In the Spotlight

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CYSTIC OVARIAN FOLLICLES IN DAIRY CATTLE

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Introduction
Cystic ovarian follicles (COF) are an important cause of subfertility in modern dairy cattle. Prolongation of the calving interval and treatment costs of COF result in economic losses for the farmer. In the past COF was mainly associated with clinical symptoms such as nymphomania, and was therefore usually called Cystic Ovarian Disease (COD). Nowadays it is mainly seen as a cause of anoestrus leading to an increased interval parturition-first insemination without any obvious clinical symptoms. Therefore, we currently prefer to use the term COF instead of COD.

Definition
Cystic ovarian follicles develop when one or more follicles fail to ovulate and subsequently do not regress but maintain their growth. They commonly are defined as follicle-like structures, present on one or both ovaries, with a diameter of at least 2.5 cm for a minimum of ten days in the absence of a corpus luteum. It has become clear though that this definition needs to be revised.

First, the diameter limit is rather artificial since follicles might already become cystic at a smaller size. Moreover, many researchers demonstrated that COF are actually dynamic structures which can regress and be replaced by new cysts. The factors that determine whether a cyst will regress or not remain unknown, although changes in the mean LH concentrations seem to be involved. The required persistency of ten days is also questionable. In addition, in practice, veterinarians generally do not have the opportunity to perform a second examination of an animal ten days after the initial diagnosis.

The absence of a corpus luteum is another requirement to fulfill the definition. It is however shown that some hormonally inactive cysts do not influence the oestrous cycle and hence can be found in the presence of a corpus luteum. This kind of cysts not influencing the oestrous cycle and hence not being pathological is therefore called ‘indifferent cysts’.

As a conclusion, it is clear that due to the heterogeneity of the cysts it is very difficult to come to a generally acceptable definition. Based on our current knowledge and recent literature, COF can be defined as follicles with a diameter of at least 2 cm that are present on one or both ovaries in the absence of a corpus luteum and that clearly interfere with normal ovarian cyclicity.

Macrosopically, cysts can be subdivided into follicular and luteal cysts, which are considered to be different forms of the same disorder. Luteal cysts are by some authors believed to be follicular cysts in later stages. As follicular cysts secrete very little or no progesterone while luteal cysts clearly do, determination of progesterone in plasma or milk(fat) is the main method to make a distinction between the two types of cysts.
mainly because of the close monitoring of the postpartum cows. The cysts occurring during the early postpartum period do however have a self recovery percentage of 60% or even higher. As the treatment of COF is reported to be very successful and rather cheap, authors usually advice to treat the affected animals in stead of waiting for self recovery as the latter may in some cases lead to significantly increased intercalving intervals.

The incidence of COF also depends on parity. As described by several independent authors, the lactational incidence rate was significantly higher in multiparous cows (±15%) in comparison with heifers (±7%).

A genetic predisposition exists for COF but the heritability is rather low (0.07 to 0.12). Authors mentioned that although the heritability is low, genetic selection against COF has been successful.

Clinical signs that accompany ovarian cysts are variable. Anoestrus is most common, especially during the postpartum period. Irregular oestrous intervals, nymphomania, relaxation of the broad pelvic ligaments and development of masculine physical traits are other signs which may be present, especially later in lactation.

Pathogenesis of COF

Ovarian dysfunction, such as cysts occur most often during the early postpartum period when the transition from the noncycling condition during pregnancy to the resumption of regular cyclicity after calving takes place. It is generally accepted that cystic follicles develop due to a dysfunction of the hypothalamic-pituitary-ovarian axis. This dysfunction has a multifactorial etiology in which genetic, phenotypic and environmental factors are involved. When discussing the pathogenesis of COF, a distinction should be made between a primary defect in hypothalamic-pituitary function from the problems at the level of the ovary.

Hypothalamic-pituitary dysfunction

The most widely accepted hypothesis explaining the formation of a cyst is the one stating that the LH release from the hypothalamus-pituitary axis is altered: the pre-ovulatory LH-surge is either absent, insufficient in magnitude or occurs at the wrong time during dominant follicle maturation, finally resulting in cyst formation. The aberrant LH release does not seem to be caused by a lower GnRH content of the hypothalamus, nor by reduced GnRH receptor numbers or LH content in the pituitary.

