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Ovulatory Failure in Dairy Cows: A Review

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Abstract

A syndrome associated with conditions leading to anovular follicles or to cystic ovaries is that of ovulation failure. Condition is obviously multicausal, with some findings supporting the theory that is hereditary, and affected by the season of the year. However, most evidence is consistent with the lack of an LH surge being the critical underlying physiological change that leads to anovulatory condition. Diagnosis of anovulation can only be made retrospectively, by noting that a follicle persists longer than expected. It was reported that cows can spontaneously recover from ovulatory failure by mechanisms that still remain unclear. Improvement in energy status can reduce the period of anovulation. In the various hormonal treatments responses are not uniform, since they appear to be dependent on factors influencing the prevalence of ovulation failure. Therefore, no particular treatment can be recommended unequivocally for all cows. On the other hand, it seems that anovular cows can be successfuly synchronized and time inseminated using the protocols combining progesterone, GnRH and prostaglandin analogues.

Key words*: cow, cyst, ovary, ovulation*

Introduction

Descriptions of cystic cows and cows with small ovaries can be found in literature from the early part of the 1900's (Pearl and Surface, 1915; Albrechtsen, 1917). In 1948, Hancock proposed a way to classify patterns of reproductive activity in cattle based on types of ovarian activity. In that plan and after that cystic ovaries, ovarian follicular cysts, ovarian cysts, cystic ovary degeneration, and cystic ovarian disease (COD) were synonymous used to describe an anovulatory condition when follicular structure grows to and surpasses ovulatory size, yet fails to ovulate.

Ovulation is initiated by increase of LH surge which results with follicle rupture and release of the ovum (Espey, 1994). A syndrome associated with conditions leading to anovulation and/or to cystic ovarian disease (COD) is that of ovulation failure (Noakes *et al*., 2001). Sometimes, anovulation is observed with the follicle regressing and becoming atretic, and sometimes a follicle does not regress but, having reached the size of 1.6-2.5 cm in diameter, the follicle wall becomes luteinised. This structure functions in the same way as corpus luteum, either regressing after 17-18 days or, frequently, much earlier so that cow returns to oestrus at a shorter than normal interval (Hafez and Hafez, 2000;

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Noakes *et al*., 2001). After demise of the luteinised follicle, the subsequent oestrus will probably be followed by normal ovulation (Seguin, 1980). Such a structure will be < 2.5 cm in diameter and fluid-filled, with a rim of luteal tissue lining the follicle and with no evidence of a point of ovulation (Hafez and Hafez, 2000; Noakes *et al*., 2001; Zobel *et al*., 2012b).

Ovarian cysts

In short, bovine ovarian cysts are follicles that fail to ovulate at the time of oestrus. Condition has been identified and characterized by veterinarians and scientists for all of the past century, as been one of the most critical reproductive disorders disturbing the normal ovarian cycle in dairy cows resulting in a prolong interval from calving to conception.

Older papers defined ovarian cysts as anovulatory follicular structures as more than 2.5 cm in diameter that persists for more than 10 days, while some included additional criteria such as the absence of luteal tissue (Hancock, 1948; Kesler and Garverick, 1982; Laporte *et al*., 1994; Garverick, 1997). Since ovarian cysts represent anovulated preovulatory follicles (Garverick, 1999), it seemed logical to assume that the minimum size of an ovarian cyst would be similar to the size of a preovulatory follicle (Gumen *et al*., 2002). Therefore, a follicle > 16 mm diameter persisting over 6 days in the absence of a corpus luteum, could be classified as cyst (Gumen *et al*., 2002; Hatler *et al*., 2003). However, during the last decade the definition of cysts changed and advanced to: "Ovarian cysts are anovulated follicles at least 16 mm in diameter that persist for more than 6 days with no corpus luteum detectable by ultrasound" (Silvia et al., 2002).

