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Cystic Ovarian Follicles in Cattle: A Review

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Abstract

Cystic ovarian follicles are considered as important causes of reproductive failure in cattle. Economic loss to the dairy industry is mainly due to increases in days open in the postpartum period, and subsequent increases in culling rate. The disease process is a consequence of a mature ovarian follicle that fails to ovulate at the appointed time in the estrous cycle. Recent studies suggest that this anovulatory ovarian follicular structure may persist as a dominant structure, preventing further follicular growth. Alternatively, it may be replaced by another cystic follicle or it may regress, allowing initiation of a follicular wave followed by the development of a dominant follicle and ovulation. In certain cases, these cystic follicular structures are luteinized and secrete progesterone.

Our understanding of the etiology and treatment for cystic ovarian follicle is not complete at this time; however, it is critical to consider the hypotheses developed in recent years. Past findings suggested that perturbation of the hypothalamo-hypophyseal-ovarian (HHO) axis, due to many exogenous and endogenous factors, caused anovulation. One such major perturbation may be aberrant changes in the receptor expression in the HHO axis for the hormones involved in maturation, deviation, dominance and ovulation of the follicle. Besides receptors, conditions such as insensitivity of the hypothalamus to the positive feedback effect of estradiol may have a role in the etiology. Based on studies with experimentally induced and naturally occurring cystic ovarian follicles, insufficient, inadequate and inappropriate timing of luteinizing hormone (LH) release and levels around the time of ovulation has been suggested as the major cause(s) for ovulation failure. However, not all studies support this hypothesis. Hitherto, hormonal preparations that release LH from the anterior pituitary, or that have LH-like action, are used to treat cysts. Gonadotropin-releasing hormone (GnRH) fits the former category, and human chorionic hormone (hCG) the latter group. However, recent studies suggest that correcting LH deficiency may not be an efficient protocol based on the observation that there was abundance of LH in cows after formation of cystic ovarian follicles. Cystic ovarian follicles that are heavily luteinized respond to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$).

Résumé

Les follicules ovariens kystiques sont considérés comme une cause importante de l'échec reproducteur chez les bovins. Les pertes économiques encourues par l'industrie laitière sont reliées principalement à l'augmentation de la durée de la période ouverte après le vêlage et à l'augmentation subséquente du taux de réforme. La maladie prend place lorsqu'un follicule ovarien mature n'ovule pas au moment approprié dans le cycle oestral. Des études récentes suggèrent que cette structure folliculaire ovarienne anovulatoire peut demeurer dominante et prévenir toute autre croissance folliculaire. Il peut aussi arriver que cette structure soit remplacée par un autre follicule kystique ou qu'elle régresse permettant l'initiation d'une autre vague folliculaire suivie du développement d'un follicule dominant et de l'ovulation. Dans certains cas, ces structures folliculaires kystiques sont lutéinisées et sécrètent de la progestérone.

Notre compréhension de l'étiologie et du traitement des follicules ovariens kystiques est présentement incomplète. Il est toutefois important de considérer les