It is believed that an altered feedback mechanism of oestrogens on the hypothalamus-pituitary can result in an aberrant GnRH/LH release and hence in cyst formation. A GnRH/LH surge occurring prematurely during follicular growth, i.e. when no follicle able to ovulate is present, can render the hypothalamus unresponsive to the feedback effect of oestradiol which results in the formation of ovarian cysts.

An altered feedback mechanism and GnRH/LH release may be attributed to factors interfering at the hypothalamic-pituitary level. Progesterone at suprabasal levels blocks the LH-surge, thereby inhibiting ovulation but increasing the LH pulse frequency. This results in an anovulatory, persistent follicle with a larger diameter and a longer lifespan than normal, very similar to COF. In early postpartum cows, the suprabasal periph- eral progesterone levels may originate from the release of progesterone by the breakdown of fat during the negative energy balance (NEB). During late gestation when cows are in the anabolic phase and are building their fat depots as energy reserves for the next lactation, they also have high progesterone levels to sustain pregnancy. As progesterone is lipophilic, it will be deposited in the fat at that time of lactation. In the early postpar- tum phase however, cows enter NEB and break down their fat reserves as a source of energy. In this way released progesterone may cause suprabasal progesterone levels and lead to COF formation.

Also ultrasound can be useful to differentiate these two types of cystic structures. Follicular cysts have a thin wall (≤3mm), and the follicular fluid is usually uniformly anechoic, while luteal cysts have a thicker wall (≥3mm) which is visible as an echogenic rim. Also, the latter often have echogenic spots and web-like luteal structures in the follicular fluid.
Other factors known to (in)directly inhibit GnRH/LH pulse secretion at the exact moment in relation to the growth and maturation of the dominant follicle, and in this way elicit cysts are stress, intrauterine infections and seasonality.

In conclusion, an aberrant LH surge is likely to be the trigger for the development of COF. Abnormal LH release seems to be caused by an altered feedback mechanism of oestrogens on the hypothalamus-pituitary axis.

Ovarian/follicular dysfunction

Also a primary dysfunction at the level of the follicle may disrupt the hypothalamic-pituitary-ovarian axis and through this cause the formation of COF. First of all, alterations in LH receptors expression and content in the follicle may cause anovulation. Besides the changes in receptors expression and content, alterations in steroidogenesis by the dominant follicle may also be involved in cystic degeneration. After all, the dominant follicle has to stimulate an LH surge at the right time in its development by producing sufficient amounts of oestrogens. Aberrations in mRNA expression of steroidogenic enzymes have been demonstrated in cystic follicles.

Apart from the changes in mRNA expression for certain receptors and steroidogenic enzymes, cell proliferation and apoptosis in the granulosa and theca interna cells also seem to be altered in some cystic follicles. In our lab we recently demonstrated that elevated NEFA levels as occurring in dominant follicles early after calving have a significant negative effect on the proliferation of granulosa and theca interna cells in vitro. Especially the saturated fatty acids like stearic acid (18:0) and palmitic acid (16:0) caused a diminished proliferation and a higher apoptosis of the oestrogen producing follicular cells. The latter may be an important factor in the pathogenesis of COF since a reduced viability of these follicular cells may be accompanied with oestrogen levels that are too low to cause an LH surge at the exact moment.

As insulin has been shown to be an important factor that stimulates follicular cells to proliferate and produce oestrogens, the remarkably steep decrease of peripheral insulin levels in high yielding dairy cows early after calving can also be seen as an attributable factor in the pathogenesis of COF. Indeed, in a field study recently published by our group we were able to demonstrate that in some cows suffering from COF, the peripheral insulin levels near the moment of cyst formation were significantly lower than in control cows which did ovulate. Earlier, we had demonstrated using intravenous glucose tolerance tests (IVGT) that in some cows suffering from COF there was no insulin response at all after the cows were given a glucose bolus.

As a conclusion, factors that have a negative effect on the production of oestrogens by the follicular granulosa and/or theca interna cells can be seen as significant contributors to the establishment of COF. High NEFA levels (especially of saturated fatty acids) and low insulin levels seem to act in this way and seem to be important risk factors to elicit COF.

