Cystic ovarian disease in dairy cattle

J. D. Smith

Department of Pathobiology and Population Medicine, College of Veterinary Medicine,

Mississippi State University, Mississippi State, MS, USA

Abstract

Practitioners involved in the delivery of veterinary care and who provide consultation to dairy cattle owners must be able to effectively diagnose and treat common conditions which impact the economic stability of the dairy enterprise. This manuscript provides the practitioner with the information to understand the pathophysiology of cystic ovarian disease, choose an appropriate treatment and suggest possible management changes to minimize the economic impact of this disorder.

Keywords: Cystic ovarian disease; anestrus; infertility; GnRH; cattle

Introduction

Cystic ovarian disease (COD) has been recognized as a frequent cause of subfertility and poor reproductive efficiency in cattle for almost 100 years and is still considered to be one of the most economically important reproductive conditions affecting dairy cattle worldwide. The major causes of economic loss are due to increased days open in the postpartum period which extends the calving interval, costs associated with treatment and higher culling rates in affected animals.[1,2] Cystic ovarian disease has also been shown to decrease the pregnancy rate to subsequent AI which leads to an increase in services per conception resulting in increased semen costs.[3]

Terms which have been used to describe the condition of persistent anovulation of preovulatory follicles include: cystic ovarian disease, cystic ovarian follicles, cystic ovarian degeneration and cystic ovaries. The most common term used in the literature to describe this condition is cystic ovarian disease. As we understand more about this

condition and management practices have changed we should revisit the use of the term cystic ovarian disease. The most recent term used to describe this ovarian dysfunction is cystic ovarian follicles (COF).[1,3] Since "cysts" are often diagnosed in the absence of any obvious clinical signs the term "disease" should likely be replaced by "follicles" as it more accurately describes the condition.[3]

Definition

The classical definition of COD in cattle is the presence of an anovulatory structure on the ovary which is > 2.5cm in diameter and has persisted for at least 10 days in the absence of a corpus luteum (CL).[4] As more knowledge is gained regarding COD the previous definition requires refinement. The size limit of 2.5cm is arbitrary and would exclude cystic follicles which are smaller than 2.5cm. The dominant follicle of dairy cattle typically ovulates on average at a size of 1.6-1.9cm.[3] The classic definition that requires presence for 10 days should also be questioned due to the fact that cystic ovarian follicles have been shown to be dynamic structures which change over the course of time. Also cows diagnosed with COD are generally not palpated again in 10 days to totally fulfill the classical definition. The necessity for the absence of a CL is also not universally fulfilled. Cysts which are non-steroidogenic and thus hormonally inactive may not influence the estrous cycle and thus could be found in the presence of a CL. Most cows today however are diagnosed with COD on the basis of a single rectal palpation or ultrasound examination and no attempt is made to assure the structure has been present for 10 days in the absence of a CL.

A recent term and definition put forth in the literature to more accurately describe this condition is cystic ovarian follicles. Cystic ovarian follicles are defined as follicles

with a diameter of at least 2 cm that are present on one or both ovaries in the absence of any active luteal tissue and that clearly interferes with normal ovarian cyclicity.[3] This definition more clearly defines the condition in relation to our current understanding and its impact on reproduction.

Cysts are further classified as being follicular cysts or luteal cysts depending on the degree of lutenization and the level of progesterone secretion. Both are considered to be different forms of the same condition with luteal cysts being a follicular cyst which has undergone some lutenization.[2] Follicular cysts do not secrete progesterone whereas luteal cysts secrete varying amounts of progesterone however an absolute threshold has not been determined.[3] The ability to accurately classify each cyst is subject to personal interpretation based on clinical as well as laboratory findings.

