Recent Advances in Bovine Reproductive Physiology

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INTRODUCTION

The intent of this review is to give practitioners of the art and science of bovine reproduction a view of recent research findings in reproductive physiology. In some cases, practical applications of these findings have been suggested. In many cases, it has been left to the ingenuity of the practitioner to utilize the new information effectively.

The scientific literature in reproductive biology continues to increase at a very rapid rate. One welcomed trend is the increased appearance of data concerning domestic animals. A recently published textbook on reproduction by McDonald(28) which emphasizes cattle, sheep, swine, horses, dogs and cats will be of interest to many practitioners. The other text recommended is Nalbandov's *Reproductive Physiology.*(35)

The presence and importance of steroidal as well as gonadotrophic hormones have been well established for many years. It, however, has only been lately that quantitative information has become available. The development of sensitive assay procedures has been the key to our new insight into hormonal regulation of the estrous cycle, gestation and parturition. The use of gas-liquid chromatography and competitive protein-binding radioassay has allowed the quantitation of nanogram (10^{-9}gm) or even picogram (10^{-12}gm) amounts of steroidal hormones such as progesterone, estradiol-17_β and testosterone. Radioimmunoassay has enabled similar quantities of gonadotrophins (LH and FSH) to be measured. The great advantage of these techniques lies in the fact that individual animals can be sampled repeatedly resulting in a clearer dynamic picture of hormone secretion.

Gonadotrophic Control

LH changes in the systemic blood of cows during the estrous cycle were reported in 1969 by Schams and Karg(40) as shown in Fig. 1. Three points are of major interest: first, is the presence of a large preovulatory surge of LH which occurs about 15-25 hours before ovulation; second, a generally baseline level of secretion during the most of the cycle; and third, a short-lived surge observed at about day 9 (in about 40% of the

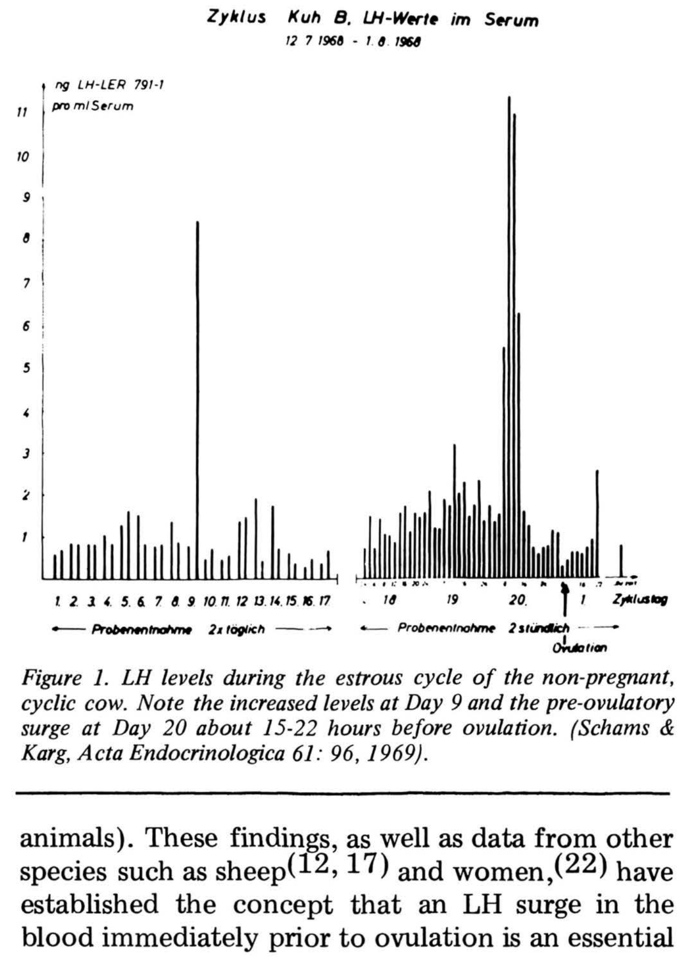

Figure 1. LH levels during the estrous cycle of the non-pregnant, cyclic cow. Note the increased levels at Day 9 and the pre-ovulatory surge at Day 20 about 15-22 hours before ovulation. (Schams & Karg, Acta Endocrinologica 61: 96, 1969).

animals). These findings, as well as data from other species such as sheep(12, 17) and women,(22) have established the concept that an LH surge in the blood immediately prior to ovulation is an essential component of this phenomenon in mammals. The significance of the LH surge at day 9 is not yet clear. It may be that LH is present in all cows but that sampling was not done often enough to detect its presence. It may be the corpus luteum (CL) that is reaching structural and functional maturity at about day 9 requires additional LH support for the maintenance of peak luteal activity through day 17 or 18 of the cycle.

