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Epidemiological Description of Cystic Ovarian Disease in Argentine Dairy Herds: Risk Factors and Effects on the Reproductive Performance of Lactating Cows

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Contents

To describe the epidemiology of cystic ovarian disease (COD), to find possible risk factors associated with the incidence of cysts and to analyse the impact of COD on the reproductive performance of dairy cows, databases from 22 dairy herds from the main dairy region in Argentina were retrospectively evaluated throughout a 3-year period (2009–2011). A total of 248 COD cases over 9156 parturitions were recorded, resulting in a cumulative incidence rate of 2.7%. Cystic ovarian disease incidence density was lower during the first 100 days postpartum (DPP) than during later stages of lactation. Seasonality had a significant influence on the disease presentation with higher incidence rates during winter and spring. Cows with a previous diagnosis of clinical mastitis showed 2.72 times more chances of developing ovarian cysts. Cystic cows had longer calving to first service and calving to conception intervals and lower conception rate than controls.

Introduction

Cystic ovarian disease (COD) is a common cause of reproductive failure in dairy cattle (Kesler and Garverick 1982). Follicular cysts have been defined by Kesler and Garverick (1982) 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. Other authors defined follicular cysts as single or multiple anovulatory follicles larger than 20 mm and 15 mm, respectively, in one or both ovaries, in the absence of a corpus luteum and lack of uterine tonicity (Bartolomé et al. 2005). Although the mechanism of cyst formation is still not fully understood, most researchers coincide that the hypothalamic–pituitary–ovarian axis presents an endocrine imbalance associated with an absent, insufficient and/or asynchronous luteinizing hormone (LH) surge (Garverick 1997; Vanholder et al. 2006). In addition, a primary dysfunction characterized by cellular and molecular changes at the follicle level such as variations in the expression of cytoskeletal and heat shock proteins and modifications in the insulin-like growth factors system and steroid receptor expression in the granulosa and theca cells has also been demonstrated (Ortega et al. 2007; Rey et al. 2010; Alfaro et al. 2012; Salvetti et al. 2012; Velázquez et al. 2013).

Cumulative incidence rates of COD in dairy herds reported by other authors range between 6 and 23% (Casida and Chapman 1951; Bartlett et al. 1986; Laporte et al. 1994; Garverick 1997; Silvia et al. 2002; Vanholder et al. 2006; Probo et al. 2011). A recent study from Norway has reported a lower incidence rate of 0.82% (Nelson et al. 2010). Some factors predisposing to COD are as follows: heredity (Kesler and Garverick 1982; Hooijer et al. 2001), high milk production (Bartlett et al. 1986; Laporte et al. 1994; Rajala and Gröhn 1998; Hooijer et al. 2001), age (Peter 2004), lactation period (Bartlett et al. 1986; Hooijer et al. 2001; Peter 2004), body condition score (López-Gatius et al. 2002), seasonality (Bartlett et al. 1986; López-Gatius et al. 2002; Peter 2004; Nelson et al. 2010) and phyto-oestrogens (Roberts 1986). Also, retained placenta, milk fever and metritis are mentioned as possible factors associated with the prevalence of the disease (Bosu and Peter 1987). Finally, stress, through its blockage of the oestrogen-induced LH surge by ACTH, has been suggested to be a major contributor to COD (Liptrap 1993; Kawate et al. 1996; Dobson et al. 2000; Amweg et al. 2011).

Few published studies around the world have focused on the epidemiological aspects of COD (Bartlett et al. 1986; Mohammed et al. 1991; Laporte et al. 1994; Hooijer et al. 2001; López-Gatius et al. 2002; Østerås et al. 2007; Nelson et al. 2010). All of them correspond to research carried out in North America and European countries. In this regard, there is a complete absence of information on the epidemiology and risk factors related to COD in dairy herds from Argentina, where the management systems, climate and cow biotypes are different from those of north hemisphere countries.

