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REVIEW ARTICLE

Follicular Cysts: A Single Sign and Different Diseases. A View from Comparative Medicine

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Abstract: Ovarian cystic follicles are the sign of important causes of reproductive failure in numerous species. In this review, some morphological, endocrinological and clinical aspects of cystic follicles in women, cows, mares, sows and bitches are discussed. Follicular cysts are the consequence of the failure of a mature follicle to ovulate at the appointed time of ovulation in the estrous cycle. Although the etiology of follicular cysts remains unknown, this review examines the evidence about the role of endocrine signaling systems in the specific disease or syndrome in each of the species mentioned above. This review also describes, the changes in the pathways of endocrine mechanisms that would trigger disturbances in the intraovarian component underlying the aberrant persistence of follicular cysts. The knowledge of the morphological and endocrinological nature of cystic follicles in different species can provide relevant information to better understand specific diseases when it is integrally analyzed from the comparative medicine viewpoint.

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Keywords: Follicular cyst, polycystic ovarian syndrome, cystic ovarian disease, cow, sow, mare, bitch.

1. INTRODUCTION

Cystic ovarian degeneration, first described by Gurlt in 1631, is an important ovarian dysfunction in both humans and domestic animals [1]. Cystic ovarian disorders occur in various mammalian species and although cystic ovaries vary in anatomical and biochemical details among species, the common features in all cases are chronic acyclicity or erratic cycles (amenorrhea or oligomenorrhea in humans), anovulation and infertility or reduced fertility in polytocous animals [2-4].

Cystic ovarian follicles are persistent anovulatory structures which occur spontaneously, and can be single or multiple (polycystic) according to the species. Since these follicles reduce fertility, this issue has become a major health concern worldwide and has received the attention of animal scientists and medical researchers for more than 50 years. Cystic follicles were initially described in terms of their morphological characteristics and effects on reproductive cyclicity and fertility [5]. Currently, it is well known that cystic follicles are also accompanied by altered endocrine profiles and different clinical phenotypes. Despite extensive research has been conducted, concluding explanations regarding cyst formation have remained elusive. While it is believed that follicular cysts result from a malfunction of the metabolic, endocrine, neuroendocrine mechanism controlling follicular development, maturation and ovulation, the nature of the defects that leads to cyst development is still unknown [5].

Cystic follicles are the result of several alterations in follicular development and ovulatory mechanisms. Ovulation is the final result of a series of events coordinated by the ovary, hypothalamus, and pituitary gland, and therefore this scenario complicates elucidating the site in which malfunction occurs. Cystogenesis in the species discussed in this review may involve different physiological pathways, and indeed different mechanisms may exist within a species. Despite this, it is considered that data on this subject in one species might complement the data in other species and will provide a superior knowledge of the problem.

As we report in this review, considerable differences exist regarding cystic ovarian disorders between mammalian species (humans, cattle, bich, mare, sow, *etc*.). Thus, the interspecies inferences for the study of follicular cysts as a sign of a certain disease or syndrome must be based on a thorough knowledge of the reproductive physiology of each species. Nevertheless, similarities in key steps of mammalian reproduction provide an attractive point for comparative medicine studies about ovarian disease, failure of ovulation and the interaction between the reproductive and metabolic pathways. This review provides details about similarities and differences among species of several disease entities, which have follicular cysts as a special sign.

2. WOMEN

The disorder currently known as polycystic ovary syndrome (PCOS) was first described in 1844 [6,7]. Later, in 1935, was described an association between large polycystic ovaries, menstrual irregularities, ovulatory failure, infertility, hirsutism and obesity as a syndrome [8,9].

PCOS, which results from complex and poorly understood interactions between environmental and genetic factors, is the main endocrine disorder and cause of ovulatory dysfunction affecting reproductive age women [10,11]. Although the expression "polycystic ovarian disease" is often used synonymously, albeit incorrectly, to describe this syndrome, it is considered a syndrome, not a disease [12]. Although it is manifested by heterogeneous clinical

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features, the clinical expression varies widely, the syndrome is classically characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries.

In 2003, during the meetings of the European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM)-Sponsored 3rd PCOS Consensus Workshop Group, an attempt was made to standardize the working definition of PCOS [13]. Since then, the presence of two of three of the following criteria have been required for the diagnosis of PCOS: (i) oligo and/or anovulation, (ii) clinical and/or biochemical signs of hyperandrogenism and (iii) appearance on ultrasound of polycystic ovaries, after the exclusion of diseases with a similar clinical presentation [14-16]. In December 2012, the National Institutes of Health (NIH) Evidence-Based Methodology Workshop on PCOS confirmed and recommended maintaining the broad diagnostic Rotterdam criteria along with the identification of the specific PCOS phenotypes for each single patient, especially for their different potential cardio-metabolic implications.

According to the type of diagnosis used, PCOS is diagnosed in 5-15% of women in reproductive age [17]. In anovulatory women with PCOS, the most prominent sign at ovarian level is follicular maturation arrest, which results in an abnormal ovarian endocrine environment characterized by chronic anovulation, hyperandrogenemia, increased peripheral conversion of androgens to estrogens, and characteristic morphological findings, including a sclerocystic appearance [18]. In addition, the etiology of the syndrome, including the mechanism of anovulation, is still unclear [19]. Polycystic ovaries are ultrasonographically diagnosed by the presence of 12 or more antral follicles (2±9 mm in size), or increased ovarian volume greater than 10 cm^3 on either ovary [17].

