

Side effects and occupational risks of using intrauterine kerosene in a mare

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Summary

Use of intrauterine kerosene is becoming popular for treatment of chronic endometritis. In this case, intrauterine kerosene was used to treat pyometra in a mare after failure of traditional treatments and adjuvants to resolve the condition. Intrauterine infusion with kerosene was followed by uterine lavage the following morning. Reflux of kerosene into the vagina resulted in chemical vaginitis with behavioral changes in the mare the morning after infusion. Five minutes after uterine lavage, the mare developed severe signs of colic and pain associated with the vaginal procedures that exacerbated the irritation. Side effects subsided with local instillation of 2% lidocaine into the vagina. In addition, kerosene eroded the obstetrical sleeve of the operator during uterine lavage, and resulted in chemical dermatitis with local redness, heat and pain for several hours. The severe side effects seen in this mare raise questions regarding animal welfare and ethical use of kerosene. The use of commercially available kerosene poses significant health risks to personnel and additional precautions are needed to minimize occupational exposure. Intrauterine kerosene should be used with caution until controlled efficacy and safety studies become available and the benefits are proven to outweigh the risks.

Keywords: Infertility, mare, kerosene, occupational hazards, safety

Background

The use of intrauterine kerosene in mares is advocated by some clinicians as an adjuvant in treatment of chronic endometritis caused by gram negative and positive bacteria, yeast or fungi.¹ Use of adjuvants in the treatment of chronic endometritis becomes a necessity since traditional therapy with uterine lavage, antibiotics and oxytocin often fails to resolve the infection. Treatment failure may occur due to recurrent contamination of the uterus, or failure to completely eliminate inflammatory exudates in mares with anatomical abnormalities or dysfunctional myometrial contractions, production of biofilm by bacteria or yeast, or abnormal mucus production by endometrial cells.^{1,2}

Biofilm is a complex structure of bacterial colonies, polymers and channels that results in a focal infection of non-dividing bacteria, covered by a matrix. This matrix confers bacteria protection from the environment and immune system, and structural support, and interferes with antibiotic penetration. Furthermore, the lack of bacterial division results in inherent resistance to most antimicrobials. Disruption of the biofilm is necessary to allow for antibiotic penetration, interaction of bacteria with the immune system and re-initiation of bacterial division. Biofilm disruptors used in mares with endometritis include ethylene diaminetetraacetic acid-tromethamine (EDTA), Tricide, N-acetyl-cysteine (NAC), dimethyl sulfoxide (DMSO) and hydrogen peroxide.^{1,2}

The mucociliary apparatus also has an important role in preventing adhesion of bacteria to the endometrium and promoting physical clearance. In addition, endometrial mucus contains bacteriostatic products like lactoferrin or lysozyme. Normal mucus maintains the endometrial surface hydration and facilitates phagocytosis. Changes in production, viscosity and elasticity of mucus can interfere with the ability of the mucociliary apparatus to remove bacteria or with antibiotic penetration. Inspissated mucus results in accumulation of bacteria and inflammatory debris within the uterus, exacerbating the problem. Therefore, mucolytics such as NAC, DMSO and kerosene are used to improve treatment success.^{1,2}

Treatment with intrauterine kerosene is becoming popular since it seems to improve pregnancy rates in chronically infertile mares. An intrauterine infusion of 50 ml of kerosene resulted in 50% and 45% foaling rate in mares with grade 2 and 3 endometrial biopsies, respectively.³ No control mares were included in the study. However, the findings were later interpreted as an improvement in fertility since foaling rates in mares with grade 3 biopsy are expected to be less than 10%.² Uterine lavage with 250 to 500 ml of kerosene also resulted in pregnancy in chronically infertile mares.⁴ Activation of

endometrial glands, reduction of mucus and exudate through desquamation and removal of the uterine epithelium, and clearance of inspissated glandular secretions were proposed as mechanisms by which kerosene seemed to improve pregnancy rate.¹⁻⁴

Histologically, intrauterine infusion with kerosene caused diffuse severe endometritis and edema, production of a serum-like exudate, and necrosis of luminal epithelium. However, these changes were transient and resolved within 14 days.^{3,4} Loss of ciliated cells occurred 24 hours after treatment. However, a regenerated muco-ciliary apparatus was re-established by four days after infusion with kerosene.⁵

While the safety of kerosene on endometrial health has been demonstrated,^{3,5} no studies have evaluated the effect of this treatment on mare health and welfare. Side effects have not been reported, although there is anecdotal evidence of transient vaginitis and discomfort immediately after treatment. This case report demonstrates the presence of severe side effects associated with the use of intrauterine kerosene in a mare and untoward effects in a clinician. These effects need to be taken into account if this treatment is to be used, and ways to prevent or mitigate them need to be installed taking patient welfare into consideration.

