Reproductive efficiency is the most important factor impacting the economics of a cow calf operation. The economic value of reproduction for commercial beef producers was reported to be five times greater than calf growth (Trenkle and Willham, 1977). Maximizing reproductive efficiency depends upon the successful completion of the following events: a heifer must reach puberty before the start of the breeding season, conceive early in the breeding season, calve unassisted, raise the calf to the time it is marketed, and the heifer/cow must conceive in time to calve early during the subsequent calving season. Any interruption in the preceding cycle will constitute reproductive loss, which is estimated to cost the US beef industry around $500 million annually (Bellows et al., 2002). Therefore, minimizing reproductive loss needs to be a high priority.

Recent years have witnessed the rapid development of technologies utilized to increase reproductive efficiency and(or) improve the genetic merit of a herd. Some of these technologies include: estrous synchronization, artificial insemination, gender-selected semen, in vitro embryo production, embryo transfer, ultrasonography, transgenics, and cloning. Of the preceding reproductive technologies, estrous synchronization and artificial insemination are among the most powerful and applicable technologies for genetic improvement of beef herds (Seidel, 1995). The development of new and improved methods of synchronizing estrus and ovulation depends on our understanding of the physiological and hormonal mechanisms controlling the estrous cycle and the initiation of estrous cyclicity in prepubertal heifers and postpartum cows. Although estrous synchronization products and protocols have changed over time, the basic physiological principles underlying how these products work have not. An understanding of the bovine estrous cycle and how estrous synchronization products work will facilitate the application of these technologies in groups of cycling and anestrous females. This article reviews the endocrine regulation of the estrous cycle with specific emphasis on the regulation of growth of a dominant follicle and the lifespan of the corpus luteum. In addition, emphasis will be given to estrous synchronization products that are commercially available, and the physiologic mechanisms by which these products synchronize estrus and(or) ovulation in cattle.

**Principles of the Bovine Estrous Cycle**

*Characteristics of the Estrous Cycle*

In cattle, the estrous cycle normally varies from 17 to 24 days and the duration of estrus is generally 10 to 18 hrs; however, considerable variation exists among individual animals (range <
8 to > 30 hr; O’Connor and Senger, 1997). The primary sign of estrus in cattle is standing to be mounted and secondary signs of estrus include frequent mounting, watery mucus from the vulva, and restlessness. There are a number of estrous detection aids available to assist producers including pressure mount detectors, tail chalk/paint, androgenized cows, and teaser bulls (rendered sterile by vasectomy, epididectomy, and(or) penile deviation). However, the HeatWatch electronic estrous detection system is the most effective estrous detection aid and provides precise information on the onset, intensity, and duration of estrus. Rorie et al., (2002) utilized the HeatWatch system with 500 Angus cows to evaluate the effect of the intensity of estrus on pregnancy rate. Estrus was synchronized with the Select Synch protocol (Gonadotropin releasing hormone [GnRH] followed seven days later with an injection of prostaglandin F$_{2\alpha}$). Length of estrus ranged from 0.5 to 24 hr and there was no effect of length of estrus on pregnancy status. However, cows that became pregnant were mounted more times per estrus than cows that did not conceive. These data are similar to another study with Angus cows in which cows that became pregnant were mounted more times per estrus than cows that did not become pregnant (Kuhlman et al., 1998).

A seasonal effect on estrous behavior has been reported in Angus x Hereford cows located in Oklahoma (White et al., 2002). In the preceding study, the length of estrus was greater in summer compared to winter or spring; however, cows were mounted more frequently per estrus in winter compared to summer or spring. Therefore, estrous detection may need to occur more frequently in winter compared to spring or summer; whereas, in summer estrous detection may need to occur for a longer duration at each check. In this study, there was no effect of season on the interval from the onset of estrus to ovulation (Mean = 31 hr). In Florida, an increase in the temperature-humidity index (THI) decreased the number of mounts per estrus (Landaeta-Hernandez et al., 2002).