Origin and causes

Two direct causes for ovarian cysts are suggested: ovulation disorder and the delay of regression, with ovulation dissorder accepted to be the main etiology of cystic ovaries (Bierschwal *et al*., 1975; Seguin, 1980; Hamilton *et al*., 1995; Isobe, 2007). This seems to be caused by deficiency of positive feedback of estrogen to the hypothalamus, leading to the lack of luteinizing hormone surge (Isobe, 2007). Some added a low circulating progesterone concentration as an important characteristic of follicular compared to luteal cysts (Roberts, 1971; Bierschwal *et al*., 1975; Seguin, 1980). Frequent rectal palpation and ultrasonography has shown that the cystic ovarian structures are not static (Garverick and Smith, 1986; Cook *et al*., 1990, 1991; Hamilton *et al*., 1995), since new follicular waves can be observed in the presence of larger ovarian follicles (Hatler *et al*., 2003). Circulating FSH appears to remain depressed following follicular deviation as the follicular cyst remains dominant (Hamilton *et al*., 1995). The continuation of the growth of the cyst seems to be due to the lack of positive feedback induced by oestradiol and thus failure of an LH/

FSH pre-ovulatory surge (Fourichon *et al*., 1999). The elevation in oestradiol affects behaviour, and cows with follicular cysts are often members of the sexually active group. Many cysts that occur in the early postpartum period self correct but some persist and further cysts can develop which may be hard to eliminate (Fourichon *et al*., 1999; Hatler *et al*., 2003).

Post partal hormonal pattern

Following calving there is a normal period of anoestrus during which uterine involution occurs. Thereafter, coordinated activity of the hypothalamic-pituitary axis and ovaries reesteblishes, culminating in ovulation and reinitiation of oestrus and ovulation (Wiltbank *et al*., 2002). Parturition is followed by resumption of FSH release and follicular development (Tennant and Peddicord, 1968; McNeilly, 1988). Richards (1980) suggested that changes in follicular function may be related to changes in numbers of gonadotropin binding sites in the follicles. However, many other studies have reported that postpartal follicles are similar to anovulatory follicles in cyclic cows in regard to concentrations of progesterone, and testosterone in follicular fluid, LH and FSH receptors in granulosa cells, and LH receptors in theca cells (Spicer *et al*., 1986; Rhind *et al*., 1992).

During the normal oestrous cycle changes in ovarian morphology occur. Near the time of oestrus, the preovulatory follicle grows and produces substantial amounts of estradiol. At later point circulating estradiol reaches a sufficient concentration and duration to induce characteristic oestrous signs and LH surge (Welsh and Johanson, 1981; Echternkamp, 1984; Spicer and Zin, 1987). It was also reported that cows with follicular cysts have high concentration of estradiol but lack an LH surge, suggesting a less responsive hypothalamic-pituitary axis (Kesler *et al*., 1979). Thus, the anovulatory condition appears to result from the lack of an LH surge (Dobson *et al*., 1987; Yoshioka *et al*., 1998). Finally, a commonly accepted hypothesis is that ovarian cystic condition is induced by neuroendocrine imbalance involving hypothalamic-hypophyseal-ovarian axis so the preovulatory follicle fails to ovulate and become cystic (Ijaz *et al*., 1987; Farin and Estill, 1993; Garverick, 1997; Peter, 1997).

Incidence

Most of the studies (López-Gatius, 2003; Lucy, 2007) reported the incidence of ovarian cysts to be between 7% and 14% of animals, presenting significant and/or one of the most significant causes of subfertility in dairy cows. López-Gatius (2003) reported ovarian cysts to be six times more frequent during the warm compared to the cool period of the year with average of 7% throughout the course of 10 years of the study period. On the other hand, Zobel *et al*. (2013) reported ovarian cysts to be almost insignificant cause of infertility for Simmental dairy cows, recorded in 4.52% of cows over the course of 5

years, and with decreasing incidence during the study period.

