Ovarian cysts in cattle: a review



Nora Mimoune*, Mohamed Yassine Azzouz, Djamel Khelef and Rachid Kaidi

Abstract

Ovarian cysts (OC) are one of the major factors affecting the fertility of dairy cattle due to their negative effects on reproductive performances, causing great losses. They have been traditionally defined as anovulatory follicular structures with a diameter exceeding 20 or 25 mm, lasting at least 10 days on the ovary in the absence of a functional corpus luteum. However, in recent years, the development of ovarian ultrasound and hormonal assays, particularly progesterone (P4), have provided additional information, thus changing the definition of this disease. These methods were proposed as the most effective combination for the diagnosis of OC. Treatments are primarily based on the use of different hormones or hormonal associations. Particularly, standard treatment is GnRH. PGF_{2a} is very effective in the case of luteal cyst. However, treatment failures observed with commonly administered hormones require the use of second-line treatments. Therefore, the Ovsynch protocol and progestogen appear to be a possible alternative in OC treatment. In order to prevent OC formation and to reduce OC incidence, strategies should focus on reducing diseases and stress and optimizing food intake during dry-off and post-partum (PP) periods. Medical prevention has been proposed with the same substances commonly used in treatment (GnRH, PGF₂₂).

Key words: cyst; ovary; cows; review

Introduction

Fertility is a very complex process and the final outcome is the result of the close and well orchestrated interaction between the hypothalamus-pituitary-ovary-uterus. The complexity of this process indicates that any factors interfering with the functioning of one or more of the organs involved will also influence the overall fertility outcome (Samardžija et al., 2006; Kočila

et al., 2009; Kovács et al., 2020). Reduced fertility, as observed in modern high yielding dairy cows, is most likely due to alterations at several consecutive steps in the reproductive process (Lucy, 2001; Dobranić et al., 2008; Szenci et al., 2018). These dysfunctions cause a delay in reestablishment of normal ovarian activity after calving (Mimoune et al., 2018).

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One of the most common ovarian dysfunctions during the PP period in cattle is ovarian cysts (OC). They have been defined as fluid filled structures. ≥ 25 mm in diameter, that persist in the ovaries for at least 10 days in the absence of a functional corpus luteum (Mimoune et al., 2018; Mimoune et al., 2020). Because of the frequency of reproduction follow-up visits to a herd (1 to 2 times per month), the dynamic nature of OC and the recommendation to administer treatment quickly after diagnosis, the criterion of persistence is rarely taken into account. The reported OC incidence in dairy cattle showed a range from 6 to 20% (Silvia et al., 2002; Mimoune et al., 2017). This discrepancy can be explained by the different definitions and diagnostic methods used during screening. These rates can be even higher, given the fact that more than 60% of cows developing OC before the first ovulation following PP can recover spontaneously (Peter, 2004; Mimoune et al., 2019).

Two types of OC exist in bovine species: a follicular cyst is formed by a non-luteinized thin wall, while a luteal cyst shows signs of luteinization and contains a thick wall, and can be considered an advanced form of the follicular cyst (Garverick, 1997). In practice, the diagnosis of the nature of the cyst is complicated by the existence of intermediate forms. This distinction is important as treatment will vary depending on the type of OC diagnosed.

OCs are associated with increased calving-first insemination, calving-conception, and finally calving-calving intervals (Hooijer et al., 2001). Treatment is recommended only from 50-60 days PP in the absence of a corpus luteum and in the presence of anoestrus. However, earlier treatment would reduce the risk of persistence, improving the chances of recovery. The main treatments for OC are different hormones or hormonal combinations. Administration of GnRH

is the most widely used treatment for this condition (Hanzen et al., 2008). However, treatment failures observed with commonly administered hormones require the use of second-line treatments (Nanda et al., 1991).

In recent years, several studies on OCs have focused on the clinical characteristics (Peter, 2004), aetiology and pathogenesis (Vanholder et al., 2006; Mimoune et al., 2019), and diagnosis and treatment (Probo et al., 2011; Mimoune et al., 2017). Despite many published studies, some aspects of the disease remain unknown and inconclusive (Mimoune et al., 2019). In this present study, the basic and current knowledge of OC in cattle is presented in the form of a literature review.

Definition

As early as 1831, abnormally large ovarian follicles, which did not ovulate and which resulted in an alteration of cyclic activity, a change in sexual behaviour and subfertility, led to the coining of the term "ovarian cyst". McMutt was the first to use the term cystic in reference to persistent follicles, with a diameter of >20 mm (Coleman, 2008).

