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Chapter 7

Regulation and Function of Gonadotropins Throughout the Bovine Oestrous Cycle

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1. Introduction

Gonadotropins are protein hormones secreted by the pituitary gland and include luteinizing hormone (LH) and follicle stimulating hormone (FSH). Both LH and FSH govern the estrous cycle i.e. the cyclical pattern of ovarian activity that facilitates the transition of female animals between periods of reproductive non-receptivity to receptivity enabling mating and subsequent pregnancy. The onset of estrous cycles occurs at the time of puberty. In heifers puberty occurs at 6–12 months of age, generally at a weight of 200–250 kg. The normal duration of an estrous cycle in cattle is 18–24 days. The cycle consists of two discrete phases: the luteal phase (14–18 days) and the follicular phase (4–6 days). The luteal phase is the period following ovulation when the corpus luteum (CL) is formed (often further designated as met-estrus and diestrus), while the follicular phase is the period following the demise of the corpus luteum (luteolysis) until ovulation (often further designated as pro-oestrus and oestrus). 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. Gonadotropin regulation of follicle growth during the estrous cycle

Cattle are polyestrous animals and display estrous behavior approximately every 21 days. The estrous cycle is regulated by the hormones of the hypothalamus (gonadotropin-releasing hormone; GnRH), the anterior pituitary (follicle-stimulating hormone; FSH and luteinizing hormone; LH), the ovaries (progesterone; P4, estradiol; E2 and inhibins) and the uterus (prostaglandin F2α; PGF). These hormones function through a system of positive and negative feedback to govern the estrous cycle of cattle [1]. GnRH was first isolated from the hypothalamus of pigs and is a decapeptide [2, 3]. 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 [4].

The pulsatile 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 [5], GnRH binds to its G-protein coupled receptor on the cell surface of the gonadotroph cells [6]. This binding releases intracellular calcium which activates intermediaries in the mitogen activated protein kinases (MAPK) signaling pathway culminating in the release of FSH and LH from storage compartments in the cytoplasm [7]. 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 [8]. 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 behavioral estrus during which heifers/cows are sexually receptive and will stand to be mounted [9]. This pre-ovulatory GnRH surge induces a coincidental LH and FSH surge [10]. Only when serum progesterone concentrations are basal and LH pulse frequency increases to one per hour for 2–3 days does the DF ovulate [1]. Ovulation occurs 10–14 h after estrus and is followed by the luteal phase of the estrous cycle. The beginning of the luteal phase is also known as met-estrus and typically lasts 3–4 days. It is characterised 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 lutenize and produce progesterone in readiness for the establishment and maintenance of pregnancy and/or resumption of the estrous cycle [11]. During the di-estrous 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, due to inadequate LH pulse frequency.

The progesterone dominant luteal phase of the estrous cycle, through negative feedback, only allows the secretion of greater amplitude but less frequent LH pulses (one pulse per 3 to 4 hours) that are inadequate for ovulation of the DF [12]. Finally, during the pro-estrous period, progesterone concentrations decrease when the CL regresses in response to PGF secretion from the uterus [13].

3. Gonadotropin regulation of final maturation of the pre-ovulatory follicle and ovulation

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 fetal development with ovarian follicle growth taking a period of 3–4 months and categorized into gonadotropin independent and gonadotropin dependent stages [14]. Gonadotropin dependent follicle growth in cattle occurs in waves with 2–3 waves per estrous cycle [15, 16 Fig.1].