The number of mounts per estrus increases as the number of females in estrus increases (Helmer and Britt, 1985; Landaeta-Hernandez et al., 2002). This is likely due to the formation of sexually active groups of cattle which is known to increase the number of mounts per female (Hurnick et al., 1975; Galina et al., 1994). In nonsynchronized cattle there will be fewer sexually active groups (or fewer animals per group) and less mounting activity. Therefore, improved estrous detection efficiency is an advantage of an estrous synchronization program. However, it is also true that frequent animal handling and restraint are stressors (Dobson and Kamonpatana, 1986) and that increased handling and restraint of heifers during a synchronized estrus decreased the number of mounts per estrus (Lemaster et al., 1999). Depending upon the estrous synchronization protocol, a fixed-time insemination protocol should reduce the amount of animal handling associated with sorting estrual heifers at the time of insemination.

In contrast to other livestock species, cattle ovulate following the end of estrus (approximately 28 to 32 hr after the onset of estrus or 12 to 20 hr following the end of estrus). Although characteristics of the estrous cycle are similar among most beef breeds, important differences have been reported between Bos Taurus and Bos Indicus breeds (Galina et al., 1987; Inskeep et al., 1982). In general, it is more difficult to detect estrus in Bos Indicus females compared to Bos Taurus females. This is likely because Bos Indicus females are reported to have a shorter duration of behavioral estrus compared to Bos Taurus females (Brewester and Cole, 1941; Plasse et al., 1970). In addition, Bos Indicus females had a decreased interval from onset of estrus to...
ovulation (Randel, 1976), decreased magnitude of the preovulatory luteinizing hormone surge (Randel, 1976), smaller corpora lutea (Irvin et al., 1978), and lower luteal phase concentrations of progesterone (Adeyemo and Heath, 1980) than Bos Taurus females.

Hormonal Patterns During the Estrous Cycle

The estrous cycle is divided into three stages (follicular phase, estrus, and luteal phase) and is regulated by hormones secreted by the hypothalamus (GnRH), anterior pituitary gland (follicle stimulating hormone [FSH] and luteinizing hormone [LH]), ovary (estradiol and progesterone), and uterus (prostaglandin F$_2$α [PGF$_{2\alpha}$]). The preceding hormones serve as chemical messengers that travel in the blood to specific target tissues which contain receptors that are hormone specific and regulate the phases of the estrous cycle. The combination of hormone secretion and metabolism (liver, kidneys, and lungs) maintain the correct hormonal balance during the follicular phase, estrus, and luteal phase of the cycle. For a list of hormones, their biological functions, their role in estrous synchronization, and product names see Table 1.

A preovulatory follicle and the subsequently formed corpus luteum are the two primary ovarian structures that regulate the estrous cycle through secretion of estradiol and progesterone, respectively. Changes in a preovulatory follicle and corpus luteum, patterns of secretion of LH, estradiol and progesterone, and changes in ovarian blood flow during the ruminant estrous cycle are depicted in Figure 1.

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Figure 1. Changes in ovarian structures (preovulatory follicle and corpus luteum), hormones (luteinizing hormone, estradiol, and progesterone) and ovarian blood flow (ovary containing [luteal ovary] or not containing [nonluteal ovary] a corpus luteum) during the three phases of the estrous cycle (follicular, estrus, and luteal phase; Modified from Garverick and Smith, 1993).
**Follicular Phase**

The follicular phase (proestrus) begins with the initiation of corpus luteum regression (luteolysis) and ends with the onset of estrus. Luteolysis is accompanied by a rapid decrease in progesterone resulting in a decrease in the negative feedback on pituitary LH secretion. As circulating concentrations of progesterone decrease, LH pulse frequency increases followed by a rapid increase in follicular estradiol secretion. The production of follicular estradiol results from the coordinated actions of LH and FSH on theca and granulosa cells, respectively (Fortune, 1986; Fortune and Quirk, 1988). The follicle wall consists of two distinct cell layers (granulosa and thecal cells) that are separated by a basement membrane. Granulosa cells are located in the compartment with the oocyte; whereas, theca cells surround the granulosa cells and are in close association with a wreath of capillaries. Theca cells have membrane receptors that bind LH resulting in the synthesis of androgens that subsequently diffuse through the basement membrane into granulosa cells. Following FSH binding to membrane receptors on granulosa cells there is an increase in aromatase activity, that converts androgens to estradiol. Increased circulating concentrations of estradiol initiate estrous behavior and induce the preovulatory gonadotropin surge, which is essential for ovulation. In addition, estradiol can act within granulosa cells to increase LH receptor concentration and thereby prepare the preovulatory follicle to respond to the gonadotropin surge (Richards, 1980).

