

Cystic Ovaries in Dairy Cattle

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## **Abstract**

The objective of this literature review was to determine the potential causes and factors affecting the incidence of ovarian cysts in dairy cattle as well as to examine functionality of various preventative methods and treatments of cysts. The end product was to be a document outlining all the information available on the three different types of cysts that can develop on the bovine ovary, follicular cysts, luteal cysts, and cystic corpora lutea. The literature that was reviewed, most in the forms of research papers, articles, and reviews, came primarily from scientific journals and published books. The literature reviewed was only taken from sources with authors who were widely considered to be experts on the subject matter. From the finished literature review, further observations and conclusions could be made so that the subject of cystic ovaries in cattle is understood more fully.

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## **Introduction**

There are several types of cysts that can be found on the ovaries of the cow, which can have a significant impact on the reproductive efficiency of the animal. The cystic structures that were studied included follicular cysts, luteal cysts, and cystic corpora lutea. The objective was to determine the potential causes of and factors affecting incidence of ovarian cysts in dairy cattle and to examine functionality of various preventative methods and treatments of cysts. This was performed through the review and presentation of pertinent information on the cystic ovarian conditions.

Each type of cyst is defined and its characteristics described in addition to its causes, preventative methods and treatments. There is also information presented on the methods of differentiation between the cystic conditions as well as other anovulatory conditions that provide similar symptoms. Throughout the report, the different types of cysts are compared and contrasted in their characteristics, causes, and treatments so that connections are made between the different, yet remarkably similar, conditions.

The importance of studying cystic conditions lies in the consequences they have for the dairy producer. As most cysts are anovulatory, they cause severe delays in the reproductive efficiency of affected animals, leading to decreased milk production over time. This inevitably can affect the bottom line and cause the dairy producer to lose money. Because of the significant impact that cysts can have, they should be understood completely so that the most effective diagnoses can be made and treatments administered in order to prevent unnecessary losses from the farm.

# Follicular Cysts

## Definitions and Characteristics

There are several definitions used to describe ovarian follicular cysts, and the traditionally accepted definition is that they are “follicular structures of 2.5 cm or larger that persist for a variable period in the absence of a corpus luteum” (Youngquist and Threlfall, 2007). There are several sources however who, due to new data, define cysts differently. A 2003 study by Hatler et al. pointed out that “follicles typically ovulate at 17 mm in diameter, so follicles that persist at that diameter or greater may be considered to be ‘cystic.’” Vanholder et al. (2006) suggested that cystic ovarian follicles (**COF**) should be defined as “follicles with a diameter of at least 2 cm that are present on one or both ovaries in the absence of any luteal tissue and that clearly interfere with normal ovarian cyclicity.” So, though experts may argue on the specific wording used and the exact diameter that a follicle must reach to be considered cystic, we can consider ovarian follicular cysts to be any follicular structure on the ovary in the absence of luteal tissue, larger than normal follicular size, that persists for a significant amount of time and affects the estrus cycle of the animal.

Though we cannot determine the exact cause of ovarian follicular cysts, we can recognize that they “develop when one or more follicles fail to ovulate and subsequently do not regress but maintain growth and steroidogenesis” (Vanholder et al., 2006). It has also been determined that follicular cysts are anovulatory structures so, as long as they persist, cows will remain infertile (Youngquist and Threlfall, 2007). Cystic ovarian disease (**COD**) is the “most common endocrine pathology to be found in dairy cows,” and incidence is “believed to vary from 1 to 30% depending on herd and breed conditions” (Gordon, 1996). Holsteins are the most

susceptible to develop a cystic condition compared to other breeds, and the most likely time of diagnosis is 30-60 d. after parturition in high-yielding dairy cows (Gordon, 1996).

Follicular cysts, when compared to other ovarian cystic conditions, are characterized by thin walls and produce very small amounts of progesterone. Occasionally, a persistent condition can lead to increased testosterone levels, causing some cows to exhibit masculine aggressive and sexual behavior. However, most cystic cows will remain in anestrus as long as the condition persists. (Ball and Peters, 2004)

The fluid in follicular cysts contains many components, including hormones like estradiol, progesterone, and insulin. Anti-Müllerian hormone, a hormone strongly linked with polycystic ovarian syndrome in humans, is also present in follicular cysts, but at such a low concentration suggesting that there is no correlation between the hormone and incidence of COD in cattle (Monniaux, 2008). There are also a variety of proteins present in the fluid, 8 of which were identified in a study by Maniwa et al. (2005) as “BMFA, EAF, MeS, VEGF-receptor, GAPDH, HSP70, BLG, and SD.” All that is currently known concerning the general functions of each protein is described in the study, but it is imperative that these proteins be researched extensively as well as any other components identified in follicular cysts in the future so that the pathology of the condition is fully understood.