More recently, OCs are defined as anovulatory follicular structures (Cook et al., 1990; Silvia et al., 2002), with a diameter to >20 mm (Peter, 1997; Silva et al., 2012) or \geq 25 mm, persisting for at least 10 days on the ovary in the absence of a functional *corpus luteum* (Vanholder et al., 2006; Santos et al., 2009; Polat et al., 2015). It can occur in several animal species (ruminants, sows, bitches and rodents), and also in humans (Francou et al., 2008).

Some authors retain the same definition, though the figures vary. Calder et al. (1999) defined the cyst as a single follicular structure, > 20 mm in diameter or multiple structures, > 15

mm in diameter, persisting for at least 7 days with low P4 concentration. Other authors proposed as cystic every ovarian follicle that is at least 17 mm in diameter, persisting for more than 6 days, in the absence of a luteal structure, detectable by ultrasound exam (Yotov et al., 2014). This examination indicated that the follicle typically ovulates at 13–17 mm and persists at this preovulatory stage for 5–6 days, so any follicle persisting at 17 mm or more is considered cystic (Silvia et al., 2002).

It can be speculated that the OC definition differs between authors and in practice, and veterinarians generally do not perform a second examination on the animal within 10 days of the initial OC diagnosis to meet all the terms of the definition (Vanholder et al., 2006). Likewise, the significance of the presence of a corpus luteum is also difficult to assess. Some cysts can still be palpated after ovulation of another follicle and subsequent formation of a corpus luteum, indicating that they are not functional (Zulu et al., 2003). Conversely, a developing cyst may also be associated with regression of the corpus luteum (Yoshioka et al., 1996).

Ovarian cyst, cystic follicle, cystic ovarian degeneration or Cystic Ovarian Disease (COD) are some of the names assigned to this pathology. According to some authors, the term 'COD' no longer seems to be inappropriate and should be replaced by 'cystic ovarian follicle' which does not necessarily imply a disease state. This term is preferred instead of ovarian cyst because it indicates that it is the ovarian follicle and not other ovarian tissue that becomes cystic (Vanholder et al., 2006).

Classification

Depending on their functional (production of steroids) or structural characteristics, ovarian cysts can be

classified into follicular cysts (FC) or luteal cysts (LC) (Garverick, 1997; Douthwaite and Dobson, 2000; Silvia et al., 2002; Vanholder et al., 2006).

LC is associated with relatively high concentrations of P4 in the peripheral circulation. As for the FC, it produces little P4 and secretes more oestradiol (Silvia et al., 2002; Vanholder et al., 2006) in similar amounts to those of a normal follicle (Odore et al., 1999).

FC can also be distinguished from LC by rectal palpation or ultrasonography (Farin et al., 1992). They are thin-walled, single or multiple, and affect one or both ovaries (Jeffcoate et al., 1995). LC are thick-walled (> 3 mm) which have sufficiently luteinized, and are visible ultrasonographically as an echogenic structure (Vanholder et al., 2006). These cysts are usually unique on the ovary (Odore et al., 1999). They are late stage FC. In this type, thecal cells and granulosa cells spontaneously luteinize and secrete P4 (Figure 1) (Garverick, 1997).

FC are more common than LC; most cysts (70%) are follicular (Garverick, 1997), while Zemjanis (1970) and Carroll et al. (1990) reported that approximately 30 and 42% of cysts are luteal, respectively.

Another condition described different studies, the cavitary corpus luteum (CCL), which is often confused with LC, and is another form of a normal corpus luteum. More precisely, it is a corpus luteum occurring after ovulation with a central cavity of varying size, filled with fluid (Silvia et al., 2002; Vanholder et al., 2006). The cavity is 7-10 mm in diameter. Ultrasound examination can distinguish between LC and CCL (Hanzen et al., 2000). Some researchers did not find CCL in pregnant cows and concluded that this form could not support gestation, although others reported that a corpus luteum needs to produce only about 100 µg P4 to maintain gestation; therefore, CCL can support a gestational state (Coleman, 2008).

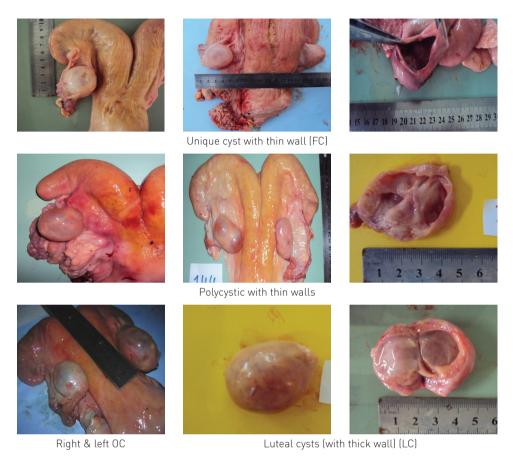


Figure 1. The different types of ovarian cysts (macroscopically)

Kastelic et al. (1990) reported, after ultrasound examination of heifers, that 79% of other forms of a normal corpus luteum contain cavities from < 2 to > 10 mm in diameter at some point in the oestrus cycle and early gestation. In the absence of gestation, CCL regresses and is considered non-pathological as long as it does not alter cycle length and does not affect fertility (Vanholder et al., 2006).