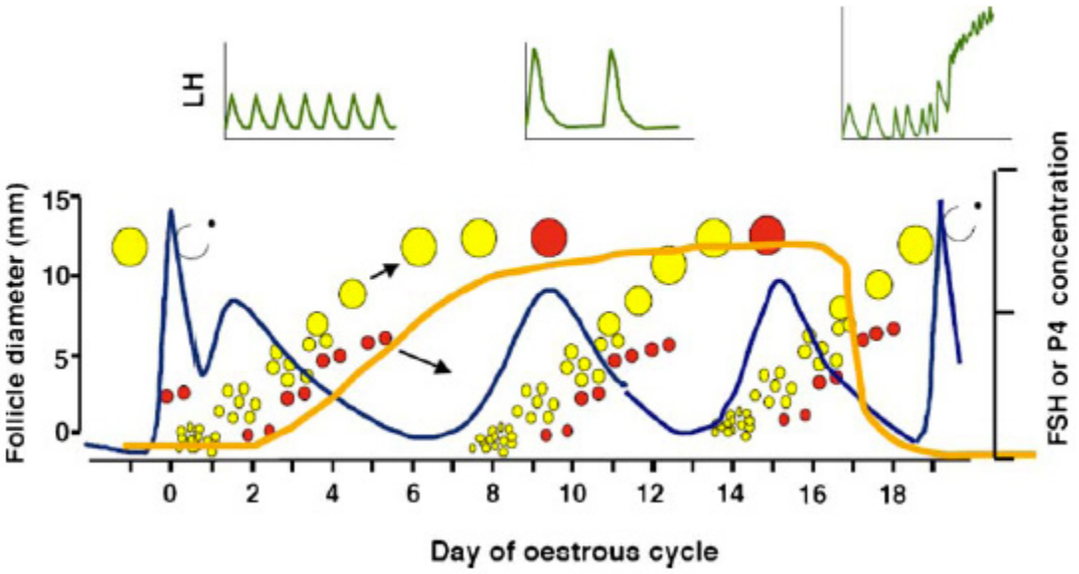

Figure 1. Schematic depiction of the pattern of secretion of follicle-stimulating hormone (FSH; blue line), luteinizing hormone (LH; green lines), and progesterone (P4; orange line); and the pattern of growth of ovarian follicles during the estrous cycle in cattle. Each wave of follicular growth is preceded 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 estrus and induces ovulation. The pattern of secretion of LH pulses during an 8-h 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. Taken from [17].

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 gonadotropin dependent follicle development is typified by the emergence of a follicle cohort typically consisting of 5–20 follicles ≥5mm and is correlated with a transient increase in FSH concentrations [10, 18]. This marks the beginning of dependency of follicle growth on FSH [19] with FSH receptors (FSH-R) localized within the granulosa cells of the follicles by Day 3 of the follicle wave [20, 21]. This enables FSH to perform its required down stream signalling effects including promoting cellular growth and proliferation [22, 23]. These 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 [24]. As the DF is selected from the cohort of follicles, the diameter increases and it is recognized as the largest healthy follicle in the cohort [25]. This increase in size leads to an increase in follicular fluid estradiol and inhibin concentrations [24]. Dominance occurs when the the DF reaches 9 mm in diameter, and it actively suppresses FSH, thus preventing further follicle wave emergence until the DF either undergoes atresia or ovulated. The increase in estradiol concentrations in concert with inhibin are the key endocrine signals that suppress FSH concentrations from the anterior

