Canine Pyometra: An Update on Pathogenesis and Treatment

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ABSTRACT: Despite six decades of research, the pathogenesis of pyometra is still not completely understood. Recent investigations question whether the previous concept of considering cystic endometrial hyperplasia (CEH)—pyometra as a complex is correct. The pathogenesis of CEH appears to have a strong hormonal component, whereas the etiology of pyometra might be more influenced by the bacterial component. However, CEH may predispose bitches to develop pyometra. Critically ill pyometra patients should be monitored for clinical criteria of systemic inflammatory response syndrome. Closed-suction abdominal drains and a different administration route for prostaglandin F\(_2\alpha\) are promising enhancements in the treatment of pyometra.

Canine pyometra is a disease syndrome that affects adult intact bitches, causing a variety of clinical and pathologic signs of genital and systemic disease. The pathogenesis of canine pyometra is not completely understood, despite decades of studies concerning the etiology of the disease. The concept of cystic endometrial hyperplasia (CEH)—pyometra, introduced by Dow,\(^1\) states that hormonal changes lead to CEH (Figure 1) and render the uterus susceptible to secondary infection, which leads to pyometra (Figure 2). Recently, it has been suggested that the classic CEH—pyometra complex description should be separated into two entities: CEH and pyometra. CEH may predispose for pyometra in some cases, but pyometra can also occur without CEH. Mounting evidence suggests that the development of pyometra is an entity separate from CEH, with a hormonal component in the pathogenesis but mainly triggered by bacterial infection.\(^2\)

ETIOLOGY—THE HORMONAL COMPONENT

The investigated factors of pathogenesis in CEH and pyometra are summarized in Figure 3.
Figure 1—The endometrium in a dog with CEH. CEH is most likely due to an exaggerated uterine response to progesterone and estrogen.

Figure 2—A severely pus-distended uterus with pyometra. The pathogenesis of pyometra may be mainly triggered by infection.

Hormone Production

Progesterone has been shown to stimulate endometrial glandular secretion and to suppress contractions of the uterus, thus creating an intrauterine environment predisposed to bacterial growth. The importance of hormonal influence on the uterus in the pathogenesis of pyometra was suspected in early research, based on the observation that the disease most commonly occurs during progesterone influence in diestrus. After concluding that few bacteria were virulent enough to be the sole cause of pyometra, Teunissen found that the cystic and inflammatory changes of the uterine wall associated with pyometra (but not the abundant pus production) could be reproduced by injections of progesterone. Estrogen alone seemed to play a less important role but appeared to enhance the endometrial response to progesterone.

Several authors have investigated whether prolonged or excessive progesterone production could be responsible for the development of pyometra but failed to measure such alterations.

Hormone Receptors

More recent investigations have evaluated whether upregulation of endometrial hormone receptors that leads to an exaggerated response to progesterone, estrogen, or androgen is responsible for the development of the disease. Expression of estrogen and progesterone receptors has been shown to be elevated in uteri of bitches with CEH but not in uteri of bitches with pyometra. It also was noted that CEH and pyometra often occur independently, and the research group has suggested that the findings indicate different pathogeneses of these two conditions. At present there is no conclusive evidence that pyometra is caused by a disturbance either in hormone production or in the uterine response to these hormones. Future researchers may need to approach CEH–pyometra with an open mind and investigate new topics, such as bacterial interaction with the uterus during the different stages in the estrous cycle.

Such considerations as a possible different pathogenesis and other major differences between CEH and pyometra (e.g., lack of a bacterial component, different blood biochemistry findings) may indicate that it is time to divide the CEH–pyometra complex into two entities.

ETIOLOGY—THE BACTERIOLOGIC COMPONENT

Past investigations of the bacteria associated with canine pyometra have been few. However, it has been well established that the most common infecting agent is Escherichia coli (Figure 4), which is isolated in 59% to 96% of pyometra cases. Occasionally, other agents (e.g., Klebsiella organisms, streptococci, staphylococci, anaerobic bacteria, pseudomonads) are isolated from the uterus of an infected animal. Sandholm and coworkers found that E. coli demonstrated adherence to receptors in progesterone-stimulated endometrium, which is one explanation for the observed predominance of this bacterium.

