

# Large Animal VETERINARY Rounds™

DECEMBER 2004  
Volume 4, Issue 10

AS PRESENTED IN THE ROUNDS OF THE DEPARTMENT OF LARGE ANIMAL CLINICAL SCIENCES  
OF THE WESTERN COLLEGE OF VETERINARY MEDICINE, UNIVERSITY OF SASKATCHEWAN

## Cystic Ovarian Disease in Cattle

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**Cystic ovarian disease is a major cause of reduced reproductive efficiency and economic loss to the dairy industry. This issue of *Large Animal Veterinary Rounds* reviews the factors involved in the pathogenesis of the disease, the methods for diagnosis, and options for treatment.**

Cystic ovarian disease (COD) is characterized by the presence of large, persistent, anovulatory follicles in the ovaries. It results from a malfunction of the neuroendocrine mechanism controlling ovulation and thus, interferes with the estrous cycle.<sup>1-4</sup> Ovarian cyst, cystic ovary, cystic ovarian degeneration, and "cystic cows" are all terms used to describe the same condition. In cattle, COD occurs primarily in dairy cows, but may occasionally be detected in dairy heifers and female beef cattle.<sup>1</sup> The reported incidence in several countries ranges between 6.7% and 13.1%,<sup>5-11</sup> while in Canada, data pooled from different studies (involving 24,356 lactations) indicates a mean incidence of 9.3%.<sup>5-7,10,17</sup>

The adverse effects of COD on fertility are related to increased intervals between calving and first service, and between calving and conception (approximately 13 and 33 additional days, respectively). Conception rates at the first service after treatment are reduced by 5% to 25%, the number of services per conception are increased by approximately 0.8 additional services compared to unaffected herdmates, and the likelihood of culling a cow that has experienced COD is increased by 20% to 50%.<sup>5-7,10,17</sup> Importantly, most cows in these studies were part of herd health programs involving regular exams during the postpartum period and prompt treatment after diagnosis. Adverse effects on fertility would likely be more pronounced in herds where routine exams are not performed.

In a 1986 United States (US) study, the cost of COD was estimated to be \$137 per lactation, when the effects on fertility and the costs of veterinary service, treatment, labour, and culling were considered. Greater milk production by affected cows did not compensate for these costs and a net loss of \$39 was estimated.<sup>6</sup> Based on these numbers, the costs of COD to the Canadian dairy industry may be millions of dollars. This indicates the importance of designing strategies to reduce COD incidence and developing efficient methods for diagnosis and treatment.

### Factors affecting COD incidence

There is a clear genetic predisposition for COD. In Sweden, the incidence was reduced from 11% in 1954 to 3% in 1977 as a result of genetic selection.<sup>2</sup> Despite this evidence, there has been a reluctance to select against COD because heritability estimates are generally low ( $h \cong 0.1$ ).<sup>10,16</sup> In addition, COD is more common in cows with greater milk production.<sup>5,6,8,11</sup> One report demonstrated that COD incidence tripled when milk yields doubled (9% and 27% incidence for lactations with 6,000 and 12,000 kg of milk, respectively).<sup>9</sup> A recent study reported a positive genetic correlation between milk production and COD. According to this study, selection based solely on milk production would increase COD incidence by 1.5% for every 500 kg increase in lactational production.<sup>10</sup> Therefore, although progress through genetic selection will be slow, ignoring the existence of a genetic predisposition for COD will only contribute to an increased incidence of the disease and related economic losses.

The incidence of COD increases with parity, especially after the first lactation; the incidence in first-lactation cows is 40% to 80% lower than in the general cow population.<sup>5,6,8,9,16</sup> The seasonal