One proposed explanation for the development of follicular cysts is that “the positive feedback of estradiol on release of gonadotropin-releasing hormone (**GnRH**) is compromised” (Bartolome et al., 2005). This would not interfere with the ability of the pituitary gland to release luteinizing hormone (**LH**) in cystic animals, but the overall function of the hypothalamic-pituitary-ovarian axis would be altered, and the preovulatory LH surge that normally induces ovulation does not occur. In cystic animals, despite the failure of ovulation by the pre-ovulatory

follicle, a surge of follicle-stimulating hormone (**FSH**) would occur, and under conditions of low progesterone concentrations and high LH concentrations, dominant follicles would be caused to grow to a larger size. These oversized follicles are termed follicular cysts, that produce high concentrations of estradiol and inhibin, cause a delay in follicular turnover and are responsible for the persistent cystic condition. (Bartolome et al., 2005; Kaneko et al., 2002)

## Causes

While there are many factors that have been linked to the predisposition of cattle to develop follicular cysts, also referred to as Cystic Ovarian Disease, the exact cause has not been defined. The factors that do predispose cows to develop follicular cysts have been suggested as genetics, hormonal imbalances, or exogenous factors, among others. And “the most widely accepted hypothesis is that COD results from a neuroendocrine imbalance involving the hypothalamic-hypophyseal-gonadal-axis” (Hooijer et al., 2001). In other words, the most likely cause of COD is a disruption along the pathway from the hypothalamus, a part of the brain that regulates hormones through the pituitary gland, to the gonads, which are the ovaries in this situation. While this general hypothesis may be accepted, it is vital to determine the specific disruption and where along the pathway it occurs in order to fully understand how follicular cysts develop and how they can be treated and prevented.

Hooijer et al. (2001) performed a study examining the correlation between genetics and incidence of COD. They initially mention that, through previous studies, the heritability of the trait has been estimated as 0.00-0.13. This means that, if there is indeed a correlation, the probability of genetically selecting against the COD trait and successfully producing desired offspring is very low. However, it has also been recognized that there is an association between high milk yield and increased incidence of COD, and that cows genetically selected for producing more milk will also be more likely to develop multiple follicular cysts over their lifetimes (Hooijer et al., 2001; Brito and Palmer, 2004; Fleischer et al., 2001). In fact, the study performed by Hooijer et al. (2001) led to the conclusion that selection for milk yield leads to an increase in COD incidence by 1.5% per 500 kg increase in milk yield. The researchers hypothesized that a possible explanation for the direct correlation between high milk yield and

increased COD incidence “is that cows in early lactation, which are trying to meet the increased requirements for milk production, are more susceptible to environmental changes with hormonal implications as a result” (Hooijer et al., 2001). In other words, it is possible that the correlation between milk yield and COD incidence is based on the state of stress on the animal during early lactation rather than a genetic correlation. While incidence of ovarian follicular cysts is likely due to both environmental and genetic factors, more research should be done in this area to identify the specific relationships between these factors. I would suggest that a good direction to pursue would be to examine the bovine genome in order to determine if there are any qualitative trait loci (**QTLs**) or single nucleotide polymorphisms (**SNPs**) that code for ovarian cysts. Doing this would be the most effective way to truly determine if there is a genetic factor affecting the incidence of COD, and specifically whether or not the possible factor is genetically tied to the genes coding for milk production. Putting all that aside, based on the study performed by Hooijer et al. (2001), it can be concluded that there is definitely a heritability factor for cystic ovaries determined by a genetic predisposition for COD in Dutch Black and White dairy cattle, and that without a reexamination of genetic selection methods, incidence of cysts will increase as long as selection for milk production traits continues.

In a 2002 study by Gümen et al, researchers hypothesized that “follicular cysts would develop if cows experienced an estradiol-induced GnRH/LH surge in the absence of an ovulatory follicle.” They further suggested that “estradiol would fail to induce a subsequent GnRH/LH surge in these cows until they were treated with progesterone” (Gümen et al., 2002). Their theories were based on the dynamic nature of cysts, evident by follicular waves due to increases in FSH, even in the presence of large anovulatory cysts. Three experiments were performed during the study to test the. Results from the experiments indicated that cows treated with

estradiol would develop an anovulatory condition after only one treatment. Researchers suggested that “if estradiol induced a GnRH/LH surge at a time when an ovulatory follicle was not present then the cow would subsequently become anovulatory due to the lack of an increase in circulating progesterone following the LH surge” (Gümen et al., 2002). The more simple interpretation is that a progesterone deficiency during the estradiol-induced LH surge is a probable cause of the development of follicular cysts on the ovaries.

In addition to the study performed by Gümen et al. (2002), there has been much investigation on the relationship between progesterone and ovarian follicular cysts. A study by Hatler et al. (2003) looked more closely at this relationship. Like many other sources, the study points out that the basic reason cysts form is because of an endocrine imbalance, and that “the vast majority of data suggest that cysts form because of a failure of the preovulatory LH surge to occur at the appropriate time in follicular maturation” (Hatler et al., 2003). The researchers wanted to further understand the role of progesterone in the formation of follicular cysts, stating that:

The objectives of the present study were to determine how often cows diagnosed with ovarian follicular cysts have intermediate concentrations of progesterone and to relate the fate of follicles that form in the presence of a follicular cyst to circulating concentrations of progesterone during their development. (Hatler et al., 2003)