Anovulation

Ovulation is followed by the formation of corpus luteum, and presents a normal physiologic progression. In the absence of ovulation, the dominant follicle becomes atretic or cystic. Cows in which dominant follicle undergoes atresia have new follicular waves, leading to the selection of a new dominant follicle (Peter *et al.*, 2009b). This condition appears to occur in all cows during the prepubertal period and commonly occurs during post partal period in lactating dairy cows. Early pregnancy is also associated with follicular turnover (Ginther *et al*., 1989a). Late gestation, however, is characterized by reduced ovarian activity (Casida *et al*., 1943; 1968) due to suppressed secretion of gonadotropins (Schirar and Martinet, 1982). Resumption of ovulation in post partum dairy cows requires that all reproductive organs recover from the previous pregnancy and parturition with ovary re-establishment followed by ovulation. The recovery of each of these tissue functions is negatively influenced by negative energy balance that occurs in periparturient dairy cows (Butler, 2003; Overton, 2011).

The size of the ovulatory follicle is highly variable between cows. For example, Holstein dairy heifers were found to ovulate follicles of 14.8 ± 0.2 mm, but lactating dairy cows ovulated follicles of 17.4 ± 0.5 mm (Schilo, 1992). Zobel *et al*. (2013) reported an ovulatory size of 18.4 ± 0.3 mm in lactating Simmental cows, while Ginther *et al*. (1989a) reported an ovulatory size of 16.5 ± 0.4 mm in heifers with two follicular waves but a smaller ovulatory size follicle (13.9 ± 0.4 mm) in heifers with three follicular waves. Nevertheless, once the preovulatory follicle increases circulating estradiol concentrations to sufficient levels for an LH surge to be induced, the ovulation follows.

Duration of post partal acyclicity is influenced by nutritional status, calving season, age, and several other factors. Although uterine involution begins and ovarian follicular waves resume soon after parturition, dominant follicles fail to ovulate, due to a failure to undergo maturation which is caused by the absence of appropriate LH pulses, a prerequisite for follicular maturation (Yavas and Walton, 2000).

Causes

Many factors are known to influence anovulatory condition, including breed, parity, heredity, season, body condition, peripartum disease, a variety of nutritional effects, and an extended period of high ambient temperature. Cows experiencing dystocia or calving with twins were more likely to be classified as anovulatory (Walsh *et al*., 2007). Similarly, retained placenta and lameness were closely associated with anovulation, when accounting for the effects of parity, season and herd (Walsh

et al., 2007; Zobel *et al*., 2009; 2012a; 2013). Anovulatory conditions with growth of follicles but not to ovulatory size is characterised by a grater negative feedback effect of estradiol than found in normally cycling cows. This condition is characterized by an insensitivity of the hypothalamus to the positive feedback effects of estradiol (Wiltbank *et al.*, 2002). The exact cause of anovulation is not presently known, but it appears that an important component in the pathogenesis of this condition is inappropriate release of gonadotropin releasing hormone at the time of oestrus.

General anovulatory causes

Season

It is generally accepted that an extended period of high ambient temperature reduces the intensity of oestrous behaviour (De Rensis and Scaramuzzi, 2003), and ovulations without oestrous signs are more common during the warmer period of the year (Rodtian, 1996). The prevalence of anovulation changes with season because heat stress reduces follicular estradiol production in dairy cows (Badinga *et al*., 1993; Zobel *et al*., 2012). Animals calving in the fall were 46% less likely to be anovular than cows calving in the winter whit the risk of pregnancy not different between cycling and anovular cows (Walsh *et al*., 2007), yet significantly higher during the hot season of the year (Zobel *et al*., 2011a; b). In addition, the risk of ovulation failure was 3.9 time higher for the hot period of the year (Zobel *et al*., 2012). Calving season is a significant factor for early cyst development. Cows calving in the warm period are 2.6 times (Hansen, 1997) and 2.1 times (Zobel *et al*., 2012) more likely to develop early cyst, compared to those calving in the cool season. As summarised by López-Gatius *et al.* (2005), the factor that the most dramatically affects ovulation is season (ambient temperature and relative humidity).

