



## Therapy of retained fetal membranes in cattle: Comparison of two treatment protocols



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### ABSTRACT

This prospective study was conducted to compare two treatment protocols for retained foetal membranes (RFM) in cattle. The routine therapy consisting of intrauterine tetracycline boluses was compared with the administration of ozone foam, both intrauterine therapies without attempts to manually remove the placenta. Cows undergoing caesarean section, suffering from uterine torsion or prolapse of the uterus, and other illnesses than RFM on the first day post-partum were excluded. Values for baseline variables as age, breed, yearly milk yield, parity, pregnancy duration, calving season and number of routine intrauterine treatments were not different between the groups. Number of days with rectal temperature > 39.7 °C within the first 10 days in milk (DIM) were greater in the ozone group. Number of escape therapies were recorded when there was imposing of this therapy as a result of cows having a fever (based on rectal temperature > 39.7 °C) and a significant reduced food intake. Escape therapies consisted of parenteral administration of tetracyclines and NSAIDs during the first 10 DIM. Number of escape therapies, however, was not different between the groups. Results from use of a logistic regression model with fever as a dichotomous variable indicated there was no effect of breed, studbook, type of stall, pasture, business and no effect of age or milk yield. In a second assessment, cows were evaluated until 200 DIM. Results from a survival analysis indicated group (Te/Oz) did not affect rate of culling from the herd.

### 1. Introduction

Retention of the fetal membranes (RFM) followed by metritis and endometritis is a common and severe problem in dairy cattle (Sheldon et al., 2006). In a review of 50 reports on the incidence of RFM, the median lactational incidence rate was 8.6% (Kelton et al., 1998). The RFM is defined as the failure to expel fetal membranes within 12–24 h after parturition (Fourichon et al., 2000; Drillich et al., 2003). The RFM is a risk factor for subsequent ketosis, displaced abomasum and mastitis (Oltenacu et al., 1990). In Switzerland as in other European countries, the routine treatment of RFM in veterinary practices consists of a local antibiotic therapy, often combined with the manual removal of the placenta (Laven and Peters, 1996; Hehenberger et al., 2015). As an intrauterine therapy, tetracycline boluses are used in > 80% of the RFM cases in Switzerland (Hehenberger et al., 2015). Antimicrobials

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administered as uterine infusions or boluses, however, do not reduce the incidence of metritis or improve fertility (Peters and Laven, 1996). The use of tetracycline, however, results in inhibition of matrix metalloproteinases and might interfere with the normal placental detachment mechanism (Eiler and Hopkins, 1992). Furthermore, the administration of antibiotics in livestock should be minimised to reduce the prevalence of resistant bacteria (Peter et al., 2018). In Switzerland, the Federal Council determined the following objectives, measures and prevention strategies of antibiotic therapy in The Swiss Antibiotic Resistance Strategy (StAR): Preventive measures such as improved hygiene, optimised management, farm hygiene and husbandry, and the development of effective alternatives to the use of antibiotics are essential (<https://www.star.admin.ch/star/en/home/star/strategie-star.html>). Instead of using tetracycline boluses for treatment of RFM, the intrauterine administration of ozone could be a valuable alternative (Djuricic et al., 2012; Zobel and Tkalcic, 2013; Djuricic et al., 2016). Ozone has a germicidal effect through oxidation of phospholipids and lipoproteins and a fungicide effect through growth inhibition (Bocci et al., 2009; Elvis and Ekta, 2011) and stimulates immunity through the induced production of cytokines (Jakab et al., 1995; Ducusin et al., 2003; Ohtsuka et al., 2006). The advantage of using ozone is the lack of known bacterial resistance development and, in animal husbandry, the lack of a withdrawal period before harvesting product as a human food source (milk, meat) (Scrollavezza et al., 1997). Values for reproductive variables in Simmental cows with RFM that were treated with ozone foam were comparable to those of a control group without RFM (Djuricic et al., 2012). The purpose of the present study was to compare the effect of intrauterine tetracycline boluses to that when there was ozone foam treatment (Riger™ spray, Novagen, Parendzana, Italy) in cases of RFM with both therapies occurring without manual removal of the placenta. Drillich et al. (2006a, 2006b) reported that 70%–85% of the cows with RFM had a fever in the first 10 DIM. In another study more than 90% of the veterinarians used systemic antibiotics if cows had a fever in cases associated with RFM (Hehenberger et al., 2015). The focus in the present study, therefore, was based on imposing the experimental treatment when there was a detection of fever during the first 10 DIM as because values for this variable are used in determining whether to administer antibiotics, parenterally. The working hypothesis for the present study was that there would be a lesser number of days when fever was evident ( $> 39.7\text{ }^{\circ}\text{C}$ ) in cows treated with ozone compared with the tetracycline bolus in the first 10 DIM. Data were collected until 200 DIM to additionally evaluate values for subsequent fertility variables and reasons for culling of animals from the herd.

