

THE OCCURRENCE OF SHORT ESTROUS CYCLES AFTER PROSTAGLANDIN
INDUCED ABORTION AT VARIOUS STAGES OF GESTATION

by

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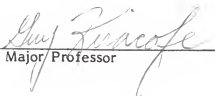

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LITERATURE REVIEW

Chapter I: Induced Abortion and Associated Physiological

Changes in Cattle

Unwanted pregnancies occur in all domestic species and are an economic as well as a physiological problem. According to a report by Schultz and Copeland (1981), many heifers are pregnant when entering feedlots. Economic loss to the feedlot operator results from lower carcass grade and a reduced price paid for heifers in late pregnancy when they are sold for slaughter. Furthermore, heifers which calve in the feedlot present a serious problem for the feedlot manager. Due to the fattened condition and suboptimal sanitary environment, there is a high incidence of dystocia and post-parturient acute metritis. There are high death losses in those cases, and heifers that do live result in economic losses for the feedlot operator.

Although unwanted pregnancies occur in many circumstances, the feedlot heifer comprises the majority of unwanted pregnancies. Abortion is a desired solution when heifers conceive too young for normal pregnancy and parturition (Schultz and Copeland, 1981), when cows purchased for training artificial insemination technicians are found pregnant (Sloan, 1977), when conception occurs to undesired sires, and when fetuses are known to contain defects.

Various methods of induced abortion have been investigated. These can be divided into two main categories. One category is the manual abortions which includes rupture of fetal or embryonic membranes per cervix, rupture of membranes per rectum, crushing or decapitating the fetus, corpus luteum

(CL) expulsion, and ovariectomy. Prostaglandin $F_{2\alpha}$ (PGF) and its analogues, estradiol-17 β and its analogues, dexamethasone and related corticoids, or any combination of these hormones are able to induce abortion at specific stages of gestation. The method chosen should be based on stage of gestation, cost, use of the animal after treatment, and a thorough knowledge of the available techniques.

Manual Abortion

The mechanism of fetal attachment in the bovine is a slow process (Chang, 1952). The faint disc-shaped cotyledon appears on the chorion where it attaches to the caruncles at about 40 d of pregnancy (Lindell, et al., 1981). Kingman (1951) stated that the chorion is self-supporting up to about 70 d, and thus, the physical connection up to this stage is a fragile one. Rupture of the fetal membranes per cervix or rectum serves to destroy the delicate physical connection between the chorion and caruncles of the endometrium. Absence of this bond induces abortion and expulsion of the uterine contents.

Maintenance of pregnancy in the bovine is known to be dependent on luteal progesterone until an ill-defined stage of gestation between 150 and 200 d (McDonald et al., 1953; Estergreen et al., 1967). Thus, removal of this ovarian progesterone source through CL enucleation or ovariectomy, would induce abortions in cattle less than 150 d pregnant.

Rupture of fetal membranes per cervix. This technique requires passage of a uterine catheter through the cervix and into the gravid uterine horn, at which point the fetal membranes are ruptured. This method was not

effective in dairy cattle pregnant an average of 85 d unless applied twice (Dawson, 1974). When abortion was induced, the interval from treatment to abortion ranged from 6 to 42 d, and the interval from treatment to first estrus ranged from 10 to 44 d. Severe endometritis occurred in all cases when abortion did result. This technique is not highly successful and many complications may develop.

Rupture of fetal membranes per rectum. Inducing rupture of the fetal membranes requires massaging the pregnant uterine horn along most of its length in such a way as to elicit "membrane slip". If the fetus is recognized, moderate pressure may be applied directly to it to crush or decapitate it (Dawson, 1974; Parmigiani et al., 1978). Rowson and Dott (1963) demonstrated that it was easy to rupture the fetal heart at 36 d of gestation if palpating for confirmation of pregnancy. Membranes rupture much easier when this technique is utilized to abort pregnancies less than 70 d (Ball and Carroll, 1963; Parmigiani et al., 1978). In addition, the conceptus is more difficult to palpate in heifers than in cows because the uteri of heifers are more turgid and their rectum is tighter and less flexible (Horstman et al., 1982). When just the membranes are ruptured in pregnancies less than 70 d, effectiveness has ranged between 33 and 100% (Ball and Carroll, 1963; Parmigiani et al., 1978; Horstman et al., 1982). If ruptured membranes are used together with crushing the fetus when gestation ranges from 35 to 66 d, success rate is comparable to or higher than rupturing the membranes only. Interval to abortion ranged from 17 to 26.5 d after treatment, and interval to estrus ranged from 27 to 38 d after treatment (Dawson, 1974; Parmigiani et al., 1978) when this technique was

used. In pregnancies 66 to 120 d, effectiveness was 100% if the fetus was decapitated at the time of membrane rupture. Days to abortion after treatment averaged 21.5, and d to estrus averaged 32 (Parmigiani et al., 1978). Dawson (1974) reported the occurrence of endometritis and the remains of a conceptus 21 d after treatment. Conception did result in four of four cows on days 6, 9, 40, and 120 after abortion. Three of the four pregnancies were in the uterine horn in which the previously aborted conceptus had been. Parmigiani et al. (1978) reported that the first estrous cycles after abortion were of normal duration in 80% of the animals treated. Thirteen percent had long cycles (>23 d), and seven percent had short cycles (<12 d).

Rupture of the fetal membranes per rectum and crushing or decapitation of the fetus appears to be an effective method of interruption of early gestation, but is highly dependent on the expertise of the palpator. It is inexpensive, and subsequent reproductive performance of beef cattle appears to be satisfactory.

Corpus luteum expulsion. The corpus luteum (CL) is the main source of progesterone during early pregnancy in the cow, although the placenta and the adrenal gland have also been shown to produce progesterone later in gestation (Balfour et al., 1957; Melampy et al., 1959). The use of CL expulsion to induce abortion was recommended over a half a century ago by Hess (1920) and Schmaltz (1921). Evidence indicates that the risk of bleeding after expulsion is much greater when a cow is pregnant than when she is open (Tanabe, 1970). Dawson (1974) found CL expulsion to be only 50% effective in females pregnant an average of 70 d. The CL could not be

expressed from 30% of the females, not cleanly expressed in 10%, and caused fatal haemorrhage in the remaining 10%. The average number of d to abortion or resorption was 6.17, and the average number of d to estrus after treatment was 11.

Corpus luteum expulsion has not been investigated in cows pregnant greater than 150 d. The CL is generally thought to maintain pregnancy until about 200 d (McDonald et al., 1953) through its synthesis and secretion of progesterone. The stage of gestation at which ovariectomy will result in abortion corresponds with the period in which PGF is a reliable abortifacient. Ovariectomy and CL expulsion have, as their end result, removal of the luteal progesterone source. Thus CL expulsion should also be effective in inducing abortion during the period in which prostaglandin is a reliable abortifacient. The stage between 150 and 200 d may be a transitional period from a time of primarily ovarian progesterone production to a time when the placenta and adrenal gland produce sufficient progesterone to maintain pregnancy in the absence of the CL (Johnson et al., 1981). As pregnancy may be maintained in the absence of ovarian progesterone after 200 d of gestation (Estergreen et al., 1967), it may be presumed that extraovarian progesterone production is adequate to maintain pregnancy at this time. Therefore, it is doubtful that CL enucleation at 200 d of gestation or later would result in abortion.

The results of the limited trials using CL expulsion as an abortifacient indicate that this method is not satisfactory for routine use, since many deleterious effects can result.

Ovariectomy. Ovariectomy was originally performed to eliminate estrous cycles and thus pregnancy in heifers; however, it is practiced on a limited basis due to the decreased rate of gain and feed efficiency of ovariectomized heifers (Horstman et al., 1982). Ovariectomy will remove a source of progesterone that is necessary for pregnancy maintenance up to 150 to 200 d (McDonald et al., 1953). Therefore, ovariectomy may interrupt an established pregnancy. Horstman and co-workers (1982), using ovariectomy, induced abortion in two of four pregnant heifers estimated to be 150 d pregnant or less. If pregnancy is maintained without the CL of pregnancy, the gestation period may be shortened, and calving difficulties and postpartum metritis secondary to retained fetal membranes may result (Estergreen et al., 1967). The two heifers which didn't abort delivered live calves 113 and 123 d after ovariectomy.

Although ovariectomy has not been effective in inducing abortion after 200 d of gestation, if ovariectomy is combined with dexamethasone or dexamethasone and prostaglandin, abortion is induced in nearly all cows. Females pregnant an average of 210 d aborted 2.8 to 7.2 d after ovariectomy plus dexamethsone or plus a dexamethasone/cloprostenol combination (Johnson et al., 1981). In those advanced stages of pregnancy the placenta and adrenal gland appear to produce sufficient progesterone to maintain pregnancy in the absence of the CL. Ovariectomy eliminates luteal progesterone, and dexamethasone may reduce adrenal progesterone through a negative feedback mechanism on the hypothalamus-anterior pituitary-adrenal axis, or it may have a direct effect on the placenta causing a reduction in placental progesterone. Ovariectomy and

dexamethasone together may constitute a reliable method to terminate pregnancies between 150 and 255 d of gestation.

Prostaglandin-induced Abortion

Prostaglandin $F_2\alpha$ (PGF) and its analogues are capable of inducing abortion in several species including human (Engel et al., 1973), rat (Fuchs and Mok, 1973), hamster (Giannia et al., 1973), goat (Bosu et al., 1979), mare (Douglas et al., 1974), pig (Podany et al., 1982), and cow (Lauderdale, 1972; Lamond et al., 1973; Brand et al., 1975). The maintenance of pregnancy in the cow is dependent on the presence of a functional CL until an ill-defined stage of pregnancy between 150 and 200 d (McDonald et al., 1953; Estergreen et al., 1967). Thus, an effective luteolytic agent will induce abortion up to 150 d of pregnancy by causing regression of the CL. The luteolytic nature of prostaglandins induces abortion in cattle during those periods when the pregnancy is dependent on progesterone synthesized by the CL (Schultz and Copeland, 1981).

Efficacy of PGF and its Analogues in Inducing Abortion at Various Stages of Gestation. Prostaglandins have been studied extensively for use as abortifacients during both early and later stages of pregnancy. Lauderdale (1972) reported successful induction of abortion in cattle between 40 and 120 d of gestation using PGF. Brand et al., (1975) induced abortion in 10 of 10 heifers pregnant 60 to 150 d using 25 and 12.5 mg on two consecutive days. Refsal and Sequin (1981) found single intra-muscular injections of 20 or 40 mg PGF to be 100% effective in inducing abortion in heifers 40 to 90 d pregnant. Sloan (1977) injected PGF intrauterine and induced abortion in 66% of cows during their second and third trimesters. Beyond 150 d of

pregnancy, abortion rates become inconsistent, but are generally poor until near term (McAllister and Lauderdale, 1979). Dinoprost tromethane, or PGF in salt form, was reported to be 100% effective in inducing abortion in pregnancies 45 to 120 d in gestation (Horstman et al., 1982).

Cloprostenol is a potent synthetic analogue of PGF. Day (1977) induced abortion in 89.5% pregnancies, and Copeland et al. (1978) reported terminating 97.6% pregnancies treated before 150 d of gestation with single doses of 500 µg cloprostenol. Ingrahm et al. (1978) and Lindell et al. (1981) treated pregnancies ranging from 39 to 146 d of gestation with 500 µg cloprostenol. Effectiveness ranged between 83 and 100%. In dose titration studies, Youngquist et al. (1977) demonstrated 250 and 500 µg cloprostenol was effective in aborting high percentages of heifers 120 d pregnant or less. If gestation length was greater than 120 d, the efficacy of 250 µg decreased, but 500 µg was still highly effective. Copeland and co-workers (1978) reported that doses less than 250 µg were not adequate to cause abortion regardless of day of pregnancy. When heifers were less than 100 d pregnant 250, 375, and 500 µg were highly effective. Between 100 and 150 d of gestation, 250 µg was less effective. Both 375 and 500 µg were able to induce abortion in pregnancies 100 to 150 d of gestation.

Prostaglandins have been shown to be reliable abortifacients when administered in the first 150 d of pregnancy (Lauderdale, 1972; Copeland et al., 1978). Their efficacy as abortifacients was decreased between 150 and 240 d of gestation (Day, 1977). To increase the efficacy from 150 to 255 d of gestation, the prostaglandins may be combined with dexamethasone. Fetal adrenal corticosteroid has been shown to initiate parturition (Liggins, 1973),

and thus, the reason for administration of dexamethasone. Using a cloprostenol/dexamethasone combination, Johnson et al. (1981) and Murray et al. (1981) induced abortion in three of four cows and eight of eight heifers pregnant more than 200 d, respectively. In a high percentage of those animals either dystocia, retained placenta, or metritis occurred.