**Regulation of Follicular Waves**: Two general patterns of antral follicular development are present in mammals. In cattle, sheep, and horses, dominant ovulatory sized follicles develop in sequential waves during both the follicular and luteal phases of the cycle. In primates, pigs, and rodents, however, dominant ovulatory follicles only develop during the follicular phase of the cycle (Fortune, 1994). The bovine estrous cycle usually consists of two to three follicular waves and each wave begins with the recruitment of a cohort of antral follicles from a pool of growing small follicles. One follicle is subsequently selected from this cohort for continued growth and becomes dominant. The remaining follicles in the cohort become atretic. During a nonovulatory follicular wave, the dominant follicle eventually becomes atretic and a new follicular wave is initiated. A viable dominant follicle present at luteolysis will generally become the ovulatory follicle (Adams, 1999). The estrous cycle length of cows that have three follicular waves is generally longer (20-24 days) compared to cows with two follicular waves (18-20 days).

In cattle, follicular waves can be detected during most reproductive states including the prepubertal period, estrous cycle, gestation, and postpartum anestrous period (Adams, 1999). The only exception to the continuous growth and development of follicular waves in cattle is during the last 21 days of gestation. During this time follicles greater than 6 mm in diameter have not been detected (Ginther et al., 1996a). Following parturition, follicular waves resumed following a rise in circulating concentrations of FSH (Schallenberger and Prokopp, 1985), and the first dominant follicle appeared between days 7 and 15 postpartum in both beef and dairy cows (Murphy et al., 1990; Crowe et al., 1993).

Follicular waves have been studied most extensively in cattle and consist of the following three stages: recruitment, selection, and dominance.
<table>
<thead>
<tr>
<th>Hormone</th>
<th>Endocrine Gland</th>
<th>Function of Hormone</th>
<th>Biological Action in Estrous Sync.</th>
<th>Product Name</th>
<th>Dosage</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>Corpus luteum</td>
<td>Inhibit estrus</td>
<td>Inhibit estrus</td>
<td>Melengestrol Acetate (MGA®)</td>
<td>0.5 mg/hd/day</td>
<td>Feed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibit ovulation</td>
<td>Inhibit ovulation</td>
<td>EAZI-BREED CIDR®</td>
<td>1 CIDR per animal (1.38 g prog)</td>
<td>Vaginal insert</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prepares animal for pregnancy</td>
<td>Induce cyclicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance of pregnancy</td>
<td>Dominant follicle turnover</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Prostaglandin F₂α</td>
<td>Uterus</td>
<td>Induce luteal regression</td>
<td>Induce premature luteal regression</td>
<td>Lutalyse®</td>
<td>5 ml</td>
<td>im inject</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ProstaMate®</td>
<td>5 ml</td>
<td>im inject</td>
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<td></td>
<td></td>
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<td></td>
<td>In Synch®</td>
<td>5 ml</td>
<td>im inject</td>
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<td></td>
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<td></td>
<td></td>
<td>Estrumate®</td>
<td>2 ml</td>
<td>im inject</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>estroPLAN®</td>
<td>2 ml</td>
<td>im inject</td>
</tr>
<tr>
<td>GnRH</td>
<td>Hypothalamus</td>
<td>Controls secretion of LH</td>
<td>Synchronize follicle wave</td>
<td>Cystorelin®</td>
<td>2 ml</td>
<td>im inject</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induces gonadotropin surge</td>
<td>Induce ovulation</td>
<td>Factryl®</td>
<td>2 ml</td>
<td>im inject</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fertagyl®</td>
<td>2 ml</td>
<td>im inject</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OvaCyst®</td>
<td>2 ml</td>
<td>im inject</td>
</tr>
<tr>
<td>Follicle Stimulating Hormone (FSH)</td>
<td>Anterior Pituitary Gland</td>
<td>Initiation of a follicular wave</td>
<td>Superovulation</td>
<td>Follitropin®</td>
<td>Depends on application</td>
<td>im inject</td>
</tr>
<tr>
<td>Luteinizing Hormone (LH)</td>
<td>Anterior Pituitary Gland</td>
<td>Stimulated by GnRH</td>
<td>Synchronize follicular wave</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Ovarian follicle</td>
<td>Estrous behavior</td>
<td>Dominant follicle turnover</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