The objectives of this observational study were to describe the epidemiology of COD in Argentine dairy herds, to find possible risk factors associated with the incidence of cysts and to analyse the impact of COD on the reproductive performance of cows.

Materials and Methods

Databases from 22 dairy herds from the central-eastern area of Santa Fe province, the main dairy region in Argentina, were evaluated throughout a 3-year period (2009–2011). Cows were managed in an all-year-round calving system and had a diet based on alfalfa pasture, oat or ryegrass grazing supplemented at different proportions (45–60%) with corn silage, alfalfa silage, corn grain, soya bean expeller and hay, according to the season of the year and production level. All cows had a dry period of at least 60 days before calving. Regular gynaecological examinations by rectal palpation made by the farms veterinarians started approximately 30 days after parturition and continued up to pregnancy confirmation at a biweekly frequency. Cows eligible for examination were all those that were open with more than 30 days post-partum (i.e. cows with history of delayed oestrus, abnormal interestrous interval or non-return to oestrus after service). Artificial inseminations started after a voluntary waiting period (VWP) of 50 DPP. In a few dairies (n = 6), repeat breeder cows (those that cycle normally, have no clinical abnormalities and fail to conceive after three services) representing on average 10–15% of all open cows were naturally mated after heat detection. For that purpose, cows in heat were taken to the bullpen to be bred. Reproductive and complementary data were recorded in a dairy herd management software system (SW Agropecuaria® – San Carlos, Santa Fe, Argentina). Descriptive epidemiology in this study included the following: COD cases distribution along lactation, seasonality of COD presentation, cumulative incidence rate during the time period analysed and incidence density rate related to the lactation period when the event occurred. All the cows that calved during the study period and had >30 DPP (n = 9156) were considered as the population at risk (Laporte et al. 1994).

A case–control study was conducted to identify possible risk factors associated with the disease. Additionally, the effects of COD on the reproductive performance of the cows were evaluated.

Case–control study

The dependent (outcome) variable for this retrospective study was the presence or absence of COD. Case definition in this study was a diagnosis of COD made by veterinarian practitioners during their regular fieldwork based on the presence of a single or multiple follicular structures >2 cm in the absence of a palpable corpus luteum, lack of uterine tonicity and that interfered with normal cyclicity (Bartolomé et al. 2005; Vanholder et al. 2006). Only ovarian cysts diagnosed for the first time during the lactation under study were considered. Due to practical inconvenience, cyst diagnosis reconfirmation 7–10 days later was not performed. However, based on Bartolomé et al. (2005), confirmation of the diagnosis may not be necessary because the lack of palpable uterine tonicity indicates that luteolysis had occurred at least 7 days before, the uterus is no longer under the effect of oxytocin, and the follicles have been growing in the absence of progesterone. Cases diagnosed after an abortion were dismissed to avoid distortion on the calving to diagnosis interval (CDI). All the cows with cysts were treated immediately after diagnosis with gonadotropin–releasing hormone (GnRH) or a combination of GnRH and a progesterone intravaginal device. Seven days after insertion, progesterone device was withdrawn and 150 μg de D+Cloprostenol was injected. Except for this specific treatment, cystic and control cows were managed in the same way.

Control cows from the same farm were randomly selected except for the calving date, which was required to be similar (<15-day difference) to that of the related case. The case/control ratio was 1 : 2 (248 : 496). Sample size was calculated based on the following assumptions: a COD estimated prevalence of 12.9% (Erb and White 1981), a minimum odds ratio to detect of 1.5, a level of confidence of 95% and a power of 80%.

Independent variables offered to the model in this study were as follows: age, parity group (primiparous or multiparous), calving ease, production of previous lactation adjusted to 305 days (PPL305), body condition score (BCS) evaluated at the end of the VWP (50–65 DPP), uterine diseases (metritis and clinical endometritis) and clinical mastitis occurred between parturition and cyst diagnosis (Table 1). Cases of metabolic disorders and pododermatitis were not considered for the analysis due to the scarce number of events recorded. The BCS variable was also categorized (BCS cat) in two groups based on the median of frequency distribution. All data were extracted from the dairy herd management software system.