Fetal Expulsion, and Uterine, Ovarian and Mammary Changes after PGF-induced Abortions. According to Day (1977), many abortions go unnoticed despite careful observation. Fetuses less than 60 d gestation were sometimes observed to be expelled during calm walking or eating, with the animal appearing to be unaware of the event. A large percentage of the fetuses greater than 2 mo of gestation were found where an animal had been lying. If fetuses were over 6 mo old, heifers sometimes went into labor to expel them.

In heifers aborted with PGF, the average time of fetal expulsion was 86.4 h after injection, with a range from 48 to 168 h (Lauderdale, 1972; Brand et al., 1975; Refsal and Sequin, 1981). The average interval from injection to expulsion in heifers aborted with cloprostenol has varied between studies. Barth et al., (1981) reported the average time of expulsions to be 124.8 h, while Youngquist et al., (1977) reports a time of 84 h. Day (1977) and Copeland et al. (1978) both reported that 98% of the fetuses are expelled by 144 h after injection. Ingrahm et al. (1978) and Lindell et al. (1981) demonstrated interval to expulsion varies with length of gestation. Heifers 39 to 71 d pregnant expel fetuses by 61.6 h (Lindell et al., 1981), 75 to 105 d, by 96 h (Ingrahm et al., 1978), and 102 to 146 d, by 82 h (Ingrahm et al., 1978; Lindell et al., 1981).

Brand et al. (1975) and Day (1977) reported that by 24 to 48 h after injection the uterus became tense, with thicker walls, and palpation per rectum provoked a further response. The tension often became too great to allow accurate palpation of the contents. Turgidity remained for 36 to 48 h, and changed the shape of the uterus, which became higher and rounder. By day five, if abortion was inevitable, the uterus became doughy, lifeless, and "heavy". Copeland et al. (1978) noted uteri were involuted by day 21, or by day 50 after injection as described by Barth et al. (1981).

Within 48 h of treatment the CL of pregnancy diminished in size to 12 to 14 mm in diameter (Lauderdale, 1972; Brand et al., 1975; Day, 1977). Regardless of day of gestation at treatment or side of CL of pregnancy, follicles were palpable by 1 to 3 d after injection on both ovaries (Day, 1977; Lindell et al., 1981). There did not appear to be any pattern of follicular development in relation to the CL of pregnancy. Day (1977) noted 63% of the CL of pregnancy were on the right ovary and 37% on the left ovary. Two days after injection of cloprostenol, ovaries were palpated again. Follicles were noted on 53% of the left ovaries and 47% of the right ovaries. In this study, it was not determined if heifers tended to ovulate on the same or opposite ovary as the CL of pregnancy. Forty-nine percent of those heifers were palpated a third time. Eighty-eight percent of the follicles had ruptured. New corpora lutea were present by day four or five at the same site of the previous follicle. Those reached maximum size by day eight after injection. In females that did not abort, the CL decreased to approximately one third of its original size, and then remained at that size. It was not determined if that CL had any physiological function.

Follicles did develop, followed by ovulation and luteinization in non-aborting females (Day, 1977). Very limited data are available on the fate of the CL of pregnancy in treated heifers which fail to abort.

Udders and teats became enlarged and an almost clear watery liquid was present in heifers aborted at 150 d or more of gestation (Day, 1977). Such development was not observed in cows. Copeland et al. (1978) detected udder development using palpation. Of 164 heifers treated, 15 exhibited some signs of mammary gland development by day nine after injection, and 32 exhibited development by day 21 after injection.

Progesterone and PGFM Profiles after PGF-induced Abortion. Serum progesterone levels in cows and heifers varied markedly between and within animals from day to day (Day, 1977). Average serum progesterone concentrations at time of treatment ranged from 3 to 40 ng/ml, with the levels most often detected being in the 6 to 10 ng/ml range (Brand et al, 1975; Day, 1977; Ingrahm et al., 1978; Lindell et al., 1981; Refsal and Sequin, 1981). Concentrations in heifers aborted after use of a prostaglandin indicated that luteal activity was virtually eliminated by 48 h after treatment. Progesterone concentrations remained low at least until day 10 after treatment. Refsal and Sequin (1981) detected concentrations greater than 1 ng/ml by day 13 after treatment suggesting the development of a new CL (table 1). Heifers which did not abort after injection of a prostaglandin exhibited a decline in serum progesterone levels 24 h after treatment. Decreased levels were maintained for several days followed by a slow increase.

TABLE 1. SERUM PROGESTERONE CONCENTRATIONS (NG/ML) AFTER PROSTAGLANDIN INDUCED ABORTIONS

Reference	Response	Hours after injection											
		0	24	48	72	96	120	144	168	192	216	240	312
Brand et al., 1975	Aborted	6-10			<1.0								
Day, 1977	Aborted	3.15	.81	.35	.46	.29	.43	.27	.24	.79	.63	.36	
Ingrahm et al., 1978	Aborted	6-12		<1.0									
Lindell et al., 1981	Aborted	6-40		1.0									
Refsal & Sequin, 1981	Aborted	3.0			0.3				0.4				1.2
Day, 1977	Not Aborted	2.82	1.75	0.98	1.58	1.13	1.7	0.49	1.24	3.1	.69		
Refsal & Sequin, 1981	Not Aborted	3.5			2.2				3.2				

The pattern of release of 15-keto-13,14-dihydro-PGF₂α (PGFM) has not been well documented. Lindell et al. (1981) noted that animals pregnant less than 80 d released short-lived peaks of PGFM following injection of cloprostenol. These elevated levels returned to pre-treatment levels at the time of expulsion of the fetus. Similar patterns were seen in animals pregnant for more than 100 d at the time of treatment. However, these animals released massive amounts of PGFM at abortion and for 2 to 5 d afterwards. In animals pregnant for 267 d, Henricks et al. (1977) observed PGFM peaking 1 h after injection and reached basal levels within 4 h. The abortifacient used by Henricks and co-workers was PGF. Thus, the change in serum PGFM may have been an artifact of the injection.

Estrual Cyclicity, Ovulation, and Fertility after PGF-induced Abortion.

Females do exhibit standing estrus after prostaglandin induced abortion. Estrus behavior persisted for as long as 36 h, but was generally 6 to 8 h in duration. Typical thrusting pelvic movements were made before and during the mounting. In the absence of a bull, the estrus animal preferred to mount rather than be mounted (Day, 1977).

Intervals from injection to estrus have ranged from 34 h (Brand et al., 1975; Day, 1977) to 36 d (Lindell et al., 1981). There is some controversy as to the percentage of aborted heifers exhibiting estral behavior and the interval to estrus as related to length of gestation at abortion. Day (1977) observed 75% of heifers aborted between 32 and 250 d of gestation in standing estrus, and Brand et al. (1975) observed 70% of heifers aborted between 60 and 150 d of pregnancy in estrus. Ingrahm et al. (1978) detected 50% and 16.6% of heifers in estrus when aborted between 75 to 105 and 105

to 135 d, respectively, while 100% of the heifers aborted between 39 and 146 d of gestation were detected in estrus by Lindell et al. (1981) and Refsal and Sequin (1981).

When interval to estrus is determined in relation to day of gestation at treatment, there appears to be some variation. Lindell et al. (1981) observed 100% of heifers aborted between 39 and 71 d in estrus 72 h after injection, while heifers aborted between 102 and 146 d were not detected in estrus until 14, 18, 24, 24, 29, and 36 d after injection. Ingrahm et al. (1978) observed heifers in standing estrus by 96 h if aborted at 75 to 105 d of gestation, and by 81 h if aborted at 105 to 135 d of gestation. The hours of peak estrual activity without regard to gestation length at abortion range from 50 to 70 h after injection (Brand et al., 1975; Day, 1977; Refsal and Sequin, 1981).

Subsequent cyclicity and fertility has been sketchily followed in some trials. When allowed to cycle through two estrous periods before breeding, cattle aborted between 32 and 250 d of gestation maintained conception rates equal to controls (Day, 1977). Ingrahm et al. (1978) demonstrated the first estrous cycles after abortion were less than 16 d in length in 50% and 66% of heifers aborted at 3.2 or 4.2 mo, respectively. In addition, 50% of those exhibiting an initial short cycle, exhibited a second cycle that was also short (Ingrahm et al., 1978). Heifers aborted between 39 and 71 d of pregnancy were able to conceive, had cycles of normal length, or had short cycles immediately after abortion. When aborted later in gestation (102-146 d), estrus wasn't detected until 24 d after treatment. Two of six heifers aborted later in pregnancy exhibited a short luteal phase prior to the first

observed estrus after abortion. Both heifers then exhibited estrous cycles less than 12 d in length. One of those had a second short estrous cycle. One of six heifers had a cycle of normal length. Cycles were not characterized in the other three heifers (Lindell et al., 1981).

Prostaglandins can induce abortions 80 to 100% of the time in cattle up to 150 d of gestation. However, beyond 150 d, combining dexamethasone with prostaglandin is necessary to increase efficacy to that level.

Estrogen-induced Abortion

Abortion due to estrogen injections results from CL regression. However, the primary luteolytic action of estrogen appears to be indirect, and operates by causing the release of PGF by the uterus (Keyes et al., 1983).

Efficacy of estrogenic compounds in inducing abortion appears to be lower than the prostaglandins. Estrogen injections into heifers between 40 and 150 d of gestation resulted in 60 to 80% of females aborting (Brand et al., 1975; Refsal and Sequin, 1981; Horstman et al., 1982). To increase the efficacy later in gestation, the estrogens may be combined with dexamethasone. Sloan (1977) reported abortion in five of five females pregnant 5 to 8.5 mo using that combination.

The interval from treatment to abortion varies depending on which estrogenic compound is used. However, the majority of females abort by day 10, with the range being 3 to 25 d (Hill and Pierson, 1958; Brand et al., 1975). Estrual behavior immediately after abortion was not reported in the literature reviewed. Sloan (1977) did report the occurrence of normal estrous cycles following abortion, but did not indicate when these cycles

resumed. Uterine tone increases 24 to 48 h after treatment, but returns to normal soon thereafter (Brand et al., 1975). The CL decreases in diameter by day five to six after injection in some females (Brand et al., 1975). When ovaries were palpated 20 d after abortion, no follicles were present (Refsal and Sequin, 1981). The concentrations of serum progesterone decrease slowly for several days reaching a nadir by day seven after injection (Refsal and Sequin, 1981).

The physiological changes observed when aborted with estrogens are similar to those observed when aborted with prostaglandins. Abortion rates are slightly lower in the estrogen treated cattle. When the estrogenic compounds are used to induce abortion, undesirable side effects including vaginal prolapse, lochiometra, endometritis, and induction of lactation often resulted. Thus, the prostaglandins are the hormonal method of choice for inducing abortion (Hortsman et al., 1982).

Conclusion

Several methods of abortion are efficacious depending on the stage of gestation at abortion. However, little is known about the cyclicity of cattle after abortion. There is sketchy evidence that short luteal phases occur after abortion, particularly when aborted in the first 4 mo of gestation. Similar short luteal phases have been described in postpartum cows (Odde et al., 1980). A return to normal cyclicity is of economical and physiological concern in both aborted and postpartum cattle. A comparison of the postpartum and post-abortion physiology in cattle might help explain important mechanisms essential to fertility in both circumstances.

Chapter II: Luteal Function After Parturition in Cattle

Reproductive efficiency in cattle is becoming increasingly important because of higher production costs and lower net return per animal. Bovine gestation is approximately 285 d; thus, to maintain a yearly calving interval, a cow must conceive within 80 d after parturition. The average interval from calving to estrus is approximately 60 d (Casida et al., 1968; Marion and Gier, 1968; Bellows and Thomas, 1976), but in two and three year old cows the postpartum interval to estrus may be longer (Wiltbank, 1970). Long postpartum intervals decrease reproductive efficiency by causing calves to be born later in the calving season (Wiltbank, 1970). Recent USDA estimates indicate that a 6 d decrease in the postpartum interval would reduce cow maintenance costs by \$112 million, and the increased calf weaning weight would be worth \$96 million (Gerrits et al., 1978). Various treatment regimens to induce early postpartum ovulations have been investigated (Pratt et al., 1982; Lishman et al., 1979; Garcia-Winder et al., 1986). Those methods have induced ovulations that are accompanied by corpora lutea which are subfunctional. Understanding the mechanisms which regulate luteal function is essential to the development of any treatments for the induction of ovulation early in the postpartum period. The understanding of those mechanisms is necessary to induce normal luteal phases for planned breeding seasons in cattle.

