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Efficacy of Different Ovarian Cysts Treatments (GnRH, hCG and PRID) in Dairy Cows

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Abstract: Cystic ovarian disease represent an unsolved problem in bovine reproduction. Despite the huge amount of literature, the exact pathogenesis of the disease is still not completely clear and therefore also the choice of treatment is still debated. The present study was aimed to compare the effective efficacy of the three most common drugs used for ovarian cystic disease treatment in dairy cows: GnRH (20 μg I.V.), hCG (3000 I.U. I.M.), PRID (for 10 days). Data obtained from 150 cystic Friesian cows showed that cure rates (GnRH 64%, hCG 66%, PRID 63%), conception rates (GnRH 45.2%, hCG 47.8%, PRID 46.2%), the overall pregnancy rates (GnRH 20%, hCG 22%, PRID 20%) and recovery times (GnRH 17.9 days, hCG 17.7 days, PRID 19.7 days) were not significant different except for a shorter recovery time for cows treated with PRID (9.7 days) but only when the day of PRID removal was considered as the day of treatment. Based on the present study findings, GnRH could be considered as the first choice drug for the treatment of cows affected by ovarian cysts, considering together efficacy, drugs costs and easy administration.

Key words: Cows, ovarian cysts, hormonal treatments, Friesian cows, Itlay

INTRODUCTION

Bovine ovarian cysts are being investigated from >60 years (Casida *et al*., 1944) and their influence on postpartum performances is well known. In dairy cows the incidence of the disease ranges between 3 and 32% (Eicker *et al*., 1996; Morrow *et al*., 1969) with an average occurrence estimated to be 10% (Garverick, 1999).

Cysts have been usually defined as anovulatory, follicular structures (>25 mm in diameter) that persist for at least 10 days in the absence of a corpus luteum (Roberts, 1971). This classical definition has already been revised from different researchers (Garverick, 1997; Bartolome *et al*., 2000; Silvia *et al*., 2002; Hatler *et al*., 2003) but even if the diameter of the follicular structure and/or his persistency on the ovary requested to diagnose a cyst has been reduced, no-one has yet suggested a really different and better definition.

Although, traditionally, ovarian cysts have been classified as follicular or luteal, based on clinical examination by per rectum palpation of the ovaries, some researchers (Farin *et al*., 1990; Hanzen *et al*., 2000; Douthwaite and Dobson, 2000) showed that ultrasonography is more precise to make this distinction but still a substantial error is possible.

Regarding the pathogenesis, furthermore, a number of different causes have been suggested for the development of ovarian cysts in cows (Kesler and Garverick, 1982; Garverick, 1997; Peter, 2004) but the exact aetiology of the disease remains poorly understood. Many factors have been implicated in the disruption of the normal postpartum hypothalamic-hypophyseal-ovarian axis function which eventually leads to anovulation and cyst formation (Vanholder *et al*., 2006).

On this basis, it is not surprising that where treatments are concerned, different approaches (chemicals, physical, surgical, etc.) have been used in the past. Focussing on the more widespread pharmacological therapies, the use of GnRH and hCG has been proposed in a number of different protocols (Garverick *et al*., 1976; Archbald *et al*., 1991; Bartolome *et al*., 2000). This is based on the evidence consistent with the lack of an LH surge being the critical underlying physiological change that leads to large follicle anovulatory condition (Wiltbank *et al*., 2002). Also, the administration of progesterone through an intravaginal releasing device has been used in different therapeutic schemes (Nanda *et al*., 1988; Todoroki and Kaneko, 2006; Todoroki *et al*., 2001), considering that some cows with large anovulatory

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follicles may be the result of low circulating concentrations of progesterone that block the normal positive feedback effects of estradiol (Wiltbank *et al*., 2002).

The doubts about the economic advantages of treatment have been debated in several articles (El-Tahawy and Fahmy, 2010; De Vries *et al*., 2006). It is obviously impossible a standard assessment of the economic benefits that are deeply influenced by farm differences in costs and management. Nevertheless, the researchers conclude that treatments are in the whole, more convenient than waiting for spontaneous recovery. Reported rates for spontaneous recover of ovarian cysts range from 20% (Youngquist, 1986; Peter, 1998) to nearly 70% (Whitmore *et al*., 1974); the cysts of the early postpartum period are known for an high percentage of spontaneous recovery (Morrow *et al*., 1966) but the cysts with heavier effects on the reproductive performances are typical of the late postpartum.