Follicular arrest in PCOS develops when granulosa cells in antral follicles normally begin to express aromatase (7 mm in size) [20,21], but an excess of intraovarian 5α-reduced androgens inhibits granulosa cell aromatase activity and impairs follicle growth [22,23]. The frequent occurrence of hyperinsulinemia in PCOS further exacerbates ovarian follicular arrest, which promotes ovarian hyperandrogenism by stimulation of 17α-hydroxylase activity in theca cells [24]. Hyperinsulinemia also amplifies luteinizing hormone (LH)-stimulated and insulin-like growth factor 1 (IGF-1)-stimulated androgen production [25], increases serum free testosterone levels through decreased hepatic sex hormone-binding globulin production, and enhances serum IGF-1 bioactivity through suppressed IGF-binding protein production [26]. Insulin excess also promotes premature follicle luteinization through enhanced follicle-stimulating hormone (FSH)-induced granulosa cell differentiation, which arrests granulosa cell proliferation and subsequent follicle growth [27,28]. Finally, overproduction of anti-Müllerian hormone (AMH) [29-31] by granulosa cells in PCOS appears to antagonize FSH action in small PCOS follicles [32], as such follicles are estrogen-deficient despite sufficient FSH bioavailability [33,34].

In women with PCOS, hyperandrogenism is associated with the android body fat distribution, characterized by accumulation of fat mainly in abdominal depots [35]. Interestingly, the presence of hyperinsulinemia is independent of obesity [36], and therefore may be an independent factor in PCOS. Whether hyperandrogenism causes hyperinsulinemia or vice versa remains to be determined, and both may be possible [37]. In addition, it is unknown whether other factors secreted by the increased follicle pool contribute to the metabolic phenotype. Women with PCOS also present higher risk of type 2 diabetes mellitus, hypertension, dyslipidemia and cardiovascular disease [38]. Moreover, insulin resistance is also a common feature in patients with PCOS [39], and approximately 50-70% of women with PCOS have insulin resistance and compensatory hyperinsulinemia [40]. The association of androgen excess, abdominal adiposity, insulin resistance and metabolic derangements in women with PCOS has been explained by the existence of a vicious circle in these women, which may start during early stages of life or even prenatally, whereby androgen excess favoring the abdominal deposition of fat further facilitates androgen secretion by the ovaries and adrenals in women with PCOS [39,41].

The etiopathology of PCOS is poorly understood, and most putative gene candidates studied to date have been unable to adequately explain its phenotype [42], suggesting that this disease has multiple (albeit undiscovered) genetic origins modified by environmental factors and perhaps fetal programming [43,44].

3. COWS

In dairy cattle, a common cause of reproductive failure is Cystic Ovarian Disease (COD) [45,46]. In cows, follicular cysts have been defined by Kesler & Garverick [45] as follicular structures of at least 2.5 cm in diameter that persist for at least 10 days in the absence of a corpus luteum. However, in practice, veterinarians generally do not have the opportunity to follow the animal by periodic examination up to 10 days after the initial diagnosis of COD to confirm this condition. Therefore, other authors have included characteristics to overcome this inconvenience, defining follicular cysts as single or multiple anovulatory follicles in one or both ovaries, with a larger diameter than the ovulatory follicle in the absence of a corpus luteum and lack of uterine tonicity [47]. The absence of a corpus luteum is a requirement which is not always fulfilled [46]. As described below, non-steroidogenic cysts which are hormonally inactive do not influence the normal estrous cycle, so they can occur together with a corpus luteum.

Cysts arise as a result of anovulation of a preovulatory follicle. Under normal circumstances, anovulation is followed by either atresia or luteinization, after which the follicle regresses. In COD, the follicle avoids this process, increasing in size and persisting. Cyst diameters range from 2.5 cm to 7.5 cm, but mostly from 2.5 to 3.0 cm [5]. Macroscopically, cysts can be classified into follicular and luteal cysts, which are considered to be different forms of the same disorder [48]. Determination of progesterone concentrations in blood plasma, milk or milk fat can help to make a distinction between the two types. Follicular cysts secrete low amounts or no progesterone, whereas luteal cysts clearly secrete progesterone [49]. However, the threshold values show important variation [50-54], which makes it difficult to set a concentration threshold. In addition, a great variation in the intermediate forms presented with limited or extensive luteinization complicates the clear identification of the cyst type. So, classification is not clear-cut and is subject to personal interpretation [46].

During cystogenesis, the initial degeneration of granulosa cells is followed by the degeneration of the oocyte and the theca interna (luteinization of theca occurs eventually), and this fact leads to the ovulation failure of an ovulatory antral follicle. The granulosa cells undergo pyknosis and karyorrhexis and finally disappear from the cyst cavity. Al-Dahash and David [55] determined that granulosa cells were absent from 50% of cysts examined in an abattoir survey, whereas Brown *et al*. [56] determined that granulosa cells were absent from many of the cysts examined from cows diagnosed as cystic prior to ovariectomy. The theca interna cells undergo pyknosis with subsequent fibrosis of the cyst wall. Luteinization of the theca interna, when it occurs, varies from small isolated areas to thick crescents usually located at the base of the cyst deep in the ovary. It has been described that variation of the cyst wall thickness is mainly due to variation in the width of the theca interna [56]. However, in the first stage of persistence, granulosa thickness decreases significantly [57]. Thickness of the granulosa layer varies in cysts containing granulosa cells. Variation has also been observed in the thickness and degree of luteinization of the theca interna [5].