GnRH = gonadotropin releasing hormone; prog = progesterone; N/A = not applicable
Recruitment. Recruitment of a cohort of follicles, around 3 mm in diameter, is stimulated on each ovary by a transient rise in FSH (Figure 2). Inhibition of both FSH and LH arrested follicular growth at 2 to 4 mm, however, when physiological levels of FSH were infused for 48 hr follicular growth from 5 to 8 mm was stimulated (Gong et al., 1996). The peak concentration of FSH occurred when the future dominant follicle attained a mean diameter of approximately 4 mm, after which concentrations of FSH declined (Figure 2; Ginther et al., 1996b), and were at basal concentrations by the time follicular selection occurred (Ginther et al., 2000a). The mechanism responsible for the initial decline in FSH concentration is unknown, however, estradiol and inhibin are follicular products that probably play a major role in the decline of FSH (Adams, 1999).

Selection. Follicular selection is the process by which a single follicle from the recruited cohort is selected to continue to grow and become dominant, while the remaining follicles of the cohort undergo atresia. With the decline in circulating FSH concentrations, small follicles are presumably unable to continue growth and the selected follicle (dominant follicle) may shift its dependency from FSH to LH (Ginther et al., 1996b). The decreased circulating concentrations of FSH at the time of selection are likely important for the selection of a single dominant follicle (Figure 2). The decline in circulating concentrations of FSH is presumably driven by increasing concentrations of estradiol (and perhaps inhibin) produced by the cohort of recruited follicles (Ginther et al., 2000b). Increased concentrations of estradiol and inhibin may feed back on the hypothalamic-pituitary axis to selectively suppress FSH secretion (Martin et al., 1988). At follicular deviation, the selected follicle continues to grow while the subordinate follicles enter atresia (Ginther et al., 1996b). In cattle, deviation usually occurs when the largest follicle reaches a diameter of approximately 8 mm, approximately 2.7 days after the initiation of a follicular wave (Ginther et al., 1997; Ginther et al., 1999) or 61 hr after the LH surge (Kulick et al., 1999).

Dominance. The dominance phase of the follicular wave occurs when a follicle has been selected and continues to grow at a faster rate than the largest subordinate follicle, and inhibits the emergence of a new follicular wave (Ginther et al., 1996b). Following selection and establishment of a dominant follicle, follicular recruitment is inhibited until dominance is lost or ovulation occurs. Inhibition of follicular recruitment may be mediated by inhibiting the transient rise in circulating concentrations of FSH (Adams, 1999). An alternative hypothesis is that the dominant follicle directly inhibits growth of small follicles through the secretion of a factor(s) that acts directly on other follicles in the ovary. Regardless of the mechanism, destruction or ovulation of a dominant follicle results in a transient rise in circulating concentrations of FSH and subsequent initiation of a new follicular wave (Adams et al., 1992).

Estrous Phase
Increasing circulating concentrations of estradiol following luteolysis initiate estrous behavior, increase uterine contractions (facilitate sperm transport), and induce the preovulatory gonadotropin surge. The preovulatory gonadotropin surge coordinates the following events that are critical to the establishment of pregnancy: resumption of meiosis within the oocyte, follicular rupture, and luteinization of follicular cells. LH is generally considered to be the primary gonadotropin that controls the preceding events; however, FSH also has been shown to cause ovulation and luteal tissue formation (Galway et al., 1990). The end of the estrus phase of the
cycle is marked by follicular rupture, which is the culmination of a complex cascade of events leading to the activation of proteolytic enzymes that digest the follicular wall and allows the egg (oocyte) to be released for fertilization. This process is similar to mechanisms associated with inflammation. Injection of GnRH will induce a surge of LH within 2 to 4 hr and ovulation of a dominant follicle will occur 24 to 36 hr after injection.

Estrus and ovulation are not always linked and frequently occur as independent events. The incidence of anovulatory estrus in peripuberal heifers was 22% and 13% for years 1 and 2, respectively and this phenomenon has been called nonpuberal estrus (Nelsen et al., 1985; Rutter and Randel, 1986). The incidence of nonpuberal estrus may be affected by age, breed, and photoperiod or season of the year (Nelsen et al., 1985). Formation of a cystic follicle can also result in estrous behavior without ovulation; however, the incidence of cystic follicles is low in beef cattle. Cystic follicles are normally treated by injecting GnRH, to luteinize the follicular tissue followed by an injection of PGF$_2\alpha$ 7 days later to regress the luteal tissue.