pituitary gland via negative feedback reducing FSH to basal concentrations [10, 26, 27]. The selected DF becomes increasingly responsive to LH [27] 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 [18] to LH dependency [28] is propagated through the presence of LH receptors (LH-R) on the granulosa cells [29]. LH-R are localised to the theca and granulosa cells of healthy follicles, at different stages of follicle development [20]. 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 [29-31]. Moreover, evidence suggests transient increases in circulating LH concentrations that occur at or around the time of follicle selection [32], allows the DF to continue E2 production and grow in the face of declining FSH concentrations [33]. During the early luteal phase lesser amplitude and greater frequency (20–30 pulses/24 h) LH pulses occur, in the mid-luteal period LH pulses are of greater amplitude and lesser frequency (6–8 pulses/24 h) both of which are of insufficient amplitude and frequency for final maturation and subsequent ovulation of the DF [12]. 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 [33, 34] 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 [10, 35, 36]. The synthesis of estradiol is dependent on the production of androgens in the theca cells and subsequent aromatisation of these androgens to estrogens in the granulosa cells known as the two cell/two gondatropin model [37]. Production of estradiol from growing follicles is dependent on sufficient LH pulse frequency [38, 39]. The binding of LH to its receptors in the theca cells drives the conversion of cholesterol to testosterone through a series of catalytic reactions [40]. Testosterone, once produced in the theca cells, diffuses out into the granulosa cells where it is converted to estrogens by the aromatase enzyme [40]. 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 pre-ovulatory 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 [10]. The increased estradiol concentrations also induces expression of estrous behavour, required for successful mating [41]. 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 [42-44], two receptors IGFR-I and IGFR-II [45], 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 [36, 46, 47], 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 [48]. 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 (TGFRI 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 [49]. Activin can increase the production of estradiol in follicular fluid [50] whereas follistatin impedes activins' positive steroidogenic effects, both of which can alter the estradiol feedback mechanism to the hypothalamus and pituitary [51]. 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 oestrous cycle [52].

4. Estrous behavior

A recent review of the literature [53] reported mean inter-ovulatory intervals of 22.9 and 22.0 days for lactating dairy cows and heifers, respectively. Standing to be mounted by a bull or herd mate is the primary and most definitive sign of oestrus in cattle. Estrogen, specifically, estradiol, is the primary signal to the brain that induces expression of estrus, but only in the absence of progesterone [54]. It appears that stressors which elevate blood concentrations of cortisol are capable of delaying or blocking the pre-ovulatory LH surge and affecting the expression of estrus without altering pro-oestrous concentrations of blood oestradiol (see review by [55]). In a recent review, Diskin [56] calculated that for dairy cows the average duration of standing estrus was 8.1 h with 9.1 standing events or mounts recorded during standing estrus. There is evidence [57] that the duration of standing estrus decreases as milk production increases (14.7 and 2.8 h in cows yielding 25 or 55 kg milk, respectively). For heifers it would appear that the duration of standing estrus is somewhat longer, 12–14 h [56]. For beef cows, kept indoors, the average duration of standing estrus has been reported to be less than 8.5 h [56]. Both the duration of standing estrus and intensity of estrous expression are affected by a range of environmental factors including under foot surface type, size of the sexually active group and the presence of a bull [56]. Breaks or quiescent interludes in standing activity have also been observed in 30% of dairy cows at [58] while breaks with an average duration of 2.6 h in 67% of beef heifers have been recorded [59]. There is no evidence from dairy cows [60], beef cows or heifers [56] that either the onset of standing estrus or end of estrus follows any distinct diurnal pattern.

5. Gonadotropin regulation of Corpus luteum function

The CL originates from the cells of the ovulatory follicle. LH, the major luteotropic hormone in cattle [61], is responsible for stimulating luteinization of the theca and granulosa cells of the pre-ovulatory follicle into luteal cells [62]. 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 gonadotropin secretion and prevent behavioral oestrus occurring. Progesterone is required for the maintenance of pregnancy with many studies reporting a positive association between progesterone concentrations and the probability of embryo survival [63-66]. The proposed mechanisms by which progesterone affects embryo survival are indirect, not acting on the embryo itself but via effects on the uterine endometrium [67, 68]. Available evidence in both cattle and sheep, has identified that sustained increased concentrations of progesterone during the luteal phase of the estrous cycle alters the expression pattern of genes in the uterus [69-73] which in turn alters the composition of the uterine histotroph i.e. availability of enzymes, carrier proteins, hormones and nutrients to the developing embryo prior to implantation [68]. Moreover, alterations in systemic progesterone during the early luteal phase have been shown to have significant effects on conceptus elongation [67, 71, 74]. 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 [75]. 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 [76]. 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 is secreted by the uterus in the bovine [77] and is the major luteolytic hormone in ruminants [78-80]. Oxytocin receptors in the uterus binds oxytocin which propagates the episodic secretion of PGF from the uterus. PGF then mediates the luteolytic mechanism via countercurrent exchange between the uterine vein and the ovarian artery (Fig. 2), 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.