The Sub-functional Corpus Luteum

The corpus luteum (CL) is a transient endocrine gland which develops from a Graafian follicle following ovulation. It is a continuation of

follicular maturation (Warbitten, 1934), and the preparation of luteal cells for the synthesis and secretion of progesterone begins prior to ovulation. The CL plays an important regulatory role because length of estrous and menstrual cycles depend on the duration of progesterone secretion.

Subnormal luteal function has been documented in humans (Strott, et al., 1970), primates (Wilks et al., 1976), sheep (Oldham and Martin, 1979; Coleman and Dailey, 1983; McLeod and Haresign, 1984), and cattle (Odde, et al., 1980; Pratt et al., 1982; Hinshelwood et al., 1982). Subnormal luteal function in cattle has been observed preceding the first ovulatory estrus in prepuberal or postpartum animals (Corah et al., 1974; Castenson et al., 1976), after early weaning of calves (Odde et al., 1980), after early postpartum injections of human chorionic gonadotropin (hCG; Pratt et al., 1982), after early postpartum injection(s) of gonadotropin releasing hormone (GnRH; Lishman et al., 1979), and after induced abortions at various stages of gestation (Ingrahm et al., 1978; Lindell et al., 1981; Keay, 1985).

Subfunctional corpora lutea can be divided into two groups. The first group includes corpora lutea having a normal lifespan, but decreased secretion of progesterone (Pratt et al., 1982; Coleman and Daily, 1983), and the second group includes corpora lutea having a short life span (Odde et al., 1980; Coleman and Daily, 1983). Since the first postpartum ovulation in cattle appears to have a predictable short life span, discussion will be primarily related to why the CL regresses prematurely rather than situations where life span is normal but there is decreased secretion of progesterone.

The first luteal tissue formed in prepuberal and postpartum cattle frequently results in short-lived corpora lutea (Berardinelli et al., 1980; Kiracofe, 1980). Macmillan and Watson (1971) reported the natural occurrence of a detectable short estrous cycle in 18% of the cattle observed, while Odde et al. (1980) reported an 8% natural occurrence. Short-lived CL or short cycles were observed in 80% of the cattle that ovulated in response to early weaning (Odde et al., 1980); 70-80% of those that ovulated in response to GnRH injection(s) (Lishman et al., 1979; Kesler et al., 1980); and 100% of those which ovulated in response to hCG injection (Garcia-Winder, et al, 1986). The percentage of short cycles increased with increasing herd size, and among second calving, three year old cows (Macmillan and Watson, 1971).

The short cycle is characteristically 7 to 12 d (Odde et al., 1980; Kesler et al., 1980; Ramirez-Godinez et al., 1982b). Serum concentrations of progesterone increase through day five after ovulation, and decline between days five and seven compared to normal cycle cows (Kesler et al., 1980). Secretion of progesterone from estrus to day five was similar for corpora lutea of short and normal life span (Ramirez-Godinez et al., 1981; Manns et al., 1983), and similar peak levels of progesterone occur (Rutter and Randell, 1984). In addition, weight and concentration of progesterone in luteal tissue 5 d after estrus were similar between the two groups (Kesler et al., 1981a; O'Shea et al., 1984). Ovulation does occur and fertilization may result. However, because the CL regresses prior to pregnancy recognition, the pregnancy is not maintained (Ramirez-Godinez et al., 1982a).

Mechanisms associated with subnormal luteal function may occur during the follicular and(or) luteal phase. Possible reasons for luteal insufficiency after the first puberal and postpartum ovulations include 1) inadequate preovulatory follicular development, 2) lack of sufficient luteotropin during the luteal phase, 3) failure of the luteal tissue to recognize a luteotropin, 4) premature release of a luteolysin, and(or) 5) increased sensitivity of luteal tissue to a luteolytic factor.

Possible Causes of Luteal Insufficiency

Inadequate Preovulatory Follicular Development. The preparation of luteal cells for the synthesis and secretion of progesterone begins during the follicular phase of the estrous cycle. Both granulosa and theca cells are involved in this development (Alila and Hansel, 1984). Thus, both extra- and intrafollicular events are important for adequately preparing follicular cells for luteinization and secretion of progesterone. Mechanisms which alter the microenvironment of the preovulatory follicle may impair the ability of the follicular cells to secrete progesterone, thus resulting in inadequate luteal function. In the follicular phase, components of the microenvironment which may be altered include inadequate gonadotropin and(or) steroid hormone concentrations, and(or) inadequate hormone receptor affinity or concentration.

Corpora lutea develop from both the theca and granulosa cells of the maturing follicle (Alila and Hansel, 1984) under the coordinated actions of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The theca cells are extrafollicular and the granulosa cells are intrafollicular.

Therefore, extra- and(or) intrafollicular events can alter subsequent luteal function. Within the theca interna, LH stimulates the synthesis of androgens. These androgens diffuse through the basement membrane towards the interior portion of the follicle. Within the granulosa cells, the androgens are aromatized to estradiol-17 β (E_2) through the FSH regulated enzyme, aromatase. Intrafollicularly, FSH also has a role in mitosis of granulosa cells, antrum formation, maintenance of granulosa cell viability (in vitro), and synthesis of gonadotropin receptors on granulosa cells (Richards, 1980).

Gonadotropins (LH and FSH) and ovarian steroids (progesterone and E_2) may alter the hormonal environment acting upon the extrafollicular and intrafollicular cells of the developing follicle. Each of these will be discussed briefly.

Lack of a Gonadotropins during the Follicular Phase. In women, decreased plasma concentrations of FSH or a decreased FSH:LH ratio during the preovulatory phase was associated with subnormal luteal function (Strott et al., 1970). In addition to FSH, plasma concentrations of E_2 were decreased in monkeys during the follicular phase prior to a shortened luteal phase (Stouffer and Hodgen, 1980). Inadequate concentrations of FSH and E_2 during the preovulatory follicular development may result in a reduction of mitosis in the granulosa cells which would contribute to a decreased number of luteal cells after luteinization. Inadequate concentration of these hormones may also lead to a depressed concentration of receptors for LH in granulosa cells (Richards, 1980) thus preventing normal luteinization.

The follicular phase in cattle and sheep is shorter than in humans and primates. However, preovulatory concentrations of FSH might be important in the development of a normal CL . Experiments that relate to the idea that FSH is the limiting factor for the formation of normal corpora lutea in postpartum cows have produced mixed circumstantial evidence. Ramirez-Godinez et al. (1982b) observed in early weaned cows that concentrations of FSH preceding the formation of corpora lutea with short life span were lower than those preceding the formation of normal-lived corpora lutea. However, administration of pregnant mare serum gonadotropin (PMSG; Sheffel et al., 1982) or FSH (Lishman et al., 1979) to postpartum cows prior to induction of ovulation failed to enhance luteal function. Pretreatment with norgestomet prior to inducing ovulation with hCG did not alter concentrations of FSH either pre- or post-ovulation in two of three experiments. Yet, luteal life span was enhanced in cows pretreated with norgestomet. Because cows pretreated with norgestomet in one experiment had lower FSH levels 5 d prior to hCG (0.6 vs 0.8 ng/ml; $P < .05$), and there was a lower incidence of corpora lutea with normal life span associated with these decreased levels of FSH, it was suggested that a minimum or threshold concentration of FSH is needed during norgestomet pre-treatment if the corpora lutea formed after hCG are to have a normal life span. Follicle stimulating hormone may only need to exceed a threshold level to adequately prepare a preovulatory follicle for subsequent secretion of progesterone (Garcia-Winder et al., 1986).

Preovulatory concentrations of LH are important for follicular maturation and normal luteal function, providing that events leading up to

the synthesis of LH receptors are adequate. In cows, mean concentrations of LH in serum were lower during anestrus than levels observed just prior to the first postpartum estrus (Williams et al., 1982). An increase in the pulse frequency of LH has been detected prior to ovulation and estrus (Walters et al., 1982a; Leung et al., 1986). In postpartum cows induced to ovulate with early weaning, number and magnitude of LH pulses increased by 48 h postweaning (Edwards, 1985). In postpartum cows induced to ovulate with hCG, Garcia-Winder et al., (1986) studied the patterns of secretion of LH in norgestomet-pre-treated and control cows. Treatment did not affect mean concentrations of LH. The frequency of LH pulses was greater five d prior to hCG in norgestomet-pre-treated than in control cows, but no differences were observed in pulse amplitude. The increased pulse frequency of LH prior to induction of ovulation was associated with increased concentrations of E_2 . Sheffel et al., (1982) reported a similar increase in plasma concentrations of E_2 when pre-treated with PMSG prior to induced ovulation. These results suggest that an increase in pulse frequency of LH in the presence of FSH may be important for the synthesis of E_2 , and may affect the preparation of the follicle to become a CL (Garverick and Smith, 1986).

The duration and magnitude of the ovulatory LH surge may be related to subnormal luteal function. The first ovulatory surge has been reported to be decreased or no different than the subsequent LH surge (Schams et al., 1978; Manns et al., 1983). In cows, the duration of the surge of LH induced by a single injection of GnRH was shorter than the spontaneous surge of LH (Troxel et al., 1984). Vincent (1984) showed that treatment of postpartum

anestrous ewes with GnRH in gelatin capsules, which produced a more prolonged release of LH than a single im injection of GnRH in saline, enhanced luteal function. In accord with these results, pulsatile injections of GnRH for 72 h prior to a GnRH challenge in postpartum anestrous dairy cows resulted in normal length estrous cycles; whereas a GnRH challenge preceded by saline injections resulted in short cycles (Mollett et al., 1983). In addition, progestogen treatment prior to injection of GnRH has been associated with greater GnRH-induced LH release, increased peak concentrations of LH, and enhanced luteal function (Smith et al., 1983; Troxel and Kesler, 1984b).

In contrast, pulsatile low dose injections of GnRH for 72 h in prepuberal heifers (5 mo old) did induce preovulatory LH surges with a coincident FSH surge. This was not followed by normal luteal function (normal = $P_4 > 1.0$ ng/ml for 10 or more d; McLeod et al., 1985). Intermittent small dose injections of GnRH for 96 h in postpartum cows induced ovulation and continued cyclicity, but a large percentage of cows had short first estrous cycles. Exogenous E_2 appeared to overcome this problem as a high percentage of cows receiving intermittent GnRH plus E_2 had normal length first estrous cycles (Walters et al., 1982b). Utilizing single or double pulses of GnRH, with or without progesterone pretreatment, did induce ovulations in postpartum dairy cows. However, neither progesterone priming nor repetitive injection of GnRH enhanced pituitary LH or FSH secretion compared to a single GnRH injection. Progesterone pretreatment did enhance luteal function, but this appeared to occur via an ovarian

mechanism which was independent of pituitary gonadotropin secretion (Williams et al., 1982).

Pretreatment with progesterone, (Ramirez-Godinez et al., 1981), E_2 (Walters et al., 1982b), pulsatile injections (Mollett et al., 1983), or prolonged release of GnRH (Vincent et al., 1984) prior to induction of ovulation have all enhanced luteal function in the postpartum cow and/or ewe. In these studies, it is unclear whether increased luteal function is due to increased follicular maturation, a prolonged surge of LH, and/or increased frequency of LH pulses, or if the response is independent of pituitary gonadotropic secretions.

Lack of Gonadal Steroids during the Follicular Phase. In addition to pituitary hormones, estradiol contributes to the preovulatory endocrine environment and may alter subsequent luteal function. Ramirez-Godinez et al. (1982b) compared serum E_2 concentrations between the first and second postpartum estruses. Their data suggested E_2 may be somewhat lower at the first estrus, but no significant differences were found. Walters and co-workers (1982b) pre-treated cows with E_2 prior to induction of ovulation with pulse injections of GnRH. Luteal function was prolonged in these cows compared to early weaned cows and cows treated with GnRH alone. Garcia-Winder et al. (1986) investigated levels of E_2 in postpartum cows induced to ovulate with hCG. Cows pretreated with norgestomet exhibited increased levels of E_2 1 d prior to hCG. These results are similar to those of Sheffel et al. (1982) in which concentrations of estradiol were higher in norgestomet pretreated cows 2 d prior to hCG. In cows with adequate FSH, pretreatment with norgestomet apparently caused subtle increases in

secretion of LH, which enhanced the development of a dominant follicle characterized by a higher production of E_2 (Baird, 1983). Estradiol-17 β has many roles in follicular development such as increasing granulosa cell proliferation, enhancing the stimulation of synthesis of progesterin by gonadotropins, and synthesis of LH receptors in granulosa cells (Richards, 1980). Thus, elevated concentrations of estradiol may be essential for adequate preparation of follicular cells to secrete progesterone.