Alternatively, ovulation without estrus is not uncommon in beef cattle. The first ovulatory estrus in heifers and postpartum cows is preceded by a transient increase in progesterone (short luteal phase; Gonzalez-Padilla et al., 1975). This is presumably due to ovulation without estrus. Increased concentrations of progesterone may be involved in preparation of the uterus for the possibility of pregnancy or in the establishment of patterns of gonadotropin secretion characteristic of cycling females. Short-term exposure of prepuberal heifers or anestrous postpartum beef cows to a progestin (Melengestrol Acetate [MGA] or Controlled Internal Drug Release [CIDR]) has been used extensively in estrous synchronization protocols to mimic this short period of progesterone exposure and will be discussed in more detail later.

**Luteal Phase**

The luteal phase spans the time of corpus luteum formation and maintenance which begins with ovulation and ends with luteolysis. Progesterone is the primary secretory product of the corpus luteum and is regulated by secretions of the anterior pituitary, uterus, ovary, and embryo (Niswender et al., 1976). The regulation of progesterone secretion is likely controlled by a balance of luteotropic (stimulate progesterone) and luteolytic (inhibit progesterone) stimuli, given that both types of stimuli are secreted concurrently during the estrous cycle. In ruminants, LH is considered to be the primary luteotropic hormone and concentration of luteal LH receptors is positively correlated with changes in progesterone and luteal growth (Niswender et al., 2000). Corpora lutea receive the majority of the ovarian blood flow (Figure 2) and blood flow to the luteal ovary and progesterone secretion are highly correlated (Niswender et al., 1976). Progesterone has a central role in the regulation of the estrous cycle as it determines estrous cycle length and is required for the maintenance of pregnancy.

In cattle, PGF$_2\alpha$ is the uterine luteolysin and is commonly used to synchronize estrus in cattle. In the absence of an embryo, the uterine concentrations of PGF$_2\alpha$ increase during the late luteal phase and PGF$_2\alpha$ is secreted as pulses into the uterine veins on days 17 to 20 following estrus (Figure 4; day 0 = estrus; Inskeep and Murdoch, 1980). PGF$_2\alpha$ is transported from the utero-ovarian vein into the ovarian artery via a counter-current transfer mechanism (Hixon and Hansel, 1974; McCracken et al., 1972) and is transported to the corpus luteum. PGF$_2\alpha$ may have both a direct and an indirect effect on a ruminant corpus luteum to cause luteolysis. In the presence of
an embryo, pulsatile secretion of PGF$_{2\alpha}$ is reduced and the corpus luteum does not regress. Maintenance of high circulating concentrations of progesterone in pregnant animals prevents the expression of estrus and ovulation.

**Follicular Determinants of Corpus Luteum Function**

Corpora lutea are a continuation of follicular maturation; consequently, changes in the hormonal stimulation of a preovulatory follicle may have a subsequent effect on luteal progesterone secretion. The endocrine microenvironment of a preovulatory follicle is unique relative to surrounding nonovulatory follicles and is important for preparation of follicular cells for luteinization and secretion of progesterone (McNatty et al., 1975). McNatty et al. (1979) suggested that development of a normal corpus luteum may depend upon a preovulatory follicle meeting the following criteria: 1) an adequate number of granulosa cells, 2) an adequate number of LH receptors on granulosa and theca cells, and 3) granulosa cells capable of synthesizing adequate amounts of progesterone following luteinization. Furthermore, the ability of luteinized human granulosa cells to secrete progesterone increased when the cells were collected from follicles having increased follicular fluid concentrations of estradiol compared to granulosa cells collected from follicles that had lower concentrations of estradiol (McNatty et al., 1979). Premature induction of ovulation in ewes was associated with luteal insufficiency (Murdoch et al., 1983). These data are relevant to fixed-time insemination protocols in which physiologically immature dominant follicles are induced to ovulate at AI and the subsequent circulating concentrations of progesterone are lower than in cows in which a larger dominant follicle is induced to ovulate with GnRH (Perry et al., 2005). Inadequate luteal function following induced ovulation may be due to a reduced number of follicular cells and(or) inadequate preparation of follicular cells for luteinization and secretion of progesterone.

