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Cystic Ovarian Disease in Dairy Cattle - A Review

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Abstract: Ovarian cysts are characterized by rectal palpation as structures greater than 2.5 cm (Approximately 1 inch) in diameter remaining on an ovary for more than 10 days. Major categories of cysts include follicular cysts, luteinized follicular cysts and cystic corpora lutea. Follicular cysts result from failure of ovulation and luteinization. Follicular cells that once produced estrogen change into luteal cells of the new corpus luteum that secrete progesterone. Follicular cysts are blister-like structures, flaccid to the touch. Luteinized cysts apparently fail to ovulate, but some luteinization occurs. Because of the varying degree of luteinization, Luteinized cysts are firmer to the touch than follicular cysts though not as solid as corpus luteum. Cystic corpora lutea are corpus luteum with a fluid filled center. The actual cause of cystic ovarian disease is unknown. The basic pathophysiology of cystic ovarian disease involves a neuroendocrine dysfunction of the hypothalamic-pituitary-ovarian axis resulting in ovulation failure. Research evidence incriminates each part of the hypothalamic pituitary ovarian axis as the causative organ. An abnormal pattern of estrous behavior is the most noticeable sign of cystic ovarian disease. A cow with an ovarian cyst might exhibit "Constant "estrus (Nymphomania), no estrus (Anestrus) or anerratic combination of estrus and anestrus. Past evaluations of ovarian cysts using transrectal palpations have increased and accurate diagnosis currently employs a combination of transrectal palpation, transrectal ultrasonography and plasma progesterone assay. During earlier times, the manual rupture of ovarian cysts was advocated. Yet during the past several years, single or combinations human chorionic Gonadotrophin, Gonadotrophin releasing hormone, progesterone and prostaglandins have been frequently used in clinical practice. The success of therapy is governed by many confounding variables such as persistence of the cystic follicles and initiation of therapy as pathological alterations that occur following ovarian cysts persistence require some time for spontaneous recovery.

Key words: Anestrus · Corpus Luteum · Gonadotrophin Releasing Hormone · Nymphomania

INTRODUCTION

Over the past few decades, milk yield per dairy cow had increased considerably due to continuing genetic selection and improvement of nutrition and herd management. Simultaneously with this selection for production characteristics, dairy cow fertility had declined significantly [1]. Reproductive performance is however an important factor in determining dairy herd profitability. In addition, the cows' reproductive performance play an important role in the culling decisions. So, the good reproductive performance positively affected the cow's active herd life and played an important role in dairy herd economics [2].

Fertility is a very complex process and the final outcome is the result of a close and well-orchestrated interaction between hypothalamus-pituitary-ovary-uterus. The complexity of this process indicated that any factors which interfere with the functioning of one or more of the organs involved will also influence the overall fertility outcome. The reduced fertility, observed in modern high yielding dairy cows, is most likely due to alterations at several consecutive steps in the reproductive process. One of the most common ovarian dysfunctions during the postpartum period was the formation of ovarian cysts after ovulation failure [3].

Cystic ovaries could be diagnosed by the detection of one or more fluid filled structures larger than a mature

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follicle (i.e.>2.5 cm diameter), which are persistent for longer than 10 days and which result in aberrant reproductive function. The definition sometimes specifically excluded the presence of a corpus luteum. Cysts arise as a result of anovulation of the Graffian follicle. Under normal circumstances, anovulation is followed by either atresia or luteinisation, after which the follicle undergoes regression. In cystic ovarian disease, the follicle increases in size and persists, for at least 10 days with the degeneration of the granulosa cell layer, which eventually alter the normal cyclical activity of the cow. The cows encounter cystic ovaries demonstrates the signs of either anestrum or nymphomania. Many cows developed large, fluid-filled structures in the ovaries during the immediate postpartum period. It has been reported that up to 60% of cows developed cysts before the first postpartum ovulation [4].

These normally go undetected, unless the cow is examined transrectally. Cystic ovarian structures during the first postpartum ovulation usually regress spontaneously without any extension in the interval to first estrus or evidence of nymphomania and should not be considered as true ovarian cysts. Non-steroidogenic cysts which are hormonally inactive do not influence the normal estrous cycle, so they can occur together with a corpus luteum. Therefore, the recent definition of ovarian cysts (OC) differed and became more logically. Cystic Ovarian Disease (COD) is a common and economically significant condition of dairy cattle. It was first described in the early 1900's and was recognized as an important cause of reproductive loss in cattle [5]. Therefore, the objectives of this review were to highlight the classifications, potential causes, pathogenesis, symptoms and diagnosis of ovarian cysts and describe functionality of various treatment methods and recommended treated of each type of ovarian cysts.