Since, the 1970s, hCG and GnRH analogues have been used to treat ovarian cysts in cows and both appear to be equally effective as regards treatment response and fertility (Nakao *et al*., 1992; Peter, 2004). The hCG provided recovery rates between 65 and 80% (Kesler and Garverick, 1982). In a study employing various doses of GnRH, Bierschwal *et al*. (1975) found a recovery rate of 64-82%, a mean time from treatment to oestrus of 22.2-22.8 days and a conception rate of 72-87%; similar results were also found by Ijaz *et al*. (1987) with 65-80% of cows re-establishing ovarian cyclicity after GnRH treatment. Between the two, the use of GnRH and its analogues has been considered more interesting, due to its satisfactory success rate, irrespective of type of cyst, absence of antigenic effects and low pharmaceutical cost (Carruthers, 1986; Ngategize *et al*., 1987). Nevertheless, poor or no response by luteal cysts to GnRH has also been earlier reported (Dobson *et al*., 1977; Sprecher *et al*., 1990) and opinions vary among bovine practitioners regarding differing recovery rates after GnRH treatment in cows with luteal or follicular cysts.

The use of PRID, tested by Nanda *et al*. (1988), showed a 68% of cyst recovery with or without a display of estrus.

The aim of this study was to compare the clinical effects of hCG, GnRH and PRID, the three more common pharmacological therapies for cows ovarian cysts, considering cure rate, time to first oestrus and first estrus conception rate as well as overall pregnancy rate considered as the number of obtained pregnant cows among all the treated cows.

In addition, also unwanted potential side effects of each compound as well as drugs costs have been considered in the evaluation of treatment choice.

MATERIALS AND METHODS

Farms, animals and treatments: The study took place >4 year period in five herds (200-300 cows each) located in Northern Italy. The herds were characterized by mean annual milk yield of 8750 kg per cow (8650-8900 kg) with 3.8% fat (3.7-3.75%) and 3.5% proteins (3.3-3.7%). The diet was formulated to provide 23 kg day^{-1}, 16.0% crude protein, 1.90 Mcal kg^{-1} net energy of lactation, 31.4% neutral detergent fiber, 40.5% non-structural carbohydrates and 6.1% crude fat.

The genital tracts of 1470 Friesian cows were evaluated during the routine Postpartum (PP) clinical check. The clinical evaluation was performed once a week from the 4rth week after calving by both rectal palpation and ultrasonographyc examination (real-time linear array, 7.5 MHz rectal probe, Esaote Pie Medical, Florence, Italy) of the genital tract.

Cows bearing ovarian follicular structures with diameter >25 mm, persisting for at least 7 days in the absence of any corpus luteum were considered as affected by ovarian cysts. On a total of 1470 examined cows, 150 were affected by ovarian cysts.

Because the treatment regimens proposed are effective for both follicular and luteal cysts, no attempt to distinguish between the two conditions was done.

At the time of diagnosis confirmation, between 55 and 65 days PP, all cystic cows were randomly assigned to one of the three following groups of treatment:

- Group A (n = 70) 20 μg buserelin (GnRH-analogue) I.V.
- Group B (n = 50) 3000 hCG I.M
- Group C (n = 30) PRID Delta for 10 days

After treatment, animals were clinically checked twice a day to detect estrus, confirmed by the ultrasonographic finding of a preovulatory follicle. Cows were considered responsive to the treatment if estrus was detected within 30 days. The time between treatment and standing estrus was considered as recovery time. The ratio between cows in estrus within 30 days after treatment and treated cows was defined as cure rate. When normal conditions of the genital tract (uterine tone, cervical mucus) were found, the cows were artificially inseminated 12 h after estrus detection with semen of proven fertility. Pregnancy diagnosis was carried out by palpation per rectum within

7 weeks from artificial insemination. First estrus conception rate (pregnant cows/inseminated cows) and overall pregnancy rate (pregnant cows/treated cows) were considered. Apart from first estrus conception rates, considering only cows artificially inseminated after estrus induced by treatment also the overall pregnancy rate has been evaluated. In fact, although it could seem a non-sense measurement, from an economic point of view, the farmer evaluates how many pregnancy are obtained on a total of actually treated cows.

Statistical analysis: Cure, first estrus conception and overall pregnancy rates were evaluated with the Fisher test while recovery time by the t-test for independent samples. Data were checked for normality by the Shapiro-Wilk test. Statistical significance was set for $p<0.05$.

RESULTS

Irrespectively of type of cyst, 150 cows with cysts out of a total of 1470 animals were detected with a prevalence of 10.2%. The results related to cure, conception and overall pregnancy rates in the three treatment groups are shown in Table 1 and 2 while recovery times are reported in Table 3.

Regardless the type of treatment, an overall of 97 cows (64.7%) displayed estrus within 30 days from therapy but 30 (30.9%) were not inseminated due to inadequate genital tract conditions.