Early weaning (Ramirez-Godinez et al., 1981), injection of GnRH (Pratt et al., 1982; Troxel and Kesler, 1983), or injection of hCG (Garcia-Winder et al., 1986) into anestrus postpartum cows resulted in formation of short lived corpora lutea, unless the animals were pretreated with a progestogen. It is not clear whether progesterone priming enhances luteal function by modulating the secretion of gonadotropins and(or) by directly affecting the preovulatory follicle. As mentioned previously, progesterone pretreatment has been shown to increase LH pulse frequency, and increased concentrations of E_2 (Garcia-Winder et al., 1986). In anestrus ewes pretreated with progesterone and injected with repeated low doses of GnRH, the surge of LH was delayed (McLeod et al., 1982) and normal luteal phases were exhibited. Estradiol secretion by follicles collected at the time of the LH surge was enhanced in vitro compared to follicles collected 14 h prior to the LH surge (Hunter et al., 1986). A delayed surge of LH might extend preovulatory follicular development, increase exposure time to gonadotropins, and(or) enhance mitotic divisions of granulosa cells (Garverick and Smith, 1986), thus enabling the final maturational stages of follicular development to ensue.

Preovulatory follicular development includes extrafollicular changes, as discussed up to this point, and intrafollicular changes. The endocrine environment within the preovulatory follicle is unique in relation to surrounding non-ovulatory follicles. Factors which may be altered within the follicle include granulosa cell numbers, ability of the cells to bind LH and secrete progesterone, as well as many other factors. Characteristics of preovulatory follicles anticipated to form subnormal corpora lutea have been compared to follicles anticipated to form normal corpora lutea. Preovulatory follicles expected to form short-lived corpora lutea were found to be steroidogenically subfunctional prior to induction of ovulation in postpartum cows (Garcia-Winder et al., 1985) and ewes (White et al., 1985). Hunter and co-workers (1986) induced anestrous ewes to ovulate with multiple injections of GnRH with or without progesterone pretreatment. Follicles were removed 14 h prior to or at the LH surge. Diameter, granulosa cell number, E_2 , testosterone, and progesterone concentrations in follicular fluid, E_2 production in vitro, and binding of 125 I-hCG to granulosa and theca cells were evaluated. No differences were detected in follicles collected 14 h prior to the LH surge. Those follicles collected at the LH surge from ewes pretreated with progesterone exhibited greater E_2 secretion in vitro and greater 125 I-hCG binding to granulosa cells. These results suggest that inadequate luteal function after repeated injections of GnRH may be due to a poor response to the LH surge indicative of a deficiency in the final maturational stages of the follicle. Further study is needed to determine if this is true and if so, to determine the mechanism

whereby progesterone pretreatment ensures that follicles do through the final maturational stages before ovulation.

Inadequate Luteal Phase Luteotropin. The synthesis and secretion of progesterone after ovulation are regulated by luteotropic and luteolytic mechanisms during the luteal phase. Since both of these stimuli are present concurrently during the estrous cycle, the stimulation or inhibition of progesterone synthesis and secretion may be dependent upon a balance of these stimuli.

Luteinizing hormone (LH) is an important luteotropin in cattle, and administration of LH can prolong luteal life span (Shomberg, et al., 1967). Decreased secretion of LH after ovulation has not been associated with decreased luteal life span. Mean concentration, pulse frequency, and pulse amplitude of this gonadotropin are similar for inadequate and adequate corpora lutea (Ramirez-Godinez et al., 1982b; Rutter et al., 1985). Peak values during the ovulatory LH surge are also similar between both groups (Manns et al., 1983).

The LH pulses are not released as frequently as the progesterone pulses (Walters et al., 1984). This suggests that hormonal or perhaps a nonhormonal factor(s), in addition to LH, stimulate progesterone secretion. Walters et al., (1984) reported that almost every FSH pulse during the early or midluteal phase in cattle was followed by a progesterone pulse. Receptors for FSH have been reported in the bovine CL (Manns et al., 1984). These results suggest that FSH may have a luteotropic role in luteal function. However, post-ovulatory concentrations of FSH are reported to be similar during subnormal and normal luteal phases (Ramirez-Godinez et

al., 1982b; Manns et al., 1983). Although some observations suggest FSH may have a luteotrophic role, other studies indicate that once an increased level of plasma FSH is established about 5 to 10 d postpartum, differences in plasma FSH have no influence in the onset of ovarian cycles (Lamming et al., 1981).

Prostacyclin (PGI_2) may also play a luteotropic role in the bovine CL. Prostacyclin is a metabolite of cyclic endoperoxide prostaglandin H_2 (PGH_2) through the enzyme prostacyclin synthetase. This enzyme has been found in high concentrations in the luteal tissue of cattle (Sun et al., 1977). Prostacyclin is the dominant prostaglandin formed when PGH_2 is incubated with bovine CL membrane preparations (Sun et al., 1977). Injections of 1 mg PGI_2 directly into the bovine CL on day 12 or 13 of the estrous cycle significantly increased peripheral plasma progesterone concentrations in normally cyclic virgin Holstein heifers (Milvae and Hansel, 1980). This affect was not due to altered levels of LH. However, PGI_2 is a potent vasodilator (Moncada and Vane, 1979) which may have enabled more luteotropin to reach the CL. Prostacyclin had a luteotropic effect on progesterone production by dispersed luteal cells that was greatest during luteal development (Milvae and Hansel, 1980). Intrauterine administration of indomethacin (a prostaglandin synthesis inhibitor) shortened luteal life span when administered days four to six of the estrous cycle (Milvae and Hansel, 1985). These results suggest that PGI_2 has luteotropic effects on the bovine CL in vivo and in vitro during the early phase of the cycle. There is no direct evidence that decreased prostacyclin concentrations are related to shortened luteal life span.

Failure to Recognize a Luteotropin. An intraluteal mechanism possibly associated with subnormal luteal function is decreased responsiveness of luteal tissue to a luteotropin. Three possible luteotropins are LH, FSH, and PGI_2 . Of these, the responsiveness of luteal tissue to LH has been the most investigated in relation to subnormal luteal function.

The ability of LH to stimulate progesterone synthesis in vitro following GnRH induced ovulation is unclear. In vitro LH stimulation increased progesterone production by dispersed luteal cells relative to unstimulated cells (Rutter et al., 1985), or had no effect (Kesler et al., 1981b). Luteal cells from cows expected to have short cycles tended to have greater basal and mean LH stimulated progesterone release than did cows expected to have normal cycles (Rutter et al., 1985). This is in contrast to the study by Kesler et al. (1981b) who reported higher basal and LH stimulated production on day seven after estrus from cycling CL compared to day seven post-GnRH induced CL. Additionally, the LH-induced secretion of progesterone in vitro was similar for bovine luteal tissue sampled following ovulation at the first compared to third spontaneous ovulations (Duby et al., 1985). A possible explanation for the contrasting results is that corpora lutea were sampled at various times after ovulation. Some luteal tissues had possibly been exposed to a luteolytic factor(s) and were in various stages of regression.

Differences in LH-induced secretion of progesterone may be due to alterations related to the LH receptor. Hormone receptor binding is dependent upon the hormone concentration, affinity of hormone binding, and receptor concentration. As discussed previously, there does not appear to

be any differences in LH concentrations between normal and subnormal luteal phases. Thus, the affinity of hormone binding or receptor concentrations might explain observed differences in LH-induced progesterone secretion.

During the normal luteal phase, secretion of progesterone rises until day five after estrus. The affinity of receptors might be expected to show a parallel increase. In cattle, an increase in LH receptor affinity has not been observed during the luteal phase (Rao et al., 1979). Receptor affinity in relation to inadequate luteal function was not reported in the literature reviewed.

The CL contains a heterogenous population of cells which differ in size and steroidogenic ability (Fitz et al., 1982). Steroidogenically active luteal cells include small and large cells. There are distinct differences in the ability of small and large cells to secrete progesterone in the absence or presence of LH. Basal progesterone secretion is lower in small relative to large cells; however, LH stimulated progesterone secretion is greater in small cells (Koos and Hansel, 1981). Luteal LH receptors are concentrated in the small luteal cells, while PGF receptors are on the large luteal cells. The ratio of large to small cells increases during the cycle suggesting there is a transformation of small to large cells (Fitz et al., 1982). Data suggests that this transformation is driven by LH (Farin et al., 1985). If this transformation was driven too rapidly during the subnormal luteal phase, there could be a decrease in LH receptors and an increase in PGF receptors. The luteal tissue would lose its ability to bind LH. No difference has been detected between subnormal and normal corpora lutea

in the ratio of large to small cells (Manns et al., 1983; Rutter et al., 1985). The concentrations of LH receptors for corpora lutea anticipated to have a short or normal life span were not different (Rutter et al., 1985), nor were differences detected in unoccupied and occupied receptors for LH between the two tissue types (Smith et al., 1985). However, the total number of luteal cells and CL size were different (Duby et al., 1985; Rutter et al., 1985). Although concentrations of receptors were not different, because number of cells was different, total number of receptors would also differ. Manns and co-workers (1983) reported that regression of the short-lived CL appeared abnormal compared to the longer lived CL in which regression was characterized by a rapid decline in progesterone and elevated blood PGFM. The authors theorized that the CL couldn't sustain its ability to secrete progesterone. Decreased total quantity of receptors may have led to early demise of the CL.

Premature Luteolytic Stimulus. In 1969, PGF was found to be a potent luteolytic agent in vivo. This compound is capable of causing the CL to regress histologically and plasma progesterone levels to fall (Horton and Poyser, 1976). Utilizing samples of uterine endometrial tissue and venous plasma, three main points about uterine secretion of PGF during the bovine estrous cycle have been characterized: 1) Concentrations in the endometrium and uterine venous plasma are low early in the estrous cycle. Significant increases are evident by day 15, and luteal regression is usually complete by day 16 to 18 (estrus = day 0). Elevated levels are maintained throughout this period; 2) Secretions of PGF occur in a series of peaks of varying frequency, magnitude, and duration. The frequency increases as the

end of the luteal phase is reached; 3) These peaks do not cease until at or near the onset of estrus, and concentrations remain high at least through day 18 of pregnancy in ewes (Horton and Poyser, 1976; Inskeep and Murdoch, 1980).

Prostaglandin $F_2\alpha$ plays a major role during parturition in most domestic species, and a prolonged release of PGF postpartum plays a role in uterine involution. One week prior to parturition, PGFM (15-Keto-13, 14-dihydro-PGF₂; main plasma metabolite of PGF) levels begin to increase, peak at parturition, and decline within 3 d to levels maintained for 1 to 3 wk postpartum. A second decline to basal levels occurs by week four in the ewe (Fredricksson, 1985). The same pattern is detected in the bovine. PGFM levels are highest on day three postpartum, and reach basal levels by day 21 (Manns et al., 1983; Madej et al., 1984, Troxel and Kesler, 1984a). These increased levels of PGF were produced by the uterus (Guibault et al., 1984). Circulating concentrations of PGFM are decreased by 20 d postpartum, a time prior to the first ovulation and occurrence of short luteal phases in postpartum beef cows.

Several studies have been conducted to investigate if subfunctional CL have an inherent short life span or if luteolytic factors cause early regression. Indomethacin, an inhibitor of prostaglandin synthesis, infused into the uterus beginning the day following GnRH induced ovulation in postpartum beef cows extended luteal lifespan (Troxel et al., 1984). However, when administered day four to six, indomethacin shortened luteal life span (Milvae and Hansel, 1985). The cause of this contrast is unknown. These results suggest that during luteal development, prostaglandin

synthesis is needed for complete development. Prostacyclin has been implicated here. During the later part of the luteal phase, prostaglandins synthesized play a role in lysis of the CL. Prostaglandin F_2 is implicated in this case (Garverick and Smith, 1986). Inhibition of PGF synthesis increases luteal life span, while inhibition of PGI_2 synthesis limits luteal development, thus decreasing luteal life span.

Wiltbank and Casida (1956), Anderson et al. (1962), and Kiracofe and Spies (1966) demonstrated the uterus is necessary for luteal regression in cattle and sheep. More recently, Copelin et al. (1985) and Schallenberger et al. (1984a) have demonstrated that the uterus is also needed for luteal regression in the early weaned beef cow and early postpartum dairy heifer, respectively. Schallenberger et al., (1984a) hysterectomized three heifers immediately postpartum and maintained three intact controls. Initial ovulations occurred between 11 and 15 d postpartum in both groups. Average LH and FSH secretion was higher and pulses more frequent in the hysterectomized group. However, gonadotropin secretion parameters were similar in both groups after the early luteal phase. Low progesterone concentrations were detected prior to the initial ovulation. Copelin et al. (1985) demonstrated that concentrations of progesterone were similar from estrus to day five for hysterectomized and intact cows (estrus = day 0). Secretion of progesterone decreased after day five in intact cows compared to hysterectomized cows. The pattern of secretion of progesterone from estrus to day 16 was similar for hysterectomized and intact (second cycle) cows. Since secretion of progesterone from day zero to 16 following the first ovulation in hysterectomized animals was similar to that during a

normal luteal phase, it is unlikely that inadequate follicular development and(or) insufficient luteotropic support are associated with subnormal luteal function in early weaned beef cows. Rather, by day eight after the first estrus, the uterus has a premature inhibitory effect on luteal life span. These results, in combination with those of Kesler et al. (1985) in which subcutaneous injections of indomethacin prolonged luteal life span, suggest that a premature release of PGF is associated with inadequate luteal phases.