Case presentation

A 12-year old multiparous Quarter Horse mare was presented in July 2016 to the Veterinary Medical Center at the University of Georgia with a complaint of infertility. The mare was recently acquired by the owner and her reproductive history was unknown. During the breeding season prior to presentation, she was mated to a stallion of unknown fertility on two estrous cycles. The owner was unable to provide information on breeding management (i.e. ovarian monitoring, timing of ovulation, number of matings, treatment of breeding-induced endometritis, semen quality, etc.), but wished to determine the reason for infertility and to artificially inseminate the mare with cooled shipped semen.

On presentation, a breeding soundness examination was performed. The mare was bright, alert and responsive. Her rectal temperature was 99.1°F, pulse was 36 bpm and respiratory rate was 24 bpm. Her general physical condition was within normal limits. Perineal conformation was within normal limits except for a slight cranial tilt of the vulva (around 20°). On palpation per rectum, the uterus was heavy and the cervix was tight. Ultrasound per rectum revealed presence of a 24 mm follicle on the right ovary, small follicles on the left ovary and mild endometrial edema. No corpus luteum was noticed. The findings were consistent with estrus. There was also a large amount of hyperechoic fluid within the uterine lumen. Upon vaginal speculum examination, a white-yellow fluid was noticed on the floor of the cranial vagina, and the cervix was closed. Digital cervical examination revealed that the cervix was not dilated and only one finger could be introduced through the lumen. Furthermore, a 2-cm cervical defect resembling a diverticulum was noted in the ventral portion of the cervical canal. The cervical lesion could also be identified on ultrasound as a hypoechoic irregular area (Figure 1).

The mare's uterus was lavaged on presentation with 5 L of 0.9% sodium chloride (NaCl) solution. A large amount of purulent material was recovered. On endometrial cytology, a large number of degenerate neutrophils were present. Endometrial bacterial culture yielded growth of *Streptococcus equi* subspecies *zooepidemicus*, *Streptococcus dysgalactiae* and an unidentifiable gram variable rod. On endometrial biopsy, ulcerated areas of endometrial epithelium were present, with a thick layer of mucus covering the epithelium and diffuse inflammatory infiltrate. Fibrosis was mild and sporadic (no glandular nests, no to one layer of periglandular fibrosis).

The mare was diagnosed with pyometra. Cervical laceration and fibrosis with failure to dilate was suspected to be the underlying predisposing factor. Treatment for pyometra initially consisted on daily uterine lavage with 0.2% povidone iodine solution (v:v) in sterile 0.9% NaCl solution for seven days during estrus to evacuate her uterus. Ampicillin sodium, 2 g, was infused into the uterus daily for five days. Antibiotic therapy continued systemically with procaine penicillin G, 22000 IU/kg IM Q12h, for five more days since the mare progressed into diestrus while still having evidence of intrauterine fluid accumulation. Antimicrobials were selected based on the result of the antibiotic sensitivity test. The mare also received oxytocin 10-20 IU IM every four h for the duration of antimicrobial treatment.

N-acetyl-cysteine (3.3% solution, 150 ml) was used as a mucolytic and anti-inflammatory on the first day of treatment. On days 2 and 3, Tricide (8mM disodium EDTA dehydrate and 20 mM 2-amino-2-hydroxymethyl-1,2-propanediol, 500 ml intrauterine) was used as a biofilm disruptor. After ten days of antibiotic and oxytocin treatment, intrauterine fluid was no longer present and treatment was discontinued. However, intrauterine fluid started accumulating again 48 hours after discontinuation.