Table 1: Cure rates (estrus whitin 30 days after treatment) and first estrus conception rates in the 150 cystic cows randomly assigned to one of the three treatments

Groups	Treated (n)	In estrus (n (%))	Inseminated (n (%))	Pregnant (n (%))
A (GnRH)	70	45/70 (64.3)	31/45 (68.9)	14/31 (45.2)
B (hCG)	50	33/50 (66.0)	23/33 (69.7)	11/23 (47.8)
C (PRID)	30	19/30 (63.3)	13/19 (68.4)	6/13 (46.2)

Table 2: Overall pregnancy rates (pregnant cows/treated cows) in the three treated groups of animals

Groups	Pregnant/Treated (n (%))
A (GnRH)	14/70 (20)
B (hCG)	11/50 (22)
C (PRID)	6/30 (20)

Table 3: Recovery time (time from treatment to standing heat) in the three treatment groups. In the PRID group both the interval from device application (PRID) and from device removal (PRID-10) have been considered

Treatment	GnRH (n = 45)	hCG (n = 33)	PRID (n = 19)	PRID-10 days (n = 19)
Days	17.9±3.1	17.7±3.2	19.7±4.7	9.7±4.7*

*<0.001

No statistically significant differences were found in cure rates, conception rates and overall pregnancy rates among the three treatment groups.

Since, the Shapiro-Wilk test provided sufficient evidence of normal distribution, comparison of recovery times with the t-test showed significantly shorter recovery time for cows treated with PRID but only when the day of PRID removal was considered as the day of treatment.

DISCUSSION

The aim of the present study was to compare the clinical effects of hCG, GnRH and PRID, the three more common pharmacological therapies for ovarian cysts in cows. Indeed, even if many researches have been published on the ovarian cysts treatment, the comparison among results obtained in different studies could be quite difficult. Difficulties relay on several experimental variabilities such as ovarian cyst definition, criteria for animals enrollment, type of drugs used for treatment, dosages and protocols and criteria for treatment response evaluation.

In the present study a prevalence of 150 cows with cysts out of a total of 1470 animals (10.2%) is consistent with results from other researchers: e.g., 12.8% (Bartlett *et al*., 1986) 5.6-18.8% (Garverick, 1997).

The choice to treat animals without differentiating between follicular and luteal cysts is in a measure, due to the difficulty to perform a certain diagnosis as previously stated. Moreover, the two type of cysts may be considered as different forms of the same disorder (Vanholder *et al*., 2006). In particular, luteal cysts are believed to be follicular cysts in later stages (Garverick, 1997).

Concerning treatments, in the cow ovarian cysts can be treated with hormones inducing the release of LH from the anterior pituitary (e.g., GnRH) or having LH-like action (e.g., hCG) (Kesler and Garverick, 1982; Woolums and Peter, 1994; Garverick, 1997; Peter, 1998, 2000). The use of exogenous progesterone for the cure of ovarian cysts in cows is also well known. The efficacy of this treatment seems to be due to its inhibiting action on LH release allowing pituitary LH replenishing (Gumen *et al*., 2002; Gumen and Wiltbank, 2002). Some researchers evaluated the efficacy of progesterone treatment for cystic cows using different posologies and studying ovarian and hormonal changes (Jeffcoate and Ayliffe, 1995; Calder *et al*., 1999; Douthwaite and Dobson, 2000; Todoroki *et al*., 2001; Zulu *et al*., 2003).

The cure rates (GnRH 64%, hCG 66%, PRID 63%), the conception rates (GnRH 45.2%, hCG 47.8%, PRID 46.2%), the overall pregnancy rates as result of the treatments

(GnRH 20%, hCG 22%, PRID 20%) and the recovery time (GnRH 17-9 days, hCG 17.7 days, PRID 19.7 days) obtained in this study were not significantly different among treatments and are in agreement with the results of other researchers (Bierschwal *et al*., 1975; Kesler and Garverick, 1982; Ijaz *et al*., 1987).

The only significant difference observed among the three treatments is a shorter recovery time for PRID but only when the interval from device removal and estrus was considered as recovery time. This evaluation although, correct from an endocrine point of view does not match the effective economic loss due to the 10 days of treatment.

Because of lack in actual differences among the three treatments, other aspects behind drugs efficacy such as costs and potential side effects have been evaluated. In this respect, GnRH because of its small molecular size is not likely to stimulate an immune reaction as it occasionally observed after hCG injection (Woolums and Peter, 1994; Peter, 1998, 2000).

From an economic point of view hCG is a more expensive drug compared to GnRH while PRID is surely more expensive than hCG.

On the other hand, hCG has been used successfully for treatment of refractory follicular cysts not responding to GnRH treatment (Woolums and Peter, 1994; Peter, 1998, 2000) and use of PRID is considered a second opportunity for cows not responding to other treatments.

CONCLUSION

The results from the present study evidenced that GnRH could be considered as the first choice treatment for cows bearing undistinguished ovarian cyst in agreement with efficacy, easy administration, costs and absence of potential side effects. hCG should be considered as a second choice drugs for cows not responding to GnRH because of higher costs and for potential decreasing effect due to the induced immune reaction. Also, the use of PRID should be considered the last alternative for cysts refractory to other treatments because of drug cost but also for the disadvantageous application and removal of device and time of treatment.

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