6. Conclusions

The estrous cycle in cattle is typically 18–24 days in duration, with estrous behavior expressed for a 2–24-h period during the late follicular phase. During normal estrous cycles there are typically two to three and occasionally four waves of follicular growth each involving a period of emergence, selection and dominance followed by either atresia or ovulation of the DF. The gonadotropin hormones FSH and LH are the main regulators of folliculogenesis and steroidogenesis with LH being the major luteotrophic hormone. LH pulse frequency is the major determinant affecting the ultimate fate of a selected DF. Pulsatile PGF of uterine origin is the main hormonal signal that induces luteolysis of the CL and the switch from the luteal to the follicular phase of the estrous cycle.

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7. References

[1] Roche JF. Control and regulation of folliculogenesis--a symposium in perspective. Rev Reprod. 1996 January 1, 1996;1(1):19-27.

[2] Baba Y, Matsuo H, Schally AV. Structure of the porcine LH- and FSH-releasing hormone. II. Confirmation of the proposed structure by conventional sequential analyses. Biochem Biophys Res Commun. 1971;44(2):459-63.

[3] Schally AV, Arimura A, Baba Y, Nair RMG, Matsuo H, Redding TW, et al. Isolation and properties of the FSH and LH-releasing hormone. Biochem Biophys Res Commun. 1971;43(2):393-9.

[4] Schally AV, Arimura A, Kastin AJ, Matsuo H, Baba Y, Redding TW, et al. Gonadotropin-Releasing Hormone: One Polypeptide Regulates Secretion of Luteinizing and Follicle-Stimulating Hormones. Science. 1971 September 10, 1971;173(4001):1036-8.

[5] Moenter SM, Brand RC, Karsch FJ. Dynamics of gonadotropin-releasing hormone (GnRH) secretion during the GnRH surge: insights into the mechanism of GnRH surge induction. Endocrinology. 1992 May 1, 1992;130(5):2978-84.

[6] Kakar SS, Rahe CH, Neill JD. Molecular cloning, sequencing, and characterizing the bovine receptor for gonadotropin releasing hormone (GNRH). Domest Anim Endocrinol. 1993;10(4):335-42.

[7] Weck J, Fallest PC, Pitt LK, Shupnik MA. Differential Gonadotropin-Releasing Hormone Stimulation of Rat Luteinizing Hormone Subunit Gene Transcription by Calcium Influx and Mitogen-Activated Protein Kinase-Signaling Pathways. Mol Endocrinol. 1998 March 1, 1998;12(3):451-7.

[8] Farnworth PG. Gonadotrophin secretion revisited. How many ways can FSH leave a gonadotroph? J Endocrinol. 1995 June 1, 1995;145(3):387-95.

[9] Frandson R, Wilke WL, Fails AD. Anatomy and physiology of farm animals. Lippincott Williams and Wilkins, Baltimore. 2003.

[10] Sunderland SJ, Crowe MA, Boland MP, Roche JF, Ireland JJ. Selection, dominance and atresia of follicles during the oestrous cycle of heifers. J Reprod Fertil. 1994 August 1, 1994;101(3):547-55.

[11] Niswender G. Mechanisms controlling luteolysis. Raven Press, New York 1981.

[12] Rahe CH, Owens RE, Fleeger JL, Newton HJ, Harms PG. Pattern of Plasma Luteinizing Hormone in the Cyclic Cow: Dependence upon the Period of the Cycle. Endocrinology. 1980 August 1, 1980;107(2):498-503.

[13] Hansel W, Convey EM. Physiology of the Estrous Cycle. J Anim Sci. 1983 July 1, 1983;57(Supplement 2):404-24.