Evaluation of the effects of COD on the reproductive performance of the cow

Considering COD diagnosis as the starting point, cows were allocated in two groups: one including all cows that developed cysts after parturition, and the other including cows used as controls in the case–control study. The outcome variables studied in this case were as follows: calving to first service interval (CFSI) for those cows that presented COD before their first service, calving to conception interval (CCI), cumulative pregnancy rate up to the end of lactation (PR), abortion and production of concurrent lactation adjusted to 305 days (PCL305).

Statistical analysis

Descriptive epidemiology

The overall cumulative incidence rate was calculated as the total of COD cases diagnosed during the study period divided by the population at risk. The COD incidence density rate related to the lactation period when the event occurred was calculated as COD cases per lactation period divided by the number of open cows months at risk for each period (Dohoo et al. 2003). To evaluate the effects of seasonality and stage of lactation on COD incidence rates, chi-square tests were conducted.

Case–control study

To identify potential risk factors associated with COD incidence, a two-stage analysis was conducted (Dohoo

Table 1. Description of independent variables included in the case–control study

Variable	Description
Age	Months of age since born
Parity group	Cows were categorized into two groups primiparous and multiparous
Calving	Parameters considered were calving date and calving ease (normal or assisted)
PPL305	Total milk production of previous lactation adjusted to 305 days. Lactations with <200 days were dismissed
Body condition score	Scales 1 to 5 with 0.25 point increases (Edmonson et al. 1989), evaluated once after the voluntary waiting period
Diseases	Cases of metabolic diseases, uterine infections, pododermatitis and clinical mastitis recorded

et al. 2003). In the first stage, associations between the dependent variable (case of COD) and each of the independent variables were screened by univariate chi-square test for dichotomous variables (BCS cat, calving ease, uterine diseases and clinical mastitis) or independent-samples t-test analysis for continuous variables (age, lactation number, BCS and PPL305). Variables with a $p < 0.15$ were then considered for further analysis provided that there was no co-linearity ($r < 0.60$) between them. Co-linearity between variables was assessed pairwise by calculating Spearman rank correlations. In the second stage, associated variables with $p < 0.15$ in the univariate analysis were offered to a logistic regression analysis. In the final model, variables with $p < 0.05$ were considered statistically significant and retained in the model.

Effects of COD on the reproductive performance of the cow

The impact of COD on cow's fertility was evaluated considering the following parameters: CFSI, CCI, PR, PCL305 and abortion. Continuous outcome variables (CFSI, CCI and PCL305) were analysed by performing a generalized lineal model, whereas dichotomous variables (PR and abortion) were analysed by mixed-effects logistic regression (INFOSTAT®; Universidad Nacional de Córdoba, Córdoba, Argentina). In both analysis, group, age, year of COD diagnosis, calving and COD diagnosis season, BCS, parity and calving ease were considered as fixed effects, whereas herd was used as a random-effects variable.

Results

Descriptive epidemiology

The number of milking cows per herd, mostly Argentine Holstein cows, ranged from 75 to 494. Mean production per 305-day lactation of the whole population under study was 7817 ± 1805 kg. Cows averaged 3.0 ± 1.7 lactations. The cumulative incidence rate of COD during the study period was 2.7% (248 cases over 9156 cows at risk), and the mean partum to diagnosis interval was 158 ± 115 days. Open cows with <100 DPP presented a lower COD incidence rate than those at later stages of lactation ($p < 0.05$; Table 2). Cystic ovarian disease cases were more frequently diagnosed during winter and spring ($p < 0.05$; Table 3). In addition, COD incidence was higher among cows that calved during autumn and winter ($p < 0.05$; Table 4).