FSH levels in the blood of cows are not yet available. FSH data from women(22) indicate that a FSH surge occurs simultaneously with the preovulatory rise of LH. Further, it appears that the concomittant release of both LH and FSH is an essential prerequisite for ovulation. Although FSH levels in women are higher in the follicular phase

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and lower in the luteal phase (possibly due to the amount of gonadal hormones secreted), FSH concentrations remain at a fairly constant baseline level during the rest of the menstrual cycle. While it is somewhat hazardous to interpolate from species to species, it is quite probable that a similar pattern of FSH will be found in the cow, namely a preovulatory surge with relatively steady base levels the rest of the cycle. Prolactin levels in the cow do not appear to follow any discernible pattern.[25]

The essentiality of LH secretion for maintenance of the bovine CL (luteotrophin) as well as stimulation of hormone production (steroidogenesis) during the estrous cycle is still not clear. Donaldson *et al.*[7] demonstrated a luteotrophic effect of LH in the cow by prolonging estrous cycles through the administration of LH. Hendricks *et al.*[19] showed that transecting the hypophyseal stalk early in the cycle did not prevent the development of the CL although steroidogenic function was less than control CL. Short[42] has pointed out that the ability of LH to prolong luteal life span is more pronounced *in vivo* than is stimulation of hormone production. Critical experiments remain to be done in the hypophysectomized, hysterectomized cow.

A major area of advancement in reproductive physiology in the last decade concerns the realization that hormonal substances (releasing factors) produced in the hypothalamus are carried via the hypothalamo-hypophyseal portal system and effect synthesis and release of trophic hormones from the pituitary[18]. Thus the "master gland" concept of the adenohyphysis has been modified to one of subordination to the hypothalamus. Work remains to be done to show the importance of these factors in the cow.

Gonadal Steroids

Progesterone has been determined in the systemic blood of cows during the estrous cycle [39, 44] and has been shown to accurately reflect CL function (see Fig. 2). Corpus luteum activity in cows with 21-day cycles increased rapidly from *Day* 3 (estrus = *Day* 1; ovulation = *Day* 2) until about *Day* 8 or 9 with peak secretory activity attained from *Day* 9 to about *Day* 17[44]. These cows showed a progesterone decrease of more than 50% from the previous day on *Days* 18 (two cows), 19 (one cow) and 21 (two cows). Two other cows with cycles of 22 and 23 days' duration both had a similar decline on *Day* 20. This decrease represents the time of regression of the CL. Thus CL regression in the cow occurs 1-4 days before the onset of the next cycle with luteal activity maintained up to or through *Day* 17 in cows with 21-day cycles. It is to be emphasized that regression of the bovine CL is very precipitous both from a functional and structural view. The decided reduction in the size of the CL that occurs within 24 hours following the initiation of regression should be of aid to practitioners in determining the current status of ovarian activity. It should be possible to pinpoint the time of CL regression through palpation *per rectum* particularly if daily examinations can be made. This could allow a more accurate assessment of the stage of the estrous cycle to be made.

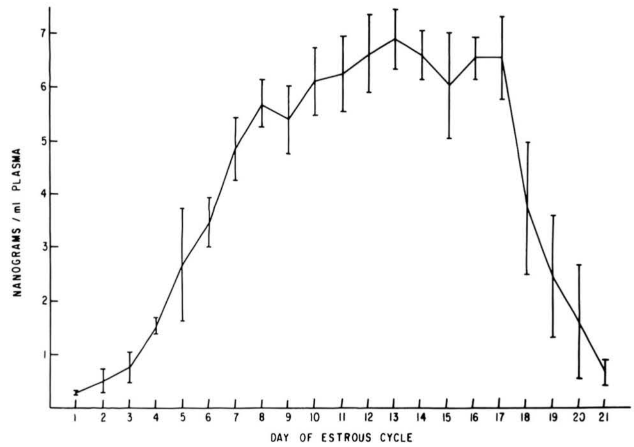

Figure 2. Progesterone concentration in jugular venous plasma from four cows with 21-day estrous cycles (estrus = Day 1). Vertical bars represent the SEM. (Stabenfeldt et al., J. Reprod. Fertil. 19: 433, 1969).