The incidence of COD in dairy herds varies from 5 to 30% [46,49,58-63]. This condition generates significant economic losses to the dairy industry by increasing calving-to-conception and intercalving intervals and, if the condition persists, the animals may be eliminated from the herd [63,64]. The incidence of cystic follicles

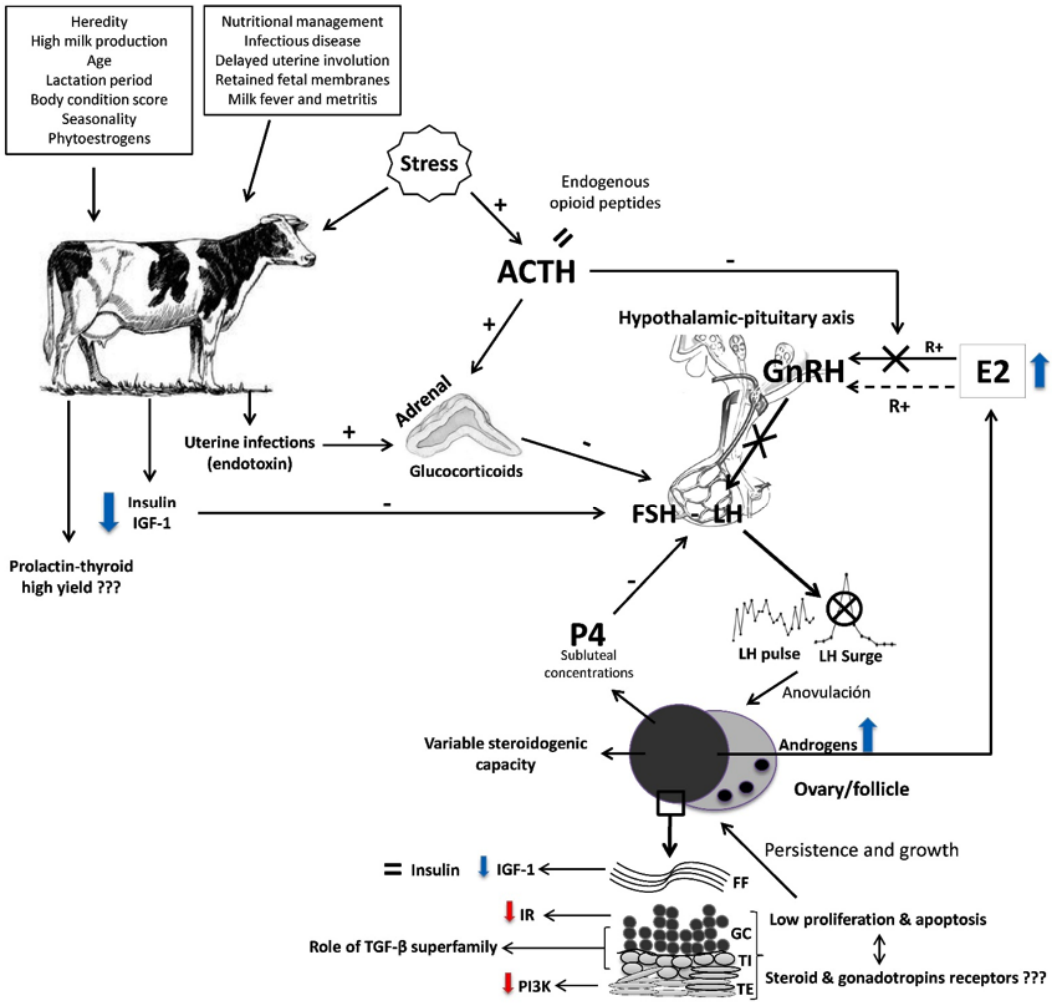

Fig. (1). Schematic representation of the multifactorial etiopathogenesis and possible pathways involved in bovine cystic ovarian disease. In the scheme are indicated all factors that alter the response mechanisms of the hypothalamic-pituitary-gonadal axis. Stressors, subluteal concentrations of progesterone, modification in estradiol feedback mechanism and important changes into the ovary (growth factors, gonadotropins and steroids receptors, insulin pathway signaling, proliferation and apoptotic mechanism) can modify the physiological patterns of hormones release at the hypothalamic (GnRH) and pituitary (FSH and LH) levels, leading to the ovulatory fail, follicular persistence, and cyst formation. Plus sign: stimulating effect. Minus sign: inhibitory effect. Blue up arrows: high concentration. Blue down arrows: low concentration. Red down arrows: reduced expression. Dashed arrow: induced modifications. R+: positive feedback. GC: granulosa cells. TI: theca interna cells. TE: theca externa cells. FF: follicular fluid. IR: insulin receptor. PI3K: phosphatidylinositol-3-kinase. TGF-β: transforming growth factor beta. IGF-1: insulin-like growth factor-1. P4: progesterone. E2: estradiol. LH: luteinizing hormone. FSH: follicle-stimulating hormone. GnRH: gonadotropin-releasing hormone.

could be higher, considering that 40-60% of cows that develop COD before the first postpartum ovulation spontaneously recover a healthy status and present no more cystic follicles [65]. Even more, if the postpartum period when resumption of normal ovarian cycles occurs from 30 to 60 days post partum, higher percentage could be detected [66,67]. COD has been observed more frequently in cows during their second to fifth lactation. Consequently, subsequent lactations have a negative impact on the reproductive efficiency in the affected animals [63].