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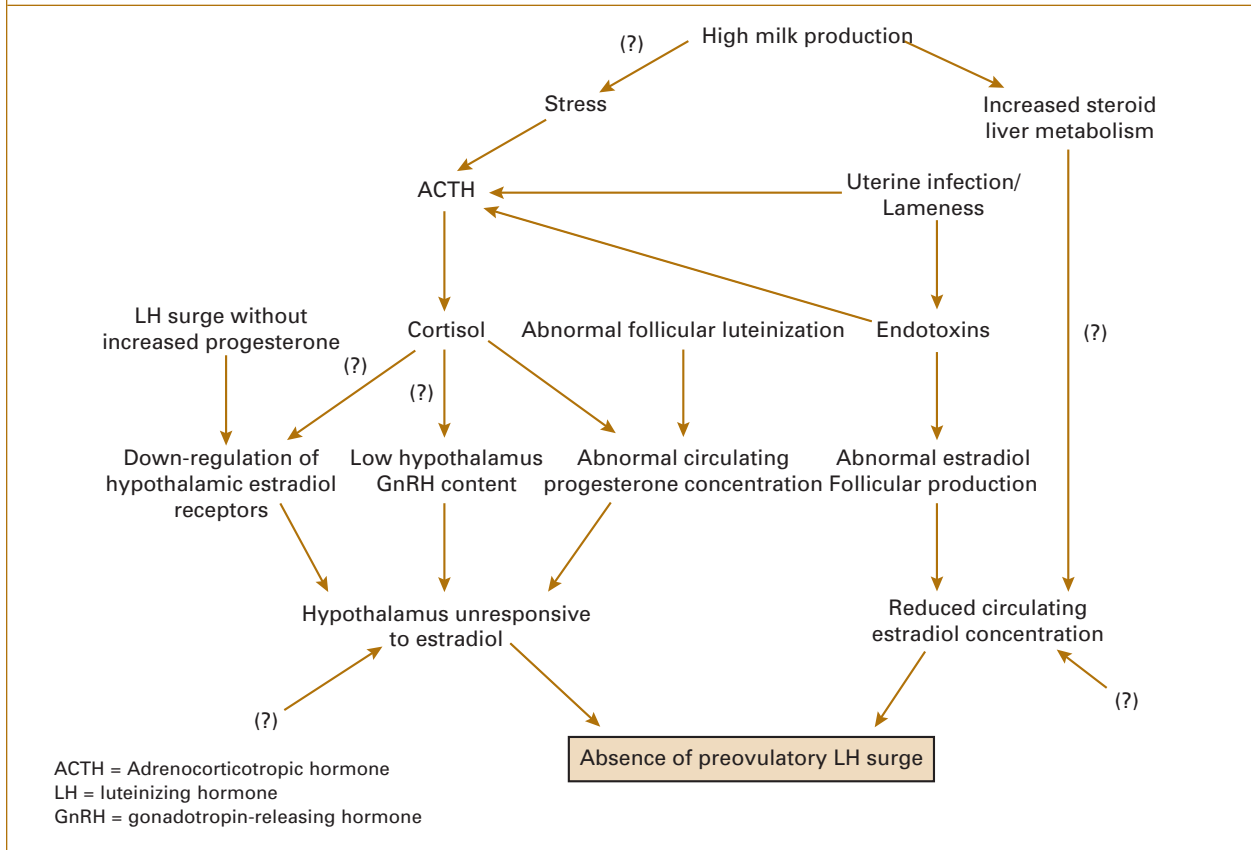
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The Canadian Veterinary Medical Association recognizes the educational value of this publication and provides support to the WCVIM for its distribution.

**Figure 1: The pathogenesis of cystic ovarian disease in cattle involves the absence of the preovulatory LH surge resulting from a disturbance in the positive feedback effect of estradiol on the hypothalamus. This disturbance is caused by hypothalamic unresponsiveness or by reduced circulating estradiol concentration.**



effect on COD incidence is not clear. Some studies were unable to demonstrate any effect,<sup>6,10</sup> while others described an increased incidence during fall-winter,<sup>8</sup> winter,<sup>18</sup> or summer.<sup>11</sup> Cows with abnormal postpartum conditions including retained fetal membranes, metritis, ketosis, and lameness are 1.4 to 2.9 times more likely to develop COD than cows having a disease-free postpartum period.<sup>5,8,11,15,18,19</sup> Therefore, measures to reduce other postpartum problems should also reduce COD incidence.

