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# Treatment of ovarian cysts in dairy cows with simultaneous administration of GnRH and PGF2α has no clear advantage over the use of GnRH alone

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**Abstract**

The aim of the study was to determine the therapeutic efficacy of simultaneous administration of GnRH and PGF2α in dairy cows with ovarian cysts. Ovarian cyst-affected dairy cows were divided into two experimental groups: 54 cows treated with GnRH and PGF2α, and 42 cows treated with GnRH alone, whereas 22 untreated cows served as the control group. Clinical response and reproductive performance were evaluated. The cumulative disappearance was better in treated cows than in the control group; however, there were no differences between the treatment groups (92.6; 95.2% *vs.* 72.3%). The mean interval from calving to conception was not significantly shorter (being so by 29 d) in the GnRH/PGF2α group than in the cows treated with GnRH alone ($P > 0.05$). The intervals from treatment to conception were also similar in these groups. The pregnancy rate in both treated groups was similar (62%) and higher than in the control cows (53%). In the cows with luteal cysts, the total pregnancy rate was higher in all experimental groups; however, only in GnRH-treated cows was this difference statistically significant (77.8% *vs.* 50.0%, $P < 0.05$). With time after parturition, the pregnancy rate decreased in all groups. In general, the cows treated with GnRH and PGF2α simultaneously displayed a good clinical response and slight improvement in reproductive performance compared to the single-therapy GnRH group; however, this was not fully convincing.

**Keywords:** dairy cows, ovarian cysts, treatment.

## Introduction

Currently, cystic ovarian follicles (COF) are defined as fluid-filled structures of at least 17-25 mm diameter persisting on the ovary for 6-10 d and interfering with normal sexual behaviour (14, 24, 26, 28). Cystic ovaries are the result of an interaction between hereditary factors, milk yield, stress, and unbalanced nutrition (4, 14, 16, 18, 19). This disorder is a significant cause of reproductive losses with great economic impact on dairy farms. The incidence of COF is high, since in many herds this disorder has been estimated at 10%-30% of the population (10, 22, 28). Economic losses are caused by an increase in the number of days open, increased culling rate because of infertility, and high treatment costs (8).

Ovarian cysts are anovulatory follicles developing during the puerperal phase. In general, a dysfunction of the hypothalamus-pituitary-ovarian axis, which leads to an abnormal release of gonadotropin-releasing hormone (GnRH) and luteotropic hormone (LH) is suggested as the main pathogenic mechanism of cystic structure development (24, 26, 28). Cysts either regress or persist beyond puerperium as follicular or luteal cysts, depending on their structural and functional characteristics. Whereas follicular cysts are thin-walled and secrete little progesterone and more oestradiol, luteal cysts have a thicker wall and secrete progesterone (6, 24). A clinical problem, such as anovulatory anoestrus, emerges when cysts block ovulation and cause aberrant behaviour, mainly anoestrus.

Diagnosis and therapy of ovarian cysts might be an important factor in minimising economic losses and improving herd fertility. So far, most cysts are treated using reproductive hormones. Cystic cows often respond to substitution therapy with GnRH or human chorionic gonadotropin (hCG) leading to restoration of

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normal cyclicity and to oestrus within three weeks after treatment (5, 24). Under field conditions, GnRH injections are the treatment of choice. In general, after administration of GnRH, within three weeks there is a resumption of the normal oestrus cycle in 60%-95% of treated cows, followed by pregnancy rates of 60% -85% (20). The hCG compound has been used successfully for treatment of refractory cysts, which do not respond to GnRH therapy (24). Alternatively, ovarian cysts can be treated with intravaginal progesterone-releasing devices. The success of therapy with long-acting gestagens is high because usually 70%-85% of cystic cows recover within two weeks and conceive within three inseminations (20).

Prostaglandin F2α (PGF2α) or its analogues are used in the treatment of choice for luteal cysts (12). Moreover, this therapy could be combined in the treatment of follicular cysts with GnRH/hCG to shorten the induced luteal phase (14).