Clinically, ovarian cysts in dairy cows are associated with nymphomania or with anestrus. Veterinarians usually diagnose COD based on the history of animals (multiple mating behavior and unsuccessful inseminations), rectal palpation and ultrasonography (Table **1**) [68,69].

The causes of COD in dairy cows have remained an enigma since they were first described in 1813 [70]. In addition, the mechanisms leading to the development and maintenance of the disease are still object of speculation and research, remaining poorly understood [71]. The disease has a multifactorial etiology, with different clinical, environmental and hereditary factors implicated in the disease pathogeny [1,5,49,65,72-77]. Regardless of the causes, the dominant follicle fails to ovulate and becomes an anovulatory cystic structure [64].

The etio-pathogenia of COD in dairy cattle is a complex process involving dysfunctions in folliculogenesis and ovulation, and other factors such as stress, nutritional management and infectious disease can co-exist (Fig. **1**) [61]. Specifically, some factors predisposing to COD are: heredity [45, 78], high milk production [59,60,78,79], age [64], lactation period [59,64,78], body condition score [80], seasonality [59,64,80,81] and phytoestrogens in the food [82]. Retained placenta, milk fever and metritis are also mentioned as potential factors associated with the prevalence of the disease [73]. Finally, of all these factors, stress has been suggested to be a major contributor to COD through its blockage of the estrogen-induced LH surge by adrenocorticotropic hormone (ACTH) [83-86].

Table 1. Summary of morphological, functional, clinical and endocrinological events in bovine COD.

Morphology	Functional	Clinical	Ultrasonography	Follicular fluid
Type 1: Presence of granulosa and theca cells layers	Follicular	Nymphomania	Wall thickness ≤ 3mm uniformly nonechogenic content	Type 1: P4 < 100ng/mL E2 > 100ng/mL
Type 2: Evidence of reduced thickness, atretic or missed granulosa and theca cells layers				
Type 3: Only the theca cells layer are present. A flat theca externa cell layer are juxtaposed to the theca interna cell layer.	Androgenic in some cases	Nymphomania/ Anestrus		Type 3: P4 < 100ng/mL E2 < 100ng/mL
Type 4: Only luteinized theca cell layers are presents	Luteal	Anestrus	Wall thickness > 3mm Granular or grid patern echogenic content	Type 2: P4 > 100ng/mL E2 < 100ng/mL

Considering the pathogenesis of COD, a distinction may be made between a primary defect in the hypothalamic-pituitary axis and a primary defect in the ovarian follicle. Although cysts may be developed from defects at both levels, *i.e.* ovary/follicle and hypothalamus/pituitary, and although it is accepted that an altered function of the hypothalamus-pituitary-ovarian axis is the main component of the etiopathogenia of COD [1,5,45,49,65,72,73,75-77,85,87,88], the persistence of follicles over time is associated with an intra-ovarian component [61,89]. Abnormal gonadotropin release has been suggested as a cause of cystic follicles in cattle [90]. In particular, a deficiency in the hypothalamic response to estrogen-positive feedback or in the pituitary response to GnRH could lead to subnormal LH release, anovulation, and cyst formation. However, the role of LH in the disease process is still under debate [91], and it has been suggested that a reduction in LH pulses could be involved in anovulation [77,85].

Regarding metabolic disorders, it has been proposed that insulin resistance or hyperinsulinemia may not have a role in the etiology of COD in cows [92]. However, we have reported several variations in the insulin signaling and IGF system mainly at ovarian level [93-97]. In the ovary, insulin and IGF-1 are able to modify the sensitivity to gonadotropins. Since in postpartum dairy cows the concentrations of IGF-1 and insulin are low, a lesser sensitivity to LH and FSH has been proposed [98]. This prevents the normal resumption of cyclicity and leads to follicle persistence and consequent cyst formation. Our results have shown reduced concentration of IGF-1 in follicular fluid of cystic cows that could have an active role in this process [95,99]. Furthermore, it has been suggested that IGF-1 is involved not only in the ovulatory failure, but also in the maintenance of COD in cattle [62,100]. In this disease, while IGF-1 levels are known to be lower during cystogenesis [100-102], intrafollicular IGF-1 can be even lower than serum concentrations [95,99].

The relevance of insulin for the final development and ovulation of follicles and for the stimulation of steroidogenesis is widely accepted [103-106]. In our laboratory, we have found lower presence of insulin receptor in granulosa cells of cystic follicles in spite of similar insulin concentration in follicular fluid of cystic and control cows. We have also reported reduced expression of the downstream intermediate phosphatidylinositol-3-kinase (PI3K) in theca cells, a novel finding that could indicate an altered insulin final response in these structures [97]. Apparently, the similar levels of insulin would not be associated with a potential different local response to this hormone in cows with COD, being the variations in the intermediates of the signaling pathway the ones that could modify the final response.

Another contributing factor that may play a role in the pathogenesis of COD is delayed uterine involution and early postpartum problems such as retained fetal membranes, milk fever and metritis [64,73]. It has been proposed that postpartum uterine infections might stimulate prostaglandin F2α (PGF2α) and glucocorticoids secretion, which predisposes cows to COD [73]. In addition, bacterial endotoxins released in the uterus may stimulate cortisol secretion, which in turn modulates or even suppresses pre-ovulatory surge-like release of LH by an unknown mechanism [73,107-110]. Consequently, endotoxins and their mediators might disturb the hormonal control of normal folliculogenesis and ovarian function [111,112].