Diet regimen

According to Bossis *et al*. (1999), growth rate and ovulatory follicle diameter, as well as concentrations of LH, and estradiol are reduced in heifers having lower body condition score (BCS). In dairy cattle, there is a period of negative energy balance during the first few weeks postpartum as food intake increases to meet energy demands (Roche *et al*., 2000). It seems likely that, during the early postpartum period, under nutrition may trigger a state similar to the prepubertal state in which estradiol is inhibitory to hypothalamic GnRH secretion (Schillo, 1992; Beam and Butler, 1999; Butler, 2000). Additional metabolic risk factor for ovarian cysts is over conditioned cows, leading to reduction in insulin (Vanholder *et al*., 2005). Cows with abnormal puerperium were 1.9 times more likely to develop cysts while an increase of 1 unit of BCS increased the risk 8.4 times, thereby indirectly implicating nutrition as a secondary causative factor for ovarian cysts (Lopez-Gatius *et al*., 2002). The same authors suggested that gain in

nutritional status prepartum can impair post partal ovarian function and been of major risk for cystic condition. In addition, overfeeding during the dry period predisposes the animal to fat accumulation, increased lipolysis post partum and to a lower ability of the adipose tissue to re-esterify mobilised fatty acids (Macmillan *et al*., 1996; Rukkwamsuk and Geelen, 1999).

Heredity

Although there are many predisposing factors for ovarian cysts (Melendez, 2003), it has also been reported that condition is hereditary (Roberts, 1971; Abd-Allah, 1998; Zobel *et al*., 2012). Ijaz *et al*. (1987) reported that because ovarian cysts in cows are frequently due to an inherited weak hormonal constitution, the treatments are of only temporary value. Alternatively, it is better to select against ovarian cysts to reduce their incidence. In a 20 years retrospective study of ovarian cysts in cows conducted by Cole *et al*. (1986), the incidence ranged from 0% in 1963rd to 52.3% in 1983rd. In addition and supporting the previous results, the incidence of anovulation showed a steady increase over the 5-year period with analysis of data and a pedigree of affected cows supporting the theory of hereditary condition (Zobel *et al*., 2013).

Milk yield

The occurrence of ovarian cysts is closely associated with milk production, and is more common in high producing cows (Roberts, 1971; López-Gatius *et al*., 2002). It has also been reported that increased milk production is a risk factor for this condition (Heuer *et al*., 1999). However, there are many other predisposing factors for ovarian cysts (Melendez, 2003) and contradictory opinions. Recent studies have reported higher reproductive performance, with reduce incidence of ovarian cysts and anovulatory conditions, in high milk producing herds compared to low producing herds, so concluded that this was likely due to better nutritional and reproductive management in high producing herds (LeBlanc, 2010).

Endometritis/metritis

There is general, but not unanimous, agreement that endometritis does have a detrimental effect on subsequent fertility. Erb *et al*. (1981a;b) reported that metritis prolongs calving interval directly, and in the relationship between placental retention, anovulation, and cystic ovarian disease. Curtis *et al*. (1985) noted that all reproductive disorders are interrelated in some point. Francos (1979) found an inverse relationship between the incidence of diagnosed metritis, repeat breeder and cystic cows within herds. On the other hand, Miller *et al*. (1980) reported no significant effect of mild metritis. Several studies reported a link between puerperal uterine infection and abnormal post partal ovarian function (Bosu and Peter, 1987; Opsomer *et al*., 2000; Mateus *et al*., 2002). There is some evidence that endotoxins released by bacteria in the uterus play a significant

role in the occurrence of abnormal ovarian function (Peter *et al*., 1989). Chronic uterine infection was associated with disruption of the LH surge, thus failure of ovulation (Karsch *et al*., 2002). As shown, the relationships among uterine bacteria, the immune or inflammatory response, and ovarian function are complex and require more investigation, although it appears that uterine diseases are associated with anovulatory oestrus and cystic ovarian disease (Zobel *et al*., 2011a, 2012, 2013).