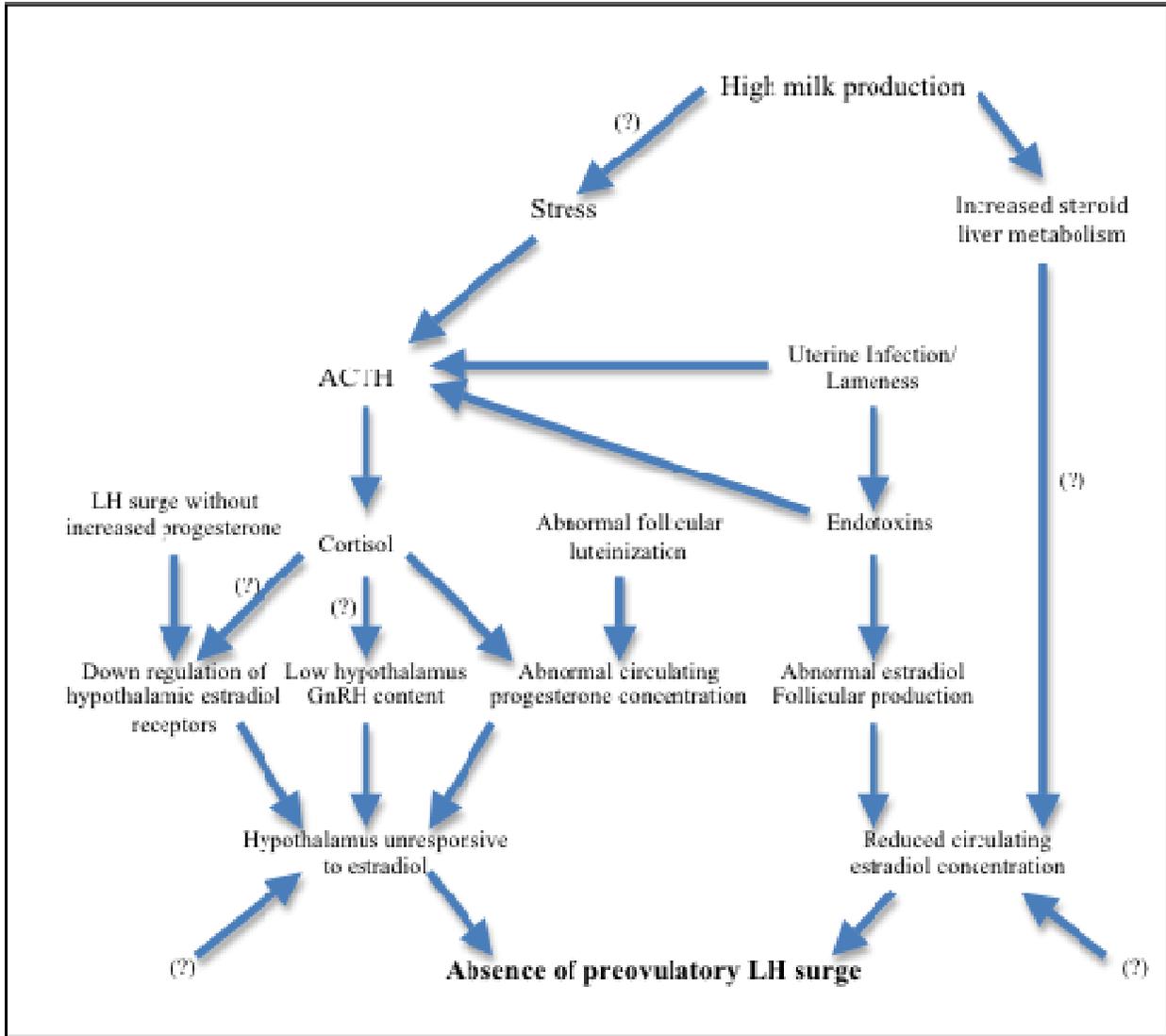
Results of the aforementioned study suggested that the majority of cows with anovulatory cystic follicles did have intermediate concentrations of progesterone at the time of diagnosis. They also observed that developing dominant follicles, when in the presence of follicular cysts and especially those with intermediate progesterone concentrations, developed into new

follicular cysts themselves. The ultimate conclusion was that “intermediate levels of progesterone commonly associated with cysts may predispose subsequent follicles to form cysts and contribute to the phenomenon of cyst turnover” (Hatler et al., 2003). My interpretation of this data is that there is a definite relationship between endogenous concentrations of progesterone and the incidence of follicular cyst formation. Further research should be performed in order to distinguish the exact role of progesterone in the development of ovarian follicular cysts.

A 2002 study performed by López-Gaitus et al. examined risk factors that lead to the development of COD. While the researchers did not determine any true cause of ovarian cysts, they examined several factors that would predispose cows to develop a cystic condition. One of the factors examined was body condition, and results suggested that “a gain in nutritional status prepartum can impair postpartum ovarian function, thus being a major risk factor for early cyst development that continues to the late cystic condition” (López-Gaitus et al., 2002). Another risk factor that was identified was calving season, and results indicated that cysts were 2.6 times more likely to develop in warm periods than during cooler seasons. The researchers also examined abnormal puerperium as a risk factor for ovarian cysts, defining the term broadly as any of the disorders that include twinning, retained placenta, primary metritis, and ketoneuria, or a combination of the conditions. The cows that did have an abnormal puerperium were about twice as likely to develop new follicular cysts, but the condition was not determined to be a risk factor for late ovarian cysts. López-Gaitus et al. (2002) also recognized the effect of high milk production on cyst incidence, and determined that older cows were more likely to develop a chronic cyst condition than those in earlier lactations. All of these risk factors should be

thoroughly considered in the management of dairy facilities, and based on the knowledge of their existence, measures should be taken to prevent increased incidence of ovarian cysts.