The mechanism associated with the timing of PGF release following the first formation of luteal tissues in postpartum cows is unknown. Hormonal factors known to affect the release of PGF from the uterus in the normally cyclic animal are oxytocin and E_2 .

Oxytocin induced an increase in the concentration of PGFM in systemic circulation if injected into ovariectomized ewes only after a sequence of progesterone injections followed by an E_2 injection (Caldwell et al., 1972), in anestrus ewes (Sharma and Fitzpatrick, 1974), in pregnant and early postpartum (<17 days) ewes (Mitchell et al., 1975), in early postpartum cows (Troxel et al., 1984), and in heifers day 17 to 19 postestrus or postconception (LaFrance and Goff, 1985). However, this increase was not exhibited when oxytocin was injected on days 3, 8, or 13 of the ovine estrous cycle (Roberts et al., 1975), or on days 6 or 13 of the bovine estrous cycle (LaFrance and Goff, 1985). This suggests that the responsiveness of the prostaglandin-synthetic mechanism to oxytocin varies with the estrous cycle, indicating at least a partial dependence on the gonadal steroid status of the animal.

The oxytocin induced PGF release is enhanced if E_2 is injected 24 h prior to the oxytocin injection in anestrus ewes. Estradiol-17 β alone in anestrus ewes induces greater release of PGF than does oxytocin alone (Sharma and Fitzpatrick, 1974). As discussed previously, PGF increases on day 14 in the intact ewe. This increase does not occur in ovariectomized ewes unless E_2 is injected following a sequence of progesterone injections (Caldwell et al., 1972). Infusions of physiological amounts of E_2 on day 14 of the ovine estrous cycle increased PGF release from 1.4 μ g/h to 102 μ g/h. This increase does not occur on days 6 and 10 of the estrous cycle. This finding suggests that E_2 can induce PGF release only after a prior period of progesterone (Roberts et al., 1975).

The corpora lutea in sheep contain high levels of oxytocin (Wathes and Swann, 1982) and secrete it into the ovarian vein (Flint and Sheldrick, 1982). Active immunization against oxytocin leads to prolonged luteal life span (Sheldrick et al., 1980), while immunization against E_2 leads to low or undetectable levels of PGF in jugular blood (Caldwell et al., 1972). Systemically administered oxytocin is somewhat luteolytic in the cow (Armstrong and Hansel, 1959), and this luteolytic effect can be prevented by hysterectomy (Hansel and Wagner, 1960). During the ovine estrous cycle, peak levels of E_2 and PGF in utero-ovarian venous blood are detected on day 15 just prior to the demise of the CL (Roberts, et al., 1975). Concurrent with these peak levels is the depletion of oxytocin from the luteal tissue (Flint and Sheldrick, 1983). Recently Schramm and co-workers (1986) demonstrated that oxytocin could be locally recirculated to the ovaries, oviduct, and tip of the uterine horn through the network of blood

vessels in the ovarian pedicle in sheep. These findings are consistent with the mechanism proposed by Roberts et al. (1976) to account for the increase in uterine PGF production at luteal regression, i.e. that a rise in follicular E_2 production causes an increased endometrial oxytocin receptor concentration, thereby facilitating the stimulatory effect of oxytocin on PGF production. Evidence in support of this includes a mid-cycle peak of E_2 (Shemesh et al., 1972) which might initiate the development of oxytocin receptors at the end of the cycle in sheep (Roberts et al., 1976), uterine oxytocin receptors are stimulated in the rat by E_2 (Soloff, 1975), and other factors as discussed above. Luteal secretion of oxytocin may amplify the luteolytic signal through a local positive feedback pathway (see Figure 1), and ensure rapid completion of luteal regression (Flint and Sheldrick, 1983; Flint et al., 1986).

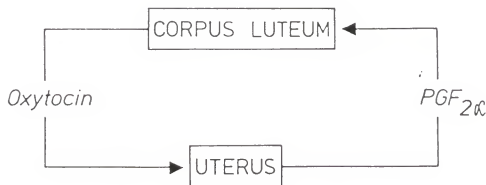


Figure 1. Postulated positive feedback loop showing possible interactions between the corpus luteum and the uterus to ensure episodic secretion of $PGF_{2\alpha}$. (Flint et al., 1986)

Luteal regression as proposed by Roberts et al. (1976) is supported by considerable evidence. Several studies also support the theory that the short luteal phase in the postpartum cow results from a premature release of a luteolytic factor, presumably PGF, from the uterus. Studies to investigate the factors associated with the release of PGF from the uterus in the postpartum cow which compare short and normal estrous cycles are limited. When hysterectomy was used to prevent the short estrous cycle, no differences were detected in E_2 or oxytocin levels between intact and hysterectomized early postpartum dairy heifers (Schallenberger et al., 1984a). In both groups, E_2 was low initially and increased to preovulatory levels between 9 and 12 d postpartum. Ovarian oxytocin was low (1-3 pg/ml) until a preovulatory follicle developed. After ovulation (day 11-15 postpartum), oxytocin remained elevated until day 14 of the luteal phase in both groups. Hysterectomized heifers maintained the CL until at least 58 d postpartum. Length of estrous cycles in intact heifers was not presented in this study. Although removal of the uterus prevents the short estrous cycle, it cannot be assumed that other physiological traits such as ovarian secretion of E_2 and(or) oxytocin are altered by hysterectomy. Luteal regression in these animals may be prevented strictly due to removal of the source of luteolysin rather than any alteration of ovarian function.

Garcia-Winder and co-workers (1986) compared endocrine profiles from progesterone pretreated and control cows induced to ovulate with hCG. Estradiol 17 β was higher in the norgestomet pretreated cows 1 d after implant removal. Sheffel et al. (1982) reported similar results. In cows with adequate FSH, pretreatment with norgestomet caused subtle increases

in secretion of LH, which enhanced the development of a dominant follicle characterized by a higher production of E_2 (Baird, 1983).

Evidence supports the theory that premature release of a luteolysin from the uterus is related to the short luteal phase. Further investigation into the mechanism controlling the release of PGF from the uterus is needed.

Increased Sensitivity of Luteal Tissue to a Luteolysin. Induced corpora lutea in prepuberal gilts have been shown to be more sensitive to luteolysis by PGF than spontaneously formed CL of the mature gilt (Puglisi et al., 1979). Sensitivity to PGF is related to the concentration of receptors for this compound. In luteal tissue, the receptors for PGF are concentrated on the large luteal cells when compared to the small luteal cells (Fitz et al., 1982). During the estrous cycle, there appears to be a shift from small to large cells that is driven by LH (Farin et al., 1985). If this shift were premature in the subnormal CL, this tissue would be sensitive to a luteolysin earlier in the cycle. There is no difference in the ratio of large to small luteal cells in subnormal and normal corpora lutea (Rutter et al., 1985). However, sensitivity is also related to other factors as discussed previously. Smith et al. (1986) allotted cows at calving to be hysterectomized-control or hysterectomized-progestogen implanted. The implanted cows received a norgestomet implant after calving that was removed 9 d later. Ovulation was induced in both groups with GnRH. Hysterectomy was performed 2 to 3 d after GnRH, and cows were challenged with low doses of PGF on day seven following GnRH. Response was monitored via blood progesterone. Results demonstrated that

sensitivity of corpora lutea anticipated to be short lived to PGF was not greater than corpora lutea anticipated to be normal. In contrast, Niswinder (1986) reported that CL expected to be short-lived had more receptors for PGF on day seven after the LH surge compared to CL expected to have a normal life span. This was concluded from only two observations. More investigation of the luteal sensitivity to luteolytic factors is needed.

Conclusion

At present, it is not known if the short estrous cycles after abortion referred to in chapter I are a result of the same mechanisms as short estrous cycles in the postpartum cow. However, length of luteal life span appears similar, and the aborted heifer provides a different experimental model that can help substantiate or refute some of the hypothesis currently proposed in the postpartum cow. Characterization of cycling after abortion is the main objective of this thesis, and hopefully it will help explain some of the physiological mechanisms involved in resumption of normal cycles after parturition as well as after abortion.

EXPERIMENT I

ABORTION IN BEEF HEIFERS AT VARIOUS STAGES OF GESTATION:

SUBSEQUENT WEIGHT AND PHYSIOLOGICAL CHANGES

Summary

Ninety-one pregnant crossbred Angus heifers aborted after receiving an injection of a prostaglandin analog at an average of 50, 75, 100, or 125 d of gestation. Uterine involution, weight changes, and other changes associated with abortion were followed during the first 3 wk after administration of prostaglandin. The average interval from injection to estrus was 5.2 d, and fetuses were usually expelled soon after estrus. Uterine involution was more rapid in heifers aborted earlier in gestation. There was more udder development, vaginal discharge, and retained membranes in heifers aborted later in gestation. No detrimental effects were noted in those heifers aborting at 50 or 75 d of gestation, and growth was not altered when compared to heifers which failed to abort (1.13, 1.50, and 1.27 kg/d, respectively). Those heifers aborted at 100 d of gestation experienced a decreased growth rate; those aborted at 125 d of gestation lost weight during the first 3 wk after abortion.

Introduction

It is well established that prostaglandin F_2^α (PGF) and its analogues administered by various routes can induce functional and morphological regression of the corpus luteum (CL) in cattle up to 150 d of gestation (Lamond et al, 1973; Brand et al., 1975; Copeland et al, 1978). Maintenance of pregnancy in the cow is dependent on the presence of a functional CL until this time (McDonald et al., 1953; Estergreen et al., 1967). Prostaglandins are 80 to 100%

effective in inducing abortion in cattle up to 150 d of gestation (McAllister and Lauderdale, 1979).

In the United States, a large percentage of heifers enter feedlots pregnant (Edwards and Laudert, 1984). In 1972, a market research survey indicated that 1.42 million feedlot heifers are aborted each year (McAllister and Lauderdale, 1979). Pregnant heifers are recognized as a liability to the cattle feeder. Economic losses to the feedlot operator result from the lower prices paid for heifers in late pregnancy when sold for slaughter. Heifers that calve in the feedyard require additional treatment and labor costs and are less valuable when sold (Schultz and Copeland, 1981). Edwards and Laudert (1984) determined heifers aborted in the feedlot before 120 d of gestation are worth \$17 per head more than heifers pregnant at slaughter, although pregnant heifers gained 15% faster.

In general, research to date has been related to testing the efficacies of various compounds in inducing abortion. It is clear that aborting heifers early in pregnancy is cost effective if they are fed for slaughter. However, more information is needed concerning weight and physiological changes after abortion. The purpose of the current study was to determine the magnitude of weight change after abortion at various stages of gestation, and to observe any other physiological changes and complications associated with abortion.

Materials and Methods

One hundred three pregnant crossbred Angus heifers, verified pregnant by rectal palpation to known artificial insemination dates, were maintained in dry lots at Kansas State University. Heifers were fed a ration of sorghum silage and

protein supplement calculated to meet NRC (1984) requirements for growing, medium frame heifers. Mineral blocks and water were available at all times.

Heifers were randomly allotted to be aborted an average of either 50, 75, 100, or 125 d of gestation. Animals were palpated again to reconfirm pregnancy just before an injection of a prostaglandin analogue. Seventeen, 18, and 17 pregnant heifers were injected im with 15 mg Luprostiol at 45 to 60 d, 71 to 79 d, and 94 to 101 d of gestation, respectively. On days 117 to 132 of gestation, three groups of 17 heifers each received either 15 mg Luprostiol im, 15 mg Luprostiol sc, or 2 mg fenprostelene sc. Beginning at injection, animals were observed twice daily for signs of estrus, fetal expulsion, or other signs of abortion. Observation periods were 30 min in duration. Observations continued until at least one normal estrous cycle (16-24 d) was exhibited or for 50 d after injection if a normal estrous cycle was not observed.

Heifers were palpated via rectum once weekly for 3 wk after treatment to monitor changes in uterine size and tone. The uterus was scored on a scale of 0 to 5 (0=complete involution; 5=distended to size of a 125 d pregnancy) in heifers injected at 125 d of gestation.

The initial weight was taken at time of treatment (Wt 1). A second weight was taken 1 wk after treatment (Wt 2), and a third weight was taken 3 wk after treatment (Wt 3). Average daily gain (ADG) was calculated as Wt 3 minus Wt 1 divided by 21 d. All weights were taken between 0600 and 0900 h, and heifers had not been held off feed or water prior to weighing.