Estrogen changes in the peripheral blood of cows during the estrous cycle have not been determined. Results from other species, however, have recently become available. From human studies utilizing both blood and urine [4] there appears to be a surge of estradiol-17_β that coincides with or just precedes the LH surge. Also, studies in anestrous ewes have shown that intravenous injection of as little as 0.003 mg of estradiol-17_β can elicit a surge of LH which is similar to that observed during estrus of the cyclic ewe[17, 32]. It thus appears that a surge of estrogen presumably of follicular origin initiates the LH release which leads to ovulation. While this may be the situation in the cow, it still remains to be demonstrated.

Anestrus has been a common cause of reproductive loss in cattle. The capability of estrogen to initiate follicle activity has been doubted, although Gibbons and Kiesel[13] have reported ovulation on the induced heat with normal conception at this time. Estrogen administration has been commonly used to induce behavioral estrus. Recent work[5] has emphasized the small amount of estrogen needed to induce behavioral estrus (in this instance in spayed heifers); 0.121 mg estradiol benzoate was effective in producing estrus. In addition, this dosage did not induce an estrogen refractory state. Animals given 10 mg of estradiol benzoate on similar schedules became refractory to the more physiological amounts of estrogen (400 μg) which followed. The modification of this estrogen refractory state by progesterone was suggested as being due to a conditioning of neural centers by progesterone. The practical point to be gained is that the doses of estrogen that are often used by practitioners are pharmacological in amount and can cause long-lasting changes in steroid sensitivity of the brain with possible deleterious effects on reproductive function (gonadotrophin synthesis and/or release). Veterinary practitioners should reconsider the amount of estrogen traditionally administered to cattle for modification of reproductive function.

Hewetson[20] has recently reported that two doses of progesterone (40 mg) administered 48 hours apart resulted in estrus manifestation in 80% of the animals within 3½ days of the last injection; fertility was normal. The mechanism of action is not known but it may be that a temporary suppression of gonadotrophin release (by progesterone) is followed later by a rebound release which results in follicular growth and ovulation.

Luteal and Follicular Cysts

The contribution of luteal cysts to reduced fertility in the cow has been of interest to many veterinarians. The occurrence of luteal cysts is quite common. In one study in Australia, 14% of 168 CL examined had cavities 8 mm or larger while 34% of 119 CL examined in New York had similar cavities.[8] The conclusion of this study was that the majority of these cysts were not pathological. Unless the luteal cyst is thin-walled, most CL with central cavities appear to produce quantities of progesterone that are compatible with normal reproductive function.

The occurrence of follicular cysts continues to be a problem, especially in dairy cattle. The variety of clinical syndromes of cows with cystic ovaries ranging from nymphomania to anestrus suggests the possibility of multiple causes. One hypothesis, namely a malfunction of the adrenal cortex with excess production of estrogens and androgens is supported by the assumption of male characteristics by some females and also by a significant increase in urinary 17-ketosteroids[11,35]. Cupps *et al.*[6] have supported this idea through the observation of adrenal hyperplasia in some cows with follicular cysts. If the adrenal cortex produces abnormal end products such as estrogen and androgens, feedback inhibition of ACTH secretion does not occur. Continued ACTH release could effect further release of estrogens and androgens from the adrenal cortex[46]. This, in turn, could lead to suppression of gonadotrophin secretion, particularly LH. It should be remembered that biosynthetic pathways in endocrine tissues are similar with progesterone being a common point of divergence. Besides converting progesterone to corticoids, the adrenal cortex has the capacity to change progesterone into an androgen, androstenedione, which can be converted to testosterone. Androstenedione can also serve as a precursor for estrogen synthesis. A modification of enzyme systems in the adrenal cortex could lead to the formation of abnormal end products, namely, androgens and estrogens.