### Pathogenesis

Ovarian cysts can be classified as follicular or luteal depending upon steroid production; luteal cysts produce more progesterone (circulating concentration  $\geq 1$  ng/ml). Younger follicular cysts have a thicker granulosa cell layer that gradually disappears with age. Luteal cysts are follicular cysts in later stages of development that have undergone luteinization.<sup>20</sup> Ovarian cysts are not static structures. Their dynamics are characterized by regression and the development of new follicles that also become cysts (cyst turnover). Follicular waves continue to occur in the presence of cysts and are associated with follicle-stimulating hormone (FSH) surges similar to those in normal, cycling cows.<sup>21-23</sup> Growth rates are similar for normal follicles and follicles destined to become cysts, but cysts continue to grow after reaching the expected ovulatory size.<sup>22</sup> Therefore, interfollicular wave

intervals are longer in cows with COD (>13 days) than in normal cows (8-9 days).<sup>22,23</sup>

In normal cows, increased circulating estradiol concentrations have positive feedback effects on the hypothalamus when circulating progesterone concentrations are low. This results in the release of gonadotropin-releasing hormone (GnRH) that, in turn, stimulates the pituitary to release the preovulatory luteinizing hormone (LH) surge. Cystic ovarian disease develops as a result of the absence of a preovulatory LH surge that is caused by a disturbance in the positive feedback effect of estradiol on the hypothalamus.<sup>2-4</sup> This may involve unresponsiveness of the hypothalamus, either inherent or from interference by abnormal circulating progesterone concentration, or reduced circulating estradiol concentration, either as a consequence of abnormal follicular production or increased metabolism (Figure 1).

Probably the most common cause of COD is hypothalamic unresponsiveness to estradiol.<sup>2-4</sup> Cows that develop COD do not have a preovulatory LH surge even when the dominant follicle secretes high concentrations of estradiol.<sup>24,25</sup> Moreover, exogenous estradiol treatment either cannot elicit an LH surge in cows with COD or the surge is delayed.<sup>23,24</sup> Unresponsiveness to estradiol may be associated with decreased hypothalamic GnRH content<sup>21</sup> and may develop if an LH surge is not followed by ovulation. After an LH surge, exposure to progesterone may be necessary to

up-regulate estradiol receptors in the hypothalamus and re-establish responsiveness to estradiol.<sup>26,27</sup>

Abnormal circulating progesterone concentrations interfere with hypothalamic responsiveness to estradiol and result in the formation of cysts.<sup>28</sup> In a recent study, 66% of cows with cysts and no detectable luteal tissue in cyst or ovary, had intermediate circulating progesterone concentrations (0.1–1 ng/ml), and only 10% of the newly-developed follicles ovulated in these cows.<sup>29</sup> In this study, it could not be determined if the original cysts formed because of abnormal progesterone concentration, possibly due to luteinization of a previous preovulatory follicle. Nevertheless, the results indicated that a self-perpetuating mechanism exists; follicles that develop in the presence of cysts producing abnormal amounts of progesterone are likely to become cysts themselves.

Reduced circulating estradiol concentrations may also be involved in the pathogenesis of COD, as demonstrated by the formation of cysts after estradiol immunoneutralization.<sup>30</sup> Decreased circulating estradiol concentrations can result from factors directly affecting follicular production (eg, endotoxins) or as a consequence of increased steroid liver metabolism in highly productive dairy cows. Circulating estradiol concentration in lactating dairy cows is lower than in heifers and is also associated with lower preovulatory LH peak levels.<sup>31</sup> Whether or not reduced circulating estradiol in lactating cows is associated with COD remains to be demonstrated.

Adrenocorticotrophic hormone (ACTH) and cortisol also likely play a role in the pathogenesis of COD. Treatment with ACTH delays the normal decrease in circulating progesterone concentrations during the last third of the estrous cycle (either by interfering with luteolysis or by causing adrenal progesterone production), and suppresses the preovulatory LH surge.<sup>32,33</sup> Furthermore, estradiol treatment is unable to stimulate an LH surge in heifers with ACTH-induced COD.<sup>34</sup> Therefore, it appears that ACTH and cortisol may have a direct effect on the hypothalamus and/or an indirect effect by causing abnormal circulating progesterone concentrations. High milk production and stress may be associated with COD through increased ACTH and cortisol secretion.