It has been shown that hormonal programmes for ovulation synchronisation using a combination of GnRH/PGF2α (Ovsynch) can also be used for the treatment of cysts; however, with a different success rate (1). A few reports exist about simultaneous application of GnRH and PGF2α, partially as a constituent of other hormonal protocols (5, 7, 17). Due to the synergistic effect of both hormones on LH release, this treatment seems to have an advantage over the use of GnRH alone (17). This method has been also considered as an efficient method of treatment under field conditions, since it is applicable without the need to distinguish between two types of ovarian cysts (17). Diagnosis of ovarian cysts itself is easy, but accurate differentiation between follicular and luteal structures is difficult (12). Therefore, under field conditions, ovarian cysts are very often treated without clinical differentiation. It should also be stressed that most cysts can be classified as intermediate forms with partial luteinisation of the wall (24).

Surprisingly, simultaneous treatment with GnRH/PGF2α is rather rare compared to other treatment methods; information about its cure rate is therefore limited and controversial (5, 7, 17).

In this field study, simultaneous application of GnRH and PGF2α for the treatment of ovarian cysts was evaluated using clinical criteria and reproductive measures.

## Material and Methods

**Animals.** The study was performed on three herds of 50-120 cows of Polish Holstein-Friesian breed. The cows were three to six years of age, with a milk yield between 6000-9000 litres. The cows were kept in loose-housing barns and fed grass and maize silage, concentrates, and vitamin and mineral supplements. Total mixed ration feeding systems were used.

Standard practice for reproductive management was followed with all cows during the *post partum* and breeding periods. The cows were inseminated by technicians after oestrus detection by the owners. Pregnancy was diagnosed by rectal palpation and ultrasonography between days 35 and 45 after insemination.

**Study design.** The cows with ovarian cysts were selected by routine rectal palpation within a reproductive herd health programme for 40-80 d after parturition, or diagnosed in a group of cows with anoestrus during the breeding period. All selected cows had no clinical endometritis upon examination.

Ovarian follicular cysts were diagnosed using rectal palpation and ultrasonography (Honda HS 1500V, linear probe, 5 MHz, Honda Electronics Ltd, Japan). The size of the cysts was measured as the diameter of the external border of the structure.

Ovarian cysts were defined as follicular structures with a diameter over 25 mm coinciding with the absence of the corpus luteum and with altered sexual behaviour and anoestrus. The exact diameter of cysts and their walls, as well as the presence or absence of other ovarian structures, were determined by ultrasound examination on the day of diagnosis. Follicular and luteal cysts were distinguished according to the following classification: follicular cysts were anovulatory single or multiple thin walled follicles on one or both ovaries; luteal cysts were anovulatory follicles with partial luteinisation of the wall thicker than 3 mm, occurring usually as a single structure on one ovary.

All cows with ovarian cysts were assigned randomly to two treatment groups and one control group. Group 1 (n = 54) simultaneously received GnRH (20 μg, IM, Buserelin (Receptal®), MSD Animal Health, part of Merck Animal Health and formerly Intervet, Germany) and PGF2α (25 mg, IM, Dinoprost (Dinolytic®), Pfizer, Belgium). Group 2 (n = 42) was treated only with GnRH with the same dose. A total of 22 cows with ovarian cysts were left untreated and served as a control group (Group 3).

After the first treatment or examination of the control group, the cows were inspected for oestrus signs at least three times daily. Cows which returned to oestrus were inseminated with frozen semen and after day 35, pregnancy detection was performed.

The cows without oestrus signs were subjected to the second examination and treatment 14 d later, and the response to therapy was examined. If the follicular structures were found to be unchanged (location, size, and character) and there was no corpus luteum, they were considered to be ovarian cysts. In such cases, the second treatment was performed using the same method. After the following 14 d, the same procedure was repeated, and cows that did not respond, were treated for the third time using the same method.