Data on weight changes were analyzed by the SAS General Linear Model (1982) procedure.

Results and Discussion

Twelve of 103 heifers did not abort by 50 d after injection. Two of those were heifers injected at 50 d of gestation, four at 75 d, four at 100 d, and two at 125 d (table 2). No differences in abortion rate were related to weight at treatment. Copeland et al. (1978) also reported that treatment response wasn't related to weight at prostaglandin administration. It was not the objective of the current study to determine the efficacies of the PGF analogues or modes of administration used on heifers in the 125 d-group. In heifers that did abort, response after abortion was not related to analogue or mode of administration that was used. A higher percentage of heifers tended to abort when treated later in gestation. Efficacy of treatment in relation to day of gestation at treatment during the period when pregnancy is dependent on luteal progesterone was not reported in the literature reviewed.

All heifers that aborted exhibited estrus after treatment. Previous reports on the occurrence of estrus after abortion have varied from 16.6% of heifers aborted between 105 and 135 d exhibiting estrus (Ingrahm et al., 1978) to 100% of heifers aborted between 39 and 146 d exhibiting estrus (Lindell et al., 1981; Refsal and Sequin, 1981).

The average interval from prostaglandin administration to estrus was 5.2 d. Interval to estrus after abortion was not related to day of gestation at treatment or weight at treatment. There was a tendency for heifers aborted at 125 d to have a longer interval to estrus (table 2). The longer interval to estrus in heifers aborted at 125 d of gestation may have been related to the higher percentage of retained membranes (26.5%) experienced by those heifers. Heifers retaining membranes experienced an average interval to estrus of 8.65 d. If

TABLE 2. CHARACTERISTICS OF HEIFERS BY DAY OF GESTATION AT TREATMENT

Item	Average day of gestation at treatment			
	50	75	100	125
Number of heifers which aborted	15 (88.2) ¹	14 (77.8)	13 (76.5)	49 (96.1)
Average interval from injection to estrus (days) ²	3.6	4.2	3.7	6.4
Number of fetuses observed after injection	2 (13.3) ¹	9 (64)	13 (100)	49 (100)
Average interval from injection to fetal expulsion (days) ²	6.25	4.5	4.1	3.6

¹Percentages in parenthesis.

²Heifers observed every 12 h.

those heifers plus one with an interval to estrus of 49 d, are removed from the calculation of interval to estrus, the heifers which didn't have retained membranes had an interval to estrus of 4.5 d. Previously reported intervals to estrus after prostaglandin administration have ranged from 34 h (Brand et al., 1975; Day, 1977) to 36 d (Lindell et al., 1981). Retention of fetal membranes was not reported in the studies with long intervals to estrus, but retained membranes appeared to extend the interval to estrus in heifers aborted at 125 d of gestation in the present experiment. Extended intervals to estrus after treatment have been reported to be related to length of gestation at abortion (Ingrahm et al., 1978; Lindell et al., 1981), although such a relationship was not detected in the current study.

Most estruses were exhibited between 2 to 6 d after treatment (100%, 93%, 100%, and 80% for heifers aborted at 50, 75, 100, and 125 d, respectively). Fetuses were generally expelled after estrus, with all fetuses being expelled by 6.5 d after injection. Fetuses were expelled with or without membranes intact. Those heifers treated at 50 d of gestation appeared to expel very few fetuses (13%) and no signs of discomfort were observed. In other groups, fetal expulsion occurred in nearly all cases (64%, 100%, and 100% in heifers aborted at 75, 100, and 125 d, respectively; table 2). Most fetuses were found where the heifer had been lying, but actual expulsion wasn't witnessed. Signs of discomfort were not observed in heifers treated at 75 d, but nervousness, hyperactivity, and fence walking were common in heifers treated at 100 and 125 d of gestation. Only heifers in the 125 d group had retained membranes for more than 2 d (26.5%), and(or) detectable uterine infection (8%). Similar characteristics of fetal expulsion have been described by Day (1977). In prior

abortion studies, the intervals from prostaglandin injection to fetal expulsion have ranged from 48 to 168 h, with the average reported interval being 3.4 d (Lauderdale et al., 1972; Brand et al., 1975; Day, 1977; Ingrahm et al., 1978; Lindell et al., 1981; Refsal and Sequin, 1981). The interval to expulsion may be related to length of gestation at treatment (Ingrahm et al., 1978; Lindell et al., 1981). Heifers aborted between 39 and 71 d exhibited an interval to expulsion of 61.6 h; heifers aborted between 75 and 105 d exhibited an interval to expulsion of 96 h (Lindell et al., 1981); and heifers aborted between 102 and 146 d had an interval to abortion of 82 h (Ingrahm et al., 1978). Such a relationship was not detected in the current investigation.

Visible udder development was detected in 40.8% (20 of 49) of those heifers aborted near 125 d of gestation. Udder development was detected only in heifers aborted after 100 d. Enlargement of the mammary gland and teats has also been reported by Day (1977) in heifers aborted at 150 d or more of gestation. This development was also accompanied by secretion of an almost clear, watery fluid which was not detected in the current study. In heifers aborted between 50 and 160 d pregnant at treatment, 19% (31 of 164) exhibited slight to moderate development of udders (Copeland et al., 1978).

Changes in uterine tone and size were recorded during the first 3 wk after treatment. Abortion could be verified by palpation in all heifers 1 wk after injection. As day of gestation at treatment increased, more heifers had distended uteri during the first wk after prostaglandin administration (53%, 86%, 100%, and 100% for heifers aborted at 50, 75, 100, and 125 d, respectively; table 3). All groups exhibited a detectable decrease in uterine size during week two. At the conclusion of week three, 93% of the heifers aborted at 50 d had

TABLE 3. CLASSIFICATION OF UTERINE
INVOLUTION IN BEEF HEIFERS ABORTED
AT VARIOUS STAGES OF GESTATION

Day of gestation at injection	Week post-injection	Percent of heifers with distended uteri ¹
45-60	1	53.3
	2	40
	3	6.7
71-79	1	85.7
	2	50
	3	26.7
94-101	1	100
	2	84.6
	3	38.5
117-132	1	100
	2	95.9
	3	67

¹Percentage includes only heifers that aborted. A uterus was classified as distended if the enlargement due to a recent pregnancy could be detected at palpation; all others were classified as involuted.

completely involuted uteri, while 73%, 61%, and 33% of heifers aborted at 75, 100, and 125 d of gestation, respectively, had completely involuted uteri. Uterine scores given to heifers treated on day 125 demonstrated a gradual decrease over the 3 wk period after injection (wk 1, 3.98; wk 2, 2.55; wk 3, 1.94). Copeland et al. (1978) noted uteri were involuted by day 21, or by day 50 as described by Barth et al. (1981).

Initial weight at treatment was significantly different between treatment groups (table 4). Heifers aborted at 100 and 125 d were heavier than heifers aborted earlier in gestation as a result of the experimental design. All heifers were allotted to treatment after determined pregnant during the same breeding period. Thus, heifers were older and heavier as a result of being treated later in gestation. Weight gain 1 wk after abortion was similar for the 50, 75, and 100 d groups, but heifers in the 125 d group had a significant weight loss ($P<.001$). Although average daily gain (ADG) during the first 3 wk after abortion was significantly different between the 50 and 75 d groups, both were similar to ADG in heifers that were injected, but failed to abort (Table 4), indicating the different ADG was not associated with abortion. Weight gain was lower ($P<.001$) in heifers aborted at 100 d of gestation compared to heifers aborted earlier and those that failed to abort. Heifers treated at 125 d of pregnancy lost 0.11 kg/d during the 3 wk following treatment. The weight changes exhibited by all treatment groups were found to be related to length of the first estrous cycle exhibited after abortion ($P<.05$). However, this may be due to an interaction between cycle length and treatment group ($P<.5$). Heifers aborted later in gestation exhibited more short estrous cycles (<13 d) after abortion, and also had greater weight losses. Increased numbers of short estrous cycles and

TABLE 4. COMPARISON OF WEIGHT CHANGES IN BEEF HEIFERS ABORTED AT 50, 75, 100 OR 125 DAYS OF GESTATION

Item	Average day of gestation at treatment				Heifers not aborting
	50	75	100	125	
No. of heifers	15 ¹	14	13	49	12 ²
Initial weight (kg) ³	379.21 ^a	382.75 ^a	399.85 ^b	427.97 ^c	398.26 ^{ab}
Weight, 1 wk after treatment (kg) ³	387.51 ^a	392.77 ^{ab}	407.56 ^{bc}	415.91 ^c	408.69 ^{bc}
Wt. change 1 (kg) ³	8.44 ^a	10.02 ^a	7.71 ^a	-12.02 ^b	10.43 ^a
Weight, 3 wk after treatment (kg)	403.11	414.00	413.96	425.98	424.57
Total weight change (kg) ³	24.04 ^a	31.25 ^b	4.11 ^c	-1.98 ^d	26.31 ^{ab}
Avg. daily gain (kg/day) ³	1.14 ^a	1.49 ^b	.67 ^c	-.11 ^d	1.25 ^{ab}

¹Weights not collected for one heifer that did abort; therefore, data are based on 14 heifers.

²The 12 heifers are made up of two heifers that did not abort in the 50-day group, 4 in the 75-day group, 4 in the 100-day group, and 2 in the 125 day group.

³Values in the same row with no common superscripts differ (P<.001).

increased weight losses could both be a result of increased stage of gestation at treatment. These results concur with those reported by Horstman et al. (1982) in which heifers aborted between 45 and 120 d pregnant gained equal to the open controls during the first 15 d after treatment. In addition, Edwards and Laudert (1984) and Riley et al. (1983), reported that heifers aborted at greater than 120 or 138 d of gestation exhibited decreased gains to slaughter compared to heifers aborted early in gestation, pregnant controls, and open controls. After slaughter, when ADG was adjusted to the same carcass yield as open heifers, those heifers aborted late in gestation still expressed decreased gains. The weight loss could be attributed to the losses experienced at abortion which were detected in the current trial.

Data indicate that weight gains in heifers aborted up to 75 d of pregnancy are not effected and heifers show no side effects or detrimental effects on uterine involution. Reduction in weight gain and complications such as udder development, retained placentas, and uterine infections can be expected in heifers aborted after 100 d.

EXPERIMENT II
SHORT ESTROUS CYCLES AND ASSOCIATED SERUM PROGESTERONE
IN BEEF HEIFERS ABORTED
AT VARIOUS STAGES OF GESTATION

Summary

Estrous cycles were observed after abortion in crossbred Angus heifers that were injected with a prostaglandin analog at day 50 (15 heifers), 75 (14 heifers), 100 (13 heifers), or 125 (49 heifers) of gestation. The average interval from injection to first estrus was 3.6, 4.2, 3.7, and 6.4 d for heifers injected at 50, 75, 100, or 125 d of gestation, respectively. Cycles less than 13 d were classified as "short", those 13 to 16 d as "intermediate", those 16 to 24 d as "normal", and those greater than 24 d as "long". Heifers aborted at 50 d of gestation had seven short and eight normal first cycles; heifers aborted at 75 d of gestation had 11 short cycles, two normal cycles, and one long cycle; heifers aborted at 100 d of gestation had 12 short cycles and one normal cycle; whereas, heifers aborted at 125 d of gestation had 25 short cycles, 13 normal cycles, two long cycles, six intermediate cycles, and three heifers failed to exhibit a second estrus by 50 d after abortion. Of those heifers having short first cycles, short second cycles occurred in one of seven heifers aborted at day 50, three of 11 at day 75, seven of 12 at day 100, and 18 of 25 at day 125. Serum progesterone was measured at 0, 24, and 48 h after injection, and at 5 d and 10 d after the first exhibited estrus. Progesterone concentration declined before estrus, then increased by 5 d after estrus in all cases. Progesterone

concentration continued to increase between 5 and 10 d after estrus in heifers exhibiting normal estrous cycles, but decreased in heifers having short cycles. Data indicate that the percentage of heifers having short cycles after abortion increases as the length of gestation increases to 100 d, and the percentage of those heifers having two short cycles after abortion also increases.

Introduction

The most widely accepted technique to induce abortion in beef cattle is administration of prostaglandin F_2^α (PGF; Schultz and Copeland, 1981; Horstman et al., 1982). Previous data indicates that prostaglandins will effectively abort cattle up to 150 d of gestation (Lauderdale, 1972; Brand et al., 1975; Schultz and Copeland, 1981; Edwards and Laudert, 1984).

