1] Nutztiere & Pferde

[2] 5 Teilnehmer arbeiteten an Universitäten oder im Bereich Lebensmittelsicherheit und konnten somit nicht in eine der gewählten Gruppen eingeordnet werden. Demnach entsprechen die Zahlen der „Gesamt"-Spalte nicht der Summe der einzelnen Gruppen.

Tab. 2 Angaben zur Qualifikation unter Berücksichtigung des Tätigkeitsfeldes

Table 2 Data concerning qualification considering several disciplines

	Gesamt[3] (n=293)		**Kleintierpraktiker (n=128)**		**Großtierpraktiker[1] (n=51)**		**Gemischtpraktiker (n=109)**	
Aussage	Absolut	%	Absolut	%	Absolut	%	Absolut	%
Praxiserfahrung								
< 5 Jahre	83	28,6	32	25,2	16	32,0	32	29,6
5-15 Jahre	105	36,2	52	40,9	23	46,0	29	26,9
> 15 Jahre	102	35,2	43	33,9	11	22,0	47	43,5
Weitergehende Qualifikationen[2]								
keine	127	43,9	42	33,3	25	49,0	57	53,3
Promotion	142	49,1	73	58,0	24	47,1	44	41,1
Fachtierarzt	49	16,9	26	20,6	4	7,9	17	15,8
Zusatzbezeichnung (en)	21	7,3	3	6,0	3	6,0	7	6,6
Englischkenntnisse[2]								
mangelhaft	19	6,5	2	1,6	1	2,0	12	11,1
Schulenglisch	74	25,3	19	15,1	13	25,5	42	38,9
Alltagsgespräch	98	33,7	46	36,2	18	35,3	33	30,7
Fachvortrag / Publikation	138	47,4	74	58,3	28	54,9	28	26,9

[1] Nutztiere & Pferde

[2] Mehrfachnennungen sind aufgetreten

[3] 5 Teilnehmer arbeiteten an Universitäten oder im Bereich Lebensmittelsicherheit und konnten somit nicht in eine der gewählten Gruppen eingeordnet werden. Demnach entsprechen die Zahlen der „Gesamt"-Spalte nicht der Summe der einzelnen Gruppen wieder.

Tab. 3 Angaben zum Fortbildungsverhalten unter Berücksichtigung des Tätigkeitsfeldes
Table 3 Data regarding continuing education considering several disciplines

	Gesamt[3] (n=293)		**Kleintierpraktiker (n=128)**		**Großtierpraktiker[1] (n=51)**		**Gemischtpraktiker (n=109)**	
Aussage	Absolut	%	Absolut	%	Absolut	%	Absolut	%
Absolvierte ATF-Std								
<10 Std pro Jahr	11	3,8	1	0,8	7	14,0	3	2,8
10-20 Std pro Jahr	117	40,8	36	28,6	19	38,0	61	56,5
20-40 Std pro Jahr	119	41,5	63	50,0	19	38,0	36	33,3
> 40 Std pro Jahr	40	13,9	26	20,6	5	10,0	8	7,4
Lesen regelmäßig vetmed Journals[2]								
Nein	30	10,4	17	13,5	5	10,2	8	7,3
Ja, deutschsprachig	251	86,9	106	84,1	41	83,6	99	90,8
Ja, englischsprachig	60	20,8	31	24,6	14	28,5	13	11,9
Zeit zum Suchen & Durcharbeiten med Info								
< 1 Std pro Woche	22	7,7	6	4,8	5	10,4	11	10,1
Ca. 1 Std pro Woche	84	29,3	37	29,6	16	33,3	31	28,4
2-5 Std pro Woche	144	50,2	67	53,6	18	37,5	58	53,2
> 5 Std pro Woche	37	12,9	15	12,0	9	18,8	9	8,3

[1] Nutztiere & Pferde

[2] Mehrfachnennungen sind aufgetreten

[3] 5 Teilnehmer arbeiteten an Universitäten oder im Bereich Lebensmittelsicherheit und konnten somit nicht in eine der gewählten Gruppen eingeordnet werden. Demnach entsprechen die Zahlen der „Gesamt"-Spalte nicht der Summe der einzelnen Gruppen wieder.