hypothèses développées récemment. Les résultats antécédents suggéraient qu'une perturbation de l'axe hypothalamo-hypophyso-ovarien (HHO), causée par plusieurs facteurs endogènes et exogènes, entraînait l'anovulation. Une source possible de perturbation impliquerait des changements anormaux dans l'axe HHO au niveau de l'expression des récepteurs d'hormones impliquées dans la maturation, la déviation, la dominance et l'ovulation du follicule. Au-delà des récepteurs, l'insensibilité hypothalamique à la rétroaction positive de l'estradiol pourrait aussi jouer un rôle dans l'étiologie. Sur la base d'études impliquant des follicules ovariens kystiques présents naturellement ou induits expérimentalement, il semble qu'une cause majeure d'échec de l'ovulation soit associée à la production insuffisante, inadéquate et au mauvais moment de l'hormone lutéinique (LH) au moment de l'ovulation. Toutefois, toutes les études ne supportent pas cette hypothèse. Des préparations hormonales, qui déclenchent la production de la LH à partir de la glande pituitaire antérieure ou qui ont un mode d'action similaire à la LH, sont donc utilisées pour traiter les kystes ovariens. La gonadoréline (GnRH) est un exemple d'une hormone pituitaire, alors que l'hormone gonadotrophine chorionique humaine est un exemple d'hormone à mode d'action similaire à la LH. Toutefois, des études récentes semblent indiquer que l'ajustement des niveaux de la LH n'est possiblement pas un bon plan car on observe une grande quantité de LH chez les vaches après la formation de follicules ovariens kystiques. Les follicules ovariens kystiques qui sont fortement lutéinisés réagissent à la prostaglandine $F_{2\alpha}$ ($PGF_{2\alpha}$).

Introduction

Ovarian follicular growth occurs in two or three waves during the normal bovine estrous cycle.[39,41,45] Each wave is characterized by recruitment of 2-6 follicles, 4-5 mm in size, followed by selection of one follicle that grows to become a dominant follicle. A recent review has provided a simple model to explain the relationship between action of hormones and the growth of follicles from emergence to ovulation.[45] In 10-15% of cases, this dominant follicle(s) fails to ovulate and continues to grow into cystic follicle(s). Cystic follicles are one of the most common causes of reproductive failure in cattle.[6,32,48] A cystic follicle is defined as an anovulatory follicle-like structure (greater than 2 cm in diameter) that may persist on the ovary (usually for more than 10 days) with or without the presence of a corpus luteum.[32] Currently, this structure is believed to be dynamic in nature, and spontaneous recovery occurs in some cases.[9] However, in certain cases these structures persist on one or both ovaries resulting in an abnormal reproductive function.[34] This condition can result in significant economic losses to the dairy industry due to both increased calving to conception and calving intervals. Cystic follicles reportedly cause the number of days open to increase by 22 to 64 days, resulting in an estimated economic loss of $137 per lactation.[14] In addition, cows affected may be at greater risk of being culled because of poor reproductive performance. It is most common in milking dairy cows, however, it has also been diagnosed in heifers, dry cows and beef cows.

The mechanisms leading to follicular cysts have been the object of speculation and research for many years,[45] but remain poorly understood. It is believed that the condition has a multifactorial etiology with a number of clinical, environmental and hereditary factors responsible for the disease process.[2,6,10,19,33,46-49] Regardless of the causes, the dominant follicle fails to ovulate and becomes an anovulatory cystic structure. This dominant follicle is recruited from the cohort of follicles by a yet unknown mechanism. Earlier we have discussed the pathogenesis, diagnosis and treatment of the condition, including the process of folliculogenesis and ovulation.[46,47] The purpose of this review is to present advances that have been made in our understanding of pathogenesis, fate and treatment of cystic follicles.

Pathogenesis

Hypothalamic-hypophysial dysfunction

The most widely accepted hypothesis involves a neuroendocrinological dysfunction of the hypothalamic-pituitary-gonadal axis.[2,6-8,19,32,34] As per this hypothesis, the primary cause of cystic follicles is a deficiency in the preovulatory surge-like release of luteinizing hormone (LH), or an aberrant release pattern of this hormone. It has been established that the preovulatory follicles secrete estrogens that cause positive feedback on the hypothalamo-hypophysial axis to release LH responsible for ovulation. It is believed that aberration in this process can result in the failure or inadequate release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. The hypophysis response to this event is one of either inadequate or inappropriate timing in the release of LH. Furthermore, there is also lack of hypophyseal responsiveness or refractoriness to the positive-feedback effect of estrogens on gonadotropin release. Besides the hypophysis, the insensitivity of the hypothalamus to the positive feed-back effect of estradiol may contribute to ovulatory failure.[45] Based on this concept, a model has been suggested to explain the formation of follicular cysts.[45]