Classification, Characteristics and Causes of Ovarian Cysts: 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 [6].

Follicular Cysts: Several definitions were 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 [6]. There are several sources however who, due to new data, define cysts differently. Hatler *et al.* [7] stated 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.* [8] 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 clearly interfere with normal 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 [6].

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 remained in anestrous as long as the condition persists [9]. 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 [10].

Many factors linked to the predisposition of cattle to develop follicular cysts, also referred to as Cystic Ovarian Disease, the exact cause has not been defined. Factors predisposed cows to develop follicular cysts included genetics, hormonal imbalances, or exogenous factors. The most widely accepted hypothesis stated that Cystic Ovarian Disease (COD) resulted from a neuroendocrine imbalance involving the hypothalamic-hypophyseal-gonadil-axis". In other words, the most likely cause of COD was a disruption along the pathway from the hypothalamus, a part of the brain that regulates hormones through the pituitary gland to ovaries [11].

Hooijer *et al.* [11] correlated genetics with incidence of COD estimated heritability of 0.00-0.13 between them. This means that, if there was indeed a correlation, the probability of genetically selecting against the COD trait and successfully producing desired offspring was very low. However, it had also been recognized that there was an association between high milk yield and increased incidence of COD and that cows genetically selected for producing more milk was more likely to develop multiple follicular cysts over their lifetimes [12].

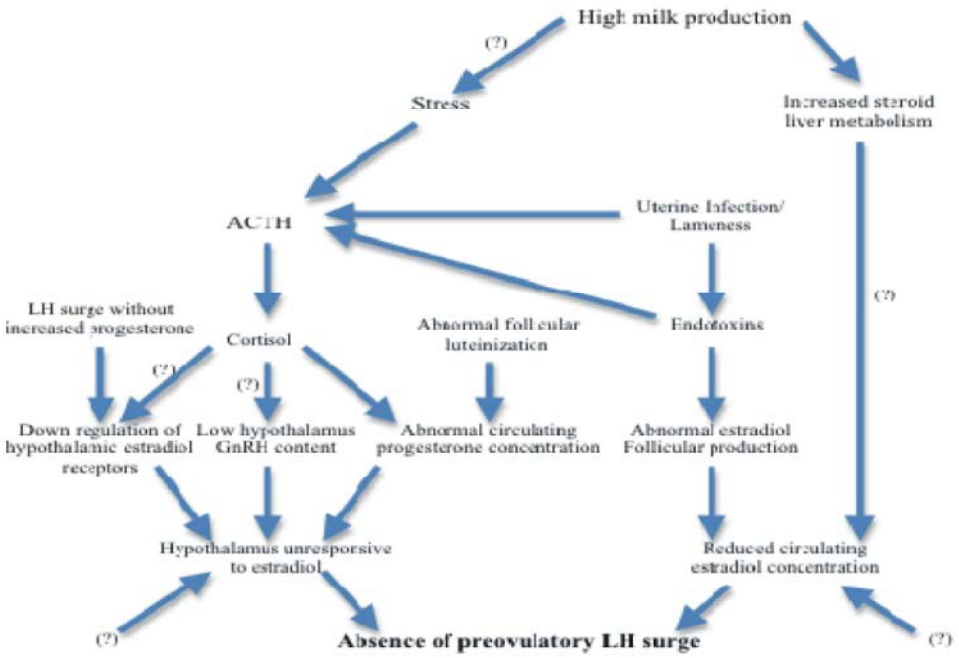

Fig. 1: Possible explanations for the absence of a preovulatory LH surge that causes follicular Cysts [16]

In fact, selection for milk yield leads to an increase in COD incidence by 1.5% per 500kg 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, were trying to meet the increased requirements for milk production, were more susceptible to environmental changes that implicated their hormonal status [11]. Gümen *et al.* [13] 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". 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 and confirmed his theory by detecting anovulatory condition when cows were treated by one treatment dose of estradiol.

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." The more simple interpretation was that a progesterone deficiency during the estradiol-induced LH surge was a probable cause of the development of follicular cysts on the ovaries. The basic reason was referred to the endocrine imbalance and that "the vast majority of data suggest that cysts were formed because of a failure of the preovulatory LH surge to occur at the appropriate time in follicular maturation [14].

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. They 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 first 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 [15].

