Effects of Gonadotrophin Releasing Hormone on Reproductive Performance of Dairy Cows with Retained Placenta

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ABSTRACT

The effects of gonadotrophin releasing hormone (GnRH) on the reproductive performance of dairy cows with retained placenta were studied. Three hundred and seventy-eight cows diagnosed as having retained placenta received intramuscular injections of either 2 mL sterile water or 200 μg of GnRH in 2 mL sterile water between day 8 and day 14 postpartum. Rectal palpation was performed at the time of treatment and ten to 20 days after treatment in order to determine the rate of uterine involution. Thereafter, monthly rectal examinations were carried out until insemination. Pregnancy diagnosis was made by rectal palpation at 40 days or more after breeding.

Using the entire experimental population, there were no significant differences between GnRH-treated and control cows for the rate of uterine involution, the occurrence of reproductive problems, the interval from parturition to first observed estrus, the interval from parturition to first insemination, the interval from parturition to conception, the number of services per conception, the total number of services per cow regardless of conception and the incidence of culling for infertility. When the data for herds in which breeding began earlier in the postpartum period (herds having a mean $\leq$ 80 days from parturition to first service for retained placenta cows) were considered, the GnRH treatment resulted in a significantly shorter ($p \leq 0.01$) calving to conception interval as compared to control cows. Also, there was a significant reduction ($p \leq 0.05$) in the total number of services per cow regardless of conception and a significant reduction in the interval from parturition to first service. The authors concluded that the administration of GnRH in cows with retained placenta produced improvements in certain parameters of reproductive performance, provided early postpartum breeding was practiced.

Key words: GnRH, postpartum, retained placenta, bovine, dairy.

RÉSUMÉ

Cette expérience consistait à étudier les effets de la gonadoreline sur la performance reproductrice de 378 vaches laitières qui souffraient de rétention placentaire. Elles reçurent une injection intramusculaire de 2 mL d'eau stérilisée, avec ou sans 200 μg de gonadoreline, entre le huitième et le 14^{e} jour après le vêlage. Un des auteurs procéda à la palpation rectale, au moment de l'intervention, ainsi que dix et 20 jours plus tard, afin de vérifier le degré d'involution utérine. Il effectua ensuite mensuellement ce genre d'examen, jusqu'à l'insémination, ainsi que pour procéder au diagnostic de gestation, au bout de 40 jours ou plus après l'insémination.

En tenant compte de toutes les vaches impliquées dans cette étude, on n'enregistra pas de différences appréciables entre les vaches qui avaient reçu de la gonadoreline et les témoins, relativement au degré d'involution utérine, à l'incidence de problèmes de reproduction, aux intervalles entre le vêlage et le premier oestrus ou la première insémination ultérieurs, ou la conception, ainsi qu'au nombre total d'inséminations par conception ou par vache, indépendamment de la conception ou de l'élimination pour infertilité. L'analyse des résultats obtenus dans les troupeaux où on commença à inséminer plus tôt après la période du vêlage, c'est-à-dire ceux qui affichaient une moyenne inférieure ou égale à 80 jours entre le vêlage et la première insémination des vaches atteintes de rétention placentaire, révéla que le traitement à la gonadoreline entraîna un intervalle sensiblement plus court ($p \leq 0,01$) entre le vêlage et la conception, par rapport aux témoins. On enregistra aussi une réduction appréciable ($p \leq 0,05$) du nombre total d'inséminations par vache, indépendamment de la conception, et une réduction significative de l'intervalle entre le vêlage et la première saillie ultérieure. Les auteurs conclurent par conséquent que l'administration de gonadoreline aux vaches qui souffraient de rétention placentaire améliora certains paramètres de leur performance reproductrice, lorsqu'ils les inséminaient tôt après le vêlage.

Mots clés: gonadoreline, après le vêlage, rétention placentaire, vaches laitières.

INTRODUCTION

Gonadotrophin releasing hormone (GnRH) is a naturally occurring hypothalamic decapeptide which causes a pituitary release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) in several species of animals (1,2). Systemic administration of GnRH causes a rapid increase in

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plasma LH and FSH levels in cattle (3). Clinical applications for GnRH in cattle have been extensively reviewed (4,5).

