In

the name of

God

Razi University

Faculty of Agriculture
Department of Animal Science

M.Sc. Thesis

Title of the Thesis:

The effect of Presynch-Ovsynch method according to parturition history and results of postpartum ultrasonography of ovaries on fertility of dairy cows

Supervisor:
Dr. Hamed Karami Shabankareh

By:
Meysam Afsari Akbarabadi

February 2011

پردیس کشاورزی و منابع طبیعی
گروه علوم دامی

پایان نامه جهت اخذ درجه کارشناسی ارشد رشته علوم دامی
گرایش فیزیولوژی دام

بررسی اثر روش Presynch-Ovsynch بر اساس سوابق زایش و نتایج بدست آمده از سونوگرافی تخمدان ها پس از زایش بر باروری گاوهای شیری

استاد راهنما:
دکتر حامد کرمی شبانکاره

نگارش:
میثم افسری اکبرآبادی

بهمن ۱۳۸۹

List of Contents **Page**

List of tables

List of figures

Abstract

This study was designed to evaluate the reproductive performance of lactating dairy cows (Holstein Friesian) following the injection of $PGF_{2\alpha}$ analogue on Day 15 postpartum and gonadotropin releasing hormone (GnRH) analogue on Day 23 post-AI with Presynch (2 injections of $PGF_{2\alpha}$, administered 14 d apart starting at 30–35 days postpartum) + Ovsynch-based (GnRH–7 d– $PGF_{2\alpha}$ –2 d–GnRH–16-20 h–TAI) treatment during the warm and cool periods. All cows (n = 313) were assigned to one of four groups: M_1 (n= 72): $PGF_{2\alpha}$ on Day 15 postpartum + Presynch-Ovsynch + GnRH on Day 23 post-AI; M_2 (n= 41): $PGF_{2\alpha}$ on Day 15 postpartum + Presynch-Ovsynch; M_3 (n= 100): Presynch-Ovsynch; and control (n= 100): cows were not treated and were inseminated at natural estrus. Pregnancy diagnosis was performed using ultrasonography technique within 28-35 days post-insemination. Statistical analyses were performed with the procedures GLM and GENMOD of the SAS program. Results showed that treatment with $PGF_{2\alpha}$ on Day 15 postpartum significantly decreased days to conception and the number of S/C ($P < 0.01$) and improved the FSCR ($P < 0.1$) only in those cows that were treated with M_2 protocol. Whereas, the days to first service was not influenced by treatment with $PGF_{2\alpha}$ on Day 15 postpartum ($P > 0.05$). Therefore, treatment with $PGF_{2\alpha}$ on Day 15 postpartum had a beneficial effect on the reproductive performance only in those cows that were treated with M_2 protocol. In contrast, administration of GnRH on Day 23 post-AI increased the days to conception and the number of S/C ($P < 0.01$) and decreased the FSCR ($P < 0.1$) in those cows treated with M_1 compared to M_2 protocol. Therefore, it has been concluded that Presynch-Ovsynch protocol could be more reproductively beneficial when a single treatment with $PGF_{2\alpha}$ was administered at 15 d postpartum (15 days after the $PGF2_{\alpha}$, Presynch-Ovsynch protocol was initiated). Furthermore, administration of a GnRH agonist on Day 23 after AI did not improve reproductive performance for cows receiving first postpartum TAI after Presynch-Ovsynch protocol.

Keywords: Dairy cow; Presynch-Ovsynch; Postpartum; Reproductive performance; Timed AI.