A thorough explanation for the biological cause of follicular ovarian cysts can be provided by Bartolome et al. (2005). The initial root of the problem is a dysfunction of the positive feedback of estradiol on release of GnRH. Because of this, function of the hypothalamic-pituitary-ovarian axis is altered, even though the pituitary gland is still able to release LH. Because of the hormonal imbalance, the dominant follicle does not ovulate before the transient increase in FSH occurs, stimulating a “new wave of follicular development, which occurs under conditions of low progesterone concentrations and high LH concentration” (Bartolome et al., 2005). This causes excessive growth of dominant follicles to become follicular cysts, which produce large amounts of estradiol and inhibin, therefore causing a delay in follicular turnover. Brito and Palmer’s review on COD (2004) provided a succinct flow chart that hypothesizes the different mechanisms that potentially lead to the absence of the preovulatory surge of LH that ultimately causes follicular cyst formation. This flow chart is reproduced on the following page.



**Figure 1:** Possible explanations for the absence of a preovulatory LH surge that causes follicular cysts. (Adapted from Brito and Palmer, 2004).  
 ACTH = Adenocorticotrophic hormone  
 LH = luteinizing hormone  
 GnRH = gonadotropin releasing hormone

A 2009 study by Braw-Tal et al. examined the relationships between levels of certain hormones and incidence of COD. Two hormones that they focused on were insulin and insulin-like growth factor-I (**IGF-I**), which have previously been suggested as indicators between

nutritional status and ovarian function in cattle. Both hormones have been shown to stimulate estradiol synthesis in granulosa cells and androgen synthesis in theca cells. Based on the previous studies, the researchers hypothesized that “any failure in function of the insulin/IGF-I system will lead to follicular regression and/or cyst formation” (Braw-Tal et al., 2009) Though they did find a correlation between insulin/IGF-I and cystic formation, there was very little trace of the hormones found in cystic fluid, so more research should be done in order to determine the distinct relationship between the hormone and incidence of COD. Table one shows the concentrations of several hormones, including insulin and IGF-I, and other substances found in preovulatory follicles, subordinate follicles, and follicular cysts. (Braw-Tal et al., 2009)

	<b>Progesterone (ng/mL)</b>	<b>Estradiol (ng/mL)</b>	<b>IGF-I (ng/mL)</b>	<b>IGFBPs (% bound)</b>	<b>Insulin (pg/mL)</b>	<b>Glucose (mg/L)</b>
<b>Preovulatory follicles (n = 15)</b>	54 ± 5	2034 ± 32	146 ± 42	1.4 ± 0.2	205.2 ± 22.5	0.74 ± 0.03
<b>Subordinate follicles (n = 18)</b>	390 ± 93	94 ± 28	125 ± 32	18.6 ± 2.3	20.1 ± 8.9	0.55 ± 0.05
<b>Cysts (n = 20)</b>	212 ± 31	170 ± 37	61 ± 6	14.0 ± 1.1	2.8 ± 1.4	0.36 ± 0.02
<b>Statistical variability</b>	<i>P</i> < 0.05	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.01

**Table 1:** Hormonal concentrations from follicular fluid of ovarian follicles and cysts.

(Adapted from Braw-Tal et al., 2009)

IGFBPs = IGF Binding Proteins, *n* = number of follicles/cysts tested

## Prevention and Treatments

It was shown in a study mentioned by Brito and Palmer (2004) that the most economical time to treat COD was as soon as the condition was diagnosed, even without waiting for the voluntary period during which spontaneous recovery may occur. Their research indicated that the most common treatment for COD is GnRH, which “results in an immediate increase in LH secretion and luteinization of the cysts. Ovulation of the cyst does not occur, but other follicles present at the time of treatment may ovulate” (Brito and Palmer, 2004). After the GnRH treatment and subsequent luteinization, the cyst becomes responsive to prostaglandin- $F_{2\alpha}$  ( $PGF_{2\alpha}$ ) because the steroidogenic synthesis pathway has switched from estradiol to progesterone. The newly elevated levels of progesterone are responsible for a restoration of responsiveness to the positive feedback effect of estradiol, resulting in the resumption of normal cyclic ovarian activity after the release of endogenous  $PGF_{2\alpha}$  and cystic regression. (Brito and Palmer, 2004)

Though the studies examined by Brito and Palmer (2004) do show that GnRH is the most effective at returning cows with anovulatory follicular cysts to a normal cyclic ovarian condition, there is some variability with this treatment, as there is with all treatments.

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%. In comparative studies, buserelin (a more potent GnRH analogue) or human chorionic gonadotropin (**hCG**) produced similar effects to those observed after GnRH treatment. (Brito and Palmer, 2004)

The underlying reasons for the continued state of anestrus in about 20% of the cows treated with GnRH are not clear, as there is no difference in stimulated LH release between responsive and

unresponsive cows. However, the cause could be linked to issues with endogenous progesterone as the anovulatory cows show no increase in progesterone after the release of LH. (Brito and Palmer, 2004)

Another method that has been used successfully for the treatment of COD is the Ovsynch protocol, originally designed for fixed-time artificial insemination (AI). This protocol has been shown to provide similar pregnancy rates (~27%) for both normal cycling cows and cows with cysts in a large Florida dairy herd (3000) lactating cows. Additionally, “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” (Brito and Palmer, 2004). A Study by Stevenson and Tiffany (2004) is in agreement with the usage of the Ovsynch protocol as a treatment for COD, finding it to be effective at curing the cystic condition and getting the previously cystic animal pregnant after AI.

