Practical Uses of GnRH and Prostaglandins in Bovine Reproduction

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A Review

Recent developments in reproductive endocrinology has led to a tremendous increase in the knowledge and understanding of the complex physiologic mechanisms controlling the reproductive processes in domestic animals. The practical implications and applications of these physiologic findings for improving reproductive efficiency in domestic animals have been widely reviewed (34, 37, 59, 62).

Undoubtedly the two most significant developments in the field of bovine reproduction in the past decade have been the commercial availability of Gonado-tropin-releasing hormone (GnRH) and Prostaglandin $F_2\alpha$ (PG) and their respective analogues. The products are now extensively used in the field of bovine reproduction (34-37, 58). As often is the case with new products some practitioners have expressed satisfaction, while others have expressed disappointment with the results obtained following the use of these hormones. Two main factors account for complaints of disappointment and failures. On one hand the veterinarian is not fully informed of abberrant results that may occur when the products are used in practice. This is due to the fact that much emphasis is placed on the results obtained when the products are used in carefully selected animals under controlled experimental conditions or in clinical trials. This premise incorrectly assumes uniformity of animals to be treated and the husbandry conditions under which these products are to be used, and does not appreciate the differences in the interest, knowledge, experience and competence of practitioners who routinely use these hormones. In this regard, a careful investigation of the complaints of failures indicate that in most cases the hormones were incorrectly used.

Information regarding problems encountered by veterinarians using PG and GnRH are fragmentary. Schultz (58) reviewed the experiences and problems associated with usage of prostaglandins. It was apparent that most cases of reported disappointments and failures following field applications of prostaglandins stemmed mainly from a lack of understanding of the physiologic complexities of the reproductive process, incorrect applications and a lack of appreciation of the limitations of the product. This applies equally to GnRH. It is therefore important for the veterinarian to realize that maximum benefits from the use of GnRH and PG can be obtained only if the hormones are used in the prescribed manner (route, dose) and after an accurate diagnosis has been made. It is thus imperative that the user should have adequate knowledge of the reproductive process in the cow. Furthermore, in order to avoid overexpectations and frustrations the practitioner must also be aware of not only the potentials, but also the limitations of these hormones. Experience since commercial introduction of the drugs has shown that the extent of usage of each product depended on its availability, ease of administration, cost per treatment, a high degree of efficiency and a low incidence of failures or side effects when used under field conditions.

The aims of the present report are to review the results obtained following field application of these two products; list the common complaints or problems associated with their usage and to discuss the possible reasons for these complaints or failures and how they can be avoided under field conditions.

Applications of GnRH and Analogues in Bovine Reproduction.

Gonadotropin-releasing hormone (GnRH) also referred to as luteinising hormone/follicle stimulating hormone-releasing factor (LH/FSH-RF) or luteinising hormone-releasing factor (LH-RF), is a decapeptide of hypothalamic origin which stimulates the release of pituitary gonadotropins (FSH and LH) in farm animals (12). Since its first isolation about a decade ago, tremendous work has gone into the determination of its chemical structure, leading to the synthesis of large quantities for experimentation and finally for commercial application. GnRH and its synthetic mimics, hitherto referred to in this report as GnRH, are presently commercially available as LH-RH* in Europe, Factrel** in Canada or Cystorelin*** in the U.S.

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*LH-RH - various prepartions and analogues
**Factrel - gonadorelin HCI - Ayerst, Montreal, Canada.
***Cystorelin - gonadorelin - Abbott Labs., Chicago.

The results of experimentations and field application of GnRH in cattle have been widely reviewed (34, 37). Administration of GnRH causes dose-related increases in the serum concentrations of luteinising hormone (LH) in cattle. Of practical significance are the findings that the response to GnRH treatment is influenced by the physiologic state of the treated animal. For instance, when GnRH is used for the induction of ovulation, the best results are obtained when a suitable pre-ovulatory follicle is present. Secondly, when used in the postpartum cow, the pituitary response to GnRH was shown to increase with time after parturition (10, 24, 39, 41, 56).

Route and Dose (GnRH)

Systemic administration of GnRH using various routes (intravenous, intramuscular, subcutaneous, intravaginal and intrauterine) yields similar results in cattle (21, 34, 37, 39). The most commonly employed route of administration is i.m., although some practitioners prefer the i.v. route.

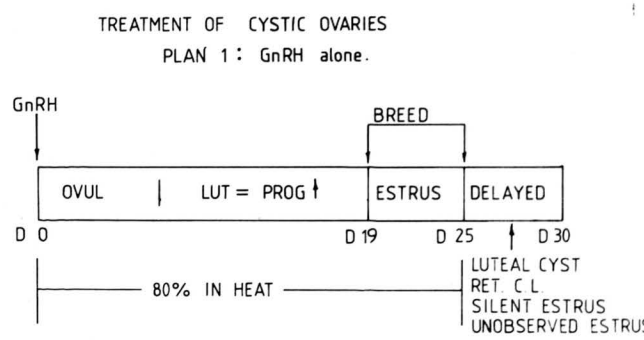
Dose response studies and results of field trials have led to the adoption of widely varying dosages of GnRH for cattle. Higher doses of GnRH (0.5 - 1.5 mg) are used in Europe; while in North America, low to medium doses (100 - 250 mg) are used. Both treatments have been shown to produce clinical cure; however, it is reported that the higher doses induce ovulation and corpus luteum formation in a high percentage of treated cows, while the lower doses are thought to produce luteinisation with a low incidence of ovulation and corpus luteum formation (4, 5, 27, 37, 53, 61, 72).