Cortisol and endotoxins may act synergistically to cause COD. Positive uterine cultures and higher bacterial growth density which, in turn, are associated with greater circulating cortisol, are more prevalent in cows with COD.<sup>35</sup> Intrauterine infusion of *Escherichia coli* endotoxin increases circulating cortisol concentration, reduces estradiol concentration, and abolishes the LH surge, demonstrating that endotoxins may directly affect follicular estradiol production.<sup>36</sup> A similar mechanism may be involved when COD develops in association with lameness. Some cases of lameness are believed to be associated with subclinical ruminal acidosis resulting in the production of endotoxins and cortisol.<sup>19</sup>

Despite the absence of the preovulatory LH surge in cows with COD, LH pulse frequency is increased.<sup>21,22</sup> However, exogenous treatments designed to mimic the increased LH pulse frequency observed in cows with COD

do not result in the development of cysts, indicating that increased LH pulse frequency may be important for sustaining the growth of cysts, but is unlikely to be the primary cause of anovulation.<sup>37</sup>

## Diagnosis

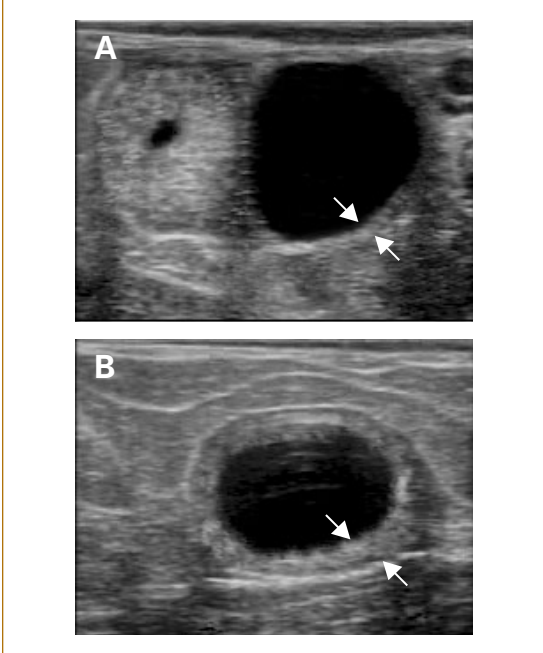
Ovarian cysts have been defined as fluid-filled structures  $\geq 20$ –25 mm in diameter that persist in the absence of a corpus luteum (CL) for  $>10$  days.<sup>1–4</sup> Considering that herd health visits are usually scheduled once or twice a month, the dynamic nature of cysts, and the recommendation for prompt treatment after diagnosis, the persistency criterion has become more a matter of academic debate than a practical consideration. The significance of the presence of a CL is also difficult to assess. Some cysts can still be palpated after ovulation of another follicle and subsequent CL formation, indicating that they are not functional.<sup>38</sup> Conversely, a developing cyst may also be associated with a regressing CL.<sup>23</sup> Therefore, from a practical point of view, the presence or absence of a CL has little significance for diagnosis. It is important to remember that ovarian cysts are anovulatory structures that should not be confused with a CL containing a central cavity. These develop after ovulation and are not pathological.

Cows with COD may have frequent, irregular, prolonged or continuous signs of estrus (nymphomania), but the majority are anestrus.<sup>1–4</sup> Relaxation of the pelvic ligaments, elevated tail-head, and development of masculine characteristics may be observed in chronic cases. The incidence of COD is bimodal with the first peak occurring during month 2 postpartum and the second peak between 4 and 6 months postpartum. The second peak is probably associated with a greater number of cows being presented for examination due to abnormal behaviour or repeat-breeding.<sup>6,13,14</sup> The same proportion of cows develop COD before and after the first postpartum ovulation, but the incidence decreases in consecutive cycles; spontaneous recovery may occur in 38% to 48% of the cases.<sup>11,18</sup>