The results were considered as positive if the cow

established a normal oestrus cycle or conceived. The experimental period was ended when the cows were either pregnant or not pregnant within 150 d after the last treatment.

**Data collection and statistical analysis.** The interval from calving to diagnosis of cysts was noted for the treatment and control groups.

During the treatment period the following clinical data was collected: cystic disappearance rate, oestrus detection rate, and pregnancy rate for the experimental groups after the first, second, and third treatments, or for the control group at the same examination times.

The cystic disappearance rate was defined as the percentage of cows without cysts after treatment. The oestrus detection rate was calculated as the percentage of cows with oestrus signs and the pregnancy rate was defined as the percentage of pregnant cows in experimental and control animals at each consecutive examination. The percentage was expressed as a percentage of the total number of cows in each group at the same period.

Additionally, on the basis of the insemination and pregnancy check records, the following reproductive performances were calculated: interval from treatment to conception (days), interval from calving to conception (days), cumulative pregnancy rate (%), and services per conception (number). Cumulative pregnancy rates (%) were also calculated in the experimental and control groups considering the type of cysts and length of the *post partum* period at treatment.

Groups with different treatment regimens and untreated animals were compared in terms of the above -mentioned clinical criteria of ovarian response and reproductive performance using the chi-square test. Values corresponding to the experimental groups were expressed as mean ±SD. Statistical analysis was performed using the Statistica data analysis software system *vs* 10.0 (StatSoft 2011, USA). The statistical significance was set at $P < 0.05$.

## Results

The distribution of cows within the experimental groups with respect to periods after parturition is presented in Fig. 1. Most cysts (>80%) were diagnosed in the period over 100 or 200 d *post partum* with a similar incidence among the experimental groups.

In general, comparison of clinical and reproductive criteria between both treatment groups and control animals showed no significant differences. Only the cumulative disappearance rate after the third treatment cycle was significantly higher ($P \leq 0.05$) in both groups treated with hormones than in untreated cows (92.6 and 95.2% vs. 72.3%).

The values of all clinical criteria in cows treated with GnRH/PGF2α (group 1) did not differ from those in cows treated with GnRH alone (group 2). The cumulative disappearance rate (>90%) and oestrus rate (>80%) after the third treatment were high and similar in both groups (Table 1). Pregnancy rates in these groups were also similar, but lower, at 62% (Tables 1 and 2).

The reproductive performance values in all experimental groups are presented in Table 2. The mean interval from calving to conception was shorter by 29 d in group 1 than in cows from group 2; however, this difference was not statistically significant ($P \geq 0.05$). Similarly, the ratio of services per conception in group 1 was better than in the two other groups (1.5 *vs*. 1.76). The pregnancy rate in both groups treated with hormones was similar (62%) and higher by about 10% compared with the control cows (Table 2).

There was a numerical difference between GnRH-treated and control cows in the calving-conception interval (324.7 *vs*. 309.7 d); however, it was not statistically significant. The intervals from treatment to conception were also similar in these groups.

Analysis of the pregnancy rates in different periods after calving demonstrated similar results in both treatment groups. There were only numerical differences which were not statistically significant (Table 3). Moreover, the pregnancy rate after both treatment methods tended to decline with the time after calving.

Subsequent pregnancy rates in treated cows with follicular or luteal cysts are summarised in Table 4. The pregnancy rate was higher in cows of all experimental groups with luteal cysts. Combined treatment (GnRH/PGF2α) gave similar results regarding both types of cysts (66.7% *vs*. 61.1%), whereas GnRH alone had better effectiveness regarding luteal cysts compared to follicular cysts (78.8% *vs*. 50.0%, $P \leq 0.05$). Interestingly, in the control group the total pregnancy rate in cows with luteal cysts was twofold higher (62.5%) than in cases with follicular cysts (33.3%).