In bovine reproduction GnRH can be used where LH therapy is indicated. Thus the practical applications of GnRH in the bovine include the treatment of cystic ovaries, management of postpartum reproductive activity and induction of ovulation.

Treatment of Cystic Ovarian Degeneration

The major use of GnRH by the bovine practitioner is for the treatment of cystic ovarian degeneration (COD) in the cow. In order to understand the use and the interpretation of the results obtained, an adequate understanding of the morphological, hormonal and clinical features associated with cystic ovaries is necessary. Cystic ovarian degeneration is by far the most predominant ovarian pathologic condition in dairy cows, the clinical incidence varying between 3 - 20% (1-3, 18). These Cysts are believed to result from failure of release of LH. Recent morphological and endocrine findings are of importance as far as the method of treatment is concerned. For instance it is important to know that two main types of Cysts occur; follicular and luteinised Cysts; and that cystic ovaries may be accompanied by the presence of a corpus luteum in the ovary (1, 2, 5, 19). Until five to six years ago, the most successful treatment of cystic ovaries consisted of the administration of products high in luteinising hormone activity; but in the last five years GnRH has become the treatment of choice. The effectiveness of GnRH for the treatment of cystic ovarian degeneration has been demonstrated by clinical trials and field applications (4, 11, 32, 53, 61, 69). Administration of GnRH results in normalising the estrous cycle. Following treatment with GnRH estrus occurs within thirty (30) days, with most of the animals exhibiting estrus during the interval of 9 - 24 days after treatment (Fig. 1). Conception rates following breeding on the first estrus after GnRH treatment are comparable to the herd average. In some cases two to three treatments may be necessary to effect a cure.

Figure 1. Events following the use of GnRH for the treatment of cystic ovarian degeneration in cows.



The most common practical queries by practitioners regarding the use of GnRH concern the volume of the dose administered; the keeping quality of the hormone following reconstitution and the anestrous condition in some cows following GnRH treatment for cystic ovaries.

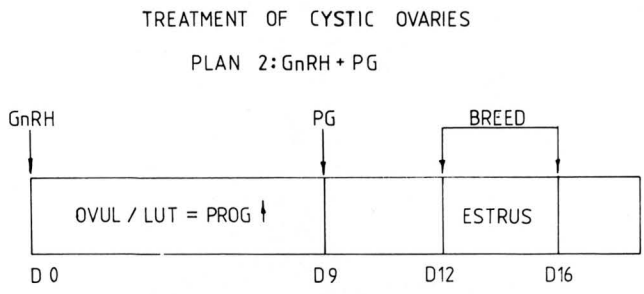
The treatment doses (100 - 1,500 mcg) of GnRH have been administered in various (2 - 10 ml) volumes of the carrier vehicle. The commonest volume used is 2 ml. Practitioners complain of the unmanageability of this small volume under field conditions. Diluent volumes of 5 ml containing the treatment dose would be preferable under field conditions. There is very little information regarding the keeping quality of the drug after reconstitution. It is advisable to use the drug soon after mixing but this may not be possible when the drug is available in multidose vials. Subsequently, the reconstituted product may be carried around for days before usage. In such instances the effect of light, heat and aging thus become a factor. It is not unreasonable to assume therefore that in some cases, failure of response may be due to the use of an inactivated product. Commercial availability of the products in single doses will eliminate this problem.

Another common query concerns the interval from GnRH treatment to the exhibition of estrus and the advice regarding breeding at estrus. A large percentage of cows with cystic ovarian degeneration exhibit estrus with 7 to 24 days

after GnRH treatment and conception to breeding at estrus is normal. The problem is with those cows that do not show estrus until 25 - 45 days after treatment. This phenomenon is of considerable concern to the practitioner and of economic importance to the dairyman. Examination of these animals has shown that unobserved estrus, luteinised cyst or retained corpus luteum may be the cause of the problem. It is thus advisable that cows, not showing estrus within 21 days after GnRH treatment for cystic ovaries should be re-examined and further treatment instituted if necessary.

In order to prevent episodes of anestrus and subsequent long intervals from treatment to breeding of cows with cystic ovarian degeneration, two modifications of the GnRH treatment have been devised. These treatments involve the sequential administration of GnRH and prostaglandins or vice versa (5, 25, 31). As illustrated in Figure 2, the first variation involves the administration of GnRH followed by the injection of prostaglandin (estrumate or lutalyse) nine to fourteen days later. Rectal palpation may be carried out

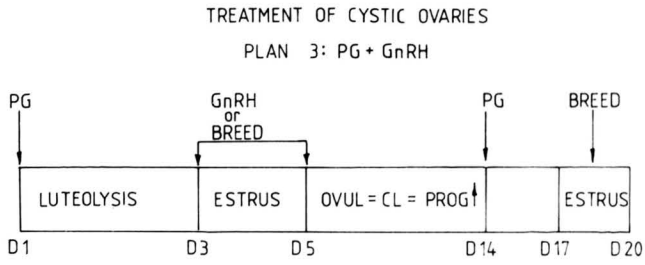
Figure 2. Treatment of cystic ovarian degeneration in cows. Events following sequential administration of GnRH and prostaglandin.



prior to the prostaglandin injection to check for luteinisation. Estrus occurs within two to five days after prostaglandin treatment and breeding on this estrus results in acceptable conception rates. A small percentage of cows may not show estrus following the prostaglandin treatment, especially if the treatment is given on Day nine post GnRH treatment. Poor or delayed luteinisation after the GnRH treatment is believed to be the cause of failure in these cases; thus the necessity of rectal examination prior to prostaglandin treatment. The problem may be avoided by delaying the prostaglandin injection until fourteen (14) days after GnRH treatment.