Another hypothesis involves hypofunction of the hypothalamo-pituitary system with insufficient release of gonadotrophins to cause ovulation. The insufficiency probably involves both LH and FSH. The reason for nymphomania in these animals is not apparent as reduced estrogen levels have been observed in cystic follicular fluid[41]. It may be, however, that steroid concentration in the follicle may not give an accurate insight into the levels of estrogens circulating in the systemic blood. It should be recognized that many disturbances in gonadotropin secretion are often transitory as witnessed by the fairly high spontaneous recovery rate of affected animals. Lactational stress, an important cause of cystic follicles, is a good example. Finally, it should be pointed out that cows that have normal estrous cycles (and fertility) should not be considered cystic even if they have large follicles.

The treatment of choice remains gonadotrophic hormones, particularly those high in LH activity. It recently has been reported that the simultaneous use (intravenous) of chorionic gonadotropin (3000 I.U.) and 125 mg progesterone is effective in treating follicular cysts.[43] The abrupt cessation of nymphomania observed may have been related to the use of progesterone.

Johnson and Ulberg[23] have shown that daily administration of either 50 or 100 mg of progesterone for 14 days is effective in treating follicular cysts. Approximately 50% of the treated animals conceived at the first post-treatment estrus, whereas only 13% of the control animals conceived. The mode of action appears to be a blockage of LH release by progesterone with increased storage of

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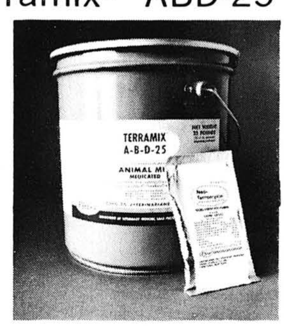

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LH occurring during the treatment. The termination of progesterone treatment allows a release of stored LH which is sufficient to cause ovulation. It may be possible to do this with shorter treatment schedules of progesterone.

The inheritability of the condition is well established. Also there is a considerable tendency for cows, even though successfully treated, to have a reoccurrence of follicular cysts. This is to suggest that practitioners need to play a more active role in modifying this condition through the elimination of these cows and not necessarily through treatment.

Utero-ovarian Relationships

Wiltbank and Casida[48] demonstrated in 1956 the importance of the presence of the bovine uterus for CL regression in the nonpregnant cow. They found prolongation of CL function occurred following complete hysterectomy.

Ginther[15] has summarized the data concerning the utero-ovarian relationships in the cow. The concept has been developed that a luteolytic substance (lyteolysis) elaborated and released by the uterus, is responsible for initiating CL regression. While the surgical evidence strongly supports this view, it must be admitted that a uterine luteolysin has not been isolated as yet. In addition, the route by which the luteolysin is transported to the ovary is not known. The most obvious route, utero-ovarian venous-arterial anastomoses, have not been found in any species[31]. The oviduct in the sheep [34] does not seem to be involved, nor is diffusion through the broad ligament[15]. The possibility of lymphatics serving as the mode of transport has not been sufficiently investigated.

Nalbandov and Cook,[36] in a rebuttal of the luteolysin concept, have pointed out that there is still no definitive evidence to support the existence of a luteolysin and that the current concept of a luteolysin is based on indirect evidence through surgical means. Recently Keyes and Nalbandov[26] have shown that normal rabbit CL in the absence of follicles (destroyed by X irradiation) cannot synthesize and release progesterone. If 2-4 μg of estradiol are given daily, the CL are maintained and produce normal amounts of progesterone. Thus we can add ovarian factors to those of pituitary and uterine origin in considering control of CL. It should be pointed out that the role of ovarian estrogens on CL maintenance in the cow is uncertain. It has been shown that pharmacological doses can cause regression. The role of physiological amounts need elucidation.

The clinical aspects of uterine influence on ovarian activity in the cow have been reviewed by Ginther[16]. Several clinical situations exist that emphasize this relationship. Cattle with uterus unicornis (one horn, both ovaries present) have been known to cycle normally if ovulation occurs in the ovary adjacent to the remaining horn; ovulation in the ovary contralateral to the intact horn can result in prolonged CL life with loss of cyclic ovarian activity (see Fig. 3).