Breed

In the study conducted over the 5 years in central Croatia, Zobel *et al*. (2013) reported the highest incidence of anovulation for Crossbreeds (Simmental/Holstein-Friesian), twofold less frequent for Holstein Friesian breed, and the lowest for Simmental breed. The similar data were previously reported by Erb *et al*. (1981b) and Bartlet (1986) recording the highest incidence of anovulation in the Holstein Friesian breed of cows. Results suggest a significant connection between anovulatory ratio and breed, with Crossbreeds and Holstein Friesian cows being the most affected.

Incidence

Interestingly, anovulatory oestrus is more common in swine and horses than in cattle and sheep. A study conducted by Peter *et al*. (2009a) revealed that the incidence ranged from 11% to 38% by 50 to 60 days after calving. The incidence of anovulation in repeat breeding crossbred cattle of Assam, and Croatia was 26.67 and 25.33%, respectively (Das *et al*., 2007; Zobel *et al*., 2013). The most important cause of subfertility for Simmental dairy cows in central Croatia was anovulatory oestrus diagnosed in 20.3% of cows, while ovarian cysts were diagnosed in only 4.52% of animals (Zobel *et al*., 2009; 2013) with tendency of decreasing over the 5-years period. The incidence of follicular cysts has been reported to be between 6 and 19% in lactating dairy cows (Garverick, 1997; Zobel *et al*., 2013) but is fairly rare in dairy heifers or beef cattle. Iglesia *et al*. (1996) indicated that 66.7% of anovulatory conditions were observed before 45 days postpartum. In the same time, the highest incidence of cysts has been reported for the intervals before 60 days (Erb and White, 1981), and peaking from 14 to 40 days post partum (Morrow *et al*., 1966).

Diagnosis

Diagnosis of anovulation can only be made retrospectively by noting, on transrectal palpation or ultrasonography, that a follicle persists longer than suspected (Noakes *et al*., 2001). The condition is not to be mixed with delayed ovulation characterised with cows ovulating as late as 96 to 124 hours following the first oestrous signs (Zobel *et al*., 2008). In the case of anovulation, the follicle will remain for 14-18 days luteinised before regressing, with ovary containing it rounded, smooth and

fluctuating, rather than irregular as when bearing corpus luteum (Adams *et al*., 1994). However, daily ultrasonography of the ovaries of anovulatory cows has shown that follicular growth continues to occur in a wave pattern (Adams *et al*., 1994; Melvin *et al*., 1999). On the other hand, transrectal examination as a diagnostic method has its limitations and can result in misdiagnosis, leading to inappropriate administration of hormones. The physiologic and endocrine status of the ovarian structures is best determined by measurement of progesterone concentrations (Peter *et al*., 2009b). Yet, it is positively known that follicular cysts usually have a thin wall and are fluctuant on palpation, whereas luteal cysts have a thick wall with luteal tissue and are hard when palpated (Seguin, 1980). Based on transrectal examination, ovarian cysts are classified as follicular or luteal according to the degree of luteinisation and progesterone secretion using laboratory analysis (Roberts, 1971). Ovarian cysts are not static structures since they may luteinise, persist for varying intervals, and become atretic (Garverick, 1999). Therefore, the size of ovarian cysts at the time of diagnosis is probably a reflection of the number of days this condition existed in relation to the time the diagnosis is made.