The second modified treatment involves the administration of prostaglandin followed in three or four days by the administration of GnRH. A second treatment of prostaglandin may be administered nine to fourteen days after the GnRH treatment, or omitted altogether (Figure 3). This method is most effective for animals with luteal cysts or where a corpus luteum and a cyst co-exist. The

Figure 3. Treatment of cystic ovarian degeneration in cows. Events following sequential administration of prostaglandin and GnRH.



prostaglandin treatment induces luteolysis followed by estrus, and the administration of GnRH results in ovulation and luteinisation and normalisation of the cycle. The second prostaglandin treatment if given shortens the interval from initial treatment to breeding

The attraction of these modified methods is the considerable saving of time from initiation of treatment to breeding when compared to GnRH treatment alone. On the other hand these treatments involve added costs in the form of two or three hormone injections. However in view of the interest shown by veterinarians and dairymen for these two methods further studies are needed to evaluate their efficacy in comparison to GnRH alone. Preliminary indications from practitioners are that the conception rates after the use of these two methods are comparable to those obtained when GnRH alone was used.

As GnRH increasingly became the treatment of choice for cystic ovarian degeneration instead of Human Chorionic Gonadotropin (HCG), comparison of their effectiveness was inevitable. Comparative field studies using either HCG or GnRH revealed that both are equally effective for the treatment of cystic ovarian degeneration in cows (23, 53, 61). The advantages of GnRH include a lowered risk of antibody production because of its comparatively small molecular structure, reduced risk of ovarian refractoriness following repeated injection, no danger of ovarian overstimulation since its action is central and finally, a lower cost per treatment.

Use of GnRH In The Postpartum Cow

Another major potential of GnRH in bovine reproduction is the prophylactic or therapeutic application of the drug to hasten normal cyclical activity in the early postpartum dairy cow. Such usage may contribute to early rebreeding and improved overall conception rates. The aim of the dairyman is to achieve a calving interval of 12 to 13 months. This can be attained if cows are successfully bred within 50 - 85 days after calving. The success of the first breeding in turn depends on absence of reproductive tract infections or

reproductive disorders prior to breeding. Thus the interval from parturition to conception is critical and any prophylactic measures aimed at providing a calving to conception interval of 50 to 60 days will be beneficial.

Jochle (34) reviewed the results of previous attempts using hormone treatments in the early postpartum period to enhance early resumption of cyclical activity, increase the number of ovulations prior to breeding and improve fertility. Earlier studies of the postpartum period provided scientific basis for judicious application of hormones during period (26, 40, 42, 49, 51, 52, 54, 64). These studies have characterised the patterns of follicular growth, estrus, ovulation and fertility after calving and endocrine changes associated with these patterns. The findings that are of significance regarding the use of GnRH are:

a) The interval from parturition to the development of ovarian follicles averages about 14 days and the interval to first ovulation is between 15 - 30 days.
b) LH concentrations and pituitary response to GnRH increases with time after calving in dairy cows.
c) About 10 - 15% of dairy cows manifest abnormal ovarian activity during the first two months postpartum, and
d) Fertility of dairy cows during the normal breeding period is in direct proportion to the number of estrous cycles prior to the beginning of breeding.

On the basis of these findings it can be assumed that the application of GnRH two weeks after calving would hasten normal cyclicity in the early postpartum dairy cows. In the field trials conducted to test this hypothesis, it was found that GnRH administered 8 - 23 postpartum may induce early cyclic activity, reduce the incidence of cystic ovarian disease and increase fertility in dairy cows. There was however no effect on the incidence of uterine infections (9, 52).

Further studies are required to describe the manner in which GnRH can be used in the postpartum period to obtain maximum results. In the meantime, practitioners administer 100 or 250 mg GnRH to cows two weeks postpartum; usually in cases of postpartum infections. Undocumented reports indicate improvement in the rate of uterine involution and resumption of cyclical activity. Better results are obtained in dairy herds that are under good reproductive management.

Use of GnRH to Induce Ovulation

GnRH has been recommended for assuring ovulation. In this regard, some practitioners use GnRH at breeding. The results of two field trials indicate only a moderate increase in conception rates when GnRH was administered to cows at the time of insemination (27, 57). This poor cost-benefit ratio thus mitigates against the routine usage of GnRH for this purpose. The method may however be beneficial in selected animals or herds where delayed ovulation is a problem (55, 67, 68). In such cases, GnRH may be administered either six (6) hours prior to, or at the time of breeding. Both methods have proven effective as confirmed by rectal palpations after treatment. Compared to the traditional method of multiple examinations in suspected cases of delayed ovulation, GnRH administration at breeding costs less and saves time. It must, however, be emphasized that GnRH therapy in such cases should be instituted after other causes of infertility have been eliminated, and should be accompanied by simultaneous improvement in management methods aimed at reducing predisposing factors.

GnRH has been used to a limited degree following estrous synchronization or superovulation for the sake of embryo transfer. Results of two studies indicate no improvement in conception rates in cows treated with GnRH following estrous synchronization (46) however, the ovulations were fairly well synchronized (17). The routine application of GnRH following estrus synchronization is not recommended, since the effects do not justify the additional cost and effort involved. Experiences of veterinarians involved in embryo transfer operations clearly indicate that HCG is superior to GnRH when administered for induction of ovulation to the donor cow following treatment for superovulation.