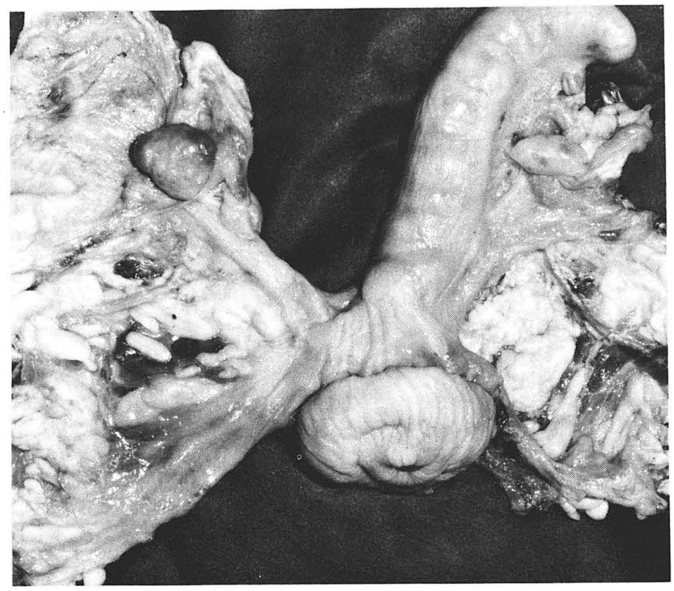

Figure 3. Reproductive tract from a unilaterally hysterectomized heifer. Estrous cycle length is greatly prolonged when the retained horn and the ovary containing the corpus luteum are on opposite sides, but not when the retained horn and the corpus luteum are on the same side. (Ginther, J.A.V.M.A. 153: 1656, 1968).

Pyometra in the cow is often associated with persistence of the CL. The self-perpetuating nature of this condition evolves from the fact that progesterone favors the development of uterine infection while destruction of the uterine endometrium (suspected source of luteolysin) favors retention of the CL. Likewise, the persistence of CL in the presence of macerated or mummified fetuses may be due to the fetal influence on the uterine endometrium through suppression of the luteolytic factor. While the association of mucometra or hydrometra (excess uterine fluid) with CL retention has not been studied, retention of CL may occur. The use of estrogens in these conditions is indicated both from the view of evacuating the uterus, as well as causing regression of the CL.[3,24]

Shortening of CL life has been shown to occur in cases of endometritis. The accidental introduction of foreign material at the time of insemination could initiate an earlier than normal release of the luteolytic substance. Also, intrauterine infusion from days 2 to 6 can shorten the cycle. While medication on the day of estrus or 1 day later is less likely to affect CL function, the possibility of causing premature regression of the CL by uterine infusion needs to be considered. This is particularly so if insemination is being carried out during the treatment cycle.

Maintenance of Pregnancy and Parturition

Analysis of progesterone in the peripheral blood of cows during pregnancy has recently added to our knowledge of bovine gestation. Progesterone levels are similar in nonpregnant and pregnant cows for the first 17 days of pregnancy. At this time progesterone concentration declines precipitously in nonpregnant cows as mentioned previously. While progesterone levels are maintained in the pregnant cow, some decline occurs by *Day* 30 to 40. These levels are maintained until about *Day* 200. Beginning at *Day* 200 a progressive increase in progesterone was noted with maximal levels achieved by *Day* 250[45] (see Fig. 4). It has been shown that ovariectomy before *Day* 200 in the

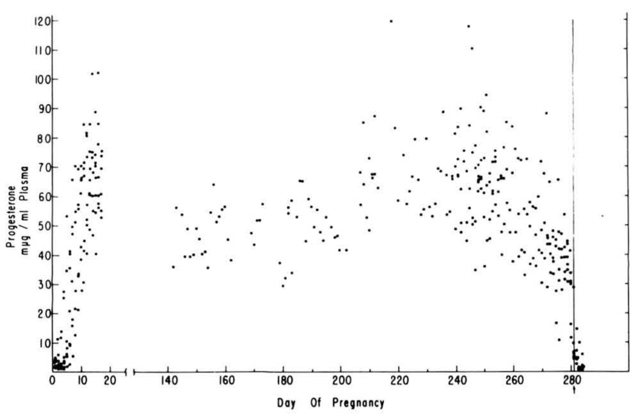

Figure 4. Peripheral plasma progesterone levels in cyclic Holstein-Friesian cows (Days 1-21) and pregnant Hereford cows (Day 140 through parturition). (Stabenfeldt et al., Am. J. Physiol. 218: 571, 1970).