Virulence Factors

Certain serotypes of E. coli, such as 02, 04, 06, 075, and 032, appear to be isolated more commonly than other serotypes from dogs with pyometra. However, the virulence factors of these serotypes have been sparsely investigated. The presence of a K antigen, an important virulence factor of E. coli–inducing cystitis, has been demonstrated in dogs with pyometra as well. The virulence factor, cytotoxin necrotizing fac-
tor, was expressed in seven of 16 serotypes associated with pyometra, and the presence of this factor was related to more severe endometrial changes.12

**Infection Route**

The route of infection was once considered to be hematogenic as well as ascending.1 Our research group performed bacterial epidemiologic studies of *E. coli* isolates from pyometra using biochemical fingerprinting, a method that has proved to be highly discriminative between clones of bacteria of the same species.13 We found a fecal strain of *E. coli* identical to the corresponding uterine isolate in each of 10 bitches with pyometra. Thus an ascending route of infection from the fecal flora into the uterus is the most logical explanation in those cases of pyometra.14

Cystitis has been shown to be commonly associated with canine pyometra.11,14,15 The *E. coli* bacteria isolated from the urinary bladder and the isolate from the uterus are descendents of the same clone of bacteria, as evidenced by biochemical fingerprinting and by restriction enzyme digestion and pulsed-field gel electrophoresis.14,16 Sandholm and coworkers11 have suggested that the urinary tract may serve as a bacterial reservoir and that bacteria ascend into the uterus during a susceptible stage in the estrous cycle. Another explanation for this phenomenon is that during pyometra, bacteria in the purulent vaginal discharge...
can easily ascend the urinary tract, especially because the urethra opening in bitches is in an anatomically dependent position.

**SYSTEMIC EFFECTS OF PYOMETRA**

The clinical signs of pyometra are not limited to the genital tract. The most frequently reported clinical signs include anorexia, vomiting, polydipsia and polyuria, lethargy, and vulvar discharge. The clinical signs are often more severe in dogs when the cervical canal is occluded, and these dogs frequently have a distended abdomen and severe lethargy. However, the cervix may spontaneously open or close during the disease, causing intermittent vaginal discharge or a sudden deterioration in the clinical status of the bitch.

**Systemic Inflammatory Response Syndrome**

Canine pyometra is often associated with systemic inflammatory response syndrome (SIRS). This syndrome is associated with any serious infectious, inflammatory, traumatic, or neoplastic foci that cause production and release of inflammatory mediators that affect the body systemically. SIRS is the common name for what previously was called sepsis, septic syndrome, or septic shock. SIRS is identified clinically in dogs by the presence of two of four criteria, including heart rate (>160 bpm), temperature (>103.5°F or <100°F), respiratory rate (>20 breaths/min or partial pressure of carbon dioxide <32 mm Hg), and white blood cell count (>12,000/µl, <4,000/µl, or >10% band neutrophils). To decrease the risk for overlooking a patient that is developing SIRS, it has been suggested that these criteria include a heart rate over 120 bpm; a temperature
below 100.6°F or over 102.6°F; and white blood cell counts of over 16,000/µl, less than 6,000/µl, or less than 3% band neutrophils. However, use of the latter criteria is associated with a high risk for overdiagnosing SIRS. Until specific markers for SIRS in dogs are developed, clinicians should use their clinical judgment in the evaluation of the individual pyometra patient, with the SIRS criteria serving as guidelines for monitoring the animal.