The third option of COD treatment, as suggested by Brito and Palmer (2004), is progesterone, and “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 works against follicular cysts by restoring the responsiveness of the hypothalamus to the positive feedback of estradiol, resulting in normal estrus and ovulation within 7 d after the implant is removed. Progesterone was such an effective treatment for COD that the resulting estrus rates range was 82-100% and conception rates at first estrus had a range of 18-28%. “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%.” (Brito and Palmer, 2004)

Brito and Palmer (2004) do not recommend manual rupture of cysts because “it may result in trauma and hemorrhage causing adhesions and contributing to fertility reduction.” The treatments that the authors have found to be effective are summarized in Table 2.

<b>Drug</b>	<b>Dose</b>	<b>Route</b>
Gonadorelin (GnRH)	100 µg	IM
hCG	10,000 IU	IM
Dinoprost (PGF <sub>2α</sub> )	25 mg	IM
Cloprostenol (PGF <sub>2α</sub> )	500 µg	IM
Progesterone	1.9 g	Intravaginal implant
<b>Treatment Protocols</b>		
(1) GnRH (or hCG) + PGF <sub>2α</sub> (day 0); PGF <sub>2α</sub> (day 9 if no estrus).		
(2) Ovsynch: GnRH (day 0); PGF <sub>2α</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).		

**Table 2:** Drug amounts, routes, and protocols for treatment of follicular cysts (Adapted from Brito and Palmer, 2004).

While many experts, such as Brito and Palmer, are against manual rupture of cysts because it comes with the risk of injury to the ovary, the Merck Veterinary Manual states that it is a valid option that should be considered:

The potential danger of traumatizing the ovary and causing hemorrhage with the subsequent local adhesions should not be overlooked, but manual rupture has been used often without problems. This method should be weighed against the cost of hormone therapy. (Kahn, 2010)

In other words, though manual rupture can potentially be harmful, it is a treatment that should be considered in cases where the cost of more reliable treatments is a concern.

Manual rupture is a common procedure used by those seeking homeopathic remedies who prefer to stay away from hormonal injections as a treatment. If the cyst will not rupture manually, experts like Hubert J. Karreman, V.M.D., the author of *Treating Dairy Cows Naturally: Thoughts & Strategies* (2007), will recommend other homeopathic remedies. If Karreman cannot gently rupture the cyst, he will prescribe “homeopathic *Apis* (for the right side) of homeopathic *Lachesis* (for the left side) twice daily for 5 days, with either one being immediately followed by homeopathic *Natrum mur*; twice daily for three days ” (Karreman, 2007). *Apis mellifica* is a common homeopathic medicine made from the female honeybee, while *Lachesis* is prepared from the fresh venom of the South American bushmaster snake and *Natrum mur* is made simply from sodium chloride, or table salt (“Homeopathy”). If this treatment doesn't work Heat Seek, a botanical herb blend typically used to enhance the observable signs of estrus, may be given, “10 tablets orally every other day for twelve doses (24 day treatment)” (Karreman, 2007). The final suggestion made, for use on “a very stubborn cyst,” is injections of vitamin B12 into the acupuncture points BL-22, 23, 24, 25 on the same side as the cyst. Though the homeopathic remedies suggested by Karreman may be effective, it is evident by the descriptions of his protocols that they are not very reliable. I would not suggest these treatments unless in necessary cases, such as on an organic dairy farm, as they would likely cause a greater delay in return to normal cyclicity than the recommended hormonal remedies.

Economics of treatment is an important factor that should be considered when choosing a treatment for ovarian cysts. The Ovsynch protocol as well as progesterone inserts are common treatments used for follicular cysts whose economic consequences are considered in a study by

De Vries et al. (2006). A summary of their findings can be seen in Table 3. Ultimately, the Ovsynch protocol was shown to be the more economical treatment, giving a profit of  $\$73.46 \pm 6.81$ , when compared to progesterone inserts, which yielded  $\$55.85 \pm 6.89$  in profit.

<b>Statistic</b>	<b>Ovsynch, \$/cow</b>	<b>Progesterone insert, \$/cow</b>
<i>Milk sales</i>	$24.99 \pm 4.80$	$24.62 \pm 5.07$
<i>Cow sales</i>	$-11.09 \pm 1.60$	$-10.37 \pm 1.83$
<i>Calf sales</i>	$22.84 \pm 0.90$	$17.23 \pm 0.98$
<i>Feed costs</i>	$-8.84 \pm 1.00$	$-5.83 \pm 1.06$
<i>Breeding costs</i>	$18.46 \pm 0.18$	$17.27 \pm 0.18$
<i>Heifer replacement costs</i>	$-46.39 \pm 7.86$	$-35.84 \pm 8.33$
<i>Other costs</i>	$0.04 \pm 0.01$	$0.03 \pm 0.01$
<b><i>Profit</i></b>	$73.46 \pm 6.81$	$55.85 \pm 6.89$

**Table 3:** Monetary gains and losses associated with Ovsynch and progesterone inserts as treatments for COD. (Adapted from De Vries et al., 2006)

A 2002 study by López-Gaitus and López-Béjar examined treatments of GnRH combined with Colostoprenol (CLP) for follicular ovarian cysts. They found that when GnRH plus CLP and CLP 14 days later was effective in resolving cysts without the need for diagnosis, and that the later dose of CLP was extremely effective in lowering cystic persistency. Table 4 shows the effectiveness of the Ovsynch protocol and another GnRH/CLP combined protocol in treating follicular cysts.

