



## Review Article

## An Overview of Bovine Cystic Ovarian Disease

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## ABSTRACT

Dairy animals are facing so many reproductive disorders and cystic ovarian disease (COD) is one of the important disease which cause major economic losses to farmers. COD affects fertility of animal which is important to reproduce young ones, that occurs due to negative impact factors on hypothalamus-pituitary stalk and normal function of the ovary which leads to alteration in follicular development, ovulation, reduced reproductive performance, unsuccessful ovulation, increased interval between parturition and conception, low conception rate, decrease in calving rate, increase in number of inseminations at each conception and finally culling. The incidence of COD is ranges from 5-30%, due to the improper management system, and the prevalence of COD is 10-13% which is associated with selection, heredity, age, environment, improper nutrition, herd size, housing, high milk production, body condition score, lactation period, seasons, retained placenta, stress, metabolic disorders and hormonal imbalance. COD is generally at highest from 30 to 60 days of postpartum. The exact pathogenesis of COD is still not confirmed, but the abnormal neuroendocrine reflex of hypothalamic pituitary dysfunction, molecular alteration in growing follicle are important components. COD has been diagnosed by animal behavioral changes, nymphomania, anestrus, repeat breeding, pelvic ligament relaxation, tails head elevation, determination of progesterone level in plasma and milk by using kits of progesterone assay, and to confirm the diagnosis of COD, mostly trans rectal palpation and trans rectal ultrasonography methods have been used. COD should be treated by using different treatment protocols such as hormonal, medicinal and homeopathic medicines.

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## Key words

Cystic ovarian disease, Infertility, Hormonal imbalance, Endocrine reproductive disorder, Treatment

## INTRODUCTION

The fertility of animals is necessary for reproduction and it depends on the neuroendocrine function. Many factors affect the hypothalamus, pituitary, and ovary function that causes decrease infertility outcomes (Kovács *et al.*, 2020). In good-yielding dairy animals,

alteration infertility occurs by the reproductive disorder (mainly normal ovarian activity) (Mimoun *et al.*, 2020; Szenci *et al.*, 2018). The reproductive disease of animals increases the calving interval, low conception rate, improper sexual behavior that causes high economic loss of industrial and non-industrial farms (Cattaneo *et al.*, 2014). In dairy animals, cystic ovarian disease (COD) is an influential reproductive dysfunction (Yimer *et al.*, 2018). It has been reported in several species of animal such as ruminants, humans, bitches and rodents (Francou *et al.*, 2008). COD is an exceeding reproductive disorder that causes a prolonged open period after parturition (Gobikrushanth *et al.*, 2016). In high producing animals, COD causes subfertility, increasing postpartum open periods, and reduced reproductive performance that causes huge economic loss in the dairy industry (Ortega *et al.*,

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2015; Garverick, 1997; Stassi *et al.*, 2019; Sayad *et al.*, 2019; Kesler and Garverick, 1982; Xu *et al.*, 2021). The frequency of COD in cattle ranges from 5-30% in all reproductive diseases (Silvia *et al.*, 2005).