Tab. 4 Angaben zur Einschätzung und Anwendung der Konzepte der Evidenzbasierten Veterinärmedizin

Table 4 Data concerning the application of evidence-based veterinary medicine

Aussage	**Trifft voll & ganz zu**		**Trifft zu**		**Trifft mäßig zu**		**Trifft nicht zu**		**Trifft gar nicht zu**	
	Absolut	%	Absolut	%	Absolut	%	Absolut	%	Absolut	%
Informations-quellen										
Chef	65	40,9	58	36,5	22	13,8	5	3,1	9	5,7
Kollege	93	32,9	142	50,2	41	14,5	6	2,1	1	0,4
Pharmaindustrie	2	0,8	50	19,9	100	39,8	55	21,9	44	17,5
Universität	33	12,4	96	36,0	84	31,5	34	12,7	20	7,5
Fachzeitschrift	54	20,1	124	46,1	68	25,3	18	6,7	5	1,9
Fachbuch	145	51,1	118	41,5	20	7,0	1	0,4	0	0,0
Literatur-datenbank	34	13,3	70	27,5	62	24,3	49	19,2	40	15,7
Suchmaschine	32	12,0	93	34,8	79	29,6	45	16,9	18	6,7
Fortbildung	40	14,8	101	37,3	97	35,8	20	7,4	13	4,8
Hohe Qualität der Informationsquellen										
Chef/Kollege	27	26,0	61	58,7	13	12,5	2	1,9	1	1,0
Pharmaindustrie	5	1,9	73	27,5	133	50,2	37	14,0	17	6,4
Universität	63	23,7	146	54,9	44	16,5	10	3,8	3	1,1
Fachzeitschrift, deutschsprachig	52	18,2	187	65,6	40	14,0	6	2,1	0	0,0
Fachzeitschrift, englischsprachig	61	25,7	137	57,8	28	11,8	4	1,7	7	3,0
Fachbuch	99	34,4	156	54,2	32	11,1	1	0,3	0	0,0

Internet	27	9,7	80	28,7	145	52,0	23	8,2	4	1,4
Fortbildung	71	24,7	185	64,2	29	10,1	3	1,0	0	0,0
Hohe Fähigkeit, Literatur										
… zu finden	33	11,6	162	57,0	179	27,8	9	3,2	1	0,4
…zu beurteilen	17	6,0	131	46,1	125	44,0	9	3,2	2	0,7