Rectal palpation is the most common method used for COD diagnosis and is effective, although false positive diagnoses may be made in approximately 10% of the cases due to the presence of large follicles adjacent to a CL or a large CL with a cavity.<sup>39</sup> Differentiation between follicular and luteal cysts cannot be made accurately by rectal palpation, and studies have shown that a correct diagnosis is achieved in only 50% of the cases.<sup>39,40</sup> Ultrasonography is a more reliable method for diagnosing COD, since ovarian structures can be visualized and true cysts can be differentiated from other ovarian structures. A CL with cavity is readily distinguished from a cyst, since the maximum CL cavity diameter is  $<20$  mm. Follicular and luteal cysts can be differentiated more accurately with ultrasonography by evaluating the thickness of the cyst wall. In follicular cysts, the wall is  $\leq 3$  mm thick, while in luteal cysts the wall is  $>3$  mm thick (Figure 2). Using these criteria, a correct diagnosis can be made in approximately 85% of the cases.<sup>39,40</sup>

Ultrasonography could be combined with analysis of circulating progesterone concentrations to improve the accuracy of COD diagnosis. By definition, progesterone

**Figure 2: Ultrasound images of the ovaries of a cow with chronic, multiple, cystic ovarian disease.** In one ovary (A) a follicular cyst (fluid-filled structure on the right) was observed; cyst cavity was 30 mm in diameter and cyst wall (arrows) was 3 mm thick. In the same ovary a corpus luteum (CL) with a cavity was observed adjacent to the follicular cyst (echodense structure on the left); note that in the CL the luteal tissue layer is very thick and the cavity is < 20 mm. In the other ovary (B) a luteal cyst was observed; this cyst cavity was 24 mm in diameter and cyst wall (arrows) was 6 mm thick.



concentration is <1 ng/ml in cases of follicular cysts and  $\geq 1$  ng/ml in cases of luteal cysts. Unfortunately, progesterone analysis is not always practical or feasible. There is great discrepancy in the literature concerning which type of cyst is more prevalent. The reported proportion of luteal cysts ranges from 25% to 77%.<sup>39-44</sup> Considering this large variation and the fact that luteal cysts are follicular cysts in later stages of development, it seems reasonable to conclude that follicular and luteal cysts have a similar incidence.

### Treatment

The results of a study using decision analysis to evaluate the most appropriate postpartum period for COD treatment, demonstrated that it was more economical to treat cows as soon as the condition was diagnosed, even before the end of the voluntary waiting period, rather than to wait for spontaneous recovery. The greatest economic benefit of treatment is a reduction in days-open.<sup>45</sup>

GnRH is the most common treatment for COD. Treatment results in an immediate increase in LH secretion and luteinization of the cyst. Ovulation of the

**Table 1: Drugs, doses, routes, and protocols for COD treatment.**

Drug	Dose	Route
Gonadorelin (GnRH)	100 $\mu$ g	IM
hCG	10,000 IU	IM
Dinoprost (PGF <sub>2<math>\alpha</math></sub> )	25 mg	IM
Cloprostenol (PGF <sub>2<math>\alpha</math></sub> )	500 $\mu$ g	IM
Progesterone	1.9 g	intravaginal implant

Treatment protocols
(1) GnRH (or hCG) + PGF <sub>2<math>\alpha</math></sub> (day 0); PGF <sub>2<math>\alpha</math></sub> (day 9 if no estrus).
(2) Ovsynch: GnRH (day 0); PGF <sub>2<math>\alpha</math></sub> (day 7); GnRH (day 9); fixed-time AI, 16 h after last GnRH treatment.
(3) Progesterone implant for 12 days (not for dairy cows).

cyst does not occur, but other follicles present at the time of treatment may ovulate.<sup>41-44</sup> After luteinization, the steroidogenic synthesis pathway switches from estradiol to progesterone and the cyst becomes responsive to prostaglandin-F<sub>2 $\alpha$</sub>  (PGF<sub>2 $\alpha$</sub> ). Elevated progesterone concentration restores the responsiveness of the hypothalamus to the positive feedback effect of estradiol and normal cyclic ovarian activity resumes after endogenous PGF<sub>2 $\alpha$</sub>  release and regression of the cyst. Return to normal cyclic ovarian activity occurs in 72% to 85% of the cows treated with GnRH; the interval from treatment to the first estrus is 19 to 23 days, and pregnancy rates at first estrus range from 46% to 58%.<sup>41-44</sup> In comparative studies, buserelin (a more potent GnRH analogue) or human chorionic gonadotropin (hCG) produced similar effects to those observed after GnRH treatment.<sup>42,44</sup> The reasons why normal ovarian activity does not resume in approximately 20% of the cows treated with GnRH are not clear, since stimulated LH release after treatment is similar in responsive and unresponsive cows. However, there is no subsequent increase in the concentration of circulating progesterone in cows failing to resume cyclic ovarian activity.<sup>41,43</sup>