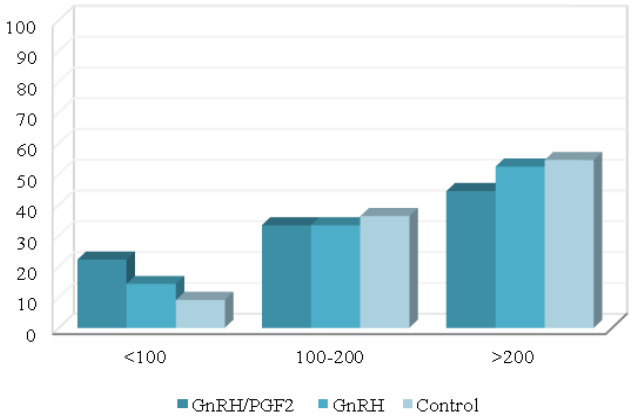



**Fig. 1.** Distribution of treated and control cows with cysts in respect of the interval from calving to diagnosis

**Table 1.** Disappearance, oestrus, and pregnancy rates in experimental and control groups after the first, second, and third treatment/examination; [a,b] – difference significant at P < 0.05

| Treatment method | Disappearance rate (% cows) | | | Oestrus rate (% cows) | | | Pregnancy rate (% cows) | | |
|---|---|---|---|---|---|---|---|---|---|
| | I | I + II | I + II + III | I | I + II | I + II + III | I | I + II | I + II + III |
| GnRH +PGF2α n = 54 | 37.04 | 70.37 | 92.59[a] | 29.63 | 59.26 | 81.48 | 22.22 | 48.15 | 62.96 |
| GnRH n = 42 | 38.10 | 66.67 | 95.24[a] | 28.57 | 52.38 | 80.95 | 23.81 | 42.86 | 61.90 |
| No treatment n = 22 | 63.64 | 63.64 | 72.73[b] | 54.55 | 54.55 | 63.64 | 45.45 | 45.45 | 54.55 |

**Table 2.** Reproductive performance: interval from treatment to conception, overall pregnancy rate and services per conception in experimental and control groups

| Method of treatment | Reproductive performance | | | |
|---|---|---|---|---|
| | Interval from treatment to conception (days) | Interval from calving to conception (days) | Overall pregnancy rate (%) | Services per conception (number) |
| | x ± SD | x ± SD | | |
| PGF2α + GnRH n = 54 | 117.88 ± 75.40 | 295.41 ± 122.98 | 62.96% | 1.5 |
| GnRH n = 42 | 115.13 ± 61.57 | 324.67 ± 133.06 | 61.90% | 1.76 |
| No treatment n = 22 | 104.57 ± 74.48 | 309.71 ± 140.16 | 54.55% | 1.76 |

**Table 3.** Pregnancy rates in experimental and control groups and different periods after calving

| Treatment | Pregnancy rate (%) | | |
|---|---|---|---|
| | <100 d *post partum* | 100-200 d *post partum* | >200 d *post partum* |
| PGF2α + GnRH n = 54 | 83.33 | 77.78 | 41.67 |
| GnRH n = 42 | 100.00 | 57.14 | 54.55 |
| No treatment n = 22 | 0.00 | 75.00 | 50.00 |

**Table 4.** Pregnancy rates in experimental and control cows with follicular and luteal cysts; [a,b] – difference within rows significant at P < 0.05

| Treatment | Pregnancy rate (%) | |
|---|---|---|
| | Follicular cysts | Luteal cyst |
| GnRH + PGF2α | 61.1 | 66.7 |
| GnRH | 50.0[a] | 77.8[b] |
| No treatment | 33.3 | 62.5 |

## Discussion

The main goal of this field study was to evaluate the clinical efficacy and influence on reproductive performance of simultaneous GnRH/PGF2α administration in the treatment of ovarian cysts in cows. Surprisingly, information on this therapeutical regime is very limited in the literature and earlier results are controversial (5, 17). Our study reveals that, regarding clinical response, this treatment method was similar or only slightly better compared with GnRH alone and withheld treatment respectively.