Some Potential and Practical Uses of Prostaglandin* In Bovine Reproduction

The earlier reports indicating that $PGF_{2\alpha}$ is a potent luteolytic agent in cattle were followed by controlled experiments and field trials aimed at describing the details of prostaglandin action and fertility following prostaglandin treatment in cows (33, 45, 48). The great potential of these findings subsequently led to the synthesis and commercial availability of various synthetic analogues (13, 58). The commercially available products include $PGF_{2\alpha}$ (PG) or dinoprost as tromethamine salts (Lutalyse, Prostin F_2, Dinolytic); Clorprostenol (CP) (Estrumate) and protalene (Synchrocept). The former two are the most common forms used in bovine reproduction. The commercial availability of these products vary from country to country.

The primary application of PG or the analogues in bovine reproduction utilises their ability to induce functional and morphological regression of the corpus luteum followed by estrus and ovulation. Prostaglandins are effective when a suitable corpus luteum is present, for instance during Days 5 to 18 of the estrous cycle. A summary of the applications of PG and CP in bovine reproduction is provided in Table 1.

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* *Prostaglandin - PG. - Term used collectively for $PGF_{2\alpha}$ and synthetic analogues in this report.*

TABLE 1

Summary Of Uses Of PG and Analogues In Bovine Reproduction

Indication	Uses
Induction of Luteolysis	1. Treatment of anestrus; silent estrus; unobserved estrus. 2. Treatment of luteinised cysts.
Induction of Luteolysis & evacuation of uterus	1. Treatment of pyometra; endometritis. 2. Treatment of mummified fetus. 3. Induction of abortion. 4. Induction of parturition. 5. Treatment of prolonged gestation.
Induction of Luteolysis	1. Estrus synchronization. 2. Superovulation.

Routes and Dosages

$PGF_{2\alpha}$ and analogues are administered systemically using various routes (Table 2). Consistent results in the field are obtained when the subcutaneous i.v. and i.m. routes are used. The i.m. route is the most convenient and the commonest route for treatment of groups of cattle. The intrauterine route of administration is rarely used, although some practitioners prefer this route in cases of endometritis, where the product is administered along with the antibiotic solution used for infusion. The intrauterine treatment requires skill of catheterisation of the cervix, a procedure that may be difficult in some cows and heifers. Furthermore its use involves the risk of introducing infection into the uterus. The dosages employed depend on the route of administration, the minimum dosage being used when the substances are administered intrauterine and the highest when the subcutaneous, intramuscular or intravenous routes are employed. Clorprostenol 500 mcg i.m. or PG 20 - 30 mg. i.m. are commonly used for induction of luteolysis. A split dose administered at 6 to 24 hours apart is effective and is believed to reduce the incidence of incomplete luteolysis (Table 3). A lower total dosage is used for split treatments, but the disadvantage is that such treatment requires more effort (36). The incidence of side effects following the use of prostaglandins is low. Side effects have been reported following the administration of high doses of $PGF_{2\alpha}$ intravenously. The signs included restlessness, increased salivation, increased rumination combined with regurgitation and diarrhea. All signs disappeared in two to three hours (75).

TABLE 2

Recommended and Common Dosages Used: $PGF_{2\alpha}$ (PG) and CP*

Luteolysis	—	PG 20 - 30 mg im/subcut; CP 250 to 500 mcg i.m.
	—	PG Split dose 8 mg and 4 mg 6, 12, or 24 hrs. apart.
	—	PG 1 - 5 mg intrauterine.
Pyometra	—	PG 12.5 mg i.v. or 25 mg i.m.; CP 500 mcg i.m.
Abortion	—	PG 20 - 40 mg im/subcut
	—	PG Split dose 12.5 mg; 12.5 mg i.m. 12 hrs. apart
	—	CP 250 mcg Day 1 - 120; 500 mcg Day 120 - 150
Mummified Fetus	—	PG 25 mg i.m.; CP 500 mcg i.m.
Parturition	—	PG 20 - 50 mg im/iv
	—	PG Split dose 20 mg; 15 mg 24 hrs. apart
	—	PG 30 - 50 mg into fetal fluids
	—	CP 500 mcg i.m.
Estrus Synchronization:		PG 20 - 30 mg im/subcut 11 - 14 days apart
		CP 500 mcg i.m. 11 - 14 days apart.

CP* - Clorprostenol.

Treatment of "Anestrus": Due to unobserved estrus, no visible estrus (silent estrus).

The major use of prostaglandins by the bovine practitioner is for the treatment of various conditions characterised by anestrus. The common problems include unobserved estrus; no visible estrus and weak estrus. Examination of cows with these conditions reveal the presence of a corpus luteum in the absence of a conceptus or palpable uterine lesions. More often than not, when these conditions occur, they are usually due to poor estrus detection. Prostaglandin administration effectively induces luteolysis and estrus in these animals (14, 20, 60). Two methods of prostaglandin treatment have been used in the management of unobserved estrus. The first method involves the administration of prostaglandin followed by insemination at observed estrus, or at a fixed time, usually eighty (80) hours after treatment. The advantage of this method is that estrus is more likely to be detected when looked for at expected intervals following treatment; while breeding at a fixed time after prostaglandin treatment eliminates the necessity of estrus detection. The second approach involves administration of two injections of prostaglandins at eleven to fourteen day intervals followed by breeding at observed estrus, or at a fixed time after the second prostaglandin injection. The advantage of this method is that estrus exhibition is greater following the second prostaglandin injection; but this approach is considered by some to be time consuming and involves the added cost of a second prostaglandin administration.

