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REVIEW

Theriogenology

Ovarian cysts, an anovulatory condition in dairy cattle

Silviu-Ionuț BORȘ[1)]* and Alina BORȘ[2)]

[1)]Research and Development Station for Cattle Breeding, 707252 Dancu, Iaşi, Romania
[2)]Department of Public Health, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine, 700489 Iasi, Romania

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ABSTRACT. Ovarian cysts are one of the most common ovarian dysfunctions in dairy cattle, which can lead to a considerable economic loss through its high incidence and can reduce the reproductive performance. Anestrus is the most significant clinical sign observed in dairy cattle suffering from this condition. For diagnosis, most of the veterinarians use a combination of methods, from ultrasonography as an additional approach to trans-rectal palpation and symptomatology when assessing ovarian cysts. Although the Ovsynch treatment seems to be preferred, the pregnancy rate after this treatment is relatively low. Despite such reports on dairy cattle ovarian cysts, the data is insufficient to validate all the characteristics of this condition. This review summarizes what the literature has so far provided from definition to treatment of ovarian cysts in dairy cattle.

KEY WORDS: anestrus, dairy cattle, oligogenic disorder, ovarian cysts, reproductive failure

The failure in dairy cattle to perform one-year calving interval (CI) is a sign of fertility problems that can generate an important economic loss. The CI in dairy cattle is influenced by a time lag between calving and the resumption of ovarian activity in the postpartum period [59, 73, 82, 85]. The most important factor that generates reproductive failure is the delayed resumption of postpartum ovarian activity [57]. Ovarian cysts represent an important cause of reproductive failure in dairy cattle. Such circumstance can lead to a considerable economic loss through ovarian cysts high incidence, to an increase in the number of days to first service, and increase in the number of open days [95].

There are some controversies regarding the definition of ovarian cysts in dairy cattle. Although in time some definitions describing the ovarian cysts have been proposed, lack of consensus persists and a clear definition of the condition is missing [39]. Previously ovarian cysts were defined as enlarged anovulatory follicle like structures (greater than 25 mm in diameter) and persisting for 10 or more days [67, 97]. In 2002 Silvia *et al.* [74] defined this condition as follicular like structure of at least 17 mm in diameter that persist on the ovary for more than 6 days in the absence of corpus luteum and clearly interfering with normal ovarian cyclicity. One of the latest definitions describes ovarian cysts as follicles with a diameter of at least 20 mm that are present on one or both ovaries in the absence of any active luteal tissue and that clearly interfere with normal ovarian cyclicity [87]. Recently, we defined ovarian cysts (follicular or luteal) as anovulatory ovarian structures with a cavity greater than 20 mm in diameter in the absence of a corpus luteum [14]. The difference between follicular and luteal cysts is that the wall is less than 3 mm in follicular cyst and greater than 3 mm in luteal cyst [16].

Wills [92] identified three types of cysts in dairy cattle 1) Large thin walled anovulatory follicular cysts, characterized by high estradiol secretion 2) Thick walled anovulatory luteal cysts characterized by prolonged and elevated progesterone secretion. 3) Follicular cysts that luteinize.

There have been various names associated with this condition over the past century including adrenal virilism, nymphomania, cystic ovarian degeneration, cystic ovaries, and ovarian cysts [30]. The most used term, “Cystic Ovarian Disease” seems inadequate and should be replaced by the term “Cystic Ovarian Follicle” [87] but some of the cysts are luteal, which can create confusion for the differential diagnosis. In our opinion, an appropriate term could be “Ovarian Cysts” because the condition describes an ovarian disorder characterized by the abnormal ovarian cavity structures which failed to ovulate (anovulation) or to regress. In fact, it is similar to the condition that applies to women, which manifests itself in an oligogenic disorder triggered by the interaction of a number of genetic and environmental factors determining a heterogeneous, clinical, and biochemical phenotype [93]. However, the pathogenesis of this disorder in women and cows has not yet been fully elucidated, regardless of the numerous studies of the metabolic and endocrine disturbances in women with polycystic ovarian syndrome and despite the relationship between metabolic changes in early lactation and the impaired reproductive performance in dairy cattle [40].