**Hormonal Management of the Luteal Phase for Synchronization of Estrus**

Successful estrous synchronization protocols require control of the timing of both dominant follicle development and luteal regression. During the estrous cycle when a corpus luteum is present and circulating concentrations of progesterone are high, standing estrus and ovulation are inhibited; however, when the corpus luteum regresses and progesterone concentrations decrease, circulating concentrations of estradiol increase and the animal returns to standing estrus. Progestins mimic the actions of progesterone produced by the corpus luteum and inhibit estrus/ovulation which can delay the interval to estrus when luteal tissue is not present. Following the removal of the progestin, progesterone concentrations will be low and standing estrus and ovulation will occur.

**Progestins**

Two progestin products that are commercially available for estrous synchronization include Melengestrol Acetate (MGA) and the CIDR (Controlled Internal Drug Release). In cycling cows and heifers, administration of MGA or CIDRs does not affect the time of corpus luteum regression. However, once corpus luteum regression has occurred, progestin administration can prevent a cow or heifer from showing estrus and ovulating. Consequently, progestin administration in cows that have experienced corpus luteum regression will delay the expression of estrus and ovulation until after progestin withdrawal.
**Role of Progestins in Anestrus.** At the start of a breeding season, most herds consist of a mixture of cycling and anestrous females. An effective estrous synchronization protocol must be able to induce a fertile estrus or ovulation in both anestrous and cycling heifers and cows. A short luteal phase usually occurs in prepuberal heifers and postpartum beef cows following the first ovulation (Perry et al., 1991; Werth et al., 1996). This short exposure to progesterone is believed to be necessary for reprogramming the reproductive axis to resume normal estrous cycling. Therefore, in herds that have a large proportion of prepuberal heifers or anestrous cows, progestin pretreatment before induction of ovulation can initiate estrous cycling status and eliminate or at least reduce the occurrence of short estrous cycles.

Administration of low levels of a progestin (i.e. MGA) in the absence of a corpus luteum, can result in the formation of a persistent follicle (see below). However, the effect of progestin treatment on persistent follicle formation differs between cycling and anestrous animals. Administration of low concentrations of progestins did not induce persistent follicle formation in early postpartum anestrous dairy heifers (Rhodes et al., 1997) or anestrous postpartum beef cows (Perry et al., 2002). It is not clear why persistent follicles did not form in anestrous cows.

**Progestin Administration and Formation of Persistent Follicles.** Persistent follicles are characterized by an extended dominant follicle life span and increased estradiol production (Zimbelman and Smith, 1966b; Siriois and Fortune, 1990; see review by Fortune and Rivera, 1999). Treatment of cycling heifers or cows with low levels of a progestin, following luteolysis, resulted in the formation of persistent follicles that had a large diameter, extended lifespan, and increased production of estradiol (Zimbelman and Smith, 1966a; Siriois and Fortune, 1990; Fortune et al., 2001). Administration of low (subluteal) concentrations of progestins to cattle, in the absence of luteal tissue, increased LH pulse frequency (Savio et al., 1993; Kojima et al., 1995; Kinder et al., 1996); however, midluteal phase concentrations of progesterone decreased LH pulse frequency and persistent follicles did not form (Siriois and Fortune, 1990; Savio et al., 1993). Thus, the formation of persistent follicles has been associated with increased LH pulse frequency, and infusion of exogenous LH induced persistent follicle formation (Duffy et al., 2000).

Insemination immediately following long-term progestin treatment and ovulation of a persistent follicle has been associated with decreased fertility (Mihm et al., 1994). No difference was reported in fertilization rate following ovulation of persistent follicles, but fewer zygotes developed into embryos containing 16 or more cells compared to ovulation of oocytes from control follicles (Ahmad et al., 1995). Decreased fertility following formation and ovulation of persistent follicles may result from alterations in the uterine environment due to increased estradiol secretion (Butcher and Pope, 1979) and(or) premature resumption of meiosis due to prolonged exposure to increased LH pulse frequency (Mattheij et al., 1994).

