

Cystic Ovarian Disease in Dairy Cow

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ABSTRACT

Cystic ovarian (OC) condition is an important ovarian dysfunction and a major cause of reproductive failure in dairy cattle. Previously defined as enlarged anovulatory follicle like structures (<2.5 cm) and persisting for 10 or more days OC in dairy cows are currently defined as cystic ovarian follicular structures of at least 17 mm that persist for more than 6 days in the absence of corpus luteum (CL). Past evaluations of OC using trans-rectal palpations have increased, and accurate diagnosis currently employs a combination of trans-rectal palpation, trans-rectal ultrasonography and plasma progesterone assay. Previously the manual rupture of OC was advised, but during the past several years single or combination hCG, GnRH, progesterone and prostaglandins have been frequently practice. Other therapies include clomiphene citrate and trans-vaginal ultrasound guided cystic follicle aspiration. Among the various therapies the Ov-Synch treatment appears to be the most logical approach, yet the pregnancy rates with timed inseminations following therapy with the OvSynch treatment are low, as with other hormonal treatments. It can be concluded that OC can be diagnosed easily yet in spite of many therapeutic options the establishment of pregnancy in cows with OC requires a longer time.

Keywords: ovarian cyst, CL, follicles, GnRH, ovsynch, ultrasonography

Milk yield per dairy cow has increased considerably due to continuing genetic selection and improvement of nutrition and herd management. Simultaneously with this selection for production characteristics, dairy cow fertility has declined significantly. One of the most common ovarian dysfunctions during the postpartum period is formation of cyst following ovulation failure. Ovarian Cyst (OC) is a common and economically significant condition of dairy cattle affecting fertility. McNutt first to use the term “cystic” to persistent follicles >20 mm in diameter (McNutt, 1927). It has been estimated that the incidence of ovarian cyst range from – 5 to 10 % in most herds. In mature cow the incidence is almost 39%. In breeding age heifer it is nearly 3 to 6% and in calf heifer it is 11%. Beef cow have a relatively low incidence of COD than dairy cattle.

Economic impact

There is a increase in calving interval of 22 to 64 days. Increase the no of culling animals and lost of cost nearly 137 dollar per lactation.

Definition

Cystic ovarian follicles develop when one or more follicles fail to ovulate and subsequently do not regress but maintain their growth and steroidogenesis. They are defined as follicle-like structures, present on one or both ovaries, with a diameter of at least 2.5 cm during a minimum of ten days in the absence of luteal tissue (Kesler and Garverick, 1982; Youngquist, 1986; Day 1991a; Woolums and Peter, 1994a). Based on the current knowledge and recent literature OC may be 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. Macroscopically, cysts can be subdivided into follicular and luteal cysts, which are considered to be different forms of the same disorder (Opsomer *et al.* 1997). Determination of progesterone concentrations in blood plasma, milk or milk fat can help to make a distinction between the two types. Follicular cysts secrete little or no progesterone while luteal cysts clearly do (Garverick, 1997). Rectal USG can be differentiated to both of them. Follicular cysts have a thin wall (≤ 3 mm) and the follicular fluid is an-echogenic, while luteal cysts have a thicker wall (> 3 mm), which is visible as an echogenic rim.

Predisposing factor of COD

COD are mainly observed in high yielding dairy cows during the first months postpartum and milk yield is generally considered a risk factor. Moreover, besides the fact that COD are hereditary (see above), a genetic correlation between cysts and milk production traits was established. However, the fact that cows do not develop a cyst during every lactation and during every ovarian cycle indicates that the gene(s) expression may be promoted by, or gains functional importance under, certain stressors, for example high milk yield and the associated negative energy balance (NEB) during the early postpartum period. At this time, energy demands to sustain milk yield are higher than energy intake thus causing a NEB. This NEB is accompanied by several hormonal and metabolic adaptations, affecting ovarian function. Energy balance may be a more accurate parameter than milk yield to further elucidate the association between COD and production. The possible underlying mechanism(s) is (are) also still unclear, but NEB may affect COD formation at both the level of the hypothalamus/pituitary and the ovary/follicle through associated hormonal and metabolic changes (Diskin *et al.* 2003; Lucy, 2003) During NEB, circulating concentrations of IGF-1, insulin, glucose and leptin are reduced, while concentrations of