**Endotoxemia and Systemic Effects**

Lipopolysaccharide, or endotoxin, is a cell wall component of *E. coli* and other gram-negative bacteria and can be released either as a result of bacterial death and disruption or during vigorous growth of the bacteria. Experimentally, sublethal doses of endotoxin have been shown to cause fever, lethargy, and increases in heart and respiratory rates. Higher doses in dogs give rise to cardiovascular and gastrointestinal effects, such as mucoid, bloody diarrhea and vomiting. The hemodynamic changes are initially transient if compensated by adequate support and treatment. If the hemodynamic changes are uncompensated, endotoxic shock often leads to myocardial failure and death. The outcome in canine pyometra has been shown to relate to blood endotoxin concentration in which high plasma endotoxin concentration was associated with mortality. Severity of clinical signs has also been related to the degree of immunosuppression in dogs with pyometra.

Endotoxemia is a possible cause of impaired lymphocyte activity, one of the features of immunosuppression seen in canine pyometra. However, the evidence for endotoxemia in bitches with pyometra conflicts. Studies conducted by our research group did not reveal endotoxemia in 50 of 53 cases, but these dogs were all in good general health, which is in accordance with a previous study. Experimentally induced endotoxemia in dogs is associated with severe clinical signs, such as cardiovascular depression or collapse, and persistent endotoxemia should be expected mainly in critically ill dogs.

**Endotoxemia and Polyuria**

Polyuria and polydipsia are common features of pyometra, a fact that has intrigued many investigators. IV injection of killed *E. coli* was shown to induce a reversible reduction in renal concentrating ability. The dysfunction was not associated with decreased release of antidiuretic hormone (ADH) and could not be reversed with exogenous ADH administration. Therefore, this effect is likely a result of decreased renal response to ADH, but the exact mechanism is unknown. Later work has found evidence of both glomerular dysfunction and renal tubular damage associated with pyometra. The classical polyuria and polydipsia seen in canine pyometra are probably of multifactorial origin (i.e., decreased response to ADH, glomerular dysfunction, renal tubular cell damage). In general, polyuria is reversible after ovariectomy and is most likely a result of bacterial

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**Table 1. Common Laboratory Parameter Abnormalities in Bitches with Pyometra**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clinical Abnormality</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>Leukocytosis</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td></td>
<td>Left shift</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Anemia</td>
<td>Mild</td>
</tr>
<tr>
<td>Packed cell volume</td>
<td>Anemia</td>
<td>Mild</td>
</tr>
<tr>
<td>Serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>Normal or decreased</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Albumin</td>
<td>Hypoalbuminemia</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Increased</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>Increased</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Bilirubinemia</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>Increased in 15%–21% of cases</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Hypercholesterolemia</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>Increased</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Increased in 17%–31% of cases</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Globulin</td>
<td>Hyperglobulinemia</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>Increased</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Urine</td>
<td>Proteinuria</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td></td>
<td>Sediment</td>
<td>&gt;10^4/µl</td>
</tr>
</tbody>
</table>

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components, such as endotoxin, or bacterial products gaining access to the systemic circulation.

**COMMON LABORATORY PARAMETER ABNORMALITIES**

The systemic effects of pyometra are reflected by several laboratory parameters (Table 1). Anemia in typical cases is caused by reduced production of erythrocytes resulting from the systemic inflammatory response. Hyperglobulinemia is a result of inflammation and hypoalbuminemia, which is considered part of an acute phase reaction. Elevated levels of alkaline phosphatase, bilirubin, and serum cholesterol are considered to result from intrahepatic cholestasis rather than from hepatocyte damage. This is in accordance with the observed low activity of alanine aminotransferase, which indicates that hepatocellular necrosis has not occurred. Examination of liver biopsy specimens confirmed these interpretations because fatty infiltration and bile pigments, but no gross hepatocellular necrosis, were observed.