Treatment

Since medical treatment alone failed to resolve the condition, cervical wedge resection together with embryo technologies (embryo transfer or intracytoplasmic sperm injection) were recommended. These options were declined and the client insisted on having the mare carry the pregnancy. Given the presence of a layer of mucus on biopsy and the failure of traditional treatment with adjuvants to clear the infection, chemical curettage with kerosene was elected as a last resort.

Commercial kerosene (Klean-Strip® 1-K Kerosene Heater Fuel), 240 mL, was infused into the uterus of the mare during estrus in the afternoon. Uterine lavage to remove kerosene and debris was planned for the next morning. The following morning, it was noticed that the mare was showing behavioral changes. She had a decreased appetite, was reluctant to approach people and seemed restless and aggressive. Ultrasonographic character of the uterine contents had changed from anechoic the day before infusion, to hyperechoic and heterogeneous the day after infusion (Figure 2). Uterine lavage was performed until the effluent was clear, requiring 8 L of 0.9% NaCl. The effluent initially contained a large amount of debris and sloughed material (Figure 3). The mare was restless in the stocks during the procedure. Within five minutes of finalizing the uterine lavage and returning to the stall, the mare started showing signs of colic, lying down, rolling and flank watching. The signs were severe and did not subside after administration of flunixin meglumine, 1.1 mg/kg IV once. A complete colic examination was performed to rule out a gastrointestinal source of acute abdominal pain. This examination included palpation per rectum, percutaneous abdominal ultrasound and nasogastric intubation. Findings were within normal limits and gastrointestinal pain was ruled out.

Chemical irritation of the vagina caused by reflux of kerosene through the cervix was suspected. It was thought that the vaginal and cervical manipulations done during the lavage may have worsened the discomfort. The mare's vagina was lavaged with 1 L of 0.9% NaCl to remove any residual kerosene, and 20 ml of 2% lidocaine were infused into the vagina with an insemination pipette to provide local analgesia.

An additional unexpected finding was the development of skin redness, heat and pain in the arm of the operator performing the uterine lavage (Figure 4). These signs became evident within five minutes of the uterine lavage while the mare's colic was being monitored. During the uterine lavage, it was noticed that backflow of kerosene into the vagina resulted in erosion of the obstetrical sleeve that the operator was wearing, which had to be replaced. Direct contact of kerosene with the operator's skin resulted in chemical dermatitis. The skin was washed with abundant water and detergent.

Outcome

The signs of discomfort resolved after vaginal infusion of lidocaine, and the mare remained comfortable thereafter. Skin inflammation and pain in the operator's arm also subsided within two hours with no further complications. Uterine lavages continued daily with no further complications for three more days. On the third day, cellular debris were no longer present in the effluent and lavage was discontinued. Oxytocin therapy with 20 IU IM every four hours continued for one more day. Intrauterine fluid was no further noticed at the end of treatment. However, anechoic intrauterine fluid was again present 48 h after discontinuing oxytocin injections (Figure 2). A final uterine lavage was performed at that time to determine the character of the effluent. The effluent was mucoid in nature, and mucometra was suspected at that moment. Uterine cytology was not performed to confirm the absence of inflammatory cells.

Due to recurrence of intrauterine fluid accumulation, hysteroscopy was performed to rule out a foreign body, endometrial adhesions or other pathology acting as a source for re-contamination or

impeding physical clearance. The cervix was fibrotic, tortuous and closed, and there were focal areas of endometrial inflammation within the uterine body (Figure 5). Two blister-like structures were present at the uterine body and the bifurcation of the uterine horns (Figure 5). The mare was discharged with the recommendation to perform cervical wedge resection and embryo technologies. Oocyte aspiration and intracytoplasmic sperm injection was recommended since exposure of the embryo to an altered uterine environment would likely decrease the success rate of embryo transfer.

Discussion

Pyometra is the accumulation of purulent contents within the uterine lumen. This condition often results from failure of the cervix to dilate due to fibrosis, tortuosity or transluminal adhesions, or ineffective uterine contractions that fail to physically evacuate uterine contents.⁶ *Streptococcus zooepidemicus* is the most commonly isolated bacterium, often in the context of mixed infections.⁶ Treatment of pyometra consists of uterine lavage and intrauterine infusion with antibiotics. Uterotonic drugs and exercise are used to encourage expulsion of uterine contents. Unfortunately, medical treatment of pyometra is often unsuccessful due to persistence of the predisposing factor leading to mechanical impairment of uterine evacuation.