The effects of administration of GnRH in early postpartum dairy cows have also been recently reviewed (6). The LH response produced by GnRH injection in postpartum cows is similar to that seen following its use in cycling cows (7) but is not normally restored until seven to ten days postpartum (8,9,10). Gonadotrophin releasing hormone-induced ovulation is significantly affected by follicle size and by plasma estradial 17-beta levels at the time of treatment (11,12).

Field studies designed to investigate the effect of GnRH administered in the early postpartum period of dairy cows on reproductive performance have produced equivocal results (6). The administration of GnRH has been shown to reduce the frequency of ovarian cysts and decrease the incidence of culling due to infertility (13,14). It has been also shown to improve fertility through a decrease in open intervals and a decrease in the number of services per conception (13,15). In a recent German study, GnRH treatment in cows with retained placenta (RP) resulted in shorter open intervals and a reduced number of services per conception (15). Other studies have demonstrated no beneficial effects of GnRH administration in the early postpartum period (16,17,18). One recent field trial described significantly increased open intervals and incidence of pyometra in cows treated with GnRH at day 15 postpartum as compared to cows treated with cloprostenol at day 24 postpartum (19).

The influence of early postpartum breeding on the economic efficiency of dairy cattle has been extensively studied (20,21,22). Maximum lifetime production of milk and offspring can be achieved if calving intervals are 12 months or less. In order to accomplish this, cows should conceive no later than 85 days postpartum (20). Dairy cattle with RP may have significantly delayed uterine involution (23), delayed return to cyclic ovarian activity (24) and reduced reproductive efficiency in the subsequent breeding period (25,26,27). The influence of RP on reproductive efficiency may be dependent upon the proportion of cows with RP that develop metritis complex (28). The number of estrous cycles prior to the intended breeding period (60 days postpartum) is an important factor in determining fertility in the 60 to 80 day postpartum period (29).

The purpose of this field trial was to evaluate the reproductive performance of dairy cows with RP following treatment with GnRH on day 8 to day 14 after parturition. The effect of early postpartum breeding on this relationship was studied.

MATERIALS AND METHODS

The cows used in this study were from herds receiving health care service from the Ambulatory Clinic of the Ontario Veterinary College. The field trial was carried out between February 1979 and November 1980. Only Holstein-Friesian cows which had RP for 48 hours or longer after parturition and had shown evidence of delayed uterine involution were included in the trial. The criteria used for delayed involution of the uterus was the previously gravid uterine horn being 20 cm diameter or greater on day 8 postpartum, or greater than 15 cm on day 14 postpartum (24). In order to maintain uniform assessment of the rate of involution, all initial rectal palpations were performed by one person (KEL).

The study was conducted as a double-blind experiment and was based on generally accepted concepts of field trial design (30). Each cow received an intramuscular injection of either 200 μg gonadorelin hydrochloride (Factrel, Ayerst, Montreal) in 2 mL sterile water or 2 mL of sterile water alone. The cows were treated between day 8 and day 14 postpartum, inclusive. Experimental vials were coded with a balanced, randomly distributed numbering sequence and were assigned on a per farm basis. This procedure aided in maintaining equal numbers of GnRH-treated and control cows on any individual farm without sacrificing the random assignment and double blind standards of the trial.

Between ten and 20 days after treatment rectal examination was carried out to determine the stage and rate of uterine involution. Thereafter, reproductive status, as determined by rectal palpation, was assessed on a regular monthly basis in conjunction with the monthly herd health visit. All estrus and breeding dates were recorded. Cows bred 40 days or more, at the time of a regular herd visit, were examined for pregnancy. In addition, reproductive abnormalities observed or detected during the postpartum period were recorded. These were identified according to standard definitions (31). These included postpartum subestrus defined as failure to exhibit estrus in the absence of palpable or observable reproductive abnormalities; and postbreeding subestrus which was applied to cows bred and not exhibiting subsequent estrus but on pregnancy examination were found to be nonpregnant in the absence of demonstrable abnormalities.

The criteria used to evaluate the response to therapy in this clinical trial were as follows: rate of uterine involution; occurrence of reproductive abnormalities, such as pyometra or cystic ovarian degeneration; interval from parturition to first observed estrus; interval from parturition to first service; open interval; services per conception; total services per cow, regardless of whether pregnancy resulted or not; and numbers of cows culled for infertility.