Brito and Palme [16] provided a succinct flow chart (Figure 1) that hypothesizes the different mechanisms that potentially lead to the absence of the preovulatory surge of LH that ultimately causes follicular cyst formation.

Luteal Cysts: The Merck Veterinary Manual [17] described 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 [9]. Call these cysts; luteinized cystic follicles and define them as cysts with thicker walls that produce high levels of progesterone. In appearance, they looked smooth and rounded, with a spherical cavity that is lined by a layer of fibrous tissue surrounded by the luteinized cells [18].

Luteal cysts are considered anovulatory cysts and are associated with infertility and mucometra in cattle. 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 [9]. Luteal cysts developed when ovulation failed to occur and the theca undergoes luteinization [18]. They are also often considered to be the later form of ovarian follicular cysts [8] 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. Luteal cyst incidence increases with age and most often affects cows with high milk production [19].

Cystic Corpora Lutea: A cystic corpus luteum in a cow was defined as "luteal tissue initiating from a corpus hemorrhagicum and containing fluid in a central cavity greater than 7 mm in diameter". 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" [20]. Incidence of cystic CLs ranged from 25.2% to 78.8% during diestrus and decreased with progression of the estrous cycle. Because cystic corpora lutea were found in cows that are normally cycling or pregnant, they were considered to be a normal stage or variation of CL development. The Merck Veterinary Manual thoroughly described the physical properties of cystic CLs and their similarities and differences to normal corpora lutea: Cystic CLs 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. 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 was 5-7 day after estrus. At this point in time, the ovarian structure was near the end of the corpus hemmorhagicum stage of development [17].

Pathogenesis of Ovarian Cysts: Ovarian dysfunctions like cysts occur most often during the early postpartum period when there was a transition from the noncyclic condition during pregnancy to the establishment of regular cyclicity. It was generally accepted that cystic follicles developed due to a dysfunction of the hypothalamic pituitary-ovarian axis. This dysfunction has got multifactorial etiology, in which genetic, phenotypic and environmental factors are involved. When discussing the pathogenesis of COD, a distinction may be made between a primary defect in the hypothalamus-pituitary and a primary defect at the level of the ovary in the follicle itself. However, COD formation resulted from defects in both ovary/follicle and the hypothalamus/pituitary as well [19].

Hypothalamic-Pituitary Dysfunction: The most widely accepted hypothesis explaining the formation of a cyst was that LH release from the hypothalamus-pituitary altered the pre-ovulatory LH-surge was either absent, insufficient in magnitude or occurs at the wrong time during dominant follicle maturation, which leads to cyst formation. This aberrant LH release does not seem to be caused by a lower GnRH content of the hypothalamus, nor by reduced GnRH receptor numbers. It is believed that an altered feedback mechanism of estrogens on the hypothalamus-pituitary resulted in an aberrant GnRH/LH release and cyst formation. GnRH/LH surges occurred prematurely during follicle growth, i.e. when no follicle capable of ovulation was present, can render the hypothalamus unresponsive to the feedback affected oestradiol which resulted in the formation of ovarian cysts [13].

This physical state of hypothalamic unresponsiveness to estrogens in the majority of cows with COF, was illustrated by the failure of an exogenous estradiol treatment to elicit a timely LH surge. Consequently, a similar state of hypothalamic refractoriness to estrogens and subsequent cyst formation can be achieved. However, the refractoriness of the hypothalamus-pituitary for estradiol in cows with COF was a consequence rather than a cause of the disease. To restore the feedback mechanism, the hypothalamus needs to be exposed to progesterone. Removal of the cystic ovary by ovariectomy restores the feedback mechanism and the capacity of oestradiol to elicit an LH surge, although the underlying mechanism is not known [21].

Progesterone at suprabasal concentrations blocked the LH-surge, thereby inhibited ovulation, but increased the LH pulse frequency. This results in an anovulatory,