*Correspondence to: Borş, S.-I.: bors.ionut@yahoo.com

INCIDENCE OF OVARIAN CYSTS IN DAIRY CATTLE

The incidence of ovarian cysts in dairy cattle may vary from 2.7% to 15.1% [13, 17] or from 6% to 30% [30, 45] with peak incidences between the interval of 14 and 40 days postpartum [25, 46, 50, 95]. Some studies have also reported that up to 70% of the ovarian cysts occur between days 16 and 50 after calving, with the highest occurrence between days 30 and 40 after calving [25, 46]. The period before day 16 and the period after day 50 post-calving show the lowest incidence of ovarian cysts [8]. Roth *et al.* [66] identified an increase of ovarian cysts in dairy cattle over time, and this has had a negative effect on the reproductive performance of today's dairy cattle population. The genetic correlations between ovarian cysts and yield traits prove that ongoing selection for production will increase the incidence of ovarian cysts [38] and in addition to that, the incidence of this disorder will increase without a reexamination of the genetic selection methods. The conclusion of the study of Hooijer *et al.* [38] is that, without further measures, the selection for milk yield increases the ovarian cysts incidence by 1.5% per 500 kg increase of milk yield.

ETIOLOGY AND PATHOGENESIS OF OVARIAN CYSTS IN DAIRY CATTLE

It is not yet completely explicit which exact mechanism generates ovarian cysts in dairy cattle. The most accepted hypothesis explaining the ovarian cysts formation is that the release of luteinizing hormone (LH) by the hypothalamic-pituitary-gonadal (HPG) axis is altered. Abnormal LH release seems to be caused by an altered feedback mechanism of estrogens on the hypothalamus-pituitary axis [87]. In addition, several factors can influence gonadotropin-releasing hormone/luteinizing hormone (GnRH/LH) release at the hypothalamo-pituitary level. At the ovarian level, cellular and molecular changes in the growing follicle may contribute to anovulation and cyst formation [87]. It is well documented that the increased levels of kisspeptin increased circulating concentrations of LH in Holstein cows and ovariectomized Jersey cows [91]. *Kiss1* neurons are key regulators of GnRH release and modulation of the HPG axis. The *Kiss1* neurons are positioned as an ideal hub receiving afferent inputs from other brain regions in response to the internal homeostatic and external signal. Also, careful considerations need to be implemented to distinguish direct actions of the neuropeptides on GnRH neurons or effects mediated through *Kiss1* neurons in the arcuate region of the hypothalamus ($Kiss1^{ARC}$) [94]. The inhibition of $Kiss1^{ARC}$ may be the key factor in the alteration of GnRH/LH secretion during lactation which can cause anovulation.

Although some authors assigned this to the disruption of the HPG axis, which cause cyst formation [2, 30, 87], the persistence of follicles over time connects with an important intraovarian component [74]. Some studies explain that an altered expression of steroid and gonadotropin receptors can disturb the endocrine signaling pathways [52, 69]. As for the cellular changes, the most agreed hypothesis shows that follicular cysts represent a distinctive stage of follicular differentiation, with a specific protein and gene expression profile in ovarian cells that differs from the one identified in atretic follicles or other follicular categories [53, 69, 89]. A delay in follicle regression after ovulation (alteration in the proliferation/apoptosis balance) is bound to trigger the ovarian cysts pathogenesis because the preovulatory follicles that can neither be ovulated nor become atretic will disturb the ovarian function, generating a starting point for follicular persistence and establishment of follicular cysts [60, 68]. The persistence of these structures enables them to continue to secrete altered levels of cytokines, growth factors and hormones, and therefore contributes to ovarian cysts pathogenesis [80]. The increment in the expression for bovine vascular endothelial growth factor (VEGFA-164, VEGFA-164b and VEGFR2) found in cysts with respect to dominant follicles and the emerging changes detected from the precise moment of anovulation could indicate that these growth factors play important roles in this process and thus contribute to the pathogenesis of ovarian cysts and its angiogenic dysregulation [81].