## 2. Materials and methods

This prospective study was performed with permission and in accordance to the Swiss law (<https://www.blv.admin.ch/blv/en/home/tiere/tierversuche.html>; Nr. BE81/15).

### 2.1. Cows, inclusion and exclusion criteria

Primiparous and multiparous dairy cows of the breeds Holstein Friesian, Red Holstein, Brown Swiss, Simmental and the respective crossbreds with RFM were included in the study. Pregnancy duration had to be  $\geq 265$  d for inclusion in the study. Only one cow per day and per farm was included to prevent cluster effects. Cows after cesarean section, uterine torsion, prolapsed uterus and fetotomy were excluded from the study. Additionally, cows having a displacement of the abomasum, acute mastitis or pneumonia as well as recumbent cows on the first day of treatment were excluded from the study. Cows were assigned to a group in which there was ozone foam treatment ( $n = 65$ ) or tetracycline bolus treatment ( $n = 70$ ) based on odd or even ear-tag numbers, respectively.

### 2.2. Treatment

Cows with RFM were examined clinically within the first 24 h after parturition (body temperature, heart and respiratory rates, vaginal and rectal palpation). Upon vaginal examination, the retention of the placenta was confirmed, but no attempt was made to manually remove the placenta. There was placement in cows with an even ear tag number (0, 2, 4, 6, 8) of ozone foam (group Oz) into the body of the uterus (Riger™ spray, Novagen, Parendzana, Italy) for 5 s corresponding to 8–10 ml (Djuricic et al., 2012). The examiners hand formed a shield at the intrauterine tip of the sterile catheter to prevent lesions of the uterine mucosa. The cows in the Te group (odd ear tag number: 1, 3, 5, 7, 9) ( $n = 3$ ) were administered tetracycline boluses into the uterine horn where there had been the location of the conceptus prior to parturition (Tetrabiotic mite® 1 g each, Provect AG, Bern, Switzerland) by manual application. Cows were then re-examined on days 4, 7 and 10 post-partum and the initial therapy was repeated on days 4 and 7.

### 2.3. “Escape therapy”

The farmers were instructed to assess the rectal temperature of the cows and score their food intake ( $\geq 50\%$ ;  $< 50\%$  of the ration) daily from day 1–10 post-partum. Cows with a rectal temperature  $> 39.7\text{ }^{\circ}\text{C}$  combined with less than 50% food intake were treated using a regimen of “escape therapy” consisting of the administration of a long-acting oxytetracycline i.m. (Cyclosol LA® Dr. E. Gräub AG, Bern, Switzerland, 20 mg/kg BW) and the NSAID flunixin meglumin i.v. (Flunixinim® Dr. E. Gräub AG, Bern, Switzerland, 2.2 mg/kg BW). If on day 4 after the initiation of the “escape therapy” treatment regimen, temperature remained  $> 39.7\text{ }^{\circ}\text{C}$  and food intake less than 50%, the “escape therapy” was repeated one time.

### 2.4. Variables evaluated

The following data were collected at the farms where the experiment was conducted: Number of animals per farm, farming system

including studbook (yes/no), type of stall (freestall/tiestall), pasture (yes/no) and farmer's business (main/side). For experimental cows, data collected were breed, age, parity, milk yield (305 d of preceding lactation), pregnancy duration, and therapy (routine, "escape") including number of days when a fever was detected.

### 2.5. Follow-up evaluations

The interval between parturition and conception, number of inseminations per pregnancy and reasons for culling of animals from the herd were recorded until 200 DIM for experimental cows.