metabolites such as non-esterified fatty acids (NEFA) and β -hydroxybutyrate (BHB) are increased. The IGF system plays an important role in follicle growth and development. Besides a direct effect, IGF-1 together with insulin indirectly stimulates follicular development through upregulation of the LH-receptor on granulosa cells. Therefore, low systemic IGF-1 concentrations early postpartum could contribute to anovulation and subsequent development of cystic. Also insulin itself is known to be a potent stimulator of follicle cell steroidogenesis and proliferation *in vitro* and *in vivo*. As a result, reduced circulating insulin concentrations early postpartum may play a role in cyst formation. Besides low insulin concentrations, a general state of peripheral insulin resistance is present as well in high yielding dairy cows early postpartum. However, rather insulin insufficiency not insulin resistance has been observed in COD cows. Conclusively, IGF-1 and insulin are important stimulators of follicle growth, low concentrations of one or both of the hormones may contribute to the formation of COD. Leptin is a recently "new" hormone, produced by adipocytes, and is regarded as the ultimate factor linking metabolic status to reproduction. Above a certain threshold level, leptin acts as a trigger to initiate hypothalamo-pituitary gonadotropin secretion. Besides effects on the central nervous system, this hormone also seems capable of modulating ovarian function by acting directly on follicular cells. Both bovine granulosa and theca cells possess leptin receptors. However, both basal, IGF-1 and LH-stimulated steroidogenesis and cell proliferation as well as insulin-stimulated cell growth are unaffected by leptin. This indicates that in a low leptin environment (i.e. poor body condition and poor nutrition), ovarian function is mainly regulated by gonadotropins and low insulin/IGF-1 concentrations. In a moderate to high leptin environment, as in obesity, leptin will limit ovarian steroidogenesis, stimulated by the high insulin/IGF-1 concentrations, to prevent overproduction. Therefore, leptin may play a role in cyst development. Cows developing

cysts have higher serum NEFA concentrations during the first week(s) post partum than ovulatory cows. Moreover, NEFA are cytotoxic for several cell types, including human granulosa cells. So (prolonged) exposure to high NEFA concentrations during periods of NEB may hamper follicle growth and development, disrupting the complex endocrine system and promoting the formation of ovarian cysts. Besides NEFA, increased serum ketone concentrations also affect ovarian function indicating that these metabolites may be mediators of the negative effect of NEB on follicular development. High ketone concentrations increase the risk of cyst occurrence and consequently are likely to be involved in the formation of COD. Either fails to elicit a GnRH and subsequent LH-surge or the GnRH/LH-surge is delayed. The dominant follicle, therefore, does not ovulate but, due to the ungoing LH pulsatility, continues to grow and becomes a cyst.

Pathogenesis of COD

Ovarian dysfunctions like cysts occur most often during the early postpartum period. 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.

Hypothalamic-pituitary dysfunction

The most widely accepted cause explaining the formation of a cyst is that LH release from the hypothalamus-pituitary is altered: the pre-ovulatory LH-surge is either absent, insufficient in magnitude or occurs at the wrong time during dominant follicle maturation, which leads to cyst formation. An altered feedback mechanism of estrogens on the hypothalamus-pituitary can result in an altered GnRH and LH release and cyst formation. A GnRH/LH surge prematurely occurring during follicle growth, i.e. when no follicle capable of ovulation is present, can

render the hypothalamus unresponsive to the feedback effect of oestradiol which results in the formation of ovarian cysts. Progesterone at suprabasal concentrations blocks the LH-surge, thereby inhibiting ovulation, but increases the LH pulse frequency. This results in an anovulatory, persistent follicle with a larger diameter and a longer lifespan than normal, and increased peripheral estradiol concentrations. Factors indirectly reducing GnRH/LH secretion like stress, intrauterine infections and seasonality are also considered to increase the risk of cyst formation. In cystic cows, the formation of new cysts is accompanied by increased LH pulse frequencies and amplitudes. However hypersecretion of LH does not seem to be involved in cyst formation, but it may play a role in cyst persistence. In conclusion, an aberrant LH-surge is likely the trigger for the development of ovarian cyst.