Stress can be a significant ingredient for the development of bovine ovarian cysts. The study of Ortega *et al.* [60] explained the mechanism of the stress factors in terms of developing ovarian cysts. First, adrenocorticotrophic hormone (ACTH) stimulates the release of cortisol and progesterone. Enhanced secretion of progesterone inhibits the release of GnRH whereas, at the same time, the increased secretion of cortisol reduces estradiol secretion and receptors to luteinizing hormone/choriogonadotropin (LHCGR) content in antral follicles. Subsequently the positive feedback of estradiol on the hypothalamus and the pituitary is deteriorated, the LH flow is suppressed, the ovulation does not ensue and the follicle becomes cystic. This proposed mechanism is linked with the decreased expression of LHCGR reported in the studies of the Kawate [42] and Marelli *et al.* [52].

Another hypothesis concerning ovarian cysts pathogenesis is that reduced circulating insulin concentrations during the early postpartum period may play a role in cyst formation [15, 88]. In addition, in the early postpartum period the high-yielding dairy cattle present a general state of peripheral insulin resistance [79]. However, the insulin resistance is less involved in the pathogenesis of ovarian cysts compared with insulin insufficiency, which is a more common circumstance [58]. The occurrence correlates with the altered interaction between glucose and insulin at the pancreatic level but does not combine with other distinct hormonal and metabolic alterations [88]. Insulin acts on the ovary and exerts direct and indirect stimulatory effects on granulosa and theca cell growth and steroidogenesis, both *in vitro* [34, 77, 78] and *in vivo* [51, 75]. Likewise, lower insulin levels tend to contradict the higher 17β-estradiol concentration in dairy cattle ovarian cysts. Hormonal alterations during the final stage of follicle growth and maturation may trigger cyst formation [88]. Other recent studies have explained a possible association of altered mRNA expression and activities of the Matrix Metalloproteinases and their inhibitors [61] as well as impaired insulin signaling pathway with the development of ovarian follicles in bovine ovarian cysts [37].

Hatler *et al.* [36] observed that 66% of ovarian cysts in dairy cattle were associated with supra-basal progesterone levels at the time of diagnosis and this was associated with cyst turnover. The supra-basal progesterone level blocks the pre-ovulatory LH

surge but does not suppress LH-pulse frequency the way normal luteal progesterone concentrations do. Consequently, anovulatory persistent follicle starts to develop, with a larger diameter and a longer lifespan than usual, along with increased peripheral estradiol concentrations [83].

Correlated with hormonal imbalances, the metabolic changes can influence the cyst formation [98]. The high incidence of ovarian cysts in dairy cattle during the early postpartum period reinforces this hypothesis, as that is the period when animals display negative energy balance (NEB). Concurrently, the association of ovarian cysts with a high level of milk production can only support the premise [11, 38, 48, 49]. Beam [11] registered increased milk yield and reduced mobilization of body reserves in proportion with the milk production in cows with ovarian cysts. This observation reveals that the differences in energy utilization/partitioning between cystic and ovulatory cows may be a risk factor for developing ovarian cysts [11].

It is however evident that the etiopathogenesis of ovarian cysts in dairy cattle is a complex process which implies the alteration of various physiological processes (folliculogenesis, steroidogenesis, ovulation) and some factor like stress, herd management, nutritional status, body condition, metabolic disorder, altered mRNA expression and Matrix Metalloproteinases and their inhibitors. Metabolic, endocrine and environmental changes can probably alter the neuroendocrine feedback at the level of $Kiss1^{ARC}$ neurons in an acute way, being a route to cyst formation. Thus, since several interconnected pathways are involved in the etiology of ovarian cysts, it remains difficult to identify the exact mechanism that generates this disorder.