Incidence and consequence

The incidence of OC indicated after diagnosis by rectal palpation was from approximately 6 to 30% (Allrich, 2001;

Silvia et al., 2002; Peter, 2004; Santos et al., 2009), with an average frequency of 10–15% (Garverick, 1997; Calder et al., 1999).

In other studies, the incidence detected after hormonal assay or ultrasound examination was 18–29% (Gümen et al., 2003). This rate may be higher since more than 60% of OC developing before the first ovulation following PP recover spontaneously (Garverick, 1997; Peter, 2004).

Based on calving rank, age and animal production, Allrich (2001) reported the following frequencies: pluriparous: 39%, uniparous: 11%, heifers: 3–6%. Meatproducing cows have a relatively low incidence.

Osmanu (1979) found that 26% of infertile cows in Ghana had OC as the major cause. In Canada, pooled data from different studies (including 24,356 lactations) indicated an average incidence of 9.3% (Brito and Palmer, 2004). According to Silvia et al. (2002), 47% of cystic cows have two or more cysts when they are first detected and the polycystic ovary is much more common than producing multiple ovulations in normal cows. It is determined that the percentage of dairy cows that will develop OC only once in their lifetime is 10 to 14%, and of these, 35% that will be chronically affected by this pathology (Peter, 2004).

It can be concluded that there is a large divergence among authors regarding the frequency of OC, which can be explained by the definition criteria and diagnostic methods used during screening, and also by the number of animals examined.

According to Kaikimi et al. (1983), the right ovary is more affected (5.1%) than the left ovary (1.2%), and simultaneous involvement of both ovaries is estimated to occur at a frequency of 0.5%. OC are more common during the first 60 days after calving (Vanholder et al., 2006). In 70% of cases, OC occurred between 16–50 days PP with an average of 30–40 days (Kirk et al., 1982). Nanda et al. (1991) reported a high frequency of OC in the 20–150 days PP.

Waves of follicular growth occur in cystic cows with a longer or more irregular interval than in normal cows (Hamilton et al., 1995). Indeed, the undesirable effects of this condition on fertility are linked to the increase in the calving-calving interval from 22 to 64 days (Garverick, 1997; Silvia et al, 2002), to the extension of calving-1st insemination and calving-conception intervals (approximately 13 and 33 additional days, respectively) (Brito and Palmer, 2004). According to Savio et al. (1990), the intervals [calving-1st ovulation]

in cows with OC and normal cows are 58 days and 12 days, respectively. The number of inseminations per conception increases by approximately 0.8 additional inseminations compared to other unaffected cows in the herd, and the probability of culling is 20 to 50% higher.

In a study conducted in the USA, the cost associated with OC when fertility was affected including the costs of veterinary services, treatment, labour, and reform, was estimated at \$137 per lactation. The higher milk production in cystic cows did not compensate for these costs, and net losses were estimated at \$39 (Brito and Palmer, 2004).

Ovarian cyst fate

OC are dynamic structures that can regress and be replaced by new cysts (Cook et al, 1990; Hamilton et al, 1995; Yoshioka et al, 1996; Peter, 1997). The factors determining whether the OC regresses are still poorly understood (Wiltbank et al., 2002; Peter, 2004).

Based on the work of Cook et al. (1990) on the ovaries of 23 cystic cows, marked with charcoal and then removed at 10, 20 and 40 days, three different evolutions were observed. In three cases, OC persisted with a size the same as or greater than previously recorded. In most cases (20/23), the cysts regressed and were replaced by other follicles that ovulated (7/23 cases) or transformed back into a cystic structure (13/23). None of the cysts ovulated. The new ovulation was observed on the same ovary or on the contralateral ovary.

As a result, a small percentage of OC persist and are classified as "chronic cysts" (this precise diagnosis of OC can be difficult and constitutes a real challenge for veterinarians) (O'Connor, 2009). In another experimental study, Silvia et al. (2002) found that 51% of follicles ≥ 10 mm in diameter, coexisting with OC, become cystic.