Prostaglandins have a rapid luteolytic effect which results in a short interval to abortion. Because exogenous prostaglandins are quickly metabolized, there is little interference with the endocrine system (Brand et al., 1975; Schultz and Copeland, 1981). The rapid decline in serum progesterone upon luteolysis enables a quick return to estrus after abortion with prostaglandin (Lauderdale, 1972; Brand et al., 1975; Day, 1977; Ingrahm et al., 1978; Lindell et al., 1981; Refsal and Sequin, 1981). The occurrence of ovulation at that estrus and the subsequent cyclicity of cattle have not been extensively investigated. Some researchers have noted short cycles (8-12 d) associated with the first estrus after abortion (Ingrahm et al., 1978; Lindell et al., 1981). None have reported the frequency of short cycles after abortion at specific stages of

gestation, the progesterone concentrations associated with those cycles, or the number of short cycles that occur before a normal luteal phase.

The present study was designed to observe cyclicity and serum progesterone concentrations associated with first estrus after abortion in heifers aborted with prostaglandins at various stages during the first 125 d of gestation.

Materials and Methods

One hundred three crossbred Angus heifers, verified pregnant by rectal palpation to known artificial insemination dates, were maintained in dry lots at Kansas State University. Heifers were fed a ration of sorghum silage and protein supplement calculated to meet NRC (1984) requirements for growing, medium frame heifers. Mineral blocks and water were available at all times.

Heifers were randomly allotted to be aborted an average of either 50, 75, 100, or 125 d of gestation. Animals were palpated again to reconfirm pregnancy just prior to an injection of prostaglandin. Seventeen, 18, and 17 pregnant heifers were injected im with 15 mg Luprostiol at 45 to 60 d, 71 to 79 d, and 94 to 101 d of gestation, respectively. On days 117 to 132 of gestation, three groups of 17 heifers each received either 15 mg Luprostiol im, 15 mg Luprostiol sc, or 2 mg fenprostelene sc. Beginning at injection, animals were observed twice daily for signs of estrus and(or) fetal expulsion. Observations for estrus continued until at least one normal cycle was exhibited or for 50 d after injection if estrus was not observed. Estrous cycles of less than 13 d were

classified as "short", those 13 to 16 d as "intermediate", those 16 to 24 d as "normal", and those more than 24 d as "long".

Blood samples were collected from all heifers by jugular venipuncture between 0600 and 0900 h at treatment, and 24 and 48 h after treatment. Additional samples were drawn 5 and 10 d after estrus or 9 and 14 d after injection in heifers which did not abort. Blood samples were collected in evacuated tubes, refrigerated, allowed to clot, and centrifuged within 6 h of collection. Serum was harvested and stored in plastic vials at -20°C until assayed for progesterone.

Serum progesterone was analyzed by radioimmunoassay and utilized methods previously described (Skaggs et al., 1986). Antiserum against progesterone-11-hemisuccinate:BSA was produced in rabbits. The antiserum cross-reacted with steroids as follows: progesterone, 1.00; 5 β -pregnanedione, 0.285; and 20 α -dihydroprogesterone, 20 β -dihydroprogesterone, 17 α -hydroxyprogesterone, pregnenolone, 5 α -pregnanedione, 5 α -pregnanediol, 5 β -pregnanediol, hydrocortisone, corticosterone, deoxycorticosterone, 21- α deoxycortisone, estradiol-17 α , estradiol-17 β , estrone, estriol, testosterone, and androstenedione, .001. A regression of concentrations determined from increasing volumes of a serum pool paralleled progesterone standards. After extraction of .1, .15, and .2 ml from one pool of estrus cows and from one pool of luteal-phase cows, the assay measured .49, .34, .40 ng/ml and 3.24, 3.34, 3.43 ng/ml, respectively. Progesterone was recovered quantitatively when added to serum (r=.99). Sensitivity of the assay was 25 pg/tube. Intra-assay coefficient of variation was 8.0%, and inter-assay coefficient of variation was 7.3%. In five assays 92.4% of

the progesterone in bovine serum was recovered during the extraction process, and corrections were made to account for the procedural loss that occurred.

Data concerning the incidence of short cycles and concentrations of serum progesterone were analyzed by the SAS (1982) General Linear Model procedure.

Results and Discussion

Estrous Cycles. Twelve heifers did not abort by 50 d after treatment; two were injected at 50 d, four at 75 d, four at 100 d, and two at 125 d. All heifers failing to abort had been injected with 15 mg Luprostiol im. In heifers that did abort, response after abortion did not differ due to prostaglandin analogue used or mode of administration. The interval from injection to first estrus in aborted heifers averaged 5.2 d. That interval was not different between treatment groups (table 5), and was not related to the length of the first estrous cycle after abortion. The average length of the first cycle tended to decrease as day of gestation at treatment increased through 100 d. A similar trend was detected in the average length of the second estrous cycle. However, this was masked in the heifers treated at 75 d of gestation as one heifer exhibited a long cycle (28.5 d).

The occurrence of short first cycles (<13 d) after abortion increased as day of gestation at treatment increased from 50 to 100 d (table 6; figure 2). The increasing percentage of heifers having short cycles explains the decreasing first cycle length trend noted in table 5. Heifers tended to have either short (<13 d) first cycles or normal (16 to 24 d) first cycles after abortion. As the percentage of short cycles increased, the average first cycle length decreased.

TABLE 5. ESTROUS CYCLES AFTER ABORTION AT VARIOUS STAGES OF GESTATION IN BEEF HEIFERS

Item	Average day of gestation at treatment			
	50	75	100	125
Number of heifers	15	14	13	49
Average interval from injection to estrus (days) ¹	3.6	4.2	3.7	6.4
Average first cycle length (days) ²	14.4 ^a	11.8 ^{ab}	8.8 ^b	13.4 ^{3a}
Average second cycle length (days) ²	17.7 ^{ab}	20.7 ^a	15.6 ^b	13.15 ^b

¹ Heifers observed at 12 h intervals.

² Values in same row with no common superscripts differ ($P < .05$).

TABLE 6. OCCURRENCE OF SHORT ESTROUS CYCLES IN ABORTED BEEF HEIFERS

Item	Average day of gestation at treatment			
	50	75	100	125
Number of heifers exhibiting: ¹				
Short first cycles	7 (46.7)	11 (78.6) ²	12 (92.3)	25 (51.0) ³
Normal first cycles	8 (53.3)	2 (14.3)	1 (7.7)	13 (26.5)
Repeated short cycles ⁴	1 (14.3)	3 (27.3)	7 (58.3)	18 (72.0) ⁵

¹Percentages in parenthesis.

²One heifer had a long cycle (28.5 days).

³Two heifers had long cycles (25, 32.5 days), 6 had abnormal cycles (13.5 to 15.5 days), and 3 didn't exhibit a second estrus.

⁴Number represents those exhibiting a second short cycle following an initial short cycle.

⁵Nine additional heifers exhibited short second cycles after an initial cycle that wasn't short.

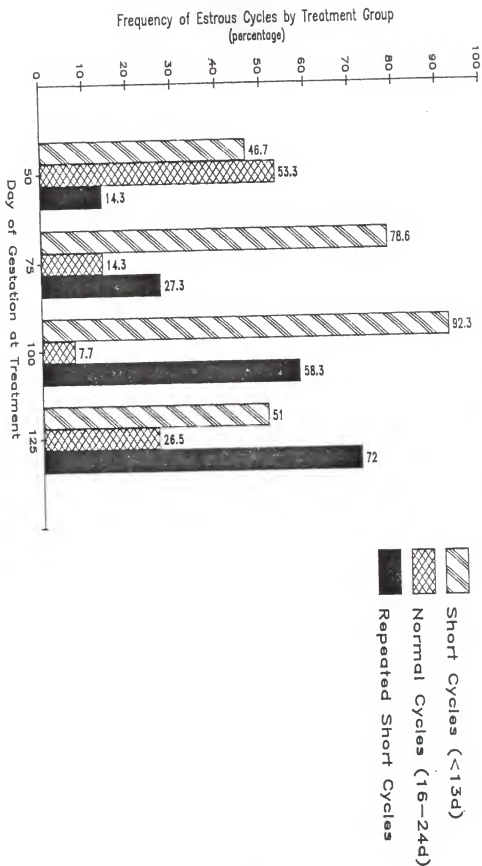


Figure 2: Percentages of aborted heifers with short or normal first estrous cycles and the percentage that had short first and second estrous cycles (repeated short estrous cycles) at various stages of gestation.

In addition, there were also more heifers that had repeated short cycles as day of gestation at abortion increased (table 6; figure 2). This explains the decreasing second cycle length trend seen in table 5.

To further analyze estrous cycle data, heifers of like first cycle classifications were compared across treatment groups. No significant differences in average weight at treatment, interval to first estrus, average second cycle length, or serum progesterone concentrations associated with the first estrus after abortion could be attributed to stage of gestation at treatment. Thus, heifers were pooled according to the type of initial estrous cycle that was exhibited after abortion and further analyzed.

In the 91 heifers that aborted, 60.4% exhibited a short first estrous cycle, 29.7% had a normal first estrous cycle, 3.3% had a long first estrous cycle, and 6.6% had an intermediate first cycle (8.5 d, 19.8 d, 28.7 d, and 15 d, respectively; table 7).

The most frequently observed short estrous cycles were between 7 and 9.5 d long, with the mode being 8 d (figure 3). In postpartum anestrous beef cows, similar short cycles have been observed after ovulation induced by weaning calves (Odde et al., 1980), injecting human chorionic gonadotropin (Pratt et al., 1982; Garcia-Winder et al., 1986), and injecting gonadotropin releasing hormone (Lishman et al., 1979).

Serum Progesterone. Serum progesterone concentration at 0, 24, and 48 h after injection was used as an indication of corpus luteum (CL) regression. Observation of an expelled fetus or fetal membranes was used as a positive indication of abortion. Abortion was verified via rectal palpation, estrus, and

TABLE 7. CHARACTERISTICS OF HEIFERS BY CYCLE CLASSIFICATION

Item	Classification of first estrous cycle after abortion ¹			
	Short	Normal	Long	Intermediate
Number of heifers ²	55 (60.4) ³	27 (29.7)	3 (3.3)	6 (6.6)
Average weight (lb)	888.4	891.1	954.5	987
Interval from injection to estrus (days) ⁴	3.9	3.4	3.2	3.6
Average first cycle length ⁵	8.5 ^a	19.8 ^b	28.7 ^c	15 ^b
Average second cycle length	14.8	17.5	14.8	13.3

¹Cycles less than 13 d are classified "short", those 16 to 24 d "normal", those greater than 24 d "long", and those 13 to 16 d "intermediate."

²Three heifers that didn't exhibit estrus cycles are not included.

³Percentages are in parenthesis.

⁴Heifers observed at 12 hour intervals.

⁵Values in row with no common superscripts differ ($P < .001$).

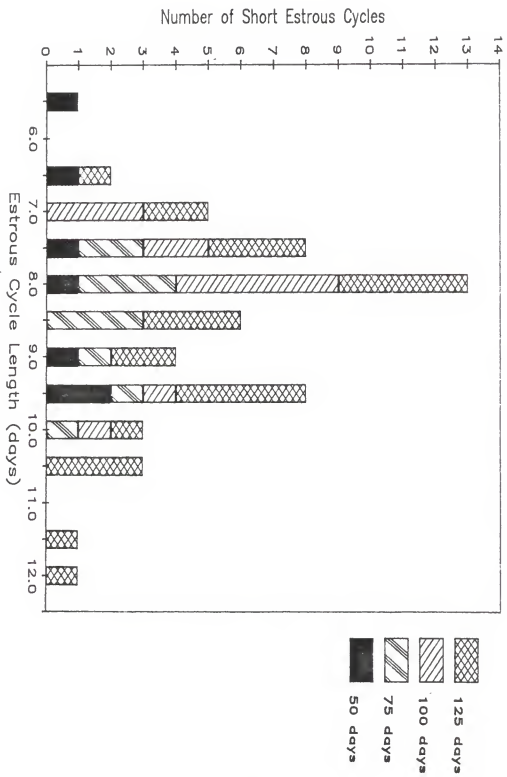


Figure 3: Occurrence of short estrous cycles in beef heifers aborted at 50, 75, 100, or 125 days of gestation.

progesterone concentrations < 1.0 ng/ml 48 h after injection. Progesterone levels 5 d after estrus were used as an indication of ovulation and luteal tissue formation. The level of progesterone 10 d after estrus was used as an indication of luteal maintenance or regression. Decreased progesterone 10 d after estrus compared to progesterone 5 d after estrus would be indicative of a short-lived CL. Increased progesterone would be indicative of luteal maintenance.