RISK FACTORS FOR OVARIAN CYSTS IN DAIRY CATTLE

The possibility of ovarian cysts occurrence increases with the yield in the current lactation [26]. Some researchers have also implied that higher milk yield in dairy cattle can increase the risk of developing ovarian cysts [15, 38, 48] yet other studies disagree with this approach [8, 86]. Such contradictory results can be explained by the fact that in the first stage of lactation, a higher milk yield generates severe NEB and in fact, this might be a more accurate parameter than milk yield. Several hormonal and metabolic adaptations, which can affect the ovarian function [12], are associated with this NEB, but the mechanism that engenders ovarian cysts is still unclear. It is possible that massive mobilization of nonesterified fatty acids (NEFA) from adipose tissue during NEB to generate their higher concentration in the follicular fluid of cystic follicles of cows with ovarian cysts which could be harmful to follicular cells, compromising normal ovarian folliculogenesis, including ovulation. These could generate an adverse microenvironment for the resumption of ovarian activity and could be a cause of the persistence of follicles and the recurrence of ovarian cysts [32]. Catabolism induced by NEB is known to affect reproduction in dairy cattle and to predispose them to have extended periods of anovulation [64, 65, 70]. A key feature in anovular cows when inseminated is that they develop the ovulatory follicle under subluteal or low concentrations of progesterone. Progesterone from the corpus luteum is pivotal for follicle development, oocyte competence, embryo growth, and endometrial function; however, many of these effects exerted by progesterone are mediated either by secretion of gonadotropins influencing follicular function and oocyte competence or by endometrial histotroph secretion influencing embryo/conceptus growth and developmental biology [71].

In the study of Laporte *et al.* [48], the most important risk factors for developing ovarian cysts, in dairy cattle, are milk production and parity. In their study, the researchers deducted that the risk increased 1.15 times in the selected group per kg of milk, while the risk increased 1.04 times in the group per parity. In comparison, Emanuelson and Bendixen [24] observed an increased risk linked with high milk production, notably if there was higher milk production compared with the performance from the previous lactation. Furthermore, the cows that experienced ovarian cysts in their last lactation grew a considerably higher hazard of suffering ovarian cysts in the current lactation [55] and this can be explained by the correlation between ovarian cysts with the cattle genetics and their environment [87]. An interesting fact is that several studies identified ovarian cysts in association with twinning [10, 24].

Environmental factors such as nutrition, feeding management and housing type are associated with the risk of developing ovarian cysts in dairy cattle [76, 87]. The housing of cows is a significant risk factor. For example, Opsomer *et al.* [59] identified a 5.7 greater risk of succumbing to ovarian cysts in dairy cattle when calving takes place indoors compared to pasture calving. Simensen *et al.* [76] identified more ovarian cysts diagnoses in free-stalls compared to tie-stalls grazing systems.

Another study performed in North-East Spain (40°N) identified the season as a risk factor of high ovarian cysts incidence. This study demonstrated that cows calving in the summer were 2.6 times more likely to develop this disorder compared with the cows calving in the winter. The researches assigned the heat stress to the seasonal variation [50]. However, some USA studies did not find seasonality to be as important as that [8, 72]. In their study, Nelson *et al.* [55] determined that autumn calving for the Norwegian dairy cattle increased ovarian cysts occurrence, compared to calving in winter, spring and summer. As a result, the cows calved during autumn would have an active reproductive period of 40 to 170 days after calving and in consequence their service period would be during the housed wintertime.

López-Gatius *et al.* [49] identified as risk factors for developing ovarian cysts some puerperium disorders such as twinning, retained placenta, primary metritis, and ketonuria, as well as any combination of these conditions. In addition, they recognized high milk yield from the puerperium period as a risk factor for developing ovarian cysts and determined that older cows were more susceptible to suffer from this disorder compared to cows at early lactation.

Although many risk factors have been associated with the likelihood of ovarian cysts occurrence, most studies identify the milk production traits as the most present factor, which may be influenced by the metabolic, genetic and health status.

CLINICAL SIGNS OF OVARIAN CYSTS IN DAIRY CATTLE

In the 1940s, the presence of cystic follicles on the ovaries was mainly associated with nymphomania and a bull-like appearance in cows [18, 29], which are clear clinical signs of a state of "disease" [87]. Before 2006, it was considered that cystic follicles were rather common, and that they could generally occur without obvious clinical signs [87]. In addition, after a flexible time period, cysts can become non-steroidogenic and then they no longer interfere with cyclicity [22, 56].

However, the clinical signs that accompany ovarian cysts are variable and depend on the extent of the luteinization of the cyst. Anestrus is most common, in 62–85% of the cases [21, 90] especially during the postpartum period [45]. Irregular estrus intervals, nymphomania [41], relaxation of the broad pelvic ligaments and development of masculine physical traits are additional signs that may be present, especially at a later time during lactation [96]. Some conditions can evolve occasionally, triggered by increasing testosterone levels, determining some cows to exhibit masculine aggressive and sexual behavior. Thus, most cows that have luteal cysts will remain in anestrus as long as the conditions persist [9].