Reproductive disorder cystic ovarian degeneration has 10-13% prevalence that affects on the fertility level and causes high economic loss (Johnson and Coates, 2004). In 60% of cows follicular cyst develops before first ovulation and as parturition occurs (Peter, 2004; Mimoune *et al.*, 2019). Alteration in normal ovulation and follicular development occurs by cystic ovarian (Ortega *et al.*, 2016). Anovulation of dominant follicle occurred by cystic structure on ovary that interfere with normal ovarian function during estrous cycle (Peter, 2004; Ortega *et al.*, 2015; Stassi *et al.*, 2019). Ovarian cyst is a bladder-like watery-filled structure of about 25mm on ovary that remains for more than 10 days (Lüttgenau *et al.*, 2016; Mimoune *et al.*, 2020; Coleman, 2008; Polat *et al.*, 2015). On ovary, one or more ovarian cyst (follicular and luteal) with size greater than 20mm in diameter in lack of corpus luteum formation. The wall of follicular cyst is less than 3mm and greater than 3mm in luteal cyst (Lüttgenau *et al.*, 2016; Todoroki *et al.*, 2001; Vanholder *et al.*, 2006). The diagnosis of follicular and luteal cyst is very difficult in field condition (Probo *et al.*, 2011; Gaebler *et al.*, 2015). Heredity, body condition score, lactation period, seasonality effect, phytoestrogen, milk fever, metritis and retention of fetal membrane are included as the cause in the occurrence of COD (Cattaneo *et al.*, 2014). Vanholder *et al.* (2006) have reported the relationship in between the mechanism of postpartum COD and endometritis. Plasma progesterone concentration in follicular cyst is less than 1ng/ml, whereas in luteal cyst it is greater than 1ng/ml (Vanholder *et al.*, 2006). Recently it is reported that in case of follicular cyst in cows, serum progesterone and estradiol concentration is 0-1ng/ml and 0-5pg/ml while its range is 8-9ng/ml and 15-20pg/ml in luteal cyst (Brodzki *et al.*, 2019).

The basic purpose of this review is to reveal about COD incidence, economic loss, causes, manage mental techniques of the basic reproductive disorder that cause low production of animals in milk, meat etc.

## INCIDENCE OF CYSTIC OVARIAN DISEASE

The COD incidence in milking animals has been reported from 5% to 30%, which are occurred due to improper management system, the prevalence of this disease occurred is mostly associated with heredity, age, high milk production, body condition score, lactation period, seasons, retained placenta, stress, metabolic disorders and hormonal imbalance (Cattaneo *et al.*,

2014). COD is generally at highest from 30 to 60 days of postpartum (Kim *et al.*, 2005). COD has occurred with increases of parity which may be associated with physiological and pathological conditions which leads to an increase in parity, such as parturient paresis or milk fever (Fleischer *et al.*, 2001). Another incidence is the selection, because most of farmers choose high milk yield animals which affects genetics and its surrounding environment may also lead to COD mostly in last lactation (Vanholder *et al.*, 2006). Herd size and housing may produce negative impact on the reproduction of animals and lead to COD because of limitations in their natural performance in herds such as in free stalls (Simensen *et al.*, 2010; Nelson *et al.*, 2010). Seasons such as in autumn and winter calving season, the occurrence of COD is higher as compared to spring and summer calving season (Peter, 2004; Cattaneo *et al.*, 2014). Nutritional management, stress, infectious diseases, decrease level of insulin in blood and increase level of blood cortisol which leads to COD (Jafari *et al.*, 2015; Silvia *et al.*, 2002). Decreased level or absence of luteinizing hormone (LH) may also lead to the occurrence of COD (Mimoune *et al.*, 2019).

## PATHOGENESIS

Due to complex disorder and clinical signs, exact pathogenesis of COD is unknown (Vanholder *et al.*, 2006). In COD, pathogenesis depends on the abnormality in neuroendocrine reflex of the hypothalamic pituitary gonadal axis (Noakes *et al.*, 2001; Scully *et al.*, 2021). And also in COD pathogenesis, molecular alteration in growing follicle is key component (Çolakoglu *et al.*, 2021; Stassi *et al.*, 2019). It is difficult to differentiate in follicular and luteal cyst diagnosis in field condition so GnRH over prostaglandin recommended for treatment (Bors *et al.*, 2018).