The phenomenon of replacement is called "turnover of cyst" which is considered to be a very serious problem, and this lasts for a period exceeding the duration of the normal oestrous cycle. The explanation for this phenomenon remains unknown; one possibility is that the physiological conditions leading to the formation of the initial OC remain present. It is still possible that the presence of OC predisposes the follicle to evolve into a cystic structure. For this, it is important to understand how the original or the first OC formed, and how its allow for the formation of additional OCs. It is also important to remember that the fate of follicles is closely correlated with the P4 concentration. Studies have shown that 66% of cows with OC had intermediate P4 concentrations (0.1-1 ng/mL) at the time of their detection. The majority of new follicles (76%) that develop in this concentration range become cystic, while only 10% ovulate (Silvia et al., 2002; Hatler et al., 2003).

Symptoms and diagnosis

OC can be accompanied by a permanent oestrus state, which justifies its association with nymphomania or at the latest with virilism, though signs of anoestrus are most frequent, with an incidence of 62–85% (Garverick, 1997; Wiltbank et al., 2002).

Usually, the physical appearance of affected cows is not different from normal cows, although the general symptoms that may be associated with this pathology are variable: absence of tone in the genital tract, relaxation of the pelvic ligaments, elevation of tail attachment, and sudden change in milk production and development of male characteristics (Allrich, 2001).

Upon transrectal palpation, FC has a thin wall that fluctuates when touched. LC is thick-walled and is firmer to palpation than FC, although it is not as strong as a corpus luteum (Coleman, 2008). CCL resembles a normal corpus luteum but is more fluctuating, soft and formed after ovulation (Roberts, 1971). Transrectal palpation is the most frequently used method, although it does not allow precise differentiation between FC and LC (Farin et al., 1992) and studies have shown that an accurate diagnosis is only possible in 50% of cases (Farin et al., 1992; Douthwaite and Dobson, 2000). False positive diagnoses occur in about 10% of cases due to the presence of large follicles adjacent to a corpus luteum or a large CCL.

Palpation of the uterus may provide additional information. FC can be accompanied by an oedematous state of the uterus that makes it firm, or in 4% of cases of mucometrium (approximately 1 litre). A flaccid uterus can be palpated with LC. In the case of hyperoestrus, vaginal mucosa may be congested and the cervix is more or less secreting. In 60% of cases, it is open enough to allow a finger or in 16% of cases to allow a thumb to pass (Al-Dahash and David, 1977).

Ultrasound is а more reliable method of diagnosing OC, since ovarian structures can be visualized. It can easily distinguish a CCL from a LC, knowing that the maximum diameter of the central CCL cavity is < 20mm. FC is anechoic and has a wall thickness < 3 mm. The LC has luteal tissue at its periphery, is more or less regular in shape, surrounding an anechoic central cavity, with a diameter from 20 to 37.6 mm (Caroll et al., 1990; Farin et al., 1992). The average wall thickness is 5.3 mm, ranging between 3 and 9 mm compared to that of CCL which is > 5 to 10 mm (Boyd and Omran, 1991) (Figures 2 and 3).

The presence of follicles > 5 mm in diameter is more frequently observed in LC, which constitutes a complementary sign of differential diagnosis (Douthwaite and Dobson, 2000). Using these criteria, a correct diagnosis is possible in about 85% of cases. Therefore, ultrasound

examination is much more accurate in diagnosing OC type than manual palpation due to its ability to detect luteal structures (Farin et al., 1992; Douthwaite and Dobson, 2000).

Ultrasound can be combined with an analysis of the level of circulating P4 to

improve diagnosis accuracy (to 92% for FC and 82% for LC) (Douthwaite and Dobson, 2000).

FC is typically associated with a plasma concentration of <1 ng/mL P4. However, concentrations varying from 0.5 to 5 ng/ml have been used as maxi-

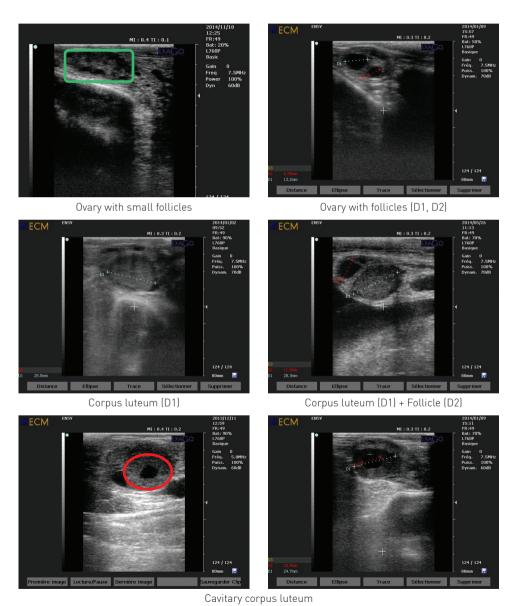


Figure 2. Normal structures on the ovary at ultrasound exam





Follicular cysts (FC)