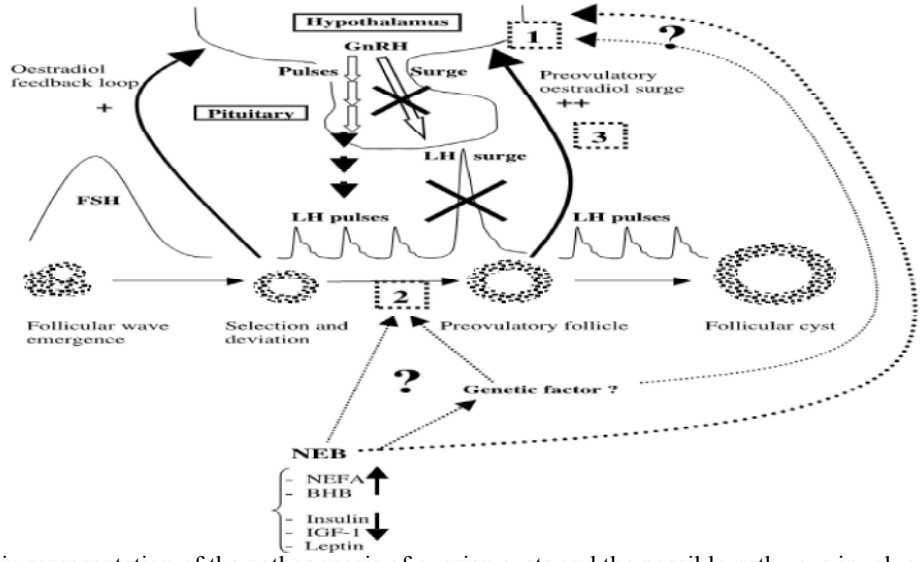

Fig. 2: Schematic representation of the pathogenesis of ovarian cysts and the possible pathways involved.

persistent follicle with a larger diameter and a longer lifespan than normal and increased peripheral estradiol concentration. Recently, at the time of diagnosis most cysts were accompanied by suprabasal progesterone concentrations, which played a role in cyst turnover. These observations together with the similarities between persistent follicles, induced by suprabasal progesterone and naturally occurring cysts, suggested a role for progesterone in the pathogenesis of COD [14].

Ovarian/Follicular Dysfunction: A primary dysfunction at the level of the follicle may disrupt the hypothalamic-pituitary-ovarian axis and cause the formation of OC. First of all, alterations in LH receptor expression and content may cause anovulation of the follicle. The LH surge initiated a complex multi-gene, multistep process in which timing is essential, finally leading to ovulation of the pre-ovulatory follicle. FSH and LH receptor numbers in granulosa cells of cysts decreased when compared to normal follicles [22]. estrogen-active cysts showed a higher expression of 3β-hydroxysteroid dehydrogenase mRNA, a steroidogenic enzyme and cows developing a cyst have increased estradiol concentrations during the early stages of follicular dominance [23].

Another receptor of interest was the estradiol receptor β(ER-β). In rodents, the importance of this receptor in follicular growth and development had clearly been demonstrated and its localization in follicle cells throughout follicular development had been described in many mammals including cattle [24]. More specifically, in rat ovarian follicles ER-β mRNA expression precedes increased expression of mRNA for the LH receptor and specific steroidogenic enzymes. Therefore, alterations in ER-β expression may be involved in the development of COF. Besides changes in receptor expression and content, alterations in steroidogenesis by the dominant follicle may also be involved in cystic development [24]. Apart from changes in mRNA expression for certain receptors and steroidogenic enzymes, cell proliferation and apoptosis in the emodelin and theca interna cell layers were altered in cystic follicles. Early cystic follicles showed an increase in apoptosis while cell proliferation was decreased [25].

Matrix metalloproteinases (MMP) could be involved in the formation of cysts: higher proMMP-2 and -9 levels were present in the follicular fluid of cysts than in the follicular fluid of normal dominant follicles. MMP played a role in follicle wall remodeling and rupture at the time of ovulation, but here to the inactive proMMP form needs to be transformed to the active MMP form. This activation was triggered by the LH-surge. Since an aberrant LH-surge caused COF formation, the higher proMMP-2 and -9 levels in the follicular fluid of COF were most likely an indication of the lack of an LH-surge [22].

Schematic representation (Figure 2) indicates the pathogenesis of ovarian cysts and the possible pathways involved. An FSH surge stimulated the emergence of a new follicular wave, from which a single dominant follicle was selected at the time of deviation. Through a positive feedback loop oestradiol stimulated GnRH and LH pulsatility, which in turn supported growth and development of the dominant follicle. Upon reaching preovulatory size, follicular steroidogenic activity reached a peak and produced a preovulatory estradiol surge. This surge either failed to elicit a GnRH and

subsequent LH surge or the GnRH/LH surge was mistimed/delayed. The dominant follicle, therefore, did not ovulate but, due to the ongoing LH pulsatility, continues to grow and becomes a cyst. The disruption of the hypothalamic-pituitary-gonadal axis produced by: (1) Factors affecting the estradiol feedback mechanism and GnRH/LH release at the hypothalamic-pituitary level. (2) An aberrant follicle growth and development with alterations in receptor expression and steroidogenesis. (3) Factors leading to an altered estradiol surge and feedback. Hypothalamic-pituitary function and follicular growth/development affected by negative energy balance (NEB) through metabolic/hormonal adaptations. In addition, in the situation of NEB, the increased expression of genetic hereditary factor(s) associated with COF promoted or the functional importance which affected follicle growth and hypothalamic-pituitary function [26].