DIAGNOSIS OF OVARIAN CYSTS IN DAIRY CATTLE-DIFFERENTIAL DIAGNOSIS

The ultrasonography is the most common tool used to diagnose and differentiate the ovarian cysts in dairy cattle although its accuracy is not absolute [14].

Several methods combined can establish increased accuracy of diagnosing ovarian cysts and differentiating follicular and luteal cysts. The difference between follicular and luteal cysts is that the cyst wall is less than 3 mm in follicular cyst and greater than 3 mm in luteal cyst [16]. However, this differentiation is difficult in field conditions [28, 62] and is often omitted from the diagnosis. Thus, per rectum palpation of the genital tract will determine if corpus luteum is absent and whether the uterus lacks tone or not. The cows with ovarian cysts fail to ovulate a preovulatory follicle and the uterus lacks tone. Ultrasonography will confirm that corpus luteum is absent, will establish the size of the follicles, if present, and will help check on luteinization. Measurement of plasma progesterone concentration will detect the degree of luteinization [7]. Follicular cysts are characterized by low plasma progesterone concentrations (<1 *n*g/m*l*) unlike luteal cysts which have high progesterone levels [23]. Therefore, the use of progesterone profile helps differentiate the luteal and follicular ovarian cysts. Besides, the employment of trans-rectal ultrasonography will achieve the exact distinction between the two cysts. The use of ultrasound is necessary to differentiate between follicular cysts and ovarian inactivity (presence of little or no follicular development), where there is low progesterone level in both cases, which would otherwise be difficult to differentiate by using progesterone analysis only. Therefore, the combined use of progesterone analysis and ultrasonography is useful to differentiate with accuracy the distinct types of ovarian abnormalities such as follicular cyst, luteal cyst, and ovarian inactivity [95]. An authentic diagnosis of ovarian cysts currently employs a combination of trans-rectal palpation, trans-rectal ultrasonography and plasma progesterone assay [39]. However, the use of on-farm progesterone kits has unfortunately not been widely adapted in many countries [84] and the threshold values used in the literature for progesterone are variable [88]. For this reason, farm veterinarians usually rely only on ultrasonography as additional method to trans-rectal palpation and symptomatology when assessing ovarian cysts [14].

There is a significant difference between luteal cyst and cystic corpora lutea (cystic CL). While luteal cysts are follicular cysts the walls of which luteinize in time, cystic CL are "physiologic and originate from follicles that have formed a cavity during corpus luteum development". The differential diagnosis between these two structures can be preceded through rectal palpation in order to determine if the formation is structurally characteristic of a corpus luteum or not. A cystic CL can be diagnosed if a line of demarcation and distortion in the shape of the ovary is detected. However, differentiation can only be successfully confirmed when rectal palpation and ultrasonography are combined [6, 20]. Thus, to avoid confusion cystic CL can be called cavitary CL, since it is not pathological.

Although ultrasonography is not ultimately accurate, it nevertheless represents a robust method for differentiating ovarian cysts in cows [14], with an accuracy ranging of 75–95%, as reported by various authors [16, 31, 35].

TREATMENT AND CONTROL OVARIAN CYSTS IN DAIRY CATTLE

The chance of spontaneous recovery from cysts that develop in early postpartum is more likely for the cows with lower production, 80% of cows with ovarian cysts in their first lactation spontaneously recovered while this figure was 30% for older cows [49]. Even if spontaneous recovery from ovarian cysts does exist, Brito and Palmer [16] recommend initiating the treatment as soon as the condition is diagnosed, for economic consideration. Another profitable option is to treat multiparous cows with ovarian cysts very early in the postpartum period, while treatment of primiparous cows should be delayed, at least until the end of the pre-service period, to provide opportunity for spontaneous recovery [49].

From all the treatments that can apply, such as manual rupture [44], cystic fluid aspiration [3, 66] and hormonal application [33, 43], the last method seems to prevail [84]. The manual rupture cannot be recommended due to the possibility of hemorrhages and adhesions [16]. In some conditions, minor ovarian manipulation can cause rupture of thin-walled cysts. However, excessive force should be avoided when performing transrectal examination of dairy cattle.