Ovarian/Follicular dysfunction

A primary dysfunction at the level of the follicle may disrupt the hypothalamic-pituitary-ovarian axis and cause the formation of COD. First of all, alterations in LH receptor expression and content may cause anovulation of the follicle. No significant differences in FSH/LH receptor mRNA were observed between these young cysts and dominant follicles, indicating that the increased LH mRNA expression in estrogen-active cysts is a consequence rather than a cause of the cystic state. Another receptor of interest is the estradiol receptor β (ER- β). Alterations in expression of the ER- β might disrupt the local intra-ovarian paracrine/autocrine system, leading to an altered follicular development and steroidogenesis and finally formation of COD. Alterations of the endocrine system precede, and perhaps cause, the observed follicular alterations in cysts. Recently, Imai *et al.* (2003) suggested that matrix metalloproteinases (MMPs) could be involved in the formation of cysts: higher proMMP-2 and -9 levels were present in the follicular fluid of cysts than in the follicular fluid of normal dominant follicles.

MMPs play a role in follicle wall remodelling and rupture at the time of ovulation but hereto the inactive proMMP form needs to be transformed to the active MMP form. This activation is triggered by the LH-surge (Robker *et al.* 2000). Since, an aberrant LH-surge causes COD formation, the higher proMMP-2 and -9 levels in the follicular fluid of COF are most likely an indication of the lack of an LH-surge rather than a cause of COD formation.

Diagnosis

Diagnostic approaches for OC in cows include history and clinical signs, transrectal palpation, ultrasonography and plasma or milk progesterone assay. The presence of cystic follicles on the ovaries was mainly associated with nymphomania and a bull-like appearance in cows. Some of the physical signs associated with OC which include: loss of tone throughout the female genital tract, relaxation or stretching of the sacrosciatic and sacroiliac ligaments giving the raised tail head (sterility hump) appearance, behavioral changes (buller cow) which are characteristic of nymphomania (i.e., excessive mounting, standing, and bawling with noticeably deeper tone) and erratic milk production. Anoestrus is most common, especially during the postpartum period. Irregular estrus intervals and development of masculine physical traits are other signs which may be present especially later during lactation. It has also been determined that follicular cysts are anovulatory structures so, as long as they persist, cows will remain infertile. When follicular cysts persist for prolonged periods in dairy cows, endometrial glands hypertrophy and pathologies in the uterus called mucometra with normal estrous cycle lengths. When compared to follicular cysts, luteinized cysts are more likely to persist over long periods of time and can lead to nymphomania in some animals. The most likely time of diagnosis is 30-60 day after parturition in high-yielding dairy cows. Ovarian cysts and normal preovulatory follicles are differentiated on the basis of number and