Clinical Signs And Diagnosis

Clinical Signs: Cystic ovarian disease has been a concern for producers and veterinarians for almost two centuries because a diagnosis of COD usually means the cow is not pregnant. A German scientist in 1831 wrote one of the earliest records of COD noting its relationship to infertility and documented some of the physical conditions associated with COD [27]. These syptoms included: Loss of tone throughout the female genital tract. Relaxation or stretching of the sacrosciatic and sacroiliac ligaments giving the raised tail head appearance. Formation of a cyst or cysts on the ovary or ovaries. Behavioral changes occurred (Buller cow) which are characteristic of nymphomania (i.e. excessive mounting, standing and bawling with noticeably deeper tone). Erratic milk production. Nymphomaniacal behavior has been so extreme that some cows have been reported to “Mount a man, especially while being led”. Most of these symptoms are still recognized in cows.

However, with earlier detection, only extreme cases tend to exhibit the relaxed ligaments, bulling and a deepening of the vocalizations. The main symptom observed in modern day dairy cattle is anestrus [4]. Nymphomania is a term that is better used as a descriptive word for a symptom in certain cases of COD, rather than a synonym for the overall condition.

Historically, the producer has recognized COD primarily on nymphomaniacal behavior. Through increased veterinary involvement with herd management and production and producer education, a strong focus has been placed on increasing milk production and reproductive efficiency of dairy cattle. With these changes in management and breeding strategy, a greater awareness of COD has occurred and anestrus is recognized as the key clinical sign [26].

Diagnosis: For many years cysts had been determined by behavioral and palpation criteria. Generally, a cyst is defined as a palpable structure on one or both of the ovaries greater than or equal to 2.5cm (Approximately one inch) irrespective of other ovarian structures. In practice, a veterinarian seldom has the opportunity to recheck a cow in 10 days. Thus, most diagnoses based on the one time detection of a large fluctuant structure meeting most of the previous criteria and treatment was usually administered at the time of diagnosis. Diagnostic approaches for OC in cows include history and clinical signs, transrectal palpation, ultrasonography and plasma or milk progesterone assay [19]. In the 1940’s, the presence of cystic follicles on the ovaries was mainly associated with nymphomania and bull-like appearance in cows. Due to many exogenous and endogenous factors, perturbation of the hypothalamo-hypophysealovarian (HHO) axis results in anovulation. Ovarian cysts diagnosed after the puerperium had a negative effect on fertility, whereas when cysts were diagnosed during the puerperium they do not affect reproduction [28].

The most likely time of diagnosis was 30-60 day after parturition in high-yielding dairy cows but the detection of anovulatory follicles during the first weeks after calving should not be considered an ovarian impairment. From a practical point of view, an ovarian impairment may be suspected when anovulatory follicles were detected from 7 weeks after calving, a time when reproductive functions are thought to be restored [29].

Ovarian cysts and normal preovulatory follicles were differentiated on the basis of number and size but mainly on the basis of uterine tonicity. During transrectal palpation, ovarian cysts were identified as multiple follicles that were typically larger than normal ovulatory follicles with an increased overall ovarian diameter along with a flaccid uterus in the absence of a corpus luteum while cows in proestrus have an erect, turgid uterus [30].

Although transrectal palpation had long been the diagnostic approach, follicular cysts cannot be differentiated from luteal cysts solely by palpation. It was difficult to distinguish between follicular and luteinized cysts without using ultrasonography in anoestrous cows. The accuracy of diagnosing ovarian cysts and differentiating follicular and luteal cysts can be increased by combining transrectal palpation of the genital tract to determine that a corpus luteum was absent and the uterus lacks tone; ultrasonography to confirm

that a corpus luteum was absent, to determine the size of follicles that were present and to check for luteinization; and measurement of plasma progesterone concentration to determine the degree of luteinization [31]. The accuracy of diagnosis can be increased by obtaining information about the reproductive history of the animal, vaginal examination and progesterone determination [32]. Kahn [17] described a luteal cyst as being characterized by enlarged ovaries with one or more cysts with thicker walls than those of follicular cysts because of a lining of luteal tissue. Ultrasonography is effective in detecting follicular and luteal cysts with high accuracy. Color Doppler sonography is superior to B-mode sonography for differentiating follicular and luteal cysts and aided in the selection of treatment [33]. More over two approaches can be considered in the diagnosis of OC.