Cows treated with prostaglandins will show heat two to seven days after treatment. Most estrus activity occur on days three, four and five after treatment. This apparent improvement in the exhibition of estrus in cows treated for unobserved estrus may be due to the fact that estrus detection is carried out at predetermined times after prostaglandin treatment. The decision regarding breeding following prostaglandin treatment depends on the circumstances of each individual case and more so the choice of the dairyman. Conception rates following breeding after prostaglandin treatment are normal; and better if the animal is bred at observed estrus.

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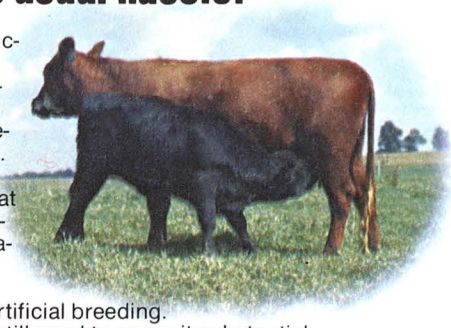

Since the introduction of Lutalyse, more and more cattlemen are taking advantage of the genetic superiority A.I. offers their herds. They're realizing that Lutalyse helps minimize the time and labor commitments needed for estrus detection prior to artificial breeding.

While cattlemen still need to commit substantial time and effort into an A.I. breeding program, it can be considerably less when they use Lutalyse to synchronize estrus. That's because labor requirements are intensified into just a few days. And the ability of Lutalyse to synchronize estrus also allows cattlemen to schedule this high-intensity labor demand into an otherwise "slow period".

By synchronizing the estrus and subsequent artificial breeding of the herd, chances are the calving season will be synchronized, too. Thus, Lutalyse makes it possible for a cattleman to schedule the herd's calving season to occur earlier. And having genetically-superior calves on the ground earlier can result in heavier calves with the potential for improved profitability at weaning.

Dairymen are improving their herds with their heifers, Lutalyse and A.I.

One very effective way for dairymen to improve their herds is by tapping the genetic potential of their heifers. To capitalize on this potential, dairymen will want to use a "proven" A.I. sire.

They know that a proven animal can sire daughters able to produce up to 1,000 pounds more milk per lactation than daughters of non-proven bulls. Probably the easiest way to instill the superiority of a proven sire into a heifer's calf is through A.I.

However, until recently A.I. has required a considerable commitment in time and labor by dairymen to observe each heifer for estrus, sort her out and then artificially breed her.

Lutalyse allows dairymen to schedule the estrus of groups of heifers at a time convenient to A.I. And while there's still a certain amount of labor needed to make a Lutalyse and A.I. program work, it's now compressed into a few manageable days.

Cooperation and coordination are the keys to successful Lutalyse breeding programs.

To assure successful results with Lutalyse for your clients, you will need a commitment of cooperation from the producer and his A.I. supplier at the outset. Only with this commitment can you help effectively coordinate the many events that will occur throughout the program.

Once everyone is working together, the next step is the development of a total breeding management program for the herd. This program normally starts with an evaluation of the herd's cycling activity, followed by a review of the herd's nutritional status, establishment of a herd health schedule, recommendations for handling facilities, advice on selection of quality semen, and use of a skilled inseminator.

You and the producer's A.I. supplier can provide the guidance and assistance needed to develop and implement this breeding management program. If the cattleman or dairyman follows this program closely, the results can be both productive and profitable.

And as the word of these successful breeding programs spreads, the number of producers wanting to utilize Lutalyse to take advantage of A.I. will increase, too. That will give you an opportunity to help other producers realize the benefits of a Lutalyse program while increasing the scope of your practice.

Yes, Lutalyse helps make timing estrus easier for your clients...and it can help the growth of your practice, too.

Lutalyse:
The Timing Is Right!

TABLE 3

Time of abortion following prostaglandin treatment of pregnant cows during the first trimester.

Cow	Treatment	Interval*		Remarks
1	25 mg PG** i.m.	116 hr.	(5d)	Fetus 116 g. C.R. 10 cm. ****Estrus 24 d.
2		93 hr.	(4d)	Fetus 121.5 g. C.R. 10 cm. Bloody mucus discharge E. 35 d.
3		95 hr.	(4d)	Fetus in vagnia; 110 g. C.R. 12 cm. E. 27 d.
4	25 mg PG i.m. for 2 days	95 hr.	(4d)	Fetus 190 g. C.R. 14 cm. E. 24 d
5		27 days		Fetus 107 g C.R. 13 cm. E. 26 d.
6		90 hr.	(4d)	Fetus 216 g. C.R. 16 cm.
7	50 mg PG i.m.	96 hr.	(4d)	Fetus 194 g. C.R. 16 cm. E. 22 d.
8		92 hr.	(4d)	Fetus in vagina; 188 g. C.R. 15 cm. E. 43 d.
9		72 hr.	(3d)	Fetus in vagina; 192 g. C.R. 16 cm. E. 27 d.
10	500 mcg CP*** i.m.	96 hr.	(4d)	Fetus 371 g. C.R. 23 cm. E. 35 d.
11		93 hr.	(4d)	Fetus 282 g. C.R. 21 cm. E. 27 d.
12		86 hr.	(4d)	Fetus 571 g. C.R. 26 gm. E. 24 d.

* Interval for treatment to abortion.
** PG - $PGF_2\alpha$ Lutalyse.
*** CP - Clorprostenol - Estrumate.
**** Estrus - Days from abortion to first estrus.