Cervical wedge resection has been used to facilitate uterine clearance and resolution of pyometra in mares.⁶ Even though this treatment impairs the ability of the mare to carry a pregnancy, offspring could be produced using *in vitro* or *in vivo* embryo technologies.⁶ However, even when cervical patency was surgically re-established, fluid accumulation persisted in 20% (1/5) of the mares.⁶ The large and prolonged fluid accumulation prior to surgery could have led to stretching of the mesometrium and ventral positioning of the uterus, or stretching of the myometrium and inefficient uterine contractions, resulting in treatment failure. The cervical diverticulum could have also acted as a reservoir and source of re-contamination after treatment. Surgical removal of the diverticulum was considered. However, due to the inability of the cervix to relax, cervical wedge resection was deemed to be a more appropriate option for this mare.

In the case reported here, cervical laceration and fibrosis was suspected to be the predisposing cause. The duration of the lesions was unknown, but there was no recollection of presence of intrauterine fluid prior to mating. Repeated mating likely resulted in bacterial contamination of the uterus. Failure to clear bacteria resulted in persistent endometritis with infertility, which then progressed to pyometra. It could be speculated that more intensive involvement of a veterinarian in the breeding management or earlier referral of the mare could have allowed for an earlier diagnosis and treatment of the condition before it progressed into pyometra, potentially improving the prognosis for fertility.

The chronic and severe endometrial irritation associated with pyometra possibly stimulated production of the mucus film seen on biopsy. It is also possible that denuded areas of epithelium allowed for bacterial adhesion and formation of biofilm. Given the complex environment associated with pyometra, mucolytics (NAC) and biofilm disruptors (Tricide) were initially used as adjuvants together with traditional uterine lavage and antibiotics. The owner of this mare initially declined the use of embryo technologies or surgical treatment. Due to the limitation to medical treatment and failure of traditional therapies to resolve the condition, use of non-traditional therapy was attempted. Chemical curettage with kerosene was deemed to be the last resort, although it was acknowledged that its efficacy in treating pyometra was unknown. Infusion of 240 ml during estrus was elected based on current practices.⁵

Kerosene has been proposed for treatment of chronic endometritis caused by gram negative organisms, fungi or yeasts as it appears to improve pregnancy rates in persistently infected mares.¹ However, the mechanism of action of kerosene is currently unknown. The presumed positive effect relates to its ability to stimulate a strong inflammatory response through chemical curettage and the activation of fibrosed endometrial glands, permitting the growth of new, functional endometrial tissue.^{1,3} Additionally, kerosene reduced mucus production through the destruction of the uterine epithelium and clearance of inspissated secretions from dilated and cystic endometrial glands.¹⁻⁴

Uterine lavage with 250 to 500 mL of kerosene in subfertile mares caused diffuse, mild endometritis and edema. Inflammation lasted one or two days, and was followed by expulsion of retained excretions from the endometrial glands and mucopurulent uterine discharge. One to three days after treatment, there was an influx of healthy leukocytes within the endometrium and uterine lumen. Lavage was performed during diestrus and mares returned to estrus within two to five days of treatment presumably due to release of endometrial prostaglandin $F_{2\alpha}$.⁴ This information was presented as a summary of a symposium. The reviewing author commented that intrauterine kerosene markedly improved the fertility of these mares and that most conceived when mated in the estrus following treatment. It was also mentioned that kerosene was not suitable for treatment of cervical lacerations, uterine adhesions or fungal infections.⁴ Unfortunately, no data are available from this study for thorough analysis and evaluation of the conclusions.