size but mainly on the basis of uterine tonicity. During transrectal palpation, ovarian cysts are identified as multiple follicles that are typically larger than normal ovulatory follicles with an increased overall ovarian diameter along with a flaccid uterus in the absence of a corpus luteum while cows in proestrus have an erect, turgid uterus. Although transrectal palpation has long been the diagnostic approach, follicular cysts cannot be differentiated from luteal cysts only by palpation. The accuracy of diagnosing ovarian cysts and differentiating follicular and luteal cysts can be increased by combining transrectal palpation of the genital tract to determine that a corpus luteum is absent and the uterus lacks tone; ultrasonography to confirm that a corpus luteum is absent, to determine the size of follicles that are present, and to check for luteinization; and measurement of plasma progesterone concentration to determine the degree of luteinization. The accuracy of diagnosis can be increased by obtaining information about the reproductive history of the animal, vaginal examination and progesterone determination. A luteal cyst is characterized by enlarged ovaries with one or more cysts with thicker walls than those of follicular cysts because of a lining of luteal tissue. Ultrasonography is effective in detecting follicular and luteal cysts with high accuracy. Two approaches can be considered in the diagnosis of OC. First, detection of multiple follicles approximately 18 to 20 mm in diameter and second, ovarian follicular waves during a period of 7 to 10 days in the absence of ovulation, absence of corpora lutea, and a lack of uterine tonicity. Luteal cysts are associated with relatively high concentrations of progesterone in the peripheral circulation while follicular cysts are associated with relatively low concentrations of progesterone. A plasma P4 concentration greater than 1 ng/ml as the minimum P4 concentration for a cyst to be considered luteal. Thus accurate diagnosis of the type of OC requires a combination of diagnostic approaches such as transrectal palpation, transrectal ultrasonography and plasma progesterone profiles.

TREATMENT PROTOCOLS

Spontaneous recovery

The spontaneous recovery percentage of early cysts is 60-65%. Steinbauer (1985) recommended treatment only after day 50 post partum, because of possible spontaneous regression of the cyst.

Manual rupture

In the past, manual rupture of OC had been suggested (Roberts, 1971) however, recently it did not recommend manual rupture of cysts because it may result in trauma and hemorrhage causing adhesions and contributing to fertility reduction.

GnRH alone

The distinction between follicular cyst and luteal cyst is not important in practice, because the response of both types of cysts to GnRH treatment is similar and usually results in luteinization of the cysts followed by estrous within 4 weeks of treatment.

hCG

Since the 1970s hCG and GnRH analogues have been used to treat ovarian cysts, and both appear to be equally effective with regards to treatment response and fertility but the next estrus would occur 5-21 days after treatment.

PGF2 α

Prostaglandin F₂ α (PGF₂ α) has been used for the treatment of luteinized cyst because of its luteolytic activity, and estrous symptoms can be observed within 2 or 3 days of treatment. It is the most effective treatment for luteinized cysts. 75% of the cows were in estrus within 7 days after treatment and pregnancy rates at first estrus were 66%. Recommended luteolytic doses of PGF₂ α as the ideal treatment for luteal cyst, with estrus being evident within 3-5 days.

Progesterone and progesterone implants

Treatment with progesterone may disrupt the endocrine environment needed to maintain ovarian follicular cysts and thus lead to their regression. Acute treatment as well as chronic treatment (9-14 days) with progesterone caused a rapid reduction in the size of persistent follicles and restored cyclic ovarian activity. Treatment with CIDR proved effective in restoring ovulation and reestablishing normal cyclicity in cows with cysts persistent for a long period. Progesterone and Estradiol Benzoate treatment administered using a PRID have a high rate of therapeutic effectiveness in cows with OC.

GnRH+ PGF2 α combination

Comparatively, ovarian cysts are less responsive to treatment with GnRH alone. GnRH plus Cloprostenol (CLP) 14 days later is effective in resolving cysts with significantly higher percentages of ovulation rates, returns to estrus, and pregnancy rates, and a much lower level of cystic persistence. However, currently GnRH followed by PG 7-10 days later is a routinely used therapy for OC.

Ovsynch protocol

Some recent protocols for synchronization of ovulation, commonly referred as Ovsynch, followed twice artificial insemination (AI) performed 16- 20 h after the 2nd GnRH injection, yields pregnancy rates of about 25% in cows suffering from OC.

Clomiphene citrate

It is an antiestrogen and may exert direct action on the pituitary gland to augment estrogen-induced LH release so a dose of 300 mg of clomiphene citrate administered to cows after a 1% copper sulphate drench has been suggested for the treatment of OCs.

Needle aspiration

Single transvaginal-guided needle aspiration

of ovarian follicular cysts is an easy and good method for the treatment of follicular cysts. Moreover, it is a safe and good alternative method against the manual, active rupturing of cysts during trans-rectal palpation but there is a tendency of the cyst to reform.