### 2.6. Statistical analyses

The primary endpoint was the number of "fever days" defined as rectal temperature  $> 39.7^{\circ}\text{C}$  in the period of 1–10 d postpartum. The study was designed as a non-inferiority study (ozone non-inferior to tetracycline). The non-inferior difference was set at a threshold of 1 d between the mean values of the two groups with an assumption of a mean number of 3 d of fever and a conservative sd of two. Power needed to be at least 80%,  $\alpha = 0.025$  resulting in a minimum of  $n = 65$  cows per group. For categorical data, frequency of categories was determined. In metric variables, mean, median, sd, 25% and 75% quartiles, minimum and maximum were calculated. Frequencies in categorical data were assessed using the Chi-square test. Non-parametric tests were used (t-test and Wilcoxon-Mann-Whitney test) for the analysis of metric data. A  $P$ -value  $< 0.05$  indicated a significant result. Data were analysed using the statistical software SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA, [www.sas.com](http://www.sas.com)). Multiple logistic regression analysis with backward elimination was conducted to determine risk factors that affected the number of "fever days". A survival analysis was conducted for culling of animals from the herd with and without groups as fixed factors. A cox regression with backward selection of possible risk factors was performed for factors affecting culling rate.

## 3. Results

### 3.1. Farm and animals

When there was assessment of farm effects, there were no significant differences between the two groups as a result of use of a studbook (yes: Oz = 86.4%, Te = 87.1%), type of stall (free range: Oz = 52.5%, Te = 42.9%), access to pasture (yes: Oz = 100%, Te = 98.6%) and farmer's business (main: Oz = 88.1%, Te = 95.7%).

Furthermore, there were no differences between the groups when there was assessments of age, yearly milk yield/cow, duration of pregnancy, and number of cows per farm. The number of breeds included in the experimental groups were not different and neither was parity or calving season (Tables 1 and 2).

### 3.2. Treatment

Median number of routine treatments was three with no differences between the groups. In the Oz treatment group, 13 cows were detected with a fever in the first 10 DIM compared to three cows in the Te treatment group. Mean number of "fever days" ( $> 39.7^{\circ}\text{C}$ ) was greater ( $P = 0.001$ ) in the cows of the Oz (0.36 d) compared with those of the Te (0.04 d) group. Data regarding the distribution of number of "fever days" are included in Table 3.

### 3.3. "Escape therapy"

Five cows were treated with an "escape therapy" in the Oz compared with four in the Te treatment group ( $P = 0.94$ ). Duration of the "escape therapy" was 3 d (Oz:  $n = 4$ , Te:  $n = 4$ ) and 6 d (Oz:  $n = 1$ ) with there being no difference in values for the two groups.

**Table 1**

Comparison of farms and cows for the treatment groups Oz/Te.

Variables	Oz Group	Te Group	*P-value
Number of cows/group	59	70	
Number of cows/farm	25 (18/50)	25 (20/38)	0.83
Age of cows (years)	5 (3.4/7)	5.6 (3.2/7.8)	0.41
Yearly milk yield/cow (kg)	7930 (7000/9051)	8000 (7246/9760)	0.35
Duration of pregnancy (d)	282 (279/288)	282 (278/286)	0.42
Number of routine treatments	3 (2/4)	3 (2/4)	0.47

There were no differences in values between the two treatments (Oz/Te) for the variables: number of cows/group and per farm, age of cows, yearly milk yield/cow, duration of pregnancy, number of routine treatments in the Te and Oz groups; 25% and 75% quartiles are in brackets; \*Wilcoxon-Mann-Whitney Test.

**Table 2**  
Comparison of farms and cows for the treatment groups Oz/Te.

Variables	*P-value
Breed (Red Holstein, Holstein Friesian, Brown Swiss, Simmental, others)	0.46
Parity (1; 2-4; $\geq 5$ )	0.65
Calving season (spring, summer, fall, winter)	0.09
Studbook (yes; no)	0.9
Stall type (freestall; tiestall)	0.27
Pasture(yes; no)	0.36
Farmer's business (main; side)	0.10
"Escape therapy" (yes; no)	0.94
"Escape therapy" (number of days)	0.49

There were no differences in values between the two treatments (Oz/Te) for the variables: breed, parity, calving season, herd book, stall type, pasture, farmer's business, escape therapy; \*Chi-square test. The "escape therapy" consisted of the administration of a long-acting oxytetracycline i.m. (Cyclosol LA® Dr. E. Gräub AG, Bern, Switzerland, 20 mg/kg BW) and the NSAID flunixin meglumin i.v. (Flunixinim® Dr. E. Gräub AG, Bern, Switzerland, 2.2 mg/kg BW).