<b>Effects</b>	<b>Control (n = 64)</b>	<b>Ovsynch (n = 64)</b>	<b>GnRH-CLP/CLP/GnRH (n = 64)</b>
Ovulation rate (%)	—	11/64 (17)	51/64 (80)
Returns to estrus (%)	21/64 (33)	8/64 (13)	22/64 (34)
Pregnancy rate (%)	23/64 (36)	2/64 (3)	18/64 (28)
Cystic persistence (%)	—	30/63 (47)	7/64 (11)

**Table 4:** Effectiveness of different treatment regimens containing GnRH and CLP. (Adapted from López-Gaitus and López-Béjar, 2002)

The Ovsynch group was treated with “100 µg GnRH i.m. on Day 0; 500 µg CLP i.m. on Day 7 followed by 100 µm GnRH i.m. 32 h later.” The GnRH-CLP/CLP/GnRH group received “100 µg GnRH i.m. plus 500 µg CLP i.m. on Day 0, 500 µg CLP i.m. on Day 14 followed by 100 µm GnRH i.m. 32 hours later.” Both groups were artificially inseminated 24 hours after the second GnRH treatment. The GnRH-CLP/CLP/GnRH treatment was shown to be much more effective at treating follicular cysts than the Ovsynch protocol, with significantly higher percentages of ovulation rates, returns to estrus, and pregnancy rates, and a much lower level of cystic persistence. I suggest that more research be done on using different combinations of GnRH and CLP as treatments for COD in order to combat the disease to the fullest. (López-Gaitus and López-Béjar, 2002)

# Luteinized Cysts

## Definitions and Characteristics

The Merck Veterinary Manual (Kahn, 2010) describes luteal cystic ovary disease as being “characterized by enlarged ovaries with one or more cysts, the walls of which are thicker than those of follicular cysts because of a lining of luteal tissue.” Ball and Peters (2004) call these cysts luteinized cystic follicles, describing them as cysts with thicker walls that produce high levels of progesterone. In appearance, they are smooth and rounded, with a spherical cavity that is lined by a layer of fibrous tissue surrounded by the luteinized cells (Schlafer, 2007). “Luteal cysts are considered anovulatory cysts and are associated with infertility and mucometra in cattle” (Foley, 1996). When compared to follicular cysts, luteinized cysts are more likely to persist over long periods of time and can lead to nymphomania in some animals (Ball and Peters, 2004).

## Causes

Luteal cysts “develop when ovulation fails to occur and the theca undergoes luteinization” (Schlafer, 2007). They are also often considered to be the later form of ovarian follicular cysts (Vanholder et al., 2005), and therefore the causes pertaining to follicular cysts can also be considered the original causes of luteal cysts. The luteal cyst occurs when the cells of the follicular cyst (granulosa and theca) become luteinized and start producing progesterone (Peter et al., 2009). Luteal cyst incidence increases with age and most often affects cows with high milk production (Foley, 1996).

## Prevention and Treatments

When cows with luteal cysts are treated with GnRH or hCG, regression can be induced 7 to 9 days later with exogenous PGF<sub>2α</sub>, shortening the length of time between treatment and the return to normal ovarian cyclicity. PGF<sub>2α</sub>, on its own, is also the most effective treatment for luteinized cysts, and “in one study, 75% of the cows were in estrus within 7 days after treatment and pregnancy rate at first estrus was 66%” (Brito and Palmer, 2004). Additionally, “in a recent study, simultaneous treatment with GnRH and PGF<sub>2α</sub> allowed an early return to estrus in cows with luteal cysts (50% of the cows were in estrus before a second PGF<sub>2α</sub> treatment 14 days later).”

The Merck Veterinary Manual (Kahn, 2010) recommends luteolytic doses of PGF<sub>2α</sub> as the ideal treatment for luteal cystic ovary disease, as long as the animal was diagnosed correctly, with estrus showing within 3-5 d. However, it is also stated that the treatment can be variable as “there is difficulty in accurately estimating the amount of luteal tissue present” (Kahn, 2010). If a luteal cyst is diagnosed when the structure is actually a normally developing CL or cystic CL, the cow may not respond to the luteolytic action of PGF<sub>2α</sub>, as it is only effective until the 6<sup>th</sup> day following estrus. (Kahn, 2010)

“Luteal cysts also respond to human chorionic gonadotropin and GnRH therapy that is effective in the treatment of follicular cysts, but the next estrus could occur 5-21 days after treatment” (Kahn, 2010). This combination of hormones as a treatment is not as effective as PGF<sub>2α</sub>, but it should be noted that it can be a very useful treatment if the administrator has not determined whether or not the cyst is follicular or luteinized, as it will work on both types. Because estrus detection methods are poor on many farms, the Ovsynch protocol for fixed time artificial insemination, which will work on both follicular and luteal cysts, is considered to be the

treatment of choice as it results in timely breeding after treatment for cows with either condition. Contrarily to follicular cysts, however, luteal cysts should not be ruptured manually, as trauma is much more likely to occur.

## Cystic Corpora Lutea

A cystic corpus luteum (CL) in a cow is defined as “luteal tissue initiating from a corpus hemorrhagicum and containing fluid in a central cavity greater than 7 mm in diameter” (Chuang et al., 2010). The terms for cystic CLs can often be confused with those for luteal cysts, though the first is a normally functional structure and the latter a pathological condition. Because of this, “the contemporary term ‘corpus luteum with a cavity’ has been suggested to replace the classical term cystic corpus luteum” (Chuang et al., 2010). Cystic CLs occur spontaneously, when follicles become luteinized without ovulation (Pineda, 2003). Incidence of cystic CLs ranges from 25.2% to 78.8% during diestrus and decreases with progression of the estrous cycle (Kahn, 2010).