Ultrasound can be a very useful tool with which to gather information regarding the classification of cysts. Follicular cysts typically have a thin wall ($\leq$ 3 mm) whereas luteal cysts typically have a thicker wall ($\geq$ 3 mm). The follicular fluid is often hypoechoic in follicular cysts whereas in luteal cysts it may contain echogenic strands creating a web-like appearance.[5]

Incidence

The incidence of COD in dairy cattle varies amongst several studies but is typically between 5-19% with mean of 10-12%.[2] The incidence of COD could likely be even higher based on the findings that as many as 60% of cows that develop COD recover spontaneously prior to their first postpartum ovulation and could easily remain undiagnosed. The majority of COD is diagnosed by routine rectal palpations during the first 60 days postpartum at which time cows are being examined prior to breeding. Cases

are also commonly diagnosed between 120-210 days postpartum. These cases are typically diagnosed in cows which have been presented for examination after extended periods of anestrus.

There is a genetic predisposition for COD in dairy cattle, however the heritability is low at 0.07 to 0.12.[6,7] Cystic ovarian disease seems to occur more often in certain cow families. Genetic selection attempting to remove sires who produced daughters that developed COD from the breeding pool has been shown to significantly reduce the incidence of COD in Swedish herds.[3] Reduction in the incidence from 10% to 3% was achieved by selection against sires that produced daughters with COD.[8] Genetic selection as a prevention for COD will be a lengthy endeavor due to the low heritability but can be effective.

With routine use of synchronization programs (i.e., Pre-sync, Ovsync) during the voluntary waiting period to synchronize the first postpartum AI the incidence of COD as diagnosed by rectal palpation could likely be lower than previous studies have identified. However, as the modern dairy cow is under tremendous dietary and production stressors which can predispose her to COD the apparent affect of these programs on clinical incidence may be modulated.

Clinical signs

Behavioral signs seen in cows with COD are variable but can generally be classified into two groups, anestrus and nymphomania. The most common clinical sign observed in cows with COD is anestrus, this is especially evident in the early postpartum period. Approximately 80% of cows that develop COD early in the postpartum period exhibited anestrus.[4] These cows are often presented for examination after failure of the

herdsman to detect normal postpartum cycling activity. Nymphomania is yet another clinical sign which can be seen in cows with COD. These cows often attempt to ride other cows but generally will not stand for mating themselves.[4] Approximately 10% of cows affected with COD show signs of nymphomania. It appears that as the number of days following calving at which COD is diagnosed increases the likelihood of nymphomania being a clinical observation also increases.[4] Irregular estrous cycles can also frequently occur in cows with COD which often leads to inappropriate breeding of these cows based on poor or weak signs of estrus.

Pathogenesis

A dysfunction in the normal hypothalamic-pituitary-gonadal axis leading to ovulation failure is the most common accepted mechanism of COD.[1,2,9-11] The precise mechanisms leading to the aforementioned dysfunction have yet to be fully elucidated. It is believed that there is a multi-factorial cause with genetic, phenotypic, environmental and management factors involved.[3]

The most widely accepted hypothesis involves the altered release of luteinizing hormone (LH) from the pituitary gland. The pre-ovulatory surge of LH is either absent, insufficient in magnitude or is improperly timed whereas the dominant follicle does not ovulate leading to cyst formation.[1-3] There does not appear to be a reduction in GnRH content in the hypothalamus or a reduction in GnRH receptors in the pituitary.[3] Luteinizing hormone content in the pituitary also does not appear to be reduced in cows with COD.[3,12] Normally pre-ovulatory follicles secrete estrogen which has a positive feedback on the hypothalamic-pituitary axis causing release of LH which is responsible for the subsequent ovulation. There appears to be a lack of responsiveness of the

hypothalamus to the positive feedback mechanism of estrogen leading to the altered release of GnRH and/or subsequently LH causing the anovulatory state of COD.