Another review suggested that the magnitude and timing of LH surge depends on the re-establishment of estrogen-mediated positive feedback effect at the hypothalamus.[46] Besides the irregularities in this surge, the LH pulse pattern during the periovulatory period might

have a critical role to play in the successful process of ovulation. The exact role of LH in the disease process is still not clearly understood.[14] Using a well-established model,[18] cystic follicles were induced in heifers to determine the subtle, but yet critical, changes in LH around the time of expected ovulation, and the findings suggested that the reduction in LH pulses may be involved in anovulation.[36]

Ovarian dysfunction

Studies in the past suggested the alterations in the receptor expression and content, particularly for LH, may be a factor in the process of anovulation. A recent report, based on steroid receptor content in cysts, suggested that alteration in the steroid receptors, particularly progestins and estrogens, may result in anovulation.[25]

Despite much research, the pathogenesis of cystic follicles remains inconclusive, and further studies are needed to address this condition, among other issues facing the dairy industry. The LH-induced transition of a preovulatory follicle to one that can ovulate is a complex multi-gene, multi-step process in which timing is of the essence.[38] Some of the genes involved in the process are known. Many genes involved in this process remain to be documented to fully understand the process of ovulation and the molecular pathology around anovulation.

Predisposing factors

Several factors have been linked to the development of cystic follicles in cows.[1,17,48] Some of these factors have a confirmed role in the pathogenesis, while others are speculative, and their exact role or mechanisms are ill defined. The heritability of this condition is believed to be low. However, it seems to occur more frequently in certain bloodlines of cattle. It is possible that in breeds with genetic predisposition to this condition, selection to increase milk production can increase the incidence.[12] This condition has been observed more frequently in older cows during their second to fifth lactation. The occurrence is also believed to be higher during winter months. Lack of exercise and feeding rations high in protein to increase milk production are thought to be contributing factors in the development of cystic follicles during winter months. However, photoperiod was not determined to affect hypothalamic function that may predispose cows to cystic follicles. The role of nutrition and milk production is interrelated. This condition is commonly seen in high-producing cows[45] during early lactation. At this time, much of the cow's energy is devoted to milk production, in addition to basic maintenance requirements, leaving the cow vulnerable to metabolic and endocrine disturbances. It is becoming clear that there exists a negative relationship between high milk production and reproductive efficiency.[20] Occurrence of cystic follicles in high-milk-producing cows[12] may be one of the factors contributing to this relationship. With regard to metabolic disorders, it has been suggested that insulin resistance attended by a hyperinsulinemia may not play a role in the pathogenesis of cystic follicles in cows, but lower insulin response may have a role.[26]

The role of phytoestrogens is not fully elucidated. However, it has been suggested that forages containing high concentrations of estrogenic compounds might be associated with a higher incidence of cystic follicles.[37] Another contributing factor that may play a role in the pathogenesis is delayed uterine involution and early postpartum problems, such as retained fetal membranes, milk fever and metritis.[2] It is suggested that postpartum uterine infections might stimulate prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and cortisol secretion that predisposes cows to follicular cysts.[2] In addition, bacterial endotoxins released in the uterus may stimulate cortisol secretion, which in turn suppresses preovulatory LH surge release.[2] In this regard, it has been shown that endotoxin can modulate the preovulatory LH surge release in heifers[27,29,30,42] by an unknown mechanism. High-producing cows under such stressors are prone to various reproductive problems, especially cystic follicles. The role of stress in the pathogenesis of cystic follicles is believed to be mediated by the release of endogenous cortisol through inhibition of LH release. Endogenous opioid peptides produced in the hypophysis and brain are thought to block the estrogen-induced LH surge and the release of hypothalamic GnRH.[21] Stress may mimic the action of these peptides in postpartum cows. Additional evidence for the role of corticotropins in the pathogenesis of this disease is apparent by the ability to experimentally induce the disease in cows by the administration of ACTH.[18,36]