Because cystic corpora lutea are found in cows that are normally cycling or pregnant, they are considered to be a normal stage or variation of CL development (Kahn, 2010). The 10<sup>th</sup> edition of the Merck Veterinary Manual thoroughly describes the physical properties of cystic CLs and their similarities and differences to normal corpora lutea:

Cystic CL have a soft, mushy core area, due to presence of fluid from a degenerating blood clot, compared with the homogeneous, liver-like consistency of the base of a typical CL... The cystic CL as well as the typical CL may or may not have an ovulation crown or papilla at its apex. Absence of this ovulation crown or papilla should not be considered diagnostic of the cystic condition because 10-20% of functional, normal CL fail to develop this feature. (Kahn, 2010).

Although diagnosis is not essential as cystic CLs are not pathological and therefore do not require treatment, the ideal time for detection of the structure is 5-7 d after estrus. At this point

in time, the ovarian structure is near the end of the corpus hemorrhagicum stage of development. (Kahn, 2010)

# Diagnosis of Ovarian Cysts

## Differentiation of Cystic Conditions

As follicular cysts and luteal cysts are similar in size and function, it may be difficult to differentiate the two. The key to proper diagnosis is a combination of physical examination, ultrasonography, and plasma progesterone testing:

The accuracy of diagnosing ovarian cysts and differentiating follicular and luteal cysts can be increased by combining per rectum palpation of the genital tract to determine that a corpus luteum is absent and the uterus lacks tone; ultrasonography to confirm that a corpus luteum is absent, to determine the size of follicles that are present, and to check for luteinization; and measurement of plasma progesterone concentration to determine the degree of luteinization. (Bartolome et al., 2005)

Though it is important to understand the differences between these two types of cysts, treatment is similar between the two conditions so differentiation is not always necessary. (Bartolome et al., 2005)

There is a significant difference between luteal cysts and cystic corpora lutea (cystic CLs). While luteal cysts are originally pathological follicular cysts that have luteinized with age, cystic CLs are “physiologic and originate from follicles that have formed a cavity during corpus luteum development” (Bartolome et al., 2005). These cystic structures can be differentiated through rectal palpation to determine if the structure is structurally characteristic of a corpus luteum. A cystic CL can be diagnosed if there is detection of a line of demarcation and distortion in the shape of the ovary. However, differentiation can only be successfully confirmed when rectal palpation and ultrasonography are combined. (Bartolome et al., 2005)

When differentiating between ovarian follicular cysts and normal pre-ovulatory follicles, one should look at the number and size of the structures but should especially base their judgement on the basis of uterine tonicity. Upon rectal palpation, cows with ovarian cysts will be found to have “multiple follicles that are typically larger-than-normal Graafian follicles with a flaccid uterus in the absence of a corpus luteum” (Bartolome et al., 2005). Contrarily, cows in proestrus with normal follicles will have an erect, turgid uterus. This uterine tonicity is in response to luteal oxytocin secreted by the ovaries of non-cystic cows. This method is the most effective at differentiating between follicular cysts and normal follicles, however an ultrasound should also be used to determine the number and size of ovarian follicles in order to confirm the diagnosis. (Bartolome et al., 2005)

Some may have a difficulty determining whether a cow has ovarian cysts or it is in postpartum nutritional anestrus. Though a cystic condition may often be the first guess for the cause of prolonged anestrus, “several physiologic (eg, pregnancy), pathophysiologic (eg, postpartum and nutritional anestrus and ovarian cysts), and pathologic (eg, pyometra, hydrometra, ovarian hypoplasia, and granulosa cell tumor) conditions result in a lack of cyclic activity, anovulation, or anestrus” (Bartolome et al., 2005). Shallow postpartum nutritional anestrus is an anovulatory condition that can occur during the early postpartum period, and it's characterized by regular follicular waves and lower than normal secretions of luteinizing hormone (**LH**) and insulinlike growth factor 1 (**IGF-1**). These conditions cause the animal to be unable to support complete follicular development and lead to insufficient estradiol concentrations for ovulation. While this condition is associated with animals in negative energy balance, cows with cystic ovarian degeneration are in positive energy balance. Cows may also have deep postpartum nutritional anestrus, during which the ovaries are small with limited

follicular development and follicle stimulating hormone (**FSH**) secretions are low. Because of this, a simple rectal palpation and/or ultrasound exam can identify whether or not the anovulatory condition is caused by deep postpartum nutritional anestrus. “Ovarian cysts are differentiated from shallow anestrus on the basis of the number and size of the follicles, occurrence of follicular waves, body condition score (**BCS**), and stage of lactation.” (Bartolome et al., 2005)

## **Other Ovarian Abnormalities**

### **Ovaro-bursal Adhesions**

Ovaro-bursal adhesions are structures that “occur as fibrous bands between the surface of the ovary and the ovarian bursa. Their severity varies from the presence of a few very small strands of fibrous tissue”. Though there is no definitive cause of adhesions, they are most likely the result of excessive follicular hemorrhaging during ovulation, trauma to the ovary or bursa caused by rectal examination, an infection from the uterus, or damage during calving. (Ball and Peters, 2004)