Predisposing factors

Numerous factors have been associated with the development of COD in cows. This condition appears to more commonly affect high producing dairy cows in their second through fifth lactation. Early in lactation when the cow is often in a negative energy balance metabolic disturbances are more common and are often followed by COD. There appears to be a higher incidence of COD during winter months, however photoperiod does not appear to have an effect on the hypothalamic-pituitary-ovarian (HPO) axis. Other factors which have been associated with depression of GnRH/LH release and subsequent cyst formation include uterine infections, retained fetal membranes, lameness and stress.[3,11] Postpartum uterine infections are thought to stimulate cortisol secretion which can suppress the pre-ovulatory surge of LH leading to anovulation and subsequent cyst formation.[1] The associated endotoxins and inflammatory mediators can disrupt the normal hormonal pathways that ultimately control ovarian function including ovulation.[13] The role of stress in COD is believed to be related to the release of cortisol which appears to block the estrogen induced LH surge.[1,10,14]

Diagnosis

The diagnosis of COD has historically been made based on the finding during rectal examination of the cow along with her reproductive history. However the collective findings of a rectal examination, an ultrasonographic evaluation of the reproductive tract including the ovaries, progesterone concentrations in blood or milk and

behavioral abnormalities will allow for a more accurate diagnosis. The accuracy with which a skilled palpator can identify the type of cysts based on palpation alone is relatively poor.[15] The dynamic nature of both cysts and developing corpora lutea can complicate the diagnosis when palpation alone is used. A study by Farin et al., showed 10% of cows that were diagnosed as having cysts based on rectal examination were found to have a structure consistent with a normal corpus luteum by transrectal ultrasound examination.[16] In one study evaluating the use of ultrasound the accuracy of a correct diagnosis being made was 74% of follicular cysts and almost 90% of luteal cysts.[17] Progesterone concentrations have been shown to correlate very well with cyst wall thickness with 3 mm being the threshold between follicular and luteal cysts.[1,18] When one combines progesterone concentrations in addition to rectal examination and ultrasound findings the accuracy of diagnosis of the cyst type approaches 100% however this is rarely done outside of research settings. Although using progesterone testing to accurately determine the cyst type would aid in treatment decisions it is rarely used in practice situations due to the economic considerations.

Treatment options

Probably the oldest treatment of COD in cattle is manual rupture of the cyst via rectal palpation. With the advances in our understanding of COD and the availability of effective medical options this treatment can no longer be recommended. The possibility of oviductal or ovarian bursal adhesions arising secondary to the trauma associated with manual rupture and their affects on subsequent fertility are too great to ignore.[4]

Hormone therapy aimed at either causing (GnRH) or mimicking (human chorionic gonadotropin; hCG) an LH surge can be used to treat follicular cysts. Of these

two, GnRH is generally chosen first due to its small molecular size which reduces the likelihood of an immune reaction.[1,10] After an injection of GnRH a surge of LH from the pituitary occurs within 2 hours.[19] This LH surge can cause lutenization of follicular cysts which will undergo spontaneous luteolysis in about 18 days at which time a normal estrous cycle begins. Another possibility following GnRH treatment in cows with follicular cysts is ovulation of a dominant follicle followed by a subsequent normal luteal phase. Since cystic cows continue to have follicular waves, the response to GnRH is likely due to ovulation of a dominant follicle present with recruitment of a new cohort of follicles rather than lutenization or regression of the cysts.[20] The subsequent increase in progesterone concentrations causes the re-setting of the normal HPO axis and resumption of normal cyclicity in most cows. In one study that evaluated the effectiveness of a single injection of GnRH for treatment of cows with ovarian cysts, 72% of cows resumed normal cycling within 20 days of treatment compared to 16% of control cows.[19] However other studies have not borne out the same results. A study that evaluated the effectiveness of GnRH as a sole treatment for follicular cysts showed no difference in treated animals versus controls. The lack of agreement between numerous studies evaluating the efficacy of GnRH is likely due to the lack of control animals and the number of cows which recover spontaneously. There was no difference in the period of time between treatment with GnRH and resolution of the cyst or in the period of time until a CL was evident.[21] This study brings to light the high incidence of spontaneous recovery and somewhat brings into question the effectiveness of GnRH alone as a sole treatment for cows with COD. Timing of treatment in the postpartum period does not appear to affect treatment response. In one study, cystic cows were treated with GnRH

either before or after 60 days following calving. There was no difference in treatment response in the two groups however there were no control animals with which to compare.[22] In accurately diagnosed cases a relatively large percentage of cows return to cyclicity following an injection of GnRH, however some of this response could be attributed to spontaneous resolution.