چکیده

مطالعه حاضر به منظور بررسی عملکرد تولیدمثلی گاوهای شیری در پی تزریق $PGF_{2\alpha}$ در روز ۱۵ پس از زایش و GnRH در روز ۲۳ پس از تلقیح در تکمیل پروتکل درمانی Presynch (۲ تزریق $PGF_{2\alpha}$ به فاصله ۱۴ روز، ۳۰ تا ۳۵ روز پس از زایش) و Ovsynch (تزریق GnRH، ۷ روز بعد تزریق $PGF_{2\alpha}$، ۲ روزبعد تزریق دومین GnRH، سپس ۱۶ تا ۲۰ ساعت بعد تلقیح مصنوعی در زمان ثابت) در طول فصول گرم و سرد، طراحی و اجرا شد. تعداد ۳۱۳ راس گاو شیری نژاد هلشتاین در ۴ گروه مورد بررسی قرار گرفتند: گروه اول (M_1، n= ۷۲)، تزریق $PGF_{2\alpha}$ در روز ۱۵ پس از زایش + Presynch-Ovsynch + تزریق GnRH در روز ۲۳ پس از تلقیح؛ گروه دوم (M_2، n= ۴۱) تزریق $PGF_{2\alpha}$ در روز ۱۵ پس از زایش + Presynch-Ovsynch؛ گروه سوم (n= ۱۰۰ ، M_3) Presynch-Ovsynch و گاوهای متعلق به گروه چهارم (n= ۱۰۰ ، Control) بدون درمان پس از مشاهده علائم فحلی، تلقیح شدند. تشخیص آبستنی به روش سونوگرافی بین روزهای ۲۸ تا ۳۵ پس از تلقیح انجام گرفت. داده های بدست آمده با استفاده از روشهای GLM و GENMOD مربوط به آزمون SAS مورد تجزیه و تحلیل قرار گرفتند. نتایج نشان داد که درمان با $PGF_{2\alpha}$ در روز ۱۵ پس از زایش بطور معنی داری باعث کاهش فاصله زایش تا آبستنی و تعداد سرویس به ازای آبستنی ($P < 0.01$) و بهبود نرخ آبستنی با اولین تلقیح (FSCR) ($P < 0.1$) تنها در آن دسته از گاوهایی که با پروتکل M_2 درمان شده بودند، گردید. در حالیکه فاصله زایش تا اولین سرویس تحت تاثیر درمان با $PGF_{2\alpha}$ در روز ۱۵ پس از زایش قرار نگرفت ($P > 0.05$). بنابراین درمان با $PGF_{2\alpha}$ در روز ۱۵ پس از زایش دارای تاثیر مثبت بر عملکرد تولید مثلی گاوهای گروه M_2 ، بود. در مقابل، تزریق GnRH در روز ۲۳ پس از تلقیح باعث افزایش فاصله زایش تا آبستنی و تعداد سرویس به ازای آبستنی ($P < 0.01$) و کاهش FSCR ($P < 0.1$) در آن دسته از گاوهایی که با پروتکل M_1 در مقایسه با M_2 درمان شده بودند، گردید. یافته های این مطالعه نشان داد که تزریق $PGF_{2\alpha}$ در روز ۱۵ پس از زایش می تواند باعث بهبود بیشتر عملکرد پروتکل درمانی Presynch-Ovsynch شود. بعلاوه تزریق GnRH در روز ۲۳ پس از تلقیح تاثیری بر عملکرد تولیدمثلی گاوهایی که با پروتکل Presynch-Ovsynch درمان شده بودند، نداشت.

کلمات کلیدی: گاو شیری، Presynch-Ovsynch، پس از زایش، عملکرد تولیدمثلی، تلقیح مصنوعی در زمان ثابت.

Chapter 1

Introduction

Reproductive efficiency in dairy cows has declined over the last several years and is considerably lower than desired (de Vries and Risco, 2005). Decreased reproductive efficiency is due to many factors including inefficiency and inaccuracy of estrous detection, improper timing of insemination, delayed ovulation and anovulation, management, negative energy balance and nutrition, genetics and inbreeding (Lucy, 2001; Chagas et al., 2007). Detection of estrus is an essential component of postpartum breeding programs that depend on overt signs of estrus for optimal timing of insemination. About 50% of standing heats are undetected during the postpartum period (Washburn et al., 2002). Timed artificial insemination (TAI) has been advised to overcome the problem of inefficient estrous detection. The purpose of successful estrous synchronization and timed insemination program in dairy cows is to precisely control estrus and breeding without the need for estrous detection. Potential benefits from estrous synchronization in dairy cattle include reduced time devoted to estrous detection and reduced variability in days from parturition to first service, leading to reduced variability and length of calving intervals within a herd.

Use of Presynch (postpartum regimen using two injections of $PGF_{2\alpha}$ to synchronize estrous cycles before applying Ovsynch (Navanukraw et al., 2004)) + Ovsynch (GnRH–7 d– $PGF_{2\alpha}$ –2 d–GnRH–16-20 h–TAI) effectively synchronizes ovulation for first postpartum TAI, and Presynch + Ovsynch has been widely adopted by the dairy industry based on a survey in which 75% of dairy producers reported use of synchronization for submitting cows for first postpartum TAI (Caraviello et al., 2006). This Presynch-Ovsynch program enhanced fertility to first service in lactating cyclic cows (Moreira et al., 2001).