Regression of luteinized cysts that result from GnRH or hCG treatment can be induced 7 to 9 days later with exogenous PGF<sub>2 $\alpha$</sub>  to shorten the interval from treatment to estrus and increase the degree of estrus synchrony.<sup>43</sup> PGF<sub>2 $\alpha$</sub>  is also the most efficient treatment for luteal cysts. In one study, 75% of the cows were in estrus within 7 days after treatment and pregnancy rate at first estrus was 66%.<sup>46</sup> In a recent study, simultaneous treatment with GnRH and PGF<sub>2 $\alpha$</sub>  allowed an early return to estrus in cows with luteal cysts (50% of the cows were in estrus before a second PGF<sub>2 $\alpha$</sub>  treatment 14 days later). Combined treatment with GnRH and PGF<sub>2 $\alpha$</sub>  also increased the number of

cows with follicular cysts responding to the second PGF<sub>2α</sub> treatment when compared to GnRH alone.<sup>47</sup> Because differentiation between luteal and follicular cysts is difficult, and because PGF<sub>2α</sub> treatment may also be beneficial when treating follicular cysts, combining PGF<sub>2α</sub> with the GnRH treatment is recommended.

The Ovsynch protocol, designed for fixed-time artificial insemination (AI), has been used successfully for the treatment of COD. In experiments with a large Florida dairy herd (3000 lactating cows), similar pregnancy rates (~27%) were reported using the Ovsynch protocol in both normal cycling cows and cows with cysts.<sup>48,50</sup> A modified Ovsynch protocol, combining PGF<sub>2α</sub> with the first GnRH treatment, has been reported to increase pregnancy rates compared to the standard protocol. Pregnancy rates using this modified Ovsynch protocol were similar to those in normal cows bred using AI after estrus detection (28% and 36%, respectively).<sup>47</sup>

Another option for COD treatment is progesterone. Treatment with intravaginal implants for 9 to 12 days decreases LH secretion, and results in cyst regression and emergence of a new follicular wave, 5 days after implant insertion. Progesterone restores the responsiveness of the hypothalamus to the positive feedback effect of estradiol and estrus is followed by ovulation within 7 days after implant withdrawal.<sup>38,40,51</sup> Estrus rates ranging from 82% to 100% and conception rates at first estrus ranging from 18% to 28% have been reported after progesterone treatment.<sup>38,40</sup> In embryo donor cows that developed COD after superovulation, progesterone treatment for 12 to 15 days resulted in estrus and ovulation in all cows within 10 days of implant withdrawal.<sup>52,53</sup> Moreover, when progesterone was used for estrus synchronization after embryo collection instead of PGF<sub>2α</sub>, the proportion of cows developing COD decreased from ~25% to <3%.<sup>53</sup> In Canada, the use of currently available progesterone implants must be limited to female beef cattle, since they are not licensed for use in dairy cows.

Manual rupture of cysts is not recommended because it may result in trauma and hemorrhage causing adhesions and contributing to fertility reduction. Recommended drugs, doses, and protocols for COD treatment are described in Table 1.

## Conclusions

Strategies to reduce the incidence of COD should focus on reducing postpartum disease and stress. A long-term goal should be to select cow families with superior milk production, but no genetic predisposition for COD. Ultrasonography has greatly improved the ability to diagnose COD and the combination of PGF<sub>2α</sub> and GnRH in various protocols has proven advantageous over the use of GnRH alone for COD treatment. Further elucidation of the complex pathogenesis of the disease will continue to improve our capacity to prevent, diagnose, and treat COD.

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This publication is made possible by an educational grant from  
**Schering-Plough Animal Health**

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