A recent pharmacokinetic study attempted to find the optimal dose of GnRH for treatment of cows with COD. The dose of GnRH which was found to guarantee production of a critical maximum plasma LH concentration of 5 ng/ml was 74 ug of GnRH.[23] Therefore the standard 100 ug dose of GnRH used to treat cows with COD was found to generate a LH concentration of 5.86 ng/ml and should be adequate in most cases of COD. [23]

Human chorionic gonadotropin has been used successfully to treat refractory follicular cysts that fail to respond to GnRH. It has LH-like properties and causes the cyst to lutenize and begin producing progesterone. Once the cyst has lutenized it can then be treated with prostaglandin to restore the normal cyclical pattern. Its use is often relegated to cases in which GnRH has failed to render a cure. Its use has occasionally been noted to stimulate an immune reaction however the importance of this reaction is poorly understood.[1]

Prostaglandin is the treatment of choice for luteal cysts and cysts that have undergone lutenization after being treated with GnRH or hCG.[1,2,10,20] Prostaglandin has no effect on follicular cysts so it is important to accurately diagnose the type of cyst before using prostaglandin alone. After prostaglandin administration luteal cysts regress with estrus occurring in 90% of cows by day 8 post treatment. Prostglandin is commonly

used in the treatment of cysts after a previous injection of GnRH as part of an Ovsync protocol.

Protocols involving a series of hormonal injections aimed at treating the cysts and restoring the cow to normal cyclicity have been proposed.[1,11,24-27] The classical Ovsync protocol has been employed as a treatment for cysts irrespective of their type. The rational in using an Ovsync protocol is to both treat the cyst and eliminate estrus detection and breed the cows with timed AI.[11,24-27] Progesterone levels in cows with COD which are treated with GnRH are elevated five days after treatment and therefore could be treated with traditional Ovsync with good results.[24] When cows with COD are subjected to the Ovsync protocol pregnancy rates to subsequent timed insemination has range from 17-25%.[25,28]

Use of progesterone as a treatment for cows with COD has been proposed for over 40 years.[29] Now that progesterone impregnated vaginal pessaries have been approved for use in lactating dairy cattle in the United States recent emphasis has been placed on their use in the treatment of COD. Progesterone administration has been shown to re-establish the normal feedback mechanisms involving the HPO axis and allow cows with COD to resume normal cyclicity. The duration of progesterone treatment which is sufficient to re-establish normal hypothalamic responsiveness to estradiol appears to be as short as three days.[30] There was no difference in the pregnancy rates of dairy cattle with COD when treated with either the Ovsync protocol or use of a progesterone-releasing pessary for seven days with prostaglandin administration at the time of pessary removal followed by breeding after heat detection suggesting that use of intravaginal progesterone as a treatment for COD can be effective.[27] Use of

progesterone-releasing pessaries in combination with the Ovsync protocol has been studied as a treatment for cysts as well. Results showed an increase in pregnancy rates in cystic cows treated with Ovsync plus progesterone (37.5% pregnancy rate) compared to Ovsync alone (16.7% pregnancy rate).[26]

In a recent study, the effectiveness of the opioid antagonist naloxone as a treatment for cows with COD was examined.[31] It has been shown that stress may be a contributor to the pathogenesis of COD in cattle. Endogenous opioid peptides are involved in many responses to stress including the regulation of various endocrine systems.[31] Endogenous opioid peptides are believed to block the release of GnRH from the hypothalamus as well as the estrogen-induced LH surge.[14] It has been shown that administration of the opioid antagonist naloxone results in elevated LH release in cattle under various physiological states.[32] Cows diagnosed with COD were treated with naloxone as well as the GnRH agonist buserelin. In this study 77.5% of treated cows had begun cystic regression as viewed with ultrasonography or had begun cycling normally within two weeks post-treatment.[31] Further investigation of the use of naloxone is warranted and specifically its use in the absence of GnRH products which confound the interpretation of this particular study.