**TREATMENT**

**Surgical Options**

Ovariohysterectomy, the treatment of choice in most cases of pyometra, generally results in a rapid recovery with minimal risk for recurrence and also negates the risk for ovarian or uterine neoplasia or unwanted pregnancy. Reported complications of surgery include anesthetic complications, hemorrhage, peritonitis, incomplete removal of the ovaries, wound swelling, wound infection, and fistulous tracts. Surgical and anesthetic complications can be decreased if severely ill bitches receive appropriate therapy to stabilize their condition before surgery. Postsurgical mortality in bitches with pyometra has been found to be approximately 5%.

Preoperative stabilization of a bitch with pyometra must be tailored to the findings of physical examination and laboratory results. In Scandinavia, dogs are not routinely spayed and neutered, and the prevalence of pyometra is very high. Recently published data from an epidemiologic study of approximately 200,000 dogs covered by insurance in Sweden have shown that approximately 1,800 bitches were treated for pyometra in 1996. According to these data, the risk of an intact bitch to develop pyometra before 10 years of age is 23% to 24%. The author’s experience (B. A. F.) as a surgeon at the Swedish University of Agricultural Science has included treating 210 cases of pyometra. Subjectively, signs of severe systemic illness were noted in few of these bitches. The routine preoperative stabilization of bitches with uncomplicated pyometra mainly included rehydration by IV infusion of a balanced electrolyte solution (acetated Ringer’s solution). Routine anesthetic premedication included acepromazine (0.03 to 0.05 mg/kg IV) and buprenorphine (0.005 to 0.01 mg/kg IV); for anesthesia, induction was most commonly accomplished with thiopental (5 to 15 mg/kg IV) and maintained with isoflurane inhalation. Antibiotic therapy was not used unless signs of systemic illness were present. The author (B. A. F.) currently recommends the use of IV broad-spectrum antibiotics at

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**“Rule of 20”—Parameters to Monitor in Patients with SIRS**

1. Fluid balance
2. Blood pressure/perfusion
3. Cardiac function
4. Albumin
5. Oncotic pull
6. Oxygenation/ventilation
7. Glucose
8. Electrolyte/acid–base balance
9. Mentation
10. Coagulation
11. Packed cell volume
12. Renal function/urine output
13. White blood cell count/antibiotic therapy
14. Gastrointestinal motility/integrity
15. Drug metabolism/doses
16. Nutrition
17. Pain control
18. Nursing mobility/catheter care
19. Bandage/wound care
20. Tender loving care

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the time of induction to counteract possible bacteremia from manipulation of the uterus; the dose should be repeated if the operation lasts more than 90 minutes. These guidelines represent the standard perioperative antibiotic use at our hospital and were originally based on the prevention of postoperative infection in dogs after orthopedic procedures. Antibiotic therapy should be continued after surgery in systemically ill dogs or in dogs with increased risk of complications. In pyometra cases with physical examination or laboratory findings consistent with SIRS, it is wise to proceed more cautiously before the surgical procedure. Pre- and postoperative therapy and monitoring are performed according to the “Rule of 20” (see box on page 607).

Anesthesia and ovariohysterectomy should be performed without delay when cardiovascular parameters are as stable as possible. In these patients, induction with a combination of diazepam and oxymorphone (0.5 mg/kg and 0.1 to 0.2 mg/kg, respectively, administered alternately) or diazepam and ketamine (mixture of 0.5 mg/kg diazepam and 10 mg/kg ketamine, given to effect) might cause less severe cardiovascular side effects than thiopental.

The recommended surgical technique has been described previously. Compared with the regular spay, the incision is extended and the surgeon must manipulate the pus-distended and often friable uterus with extreme care to avoid penetration. The uterus should be packed off with laparotomy sponges before manipulation and transection. The suspensory ligament is often stretched from the weight of the uterus and generally does not require strumming. The vessels in the broad ligaments might be enlarged due to the uterine inflammation and need to be ligated with 2-0 or 0 monofilament absorbable suture. Because triple

Table 2. Selection Criteria for Ideal Candidates for Medical Management with PGF$_{2\alpha}$