In another study, 50 ml of commercial kerosene was infused into the uterus during diestrus to avoid reflux of the kerosene into the vagina. On day 1, all mares had a moderate-to-severe inflammation, with or without necrosis of the luminal epithelium. Inflammation resolved by 14 days. A marked increase in the secretory activity and mitotic index was observed in the glandular epithelium on Days 4 and 7, but there was no reduction in the number of glandular nests or overall improvement of the degree of endometrial degeneration after treatment with kerosene.^{3,4}

Loss of ciliated cells also occurred one day after kerosene infusion. However, a regenerated muco-ciliary apparatus was re-established by four days.⁵ These three studies provide evidence for a transient effect of kerosene on the endometrium, with resolution of inflammation, edema and necrosis by two weeks after treatment and regeneration of the muco-ciliary apparatus. Therefore, there seem to be no long-term deleterious effects of intrauterine kerosene on the endometrium. On the other hand, there seem to be no beneficial effects or improvement of degenerative changes.³⁻⁴

With respect to pregnancy rates, kerosene was proposed to improve pregnancy rates in mares with chronic infertility. Pregnancy rate after kerosene infusion was 50% in mares with category I and II endometrium, and 82% (9/11 mares) in those with category III endometrium. While pregnancy rate was high in mares with severe endometrosis, 44% (4/9) mares aborted between 40 and 100 days of gestation. Foaling rate in these mares was 45% (5/11).³ This was later interpreted as an improvement in fertility since foaling rate in mares with category III endometrium is expected to be less than 10%.² It must be noted that another study reported a foaling rate of 35% in mares with category III endometrium.⁷ It is unknown if a 10% increase in foaling rates would be statistically significant. In addition, use of kerosene in mares with category II endometrium did not seem to provide an advantage, since foaling rate in mares with moderate endometrosis is expected to be around 50%.^{7,8} In a later symposium, Bracher et al. commented that these findings tended to “confirm the rather short-term benefits of kerosene therapy, without a desired long-term improvement”.⁴ Therefore, while use of kerosene may be of value treating chronic endometritis, controlled studies or large clinical trials with appropriate control groups are needed to determine the true efficacy of this treatment and its real impact on fertility.

Nevertheless, the use of kerosene has recently gained in popularity among clinicians due to the perceived improvement in pregnancy rates. However, there is little documentation of the risks of such a procedure beyond its effect on the endometrium. Side effects have not been reported, although there is anecdotal evidence of transient vaginitis and discomfort immediately after treatment. The risks of occupational exposure to kerosene are also often overlooked. Kerosene is an oil distillate that consists of 78 to 96% paraffin or naphthene, and 4 to 25% aromatic compounds, which act as mild irritants.⁴ According to the World Health Organization Chemical Hazards and Poisons Division, exposure to commercially available kerosene can have toxic effects on the dermis, mucous membranes, central nervous system and respiratory system.⁹ Cardiac arrhythmias and ventricular fibrillation can also occur in some individuals after exposure to commercially available kerosene.⁹ One of the most frequent risks of exposure to kerosene is local skin irritation. A small percentage of individuals can sustain chemical burns following acute dermal exposure.⁹

In this case, reflux of kerosene into the vagina caused severe vaginal irritation. The behavioral changes noted the morning after kerosene infusion likely represented discomfort associated with vaginitis.

The vaginal manipulation and friction created during uterine lavage likely exacerbated the discomfort leading to severe pain that affected the mare's welfare. While there is anecdotal evidence of discomfort caused by kerosene reflux, controlled studies are needed to evaluate the effect of this treatment on animal welfare and the individual variation in the severity of the response. Additionally, treatments to mitigate pain and discomfort should be evaluated. In this mare, intravaginal irrigation with lidocaine was a suitable option for analgesia. Also, while the current practice is to infuse 250 ml of kerosene during estrus,^{2,5} use of a lower volume during diestrus as reported in other studies^{3,4} may help prevent reflux into the vagina and minimize undesirable side effects.

An often overlooked aspect of veterinary practice is occupational exposure to hazardous chemicals. In this case, the kerosene eroded the obstetric sleeve and caused contact dermatitis in the arm of the operator, also leading to pain for several hours. Therefore, the risk of human exposure to such chemicals should also be considered when selecting treatments.

The use of kerosene remains controversial, and the documentation of improved fertility requires the institution of controlled studies or large properly designed clinical trials. The side effects noted during this case were severe and call into question the welfare of the animals and personnel. Selection of treatments should be based on solid evidence of their efficacy and lack of side effects. The definition of safety in reproductive medicine is often limited to the effect of chemicals on the endometrium or fertility. The welfare of animals and veterinarians is often overlooked and should be an integral part of a responsible decision making process. The use of intrauterine kerosene may be efficacious and with time it may prove to be a valuable adjuvant in the treatment of infertility. However, such use should be done with caution until controlled efficacy and safety studies become available and the benefits are proven to outweigh the risks.