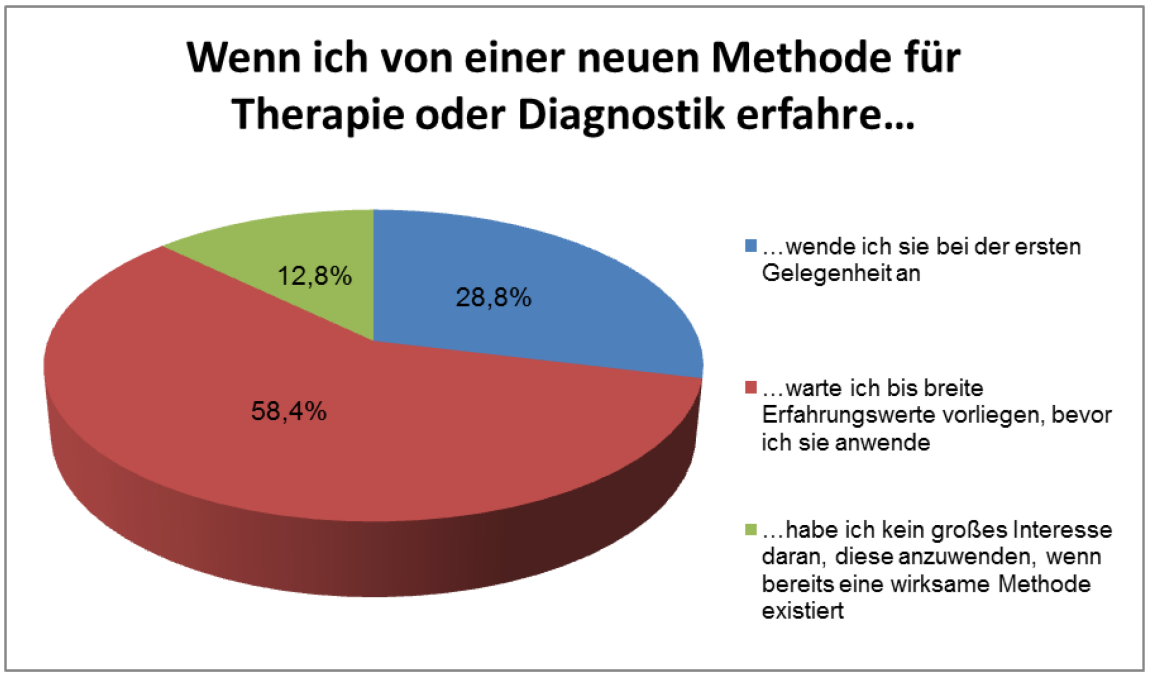

Abb 1 Standpunkt hinsichtlich des Einsatzes neuer medizinischer Methoden

Fig. 1 Attitude towards applying new methods

3. DISCUSSION

The overall objective of the conducted studies was to elucidate the status quo concerning the evidence of available literature and the implementation of evidence-based veterinary medicine (EBVM). Specifically, the objectives were 1) to evaluate the quality and comparability of published literature concerning the treatment of bovine endometritis with $PGF_{2\alpha}$, 2) to assess the efficacy of the treatment of bovine endometritis with $PGF_{2\alpha}$ by means of meta-analysis, and 3) to outline the current assessment and employment of EBVM with the help of a survey among practitioners concerning continuing education and their skills in obtaining and evaluating scientific information.

The results of the first study show a wide discrepancy between research results investigating the efficacy of $PGF_{2\alpha}$. However, our investigation encompassed studies conducted in four different decades. Considering the significant changes seen in the dairy industry, particularly with respect to housing, feeding, and management (LeBlanc et al., 2006), one might question whether comparability among those studies can be assessed at all. Furthermore, the results of the first study showed that the evidence for the efficacy of $PGF_{2\alpha}$ for the treatment of chronic bovine endometritis is limited. As an example, only about one third of all trials was controlled and randomized. This deficiency might be due to the high costs involved and ethical issues related to leaving diseased animals untreated which might cause serious animal welfare concerns.

Concerning the efficacy of $PGF_{2\alpha}$, the conducted meta-analysis did not reveal an improvement of reproductive performance of cows with endometritis after treatment with $PGF_{2\alpha}$. Even though, since there is a shortage of comparable high quality studies dealing with this topic, the performed meta-analysis did allow the consideration of six (calving to conception interval) and five (calving to first service interval) studies, respectively. In addition, significant heterogeneity was found among those studies. Furthermore, due to deficiencies regarding evidence, also non-randomized trials had to be included. Due to those facts, the findings of the conducted meta-analysis must be considered with caution since these methods have been developed to summarize the results of randomized, controlled trials. Consequently, extending its use to observational studies must account for the variability of study designs and populations employed (Fourichon et al., 2000).

There are also aspects of evidence-based medicine that need critical discussion. Arlt and Heuwieser (2005), for instance, pointed out several controversial aspects. Clinical freedom is constrained by the “best kind of medical treatment” provided by evidence-based medicine. Furthermore, they criticized that meta-analyses which, according to Bassler and Antes (2000) represent the highest level of evidence, can only provide retrospective information, and therefore are hardly up-to-date. In addition, Brosteanu and Löffler (1998)

pointed out that meta-analyses might relate studies which due to differences in quality and design are not comparable. Also, may meta-analyses reveal flaws concerning methodology as well as reporting (Jefferson et al., 2002).

Meta-analyses are systematic summaries of a large collection of results from individual studies (Glass, 1976). Therefore, they can support practitioners, mostly facing a lack of time (Dicty, 2007), in making clinical decisions (Eisend, 2004). However, reading and understanding a meta-analysis might be challenging for the reader. This is supported by Lam and Kennedy (2005) who point out that it is important for clinicians to understand the key principles of meta-analysis to properly evaluate the relevance of the results. Hence, as an alternative in urgent cases, one should promote answering a clinical question with the help of critically appraised topics (CATs). That is a standardized summary of research evidence regarding a clinical question (Sauve et al., 1995) generated from a specific patient situation or problem (Foster et al., 2001).

In combination with most recent results (Dubuc et al., 2010b), we suggest to critically reconsider the use of $PGF_{2\alpha}$ as a “best practice” standard treatment for endometritis. Further research in form of controlled, randomized and blinded trials is urgently required to assess and quantify efficacy of this treatment.