Uterine involution or follicular development may be hastened which may advance ovarian cyclicity. Evidence exists that $PGF_{2\alpha}$ is involved in short luteal phases, which often accompany postpartum return to ovarian cyclicity. In addition, $PGF_{2\alpha}$ stimulates myometrial contractility and has been suggested to increase pituitary responsiveness to GnRH to release luteinizing hormone (LH) in postpartum cows (Randel et al., 1996), thereby stimulating follicular growth and enhancing ovulation (Weems et al., 2006). Due to its various biological actions, $PGF_{2\alpha}$ and its analogues have been used for a multitude of purposes in cattle reproduction, including the induction of parturition, synchronization of estrus, and treatment of uterine and ovarian diseases (Weems et al., 2006; Richterich and Wehrend, 2009). Administration of $PGF_{2\alpha}$ in the early postpartum period would be more consistently effective in increasing motility and evacuation of bacterial contamination of the postpartum uterus if it was administered when there is a CL in the ovary. On the other hand, Young et al., (1984) indicated that a single intramuscular injection of $PGF_{2\alpha}$ in the early postpartum period reduced the postpartum interval to conception.

For conception rates to increase, embryo survival was improved as a result of additional progesterone resulting from accessory CL (Stevenson et al., 2007). The importance of adequate progesterone secretion for early embryonic development, including embryonic secretion of interferon-τ which prevents the regression of the CL, has been previously clearly demonstrated in cattle (Mann, 2002). One proposed method to increase luteal concentrations of progesterone is to increase the rate of growth of the corpus luteum (Binelli et al., 2001). Administration of hCG or GnRH after insemination at specific times coincident with the presence of the dominant follicle/s of the first and second follicular

waves may stimulate CL function, induce accessory CL formation, increase progesterone and reduce estrogen production with a consequent positive effect on embryo survival (Thatcher et al., 2003; Stevenson et al., 2007). According to the distribution of return estruses after insemination, giving GnRH 23 d after previous service may be appropriate to induce an ovulation and synchronize follicular development (Bartolome et al., 2005). However, treatment with GnRH is followed by a rapid secretion of LH, and is also associated with a transitory increase in plasma estradiol (Stevenson et al., 1993). Estradiol is a component of the process that leads to endometrial section of $PGF_{2\alpha}$ (Silvia et al., 1991). In sheep, McCracken et al., (1984) suggested that prior to luteolysis, progesterone action on the uterus declines and permits estradiol to stimulate synthesis of oxytocin receptors. Binding of oxytocin to its receptor stimulates secretion of $PGF_{2\alpha}$ from the uterus. $PGF_{2\alpha}$ stimulates release of oxytocin from the corpus luteum (Flint and Sheldrick, 1982). All these events may stimulate the secretion of $PGF_{2\alpha}$, which could result in luteolysis and terminate pregnancy. Chebel et al. (2003) indicated that the administration of GnRH on Day 21 after AI to lactating dairy cows of unknown pregnancy status did not affect pre-enrollment pregnancy rates determined on Days 28 and 42 after insemination. Therefore, the potential use of GnRH in the early post-AI period warrants further investigation.

The objectives of this study were (1) to compare reproductive parameters in dairy cows subjected to a Presynch-Ovsynch protocol, with or without a $PGF_{2\alpha}$ treatment at 15 d postpartum (15 days after the $PGF2_{\alpha}$, Presynch-Ovsynch protocol was initiated); and (2) to determine the effect of administration of GnRH-agonist at 23 d after insemination on the reproductive parameters in dairy cows subjected to a Presynch-Ovsynch protocol during the warm and cool periods of the year.