After three treatment cycles, high disappearance (>90%) and oestrus (>80%) rates in both groups of treated animals were observed. These results are in line with the observation of many authors, who reported high recovery and resumption of normal ovarian cycle in 65%-90% of cows treated with GnRH (21, 23). The clinical response of animals treated with a combined application of GnRH/PGF2α was also satisfactory (5, 17). Our results are within the ranges reported earlier. However, studies testing the efficacy of single-hormone GnRH treatment of ovarian cysts are partially controversial, because some of them suggested that there was no difference between treated and untreated

cows in ovarian response (15). This may suggest that GnRH may not be as effective as it was thought to be.

There is a general opinion that the treatment of spontaneously-occurring ovarian cysts is difficult to study due to the variation among cases as well as the environmental factors influencing this disorder at the herd level (19). Moreover, some studies are incomplete because the response to treatment was not compared with a control group (20, 29). Hence, it is difficult to determine the real efficacy of the particular treatment method, and to compare the results of different studies.

Our study was performed with two treatment groups and the results obtained in the GnRH/PGF2α group were compared with those in the GnRH group and with untreated animals. This latter group served as a control group. It could be expected that the clinical and reproductive responses in cows treated with GnRH/PGF2α would be better than in the two other groups. This treatment regime, due to the synergistic effect of both hormones, induces a high hypophysial LH release (12). It is generally accepted that release of this gonadotropin is a key mechanism for cyst recovery (3, 27). In our study, we did not measure LH, but on the basis of clinical observation we did not confirm the above suggestion, because clinical response was similar in the GnRH- and GnRH/PGF2α-treated groups. In contrast, cyst disappearance and oestrus rates in both groups with hormonal treatment were better than in untreated cows; however, only the difference in disappearance rate after the third treatment cycle was statistically significant.

Dinsmore *et al.* (5) performed a study on 75 cows from 32 herds and observed that simultaneous administration of GnRH and PGF2α appeared to have no advantage over GnRH alone. Lopez-Gatius and Lopez-Bejar (17) obtained satisfactory results after treatment with GnRH/PGF2α as a part of modified Ovsynch protocol; however, the results of this study were not compared with the group administered GnRH alone. In general, the results of the clinical response are difficult to compare, partially because of methodological diversity. Moreover, in the opinion of Lopez-Gatius and Lopez-Bejar (17), the response of cystic ovaries to treatment may be masked by factors acting at the herd level such as management, oestrus detection, and unbalanced nutrition. The study of Dinsmore *et al.* (5) was performed in small herds with probably very different environmental conditions. On the other hand, our clinical results from the GnRH-treated group are probably more reliable. It can hence be speculated that it would be difficult to achieve a further improvement with simultaneous administration of GnRH and PGF2α.

In this study, we also compared the reproductive performance of cows subjected to both kinds of treatment and untreated animals. It has been suggested that, besides the clinical response, reproductive performance should be considered as treatment success, especially from the economic point of view (11). In our study, the best reproductive results were associated with GnRH/PGF2α treatment and took the form of a higher pregnancy rate (63%) than in the control group (54%) and a shorter calving-conception period than in GnRH and control groups. In contrast, the interval from treatment to conception was similar in all groups and this is difficult to explain. The mean calving-conception interval was shorter by about 20 or 29 d respectively; however, this difference was not confirmed statistically. In spite of this, these numerical differences may have a significant effect on the economic benefit of GnRH/PGF2α treatment at the herd level. Moreover, lack of statistical significance may be explained by a large variation in the individual calving-conception interval. In our study, a shorter calving-conception interval is in line with the better service conception rate in the GnRH/PGF2α group than in the GnRH and control groups (1.50 *vs.* 1.76). In contrast, Dinsmore *et al.* (5) did not improve the fertility of cows treated with GnRH/PGF2α as compared to treatment with GnRH alone, but these authors used other fertility measures. This result is in line with the study by Hauke (13), who did not observe an increased pregnancy rate after simultaneous treatment with GnRH/PGF2α compared to treatment with GnRH and PGF2α 7 d apart. In other studies, a modified Ovsynch protocol, combining PGF2α with the first GnRH treatment increased the pregnancy rate compared to the standard protocol (7, 17). Although, in general, it is difficult to compare the reproductive performances obtained in this study with the results of other studies, it seems that the GnRH/PGF2α treatment protocol slightly improves reproductive performance over that of cows treated with GnRH alone.