First, detection of multiple follicles approximately 18 to 20 mm in diameter and second, ovarian follicular waves during a period of 7 to 10 days in the absence of ovulation, absence of corpora lutea and a lack of uterine tonicity. Determining the presence of ovarian follicular waves during a 7 to 10 day period with follicles that reach ovulatory size (12 mm) can be used to retrospectively differentiate ovarian cysts from shallow nutritional anestrus with low body condition score (BCS) [31].

In general, luteal cysts were associated with relatively high concentrations of progesterone in the peripheral circulation while follicular cysts were associated with relatively low concentrations of progesterone. Many researchers have used a plasma P4 concentration greater than 1 ng/ml as the minimum P4 concentration for a cyst to be considered luteal. Thus accurate diagnosis of the type of OC requires a combination of diagnostic approaches such as transrectal palpation, transrectal ultrasonography and plasma progesterone profiles [34].

Treatment And Prevention

Treatment: The OC therapy appears to be simple however, regaining fertility, which often requires longer time due to perturbations in endocrinology and uterine pathology that followed in long standing cases [35] seemed to be more important. Treatments for OC were numerous and variable and had changed considerably over the years [19,35]. Economically, the decision to treat an animal was influenced by the costs and the expected treatment benefits, the costs of replacement and the breeding value of the animal [36]. Many endocrine based treatments for cysts had been evaluated including steroids, Gonadotrophin and GnRH. The success of therapy in terms of disappearance of OC with different hormonal treatments was good, yet the establishment of pregnancy required variable times due to formation of new OC and pathological alterations that occur in the uterus with long term persistence of OC. Many variables such as OC time of diagnosis, OC persistence period, presence of mucometra and milk production determine the outcome of therapy [35].

Manual Rupture: In the past, manual rupture of OC had been suggested. But, currently it is no longer suggested due to potential dangers of hemorrhages and adhesions that may contribute to fertility reduction [16].

Gonadotrophin Releasing Hormone Alone: The distinction between follicular cyst and luteal cyst became not important in practice, because of the similar response of both types of cysts to GnRH treatment and usually resulted in luteinization of the cysts followed by estrous within 4 weeks of treatment. GnRH is most effective for returning cows with anovulatory follicular cysts to a normal cyclic ovarian condition, it induced the release of LH with a maximum plasma LH concentration being reached 90 to 150 minutes after application, which initiated the formation of active luteal tissue, as indicated by increased serum progesterone levels 7 days after treatment onwards. In response to treatment with GnRH, ovulation of the cyst did not occur, but other follicles present at the time of treatment ovulated [16].

GnRH had no effect on intervals from treatment to CL detection or from treatment to cyst disappearance and that CL detection and cyst disappearance were not correlated; also no association observed between the gonadotropin response to GnRH and the interval from treatment to CL detection. Thus, a single GnRH treatment has been the standard treatment for cows with ovarian cysts. There was CL approximately 7 days after the treatment with GnRH indicating that the CL formed from ovulation of an ovarian follicle and not the existing ovarian cyst [37].

After the GnRH treatment and subsequent luteinization, the cyst became responsive to the prostaglandin-F2α (PGF2α) because the steroidogenic synthesis pathway has switched from estradiol to progesterone. The newly elevated levels of progesterone were responsible for a restoration of responsiveness to the positive feedback effect of estradiol, resulted in the resumption of normal cyclic ovarian activity after the release of endogenous PGF2α and cyst regression [16].

Gonadotrophin Releasing Hormone Analogs: The epidural administration of lecirelin (A GnRH analogue) promoted the remission of follicular cysts and an improvement of reproductive parameters [38]. A single intramuscular injection of buserelin at a dose of 10µg or higher is recommended for the treatment of ovarian follicular cysts in cows. A single injection of 20µg buserelin and 200µg fertirelin have equal therapeutic effects in lactating cows having OC Buserelin, a nanopeptide GnRH analog, has 10 to 20 potentancy than fertirelin acetate in eliciting the release of LH and FSH. In comparative studies, buserelin (a more potent GnRH analogue) or human chorionic gonadotropin (HCG) produced similar effects [16]. A recent study found beneficial effects of a single IM administration of 0.1mg lecirelin acetate in the therapy of cows suffering from OC [39]. Since the 1970s HCG and GnRH analogues have been used to treat ovarian cysts and both appear to be equally effective with regards to treatment response and fertility, but the next estrus occured 5-21 days after treatment. GnRH and HCG elicited equivalent endocrine and clinical responses, but GnRH had an advantage over HCG in its minimal antigenicity [17].