The common complaints by practitioners using prostaglandins for the treatment of anestrus conditions include absence of estrus exhibition in some cows following treatment, variation in intervals from treatment to estrus exhibition; and poor conception rates following breeding on prostaglandin induced estrus.

Absence of estrus following prostaglandin treatment may be due to failure to detect estrus, especially on farms where poor estrus detection is a major problem. A small proportion of cows, however, do not show overt estrus associated with ovulation following a single prostaglandin treatment. The above two problems are easily corrected by improving estrus detection techniques and breeding at fixed time intervals following PG treatment or adopting the two dose schedule since estrous exhibition is better following this regimen of PG treatment. Failure of estrous exhibition may also be due to failure of luteolysis, which may occur in cases where the treatment is given during the insensitive period, usually due to misdiagnosis of the status of the corpus luteum. Prostaglandins induce luteolysis in corpora lutea aged five to seventeen days. Another possible cause of failure to respond to PG treatment may be the ineffectiveness of the doses commonly employed in some cows, possibly due to variation in individual response. In this regard, it is also recognized that the recommended dose of PG or CP* is close to the minimal effective dose. Finally the use of an inactivated or expired product will result in no response. The effects of sunlight, heat and other factors on the drugs have not been documented. When inactivated, the products become grey and cloudy. Variations in the interval from treatment to estrus is a major problem after a single prostaglandin treatment. A majority of cows and heifers with mature corpora lutea will show heat within two to four days after a single prostaglandin treatment. This interval to estrus may vary from two to seven days, leading to increased farm labour involved in estrus detection and poor conception rates if the cows are bred at predetermined times after treatment. The variation in the interval from treatment to onset of estrus is believed to be due to animals being in various stages of diestrus at the time of treatment or to misdiagnosis of the status of the corpus luteum. In order to circumvent the problem of varying intervals it is recommended that only animals showing estrus 48 to 96 hours after PG treatment should be bred, the remainder are bred following a second PG treatment eleven to fourteen days after the first.

Complaints concerning poor conception rates following PG treatment in cows are not uncommon, although it has been fairly well established in several clinical trials that the pregnancy rates in cows following prostaglandin treatment are normal (14, 20, 70, 73). The source of the disappointment with the pregnancy rates obtained following prostaglandin treatment may in part be due to the failure of the practitioner to realize that the treatment does not increase fertility rate, and that the conception rates after PG treatment will be equal to the normal for the herd. Thus the fertility of the herd and the individual animal will influence the conception rates following prostaglandin treatment. *Prostaglandin treatment is no panacea for correcting poor husbandry or infertility problems in a herd.* The maximum benefits following prostaglandin can be achieved only through close cooperation between the veterinarian and the dairyman. The veterinarian is responsible for detecting the presence of a corpus luteum and diagnosis of other problems that may lead to infertility, while the dairyman is responsible for estrus detection and ensuring that the cows are bred at the recommended time following prostaglandin treatment.

Treatment of Cystic Ovaries - Luteal Cysts

Another common condition characterized by anestrus which responds well to prostaglandin treatment is luteinized cysts or luteal cysts. Prostaglandin administration in cows with luteinized cysts is followed by estrus within two to five days (40, 60). Breeding may or may not be carried out on induced estrus depending on the time interval after parturition and the wish of the dairyman. The few reports available and the experiences of various practitioners indicate acceptable conception rates following breeding. One common problem encountered after prostaglandin treatment for cystic ovarian degeneration is the recurrence

* *CP - Clorprostenol*

of the condition, which may be avoided by the use of sequential administration of GnRH and PG described earlier, although this involves added cost.

Treatment of Pyometra

Pyometra, which may occur in the postpartum cow or after insemination represents a deadlock situation characterized by a swollen, soft, doughy uterus containing varying amounts of pus and the presence of a corpus luteum in the ovary. The aims of treatment of pyometra are to induce luteolysis, evacuate the uterus and restore fertility. Prostaglandins (PG and CP) have been effective for this purpose. Systemic administration of PG results in regression of the corpus luteum and evacuation of the uterus within three to seven days (14, 29, 70). After prostaglandin treatment, mucopurulent vaginal discharge is obvious by the third day, and uterine evacuation is completed by five to seven days. The evacuation of the uterus is associated with signs of estrus. Success of the treatment is indicated by the return of the uterus to a normal palpable condition within seven to ten days. A small percentage of animals fail to show completely clean vaginal mucus after initial treatment; a second prostaglandin treatment eight to twelve days after the first results in complete clearance of the condition. Although most cases are cleared by prostaglandin treatment alone, simultaneous intrauterine antibiotic infusion at the second injection may be beneficial.

In this case the second prostaglandin dose may be mixed with the antibiotic solution for uterine infusion. Breeding following treatment for pyometra, should be attempted only if the vaginal mucous discharge at estrus is clear. The conception rates following PG treatment for pyometra range from 40 - 65%, and are better if breeding is delayed for at least one cycle following treatment. Sexual rest for one to two cycles and intrauterine antibiotic infusions may contribute to improved conception rates.

Treatment of Mummified Fetus

This condition is usually characterized by a persistent CL and can be treated with prostaglandins. A single systemic or series of intrauterine administrations of PG induce luteolysis and subsequent expulsion of bovine fetal mummies (14, 63, 66, 71). The systemic route of administration is preferred. Following PG injection cervical dilation occurs within 24 hours and the mummified fetus passes through the cervix within two to five days. The dry nature of the mummified fetus may necessitate manual delivery from the vagina. A practical method of aiding expulsion from the vagina involves the insertion of a large cotton wad liberally soaked in 0.2% Furasone*. This provides vaginal lubrication which facilitates delivery of the mummified fetus without further assistance. Resumption of normal cyclical activity after expulsion of a mummified fetus is prompt and although reports on conception rates are few, they suggest that fertility is normal following this treatment regimen.