Ovaro-bursal adhesions generally do not cause reproductive problems in affected cows, unless, in severe cases, where the adhesion is so large that the fallopian tubes are blocked and fertilization of the ovum is prevented. Additionally, “in extreme cases, adhesions may extend to the opening of the ovarian bursa, resulting in a very narrow opening that may affect fertility. This condition is referred to as perisalpingitis and is rare” (Peter et al., 2009). Diagnosis of ovaro-bursal adhesions is typically difficult in live animals, but adhesions may be suspected in cows that persistently return to estrus after breeding. Further examination of the suspected animal’s reproductive history and previous treatments for reproductive disorders in combination with ultrasonographic examination can then be used as a basis for diagnosis. (Ball and Peters, 2004; Peters et al., 2009)

## **Parovarian Cysts**

Parovarian cysts are cystic structures that do not occur in the ovaries themselves, but rather in the broad ligament close to the ovaries and the uterine tubes. Palpation or ultrasonography can be used to detect them, and they appear as “fluid-filled anechoic structures and are usually round or oval in shape, occur as a single cystic structure, and range from 1-5 cm in diameter” (Peter et al., 2009). A larger form of paraovarian cysts may also occur, but this structure is called hydatid of Morgagni, and is similar to a reproductive complication in ewes and sows. There are two different types of paraovarian cysts; those derived from the cranial mesonephric tubules are called epoophoron, while those from the caudal tubules are referred to as paroophoron. All paraovarian cysts are benign, with no negative effects on reproduction and fertility. (Peter et al., 2009)

## **Fibrin Tags**

Ovulation tags are small tags of fibrin that most commonly occur in heifers due to bleeding after ovulation. They are “frequently attached to the ovary at the site of a previous ovulation or on the medial attachment of the ovary to the uteroovarian ligament” (Peter et al., 2009). While there is very little information on ovarian fibrin tags, it seems that they cause no complications to the estrous cycle or conception. (Peter et al., 2009)

## **Granulosa-theca Cell Tumors**

Granulosa-theca cell tumors are made of both type of follicular cells, and are the most common variety of ovarian tumors in cattle, even though they are rare (<0.5%). “This type of tumor arises from the sex cord stromal tissue within the ovary and may be relatively small, solid, and yellow to white or large, filled with cysts of varying sizes and weigh 11.9-12.3 kg” (Peter et al., 2009). Granulosa-theca cell tumors are most commonly benign but may be malignant and often hormonally active. “If undiagnosed and left intact, clinical signs progress through various stages beginning with nymphomania and ending with virilism. In some instances, mammary development is observed” (Peter et al., 2009). Diagnosis can be made through observations of clinical signs combined with transrectal palpation and ultrasonography. Clinical signs are “abnormal estrous cycles and follicular and luteal inactivity on the contralateral ovary.” (Peter et al., 2009)

## **Rete Ovarii**

“In the hilus region of a mature ovary, the rete ovarii is found as a network arrangement of medullary tubules or cords near the mesoovarian” (Peter et al., 2009). The medullary cords of the rete ovarii are lined with both cuboidal and columnar epithelium, differentiating to form granulosa-like cells that have a secretory function. Cysts associated with rete ovarii are not pathological in function, but may inhibit ovarian function if the rete ovarii has a space-occupying lesion. Diagnosis and differentiation from other ovarian structures can be accomplished through transrectal ultrasonic examination of the reproductive tract.

## **Ovarian Hypoplasia**

The hypoplastic ovary is essentially an underdeveloped ovary that does not function properly. The condition is characterized by incomplete development, or ovarian dysgenesis, so that the ovary is lacking in primordial follicles. Hypoplasia can occur partially or completely, on one or both ovaries. “In heifers, hypoplastic ovaries may be small such that they are difficult to locate by transrectal palpation. The ovaries may feel like thin, narrow, firm cord-like structures” (Peter et al., 2009). Like many other ovarian cysts and abnormalities, hypoplasia causes anestrus and therefore the condition must be differentiated from the others. Despite the difficulties posed by smaller structures, the most effective method of diagnosis is through transrectal examination.

## Conclusion

The majority of the literature found to be reviewed was primarily concerning follicular cysts, rather than the other two varieties. Due to this uneven concentration of information, the largest section of the review with the most information is the section on follicular cysts. Of the three conditions, the least information was found on cystic corpora lutea, with luteal cysts falling in the middle. Because luteinized cysts are often considered to be just the later form of follicular cysts, it is likely that researchers find it more important to examine the initial cause of the cystic follicle than the pathogenesis of the luteal cyst. A likely explanation for the lack of literature on the cystic CL is the “harmlessness” of the condition when compared to follicular and luteal cysts. The first is considered to be a variation of a normal corpus luteum that does not affect cyclicity, while the latter conditions both cause a state of anestrous in affected animals.

In order to minimize losses due to ovarian cysts, it is imperative that one is able to differentiate between the different types of cysts and other conditions that lead to anestrous. It is also necessary to be aware of other abnormalities of the ovary so that a lesion found during palpation is not immediately diagnosed as cystic, but rather examined completely so that the proper diagnosis can be made. All of this should be taken into consideration before decisions on treatments are made in order to effectively cure animals of the condition they have. Cystic ovaries significantly decrease reproductive efficiency of affected animals, causing losses in milk production and, overall, monetary losses to the dairy. Therefore, ovarian cysts should be continually researched in order to assure that they do not pose a serious problem to the dairy industry.

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