Besides the demonstrated shortage of high quality veterinary literature, the third study, a survey among practitioners, revealed that most practitioners are hardly able to assess the evidence of scientific information. However, about two-thirds of the respondents assessed their ability to find eligible literature as high or very high. As Dicty (2007) pointed out, high-quality research is only useful if the results are published in a high-quality manner and can be found with minimal amount of labour input involved. Thus, it can be concluded that the best sources of information are those offering relevant and valid data which can be obtained by a minimum of labour input (Smith, 1996). Moreover, Dicty (2007) emphasized the necessity for bundled information accessible fast and with moderate costs involved. Due to the fact that, in contrast to human medicine, there is neither an institution comparable to the Cochrane Collaboration nor an online database offering systematic reviews and clinical trials exclusively for veterinary topics, the allocation of scientific literature in the field of veterinary medicine is especially crucial (Dicty, 2007).

Due to the insufficient knowledge concerning the assessment of the evidence of scientific information, courses that introduce EBVM should be taught in veterinary clinical education and post graduate training to enable critical appraisal of information and to support decision-making based on valid, clinically relevant data.

4. SUMMARY

Peggy Haimerl: Therapy of Bovine Endometritis with Prostaglandin $F_{2\alpha}$ - An Evidence Based Approach

The decision making process of practicing veterinarians as well as farm personnel and animal scientists should be based on objective information. Therefore, the implementation of evidence based medicine becomes increasingly important. However, 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. Also, there is a remarkable variation in the quality of studies in veterinary and animal science. Hence, in veterinary medicine the increase of knowledge is mainly based on reviewing field reports rather than randomized, controlled clinical studies. Nevertheless, randomized, controlled, double blinded studies are the gold standard with regard to the evaluation of a given treatment.

Postpartum uterine infections are a frequent disorder in dairy cattle with a prevalence up to 57.7%. In addition, they are reported to have an immense negative impact on reproductive performance resulting in high opportunity costs for the farmers.

The overall objective of the conducted studies was to elucidate the status quo concerning the evidence of available literature and the implementation of evidence-based veterinary medicine (EBVM).

In the first study, the quality and comparability of published literature concerning the treatment of bovine endometritis with $PGF_{2\alpha}$ was evaluated.

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 utilising 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 was controlled and randomized, while 3 of those (4.4%) were also blinded. In conclusion, the first study showed a wide discrepancy between research results investigating the efficacy of $PGF_{2\alpha}$.

The second study aimed at a quantitative assessment of the efficacy of the treatment of bovine endometritis with $PGF_{2\alpha}$ by means of meta-analysis.

After applying specific exclusion criteria and evaluating specific evidence parameters, a total of five publications, comprising six trials, were eligible for being analysed by means of meta-analysis. Data for each trial were extracted and analysed using meta-analysis software Review Manager 5.1. Estimated effect sizes of $PGF_{2\alpha}$ were calculated on calving to first service and calving to conception interval. $PGF_{2\alpha}$ treatment of cows with chronic endometritis had a negative impact on both reproductive performance parameters. Heterogeneity was

substantial for calving to first service and calving to conception interval [I^2 (measure of variation beyond chance) = 100% and 87%, respectively]; therefore, random effects models were used. Sensitivity analysis as well as subgroup analysis showed that the performance of randomization was influential in modifying effect size of $PGF_{2\alpha}$ treatment. The funnel plot illustrated a publication bias towards smaller studies that reported a prolonged calving to conception interval after a $PGF_{2\alpha}$ treatment. In conclusion, the investigation of this subject by means of meta-analysis did not reveal an improvement of reproductive performance of cows with endometritis after treatment with $PGF_{2\alpha}$.

The objective of the third study was to outline the current assessment and employment of evidence-based veterinary medicine with the help of a survey among practitioners concerning continuing education (EBVM) and their skills in obtaining and evaluating scientific information.

For this purpose, a survey amongst veterinary practitioners was conducted throughout five conferences between Mai 2010 and November 2011. The questionnaire contained 32 questions concerning demographic data and profession (n = 4), qualification (n = 3), continuing education (n = 5) and skills concerning EBVM (n = 20). Besides evaluating the statements of all participants, veterinarians were classified based on the type of practice and their statements compared.