Data collected in this study were coded numerically and statistical analyses were performed using standard methods (32). Differences between GnRH-treated and control animals for age and other periparturient characteristics were tested in order to determine the similarity of the groups. Chi-square analysis was used to test for equal distributions of discrete variables, such as antibiotic treatment and concurrent diseases. For continuous variables such as days from parturition to treatment, differences were compared using Student's t-test. Differences between groups for outcome variables were calculated in a similar manner.

The importance of variables such as age, interval from parturition to treatment, antibiotic therapy and days from reconstitution to use of GnRH were analysed. The reproductive performance outcome parameters of GnRH-treated versus control cows were statistically compared within these subgroups. In addition, the differences between GnRH-treated and placebo-treated groups were analysed using discriminant analysis to eliminate distortion or bias from intervening variables (32).

A final analysis was done to assess the effects of GnRH administration on reproductive performance when early postpartum breeding was used. The mean interval from parturition to first service was calculated for each individual farm using both GnRH-treated and control cows. An arbitrary interval of 80 days average from parturition to first insemination was used to identify farms with early postpartum breeding practices. Gonadotrophin releasing hormone-treated and control animals from these farms were compared for parameters of reproductive performance using the previously described statistical analysis.

RESULTS

Three hundred and eighty-four Holstein-Friesian cows diagnosed as having RP accompanied by delayed uterine involution were studied. Six cows, which were the only RP cases on a particular farm, were eliminated from the analysis in order to avoid any bias introduced by unequal numbers of GnRH-treated and control cows on a farm. Thus, the remaining 378 cows constituted the experimental population on which the analysis of data was based. This population included 187 animals treated with GnRH and 191 placebo-treated controls.

The age and periparturient characteristics of GnRH-treated cows were not significantly different from control cows suggesting equality of the groups prior to treatment (Table I).

The reproductive performance parameters in RP cows treated with GnRH and RP placebo-treated cows are presented in Table II. There were no statistically significant differences between groups for any parameter of reproductive performance ($p \geq 0.05$). The frequency of diagnosed reproductive abnormalities were not significantly different between cows treated with GnRH and cows given a placebo ($p \geq 0.05$) (Table III).

Since a comparative analysis using the entire experimental population did not reveal significant differences

TABLE I. Age and Periparturient Characteristics of GnRH-treated Cows and Control Cows

Periparturient Characteristics	Number of Cows	
	GnRH-treated	Controls
Total number of cows	187	191
Mean cow age (Years ± SD)	5.10 ± 2.8	5.18 ± 2.7
Mean interval from calving interval to experimental treatment (Days ± SD)	9.87 ± 1.8	9.68 ± 1.6
Sex of calf: Male	80	82
Female	60	70
Multiple births	47	39
Dystocia	24	20
Stillborn calves	25	31
Clinical metritis	66	66
Acute mastitis	9	9
Milk fever	22	21
Abomasal displacement	7	7

Differences between GnRH-treated and control groups for all characteristics were not statistically significant ($p \geq 0.05$)

TABLE II. Reproductive Outcome Parameters of GnRH-Treated Cows and Control Cows

Reproductive Outcome Parameter	GnRH-treated Cows	Control Cows
1. Categories of uterine change (Absolute Number)	4.06	4.13
2. Days postpartum to first observed estrus (Mean ± SD)	80.2 ± 37.2	74.7 ± 31.8
3. Days postpartum to first insemination (Mean ± SD)	96.5 ± 33.7	91.8 ± 27.7
4. Days postpartum to conception (Open Interval) (Mean ± SD)	123.8 ± 52.5	125.9 ± 60.4
5. Services per conception (Mean ± SD)	1.8 ± 1.1	2.1 ± 1.6
6. Total services per cow (Mean ± SD)	1.96 ± 1.30	1.1 ± 2.0
7. Cows culled for infertility (Absolute Number)	16	15

Differences between GnRH-treated and control groups for all characteristics were not statistically significant ($p \geq 0.05$)

TABLE III. The Number of Diagnosed Reproductive Abnormalities in GnRH-treated Cows and Control Cows

Reproductive Abnormality	Number of Cows	
	GnRH-treated	Controls
Number of cows	187	191
Pyometra	24	28
Chronic endometritis	29	29
Cystic ovarian degeneration	23	18
Postpartum subestrus	16	17
Resorption of pregnancy	8	5

Differences between GnRH—treated and control groups for all characteristics were not statistically significant ($p \geq 0.05$)

between GnRH-treated and control groups, the roles of selected potentially important variables were examined. For example, the population was divided into subgroups according to age, interval between reconstitution and injection of the treatment solution, the use of systemic or local antibiotic therapy and the interval between parturition and treatment. There were no significant differences between GnRH-treated and control cows for any outcome parameter within these population subgroups indicating that these variables were not particularly important. In addition, discriminant analysis, which simultaneously statistically adjusts for the effects of these variables, revealed no significant differences between GnRH-treated cows and control cows.