High producing cows under stressing factors are predisposed to various reproductive problems, especially COD. The role of stress in the pathogenesis of COD is believed to be mediated by the release of endogenous cortisol through inhibition of LH release [64]. In postpartum cows, stress may mimic the action of endogenous opioid peptides (produced in the hypophysis and brain), which are believed to block the estrogen-induced LH surge and the release of hypothalamic GnRH [113,114]. Additional evidence of the role of stress in the pathogenesis of COD comes from experiments in which the disease is experimentally induced in cows by administration of ACTH [72,77,85,86,115]. Studies have shown a reduced LH response to GnRH, a reduced self-priming effect of GnRH upon the pituitary, and a delayed LH response to estradiol after ACTH administration [116]. These alterations closely resemble those occurring in COD, suggesting that stress, such as that mediated by the ACTH-adrenal cortex axis, may significantly contribute to the development of ovarian cysts. The importance of this mechanism in the generation of cysts was emphasized by Nanda and Dobson [117], who found abnormal LH surge characteristics in cows that had stress-induced increases in corticosteroid concentrations. Nanda and Dobson [117], also examined the role of endogenous opioid peptides in the etiology of cystic ovaries, and found that these peptides, which affect both GnRH secretion and the LH response of the pituitary, are also produced during stress and may, therefore, be involved in the generation of cysts.

While most evidence indicates that the development of ovarian cysts may be primarily due to deficiencies of LH secretion during the preovulatory surge, it is also feasible that the asynchrony of the

hormonal events of the preovulatory period also contributes significantly to their development [118].

Finally, there is evidence that the prolactin-thyroid system may be involved in the development of ovarian cysts. Hypothyroidism has been associated with cystic follicles in several species, and thyroxine concentrations are negatively correlated with milk production, such that high-yielding cows have lower concentrations than low-yielding ones. Hence, an association between hypothyroidism and COD in cattle has been postulated [5]. Hafez [119] suggested that ovulatory failure and cyst formation are related to high prolactin secretion (*i.e.* as associated with high yield) and, although McNeilly [120] considered that prolactin is not involved in regulating FSH and LH release at ovulation, the administration of bromocriptine (a prolactin inhibitor) blocks cyst formation in hypothyroid rats [121].

Although many studies have characterized the dynamics of follicular growth, our understanding of the cellular and molecular changes that occur within the ovarian follicle prior to the process of anovulation is still limited. As described above, the general agreement assumes that cysts develop from preovulatory follicles that fail to ovulate, persist in the ovary, and therefore interfere with normal ovarian function [46]. Some studies define persistence as a temporal stage of the life span of the cyst [88,122], whereas others consider it as a separate follicular pathology [123]. The cellular changes may be in the form of aberrant production of growth factors by the granulosa cells, the inappropriate secretion of extracellular matrix proteins or changes in cytoskeletal components [93,95,96,99,124-126].

Intraovarian alterations, as causes that contribute to follicular persistence, have not yet been clearly established. However, several studies have contributed to a better understanding of specific aspects related to the pathogenesis of cystic ovaries. In relation to endocrine signaling pathways, an altered expression of steroid and gonadotropin receptors has been demonstrated. Some authors have postulated and evaluated the intra-follicular roles of steroids in regulating follicular development [89,127-130]. Previous studies have also shown that growing and cystic follicles from cows with COD show a decrease in cell proliferation and apoptosis detected *in situ*, as well as in the expression of pro-apoptotic genes in relation to anti-apoptotic ones [131,132]. It is known that alterations in the proliferation of granulosa cells and the fate of the follicles (i.e. atresia or formation of cysts) are related specifically to steroid hormone and gonadotropin receptors. In this sense, the imbalance between proliferation and apoptosis observed in follicular cysts could explain the growth of cystic follicles and the maintenance of a static condition without degeneration and atresia, which leads to their persistence. These alterations may be due to structural and functional modifications that take place in the follicular cells and could be related to hormonal changes in animals with COD. In relation to cellular changes, it has been proposed that follicular cysts represent a distinct stage of follicular differentiation, with a characteristic protein and gene expression profile in granulosa and theca cells that differs from that found in dominant follicles and other follicular structures [126,130,132-134].

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Steroidogenesis in cystic follicles has been studied by measuring 1) plasma hormone levels, 2) steroid secretion by cyst tissue *in vitro*, and 3) hormone content of follicular fluid. The results of such studies have revealed a rather confusing and inconsistent pattern of steroid metabolism. Apparently, follicular cysts are extremely variable in their steroidogenic capacity [46]. The steroid hormone profile of cows during and shortly after cyst formation is comparable to that of cows with an ovulatory estrus [57]. Estradiol levels during estrus in cows developing cysts are similar to or higher than those of ovulating controls, and progesterone levels are also similar [57]. In cows with cysts, the estrus-like hormone profile persists throughout the early luteal phase, whereas in cows without cysts estradiol decreases and progesterone increases [57,136,137]. The evolution follicular structure of the cystic ovaries may contribute to the variation in steroids profiles. Sporadic increases in progesterone have been observed, suggesting a luteinization process of follicular cells [138]. On the other hand, a deficient aromatization by changes in the granulosa cells could be responsible for the increase in testosterone that characterizes cystic follicles during COD in cattle (Table **2**) [57,115,139].