**Table 3**  
Number of fever days for the treatment groups Oz/Te.

Number of "fever days"	Oz Group	Te Group
0	46	67
1	8	3
2	3	0
3	1	0
4	1	0

Number of "fever days" (defined as rectal temperature  $> 39.7$  °C in the period of 1–10 d postpartum) for cows in the Oz was greater than that for cows in the Te group ( $P = 0.001$ , Wilcoxon-Mann-Whitney Test).

### 3.4. Follow-up data

Neither mean number of inseminations/pregnancy until 200 DIM ( $P = 0.58$ ;  $n = 1.7$  in the Oz compared with  $n = 2$  in the Te groups, respectively) nor culling for fertility reasons ( $P = 0.21$ ; 1/13 in the Oz compared with 7/23 in Te groups, respectively) were different between groups (Table 4). Mean interval between parturition and conception was 100.5 in the cows of the Oz compared with 99 in the cows of the Te groups, respectively. Data from multiple logistic regression analysis indicated there were no significant risk factors for "fever days" (except for group). The data obtained using cox regression with backward selection of groups for factors affecting culling indicated there was only a type of stall effect ( $P = 0.02$ ) with cows in tie stalls being culled earlier than cows in free range stalls independent of treatment group.

## 4. Discussion

Fever is often observed in cows in the first 10 DIM with as many as 45% of cows without RFM (Sheldon, 2004) and as many as 95% of cows with RFM (Dinsmore et al., 1996; Drillich et al., 2003; Sheldon, 2004; Drillich et al., 2006a, 2006b). Mean number of "fever days" was  $2.5 \pm 0.3$  d in a previous study (Sheldon, 2004). The working hypothesis for the present study was based on this description, but in the present prospective study, fewer cows had a fever: only 12.4% of all cows were detected with a fever and mean number of "fever days" was 1.5. This could be explained as a result of the probability of infection being less in smaller herds where fewer cows are detected with a fever (19.1% compared with 76.7% depending on therapy for RFM) (Drillich et al., 2007). Results

**Table 4**  
Percentage of reasons for culling in the treatment groups Oz/Te.

Reasons for culling	Oz Group	Te Group
Fertility	15.4%	30.4%
Udder health	53.8%	39.1%
Claws	23.1%	8.7%
Metabolism	7.7%	4.4%
Different reasons	–	17.4%

There was no differences in values for the variables between the two treatments (Oz/Te) for the percentage of culling within 200 DIM ( $P = 0.21$ , Chi-square test).

when there is intrauterine horn treatment with antibiotics (ampicillin, cloxacillin) indicate there is a lesser fever prevalence than with systemic antibiotic (ceftiofur) (Drillich et al., 2007). When there is fever that occurs when there is an infection, this physiological response of the cows may have a protective function (Evans et al., 2015) as long as it is not a symptom of a gram-negative sepsis infection (Mackowiak, 2000). Controlling the general state of health and food intake of cows needs to be included in the decision making process as to whether an escape therapy is warranted (Sheldon, 2004). Although it was not possible to quantitatively ascertain food intake in the present study, there was reliance on the farmers' judgement and observation as to whether there was less than 50% of the expected feed consumption of the experimental animals. Escape therapies have been primarily initiated if rectal temperature exceeded 39.5 °C (Drillich et al., 2003, 2006b; Drillich et al., 2007; Djuricic et al., 2012) or  $\geq 39.7$  °C (Dinsmore et al., 1996). The antibiotic selected for parenteral administration as an “escape therapy” was tetracycline because cows of the Te group were already receiving intrauterine treatments with tetracycline because tetracycline is a first line antibiotic as recommended by the Swiss Antibiotic Resistance Strategy (StAR). Zobel and Tkalcic (2013) reported there were fewer animals with fever in the ozone treated group compared to a series of other treatments with all therapies occurring after manual removal of the placenta. Manual removal of the placenta was not performed in the present study so as to avoid damage to the endometrium (Vandeplasseche and Bouters, 1982; Bolinder et al., 1988) and suppression of the uterine leukocyte phagocytosis response (Beagley et al., 2010). The administration of ozone foam was slightly more complicated than using tetracycline boluses, which can easily be placed in the uterus. Because the wall of the uterus is often thinner in cows with RFM and during the early post-partum period, it is recommended there be use of the hand as a shield when administering the ozone foam through the catheter. In general, farmers were often skeptical about the use of ozone because of its strong odour and, also because often a crimson coloured vaginal discharge was observed until 1 week after the ozone administration. Reasons for culling of the cows from the herd were not different between the treatment groups, neither were number of inseminations per pregnancy nor the interval between parturition and conception. To conclude, the working hypothesis of the present study is not accepted because number of “fever days” was greater in the cows of the Oz group. There, however, was no difference in the number of “escape therapies” per group, because the reduced feed intake variable was included in the decision to initiate an “escape therapy”. Based on results of the present study, ozone foam is recommended as a non-antibiotic intrauterine treatment for cattle with RFM.