Fate of Cystic Follicles

Follicular growth occurs while cystic follicles are present, which is preceded by the initiation of a follicular wave by transient increases in serum follicle stimulating hormone (FSH) concentrations. Expression of receptor content for certain hormones in granulosa cells of follicular cysts have been characterized and compared to that in dominant follicles.[3] The findings suggested that dominant bovine ovarian follicular cysts expressed increased levels of messenger RNAs for luteinizing hormone receptor and 3β-hydroxysteroid dehydrogenase Δ^4 and Δ^5 isomerase compared to normal dominant follicles. In both spontaneously and hormonally induced cysts, notwithstanding the uniqueness of ovarian morphology in each case, the occurrence of intermittent follicular waves has been a constant motif.[45] This initiation may

occur in irregular and long intervals compared to cows with normal estrous cycles.[9] The follicular cysts may undergo any of the following changes by yet unknown mechanisms. Either they may lose dominance and a new dominant follicle may develop and ovulate, or they may be replaced by yet another cystic follicle. In certain cases, the cystic follicle may be luteinized or can simply persist as a cystic follicle. All but the first condition are not favorable, and render the affected animals infertile.

Diagnosis

Diagnosis of cystic ovarian disease can be made based on behavioral abnormalities, rectal palpation, transrectal ultrasonography of the ovaries and reproductive tract, and plasma or milk progesterone assays.[5,10,23,24,28,31,32,43] In a practice survey used to determine the main criteria which veterinarians used to diagnose cystic follicles in cows, the behavior of the cow (with no distinction between nymphomania or anestrus), wall thickness of the cystic follicle as determined by ultrasonography, and ovarian size as determined by rectal palpation were used by the majority of veterinarians.[24] Ultrasonographic characteristics of cystic follicles have been determined recently.[10] This report suggested that 74% of cystic follicles and 85% of cystic follicles that are luteinized could be diagnosed accurately using ultrasonography.[10] Combining ultrasonography, rectal palpation and plasma progesterone concentrations have been used to improve accuracy of the diagnosis.[10] Ultrasonography and plasma progesterone concentrations were used most accurately to determine the hormonal characteristics of the cysts.[5] It was found that plasma progesterone concentrations are positively correlated with thickness of the cystic follicle wall.[5]

Treatment

About 60% of cows with cystic follicles recover spontaneously before the first postpartum ovulation.[32] Regardless of this spontaneous recovery, increases in days open still remains a problem in the dairy industry. Prior to the advent of hormonal preparations, manual rupture of the cystic follicles during rectal palpation was practiced to treat the condition at postpartum routine reproductive examination. This method of treatment cannot be recommended because it can cause trauma or hemorrhage, which might result in ovarobursal adhesions.

Hormones that induce the release of LH from the anterior pituitary (e.g., GnRH), or have LH-like action (e.g., human chorionic gonadotropin [hCG]), or LH itself are still used to treat follicular cysts.[33] The former two are preferred over the latter one. Because of its small molecular size, GnRH is not likely to stimulate an immune reaction, which occasionally occurs after hCG or LH administration.[32] This suggestion may need further verification. Following GnRH treatment, a surge-like release of LH occurs. In most cases, luteinization of the cystic follicles occurs followed by their spontaneous luteolysis 16 to 18 days later.[32] In certain cases, a luteolytic dose of $PGF_{2\alpha}$ is necessary to initiate a follicular wave and shorten the recovery process. A recent study tested the efficacy of GnRH treatment for cystic follicles.[15] The findings of this study suggested there was no difference between treated and control cows in the interval from treatment to the observation of a CL or the disappearance of a cystic follicle.[15] This lack of difference between the treated and control group may suggest that GnRH may not be as effective as it was thought to be,[14,15] and further confirms the process of spontaneous recovery of cystic follicular conditions. Another study attempted to determine the influence of time of treatment with GnRH in the postpartum period on the recovery rate of cystic follicular conditions.[11] In this field study, cows with cystic follicles were treated with a single dose of 500 μg GnRH intramuscularly (diagnosed either before or after day 60 after parturition). There was no difference between treatment groups in the interval between treatment and first insemination. The conception rates between the groups were also similar, suggesting that GnRH treatment was effective irrespective of the timing of diagnosis and treatment.[11] The response to treatment was not compared to a control group, hence, it is difficult to determine the efficacy of the GnRH treatment. It is widely accepted that this compound is effective when the diagnosis is accurate. Further research is needed to explore the use of other treatment modalities (other than hormones) for cystic follicles.