Finally, cows with chronic cystic follicular degeneration may have lesions in several extraovarian organs, including the uterine tubes, uterus, cervix, vagina, vulva, mammary glands, adrenals, and pituitary. The mucosa of the uterine tubes becomes thick and edematous. However, unlike in women, no syndrome has been described and these lesions are the associated result of the changes produced by COD and not part of an integral syndrome.

4. MARES

Mares do not show a follicular cystic degeneration comparable to that of women and cows. In mares, the mature follicles may grow up to 70 mm [140] but should not be diagnosed as cystic. Normally, the range of maximum diameter of preovulatory follicles varies from approximately 20 to 60 mm [141].

In mares, unlike what happens in cattle, follicular cysts have not been widely studied but still occur, and there is a discussion about their actual definition. McCue [142] referred to follicular cysts as persistent anovulatory follicles, which should not be confused with hemorrhagic follicles. Sometimes, this condition shows long periods of estrus at the beginning of the breeding season but cycles become normal as the season progresses. Although the condition has been often diagnosed clinically, the macroscopic and microscopic examination of the gonads fails to substantiate the clinical diagnosis [143].

In relation to signs, two types of cases in mares have been suspected of having follicular cysts. The first type is the mare that is normal except when it is in estrus. These mares are unusually intractable during estrus and return to normal behavior after estrus or ovariectomy. The second type is described as nymphomaniac. Arthur [144] reported that this "syndrome occurs irrespective of the phase of reproductive activity and continues without abatement into the period of winter anestrus, the nervous derangement has apparently become fixed and independent of female hormone; ovariectomy cannot then be expected to effect a cure."

Occasionally, a follicular cyst can increase to a size of 100 mm or more, persists in the ovary through several estrous cycles, and

then regresses. These persistent follicles do not modify the normal development of estrous cycles, including ovulation [143]. On the other hand, large anovulatory follicles are normally encountered during transition periods of spring and autumn. Anovulatory follicles can exceed 10 cm in diameter and may persist for several weeks [145]. Frequently, the ultrasonographic image show dispersed free-floating echogenic spots as a result of the presence of blood in the follicular fluid (hemorrhagic follicles). In other cases, echogenic fibrous bands resulting from gelatinization of the hemorrhagic fluid have been observed. Although human chorionic gonadotropin or GnRH may induce ovulation, in most cases the treatment is ineffective. Fortunately, most of these anovulatory follicles regress spontaneously within 1 to 4 weeks [145].

It is worth noting that mares sometimes present an abnormality that is often confused clinically with cystic ovaries. These structures have been termed "autumn follicles" because they appear in the autumn season, although they have also been reported at other times of the year [146]. These structures are large anovulatory follicles (10-15 cm in diameter) containing blood with a liquid to gelatinous consistency [147]. The cause of this alteration is unknown, but it has been suggested that their higher incidence in autumn is related to a declining gonadotropin concentration [148].

The pathophysiology of follicular cysts remains unclear, although at present it is known that these follicles persist in the ovary and remain growing after ovulation failure, in a manner similar to that observed in ruminants [149]. The cause is likely to be abnormal estrogen production by the follicle and/or insufficient release of gonadotropins to induce ovulation [145]. In the same way as in cattle, the IGF system plays a role in both conditions, causing alterations in testosterone and estradiol concentrations. Follicular fluid from cystic follicles has higher testosterone and lower estradiol concentrations than follicular fluid from normal follicles. However, the role of the IGF system and the importance of its deregulation are still unclear and further studies should be made [149].

In any case, as in other species, cysts in mares have been associated with metabolic disorders or multisystem syndromes.

5. SOWS

Reproductive failure in sows is a common and important problem in swine farms. Some of the main clinical signs associated with this reproductive failure are anestrus, irregular estrous cycles, failure to return to heat, repeat breeding, small litter size and aggressive behavior. However, like in cows, one of the main reproductive diseases of sows is the ovarian cyst, which causes infertility and significant economic losses [150-153].

Heinonen *et al*. [152] showed that approximately 50% of the 1708 reproductive organs of sows and gilts studied had ovarian alterations and that 6.2% had variable degrees of cystic follicles. In other studies, approximately 10% of the sows culled for fertility problems showed these ovarian structures [154,155]. The presence of cysts before insemination and conception might not interfere with ovulation of other follicles but could decrease the number of normal viable eggs [155].

Although a common clinical sign in cows with cystic ovaries is nymphomania, this sign has not been described in sows. In sows, one of the most important signs is the intermittent or permanent anestrus, which could lead to misdiagnosis of pregnancy [143].

Although follicular cysts are related to hormonal imbalances, it is not easy to diagnose it on the basis of the hormonal profile. This disorder is complex because plasma concentrations of steroid hormones (progesterone and estradiol) and gonadotropins (LH) in this alteration are similar to those in sows during diestrus [155].

In sows, differently from that observed in cows and mares, and similarly to that observed in women, cysts occur as polycystic ovaries. Tsuma *et al*. [156] classified cystic follicles into two groups based on cyst size.

The first group, which is found more commonly, includes multiple large cysts that measure up to 50 mm in diameter and frequently have patches of luteal tissue in the wall. These cysts contain lower levels of estrogen and higher levels of progesterone. The second group, of unusual diagnosis, includes multiple small cysts that measure 10 to 15 mm in diameter, with little or no luteinization of the cystic wall. These cysts have high concentrations of estrogen and small amounts of progesterone.