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## Conflicts of interest

None

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## References

- Beagley, J.C., Whitman, K.J., Baptiste, K.E., Scherzer, J., 2010. Physiology and treatment of retained fetal membranes in cattle. *J. Vet. Intern. Med.* 24 (2), 261–268. <https://doi.org/10.1111/j.1939-1676.2010.0473.x>.
- Bocci, V., Borrelli, E., Travagli, V., Zanardi, I., 2009. The ozone paradox: ozone is a strong oxidant as well as a medical drug. *Med. Res. Rev.* 29 (4), 646–682. <https://doi.org/10.1002/med.20150>.
- Bolinder, A., Sequin, B., Kindahl, H., Bouley, D., Otterby, D., 1988. Retained fetal membranes in cows: manual removal versus nonremoval and its effect on reproductive performance. *Theriogenology* 30, 45–56 PMID: 16726448.
- Dinsmore, R.P., Stevens, R.D., Cattell, M.B., Salman, M.D., Sundlof, S.F., 1996. Oxytetracycline residues in milk after intrauterine treatment of cows with retained fetal membranes. *J. Am. Vet. Med. Assoc.* 209 (10), 1753–1755 PMID: 8921036.
- Djuricic, D., Vince, S., Ablondi, M., Dobranic, T., Samardzija, M., 2012. Intrauterine ozone treatment of retained fetal membrane in Simmental cows. *Anim. Reprod. Sci.* 134 (3–4), 119–124. <https://doi.org/10.1016/j.anireprosci.2012.08.023>.
- Djuricic, D., Valpotic, H., Zura Zaja, I., Samardzija, M., 2016. Comparison of intrauterine antibiotics versus ozone medical use in sheep with retained placenta and following obstetric assistance. *Reprod. Domest. Anim.* 51 (4), 538–540. <https://doi.org/10.1111/rda.12715>.
- Drillich, M., Pfützner, A., Sabin, H.-J., Sabin, M., Heuwieser, W., 2003. Comparison of two protocols for the treatment of retained fetal membranes in dairy cattle. *Theriogenology* 59, 951–960 PMID: 12517396.
- Drillich, M., Mahlstedt, M., Reichert, U., Tenhagen, B.A., Heuwieser, W., 2006a. Strategies to improve the therapy of retained fetal membranes in dairy cows. *J. Dairy Sci.* 89 (2), 627–635. [https://doi.org/10.3168/jds.S0022-0302\(06\)72126-9](https://doi.org/10.3168/jds.S0022-0302(06)72126-9).
- Drillich, M., Reichert, U., Mahlstedt, M., Heuwieser, W., 2006b. Comparison of two strategies for systemic antibiotic treatment of dairy cows with retained fetal membranes: preventive vs. selective treatment. *J. Dairy Sci.* 89 (5), 1502–1508. [https://doi.org/10.3168/jds.S0022-0302\(06\)72217-2](https://doi.org/10.3168/jds.S0022-0302(06)72217-2).
- Drillich, M., Klever, N., Heuwieser, W., 2007. Comparison of two management strategies for retained fetal membranes on small dairy farms in Germany. *J. Dairy Sci.* 90 (9), 4275–4281. <https://doi.org/10.3168/jds.2007-0131>.
- Ducusin, R.J., Nishimura, M., Sarashina, T., Uzuka, Y., Tanabe, S., Otani, M., 2003. Phagocytosis of bovine blood and milk polymorphonuclear leukocytes after ozone gas administration in vitro. *J. Vet. Med. Sci.* 65 (4), 535–539 PMID: 12736440.
- Eiler, H., Hopkins, F.M., 1992. Bovine retained placenta: effects of collagenase and hyaluronidase on detachment of placenta. *Biol. Reprod.* 46, 580–585 PMID: 1315581.
- Elvis, A.M., Ekta, J.S., 2011. Ozone therapy: a clinical review. *J. Nat. Sci. Biol. Med.* 2 (1), 66–70. <https://doi.org/10.4103/0976-9668.82319>.
- Evans, S.S., Repasky, K.E., Fisher, D.T., 2015. Fever and the thermal regulation of immunity: the immune system feels the heat. *Nat. Rev. Immunol.* 15 (6), 335–349. <https://doi.org/10.1038/nri3843>.