Learning points

- Appropriate breeding management and early referral of infertile mares allow for an early diagnosis and treatment, likely improving the prognosis for fertility.
- Medical treatment alone, in spite of addition of adjuvants and non-traditional therapy, failed to improve the uterine condition in this mare with pyometra.
- Use of kerosene to treat chronic uterine infections in mares currently lacks appropriate efficacy and safety studies to be recommended.
- The development of severe pain secondary to chemical vaginitis in this case raises questions regarding animal welfare and ethical use of kerosene.
- The use of commercially available kerosene can pose significant health risks to the operator and additional precautions are needed to minimize occupational exposure.

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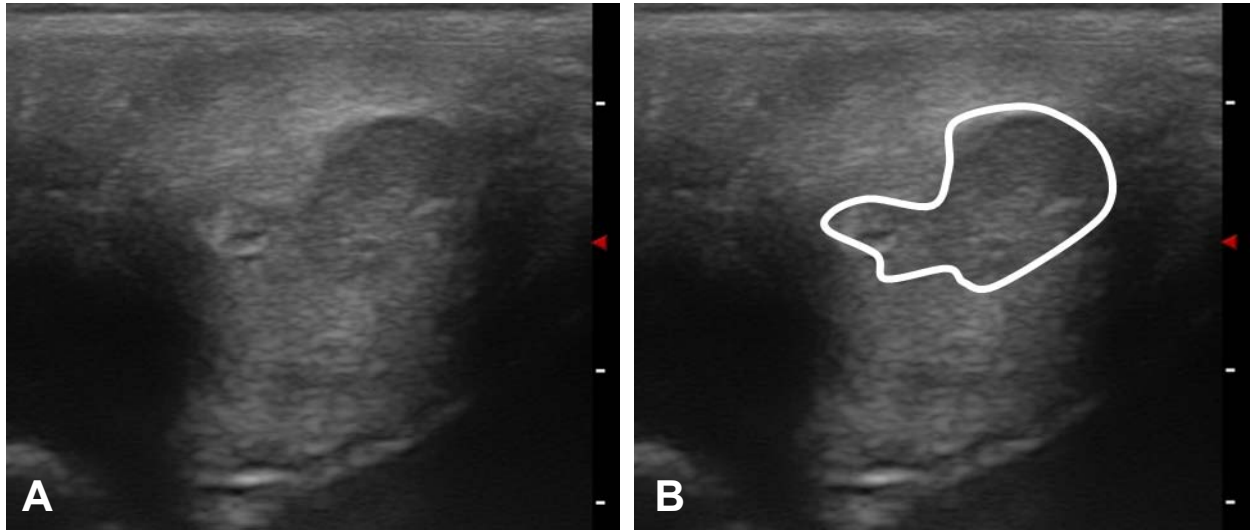


Figure 1. Ultrasonographic image of the cervical defect (A) delineated in white (B).