Conclusion

Cystic ovarian disease remains an important postpartum condition affecting dairy cattle with a substantial economic impact on the modern dairy farm. Although much effort and research has been placed on elucidating the precise mechanism(s) leading to COD its exact cause remains unclear. Currently the most effective treatments for COD appear to be those which are capable of resetting the HPO axis thereby re-establishing

normal feedback mechanisms which results in normal cyclical patterns. Both the Ovsync protocol, the use of intravaginal progesterone, or the combination of the two appear to be the most practical and effective treatments for most modern dairy operations. Due to the fact of a high incidence of spontaneous recovery in cows with COD it has made it difficult to interpret apparent response to various therapies. Further research into the cellular and molecular events that are occurring in cows with COD and the interactions of various stressors will hopefully provide us more answers to this very common condition.

References

1. Peter AT: An update on cystic ovarian degeneration in cattle. Reprod Dom Anim 2004;39:1-7.
2. Garverick HA: Ovarian follicular cysts in dairy cattle. J Dairy Sci 1997;80:995-1004.
3. Vanholder T, Opsomer G, Kruif A: Aetiology and pathogenesis of cystic ovarian follicles in dairy cattle: a review. Reprod Nutr Dev 2006;46:105-119.
4. Roberts SJ: Veterinary obstetrics and genital diseases (theriogenology), 2nd ed. Ithaca, NY: published by the author; 1971. p. 421-432.
5. Jeffcoate IA, Ayliffe TR: An ultrasonographic study of bovine cystic ovarian disease and its treatment. Vet Rec 1995;136:406-410.
6. Cole WJ, Bierschwal CJ, Youngquist RS, et al: Cystic ovarian disease in a herd of Holstein cows: a hereditary correlation. Theriogenolgy 1986;25:813-820.
7. Uribe HA, Kennedy BW, Martin SW, et al: Genetic parameters for common health disorders of Holstein cows. J Dairy Sci 1995;78:421-430.

8. Garverick HA: Ovarian follicular cysts. In: Youngquist RS, Threlfall WR, editors. Current therapy in large animal theriogenology, 2nd edition. St. Louis: Saunders; 2007. p. 379-383.

9. Woolums AR, Peter AT: Cystic ovarian condition in cattle. Part I. Folliculogenesis and ovulation. Compend Cont Educ Pract Vet 1994;16:935-942.

10. Woolums AR, Peter AT: Cystic ovarian condition in cattle. Part II. Pathogenesis and treatment. Compend Cont Educ Pract Vet 1994;16:1247-1253.

11. Bartolome JA, Thatcher WW, Melendez P, et al: Strategies for the diagnosis and treatment of ovarian cysts in dairy cattle. J Am Vet Med Assoc 2005;227:1409-1414.

12. Brown JL, Schoenemann HM, Reeves JJ: Effect of treatment on LH and FSH receptors in chronic cystic-ovarian diseased dairy cows. J Anim Sci 1986;62:1063-1071.

13. Williams CY, Harris TG, Battaglia DF, et al: Endotoxin inhibits pituitary responsiveness to gonadotropin-releasing hormone. Endocrinology 2001;142:1915-1922.

14. Malven PV: Inhibition of pituitary LH release resulting from endogenous opioid peptides. Dom Anim Endocrinol 1986;3:135-144.

15. Farin PW, Youngquist RS, Parfet JR, et al: Diagnosis of luteal and follicular ovarian cysts by palpation per rectum and linear-array ultrasonography in dairy cows. J Am Vet Med Assoc 1992;200:1085-1089.