- Fourichon, C., Seegers, H., Malher, X., 2000. Effect of disease on reproduction in the dairy cow: a meta-analysis. *Theriogenology* 53 (9), 1729–1759 PMID: 10968418.
- Hehenberger, E.M., Dohér, M., Bodmer, M., Steiner, A., Hirsbrunner, G., 2015. Diagnose und Therapie von Nachgeburtverhalten, puerperaler Metritis und klinischer Endometritis beim Rind: Ergebnisse der Online-Umfrage bei Schweizer Tierärzten. I Nachgeburtverhalten. *Schweiz. Archiv f. Tierheilk.* 157 (9), 497–502. <https://doi.org/10.17236/sat00032>.
- Jakab, G.J., Spannhake, E.W., Canning, B.J., Kleeberger, S.R., Gilmour, M.I., 1995. The effects of ozone on immune function. *Environ. Health Perspect.* 103 (Suppl 2), 77–89. <https://doi.org/10.1289/ehp.95103s277>.
- Kelton, D.F., Lissemore, K.D., Martin, R.E., 1998. Recommendations for recording and calculating the incidence of selected clinical diseases of dairy cattle. *J. Dairy Sci.* 81 (9), 2502–2509. [https://doi.org/10.3168/jds.S0022-0302\(98\)70142-0](https://doi.org/10.3168/jds.S0022-0302(98)70142-0).
- Laven, R.A., Peters, A.R., 1996. Bovine retained placenta: aetiology, pathogenesis and economic loss. *Vet. Rec.* 139 (19), 465–471 PMID: 8938967.
- Mackowiak, P.A., 2000. Physiological rationale for suppression of fever. *Clin. Infect. Dis.* 31 (Suppl 5), S185–189. <https://doi.org/10.1086/317511>.
- Ohtsuka, H., Ogata, A., Terasaki, N., Koiwa, M., Kawamura, S., 2006. Changes in leukocyte population after ozonated autohemoadministration in cows with inflammatory diseases. *J. Vet. Med. Sci.* 68 (2), 175–178 PMID: 16520542.
- Oltenacu, P.A., Frick, A., Lindhe, B., 1990. Epidemiological study of several clinical diseases, reproductive performance and culling in primiparous Swedish cattle. *Prev. Vet. Med.* 9, 59–74.
- Peter, R., Muntener, C., Demuth, D., Heim, D., Stucki, F., Mevissen, M., et al., 2018. AntibioticScout.ch: Decision support for the prudent use of antimicrobials: Application in cattle. *Schweiz. Archiv f. Tierheilk.* 160 (4), 219–226. <https://doi.org/10.17236/sat00154>.
- Peters, A.R., Laven, R.A., 1996. Treatment of bovine retained placenta and its effects. *Vet. Rec.* 139 (22), 535–539 PMID: 8961522.
- Scrollavezza, P., Ablondi, M., Pogliacomì, B., Guareschi, D., Dall'Aglio, R., Poldi, R., Pezzoli, G., 1997. Ozone treatment in mastitis, metritis and retention of fetal membranes in the cows. Page 35 in 2 Int. Symp. Ozone Application. Havana, Cuba.
- Sheldon, I.M., 2004. The postpartum uterus. *Vet. Clin. North Am. (Food Animals)* 20 (569-), 591. <https://doi.org/10.1016/j.cvfa.2004.06.008>.
- Sheldon, I.M., Lewis, G.S., LeBlanc, S., Gilbert, R.O., 2006. Defining postpartum uterine disease in cattle. *Theriogenology* 65, 1516–1530. <https://doi.org/10.1016/j.theriogenology.2005.08.021>.
- Vandeplassche, M., Bouters, R., 1982. The impact of gynaecological and obstetrical problems resulting out of pregnancy and parturition. In: Karg, H.S. (Ed.), *Factors affecting fertility in the post partum cow*. Martinus Nijhoff Publishers, The Hague, pp. 30–44.
- Zobel, R., Tkalcic, S., 2013. Efficacy of ozone and other treatment modalities for retained placenta in dairy cows. *Reprod. Domest. Anim.* 48 (1), 121–125. <https://doi.org/10.1111/j.1439-0531.2012.02041.x>.