cow almost invariably results in abortion within a few days.[9] Cows ovariectomized after *Day* 200 were able to maintain pregnancy for as long as 50 days post surgery. Stabenfeldt *et al.*[45] suggested the possibility that an extraovarian source (placenta) makes a significant progesterone contribution after *Day* 200 and thus enables the pregnancy to be maintained in ovariectomized cows to within 2-3 weeks of the normal time of labor. Many of the calves born to ovariectomized cows, however, have been weak and have died after delivery.[9] These data as well as data from corpus luteum-ablated pregnant cows (unpublished observations) clearly indicate that the cow, in most instances, is not able to complete a normal gestation period if the ovaries or CL are removed prior to about *Day* 270. The cow thus should be considered a mammal requiring the continuous support of the CL during gestation.

Progesterone levels decline from 7-8 ng/ml plasma at about *Day* 250 to about 4 ng/ml at *Day* 270. This level is maintained until about 24 hours *before* parturition at which time an abrupt drop to less than 1 ng/ml occurrs (see Fig. 5). Thus pro-

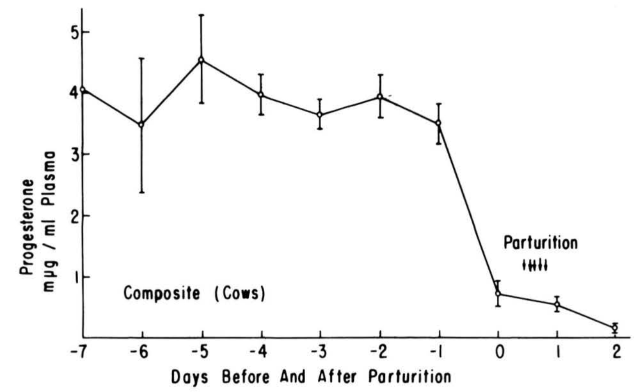

Figure 5. Peripheral plasma progesterone levels in Hereford cows (composite of five cows) during the immediate prepartum period. Vertical bars represent standard error of mean. (Stabenfeldt et al., Am. J. Physiol. 218: 571, 1970).

gesterone withdrawal is an integral part of parturition in the cow. Holm and Galligan[21] found estradiol and estrone were elevated during the last month of pregnancy of both normal cows and cows destined to have a prolonged pregnancy. In addition, cows with genetically-conditioned prolonged gestation did not show a decline in progesterone at the end of the normal term period. Thus a rise in estrogens may be important in the initiation of labor only in the presence of declining progesterone concentrations.

Recent work has been reported on experimental infection with *Vibrio fetus* in pregnant cows (*in utero*)[37]. These studies indicated that fetuses were very susceptible to the agent during the middle third of gestation and died within a few days of inoculation. Regression of the CL occurred shortly after death of the fetus with several days passing before expulsion of the fetus was accomplished. Fetuses inoculated during the third trimester were more resistant. Most survived for a longer period of time with many calves being alive at birth. The interesting point is that progesterone levels in these late aborting cows were very similar to those reported for normal cows at parturition.

The elective induction of parturition has been effected by the use of dexamethasone; 19/22 cows calved 22-56 hours after the administration of a single intramuscular dose of dexamethasone (20 mg)[1]. Adams[1] has pointed out some of the medical reasons for elective induction of labor, namely, toxemia of pregnancy, hydrops allantois or amnii, renal disease, fractures and cardiovascular disease. **Obviously, the use of desamethasone during the latter part of gestation for anti-inflammatory or metabolic reasons should be viewed with caution.**

Postpartum Activity

The importance of a relatively short and uniform interval between parturition and subsequent conception for economic productivity in cattle is well recognized. The postpartum period has been given increased attention by investigators the past several years.