Prostaglandin F2α: Prostaglandin F2α (PGF2α) has been used for the treatment of luteinized cyst because of its luteolytic activity and estrous symptoms were observed within 2 or 3 days of treatment. It still used as the most effective treatment for luteinized cysts and induced estrus in 75% of the cows within 7 days after treatment and 66% pregnancy rates at first estrus were [16].

The luteolytic doses of PGF2α as the ideal treatment for luteal cyst, induced estrus within 3-5 days [17]. Intervals from treatment to resumption of ovarian activity were affected by the characteristics of ovarian cysts, with a faster recovery for the luteal type [40].

Progesterone And Progesterone Implants: Treatment with progesterone disrupted the endocrine environment needed to maintain ovarian follicular cysts and thus lead to their regression [7]. At high doses, it exerts a strong negative feedback on LH pulse frequency which reduced LH in cows with cysts and this was followed by development of normal ovulatory follicles. Acute treatment as well as chronic treatment (9-14 days) with progesterone caused a rapid reduction in the size of persistent follicles and restored cyclic ovarian activity. Cows with persistent follicles were successfully synchronized and time inseminated using progesterone, GnRH and PGF2α, but showed a limited response to treatment with GnRH plus PGF2α [41].

Progesterone treated follicular cysts by restoring the responsiveness of the hypothalamus to the positive feedback of estradiol, resulting in normal estrus and ovulation within 7 days after removing the implant [16]. Treatments with progesterone releasing intravaginal devices (PRID) in combination with estradiol benzoate for 12 days evidenced therapeutic efficacy in resolving OC in post-partum dairy cows [42]. The effects with progesterone treatments were proposed to be mediated by restoration of the ability of hypothalamo-pituitary axis to generate an LH surge in response to an increasing estradiol [43]. Moreover, when progesterone was used for estrus synchronization after embryo collection instead of PGF2α, the proportion of cows developing OC decreased from ~25% to <3% [16].

Gonadotrophin Releasing Hormone Plus Controlled Internal Drug Release: Treatment of cows with OC with *controlled internal drug release* (CIDR) intra vaginal placement, GnRH followed by PGF2α 7 days later resulted in recruitment of new healthy follicles, synchronization of ovulation and resulted in a marked improvement in pregnancy rate [44]. Treatment with CIDR proved effective in restoring ovulation and reestablishing normal cyclicity in beef donor cows with cysts persistent for a long period [36]. Insertion of a CIDR and GnRH injection in cows with follicular cysts induced synchronous follicular wave emergence with the same pattern as observed in cows having normal estrous cycles [45]. The CIDR reduced and maintained LH secretion at normal luteal levels, thereby, induced atresia of estrogen-active cysts and prevented the formation of cysts from the newly emerged follicles [46]. Although the use of CIDR eliminated the need for evaluation of the presence of a corpus luteum at the time of PGF2α treatment [31] the combination of both minimized the risk of incorrect treatment and provided sufficient reproductive performance [47].

Gonadotrophin Releasing Hormone Plus Prostaglandin F2α: Comparatively, ovarian cysts were less responsive to treatment with GnRH alone. GnRH plus Cloprostenol (CLP) 14 days later was effective in resolving cysts with significantly higher percentages of ovulation rates, returns to estrus and pregnancy rates and a much lower level of cystic persistence. Different combinations of GnRH and CLP as treatments for OC were suggested in order to combat the problem to the fullest [41]. However, currently GnRH followed by PG *F2α 7* -10 days later was the routinely used therapy for OC [30].