Homeopathic drugs

Homeopathic remedies like homeopathic *Apis* (for the right side OC) or homeopathic *Lachesis* (for the left side OC) twice daily for 5 days, with either one being immediately followed by homeopathic *Natrummur*; twice daily for three days are effective treatments for OC (Karreman, 2007). *Apismellifica* is a common homeopathic medicine made from the female honeybee, while *Lachesis* is prepared from the fresh venom of the South American bushmaster snake and *Natrummur* is made simply from sodium chloride, or table salt.

CONCLUSION

On the basis of above review it can be concluded that ovarian cyst is a major ovarian dysfunction and an important cause of infertility of the farm animals. But it can be treated successfully if diagnosis is done at proper time. So, farmers should concern about the proper knowledge about this important problem.

REFERENCES

- Alanko, M. and Katila, T. 1980. Treatment of cystic ovaries in dairy cattle using human chorionic gonadotropin or a compound consisting of human chorionic gonadotropin with progesterone. *Nord. Vet. Med.*, **32**: 122-127.
- Albrechtsen, J. 1917. Sterility of cattle and methods of treatment. *Cornell Vet.*, **7**: 57-110.
- Ambrose, D.J., Schmitt, E.J.P., Lopes, F.L., Mattos, R.C. and Thatcher, W.W. 2004. Ovarian and endocrine responses associated with the treatment of cystic ovarian follicles in dairy cows with gonadotropin releasing hormone, and prostaglandin F_{2α}, with or without exogenous progesterone. *Can. Vet. J.*, **45**: 931-937.
- Amer, H. and Badr, A. 2007. Hormonal profiles associated with treatment of cystic ovarian disease with GnRH and PGF_{2α} with and without CIDR in dairy cows. *Int. J. Vet. Med.*, **2**: 51-56.
- Anderson, L. and Day, M. 1994. Acute progesterone administration regresses persistent dominant follicles and improves fertility of cattle in which estrus was synchronized with melengestrol acetate. *J. Anim. Sci.*, **72**: 2955-2961.
- Amer, H. and Badr, A. 2007. Hormonal profiles associated with treatment of cystic ovarian disease with GnRH and PGF_{2α} with and without CIDR in dairy cows. *Int. J. Vet. Med.*, **2**: 51-56.
- Anderson, L. and Day, M. 1994. Acute progesterone administration regresses persistent dominant follicles and improves fertility of cattle in which estrus was synchronized with melengestrol acetate. *J. Anim. Sci.*, **72**: 2955-2961.
- Annalisa, R., Debora, C., Maddalena, M., Giuseppe, M., Massimo, S. and Luigi, S.R. 2011. Epidural vs intramuscular administration of leirelin, a GnRH analogue, for the resolution of follicular cysts in dairy cows. *Anim. Reprod. Sci.*, **126**: 19-22.
- Arbeiter, K., Aslan, S. and Schwarzenberger, F. 1990. Untersuchungen über die Ovarzyste beim Rind: Entstehung, Therapieerfolge, Fruchtbarkeit. *Dtsch. Tierärztl. Wschr.*, **97**: 380-382.
- Ax, R.L., Bellin, M.E., Scheinder, D.K. and Haase Hardie, J.A. 1986. Reproductive performance of dairy cows with cystic ovaries following administration of procystin. *J. Dairy Sci.*, **69**: 542-545.
- Youngquist, R.S. 1986. Cystic follicular degeneration in the cow. In: Morrow DA (Ed.). *Current Therapy in Theriogenology*. 2nd ed. Philadelphia: WB Saunders.
- Yoshioka, K., Iwamura, S. and Kamomae, H. 1996. Ultrasonic observations on the turnover of ovarian follicular cysts and associated changes of plasma LH, FSH, progesterone and oestradiol-17β in cows. *Res. Vet. Sci.*, **61**: 240-244.
- Woolums, A.R. and Peter, A.T. 1994. Cystic ovarian condition. In: Cattle. 1. Folliculogenesis and ovulation. *Compend. Contin. Educ. Pract. Vet. (Food Anim)*, **16**: 935-942.
- Seguin, B.E., Convey, E.M. and Oxender, W.D. 1976. Effect of gonadotropin-releasing hormone and human chorionic gonadotropin on cows with ovarian follicular cysts. *Am. J. Vet. Res.*, **37**: 153-157.