Luteal cyst (LC)

Polycystic ovary

Figure 3. Ultrasound examination of the different types of ovarian cysts

mum concentrations of P4 for a FC (Farin et al., 1992; Ribadu et al., 1994). An average plasma P4 concentration of 0.29 ng/mL was reported by Douthwaite and Dobson (2000). LC is accompanied by a minimum plasma concentration > 1 ng/mL (Santos et al., 2009). However, P4 concentrations > 0 ng/mL (plasma) up to 10 ng/mL (milk) have been used (Ribadu et al., 1994).

Analysing the rates of P4 is not always practical or feasible. The data in the literature on OC type with the highest prevalence and cut-off values used vary considerably. In addition, the existence of intermediate forms with limited or extensive luteinization does not allow for a clear identification of OC type, which always remains subjective to personal interpretation (Vanholder et al., 2006).

Considering the threshold of ≥1 ng/mL or <1 ng/mL of plasma P4 during a period of 10 days in the absence of a corpus luteum, Carroll et al. (1990) and Bartolome et al. (2005) identified an OC as any structure with diameter > 25 mm and > 18 mm in 58% and 73% of cases, respectively (Caroll et al., 1990; Bartolome et al., 2005).

In milk, a threshold value of 2 ng/mL has been taken into account by some authors using the RIA system and a value of 1 (Nakao et al., 1983) or even 5 ng/mL (Sprecher et al., 1988) when the assay is performed by the Elisa method. Several studies have been published concerning the assay of steroids in cystic fluid, and here we cite the threshold values as listed by Braw-Tal et al. (2009): for FC > 100 ng/mL P4.

Cows with CCL have plasma P4 concentrations regardless of cavity size. In an abattoir study, CCL had higher P4 concentrations per gram of luteal tissue compared to a non-cavitary corpus luteum. It should be noted that the wall thickness in all types of cyst has a positive correlation with the concentration of P4 in plasma. The interest of the assay is in the evaluation of the degree of luteinization of the cystic structure present (Kastelic et al., 1990). In a P4 assay of milk, 42% of FC diagnosed by manual palpation were considered to be LC, despite the ability of ultrasound or the P4 assay to determine the age of the luteal tissue (OC or corpus luteum) (Caroll et al., 1990).

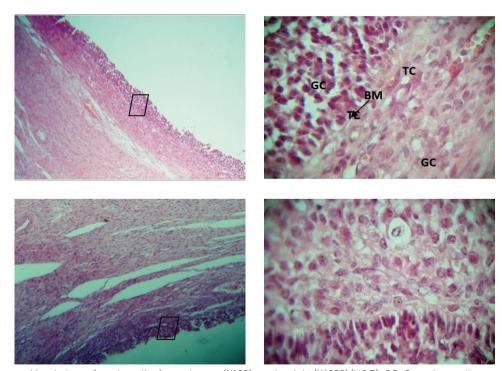
Histological studies indicate that OC has a similar morphology to the atretic follicle. In cattle, OC shows

varying degrees of theca and granulosa thickening and degeneration (Al-Dahash and David, 1977).

More recently, Braw-Tal et al. (2009), Polat et al. (2015) and Mimoune et al. (2020) described the morphological changes that are seen in parallel with the type and stage of cyst formation. These are outlined below.

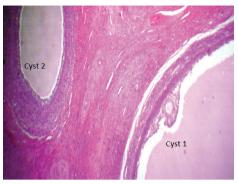
Type 1: represents young cysts (recently formed or FC)

Characterized by a partial disappearance of granulosa cells although pycnotic nuclei are rarely observed. The remaining granulosa cells preserve both morphology and function. The basement membrane is partially interrupted and allows granulosa cells to invade the internal theca. Thecal cells (theca inter-



Morphology of cystic walls, framed areas (X100), on the right (X1000) (H&E): GC: Granulosa cells, TC: theca cells, BM: basement membrane

Figure 4. Histopathological appearance of follicular cysts (FC)



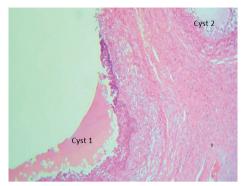
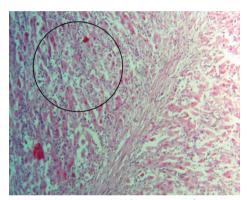
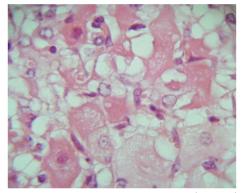