Table 2. Cystic ovarian disease (COD) incidence density rate along lactation. A total of 248 COD cases were diagnosed

	<100 DPP	101–150 DPP	151–200 DPP	>200 DPP
Cystic cows	97	47	25	79
Open cows months at risk	27775	8126	5648	17476
Incidence rate	0.35%[b]	0.58%[a]	0.44%[ab]	0.45%[ab]

DPP days post-partum. Values with different superscript letters are significantly different at $p < 0.05$.

Table 3. Seasonal cystic ovarian disease incidence density (n = 248)

Season	Cows season at risk	Cystic cows	Incidence density (%)
Summer[1]	4662	40	0.86[a]
Autumn[2]	5001	56	1.12[a]
Winter[3]	4491	78	1.73[b]
Spring[4]	3942	74	1.88[b]

Values with different superscript letters are significantly different at $p < 0.05$.
[1]January, February, March.
[2]April, May, June.
[3]July, August, September.
[4]October, November, December.

Table 4. Cystic ovarian disease cumulative incidence rate related to the calving season (n = 248)

Season	Calvings	Cystic cows	Incidence rate (%)
Summer[1]	2639	59	2.24[a]
Autumn[2]	2741	78	2.85[ab]
Winter[3]	2211	78	3.53[b]
Spring[4]	1565	20	1.28[c]

Values with different superscript letters are significantly different at $p < 0.05$.
[1]January, February, March.
[2]April, May, June.
[3]July, August, September.
[4]October, November, December.

Case–control study:

Tables 5 and 6 summarize the comparative results of univariate analysis for continuous and dichotomous variables, respectively. No association was found between age ($p = 0.484$), PPL305 ($p = 0.613$), parity group ($p = 0.416$), BCS ($p = 0.601$), calving ease ($p = 0.166$) or uterine disease ($p = 0.366$) and COD. Conversely, BCS cat ($p = 0.148$) and clinical mastitis ($p = 0.041$) were associated with COD and were offered to a logistic regression model (Table 7). Results from the analysis showed that BCS cat was not associated with the COD ($p = 0.267$). In contrast, cows that suffered a previous event of clinical mastitis had higher risk (odds ratio = 2.7; 95% CI 1.07–8.08) of having COD than cows without clinical mastitis ($p = 0.037$).

Effects of COD on the reproductive performance of the cow

The CFSI was not different between groups; however, cystic cows showed a trend for a longer interval than

Table 5. Results of continuous variables for control (n = 496) and cystic (n = 248) cows

Variable	Group	Mean	SD	p-value[a]
Age (months)	Control	66.2	25.4	0.484
	Case	64.8	24.9	
PPL305 (kg)	Control	7710	1556	0.613
	Case	7633	1441	
Lactation number	Control	3.1	1.7	0.416
	Case	3.0	1.7	
Body condition score	Control	2.76	0.4	0.601
	Case	2.79	0.5	

[a]Significance = p-value <0.15.

Table 6. Frequency distribution of dichotomous variables for control (n = 496) and cystic (n = 248) cows

Variable		Group			
		Control (%)	Cystic ovarian disease (%)	Total	p-value[a]
Calving ease	Normal	413 (66.8)	205 (33.2)	618	0.166
	Assisted	83 (73.5)	30 (26.5)	113	
Body condition score categorized	<2.75	123 (68.3)	57 (31.7)	180	0.148
	≥2.75	76 (60.3)	50 (39.7)	126	
Uterine diseases	No	432 (67.3)	210 (32.7)	642	0.366
	Yes	64 (62.7)	38 (37.3)	102	
Clinical mastitis	No	480 (67.4)	232 (32.6)	712	0.041
	Yes	16 (50.0)	16 (50.0)	32	

[a]Significance = p-value <0.15.