### *Hypothalamic-pituitary dysfunction*

Hypothalamic-pituitary gonadal axis has a great role to maintain endocrine balance for normal follicular growth, rupture of the follicle and ovulation at a time (Marelli, 2014). For ovulations, a reproductive mother hormone gonadotropin-releasing hormone (GnRH) causes discharge of luteinizing hormone (LH). While, granulosa cells, inflammatory process and dysfunction of follicle cellular components have key role in cyst formation (Silvia *et al.*, 2002; Yoshioka *et al.*, 1996; Matiller *et al.*, 2014; Baravalle *et al.*, 2015). In COD hypothalamus show an unusual response by releasing of high estradiol by which concentration of progesterone in blood circulation is increased (Diaz *et al.*, 2015). By endogenous and exogenous factor hormonal imbalance of hypothalamic-pituitary gonadal axis occur

that formed the ovarian cyst (Silva *et al.*, 2002; Cook *et al.*, 1991; Xu *et al.*, 2021). Alteration of preovulatory LH surge from hypothalamus-pituitary dysfunction leads to the formation of cyst on dominant follicle (Yoshioka *et al.*, 1996; Vanholder *et al.*, 2005). During follicular growth follicle are not able to ovulate then an unusual response of estradiol feedback from hypothalamus occurs and that results in cyst formation (Giimen and Wiltbank, 2002; Vanholder *et al.*, 2006). Cystic follicle have less reactive oxygen species (ROS) comparison to normally ovulating follicles for inflammatory reactions during ovulation (Rizzo *et al.*, 2009).

#### Ovarian/ follicular dysfunction

In cyst formation, alteration in preovulatory LH surge and steroid hormone production have great role (Mimoun *et al.*, 2017). Lack of LH receptors in granulosa cells and theca cell of ovary and irregular response of follicular cells to the preovulatory LH surge is included in cyst formation (Shimizu *et al.*, 2018). In cyst formation leutinizinghormone have great role. By the absence of preovulatory LH surge, alteration in maturation of dominant follicle occurred that altered to cyst formation (Lima *et al.*, 2019; Yoshioka *et al.*, 1996). Intermediate progesterone concentration in blood circulation can cause cystic ovaries (Silva *et al.*, 2002; Hatler *et al.*, 2003; Dhara and Sharma, 2019). Hormonal receptors have a key role for the hormone to perform the function at proper cite (Robker *et al.*, 2000). Lack of steroid receptor (follicle-stimulating hormone receptor, estrogen receptor, leutinizing hormone receptor) is included in the molecular pathogenesis of bovine ovarian cyst (Marelli *et al.*, 2014; Salvetti *et al.*, 2010). Negative energy balance occurs by imbalance of energy intake and production that effects on ovarian function by hormonal and metabolic alteration can cause COD (Opsomer *et al.*, 2000). Low insulin-like growth factor-1 and insulin in early days after parturition results in an-ovulation and cystic ovarian follicular development (Zulu *et al.*, 2002; Vanholder *et al.*, 2005) (Fig. 1).

#### Losses due to COD

The main loss that occurred due to COD is a reduction in reproductive performance which affectsthe fertility of animals by disturbing the normal ovarian cycle, failure of successful ovulation, increased interval between parturition and conception (Isobe, 2007), low conception rate, decrease in calving rate, increase in number of inseminations at each conception and because of this condition animals have been eliminated by culling from the herd which leads to financial loss to farmers (Sayad *et al.*, 2019; Ismail *et al.*, 2017; Hooijer *et al.*, 2001).

## DIAGNOSIS

The fertility of the dairy animals in the postpartum period is very important in terms of economics and dairy herd management. In this period, COD is very common without clear signs and symptoms. COD is one of the most important ovarian disorders, affecting the modern dairy cattle breeds. Most of the time, this disease is diagnosed without obvious signs, in recent times (Vanholder *et al.*, 2006).