One heifer exhibiting a long estrous cycle had been injected at 75 d of gestation, and two had been injected at 125 d of gestation. Serum progesterone concentrations suggest that each of those heifers experienced a short luteal phase followed by a normal luteal phase. The three heifers did exhibit hyperactivity at times when estrus would have been expected if a short luteal phase had occurred. Progesterone profiles of the three heifers having long estrous cycles are similar to the profiles of heifers having short estrous cycles. Apparently the heifers failed to exhibit estrus after a short luteal phase, or estrus wasn't detected.

All six heifers that had intermediate cycles were in the 125 d treatment group. Three of those heifers had retained fetal membranes for more than 2 d. Serum progesterone had declined to less than 1 ng/ml by 48 h after injection in all six heifers. Progesterone concentration increased to 0.9 ng/ml by 5 d after estrus and was near this level at 10 d after estrus. In cycling beef cows, uterine infection has been shown to extend luteal life span. It is possible that retained membranes and(or) uterine infection delayed CL regression in heifers with intermediate cycles thereby preventing the typical 7 to 12 d short cycle.

Average serum progesterone concentrations ranged from 3.6 to 5.9 ng/ml at time of treatment (table 8; figure 4). Although not significant, those heifers not aborting tended to have higher serum progesterone at the time of injection. Twenty-four hours after injection, progesterone had declined in all heifers by approximately 4 ng/ml. This decline continued to 48 h after injection in all heifers except in those failing to abort. Serum progesterone concentrations had increased by 5 d after estrus compared to 48 h after injection in all groups (tables 8 and 9; figure 4). This increase continued to 10 d after estrus in heifers exhibiting normal cycles. However, heifers having short cycles had decreased progesterone concentrations at 10 d after estrus compared to 5 d after estrus (table 9; figure 4). The heifers that didn't abort maintained serum progesterone concentrations greater than 2 ng/ml throughout the sampling period.

Serum progesterone profiles indicate that luteal tissue developed that was capable of secreting progesterone after the first estrus post-abortion, and the secretion profile appears similar to that associated with short luteal phases observed in postpartum cows. In postpartum cows, progesterone was also detectable by 5 d after estrus or ovulation, but decreased by 10 d after estrus (McNeilly et al., 1981; Ramirez-Godinez et al., 1981; Manns et al., 1983; O'Shea et al., 1984).

The characteristics of the short estrous cycle in the aborted beef heifer are very similar to short estrous cycles in the postpartum anestrous beef cow induced to ovulate. The most frequently observed short cycle after abortion was 8 d in length; the same as observed in the postpartum cow (Odde et al., 1980). Serum progesterone profiles in both models are also similar. In each case,

TABLE 8. AVERAGE SERUM PROGESTERONE LEVELS (NG/ML) AFTER INJECTION OF PROSTAGLANDIN F_2 TO PREGNANT BEEF HEIFERS CLASSIFIED BY THEIR SUBSEQUENT CYCLE LENGTH

Cycle classification ¹	Time (days after injection)		
	0	1 ²	2 ²
Short	4.9 \pm .2 ^{ab}	1.3 \pm .1 ^a	.7 \pm .1 ^a
Normal	5.1 \pm .5 ^{ab}	1.1 \pm .2 ^a	.6 \pm .1 ^a
Long	4.5 \pm 1.3 ^{ab}	1.3 \pm .4 ^a	.6 \pm .4 ^a
Intermediate	3.6 \pm .6 ^b	1.2 \pm .2 ^a	.8 \pm .1 ^b
Not aborted	5.9 \pm .5 ^a	2.2 \pm .2 ^b	2.2 \pm .1 ^b

¹Cycles less than 13 d are classified "short", those 16 to 24 d "normal", those greater than 24 d "long" and those 13 to 16 d "abnormal".

²Values in columns with no common superscripts differ ($P < .005$).

TABLE 9. AVERAGE SERUM PROGESTERONE LEVELS (NG/ML) DURING THE FIRST ESTROUS CYCLE AFTER ABORTION IN BEEF HEIFERS

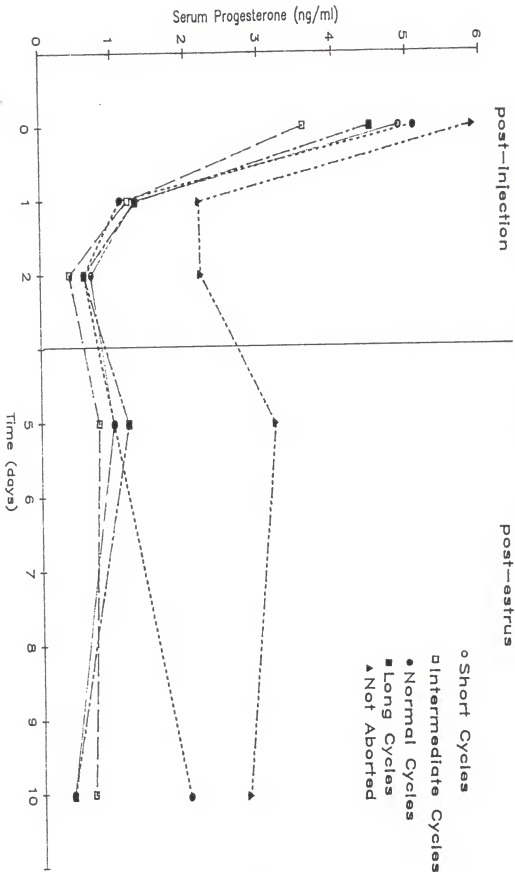
Cycle classification ¹	Time (days post-estrus)	
	5 ²	10 ²
Short	1.0 \pm .1 ^a	0.4 \pm .1 ^a
Normal	1.0 \pm .3 ^a	2.0 \pm .2 ^b
Long	1.2 \pm .1 ^a	0.4 \pm .6 ^a
Intermediate	0.8 \pm .3 ^a	0.7 \pm .3 ^a
Not Aborted ³	3.2 \pm .3 ^b	2.8 \pm .3 ^c

¹Cycles less than 13 d are classified "short", those 16 to 24 d "normal", those greater than 24 d "long", and those 13 to 16 d "intermediate".

²Values in columns with no common superscripts differ (P<.005).

³Blood collected 9 and 14 d post-injection.

Figure 4: Serum progesterone concentrations after PGF injection in pregnant beef heifers.



progesterone increased by 5 d after estrus, and decreased by 10 d after estrus. The frequency and length of short estrous cycles after abortion were predictable, suggesting the short cycles are a normal physiological phenomenon. The similarities in short estrous cycles between the aborted beef heifer and the postpartum cow suggest that the mechanism inducing early luteal regression is the same in both models.

Several reasons for early regression of the CL have been proposed: 1) inadequate preovulatory follicular development, 2) lack of a sufficient luteotropin during the luteal phase, 3) failure of luteal tissue to recognize a luteotropin, 4) premature release of a luteolysin, and(or) 5) increased sensitivity of luteal tissue to a luteolytic factor (Odde et al., 1980; Garverick and Smith, 1986). Considerable support can be cited for each of those possible mechanisms (see review by Garverick and Smith, 1986).

Only two experimental methods have effectively prevented the short luteal phase in postpartum cows: 1) hysterectomy (Copelin et al., 1985; Copelin et al., 1986), and 2) progestogen pretreatment prior to ovulation (Ramirez-Godinez et al., 1981; Pratt et al., 1982; Troxel Kesler, 1983; Garcia-Winder et al., 1986). Current investigations suggest that removal of the uterus does prevent early regression of the developing CL, establishing that the short luteal phase is at least in part due to release of a luteolytic factor from the uterus. In the aborted heifer, the uterus could be producing high levels of PGF (Lindell et al., 1981) as does the uterus of the postpartum cow (Manns et al., 1983; Madej et al., 1984; Troxel and Kesler, 1984a). The occurrence of short luteal phases and repeated short cycles increased as day of gestation at abortion increased. It is

possible that as gestation progresses and the uterus increases in size due to conceptus growth, more PGF is produced and for a longer period of time after abortion.

The mechanism whereby pretreatment with progesterone in postpartum cows prevents early demise of the CL has been extensively investigated. If the cause of early luteal regression is a premature release of a prostaglandin from the uterus, it would appear that progesterone pretreatment may play a role in controlling this release. In the aborted heifer, there would be no lack of prior progesterone. However, secretion of PGF from the uterus may be too active to be regulated by progesterone immediately after abortion. In heifers aborted later in gestation, more PGF may be released and for longer periods of time due to increased uterine distention. When PGF levels decline to levels that can be regulated by progesterone, the short cycles would no longer occur, and normal cyclicity should ensue. The same may be true for the nursed beef cow. If the postpartum nursed beef cow ovulated shortly after parturition, she may have repeated short cycles until active prostaglandin secretion from the uterus is decreased enough to be regulated by progesterone. Further research is needed to determine if progesterone plays a role in regulating the release of PGF from the uterus before a normal luteal phase can occur.

Heifers aborted with a PGF analog between 50 and 125 d of gestation exhibited a high percentage (60.4) of short cycles immediately after abortion. The percentage of heifers experiencing short cycles increased as day of gestation at treatment increased up to 100 d of pregnancy. The number of repeated short cycles also increased as day of gestation at treatment increased.

Serum progesterone profiles indicate that luteal tissue capable of secreting progesterone after the first estrus post-abortion does develop, but luteal regression occurs by 10 d after estrus in heifers having short cycles.

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Appendix

<u>Date</u>	<u>Ration</u>
09-01/09-30	39.5 lb. silage 3.5 lb. AMCY supplement
10-01/11-06	41.0 lb. silage 3.5 lb. AMCY supplement
11-07/11-18	30.0 lb. silage 11.0 lb. rolled milo 1.5 lb. AMCY supplement
11-19/11-22	21.0 lb. silage 13.0 lb. rolled milo 1.3 lb. AMCY supplement
11-23/11-30	14.0 lb. silage 16.0 lb. rolled milo 1.3 lb. AMCY supplement

AMCY Supplement

57.5% soybean meal
31.6% rolled milo
5.0% dicalcium
2.5% limestone
2.0% salt
1.0% tallow
0.3% Z-10 trace mineral
0.2% Vitamin A (30,000 IU/g)

THE OCCURRENCE OF SHORT ESTROUS CYCLES AFTER PROSTAGLANDIN
INDUCED ABORTION AT VARIOUS STAGES OF GESTATION

by

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Abstract

Estrous cycles, weight changes, and other physiological responses were observed in heifers aborted with a prostaglandin analog at 50, 75, 100, or 125 d of gestation. Serum progesterone concentration after prostaglandin injection and during the first estrous cycle after abortion was also measured.

One hundred three crossbred Angus beef heifers with known conception dates were injected with a prostaglandin analogue on day 50 (n=17), 75 (n=18), 100 (n=17), or 125 (n=51) of gestation. Heifers were observed twice daily for estrus and other physiological changes associated with abortion. Cycles less than 13 d were classified as "short", those 13 to 16 d as "intermediate", those 16 to 24 d as "normal" and those greater than 24 d as "long". Heifers were palpated once weekly to measure changes in uterine tone and size. Animals were weighed at treatment and 1 and 3 wk after prostaglandin administration. Serum samples collected at injection, 24 and 48 h after treatment, and 5 and 10 d after the first observed estrus were analyzed for progesterone.

Twelve heifers did not abort by 50 d after prostaglandin administration. Two of those were heifers injected at 50 d of gestation, four at 75 d, four at 100 d, and two at 125 d. No differences in abortion rate were related to weight at treatment or day of gestation at treatment. The average interval from injection to estrus was 5.2 d, and fetuses were expelled by 6 d after injection. Uterine involution was more rapid in heifers aborted earlier in gestation. There was more udder development, vaginal discharge, and retained membranes in heifers aborted later in gestation. Growth was not altered in heifers aborting at 50 or 75 d of gestation when compared to heifers which failed to abort (1.13, 1.50, and 1.27 kg/d, respectively). Heifers aborted at 100 d of gestation experienced a decreased growth rate (.67 kg/d), but no retained membranes, uterine infection, or signs of discomfort were observed. Those

aborted at 125 d of gestation lost weight during the first 3 wk after abortion (-.11 kg/d). No heifers in the 50-, 75- or 100-d groups had uterine infections or retained membranes for more than 2 d. In the 125-d group, 26.6% had retained membranes and 8% had detectable uterine infection.

The percentage of heifers having short estrous cycles after abortion increased as length of gestation increased to 100 d (46.7%, 78.6%, 92.3%, and 51% for heifers aborted at 50, 75, 100, and 125 d, respectively.) The percentage of heifers having a second short cycle after an initial short cycle also increased with day of gestation at treatment. Progesterone concentration declined before estrus, then increased by 5 d after estrus in all cases. Progesterone concentration continued to increase between 5 and 10 d after estrus in heifers exhibiting normal estrous cycles, but decreased in heifers having short cycles.