16. Farin PW, Youngquist RS, Parfet JR, et al: Diagnosis of follicular cysts in dairy cows by sector scan ultrasonography. Theriogenolgy 1990;34:633-642.

17. Hanzen C, Pieterse M, Scenczi O, et al: Relative accuracy of the indentification of ovarian structures in the cow by ultrasonography and palpation per rectum. Vet J 2000;159:161-170.

18. Dobson H, Ribadu AY, Noble KM, et al: Ultrasonography and hormone profiles af adrenocorticotrophic hormone (ACTH)-induced persistent ovarian follcles (cysts) in cattle. J Reprod Fertil 2000;120:405-410.

19. Cantley TC, Garverick HA, Bierschwal CJ, et al: Hormonal response of dairy cows with ovarian cysts to GnRH. J Anim Sci 1975;41:1666-1673.

20. Kesler DJ, Elmore RG, Brown EM, et al: Gonadotropin releasing hormone treatment of dairy cows with ovarian cysts I. Gross ovarian morphology and endocrinology. Theriogenolgy 1981;16:207-217.

21. Jou P, Buckell BC, Liptrap RM, et al: Evaluation of the effect of GnRH on follicular ovarian cysts in dairy cows using trans-rectal ultrasonography. Theriogenolgy 1999;52:923-937.

22. Hooijer GA, Frankena K, Valks MMH, et al: Treatment of cystic ovarian disease in dairy cows with gonadotropin-releasing hormone: a field study. Vet Q 1999;21:33-37.

23. Monnoyer S, Guyonnet J, Toutain PL: A preclinical pharmacokinetic/pharmacodynamic approach to determine a dose of GnRH, for treatment of ovarian follicular cysts in cattle. J Vet Pharmacol Ther 2004;27:527-535.

24. Bartolome J, Sozzi A, McHale J, et al: Resynchronization of ovulation and timed insemination in lactating dairy cows II: assigning protocols according to stages of

the estrous cycle, or presence of ovarian cysts or anestrus. Theriogenolgy 2005;63:1628-1642.

25. Bartolome JA, Archbald LF, Morresey P, et al: Comparison of synchronization of ovulation and induction of estrus a therapeutic strategies for bovine ovarian cysts in the dairy cow. Theriogenolgy 2000;53:815-825.

26. Bartolome JA, Sozzi A, McHale J, et al: Resynchronization of ovulation and timed insemination in lactating dairy cows III. administration of GnRH 23 days post AI and ultrasonography for nonpregnancy diagnosis on day 30. Theriogenolgy 2005;63:1643-1658.

27. Crane MB, Bartolome J, Melendez P, et al: Comparison of synchronization of ovulation with timed insemination and exogenous progesterone as therapeutic strategies for ovarian cysts in lactating dairy cattle. Theriogenolgy 2006;65:1563-1574.

28. Ambrose DJ, Schmitt EJ-P, Lopes FL, et al: Ovarian and endocrine responses associated with the treatment of cystic ovarian follicles in dairy cows with gonadotropin releasing hormone and prostaglandin F2alpha, with or without exogenous progesterone. Can Vet J 2004;45:931-937.

29. Johnson AD, Ulberg LC: Influence of exogenous progesterone on follicular cysts in dairy cattle. J Dairy Sci 1967;50:758-761.

30. Gumen A, Wiltbank MC: Length of progesterone exposure needed to resolve large follicle anovular condition in dairy cows. Theriogenolgy 2005;63:202-218.

31. Palomar MM, Acosta JC, Salvetti NR, et al: Treatment of cystic ovarian disease with naloxone in high production dairy cows. J Vet Pharmocol Ther 2008;31:184-186.

32. Byerley DJ, Kiser TE, Bedrand JK, et al: Release of lutenizing hormone after administration of naloxone in pre- and peripubertal heifers. J Anim Sci 1992;70:2794-2800.