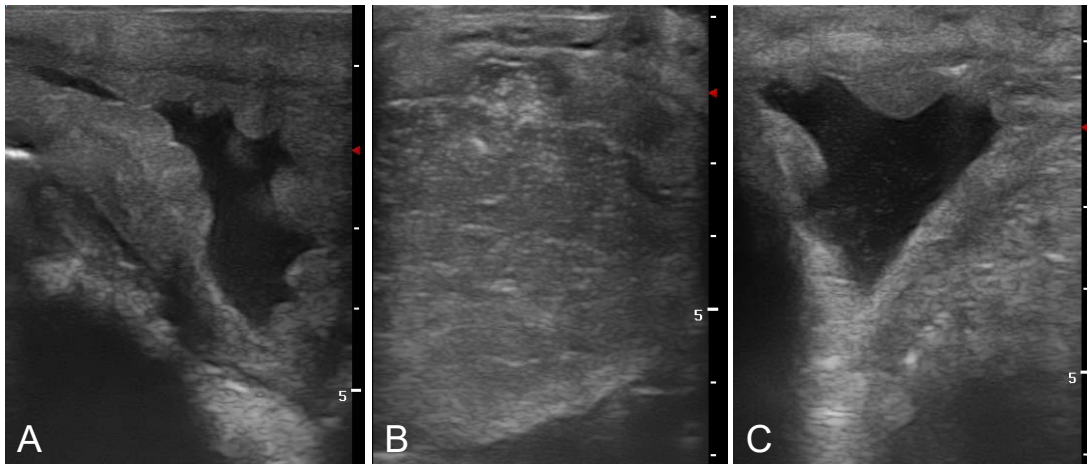


Figure 2. Ultrasonographic image of the uterine contents one day before (A), one day after (B), and 6 days after (C) intrauterine infusion with kerosene.



Figure 3. Debris and sloughed material present in the effluent recovered from the uterus the day after infusion with kerosene.

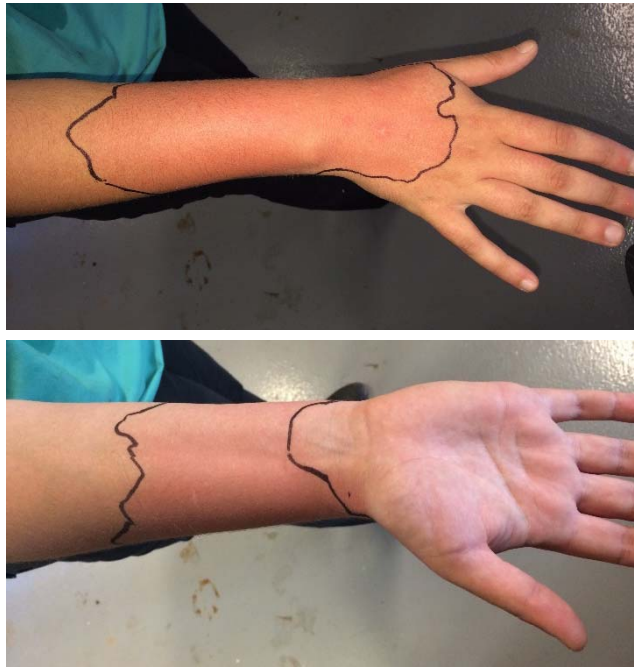


Figure 4. Kerosene eroded the obstetric sleeve during the uterine lavage and caused contact dermatitis and pain in the clinician's arm.

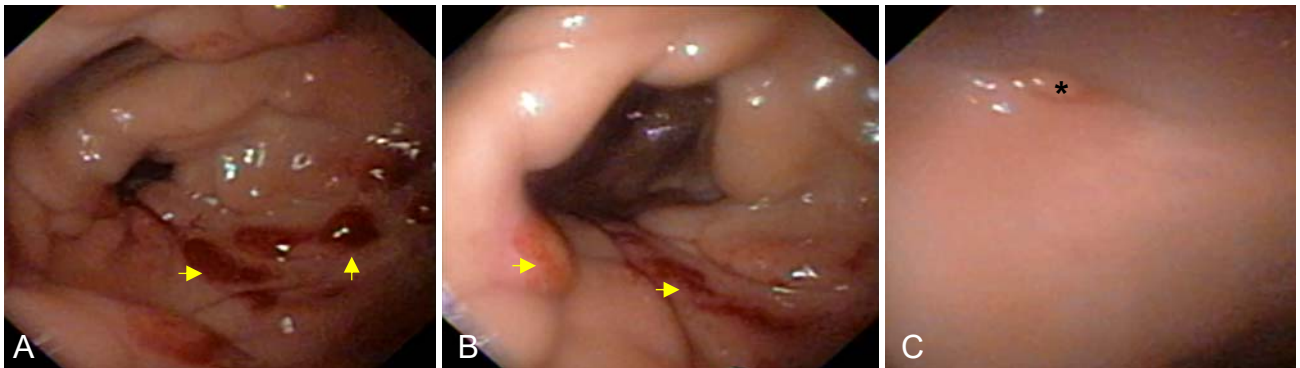


Figure 5. Endoscopic view of focal areas of endometrial inflammation (arrows) within the uterine body (A,B) and blister-like structure within the uterine body (C).

(Editor's note: Photographs in this manuscript are available in color in the online edition of Clinical Theriogenology.)