Taktaz *et al.* [84] observed that simultaneous treatment of ovarian cysts with human chorionic gonadotropin (hCG) or GnRH and cloprostenol had no obvious advantage over the conventional treatment in dairy cattle, that is GnRH alone. However, their recommendation for ovarian cysts treatment in dairy cattle is to use a single dose of GnRH followed by prostaglandin F2-alpha

(PGF2α), 10 days later.

Among the various therapies suggested for ovarian cysts, the Ovsynch treatment appears to be the most used, yet the pregnancy rates with timed inseminations following therapy with the Ovsynch treatment are low [5, 27, 54]. In addition, according to literature there are concerns of the consumers regarding the extensive use of hormones in cattle production. The treatment should be based on an accurate diagnosis. [63]. In our opinion, excessive use of hormonal products should not be encouraged but rather limited to situations where other options are inefficient or inexistent. When differentiation between follicular cyst and luteal cyst is not possible, GnRH agonists provide effective treatment against ovarian cysts. Thus, when diagnosis reveals the presence of luteal cyst, PGF2α treatment should be preferred, whereas its use against follicular cyst is less effective [14]. This treatment can generate a rate of estrus manifestation of 75% and a pregnancy rate of 66% [16]. Additionally, Khan [44] recommended luteolytic doses of PGF2α as the ideal treatment for luteal cyst and the estrus manifestation should appear within 3–5 days.

Another option for ovarian cysts treatment is the treatment with intravaginal progesterone implants for 9 to 12 days, which will decrease LH secretion and result in cyst regression and emergence of a new follicular wave, 5 days after implant insertion. This treatment restores responsiveness of the hypothalamus to the positive feedback of estradiol, resulting in normal estrus and ovulation within 7 day after the implant is removed [16].

Recently the study of Abdalla *et al.* [1] reported an improvement of the pregnancy per artificial insemination (P/AI) in cows with ovarian follicular cyst, which were pre-treated with GnRH, until a luteal structure is identified, before initiating the Ovsynch treatment regimen. However, another study reported reduced P/AI following treatment with Pre-GnRH [6].

The genetic selection can be a useful tool to control the incidence of the ovarian cysts in dairy cattle. For example, back in 2007, Canada launched a national data management system for dairy cattle health and disease, available to voluntary producers recording at least eight diseases, including ovarian cysts [47]. Casida and Chapman [19] investigated the incidence of cystic ovaries on a US Holstein herd and estimated a 0.43 heritability for the occurrence of cystic ovaries in the life of a cow. Thus, this data is useful to genetic evaluations and can provide fruitful information for selection purpose, especially for the incidence of any disease. Although the heritability rate is low, genetic selection to reduce the incidence of ovarian cysts can be successful [4]. For example, Sweden reduced the clinical incidence of ovarian cysts from 10.8% to 3.0% from 1954 to 1977 due to genetic selection [45].

As an outcome, for this particular condition, genetic selection can play an essential role in controlling it. Although the Ovsynch treatment seems to be preferred, the pregnancy rate after this treatment is relatively low. At the same time, the use of Ovsynch treatment shows no advantage over the conventional treatment: GnRH for treating follicular cysts and PGF2α for treating luteal cysts. The pre-treatment with GnRH before initiating the Ovsynch protocol when luteal structures is identified, seems to be a very good alternative for treating ovarian cysts.

CONCLUSIONS

• Ovarian cysts (follicular or luteal) in dairy cattle can be defined as anovulatory ovarian structures with a cavity greater than 20 mm in diameter in the absence of a corpus luteum characterized by a combination of signs and symptoms of hormonal disorder and ovarian dysfunction, in which the interaction of a number of genetic and environmental factors determine the heterogeneous, clinical, and biochemical phenotype;

• Therapeutic approaches should target to restore the ovarian function and to improve the pregnancy rates;

• We do not know all the aspects relating to the pathogenesis of ovarian cysts. Possibly the study of neuroendocrine feedback at the level of $Kiss1^{ARC}$ neurons in relation with ovarian cysts formation would help elucidate this detail.

CONFLICTS OF INTEREST. The author declares no conflict of interest related to this review article.

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