In total, 293 questionnaires were returned. The majority of small animal practitioners (58.3%) and those working with food animals (54.9%) declared being capable of comprehending scientific talks or papers in English without difficulty. 10.4% of all practitioners negated reading veterinary journals on a regular basis, while 20.8% stated to regularly read English veterinary journals. The majority of the practitioners sought advice from their employer or a colleague. They attribute a high or very high quality to both information sources. Almost every participant (92.6%) stated to consult medical books, and 88.6% certify this information source a high or very high quality. 68.6% of the practitioners evaluated their skills in finding suitable literature as high or very high. However, only about half (52.1%) of all participants attributed themselves a high ability to evaluate the quality of the found literature.

Based on these findings, it can be concluded that most practitioners are hardly able to assess the evidence of scientific information. Therefore, courses that introduce EBVM should be taught in veterinary education and post graduate education to train critical appraisal of information and to support decision-making based on valid, clinically relevant data.

5. ZUSAMMENFASSUNG

Peggy Haimerl: Behandlung der bovinen Endometritis mit Prostaglandin $F_{2\alpha}$ - Ein evidenzbasierter Ansatz

Entscheidungsfindungen in der täglichen tierärztlichen Praxis und Wissenschaft sowie durch Mitarbeiter landwirtschaftlicher Betriebe sollten stets auf objektiven Informationen basieren. Deshalb gewinnt die Anwendung der Evidenzbasierten Medizin zunehmend an Bedeutung. Allerdings sehen wir in der Veterinärmedizin einen Mangel an gründlich und systematisch durchgeführten groß angelegten klinischen Studien, was wiederum einen Mangel an Forschungsergebnissen hoher Evidenz nach sich zieht. Zusätzlich beobachtet man eine enorme Variation hinsichtlich der Qualität veterinärmedizinischer Studien. Daher basiert der Wissenszuwachs im veterinärmedizinischen Bereich v.a. auf Erfahrungsberichten anstatt auf randomisierten, kontrollierten klinischen Studien. Randomisierte, kontrollierte, doppelt verblindete Studien stellen jedoch den Goldstandard bezüglich der Beurteilung einer bestimmten Behandlungsstrategie dar.

Postpartale Gebärmutterentzündungen stellen mit einer Prävalenz von bis zu 57,7% eine häufige Störung bei der Milchkuh dar. Diese verursachen aufgrund von beträchtlichen negativen Auswirkungen auf die Folgefruchtbarkeit hohe Zusatzkosten für die Landwirte.

Daher war es das übergreifende Ziel der durchgeführten Studien, den Status Quo hinsichtlich der Evidenz der verfügbaren Literatur sowie der Anwendung bzw. der Umsetzung der Evidenzbasierten Veterinärmedizin (EBVM) einmal näher zu beleuchten.

In einer ersten Studie wurde die Qualität und Vergleichbarkeit der verfügbaren Literatur zum Thema Behandlung der bovinen Endometritis mit $PGF_{2\alpha}$ ausgewertet.

Dafür wurden mithilfe einer umfassenden, systematischen Literaturrecherche in Online Datenbanken bzw. Suchmaschinen 2723 Referenzen zu der untersuchten Thematik gefunden. Nach Anwendung spezifischer Ausschlusskriterien verblieben 68 Studien für eine weitere Auswertung. Diese Artikel wurden mithilfe eines speziellen Bewertungsbogens hinsichtlich spezifischer Parameter, wie z.B. dem Vorhandensein einer Kontrollgruppe sowie der Zuordnung zu den einzelnen Gruppen, beurteilt. Diese Auswertung zeigte, dass mehr als die Hälfte der Studien (51,5%) älter als 20 Jahre waren. Zusätzlich zeigte sich, dass etwa ein Drittel (36,8%) der untersuchten Studien kontrolliert und randomisiert waren, während 3 dieser Studien (4,4%) zusätzliche verblindet durchgeführt worden waren. Zusammenfassend lässt sich sagen, dass die Forschungsergebnisse hinsichtlich der Wirksamkeit von $PGF_{2\alpha}$ sehr unterschiedlich sind.

Aufbauend auf die erste Studie zielte die zweite Studie auf die quantitative metaanalytische Bewertung der Behandlung der chronischen Endometritis der Kuh mittels $PGF_{2\alpha}$ ab.