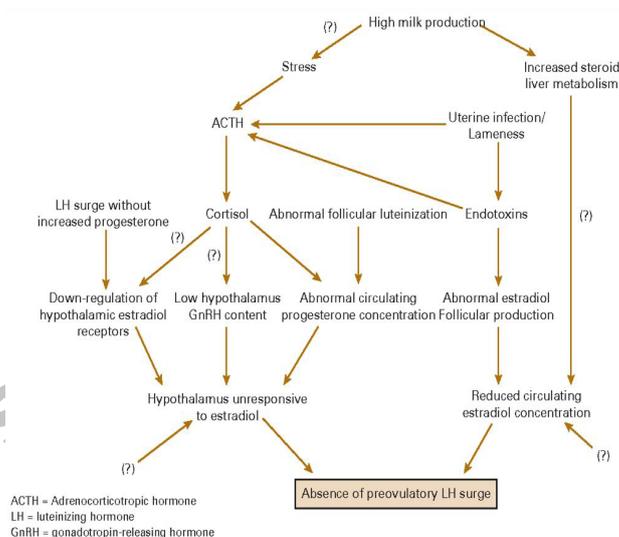


Fig. 1. The pathogenesis of cystic ovarian disease in cattle involves the deficiency of pre-ovulatory surge resulting from interruption in positive feedback outcome of estradiol on hypothalamus. This disturbance is caused by hypothalamic insensitivity or decreased circulating estradiol concentration (Brito and Palmer, 2004).

The diagnosis of COD at farm can be observed by animal behavioral changes, frequent, intermittent, extended or continuous signs of estrus called nymphomania and anestrus, repeat breeding, pelvic ligament relaxation, tails head elevation and in chronic condition masculine characteristics may be observed in bovines (Bartolome *et al.*, 2005; Brito and Palmer, 2004).

The cyst is a fluid-filled structure present on the ovary and can be detected by manual palpation through rectum of the animal. The follicular cysts are thin walled while the luteal cysts are thick. Ovaries can be examined ultrasonographically and a non-echogenic area of at least 25 mm diameter is present there. The follicular cyst has non-echogenic antrum and thin walled <3 mm while the luteal cysts has gray patches within antrum and a wall of <3 mm thick in diameter. An electronic caliper is used to

measure the internal diameters of the cysts (Douthwaite and Dobson, 2000).

For the confirmation and effective diagnosis of COD, Rectal palpation and the trans-rectal ultrasonography have been used and progesterone level in plasma and milk are analyzed by using kits of progesterone assay, mostly veterinarians rely on trans-rectal palpation and trans-rectal ultrasonography in the field with accuracy which ranges from 75-95%. (Borş *et al.*, 2018; Peter, 2004). There is about 74% of follicular cysts and 85% of luteal cysts that could have been interpreted with accuracy by using ultrasonography (Hanzen *et al.*, 2000). The cyst thickness is correlated in plasma progesterone concentration (Peter, 2004). The cyst wall thickness is analysed by using ultrasonography and the size of ovaries is diagnosed by rectal palpation, rectal palpation is the convenient technique which is mostly followed by veterinarians to diagnose COD in animal (Tebble *et al.*, 2001).

### TREATMENT OF CYSTIC OVARIAN DISEASE

There are so many efforts that have been taken to treat COD effectively to control financial losses which have been faced by farmers as a result of this disease (Stassi *et al.*, 2019). Before the first postpartum ovulation, about 60 % of the cows recover at their own place (Peter, 1997, 2000; Woolums, 1994; Kesler and Garverick, 1982). Manual rupture, injection of ovarian extract, injection of CL extract, ovariectomy, antibiotics infusion, and injections of adrenaline chloride and pituitrin are some of the oldest forms of treating COD. Administration of GnRH alone usually results in the luteinizing the cyst and the animal shows estrous within 4 weeks. The epidural injection of leirelin (GnRH analog) is good for reproductive improvements (Jeengar *et al.*, 2018).

According to a research report, prostaglandin F2-alpha (PGF2 $\alpha$ ) is the most effective treatment and used because of its luteolytic activity and the animal shows estrous signs within 2-3 days (Probo *et al.*, 2011; Brito and Palmer, 2004). In addition, to treat COD ultrasonography should be done to diagnose the type of cyst such as follicular cysts and luteal cysts, the luteal cysts should be better treated by using dinoprost (prostaglandin F2-alpha or PGF2 $\alpha$ ) or gonadotrophin releasing hormone (GnRH) analogues, whereas follicular cysts should be better treated by using with buserelin acetate (GnRH) agonist or human chorionic gonadotropin (hCG). At the farm, if an ultrasonography facility would not be available to diagnose the type of ovarian cysts, then mostly gonadotrophin releasing hormone (GnRH) has been recommended to treat COD (Borş *et al.*, 2018; De Rensis *et al.*, 2010).