Chapter 2

Literature Review

2.1. The estrous cycle

The estrous cycle represents the cyclical pattern of ovarian activity that facilitates female animals to go from a period reproductive non-receptivity to receptivity ultimately enabling mating and subsequent establishment of pregnancy. The onset of estrous cycles occurs at the time of puberty. In heifers puberty occurs at 6 to 12 months of age, generally at a weight of 200 to 250 kilograms. The normal duration of an estrous cycle in cattle is 18 to 24 days. The cycle consists of two discrete phases: the luteal phase (14 to 18 days) and the follicular phase (4 to 6 days). The luteal phase is the period following ovulation when the corpus luteum (CL) is formed (often further designated as metestrous and diestrous), while the follicular phase is the period following the demise of the corpus luteum (luteolysis) until ovulation (often further designated as proestrous and estrous). During the follicular phase, final maturation and ovulation of the ovulatory follicle occurs, the oocyte is released into the oviduct allowing the potential for fertilization.

2.1.1. Endocrine regulation of the estrous cycle

Cattle are polyestrous animals and display estrous behaviour approximately every 21 days. The estrous cycle is regulated by the hormones of the hypothalamus (gonadotrophin releasing hormone; GnRH), the anterior pituitary (follicle-stimulating hormone; FSH and luteinising hormone; LH), the ovaries (progesterone; P4, estradiol; E2 and inhibins) and the uterus (prostaglandin $F_{2\alpha}$; $PGF_{2\alpha}$). These hormones function through a system of positive and negative feedback to govern the estrous cycle of cattle (Roche, 1996). GnRH was first isolated from the hypothalamus of pigs and is a decapeptide (Baba et al., 1971; Schally et al., 1971a). Its control of the estrous cycle is mediated via its actions on the anterior pituitary which regulates the secretion of the gonadotrophs, LH and FSH (Schally et al., 1971b). The pulsitile secretion of basal levels of GnRH from the tonic center of the hypothalamus and the pre-ovulatory surge of GnRH from the surge center of the hypothalamus prevents the desensitisation of the GnRH receptor on the gonadotroph cells of the anterior pituitary. After transportation of GnRH from the hypothalamus to the pituitary gland via the hypophyseal portal blood system (Moenter et al., 1992), GnRH binds to its G-protein coupled receptor on the cell surface of the gonadotrophs cells (Kakar et al., 1993). This binding releases intracellular calcium which activates intermediaries in the mitogens activated protein kinases (MAPK) signaling pathway culminating in the release of FSH and LH from storage compartments in the cytoplasm (Weck et al., 1998). FSH is only stored in secretory granules in the cytoplasm for short periods of time, whereas LH is stored for longer periods during the estrous cycle (Farnworth, 1995).
During the follicular phase of the estrous cycle there is a hormonal environment of basal progesterone due to the regression of the corpus luteum (CL). The increased E2 concentrations, derived from the rapid proliferation of the pre-ovulatory dominant follicle (DF), concomitant with the decrease in circulating concentrations of progesterone, induces a surge in GnRH and allows the display of behavioural estrous during which heifers/cows

are sexually receptive and will stand to be mounted (Frandson, 2003). This preovulatory GnRH surge induces a coincidental LH and FSH surge (Sunderland et al., 1994). Only when serum progesterone concentrations are least and LH pulses occur every 40 to 70 minutes for 2 to 3 days does the DF ovulate (Roche, 1996). Ovulation occurs 10 to 14 hours after estrous and is followed by the luteal phase of the estrous cycle. The beginning of the luteal phase is also known as metestrous and typically lasts 3 to 4 days. It is characterized by the formation of the CL from the collapsed ovulated follicle (corpus haemorragicum). Following ovulation, progesterone concentrations begin to increase due to the formation of the CL in which the granulosa and theca cells of the ovulated DF luteinize and produce progesterone in readiness for the establishment and maintenance of pregnancy and/or resumption of the estrous cycle (Niswender, 1981). During the diestrous phase, progesterone concentrations remain elevated and recurrent waves of follicle development continue to be initiated by release of FSH from the anterior pituitary. However, these DFs that grow during the luteal phase of the estrous cycle do not ovulate. This progesterone dominant luteal phase of the estrous cycle, through negative feedback, only allows the secretion of greater amplitude but lesser frequency LH pulses that are inadequate for ovulation of the DF (Rahe et al., 1980). Finally, during the proestrous period, progesterone concentrations begin to decrease when the CL regresses in response $PGF_{2\alpha}$ secretion from the uterus in the postpubertal animal having typical reproductive cycles (Hansel and Convey, 1983) (Fig.2-1).