The reproductive performance of GnRH-treated and placebo-treated cows on farms with a mean interval to first service of 80 days postpartum or less are presented in Table IV. This analysis involved ten farms with an average of 8.2 cows on the trial and included 39 GnRH-treated cows and 43 control cows. There were significant improvements in reproductive performance in GnRH-treated cows compared to control cows on farms that utilized early postpartum breeding. The means of days from parturition to first observed estrus were similar for both groups. However, the difference in means of days from parturition to first service between GnRH-treated and placebo-treated cows (67.4 ± 17.0 vs 77.4 ± 23.7 days) was statistically significant ($p \leq 0.05$).

The greatest improvement in reproductive performance after GnRH treatment in RP cows on farms using early postpartum breeding was in open interval. The difference in average intervals from parturition to the time of conception (33 days) for GnRH-treated cows compared to control cows (97.2 ± 36.4 vs 130.6 ± 59.2 days) was statistically significant ($p \leq 0.01$). Furthermore, the total services per cow regardless of resulting conception was significantly less in the GnRH-treated group than for control cows ($p \leq 0.05$). There was no significant difference between groups for any other parameter of reproductive efficiency.

TABLE IV. Reproductive Performance Parameters for GnRH-treated Cows and Control Cows on Farms Using Early Postpartum Breeding

Reproductive Performance	GnRH-treated Cows	Control Cows
Number of cows	39	43
1. Days postpartum to first observed estrus (Mean ± SD)	63.2 ± 21.0	63.0 ± 24.4
2. Days postpartum to first insemination (Mean ± SD)	67.4 ± 17.0[b]	77.4 ± 23.7
3. Days postpartum to conception (Mean ± SD)	97.3 ± 36.4[a]	130.6 ± 59.2
4. Services per conception (Mean ± SD)	1.86 ± 0.8	2.50 ± 1.6
5. Total services per cow (Mean ± SD)	1.90 ± 0.8[b]	2.70 ± 2.0
6. Cows culled for infertility (Absolute Number)	3	1

[a]Significantly different from control values ($p \leq 0.01$)
[b]Significantly different from control values ($p \leq 0.05$)

DISCUSSION

These results indicated that the administration of GnRH in the early postpartum period of dairy cows with RP and delayed uterine involution produced significant improvements in reproductive performance in cows from herds that used early postpartum breeding. Statistically significant reductions in the open interval, in total services per cow and in interval from parturition to first service were observed in GnRH-treated cows compared to placebo-treated control cows. Similar improvements in reproductive performance, in herds that used early postpartum breeding, have been reported in studies using both normal and abnormal cows (15) and in trials restricted to cows with RP (13).

When the entire experimental population was analysed, differences between groups for all parameters of reproductive performance were not significant. Similar findings have been reported in numerous other studies (14,16,18,19). The lack of beneficial effect from GnRH treatment has been explained in two different ways. Firstly, it is expected that the reproductive performance of a reference population could be too efficient to produce statistically significant improvements in GnRH-treated animals over controls. In one study, 24 of the 54 cows on the trial had rectally palpable evidence of estrus by day 14 postpartum and ten of the 27 cows in the GnRH-treated group had already ovulated prior to treatment (18). Secondly, the reproductive management practices of the reference herds can be an extremely important influence on the effects of postpartum GnRH therapy. This factor has been stressed in one previous study (15) and is strongly supported by the results of other experiments (13,14).

In the present field trial, the management decision to breed cows at an earlier time in the postpartum period exerted a profound influence on the ability of GnRH administration to improve parameters of reproductive performance. Significant improvements in reproductive efficiency were limited to herds with a mean interval from parturition to first service for cows on the trial of 80 days or less. The economic importance of early postpartum breeding has previously been well established (20,21,22). In addition, an increase in the number of estrous cycles in the period prior to 60 days postpartum, enhanced fertility of inseminations in the period from 60 to 90 days postpartum (29). This effect did not continue into later postpartum breedings. Thus, it is understandable that the extended intervals from parturition to first service in the overall experimental population of RP cows did not yield statistically significant differences in open intervals. Similarly, in other studies intervals to first service of 88 days (14) and 83 days (15) allowed control cows enough estrous cycles to negate the advantages of early induced cycles in the GnRH-treated group.