<table>
<thead>
<tr>
<th>Candidate Feature</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient has a highly motivated owner who is informed about side effects and is willing to hospitalize the pet if it is at risk</td>
<td>Side effects, such as anxiety, hypersalivation, panting, vomiting, abdominal pain, tachycardia, and fever are common and can be dramatic; however, they usually resolve within 1 hr after treatment.</td>
</tr>
<tr>
<td>High breeding value; owners want to breed the bitch within the next estrous cycle</td>
<td>The long-term outcome of medical management has been associated with recurrence in most of the dogs treated with PGF$_{2\alpha}$.</td>
</tr>
<tr>
<td>Patient is not systemically ill</td>
<td>There is a 48-hr lag before effects of treatment can be seen, and clinical deterioration can occur in the meantime. Bacteremia can occur from therapy.</td>
</tr>
<tr>
<td>Patient has an open cervix as evidenced by vaginal discharge</td>
<td>Two cases described in the literature of uterine rupture or peritonitis after PGF$_{2\alpha}$ treatment of bitches with closed-cervix pyometra.</td>
</tr>
</tbody>
</table>

Figure 6—An alternative treatment of pyometra refractory to PGF$_{2\alpha}$. Schematic drawing shows transvaginally placed intrauterine catheters with the tip of the catheters positioned 5 to 10 cm cranial to the bifurcation. The inset shows a technique of fixing the catheters to the dorsal wall of the vagina by ligatures of 3-0 stainless steel. These drains are inserted with the aid of a specifically designed guiding device and fluoroscopy. (From Lagerstedt A-S, Obel N, Stavenborn N, et al: Uterine drainage in the bitch for treatment of pyometra refractory to prostaglandin F$_{2\alpha}$. J Small Anim Pract 28:215–222, 1987; with permission)
A low-dosage treatment

If gentamicin is used, adequate

Schematic drawing showing a guiding device

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which leads to expulsion of exudate from the

uterine lumen. Response to treatment consists of a
decrease in uterine diameter, cessation of uterine dis-
charge, and return of a normal leukogram. The side
effects associated with PGF$\alpha_2$ include abdominal pain,
emesis, defecation, tachycardia, hypersalivation, dys-
pnea, panting, and fever. A low-dosage treatment
(0.025 mg/kg injected SC q12h for 5 days or to effect)
of a natural PGF$\alpha_2$, such as dinoprost tromethamine,
has been shown to be effective and is associated with
fewer side effects than with higher doses. A systemic
bactericidal antibiotic should be administered concomi-
tantly with PGF$\alpha_2$ to prevent bacteremia, and the
antibiotic treatment should be continued for 10 to 14
days. Amoxicillin (10 to 20 mg/kg PO or SC q8–12h)
seems to be a reasonable choice in uncomplicated cases;
however, if the bitch shows fever or an affected attitude,
erythromycin (2.5 to 5 mg/kg IV or PO bid or 10
mg/kg sid) or gentamicin (2.2 mg/kg IV or SC q8h)
may be considered. If gentamicin is used, adequate
hydration must be maintained.

In cases refractory to PGF$\alpha_2$ therapy or with a closed
cervix, drainage has been performed by using catheters
placed into the uterine lumen through the vagina (Fig-
ure 6). A technique requiring a specific guiding device
showed a good outcome in nine of 12 bitches, with five
of six bred bitches conceiving (Figure 7). A newer

Medical Management

Case selection criteria for treatment of dogs with
pyometra with SC injections of prostaglandin F$\alpha_2$
(PGF$\alpha_2$) are listed in Table 2. PGF$\alpha_2$ causes contraction
of the myometrium and relaxation of the cervical
canal, which leads to expulsion of exudate from the
uterine lumen. Response to treatment consists of a
decrease in uterine diameter, cessation of uterine dis-
charge, and return of a normal leukogram. The side
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of six bred bitches conceiving (Figure 7). A newer
technique for transcervical uterine cannulation has been described that uses a hysteroscope, a rigid endoscope 25-cm long designed for use in women.\(^4\) Air is insufflated into the vagina through a channel in the operating sheath of the endoscope, and the cervix is visualized to allow introduction of a size 4 to 7 Fr (1.35 to 2.3 mm) catheter.\(^4\) However, the latter technique has not been described at present for introduction of catheters for draining purposes in pyometra cases.