Induction of Abortion

Prostaglandins are effective abortifacients when administered to cows and heifers during the first trimester. A single, or in rare cases two injections of prostaglandin are used to induce abortion in cases of mismating in dairy heifers; or for elective induction of abortion in feedlot heifers. Various doses and routes have been used by practitioners but the i.m. route is preferred. Dose response studies indicate that clorprostenol is effective at a dosage of 250 mcg up to Day 120 of gestation; and 500 mcg from Dav 120 - 150. The usual dose of $PGF_{2\alpha}$ used is 25 mg. (6, 8, 15, 16, 50, 74).

Abortions occur within three to nine days, with the majority occurring on the fourth to fifth day after prostaglandin treatment. The clinical features associated with prostaglandin induced abortion have not been described. A trial was carried out to observe and describe the clinical features associated with prostaglandin induced abortion.

Twelve Holstein cows were treated with $PGF_{2\alpha}$ or clorprostenol during the first trimester of gestation. Daily rectal palpation and vaginoscopic examinations were performed in these cows after treatment. In addition the animals were examined at frequent intervals throughout the day and night and daily blood samples were obtained for progesterone assay (Table 3). Cervical relaxation and dilation associated with a moderate amount of mucous discharge was evident in all cases within a day after treatment. Rectal palpations revealed increased uterine tone lasting from Day 1 to Day 3 after treatment. Abortions occurred between the third and fifth day after treatment and were associated with signs of estrus and mucohemorrhagic discharge at the vulva lips. In three cases the embryos were detected in the anterior vagina during the vaginoscopic examination. No episodes of metritis or systemic illness followed the abortions. Examination of the plasma progesterone patterns indicated that abortions occurred when the progesterone concentrations had decreased to 0.5 ng/ml or less. In the one cow that aborted 27 days after treatment, the cervix remained dilated from treatment until abortion and the plasma progesterone concentrations were 0.3 ng/ml or less from Day 2 after treatment until abortion occurred (6). Estrous cycles were re-established in these cows 24 - 42 days after abortion.

Failure of abortion to occur following PG administration to a heifer or cow supposed to be in the first trimester of pregnancy has been reported. This may be due to an inadequate dose of prostaglandin, ineffectiveness of the recommended dose in a particular cow or treatment may fail in animals on a supplemental source of progesterone. THe most common cause of failures however, is wrong estimation of gestation age. It is now clearly established that

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* *Furasone - 0.2% - Nitrofurasone solution N.F. - Armitage Carroll, London, Ontario.*

abortifacient efficiency of PG and analogues decreases as the gestation length approaches 150 days (74).

Data on the conception rates following induced abortion are few. The animals show normal cycles following abortion and in the absence of post-abortion complications, conception rates should be normal. Some practitioners have had cows bred on estrus following induced abortion in the first trimester with good results.

The effects of prostaglandin injection on cows during the second trimester of pregnancy are not well described. Since PG and analogues may be accidentally administered to cows during the second trimester, a small group of cows was treated with prostaglandins in order to study the effects of treatment. Six Holstein cows with known breeding dates received prostaglandin treatment during Week 26 and 28 of gestation (Table 4). Dosages of prostaglandin similar to or higher than those recommended for induction of abortion in cows were used. Daily rectal palpations and vaginoscopic examinations were carried out. Blood samples were collected daily for progesterone assay. The most significant findings included increased uterine tone and cervical dilation which were evident within two to three days after treatment. The degree of cervical dilation ranged from 2 to 6 cm. In each cow there was moderate to copious amount of mucus discharge present in the anterior vagina. The plasma concentrations of progesterone decreased from an average of 4.2 ng/ml to 0.4 ng/ml or less within 48 hours after treatment and remained low for four weeks when the observations ceased. Abortion occurred 26 days after treatment in one cow and, in another, pregnancy was terminated surgically following the diagnosis of uterine infection. In all cases mucopurulent vaginal discharge was evident within four days and this might have been due to infection introduced through the daily vaginoscopic examination. These observations indicate that administration of prostaglandins cause cervical dilation and transient increase in uterine tone in cows during the second trimester of gestation. It is therefore recommended that vaginal examinations should not be done following accidental prostaglandin treatment during the second trimester in order to lessen the chances of infection.

TABLE 4

Events Following PG Injection Into Cows During Second Trimester (Weeks 26 and 28).

Cow No.	Treatment PGF i.m.	Remarks
1 26 weeks	25 mg	Cervical dilation 48 hr., increased uterine tone 24 to 72 hrs. Moderate mucus discharge in ant. vagina, abortion 26 d. No retained placenta.
2 26 weeks	25 mg for 2 d.	Cervical dilation 48 hr., copious mucus discharge, increased uterine tone 24 to 72 hrs. No abortion.
3 26 weeks	40 mg	Bloody mucus in anterior vagina at 72 hrs., increased uterine tone 24 - 72 hrs. No abortion.
4 26 weeks	40 mg for 2 d.	Cervical dilation 72 hrs., moderate mucus discharge 72 hrs., increased uterine tone 24 - 72 hrs. No abortion.
5 26 weeks	40 mg	String of mucus at vulva 24 hrs., cervix dilated 36 hrs., increased uterine tone 24 - 48 hrs. No abortion.
6 26 weeks	50 mg	Increased uterine tone, 24 - 72 hrs., cervical dilation. moderate mucus discharge 60 hrs. No. abortion. 222
2 28 weeks	100 mg 3 days	Purulent mucus discharge in ant. vagina. No abortion.
4 28 weeks	10 mg for 3 days	Minimal mucus discharge 24 hrs. No abortion.
5	80 mg for 3 days	Blood tinged, mucopurulent discharge. Dead fetus extracted 17 days later.