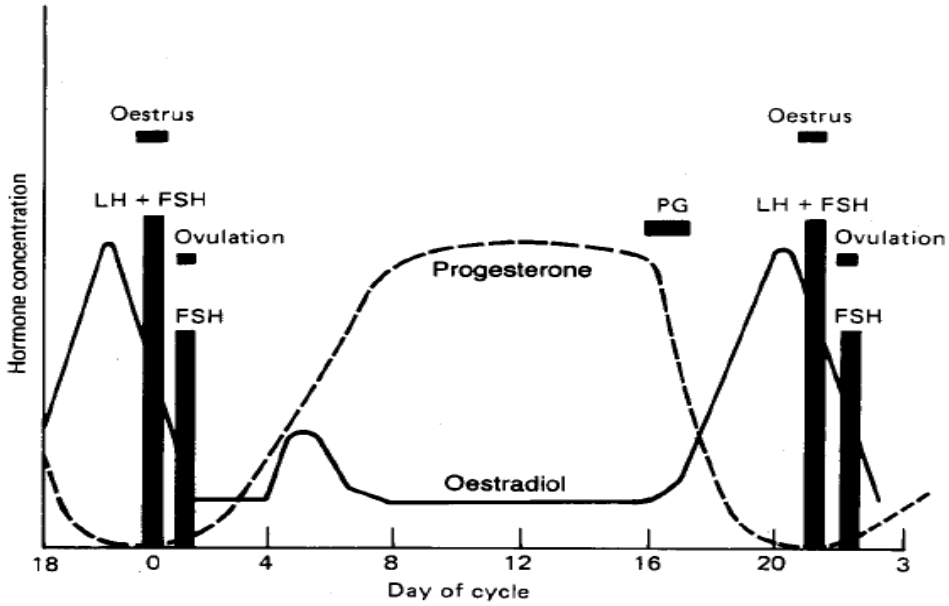

Fig.2.1. Changes in hormone concentrations during the cow's estrous cycle. (After Peters, 1985)

2.1.2. Ovarian follicular dynamics during the estrous cycle

The growth, development and maturation of ovarian follicles are fundamental processes for high reproductive efficiency in farm animals. A fixed number of primordial follicles are established during foetal development with ovarian follicle growth taking a period of 3 to 4 months and categorised into gonadotrophin independent and gonadotrophin dependent stages (Webb et al., 2004). Gonadotrophin dependent follicle growth in cattle occurs in waves with 2 to 3 waves per estrous cycle (Savio et al., 1988; Fig.2-2). Each wave of growth involves emergence, selection and dominance followed by either atresia or ovulation of the DF.

As mentioned above both FSH and LH have a prominent role in ovarian follicle development. Given that follicles are involved in the positive and negative feedback mechanisms of the hypothalamic-pituitary-gonadal (HPG) axis (estradiol and inhibins), these hormones have a governing role in the regulation of the estrous cycle of cattle. The beginning of gonadotrophin dependent follicle development is typified by the emergence of a follicle cohort typically consisting of 5 to 20 follicles ≥5mm and is correlated with a transient increase in FSH concentrations (Adams et al., 1992; Sunderland et al., 1994). This marks the beginning of dependency of follicle growth on FSH (Ginther et al., 2002) with FSH receptors (FSH-R) localised to the granulosa cells of the follicles by Day 3 of the follicle wave (Evans and Fortune 1997). This enables FSH to perform its required downstream signaling effects including promoting cellular growth and proliferation (Richards et al., 1998). This transient increases in FSH concentrations also leads to an increase in aromatase enzyme activity (P450arom; CYP19), in the granulosa cells of ovarian follicles, which converts androgen to estrogen (Hillier, 1994). As the DF emerges from the cohort of follicles, the diameter increases and it is recognized as the largest healthy follicle in the cohort (Gougeon and Lefevre, 1983). This increase in size leads to an increase in follicular fluid estradiol and inhibin concentrations (Hillier, 1994). This increase in estradiol concentrations in concert with inhibin suppresses FSH concentrations from the anterior pituitary gland via negative feedback reducing FSH to basal concentrations (Sunderland et al. 1994; Ginther et al., 2000a; b). The selected DF becomes increasingly responsive to LH (Ginther et al., 2000a) and continues growth in the face of decreasing FSH concentrations.