In the present study, there were significantly shorter intervals from calving to first insemination. However, intervals from parturition to first observed estrus were not significantly different between GnRH-treated and control cows. It must be emphasized that this reflected observed estrus and not actual cyclic activity. Neither milk or plasma progesterone assays nor repeated rectal palpations were used to plot postpartum estrous cycles. It is not known what postpartum cycle number was the first observed estrus for each group. Gonadotrophin releasing hormone-treated cows are likely to have had more estrous cycles in the early postpartum period thereby being more desirable for early breeding. Earlier studies have described the characteristics of early postpartum GnRH-induced estrous cycles (11,12). The increase in plasma progesterone after GnRH-induced ovulations was only 50% to 70% of the progesterone increase observed after noninduced ovulations. The length of subsequent cycles in the GnRH-treated group were invariably shorter than those of normal cycles, being between nine and 13 days in duration (13). In the present study, the interval between estrous cycles may have been longer in control cows thereby delaying their mean interval to first insemination.

The present field trial did not demonstrate a significant difference between GnRH-treated cows and placebo-treated cows for the occurrence of cystic ovarian degeneration or the occurrence of culling for infertility. This is contrary to other reports (2,5). These divergent findings in numbers of ovarian cysts may have been influenced by differences in the incidence of ovarian cysts in the reference population, differences in the diagnostic criteria used, or on differences in the intensity of follow-up observation. Likewise, the criteria used to decide that an animal was culled for infertility were not accurately outlined for any of the reports described, making a meaningful comparison of these values very difficult.

The design and performance of field studies to elucidate the effects of GnRH treatment vary considerably and this may produce biased or divergent findings. The characteristics of the experimental animals, such as age and breed, the number of reference herds, herd management factors and the reproductive status of experimental cows can have a profound effect on outcome variables. Also, the treatment regime, including the type of GnRH analogue, dosage, route and time of administration have been widely different. Thus, it is difficult to compare results from study to study. Of particular importance for the validity of a field trial are the methods of allocation of individuals to treatment or control groups, preferably formally randomized, and the equality of follow-up observation between groups, which is enhanced by blind techniques. With these points in mind, the authors see a need for further studies on hormonal therapy in cows during the postpartum period.

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BOOK REVIEW

ANIMAL PAIN — PERCEPTION AND ALLEVIATION. *Edited by R.L. Kitchell, H.H. Erickson, E. Carstens and L.E. Davis. Published by American Physiological Society, Bethesda, Maryland. 1983. 221 pages. Price US$40.00.*

This is an excellent book which will be of value to anyone concerned with the health and welfare of animals. To my knowledge, this is the first book that deals exclusively with pain in animals. It is particularly timely because of the advent of the animal rights movement as well as generally increased concern for the humane treatment of animals in research. Scientists, health administrators and laypeople will all find valuable information in this book.

The book consists of two parts; the first 160 pages deal with basic pain mechanisms and the last 56 pages are concerned with clinical problems. The first part contains 9 succinct chapters that provide outstanding summaries of the anatomy, physiology and psychology of pain. They are written by world-class experts in their fields and are informative and readable. The editors deserve great credit for prevailing on the authors to keep their chapters brief, to the point, and understandable despite the complexity of problems. Willis' chapter of ascending spinal pathways and Carsten's chapter on descending control over pain signals are among the clearest expositions of these topics available in the literature.

The second part, which will be of particular interest to veterinarians, deals with clinical issues. Davis provides an excellent summary of species differences in drug disposition as factors in the alleviation of pain. Lumb and his colleagues evaluate analgesic drugs in horses and Hughes and Lang present a fine summary on the control of acute pain in dogs and cats. These clinical chapters complement the expositions on basic mechanisms and the reader will frequently move back and forth among the chapters. Because the book is relatively short, this cross-referencing is easy to do.

This book is based on a symposium which was planned, organized and financed by the American Veterinary Medical Associate (AVMA) Council on Research. It was a commendable undertaking, and we must hope that this book marks the beginning of many more publications that will lead to the alleviation of pain and suffering in all animals, including man.

— *R. Melzack.*