The compound hCG has been used successfully for treatment of cystic follicles that failed to respond to GnRH treatment and have not luteinized.[32] Since this compound has LH-like action, it acts directly on the ovary and, in most cases, causes luteinization of the cysts with subsequent increase in plasma progesterone concentrations. This luteinized structure may have to be treated with $PGF_{2\alpha}$ (refer below).

$PGF_{2\alpha}$ or its analogues are the treatment of choice for cystic follicles that are luteinized.[32] $PGF_{2\alpha}$ causes regression of these cystic follicles, with estrus occurring within 8 days in 87 to 96% of treated cows. Recently, a study evaluated two combinations of GnRH with $PGF_{2\alpha}$ (day 0 - GnRH; day 7 - $PGF_{2\alpha}$; day 9 - GnRH and timed insemination 16 hours later, or day 0 - GnRH; day 7 - $PGF_{2\alpha}$, and inseminate at the induced estrus within 7 days) as treatment for cystic follicular conditons.[1] The rationale behind these regimens is twofold: 1) to treat the cystic follicles successfully, and 2) to make timed-insemination possible to eliminate estrus detection efforts in lactating cattle that have cystic follicles. The

findings revealed a few important aspects regarding conception rate and pregnancy rate in response to treatment. The conception rate was found to be better in the former group (fixed-time insemination), however, the pregnancy rate was not different between the groups. Control-group cows (cows without cystic follicles) that received the first treatment had a better pregnancy rate despite a lower conception rate. Definitely, cows with cystic follicles had reduced pregnancy rates despite the treatment, and the benefit derived from this method (OvSynch treatment) may be the fact that estrus detection is eliminated in cows with cystic follicles. Before this treatment can be recommended, the economics of this protocol must be considered in relation to the reduction in open intervals in these cows.

Administration of exogenous progesterone as a treatment for cows with cystic follicles is not new.[48] Findings from recent mechanistic studies[7,8] support this concept. In the last decade, a few studies have tried to determine the efficacy of progesterone treatment for cows with cystic follicles, particularly regarding dosage, duration of treatment, and ovarian and hormonal changes in response to progesterone administration.[4,5,13,16,44] However, much debate within the veterinary community has been centered around its use in dairy cows. Although we are not encouraging its use in this review, this compound has potential to re-establish hypothalamic function and normal cyclicity in cows with cystic follicles. In one study, exogenous progesterone administered by using two progesterone-releasing intravaginal devices (PRID) containing 1.55 g of progesterone inserted in the vagina for 9 days, decreased mean LH and LH pulse frequency, and increased FSH concentrations compared to cystic cows not treated with PRID. These hormonal changes following PRID treatment resulted in the initiation of ovulatory follicular waves, whereas follicular waves in non-treated cows with cystic follicles did not culminate in ovulation.[4] Another study evaluated the efficacy of progesterone in inducing ovulation in nine beef cows with persistent cystic follicles. A single controlled internal drug release device (CIDR) containing 1.9 g progesterone was used intravaginally for 14 days.[44] Results of this study suggested that using a single CIDR for 14 days was sufficient for restoration of normal cyclicity in all affected cows. An important observation from this study was that CIDR treatment induces atresia of estrogen-active cystic follicles, but has little or no effect on estrogen-inactive or cystic follicles that are luteinized. Although atresia of persistent follicles occurs within a short period after progesterone treatment, the above studies suggest that successful resolution of the condition requires daily administration of progesterone for 10 to 14 days, or treatment with a progesterone-releasing intravaginal device for 9 to 14 days.