- Roberts, S.J. 1986. *Veterinary Obstetrics and Genital Disease*. Woodstock, VT: Published by the author. pp. 521-522.
- Rautha Filho, M.A. and Bison, L. 2009. Homeopathic medicines for the treatment of dairy cows with cystic ovarian disease. *Braz. Homeopathic J.*, **11**: 8-13.
- Bartolome, J.A., Thatcher, W.W., Melendez, P., Risco, C.A. and Archbald, L.F. 2005. Strategies for the diagnosis and treatment of ovarian cysts in dairy cattle. *J. Am. Vet. Med. Assoc.*, **277**: 1409-1414.
- Bierschwal, C.J. 1966. A clinical study of cystic conditions of the bovine ovary. *J. Am. Vet. Med. Assoc.*, **149**: 1591-1595.
- Bierschwal, C.J., Garverick, H.A., Martin, C.E., Youngquist, R.S., Cantley, T.C. and Brown, M.D. 1975. Clinical response of dairy cows with ovarian cysts to GnRH. *J. Anim. Sci.*, **41**: 1660-1665.
- Boryczko, Z., Bostedt, H. and Hoffman, B. 1995. Comparison of the hormonal and chemical composition of the fluid from bovine ovarian follicles and cysts. *Reprod. Domest. Anim.*, **30**: 36-38.
- Butler, W.R. 2003. Energy balance relationships with follicular development, ovulation and fertility in postpartum dairy cows. *Livest. Prod. Sci.*, **83**: 211-218.
- Calder, M.D., Salfen, B.E., Bao, B., Youngquist, R.S. and Garverick, H.A. 1999. Administration of progesterone to cows with ovarian follicular cysts results in a reduction in mean LH and LH pulse frequency and initiates ovulatory follicular growth. *J. Anim. Sci.*, **77**: 3037-3042.
- Casida, L.E., McShan, W.H., Meyer, R.K. 1944. Effects of an unfractionated pituitary extract upon cystic ovaries and nymphomania in cows. *J. Anim. Sci.*, **3**: 273-282.
- Chavatte, P.M., Archbald, L.F., Risco, C., Tran, T. and Sumrall, D. 1993. Effectiveness of prostaglandin F_{2α} in the initial treatment of bovine ovarian cysts. *Theriogenology*, **40**: 745-755.
- Chenault, J.R., Kratzer, D.D., Rzepkowski, R.A. and Goodwin, M.C. 1990. LH and FSH response of Holstein heifers to fertirelin acetate, gonadorelin and buserelin. *Theriogenology*, **34**: 81-98.
- Cook, D.L., Parfet, J.R., Smith, C.A., Moss, G.E., Youngquist, R.S. and Garverick, H.A. 1991. Secretory patterns of LH and FSH during development and hypothalamic and hypophyseal characteristics following development of steroid induced ovarian follicular cysts in dairy cattle. *J. Reprod. Fertil.*, **91**: 19-28.
- Crane, M.B., Melendez, P., Bartolome, J., de Vries, A., Risco, C. and Archbald, L.F. 2006. Association between milk production and treatment response of ovarian cysts in lactating dairy cows using the Ovsynch protocol. *Theriogenology*, **66**: 1243-1248.
- Day, N. 1991a. The diagnosis, differentiation and pathogenesis of COD. *Vet. Med.*, **41**: 753-760.
- Day, N. 1991b. The treatment and prevention of cystic ovarian disease. *Vet. Med.*, **86**: 761-766.
- De Rensis, Bottarelli, F., Battioni, E., Capelli, F., Techakumphu, T., García-Ispierto, M. and López-Gatiús, F. 2008. Reproductive performance of dairy cows with ovarian cysts after synchronizing ovulation using GnRH or hCG during the warm or cool period of the year. *Theriogenology*, **69**: 481-484.
- Dinsmore, R.P., White, M.E., Guard, C.L., Jasko, D.J., Perdrizet, J.A., Powers, P.M. and Smith, M.C. 1989. Effect of gonadotropin-releasing hormone on clinical response and fertility in cows with cystic ovaries, as related to milk progesterone concentration and days after parturition. *J. Am. Vet. Med. Assoc.*, **195**: 327-330.
- Dinsmore, R.P., White, M.E. and English, P.B. 1990. An evaluation of simultaneous GnRH and cloprostenol treatment of dairy cattle with cystic ovaries. *Can. Vet. J.*, **31**: 280-284.
- Dobson, H., Rankin, J.E. and Ward, W.R. 1977. Bovine cystic ovarian disease: plasma hormone concentrations and treatment. *Vet. Rec.*, **101**: 459-461.
- Douthwaite, R. and Dobson, H. 2000. Comparison of different methods of diagnosis of cystic ovarian disease in cattle and an assessment of its treatment with a progesterone-releasing intravaginal device. *Vet. Rec.*, **147**: 355-359.
- Etherington, W.G., Martin, S.W., Dohoo, I.R. and Bosu, W.T.K. 1985. Interrelationships between postpartum events, hormonal therapy, reproductive abnormalities and reproductive performance in dairy cows: a path analysis. *Can. J. Comp. Med.*, **49**: 261-267.
- Farin, P.W., Youngquist, R.S., Parfet, J.R. and Garverick, H.A. 1990. Diagnosis of luteal and follicular ovarian cysts in dairy cows by sector scan ultrasonography. *Theriogenology*, **34**: 633-642.