Currently, the most widely accepted hypothesis about their pathogenesis is a deficiency in the LH release necessary for ovulation [155,157]. Developing cystic follicles are responsive to injection of gonadotropin during treatment known to result in experimental ovarian cysts. However, the reasons involved in the LH imbalance are not known. In this sense, it is accepted that stress, acting through the ACTH-adrenal cortical axis may be a relevant factor in the formation of cysts [158,159].

Social stress may alter the hormonal milieu that exists in the moment of ovulation and fertilization, producing an important negative effect on the reproductive performance of animals [160]. Increased secretion of ACTH is known to be accompanied by a decrease in the secretion of gonadotropins. Injections of ACTH during the follicular phase of the estrous cycle interferes with ovulation in intact sows but not in adrenalectomized sows [155,157,160]. Although the adrenal cortex may be implicated, its role is unknown. In this sense, some results suggest that progesterone of adrenal cortical origin could be involved in the development of COD in sows [158,161-163]. It has also been shown that hypothyroidism promotes the formation of ovarian cysts. The role of thyroid hormones in ovarian function has been evidenced by many authors. Moreover, some authors suggest that the development of ovarian cysts in sows is related to the seasons of the year [155].

Like in other species, an important intraovarian component has also been described in sows. Recent studies have revealed that apoptosis and cell proliferation are altered in swine cystic follicles [164]. Some studies have demonstrated that changes and destabilization of the cytoskeletal proteins (microtubules, microfilaments and intermediate filaments) of the ovary sharply decrease the production of steroid hormones and can contribute to cystogenesis [165]. Also, the development of ovarian cysts in sows has been associated with changes in the expression of cytoskeletal proteins and some growth factors [166,167]. Also, Bababola and Shapiro [4] have observed changes in steroid hormone synthesis in cystic ovaries but the precise role of steroids in the pathogenesis of COD remains unknown.

6. BITCHES

In bitches, follicular cysts do not occur as frequently as other types of pathologic ovarian cysts. The frequency of occurrence of follicular cysts in bitches has been overestimated because other types of cysts have been mistaken for follicular cysts. An incidence of 3% to 16 % has been described, being the most common type of non-neoplastic cyst in the canine ovary [168,169]. Cystic structures can vary widely in size, ranging from 0.5 cm to 7.0 cm [168,170-173].

By definition, an ovarian cyst in bitches is a fluid-filled structure [174] of any size, present outside physiological proestrus and estrus within the ovary [175]. There may be a single or multiple cysts in one or both ovaries [168], and it can be either endocrine active or inactive [174]. There are different types of ovarian cysts: follicular cysts, cysts of subsurface epithelial structures, cystic rete ovarii, lutein cysts and cystic corpora lutea [153,168,173,175]. Follicular cysts are known to be endocrine active (*e.g.* they produce estradiol and progesterone; [174]). This is also true for lutein cysts and cystic corpora lutea (*e.g*. they produce progesterone; [143,173, 175].

Table 2. Summary of morphological, functional, clinical and endocrine characteristics in different species.

Characteristics	PCOS in woman	COD in bovine	Cysts in mares	Cysts in sows	Cysts in bitches
Genetic influence	Yes [10]	Yes [46]	?	?	?
Environmental influence	Yes [10]	Yes [46]	?	Yes [155]	?
Syndrome	Yes [12]	No [143]	?	?	No [176,177]
Disease	No [12]	Yes [46]	?	Yes [155]	Yes [176,177]
Ovary dysfunction	Yes [18]	Yes [61]	Yes [149]	Yes [164]	Yes [173]
Unique cysts	No [18]	Yes [47]	Yes [143]	No [159]	Yes [168]
Multiple cysts	Yes [8,9,13]	Yes [47]	No [143]	Yes [159]	Yes [168]
Anovulation	Yes [13]	Yes [64]	Yes [142]	Yes [155]	Yes [176]
Incidence %	5 - 15 [17]	5 - 30 [63]	?	6,2 - 10 [152,154]	3 - 16 [168,169]
Cyst diameter (cm)	0,2 - 0,9 [17]	≥ 2,5 [5]	≥ 10 [143]	1 - 1,5 [159]	0,5 - 7 [170,172]
Follicular persistence	Yes [18]	Yes [45]	Yes [142]	?	Yes [175]
Alteration of the estrous cycle	Yes [8]	Yes [89]	No [143]	Yes [143]	Yes [174]
Nymphomania	No [18]	Yes/No [69]	Yes [143]	No [143]	Yes [177,174]
Spontaneous recovery	?	Yes/No [65]	Yes [145]	?	?
Gonadotropins alterations	Yes [18]	Yes [90]	Yes [145]	Yes [155,156]	?
Hyperandrogenism	Yes [13]	Yes [57]	Yes [143,149]	?	?
Estrogens (serum or follicular fluid)	High (serum) [18]	High (serum) [57]	High (follicular fluid) [143]	High (follicular fluid) [159]	High (serum) [175]
Hyperinsulinemia	Yes [24, 25]	No [46]	?	?	?
Serum IGF-1	High [26]	Low [100]	?	?	?
Serum AMH	High [30]	Equal [89]	?	?	?
Insulin resistance	Yes [39]	No [92]	?	?	?
Associated diseases	-Diabetes -Hypertension -Dyslipidemia -Cardiovascular disease -Menstrual irregularities -Infertility -Hirsutism [8,9]	-Lesions in: uterine tubes, uterus, cervix, vagina, vulva, mammary glands, adrenals and pituitary -Stress -Infectious -Retained placenta -Milk fever [143]	-metabolic disorders -multisystem syndromes. [142, 143]	- infertility: decrease the number of normal viable eggs -Stress [155,160]	- cystic endometrial hyperplasia -prolonged estrous periods -edema of the vulva -vulvar discharge - Coat and skin alterations [143,173,174,177]