Predisposing factors for COF

As mentioned earlier, COF are mainly observed in high yielding dairy cows during the first months post partum and high milk yield is generally considered as a risk factor, although not all authors agree in this. Moreover, besides the fact that a genetic predisposition for COF exists, a genetic correlation between cysts and the level of milk production has been established, indicating that an ongoing selection for production will increase the incidence of COF.

What the genetic factors are and how they promote the formation of cysts is however not known. However, the fact that cows do not develop a cyst during each lactation and during each ovarian cycle indicates that gene expression may be promoted by certain stressors like for example high milk yield and the herewith associated NEB. A lot of studies have been done in order to find a correlation between the level of milk production, the herewith associated NEB and the occurrence of COF. Although a strict consensus is lacking, we conclude from the literature that a link seems to exist between COF and the magnitude and/or duration of the NEB accompanying the current level of milk production. Etiologic factors involved may be lowered levels of glucose, insulin and IGF1 or elevated NEFA levels as explained in more detail earlier. Other significant risk factors are parity, puerperal diseases like metritis and clinical mastitis and (extreme) stress factors.

In conclusion, it can be stated that factors influencing the development of COF are still not fully understood. A major problem is that most studies measure hormone levels only after the condition had been diagnosed. Moreover, significant correlations do not necessarily indicate a causative relationship.

Treatment of COF

Once the diagnosis of COF is made, the clinician has to take the decision either to do nothing and hope for spontaneous recovery, to administer a general hormonal treatment, or to try to differentiate the type of cyst and administer a more specific treatment. Re-
Regardless of the treatment decision, the aim of the therapy is to re-establish normal oestrous cycles as soon as possible by choosing the most economical treatment. It has been demonstrated that it usually is more economical to treat ovarian cysts than to hope for a spontaneous recovery.

On the basis of the hypothesis that an absence of the LH pulse is the primary cause of COF, general treatment of cows affected by COF is directed to stimulate luteinization of the cyst which is usually followed by the re-establishment of a normal oestrous cycle. Biological preparations high in LH-like activity (e.g. human chorionic gonadotrophin) and exogenous GnRH, which acts on the pituitary gland to cause the release of endogenous LH, have been widely and effectively used for the treatment of both follicular and luteal cysts. Results of both treatments are comparable. Around 80% of the treated cows exhibit a fertile oestrus within 16 to 30 days, although pregnancy rates are slightly lower in comparison with those of normal cows. Since both types (luteal and follicular) of cysts respond similarly to this kind of treatment, differentiation is not necessary and authors agree that this approach remains the best initial therapy for the majority of cows with COF regardless of their type.

Prostaglandin therapy is also used to treat cows with luteal cysts. The response of ovarian cysts to this kind of treatment depends on the presence of luteal tissue and the veterinarian’s ability to recognize it. Because palpation per rectum has been reported to be an inaccurate method for differentiation, the diagnosis has to be based on the determination of progesterone in plasma or milk, or on the use of ultrasonography. Although the treatment with luteolytic drugs results in a shorter interval to a fertile oestrus, the cost-benefit evaluation of this kind of treatment has to incorporate the surplus costs of the immediate cyst differentiation. In this regard, it has been demonstrated that the practice of identifying all cysts as either follicular or luteal prior to treatment is questionable from an economic point of view. It has also been suggested that the use of prostaglandins given 9 to 14 days after GnRH may shorten the interval from treatment to the first fertile oestrus by about 12 days, yielding shorter intervals to conception than when GnRH is used alone. While doing the latter, one should take into account the cost of the double treatment which is another economical drawback. Cows not responding to GnRH treatment can be treated with progesterone with fairly good results. Although the mechanism by which progesterone causes regression of the ovarian cyst is not well established, it has been suggested that this treatment suppresses the release of LH, resulting in an accumulation in the pituitary and leading to an enhanced surge of LH when the progesterone treatment is withdrawn.

As the treatment results by simply injecting affected cows with GnRH or LH-agonists are reported to be relatively high, treatments based on (manual) rupture of the cyst are currently seen as outdated. Rupturing the cyst may lead to excessive bleeding especially in luteal cysts, and/or in the excessive formation of fibrin leading to the establishment of adhesions involving the ovary. The latter may negatively affect pregnancy rates once the cows are inseminated.
References


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