- Iwakuma, A., Suzuki, Y., Haneishi, T., Kajisa, M. and Kamimura, S. 2008. Efficacy of intravaginal progesterone administration combined with prostaglandin F(2alpha) for cystic ovarian disease in Japanese Black cows. *J. Vet. Med. Sci.*, **70**:1077-1083.
- Johnson, W.H. and Coates, A.E. 2004. An update on cystic ovarian disease. *In: Proceedings of the 15th International Congress on Animal Reproduction, Porto Seguro, Brazil, Porto Seguro, BA: ICAR.* pp. 60-65.
- Jou, P., Buckrell, B.C., Liptrap, R.M. and Summerlee, A.J.S. 1999. Evaluation of the effect of GnRH on follicular ovarian cysts in dairy cows using transrectal ultrasonography. *Theriogenology*, **52**: 923-937.
- Kahn, C.M. 2010. Cystic ovary disease. *In: Kahn CM, Line S (Ed.). The Merck Veterinary Manual.* 10th ed. Whitehouse Station, NJ: Merck. pp. 1243-1247.
- Karreman, H.J. 2007. Ovarian cysts. *In: Karreman HJ. Treating Dairy Cows Naturally: Thoughts and Strategies.* Austin, TX: Paradise Publications, pp. 291-292.
- Kasari, R., Fuller, D.T., Wideman, D., Jaques, J.T., Slay, L. and Lee, J. 1996. Bovine COD and the role norgestomet can play in its treatment. *Vet. Med.*, **91**: 156-162.
- Kawate, N., Watanabe, K., Uenaka, K., Takahashi, M., Inaba, T. and Tamada, H. 2011. Comparison of plasma concentrations of estradiol 17 β and progesterone, and conception in dairy cows with cystic ovarian diseases between Ovsynch and Ovsynch plus CIDR timed AI protocols. *J. Reprod. Dev.*, **57**: 267-272.
- Hatler, T.B., Hayes, S.H., Fonseca, L.F.L. and Silvia, W.J. 2003. Relationship between endogenous progesterone and follicular dynamics in lactating dairy cows with ovarian follicular cysts. *Biol. Reprod.*, **69**: 218-223.