Little is known of the inter-relation between gross pathological and endocrine appearance of ovarian cysts in bitches, although their clinical significance may be relevant [176]. As in other species, hormonally active ovarian cysts are of high clinical relevance in bitches. They are a significant source of hyperestrogenism [175], which may result in prolonged estrus [177,178] and uteropathies [174]. Besides, follicular cysts can be associated with several signs of hyperestrogenism, including prolonged estrous periods, attraction of male dogs, edema of the vulva, and vulvar discharge. However, many of them do not exhibit specific manifestations of ovarian malfunction [143,174].

It has been suggested that one or a few cysts may have the same endocrine potency as a larger number of cysts. In a previous study, increasing numbers of ovarian cysts were not correlated with increasing plasma hormone concentrations for either 17ß-estradiol or progesterone [173]. These results highlight the endocrine potency of even single ovarian cysts to disrupt normal ovarian function in bitches, which can result in hyperestrogenism and other disorders of hormonal origin (e.g. coat and skin alterations).

Different cysts located on the same ovary may exhibit differences in hormone levels, indicating that the cellular and endocrine activity of cysts is independent among them. These cysts may be formed at different stages of folliculogenesis and consequently have a varied number of granulosa and theca cells different steroids hormones [173,179,180].

Cystic follicular degeneration in bitches differs from that in other species of domestic mammals in that granulosa cells tend to persist in the wall of cystic follicles. As previously mentioned, in cows and sows, most or all granulosa cells degenerate in long-standing cysts. In some bitches, especially those manifesting signs of hyperestrogenism, proliferating cords of elongated cells with clear cytoplasm line the cysts and extend into the adjacent connective tissue. Approximately 50% of the cases in bitches have patches of lutein tissue lining the cysts [143,173].

The extraovarian lesions associated with follicular cysts in bitches have not been studied in depth. However, cystic hyperplasia of the progestational type, which leads to pyometra and cystic hyperplasia of the estrogenic type, has been seen in cases of follicular cysts in bitches. Bitches with progestational hyperplasia of the uterus have cysts with areas of luteinization, whereas those with estrogenic hyperplasia have proliferating granulosa cells lining the cysts [143]. In bitches, no metabolic changes associated with follicular cysts have been reported.

7. FUTURE RESEARCH DIRECTIONS

The current and future studies are directed to better understanding cyst development and the stressful factors that influence the normal ovarian function. In this sense, it would be interesting to evaluate different features related to ambient conditions able to affect the gestational period and consequently influence on the reproductive functions of the offsprings. Particularly, it has proposed a significant role of the epigenetic in the inheritance of physiological systems since numerous questions are still remain. To advance in these lines of studies will provide evidences of the effect of stressful events on reproduction of the future generations.

Another interesting direction is to elucidate the main factors that could predispose to the cystic disease and exert influence in follicular persistence, to infer about the ethiopatogenia of the reproductive disorders. For these reasons, the development of animal models of persistence will allow to evaluate different factors during the development of these diseases and will allow determining preventive strategies of these disorders.

Finally, the novel evidences related to metabolic system encourage delving into the knowledge of their influence on the ovarian function.

8. MAJOR CHALLENGES

Over the years numerous studies have allowed to collect evidences to better understand follicular cyst development, the determinant factors influencing their establishment and persistence, and their consequences on ovarian function. These studies provide important data on diagnosis, characterization and treatments in the immediacy of cyst formation. A great challenge would be to provide information of long term effects and the possibility to develop animal models in order to answer in this sense, making it available novel information on transgenerational effects.

On the other hand, considering that cyst formation is a result of multiple factors, integrate them is the key to an effective system analysis and to understand their development. A number of genomic, proteomic and epigenetic studies may highlight multiple factors that are involved, but the significance of such molecular targets will be dependent on the particular physiology and molecular biology of the system of interest. A comparative approach has yielded significant insight into the role of the molecular components of the stress or metabolic system and the reproductive one, but many questions remain unanswered.

CONCLUSION

As extensively described above, follicular cysts are the result of some as yet undefined malfunction in the ovulatory mechanism, together with intraovarian alterations. Since ovulation culminates after a complex series of interrelated events involving the ovary, hypothalamus and pituitary gland, determining the point at which the malfunction exists is rather difficult. Cyst formation in the five species discussed may involve different mechanisms; indeed, different mechanisms may also exist within a species (Table **2**). In addition, with a few exceptions, the findings in one species cannot be generalized to others. However, data on this subject in one species might complement those in other species and give us a better understanding of the problem. Although in all species discussed in this review, the common sign is the follicular cyst, the organs and systems affected in the associated diseases are not the same, reaching its greatest complexity in PCOS in women. Thus, studies should be conducted in each species to know the morphological and biochemical characteristics and pathogenia of cystic follicles. In particular, metabolic syndrome is significantly observed in women and not repeated in other species. Therefore, we must avoid generalizations in comparative medicine, by conducting appropriate studies for each disease, since sharing a sign does not mean that diseases and syndromes are mechanistically analogous.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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