Induction of Parturition

Prostaglandins and analogues are increasingly being employed for induction of premature parturition and for therapeutic purposes in the treatment of prolonged gestation. Various routes of administration have been used for this purpose but the i.m. and i.v. are commonly used. Parturition occurs within one to six days, usually three days after treatment. Signs of impending parturition are usually absent, but the mammary gland development is rapid and postpartum lactation is normal (38, 44, 75).

The incidence of dystocia is low during prostaglandin induced parturition; but there is an increase in the incidence of retained placenta especially if the induction is carried out too early (less than 280 days). The inability to predict the time of parturition, the absence of impending signs of parturition and the increased incidence of retained placenta reduces the management advantage gained from PG induced parturition. Fertility following PG-induced parturition has not been reported but in one study, most of the cows showed estrus within thirty days following PG-induced parturition (75).

Prostaglandins for Controlled Breeding

The greatest promise of prostaglandins is their control of the reproductive cycle in dairy and beef cattle. The use in dairy cattle has been extensive, but in beef cattle the use has been limited by several factors, particularly the labour involved.

Several regimens have been developed for the use of PG in controlled breeding programs; in each case the use of PG is being tailored to suit the program. For instance, PG has been used for controlled breeding in the postpartum dairy cow, for estrus synchronization in beef cattle and in combination with other hormones for superovulation (13, 43, 45, 47, 65).

(i) Controlled breeding of postpartum dairy cow or heifer

The use of prostaglandins for controlled breeding in the postpartum period is on the increase. Dairy cows are examined 50 to 60 days postpartum, whether they have shown heat or not. Those with corpora lutea are treated with prostaglandins and bred. The remainder are bred during

natural estrus. As discussed earlier, because of the spread of interval from treatment to estrus, absence of estrus in some cases and "poor" conception rates, some veterinarians have reservations regarding breeding cows after first prostaglanding treatment. In such cases other programs such as sequential administration of PG and GnRH or two PG injections at eleven to fourteen day intervals are recommended.

Estrous Synchronization

Various regimens using prostaglandins for estrous synchronization have been developed. Originally, the single injection method was used, but due to reservations regarding fertility rates and estrus expression the two injections at eleven to fourteen day intervals was adopted (7, 13, 30, 43, 47). Estrus manifestation is better following the second injection; ovulations are synchronized and the conception rates are normal. Some practitioners administer GnRH after the second PG injection in an attempt to tighten the interval to ovulation and increase the ovulatory rate. Experimental evidence indicate that although GnRH treatment synchronizes ovulation in treated animals, it does not improve the conception rate (17, 46).

The commonest complaint registered by practitioners after use of the two PG injection method concerns pregnancy rate. Investigation of this complaint reveals that in most cases the procedure was improperly done. Sometimes satisfactory pregnancy rates are considered disappointing simply because of ignorance of what is normal and overexpectation on the part of the owner! Some owners and practitioners expect more than normal conception rates following the use of PG. In reality, the conception rates after PG are similar to the normal rate in the particular herd. The use of prostaglandins does not improve conception rates; it may rather unearth and concentrate problems that exist in the herd.

The fact that PG is used for its luteolytic properties in this program is often overlooked by practitioners. In a study carried out to describe the events following the use of the two dose schedule of prostaglandin in dairy cattle 15 dairy cows received two prostaglandin treatments 13 days apart. Examination of the plasma progesterone patterns in these animals showed that 13 of the 15 cows ovulated following the second prostaglandin treatment (7). There was one case each of incomplete luteolysis and Cystic ovarian degeneration. Nine of the cows became pregnant but only six calved. The results of this small study serves to point out that the conception rates following PG treatment may be influenced by several factors including abnormal ovarian function following luteolysis and early embryonic death. Results of other studies also suggest that insemination at the wrong time, failure of fertilization, poor semen quality and uterine infections may contribute to lower conception rates following estrus synchronization using prostaglandin. When large herds are synchronized at one time, inadequate bull power, improper insemination technique and inseminator fatigue may reduce the results of a prostaglandin and controlled breeding program (22, 59).

In a recent study Jackson et al. (33) described two problems in cows following the two-dose schedule of PG for estrous synchronization. In one group of cows, maturation of the corpus luteum was delayed after the first PG injection so that at the second treatment, 10 days later the response was poor. Increasing the interval between treatments may be beneficial in these cases. The second problem concerned cows with short cycles, in which case the administration of the second PG dose took place during an insensitive period.

Use of Prostaglandins In Embryo Transfer Programs

At present, prostaglandin usage in embryo transfer programs is second only to its use in the treatment of anestrus. Prostaglandins are used for induction of luteolysis in the donor cow and for estrus synchronization in the recipients. In order to avoid problems of incomplete luteolysis in the donor cow, some units prefer to administer two doses of prostaglandins 12 hours apart. One common complaint regarding estrous synchronization in the recipients has been a high incidence of cystic ovarian degeneration. The cause of this is unknown but it may be due to the use of improperly cycling heifers and other management factors. The problem may be eliminated by selecting only heifers or cows which have shown normal estrous cycles as recipients.

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