Conclusions

Cystic follicles are one of the major causes of infertility. The disease process is a consequence of a mature ovarian follicle that fails to ovulate at the appointed time in the estrous cycle. Recent studies suggest that this anovulatory ovarian follicular structure may either persist as a dominant structure preventing further follicular growth, or it may be replaced by another cystic follicle, or it may regress, allowing the initiation of a follicular wave followed by the development of a dominant follicle and ovulation. In certain cases, these cystic follicular structures get luteinized and secrete progesterone. Despite much research, the pathogenesis of cystic follicles remains inconclusive, and further studies are needed to address this condition among other issues facing the dairy industry.

Response to current treatment protocols can be improved by proper diagnosis and correct treatment. As guardians of animal health, we are accountable for the production of wholesome meat, and we are responsible for the careful use of hormones in animal husbandry management. Consumers' concerns must also be considered.[35] The only way we can contribute in this process is to prevent the occurrence of cystic follicles by understanding the disease mechanism fully and limit the unwarranted use of hormones to treat such conditions. The role of puerperal uterine infection on reproductive performance has surfaced again in the literature,[22,40] particularly in the initiation of follicular growth and ovulation. Agencies such as the USDA and the veterinary/agriculture schools that administer research funds should support research that includes mechanistic studies aimed at elucidating the disease process of this condition. These studies would allow us to understand the mechanism of this disease process (gene expression), and produce cows that will ovulate easily without developing cystic follicles.[34]

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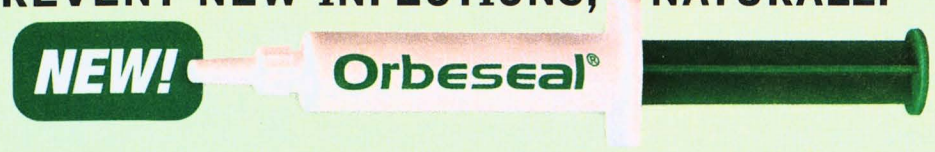
ARE YOU DOING ENOUGH TO HELP HER LOCK OUT NEW INFECTIONS?

Orbeseal® is the first and only internal teat sealant that mimics the natural keratin plug. Since teats don't always close naturally, Orbeseal provides a physical barrier against mastitis-causing bacteria, locking them out for the entire dry period.

Research has shown that cows treated with Orbeseal and a dry cow treatment program* had a significant reduction of clinical mastitis, even in a well-managed dry cow environment, when compared to a conventional dry cow treatment program alone.[1] That can mean fewer cows to treat for mastitis, optimal production, higher milk premiums and, ultimately, greater profit. Orbeseal is easy to use since only one tube per teat is required. Orbeseal, the next step in dry cow management.

PREVENT NEW INFECTIONS, NATURALLY™



Orbeseal®

Call 866-ORBESEAL (866-672-3732) or contact your Pfizer representative to learn more about how you can help your clients prevent new mastitis infections.

Pfizer Animal Health

TAKE TIME—OBSERVE LABEL DIRECTIONS

*Dry cow treatment program includes a dry cow antibiotic and a mastitis vaccine.

[1]Godden S., et al. Effectiveness of an Internal Teat Seal in the Prevention of New Intramammary Infections During the Dry and Early Lactation Periods in Dairy Cows When Used with a Dry Cow Intramammary Antibiotic. Submitted for publication. 2003. Orbeseal® is a registered trademark and Prevent New Infections, Naturally™ is a trademark of Pfizer Inc.