Irrespective of the stage of the estrous cycle during which follicles develop, the switch from FSH (Adams et al., 1992) to LH dependency (Kulick et al., 1999) is propagated through the presence of LH receptors (LH-R) on the granulosa cells (Xu et al., 1995). LH-R are localized to the theca and granulosa cells of healthy follicles, at different stages of follicle development (Camp et al., 1991). As the follicle grows, the theca cell LH-R increases and LH-R is acquired by the granulosa cells of the follicle undergoing selection to become the DF (Bao et al., 1997; Braw-Tal and Roth, 2005). Moreover, evidence suggests transient increases in circulating LH concentrations that occur at or around the time of follicle selection (Ginther et al., 2003), allows the DF to continue E2 production and grow in a lesser FSH environment (Ireland and Roche, 1983).

During the early luteal phase lesser amplitude and greater frequency (20 to 30 pulses / 24 h) LH pulses occur, in the mid-luteal period LH pulses are of greater amplitude and lesser frequency (6 to 8 pulses/24 h) both of which are of insufficient amplitude and frequency for final maturation and subsequent ovulation of the DF (Rahe et al., 1980). Thus, the DFs produced during the luteal phase of the estrous cycle undergo atresia, E2 and inhibin production decreases, and removes this negative feedback block to the hypothalamus/pituitary, FSH secretion can increase and a new follicle wave emerges. The production of high concentrations of estradiol is a defining characteristic of the DF (Ireland and Roche, 1982; 1983) and prior to visible differences in follicle diameter; the putative DF has greater follicular fluid concentrations of estradiol compared with other follicles in its cohort (Sunderland et al., 1994; Mihm et al., 2000). The synthesis of estradiol is dependent on the production of androgens in the theca cells and subsequent aromatization of these androgens to estrogens in the granulosa cells known as the two cell/two gonadotrophin model (Fortune, 1988). The binding of LH to its receptors in the theca cells drives the conversion of cholesterol to testosterone through a series of catalytic reactions (Dorrington et al., 1975).

Testosterone, once produced in the theca cells, diffuses out into the granulosa cells where it is converted to estrogens by the aromatize enzyme (Dorrington et al., 1975).

Estradiol not only has a local effect on follicle development, but it also has a systemic role via a positive feedback mechanism to the hypothalamus and pituitary gland. During the follicular phase of the estrous cycle, when progesterone concentrations are basal, this large concentration of estradiol produced by the preovulatory DF induces a GnRH surge from the hypothalamus. The resulting LH surge is of sufficient amplitude and frequency to stimulate final maturation and ovulation of the DF (Sunderland et al., 1994). The increased estradiol concentration also induces expression of estrous behaviour required for successfully mating (Ireland, 1987).

Other intra-ovarian produced factors play a role in regulating the estrous cycle either indirectly by altering the synthesis of estradiol or via direct negative feedback mechanisms to the hypothalamus and the anterior pituitary gland. The insulin like growth factor (IGF) super-family consisting of its two ligands IGF-I and IGF-II (Spicer and Echternkamp, 1995), two receptors IGFR-I and IGFR-II, (Hammond et al., 1991) and it numerous binding proteins and proteases (IGFBP 1-6, pregnancy associated plasma protein-A: PAPP-A) are responsible for the bioavailability of IGF-1 in the ovarian follicle. The bioavailability of IGF-I contributes to the growth, proliferation and steroidogenic capacity of the future DF (Mihm et al., 2000; Rivera and Fortune, 2003; Canty et al., 2006), indirectly affecting the estradiol induced negative feedback mechanism to the hypothalamus and pituitary. This in addition to early acquisition of LH receptors by the granulosa cell layer of the follicle undergoing selection are considered to be the main mechanisms facilitating the process of follicle selection (Lucy, 2007). The transforming growth factor beta (TGF) super-family contains over 30 structurally related proteins including ligands (TGF, anti-mullerian hormone, inhibins, activins, and bone morphogenetic proteins (BMP's), receptors (TGF-RI and II, activin receptor-like kinases; ALK's, accessory receptors (TGF-RIII) and downstream signaling molecules (similar to mothers against decapentaplegic; SMADS). The ligand members of this super-family were first identified in follicular fluid through their modulation of secreted FSH (Knight, 1996). Activin can increase the production of estradiol in follicular fluid (Knight and Glister, 2003) whereas follistatin impedes activins' positive steroidogenic effects, both of which can alter the estradiol feedback mechanism to the hypothalamus and pituitary (Phillips and de Kretser, 1998). Inhibins which have been detected in granulosa cells in cattle play a role in the suppression of FSH secreted in the anterior pituitary also regulating the estrous cycle (Findlay et al., 2002).