Table 7. Odds ratios of the variables included in the final logistic regression model for cystic ovarian disease

Variable	β	OR	95% CI	p-value[a]
Body condition score cat	0.278	1.32	0.808–2.156	0.267
Clinical mastitis	0.999	2.72	1.073–7.064	0.037

[a]Significance = $p < 0.05$.

controls (108 ± 63 and 81 ± 43 days, respectively; p = 0.056). Similarly, the CCI was higher in cows that previously presented COD (219 ± 122 vs 148 ± 91 days, respectively; $p < 0.001$). Cumulative pregnancy rates in cystic and control cows were 67% (166/248) and 89% (442/496) by the end of lactation, respectively ($p < 0.001$), with non-cystic cows having 4.04 times more chances to conceive than cystic cows. Cystic ovarian disease did not affect the milk production on the concurrent lactation (p = 0.721), and cysts were not associated with an increased risk of abortion afterwards (p = 0.5).

Discussion

During the 3-year period analysed in this study (2009–2011), 248 cases of COD were recorded in a population of 4945 milking cows distributed in 22 farms. The cumulative incidence rate for this time period (2.7%) was lower than those reported by other authors (Bartlett et al. 1986; Laporte et al. 1994; Garverick 1997; Silvia et al. 2002; Vanholder et al. 2006; Probo et al. 2011). As this disease has been associated with high-milk-production cows under very intensive management systems (Laporte et al. 1994; Opsomer et al. 1999; Vanholder et al. 2006), it could be expected that lower production cows on pasture-based systems such as the ones described in this study show a diminished incidence rate. Another reason that might explain the lower incidence rate could be found in the diagnostic criteria used in this study. Earlier reports on this topic considered size of a cyst to be at least 2.5 cm in diameter based on rectal palpation (Kesler and Garverick 1982). With the later implementation of ultrasound as a diagnostic tool, it has been possible to confirm COD cases in follicles structures with diameter just slightly larger than the ovulatory size (Bartolomé et al. 2005; Vanholder et al. 2006). Per rectal palpation alone might not be sensitive enough to detect such a small difference in size; thus, a certain number of cases could have been omitted of being diagnosed in the present study. However, the evaluation of uterine tone complemented with the reproductive history of the animal becomes essential complementary data that help minimizing these limitations (Hanzen et al. 2000).

Regarding ovarian cyst incidence density on the different periods along lactation, we found a lower incidence rate during the first 100 DPP than during later stages. This seems to be in disagreement with the results found by many researchers, who claimed that most cysts occur during the first third of lactation (Whitmore et al. 1974; Laporte et al. 1994; Hooijer et al. 2003; Vanholder et al. 2006). Although this could be true in terms of absolute numbers, these authors omitted to mention that during that period of time most cows are open and 'at risk' of suffering from COD. Thus, the relative number of cysts (incidence rate) during early lactation might not be as high as it seemed compared to later stages. Nevertheless, as mentioned above, some of these authors have also found that COD is related to high-yielding cows. Considering that milk production peaks within 60 DPP, by this time, these cows may be expected to have a higher incidence of cysts. Vanholder et al. (2006) suggested that a deeper and/or longer negative energy balance (NEB) could have explained this association. This may not be the case of the present study, as we failed to demonstrate that higher yielding cows had an increased COD incidence rate. These results allow us to conclude that, under the conditions described herein, NEB might not be related to cyst formation. Differences in cow biotype and/or management systems among studies could explain this controversy.

The incidence of COD presentation was strongly influenced by the season. Significantly more cases were diagnosed in winter and spring. Similarly, Roberts (1955) and Peter (2004) reported that more cases of cysts were detected during winter months and that that coincided with the months when cows were fed higher energy and protein diets (Dawson 1957; Peter 2004). In contrast, Bartlett et al. (1986) found no seasonal effect on the incidence of cysts. Regarding the influence of the calving season on COD, López-Gatius et al. (2002) reported a higher incidence of cases associated with summer parturition and concluded that heat stress could be the principal responsible for such effect. In contrast, Nelson et al. (2010) found that autumn calving was more susceptible to COD. These authors suggested that a decrease in daylight hours could have played a role in the incidence of cysts. Results of the present study showed that both autumn and winter calving were more closely associated with COD.