Another interesting aspect of this study was the comparison of the overall pregnancy rate in respect of cyst type and periods after calving at time of treatment. Our study was performed during a long period after parturition and therefore about 80% of ovarian cysts were diagnosed over 100 d after calving. It is known that with time after parturition, ovarian cysts become dynamic structures in nature (28). Follicular cysts are the first stage in the cystic condition, whereas luteal cysts are secondary structures and should be classified as a sign of recovery (17). From the clinical point of view, follicular cysts might be considered as the dominant type at the first *post partum* stage, whereas with time after calving, a predominance of luteal cysts occurs. Since we diagnosed cysts very often after d 100, it could be assumed that the majority of treated cysts were luteal cysts. GnRH/PGF2α treatment would therefore seem to be very appropriate in such cases because of the luteolytic properties of PGF2α (17). This supposition is partially in agreement with our results. In both treatment groups and the control group, the pregnancy rate in cows with luteal cysts was higher than in the cows with follicular cysts; however, statistical difference was only found in the group treated with GnRH alone. Similar results were obtained

by Drews (7). Explanation of this discrepancy between the treatment groups is difficult. We can only speculate that probably other factors such as milk yield, metabolic status, timing of insemination, etc. might influence these results. It has been stressed that the success of hormonal therapy depends on many individual and environmental factors (4, 16, 18, 24). In the opinion of Bartolome *et al.* (2), differentiation of both cyst types is not necessary because treatments and their results under field conditions are similar.

We also compared overall pregnancy rates within experimental groups and different periods after calving. The best results (80%-100% pregnancy rate) were associated with the period below 100 d after calving. With time after parturition, the results were worse. It might be possible that at earlier stages after calving, the self-recovery process was very active and successfully supported the applied treatment (9, 24, 25, 28). Surprisingly, GnRH alone gave numerically better results than GnRH/PGF2α treatment; however, this difference was not well documentated.

Our study was performed with the use of a control group. We compared clinical response and reproductive performance in cows treated with two hormonal methods with those in untreated animals. Although our results demonstrated the beneficial effect of both treatment methods, the clinical response and reproductive performance in untreated cows were also satisfactory. It is well known that the spontaneous recovery percentage of cysts is relatively high (up to 60%), especially in earlier *post partum* stages (18). However, despite this phenomenon, the hormonal treatment of cysts is recommended, due to the better reproductive performance in treated cows (11, 20, 27).

In summary, our report is one of the first studies on the clinical response and reproductive effect of combined simultaneous GnRH/PGF2α treatment of ovarian cysts. To our knowledge, no other reports, except for a paper by Dinsmore *et al.* (5), have compared GnRH/PGF2α and GnRH treatment methods. Our field study demonstrates a good clinical response and slight improvement in reproductive performance in cows treated using the GnRH/PGF2α method, compared to GnRH alone and untreated cows. However, it should be stressed that the response to the GnRH/PGF2α treatment protocol was not completely satisfactory. Further studies are necessary to characterise the cellular and molecular events that take place in the cyst wall (cystic granulosa and luteal cell function) during its development and healing and to be clear about the response to treatment. Another criticism of studies dealing with treatment of cysts is related to the use of cows with different metabolic and hormonal status and under different field conditions.

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