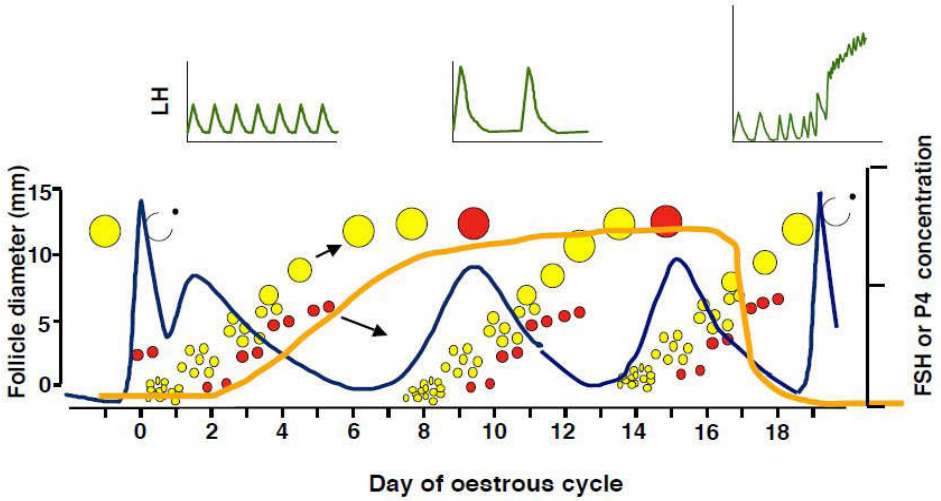

Fig.2.2. Schematic depiction of the pattern of secretion of FSH, LH, P4 and E2; and the pattern of growth of ovarian follicles during the oestrous cycle in cattle. Each wave of follicular growth is preceded by a transient rise in FSH concentrations. Healthy growing follicles are shaded in yellow, atretic follicles are shaded red. A surge in LH and FSH concentrations occurs at the onset of estrous and induces ovulation. The pattern of secretion of LH pulses during an 8-hour window early in the luteal phase (greater frequency, lesser amplitude), the mid-luteal phase (lesser frequency, lesser amplitude) and the follicular phase (high frequency, building to the surge) is indicated in the inserts in the top panel.

2.1.3. Corpus luteum function during the estrous cycle

The CL originates from the cells of the ovulatory follicle. LH, the major luteotrophic hormone in cattle (Hansel, 1966), is responsible for stimulating luteinization of the theca and granulosa cells of the pre-ovulatory follicle into luteal cells (Alila and Hansel, 1984). The function of the CL is to produce sufficient concentrations of progesterone throughout the luteal phase of the estrous cycle to maintain pregnancy (if a conceptus is present) and during pregnancy, to decrease gonadotrophin secretion and prevent behavioural estrous occurring.

Moreover, sustained increased concentrations of progesterone during the luteal phase of the estrous cycle alter the expression pattern of genes in the uterus (Forde et al., 2009). During the mid luteal phase, these sustained high concentrations of circulating progesterone down regulate the nuclear progesterone receptor in the luminal epithelium of the endometrium (Kimmins and MacLaren, 2001). This is a critical switch in allowing the synchronous increase or decrease in genes of the endometrium that are required to initiate uterine receptivity – regardless of the pregnancy status of the animal (Spencer et al., 2008). If, by Day 16 of the estrous cycle, the maternal recognition of pregnancy signal (interferon tau) has not been detected in sufficient quantities, luteolysis of the CL occurs. $PGF_{2\alpha}$ is secreted by the uterus in the bovine (Lamothe et al., 1977) and is the major luteolytic hormone in ruminants (Kindahl et al., 1976; Nett et al., 1976). Oxytocin receptors in the uterus bind oxytocin which propagates the episodic secretion of $PGF_{2\alpha}$ from the uterus. $PGF_{2\alpha}$ then mediates the luteolytic mechanism via counter-current exchange between the uterine vein and the ovarian artery (Fig. 2-3), inducing regression of the CL. This reduces circulating progesterone concentrations, estradiol concentrations increase and GnRH in the hypothalamus is stimulated as the animal enters the follicular phase of the estrous cycle.