Figure 5. Histopathological appearance of polycystic ovaries (H&E, x40)





Morphology of cystic walls (H&E, left, x40), surrounded luteinisation zones are shown on the right (at x1000) Figure 6. Histopathological appearance of luteal cysts

na) are enlarged, swollen, containing a round and broad nucleus (Figures 4 and 5). These cells lose their characteristic arrangement, parallel to the basement membrane, but still retain their secre-

tory activity, as confirmed by Hamilton et al. (1995) who reported that cysts can remain functional for an extended period. These results also confirm the work of other researchers who showed that the changes occurring during this stage of the cyst differ from those seen in follicular atresia. The mechanism involved in these changes is currently unclear (Mimoune et al., 2020).

Type 2: represents LC

They have one to two layers of flattened granulosa cells surrounding

the OC cavity. The basement membrane is absent, while thecal cells are luteinized. Follicular fluid contains a high concentration of P4 (Figure 6). The cascade of events leading to this luteinization remains obscure.

Type 3: represents cysts at a very advanced stage of formation (degenerative cyst) (Braw-Tal et al., 2009)

Complete absence of granulosa cells. Thecal cells are often not recognizable morphologically; they are swollen, with a dark and small nucleus and frequently infiltrated by fibrous tissue. The level of intrafollicular hormones is negligible.

Treatment

Non-hormonal treatment: OC manual rupture and puncture

As early as 1874, manual cyst rupture was recommended for the first time in Germany by Zschokke and the cure rate was approximately 45% (Roberts, 1971). Subsequently, studies have shown that this procedure can lead to trauma and bleeding causing adhesions and contributing to reduced fertility, although it is not expensive (Kahn, 2010).

Another method consists of puncturing the OC transvaginally under ultrasound control (Ovum-pick-up, OPU) or without ultrasound. This made it possible to obtain a first oestrus and gestation at 34 and 55 days, respectively following the puncture (Cruz et al., 2004). In addition, it is less expensive than ultrasound-guided puncture and less dangerous than manual rupture (Viana et al., 2003). Simultaneous injection of GnRH has also been suggested, followed by PGF_{2α} 7 days later (Amiridis, 2009). New oestrus was observed in 100% of cases in five cows treated with GnRH simultaneously with the OC puncture. In a study combining GnRH at the puncture and PGF₂₀ 7 days later, a total pregnancy rate of 68.4% was obtained (Cruz et al., 2004). Table 1 shows the results of OC puncture as reported in different studies.

Hormonal treatment

a) hCG (human Chorionic Gonadotropin)
Protein hormone, with luteotropic
effect. induces luteinization of OC

or other follicles present; therefore, endogenous or exogenous $PGF_{2\alpha}$ causes luteolysis and a new cycle begins. Very expensive and antigenic, this protein can cause anaphylactic shock or a refractory state in cows that has been demonstrated in rabbits (Roberts, 1971).

In response to hCG, 58 to 86% of cows develop luteal tissue. These results are obtained using the different routes of administration, from intravenous to intracystic and the different combinations of these routes (Nakao et al., 1978).

b) GnRH

Kittock et al. (1973) were the first to use GnRH to treat cysts in five cows observed to be in heat 20–24 days later. GnRH causes an immediate increase in LH secretion and luteinization of the cyst. Ovulation does not occur, but other follicles present at the time of treatment may ovulate (Garverick, 1997). After luteinization, the elevated level of P4 restores the hypothalamus response to the positive feedback of oestradiol and normal cyclic ovarian activity is restored after the release of endogenous PGF₂ and the regression of OC (Garverick et al., 1976). The percentage of cows resuming cyclicality is between 72 and 85%. The interval between treatment and 1st oestrus is 19 to 23 days, and the rate of conception at 1st oestrus ranges from 46 to 58%. The reasons for the approximately 20% of cows not responding to the treatment remain unknown, as the stimulated release of

Table 1. Comparison of the results obtained during the aspiration of the contents of ovarian cysts

Treatment	Number of animals	Diagnostic method	Rate of oestrus re-establishment	Gestation rate	Reference
Aspiration+GnRH	5 FC		100%	-	Cruz et al., 2004
Aspiration	18 FC	Ultrasound Examination	94.5%	66.6%	
Aspiration+GnRH/ PGF ₂₀	29 FC	LAGITITIATION	100%	68.4%	Amiridis, 2009

LH is similar in these cows and those that responded to the treatment. However, there is no subsequent increase in the P4 level in cows not re-establishing ovarian activity (Garverick et al., 1976).