**Prostaglandin F₂α**
Prostaglandins are naturally occurring compounds that are produced by most cells in the body and have a variety of biological actions. PGF₂α is a naturally occurring luteolytic hormone that has also been utilized to synchronize estrus and induce abortion in cattle through induction of corpus luteum regression. In the absence of an embryo, uterine concentrations of PGF₂α increase
during the late luteal phase. PGF$_{2\alpha}$ is secreted in pulses and transported to the corpus luteum via a counter-current mechanism. The mechanisms associated with PGF$_{2\alpha}$-induced luteolysis are not completely understood; however, PGF$_{2\alpha}$ probably has both a direct and indirect (decreased blood flow) action. Luteal cells are known to have PGF$_{2\alpha}$ receptors on the plasma membrane and direct inhibitory effects of PGF$_{2\alpha}$ on luteal progesterone secretion have been demonstrated (Niswender et al., 2000). In addition, PGF$_{2\alpha}$ is known to reduce luteal blood flow due to vasoconstrictor activity (Niswender and Nett, 1988).

Administration of PGF$_{2\alpha}$ to domestic ruminants does not induce luteolysis during the early luteal phase (Figure 6). For purposes of estrous synchronization, injection of PGF$_{2\alpha}$ is only effective in cycling heifers and cows (approximately day 6 to 16 following estrus; day 0 = estrus). Although functional PGF$_{2\alpha}$ receptors and signal transduction mechanisms are present in developing ovine corpora lutea (Tsai et al., 1997; Tsai and Wiltbank, 1998), the acquisition of luteolytic capacity is not established until after day 4 postestrus (Tsai and Wiltbank, 1998). Injection of PGF$_{2\alpha}$ into prepuberal heifers or anestrous cows is not effective due to the absence of luteal tissue. Furthermore, PGF$_{2\alpha}$ treatment will not induce cycling activity in noncycling cattle. Therefore, when using PGF$_{2\alpha}$ alone to synchronize estrus it is important to assess the proportion of cycling animals before initiating the treatment. In herds containing both cycling and noncycling females, the most effective estrous synchronization protocols combine treatment with a progestin and an injection of PGF$_{2\alpha}$. In pregnant feedlot heifers, PGF$_{2\alpha}$ is highly effective at inducing abortion before 100 days of gestation.

**Hormonal Management of Follicular Waves for Synchronization of Estrus**

The development of effective protocols for fixed-time insemination is dependent upon the precise synchronization of follicular waves culminating in a fertile ovulation at a predetermined time. Two approaches that have been used to synchronize bovine follicular waves include: 1) ovulating/destroying the dominant follicle and thereby initiating a new follicular wave, and 2) prolonging the lifespan of a dominant follicle (persistent follicle).

Initiation of a new follicular wave occurs following ovulation or turnover (atresia) of the dominant follicle. Administration of exogenous progesterone, estradiol, or GnRH have been utilized to turnover (progesterone and estradiol) or ovulate (GnRH) dominant follicles and to synchronize follicular waves in heifers and cows (see reviews by Bo et al., 1995; Diskin et al., 2002). Follicular turnover (atresia) of persistent follicles can be accomplished through the administration of progesterone. Progesterone as a single injection (Anderson and Day, 1994) or administered over a 24 hr period (McDowell et al., 1998) effectively regressed persistent follicles and initiated new follicular waves. Reduction of LH pulse frequency and amplitude following the administration of exogenous progesterone may be the mechanism by which persistent follicles are induced to undergo atresia (McDowell et al., 1998).

**Summary**

Understanding the basic principles of the bovine estrous cycle and how estrous synchronization products affect the cycle is essential when choosing the best protocol for heifers or cows and for determining what went wrong when pregnancy rates following a synchronized estrus are less
than expected. Three general approaches that have been used to develop estrous synchronization protocols include the following: 1) Inhibit ovulation following spontaneous corpus luteum regression (long-term progestin treatment), 2) Induction of corpus luteum regression (PGF$_{2\alpha}$ treatment), and 3) a combination of 1 and 2. Most of the protocols utilized today can be categorized under the third approach. The ability to synchronize bovine follicular waves through an injection of GnRH has added a new and important dimension to estrous synchronization and has made fixed-time AI in cows a viable option. Many of the current protocols are able to synchronize the growth of a dominant follicle in addition to the time of corpus luteum regression.

References