Production on the previous lactation showed no effect on the incidence of COD. This is consistent with the results reported by Bartlett et al. (1986) and Nanda et al. (1989), who found no association between the production of the preceding lactation and cyst formation.

Cows that had assisted calving and/or uterine disease between partum and cyst diagnosis did not show a higher COD incidence rate. In this sense, López-Gatius et al. (2002) found that cows with abnormal puerperium (including the variables previously mentioned) had almost double chances of developing early ovarian cysts (<49 DPP) but not of developing late cysts (>57 DPP). The latter might be the case of the present study, where most cysts were diagnosed after 60 DPP. In another study, Mohammed et al. (1991) found no association between metritis and COD.

Body condition score is considered a proxy parameter of NEB (Hooijer et al. 2003), and, as such, several studies have tried to correlate it with the occurrence of ovarian cysts, with controversial results (Waltner et al. 1993; Laporte et al. 1994; Beam and Butler 1998, 1999; López-Gatius et al. 2002). In this study, the analysis of BCS, which was limited to just one evaluation at the time when cows had overcome their VWP, showed no effect on COD incidence. Nevertheless, this investigation did not intend to undermine the hypothesis that COD could be associated with a NEB. In fact, cows evaluated in this study presented, in general, low BCS values (>60% of animals had a BCS <2.75). Thus, this lack of variability in BCS between the two groups would be indicating that there might be other factors related to the disease presentation.

Regarding clinical mastitis, results from the present study showed that cows with a previous diagnosis of mastitis had 2.7 times more chances of developing COD afterwards. This is in agreement with other researchers, who found an altered reproductive performance in animals that had previously suffered from clinical and subclinical mastitis (Moore et al. 1991; Barker et al. 1998; Schrick et al. 2001; Santos et al. 2004; Gómez-Cifuentes 2010). Peter et al. (1989) demonstrated that intra-uterine infusion of endotoxins in cycling heifers caused increased levels of cortisol, suppressed the LH surge and generated follicles that did not ovulate and finally turned into cysts. Our field results reinforce the findings by Peter et al. (1989), even though we are not yet in a position to state a causative effect.

As expected, the reproductive performance parameters of the COD group were markedly compromised. Although CFSI was not different among groups, cystic cows tended to consume more days to reach their first service compared to controls. Conversely, COD cows had a significantly longer CCI than controls, even though the former had been treated immediately after diagnosis. Several authors have obtained similar results (Bartlett et al. 1986; Laporte et al. 1994; Hooijer et al. 2001; Silvia et al. 2002). Moreover, cows affected by COD had 4.04 times less chances of becoming pregnant by the end of lactation. In contrast, cystic cows did not show an increased risk of abortion once the cystic condition had disappeared, and cysts had no effect on the production of the concurrent lactation.

Conclusions

This retrospective observational study intended to characterize the epidemiology of COD in typical pasture-based dairy herds of Argentina. Our data indicate that COD incidence (2.7%) was lower than that generally reported. However, its negative effects on the reproductive performance were very profound, especially on the calving to conception interval and pregnancy rate. In contrast to previous reports, cows in their first third of lactation had a lower incidence rate of COD than at later stages. A significant influence of the season on the frequency of cysts diagnosis was found, with higher incidence during winter and spring. No associations were found with age, parity group, milk production, dystocia, uterine disease, BCS or abortion. Clinical mastitis, on the other hand, was significantly related to the incidence of COD. In this regard, new studies are warranted to reconfirm this association and to find possible causal effects on the development of COD.

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Conflict of interest

None of the authors of this study has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the study.

Author contributions

Luciano Cattaneo and Marcelo L Signorini: data analysis, manuscript drafting, developing hypotheses Jose Bertoli, Julián A Bartolomé, Natalia C Gareis, Pablo U Díaz: Fieldwork, data collection, manuscript discussion Gabriel A Bó, Hugo H Ortega: Hypothesis, direction and coordination of activities.

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