Table 1: Drug amounts, routes and protocols for treatment of follicular cysts [16]

Drug	Dose	Route
Gonadorelin (GnRH)	100 µg	IM
hCG	10,000 IU	IM
Dinoprost (PGF2α)	25 mg	IM
Cloprostenol (PGF2α)	500 µg	IM
Progesterone	1.9 g	Intravaginal Implant

Treatment Protocols

(1) GnRH (or HCG) + PGF2α (day 0); PGF2α (day 9 if no estrus)

(2) Ovsynch: GnRH (day 0); PGF2α (day 7); GnRH (day 9); fixed time AI, 16 h after last GnRH treatment

3 Progesterone implant for 12 days (not for dairy cows).

Homeopathic Drugs: Homeopathic remedies like *homeopathic Apis* (for the right side OC) or *homeopathic Lachesis* (for the left side OC) administered twice daily for 5 days, with either one being immediately followed by homeopathic *NatrumMur;* twice daily for three days were effective treatments for OC. *Apismellifica* is a common homeopathic medicine made from the female honeybee, while Lachesis was prepared from the fresh venom of the South American bushmaster snake and *NatrumMur* is made simply from sodium chloride, or table salt. If this treatment doesn't work, Heat Seek, a botanical herb blend typically enhanced the observable signs of estrus, by giving 10 tablets orally every other day for twelve doses a total of 24 day treatment [48]. The use of homeopathic medicines was considered a source to study about homeopathic therapy due to its clinically and scientifically weak base [49].

Prevention: By careful genetic selection, improvements have been made by eliminating bulls that have sires daughters which have subsequently suffered from cystic ovarian disease. Ideally, cows should not be treated for cystic ovaries and certainly their progeny should not be used for breeding. Unfortunately, this places the herd manager and the veterinarian in a dilemma since, frequently, those cows that were affected were the best producers. Prophylactic use of GnRH had shown some success in reducing the prevalence of cysts in herds. It had been recommended that all cows should be treated with 100-200 µg of GnRH 12-14 days postpartum. If cystic ovaries were a direct result of stress, then COD prevention should be approached by minimizing stress and by preparing cows to cope with the stresses they inevitably encounter. Good nutrition was essential prevention and had begun with condition scoring midway through the previous lactation [49].

During the last half of lactation, cows should be fed to achieve a score of 3.5 - 3.75 at dry off and maintained at this level through to calving. Adequate (But no excessive) body reserves helped to reduce negative energy balance in early lactation. The dry cow feeding program demanded attention to the specific needs of the cow at this stage of her production cycle. In particular, close-up rations was designed with the objective of minimizing the incidence of milk fever, ketosis, displaced abomasum and other disorders which occur after calving. Trace mineral and vitamin intakes are often inadequate in the dry period when cows are not receiving supplemental grain. Several studies had demonstrated the beneficial effects of supplemental selenium along with vitamin A, vitamin E and beta-carotene in maintaining immune competency and reducing the incidence of mastitis in fresh cows [4].

CONCLUSION AND RECOMMENDATIONS

Cystic ovarian disease (COD) is the most economically important problem of dairy farm which results in anovulation, delay in reproduction, decreased milk production leading to loose of money and economic crisis for dairy producer. There are three types of ovarian cysts in dairy cattle; follicular cysts, luteal cysts and cystic CL. The most likely causes of COD are the disruption along the pathway of hypothalamus or neuro-endocrine imbalance involving the hyphothalmic-hypophyseal-gonadal axis. The most important clinical symptom to determine ovarian cysts included nymphomania and anoestrus. COD is accurately diagnosed when combination of physical examination, Ultrasonography and plasma progesterone testing are applied. The most effective treatment after accurate diagnosis of COD is GnRH followed by PGF2α and prevention is directed against the removal suspected cause (Reducing stress and by genetic selection). Most of literatures that I reviewed were primarily concerned with follicular cysts and the least information was found for cystic CL. Because of luteinized cysts are of considered to be just later form of follicular cysts, it is likely that researchers find it more important to deal with initial causes of follicular cysts than luteal cysts. A likely explanation for the shortage of literature on cystic CL is the harmlessness of the condition; that it is considered to be variation in normal CL that does not affect ovarian cyclicity when compared to follicular and luteal cysts. Based on above conclusive remarks the following recommendations are forwarded: waiting until approximately one month post-calving before attempting

to diagnose cystic ovarian disease is practical to provide time to spontaneous recovery. After this time, cows diagnosed by an experienced palpater as having an ovarian cyst should be treated with GnRH at first diagnosis. Cows should be palpated a second time within 7 to 10 days if possible and retreated if necessary. Elimination and removal of bulls that have sire daughters suffered from COD from dairy farm is also important to reduce genetically correlated occurrence of COD. Since COD significantly reduces the reproductive efficiency as well as the expected output of dairy farm, the dairy producer must be awared of the condition and brought the cow to veterinary clinic while she shows an abnormal estrus behavior or nymphomania and fails to conceive twice or more times after insemination. Further research should be performed in order to determine the exact etiology of COD as well as preventative methods.

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