Treatment

Manual rupture of cysts via transrectal palpation is not recommended because of the reduced efficacy compared to hormonal treatment (Ijaz *et al*., 1987), and because consequential adhesions around the ovary may impair future fertility (Garverick, 1999). As Morrow *et al*. (1966) reported that nearly one half of the cows recovered from follicular cysts without treatment, it was obvious that improvement in energy status providing optimal nutrition during the transition period, and early lactation, can reduce the period of anovulation (Beam and Butler, 1999; Butler, 2000). In suckling cows, an improvement in energy status and/or reduction in suckling stimulus can increase LH pulses and reduce the time to first ovulation (Stag *et al*., 1998). For example, reducing the suckling frequency to once or twice a day has shown to increase the percentage of cows that resume cyclicity (Yavas and Walton, 2000).

Among the first dealing with hormonal treatment of anovulatory follicles, Casida *et al*. (1944) reported that administration of pituitary extracts rich in gonadotropic substances could resolve the anovulatory condition in cystic dairy cows. Since the 1970's hCG and GnRH analogues were used for the treatment of ovarian cysts. Numerous studies have shown variable results following treatment of cystic and anovular cows with an LH, GnRH, or hCG products (Bierschwal *et al*., 1975; Garverick *et al*., 1976; Ribadu *et al*., 1999). If energy requirements meet the demands of production, hormonal treatment can be used for these static follicles. Treatment of anovular lactating dairy cows with GnRH for four days after timed artificial insemination (TAI) failed to improve conception rate since only

half of the cows ovulated (Sterry *et al*., 2009). It has been reported that following treatment with GnRH ovarian cysts may luteinise, but they never ovulate (Garverick, 1999).

Various combinations of GnRH analogues and $PGF_{2á}$ have been used to initiate ovarian cyclicity. In the various hormonal treatments, responses to treatments are not uniform either across herds or cows within herds since they appeared to be highly dependent on factors influencing the prevalence of anestrus (Peter *et al*., 2009b).. Therefore, it can be concluded that no particular treatment can be recommended unequivocally for all herds.

Where there are increased numbers of cows in anovulatory oestrus, or where there is excessive loss in body condition in the post partum period, then a progesterone-based treatment is preferred (López-Gatius *et al*., 2008). The method of choice would be 7-10 days of treatment with a CIDR or PRID in addition to PGF injection 1-2 days before removal of the device (Peter *et al*., 2009b). There is an option of including GnRH at the start of the progesterone treatment to induce a new follicle wave emergence, so that the subsequent dominant follicle is present for no more than nine days to ensure optimal pregnancy rates (Lane *et al*., 2008). The same author reported that administration of 3000 IU of hCG immediately after AI resulted in ovulation in all and conception in five out of six anovulatory animals. Treatments that increase circulating progesterone concentrations can help in the treatment of condition by increasing a GnRH/LH pulses and allowing the final stages of follicular growth or resetting the hypothalamic responsiveness to the positive feedback effects of estradiol (Wiltbank *et al*., 2002; Das *et al*., 2007). As shown by Peter (2004), GnRH and hCG appear to be equally effective in the treatment of anovulatory condition. Another option for treatment of cystic ovaries is prostaglandin $F_{2á}$ and its synthetic analogues. Prostaglandins act within 2 to 5 days in over 90% of cases, and are significantly faster compared to GnRH. Prostaglandins cause lysis of luteal cysts, resulting in normal oestrus and fertility. In contrast, luteal ovarian cysts seem to be less responsive to treatment with GnRH alone (Dobson *et al*., 1997; Zobel *et al*., 2013b). In the same time, the response to prostaglandins by cows with follicular cysts is poor (Leslie and Bosu, 1983). Interestingly, it was reported that if all cysts are treated with GnRH and prostaglandins at the same time, it would not matter whether the cyst is luteal or follicular and the interval from treatment to oestrus would be reduced (Dinsmore *et al*., 1990; López-Gatius *et al*., 2012). Finally, it can be suggested that lactating cows with ovarian cysts can be successfuly synchronized and time inseminated using the protocol combining GnRH and prostaglandins by simultaneous administration of both products.

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