Nessan et al. (1977) performed a comparative study between hCG and manual rupture, GnRH and manual rupture, and GnRH alone. All three groups had pregnancy rates between 40– 47%, and they concluded that HCG and manual rupture are not necessary when GnRH is used. In another comparative study, buserelin (a more potent GnRH analogue) produced effects similar to those seen after treatment with GnRH. Probo et al. (2011) reported that of 133 cystic cows, 71% resumed their ovarian activity after administration of 20 µg buserelin. Lecirelin (another analogue) has also been shown to be effective in treating OC in cows, especially if administered epidurally.

Doses of GnRH between 50 and 500 µg lead to a pregnancy rate in 1st insemination between 49 and 65%, a total pregnancy rate of 70 to 100% and an average time to obtain a gestation of 34 to 87 days. Since it is less antigenic and less expensive than hCG, GnRH is the most effective conventional treatment for OC in cattle (Peter, 2004).

c) $PGF_{2\alpha}$ and hormonal associations

LC regression resulting from treatment with GnRH or hCG can be induced 7 to 9 days later using exogenous PGF_{2 α} in order to shorten the interval between treatment and oestrus and to increase the degree of oestrus synchronization. PGF_{2 α} is also the most effective treatment for LC (White and Erb, 1980).

In a study by Leslie and Bosu (1983), cows with OC at low P4 concentration that did not respond to treatment with PGF2 α alone, had a high percentage of cyst turnover compared to those with a high P4 level. In addition, 75% of cows were in oestrus within 7 days of this

treatment, and the conception rate at 1st oestrus was 66%.

Although some authors have not been able to demonstrate the benefit of simultaneous administration of GnRH and $PGF_{2\alpha}$ (Archbald et al., 1991), a recent study reported that simultaneous treatment with these two substances resulted in early oestrus re-establishment in cows with LC (50% of cows were in oestrus before a 2nd treatment with PGF₂, 14 days later). It also increased the number of cows whose FC responded to a 2nd treatment with PGF_{2a} compared to GnRH administered alone (López-Gatius and López-Bejar, 2002). This treatment is beneficial since the differentiation between FC and LC is difficult.

The Ovsynch protocol, designed for fixed-time artificial insemination (AI), has been used successfully in oestrus synchronization programmes and ovulation (Hanzen et al., 2003a; 2003b). It consists of:

- 1st injection of GnRH to stimulate follicular growth and induce ovulation of the dominant follicle, which may be present and the subsequent formation of a corpus luteum;
- an injection of PGF_{2α} 7 days later in order to stop the P4 synthesis and to allow the dominant follicle, if present, to continue to grow and to ovulate;
- a second injection of GnRH after 48 hours, to obtain better synchronization of ovulation and the need to prevent the absence of ovulation, and
- systematic AI carried out 16 to 20 hours later (Hanzen et al., 2008).

In experiments with a large dairy herd (3000 lactating cows) in Florida, a similar gestation rate (approximately 27%) was reported using this protocol in cycling cows and cystic cows (Bartolome et al., 2003). In another experiment that compared cyst aspiration and hormone treatment, cows that underwent cyst puncture followed by treatment with

GnRH and PGF_{2 α} had better recovery rates compared to those undergoing the puncture or hormone treatment only (Amiridis, 2009).

d) Progestogens

Treatment with intravaginal implants (CIDR: Controlled Intravaginal Device Release; PRID: Progesterone Releasing Intravaginal Device) for 9 to 12 days reduced the frequency of the LH pulses over the next 6 to 24 hours (Calder et al., 1999). Therefore, P4 reduces the risk of OC persistence as LH remains stored in the pituitary level and upon implant removal; GnRH stimulates LH discharge which subsequently induces ovulation (Nakao et al., 1978). P4 restores the hypothalamus's response to the positive feedback effect of oestradiol, and oestrus is followed by ovulation within 7 days of implant removal (Douthwaite and Dobson, 2000).

Oestrus rates ranging from 82 to 100% and conception rates at 1st oestrus ranging from 18 to 28% have been reported after treatment with P4 (Douthwaite and Dobson, 2000; Zulu et al., 2003). According to Iwakuma et al. (2008), treatment of OC with the CIDR implant followed by $PGF_{2\alpha}$ upon removal ensured good reproductive performances.

Another study showed that the addition of CIDR to the Ovsynch protocol had no effect on steroid production and the rate of conception. By comparing the three hormonal treatments (GnRH, hCG and PRID), Mollo et al. (2012) found suitable results (Table 2) and concluded that GnRH is the first choice to treat OC, followed by hCG. PRID is the last attempt after other treatments have failed, given its cost and the disadvantages of its application and withdrawal.