Nach der Anwendung spezifischer Ausschlusskriterien und der Bewertung der verbliebenen Studien hinsichtlich bestimmter Evidenzparameter konnten 5 Publikationen, welche insgesamt 6 Studien umfassten, in die Metaanalyse eingeschlossen werden. Die Extraktion und Auswertung der Studiendaten erfolgte unter Verwendung des Review Managers 5.1. Dabei wurden mithilfe dieser Software Effektgrößen bezüglich der Auswirkung einer $PGF_{2\alpha}$ Behandlung auf Rast- und Güstzeiten berechnet. Die Ergebnisse zeigten eine negative Beeinflussung beider Reproduktionsparameter durch eine $PGF_{2\alpha}$ Behandlung. Auch bezüglich beider Parameter zeigte sich eine beachtliche Heterogenität zwischen den Studien [I^2 (echte Varianz) Rastzeit = 100% bzw. Güstzeit = 87%]. Sowohl die durchgeführte Sensitivitätsanalyse sowie die Untersuchung einzelner Untergruppen machten deutlich, dass die Durchführung einer Randomisierung die Effektgröße durch eine $PGF_{2\alpha}$ Behandlung beeinflusste. Im Rahmen der Untersuchung auf einen Publikationsbias zeigte die erstellte Trichtergraphik eine Verzerrung durch kleine Studien, die eine verlängerte Güstzeit nach einer $PGF_{2\alpha}$ Behandlung bescheinigten. Zusammenfassend ist festzustellen, dass die Metaanalyse keine Verbesserung der Folgefruchtbarkeit nach einer Behandlung der bovinen Endometritis mit $PGF_{2\alpha}$ aufzeigen konnte.

Die dritte Studie, eine Umfrage unter praktizierenden Tierärzten, hatte zum Ziel, einen Überblick über die momentane Einschätzung und Anwendung der Konzepte der EBVM zu erhalten. Zu diesem Zweck wurden im Rahmen von 5 verschiedenen Fortbildungsveranstaltungen klinisch tätige Tierärzte/innen hinsichtlich ihres Informationsbeschaffungs-, -bewertungs- und Fortbildungsverhaltens befragt. Der Fragebogen enthielt insgesamt 32 Fragen, welche sich auf Person/Tätigkeit (n = 4), erworbene Qualifikationen (n = 3), das Fortbildungsverhalten (n = 5) sowie die Anwendung der EBVM (n = 20) bezogen. Zusätzlich zur Auswertung der Angaben aller Befragten wurden die Angaben von Kleintier-, Großtier- und Gemischtpraktikern miteinander verglichen. Insgesamt wurden 293 Fragebögen ausgefüllt. Mehr als die Hälfte aller Klein- (58,3%) bzw. Großtierpraktiker (54,9%) gaben an, ihre Englischkenntnisse reichten aus, um englischsprachige Fachvorträgen oder Publikationen ohne Mühe erfassen zu können. 10,4% aller Befragten gab an, keine veterinärmedizinischen Zeitschriften regelmäßig zu lesen, während 20,8% der klinisch tätigen Tierärzte angaben, regelmäßig englischsprachige Fachliteratur zu lesen. Der überwiegende Anteil der Tierärzte fragte im Problemfall ihren Chef oder Kollegen um Rat. Diese beiden Informationsquellen werden als qualitativ hoch oder sehr hoch eingeschätzt. Beinahe alle Teilnehmer (92,6%) gaben an, die Lösung für auftretende fachliche Probleme in einem Fachbuch zu suchen, dem ebenfalls eine hohe bzw.

sehr hohe Qualität einräumt wird. 68,6% der Befragten schätzen ihre Fähigkeit, geeignete Literatur zu finden, als sehr hoch oder hoch ein. Eine hohe Fähigkeit, die gefundene Literatur hinsichtlich ihrer Qualität (Evidenz) kritisch beurteilen zu können, schrieben sich jedoch lediglich 52,1% der Befragten zu. Schlussfolgernd ist zu sagen, dass die Mehrheit der klinisch tätigen Tierärzte nur begrenzt in der Lage ist, Informationen hinsichtlich ihrer Evidenz einzuschätzen. Daher sollte ein Ziel sein, es Tierärzten bereits im Studium sowie in ihrer postgraduellen Ausbildung näher zu bringen, sich mit medizinischen Informationen kritisch auseinanderzusetzen und klinische Entscheidungen basierend auf soliden Daten zu treffen.

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9. DECLARATION OF INDEPENDENCE

Hiermit bestätige ich, dass ich die vorliegende Arbeit selbstständig angefertigt habe. Ich versichere, dass ich ausschließlich die angegebenen Quellen und Hilfen in Anspruch genommen habe.

Berlin, den 20.02.2013

Peggy Haimerl