**CONCLUSION**

Despite over six decades of canine pyometra studies, the etiology of the disease is still unclear. The hormonal component of the etiology has been extensively investigated. Recently, it has been suggested that the role of the infecting bacteria potentially could be more important than previously believed, both in the determination of the systemic response to pyometra and in initiation of the disease. The bacterial component in the pathogenesis of pyometra is important for the development of a systemic inflammatory response. The inflammatory response to bacterial components is suspected to cause decreased survival and immunosuppression in dogs with pyometra. Information regarding virulence factors of the bacteria associated with canine pyometra is minimal, and it seems imperative to direct future studies to this area. Surgery remains the treatment of choice in canine pyometra, and the management of patients with complicated pyometra has been enhanced by the development of new products for abdominal drainage. The development of criteria for SIRS in small animals provides guidelines for monitoring and treating critically ill patients with pyometra. New treatment alternatives for the medical management of pyometra in animals with high breeding value include intravaginal administration of PGF\(_{2\alpha}\), administration of antiprogestin RU 46534, and drainage of the uterus, which has been enhanced by new techniques for transcervical uterine cannulation.

**REFERENCES**


ARTICLE #3 CE TEST

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. Choose the best answer to each of the following questions; then mark your answers on the postage-paid envelope inserted in Compendium.

1. Which bacterium is most commonly isolated from the uterus in canine pyometra?
   a. E. coli
   b. Klebsiella spp
   c. Staphylococcus intermedius
   d. Streptococcus canis
   e. anaerobic species

2. Which hormonal abnormalities have been shown to induce pyometra?
   a. upregulation of endometrial androgen receptors
   b. prolonged or excessive endogenous progesterone production
   c. upregulation of endometrial progesterone receptors
   d. upregulation of endometrial estrogen receptors
   e. none of the above

3. What stimulus is required for the endometrium to develop receptors to which bacteria adhere?
   a. estrogen
   b. progesterone
   c. androgen
   d. cortisol
   e. thyroxin

4. Which serotype of E. coli has not been commonly associated with canine pyometra?
   a. 02
   b. 04
   c. 08
   d. 04
   e. 032

5. Which is the most likely origin of the bacteria that infect the uterus?
   a. oral flora from licking the vulva
   b. pathogenic bacteria in the environment
   c. pathogenic bacteria from direct genital contact with another dog
   d. infectious bacteria transmitted between bitches in the same household
   e. ascending fecal flora from the bitch herself
6. Which concomitant infection is commonly associated with pyometra?
   a. external otitis
   b. lower urinary tract infection
   c. upper urinary tract infection
   d. bacterial enteritis
   e. none of the above

7. Which is not identified as a criterion of SIRS?
   a. capillary refill time
   b. heart rate
   c. respiratory rate
   d. temperature
   e. white blood cell count

8. Endotoxemia in bitches with pyometra has been associated with
   a. poor survival.
   b. length of hospitalization.
   c. a high cost of treatment.
   d. disseminated intravascular coagulation.
   e. leukopenia.

9. Which is the most characteristic blood work abnormality in pyometra?
   a. decreased packed cell volume
   b. leukocytosis
   c. hypoalbuminemia
   d. increase in alkaline phosphatase
   e. decrease in alanine aminotransferase

10. Which agent has been used in the management of pyometra?
    a. broad-spectrum antibiotics
    b. SC injection of PGF$_{2\alpha}$
    c. intravaginal administration of PGF$_{2\alpha}$
    d. antiprogestin RU 46534
    e. all of the above