Table 2. Results obtained after hormonal treatments of OC (Mollo et al., 2012)

	GnRH	hCG	PRID
Recovery rate (%)	64	66	63
Pregnancy rate (%)	45.2	47.8	46.2
Conception rate (%)	20	22	20
Recovery time (days)	17.9	17.7	19.7

Finally, the drugs, doses and protocols recommended for the treatment of OC are described in Table 3, adapted by Brito and Palmer (2004).

Preventive treatment

Strategies to reduce OC incidence should focus on reducing diseases

Table 3. Drugs, doses, routes of administration and protocols for the treatment of OC (Brito and Palmer, 2004)

Molecule	Dose	Administration route	
Gonadorelline (GnRH)	100 μg	IM	
hCG	10 000 U	IM	
Dinoprost (PGF _{2a})	25 mg	IM	
Cloprosténol (PGF _{2a})	500 μg	IM	
Progesterone	1.9 g	Intravaginal device	

Treatment protocol

(1) GnRH (or hCG) + PGF $_{2a}$ (day 0); PGF $_{2a}$ (day 9 in the absence of oestrus) (2) Ovsynch: GnRH (day 0); PGF $_{2a}$ (day 7) GnRH (day 9); Al at fixed time, 16 hours after the last treatment with GnRH

(3) Progesterone device over 12 days (not for dairy cows)

and stress and optimizing food intake during dry-off and PP periods (Hooijer et al., 2001). In fact, calving, the period of involution and the start of lactation are at the origin of metabolic disorders linked to an increase in the production of free radicals. The administration of antioxidants (β-carotenes, selenium) may be the most effective way to eliminate or reduce the harmful effects of this stress (Ribadu et al., 2000; Aladrović et al., 2018; Folnožić et al., 2019). The regular assessment of the body condition score makes it possible to check the evolution and duration of the negative energy balance (López-Gatius and López-Bejar 2002; Folnožić et al., 2015; 2016). The longterm objective should be to select families of cows with higher milk production that are not genetically predisposed to the disease (Hooijer et al., 2001).

In order to restore ovarian activity as quickly as possible and to reduce the incidence of OC, an injection of GnRH, 10 to 15 days PP has been recommended (Zaied et al., 1980). In order to reduce the risk of metritis, the combination of this hormone with PGF_{2 α} 10–15 days later has also been recommended (Richardson, 1983). Noseir et al. (2013) found no significant effect on fertility parameters when administering a double dose of GnRH (receptal and cystorlin) on the 14th and 21st PP days, respectively.

Conclusions

This review shows the importance of OC on dairy cow fertility. The different definitions and diagnostic methods used for this pathology are presented, with the value of each hormone for the treatment of OC. This leads the veterinary practitioner to the best therapeutic choices. Finally, the strategies aiming to reduce the incidence or prevent the formation of OC are highlighted, based on the management of risk factors. Health measures should therefore be

optimized during parturition and PP in order to avoid metabolic disorders and to optimize the ration in the peri-partum.

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Ciste jajnika u goveda: pregledni članak

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Ciste jajnika (OC) jedan su od glavnih čimbenika koji utječe na plodnost mliječne stoke uslijed njihovih negativnih učinka na reproduktivne pokozatelje, prouzročeći velike ekonomske gubike. Tradicionalno se definiraju kao anovulatorne folikularne strukture promjera većeg od 20-25 mm koje perzistiraju najmanje 10 dana na jajniku u izostanku funkcionalnog žutog tijela. Međutim, posljednjih godina, uporaba ultrazvuka u dijagnostici stanja jajnika, kao i hormonskih testova, posebice progesteronskih (P4), osigurao je dodatne informacije, mijenjajujući time definiciju ove bolesti. Ove metode predložene su kao najučinkovitija dijagnostička kombinacija za dijagnozu OCa. Glavne terapije baziraju se na uporabi

različitih hormona ili njihovoj kombinaciji. Standardno liječenje posebice predstavlja uporaba GnRH. U slučaju luteinskih cista PGF₂₀ je vrlo učinkovit. Međutim, neuspjesi liječenja zamijećeni s uobičajeno primijenjenim hormonima zahtijevaju drugu i drugačiju metodu liječenja. Stoga se Ovsynch protokol i gestageni čine kao moguća alternativa u liječenju OC-a. Kako bi se spriječilo formiranje OC-a i smanjila incidencija OC-a, strategije je potrebno usredotočiti na smanjenje bolesti i stresa i optimizaciju unosa hrane tijekom suhostaja i razdoblja nakon teljenja (PP). Predložena je medicinska prevencija s istim molekulama koje se uobičajeno rabe u liječenju (GnRH, PGF, a).

Ključne riječi: cista, jajnik, krave, pregled