Furthermore, the COD is treated by giving GnRH followed by giving PGF2 $\alpha$  after 10 days of GnRH, highest recovery of COD has been observed which was about 87% and the pregnancy rate was recorded about 65.21% in treated animals. Mostly farmers culled their animals which are infected by COD, that's why to avoid culling, cases of COD should be treated by applying other treatment procedures such as ovsynch synchronization protocol, Ovsynch+CIDR synchronization protocol and CIDR-GnRH-PGF2 $\alpha$  or potassium iodide which have equal efficacy against COD (Khalil, 2019; Ismail *et al.*, 2017; Bartolome *et al.*, 2005).

Progesterone releasing intra-vaginal devices (PRID) with estradiol-benzoate combination for 12 days are also effective therapy against COD in postpartum animals, whereas instead of PGF2 $\alpha$ , progesterone is mostly used for the process of estrus synchronization after collection of embryo, resulting in the COD developing chances in animal decreased from ~25% to <3%. The suggested drugs dose and protocols are also described in Table I to treat COD (Brito and Palmer, 2004; Hatler *et al.*, 2003; Zulu *et al.*, 2003).

**Table I. Drugs, their doses and route for treatment of COD (Teshome *et al.*, 2016).**

Drug	Dose	Route
Gonadorelin (GnRH)	100 $\mu$ g	IM
Human chorionic gonadotropin (hCG)	10,000 IU	IM
Dinoprost (PGF2 $\alpha$ )	25 mg	IM
Cloprostenol (PGF2 $\alpha$ )	500 $\mu$ g	IM
Progesterone	1.9 g	Intravaginal implant

#### Treatment protocols

- (1) GnRH (or hCG) + PGF2 $\alpha$  (day 0); PGF2 $\alpha$  (day 9 if no estrus)
- (2) Ovsynch: GnRH (day 0); PGF2 $\alpha$  (day 7); GnRH (day 9); fixed-time AI, 16 h after last GnRH treatment
- (3) Progesterone implant for 12 days (not for dairy cows)

COD can be treated by using homeopathic drugs such as homeopathic Apis which is prepared from *Apis mellifica* that is common homeopathic medicine obtained and manufactured from female honeybee, it is used to treat the right side ovarian cyst while homeopathic Lachesis which is prepared from the fresh venom of south American snake called bushmaster, is used to treat left side ovarian cyst, this treatment have been used twice (BID: bis in die) in a day daily for 5 days. Another homeopathic drug homeopathic Natrum Mur which is prepared from sodium chloride, or table salt, which is used twice in a day for 3 days for

effective treatment of COD. In addition, botanical herb called heat seek made 10 tablets can be given orally every other day, twelve doses for 24 days to enhance the estrus signs, while manual rupture of cysts is not recommended because this procedure cause trauma and haemorrhage which leads to a reduction in fertility (Teshome *et al.*, 2016).

## CONCLUSION

This review reveals the major reproductive disorder ovarian cyst (follicular and luteal cyst) in a high-yielding dairy animal. It involves the knowledge of molecular factors for the complex pathogenesis of COD. It also helps the clinician to diagnose, manage mental techniques and treatment for COD in cattle. While, strategies to reduce the incidence of postpartum disease mainly ovarian cyst by better management. The different definitions and diagnostic methods used for the pathology are accessible, with the value of each hormonal treatment. This leads the veterinary practitioner to the best therapeutic choices. It also helps to maintain animal body condition score that is the key factor to reduce the metabolic disorder and other reproduction disorders before and after parturition. Further elucidation of the complex pathogenesis of the disease will continue to improve our capacity to prevent, diagnose, and treat COD.

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### Statement of conflict of interest

The authors have declared no conflict of interest.

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