Animals with cotyledonary placentas, such as the cow, obviously experience extensive regression and regeneration of uterine tissues in the early *post partum* period. Sloughing of the caruncles is usually complete by day 12 or 13 *post partum* with epithelial regeneration complete by day 30 (14, 47). Uterine involution has not been affected by the nursing of calves.[38, 47] Likewise, neither ovariectomy nor estradiol-17$_\beta$ (physiological amounts) significantly influenced involution, although the daily administration of 30 mg of progesterone did increase the time required for involution[29].

The local influence of the previously gravid uterine horn on the adjacent ovary is striking. In one study over 90% of the ovulations occurring before day 15 *post partum* were in the opposite ovary[30]. A significant influence was noted up to day 30. The frequency of ovulation in the ovary adjacent to the previously gravid horn increased as the diameter of the uterine horn decreased. No effect of the previously gravid horn was found after a diameter of 60 mm was attained. Foote and Peterson[10] have reported data that suggest conception rates were higher in cows where ovulation occurred in the ovary opposite the previously gravid horn and in whom uterine involution was not complete.

The first ovulation in dairy cows occurs at approximately 15 days *post partum.*[30, 33] A high incidence of silent estrus ranging from 77% to 86% has been reported. The duration of the estrous cycle following the initial ovulation averaged 15-16 days which is significantly different ($P < .01$) from the 21-22 day interval between the second and third ovulations. Thus the CL formed at the first ovulation appeared to have a relatively short lifespan. Also, a high incidence of cystic follicles were found associated with the first two ovulations.[30] Follicular cysts observed during the time of reestablishment of normal uterine and ovarian function following parturition may resolve themselves and not need treatment.

While suckling of calves by beef cows does not affect uterine involution, it does significantly increase the interval from parturition to first estrus and/or ovulation. Methods of initiating *post partum* ovarian activity in the beef cow need more work.

Estrous Synchronization

The efficacy of chemical synchronization of bovine estrous cycles is well established. In spite of our ability to control ovarian activity, a major problem remains to be solved, namely, depressed fertility at the first post-treatment estrus.

A prerequisite of successful estrous synchronization of cattle is normal estrous cycles. Many breeding programs include heifers at 14 months of age. In order that puberty be attained at this age, proper nutrition is essential, especially during the two-month period immediately prior to the breeding season.[2] This same critical time period exists for preparing cows in a nutritional sense, namely, parturition plus 60 days.

Administration of oral progestins have effectively suppressed estrus in cows. The usual procedure is for the progestin to be administered in the feed for 18 days with estrus occurring a few days after removal of the drug. It has been reported that cows treated with an oral progestin developed abnormally large follicles in the absence of active CL.[50] This situation probably exists regardless of the progestin used. These results suggest that LH secretion is more sensitive to chemical control (no ovulation) as compared to FSH secretion (continued follicle growth). This effect was not seen in cows that had active CL at the onset of treatment. Also there are data to suggest animals put on progestins early to mid-cycle are more fertile at the first post-treatment estrus than cows placed on treatment the last third of the cycle. It may be that the more mature the primary follicle is when treatment is begun (*Day* 16-21 of the cycle) the greater the possibility of reduction of the fertilizing potential of the ovum at the time of subsequent ovulation.

The use of estradiol-17$_\beta$ to cause early regression of the CL has proven successful in estrous synchronization.[49] Cows were injected with estradiol valerate (5 mg) on the second day of a nine-day progestin feeding schedule. This regimen had no adverse effect on fertilization rate, ova transport, duration of estrus, or time from beginning of estrus to ovulation; 76% of the animals were in estrus within 48 hours of drug removal. This treatment allows all cows to have similar ovarian activity (CL regressed and some follicle development) at the end of the treatment schedule.

An 80% conception rate has been reported in one small study in which all cows were inseminated on the third and fourth day following drug removal.[27] In this instance the cows began coming into heat on the third day.

While additional data is needed, there is evidence to support the use of an estrogen on day two of a nine-day progestin schedule plus insemination of cows (twice at 24-hour intervals) at a fixed time following drug removal (3-4 days). In addition to this schedule, the importance of proper nutrition immediately before and during the time of estrous synchronization cannot be overemphasized for maximal success in a controlled breeding situation.

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