[14] Webb R, Garnsworthy PC, Gong JG, Armstrong DG. Control of follicular growth: Local interactions and nutritional influences. J Anim Sci. 2004 January 1, 2004;82(13 suppl):E63-E74.

[15] Rajakoski E. The ovarian follicular system in sexually mature heifers with special reference to seasonal, cyclical, end left-right variations. Acta Endocrinol Suppl (Copenh). 1960;34(Suppl 52):1-68.

[16] Savio JD, Keenan L, Boland MP, Roche JF. Pattern of growth of dominant follicles during the oestrous cycle of heifers. J Reprod Fertil. 1988 July 1, 1988;83(2):663-71.
[17] Forde N, Beltman ME, Lonergan P, Diskin M, Roche JF, Crowe MA. Oestrous cycles in Bos taurus cattle. Anim Reprod Sci. 2011;124(3–4):163-9.
[18] Adams GP, Matteri RL, Kastelic JP, Ko JCH, Ginther OJ. Association between surges of follicle-stimulating hormone and the emergence of follicular waves in heifers. J Reprod Fertil. 1992 January 1, 1992;94(1):177-88.
[19] Ginther OJ, Bergfelt DR, Beg MA, Kot K. Role of low circulating FSH concentrations in controlling the interval to emergence of the subsequent follicular wave in cattle. Reproduction. 2002 October 1, 2002;124(4):475-82.
[20] Camp TA, Rahal JO, Mayo KE. Cellular Localization and Hormonal Regulation of Follicle-Stimulating Hormone and Luteinizing Hormone Receptor Messenger RNAs in the Rat Ovary. Mol Endocrinol. 1991 October 1, 1991;5(10):1405-17.
[21] Evans ACO, Fortune JE. Selection of the Dominant Follicle in Cattle Occurs in the Absence of Differences in the Expression of Messenger Ribonucleic Acid for Gonadotropin Receptors. Endocrinology. 1997 July 1, 1997;138(7):2963-71.
[22] Richards JS. Hormonal Control of Gene Expression in the Ovary. Endocr Rev. 1994 December 1994;15(6):725-51.
[23] Richards JS, Russell DL, Robker RL, Dajee M, Alliston TN. Molecular mechanisms of ovulation and luteinization. Mol Cell Endocrinol. 1998;145(1–2):47-54.
[24] Hillier SG. Current concepts of the roles of follicle stimulating hormone and luteinizing hormone in folliculogenesis. Hum Reprod. 1994 February 1, 1994;9(2):188-91.
[25] Gougeon A, Lefèvre B. Evolution of the diameters of the largest healthy and atretic follicles during the human menstrual cycle. J Reprod Fertil. 1983 November 1, 1983;69(2):497-502.
[26] Ginther OJ, Bergfelt DR, Kulick LJ, Kot K. Selection of the Dominant Follicle in Cattle: Role of Two-Way Functional Coupling Between Follicle-Stimulating Hormone and the Follicles. Biol Reprod. 2000 April 1, 2000;62(4):920-7.
[27] Ginther OJ, Bergfelt DR, Kulick LJ, Kot K. Selection of the Dominant Follicle in Cattle: Role of Estradiol. Biol Reprod. 2000 August 1, 2000;63(2):383-9.
[28] Kulick LJ, Kot K, Wiltbank MC, Ginther OJ. Follicular and hormonal dynamics during the first follicular wave in heifers. Theriogenology. 1999;52(5):913-21.
[29] Xu Z, Garverick HA, Smith GW, Smith MF, Hamilton SA, Youngquist RS. Expression of follicle-stimulating hormone and luteinizing hormone receptor messenger ribonucleic acids in bovine follicles during the first follicular wave. Biol Reprod. 1995 October 1, 1995;53(4):951-7.
[30] Bao B, Garverick HA, Smith GW, Smith MF, Salfen BE, Youngquist RS. Changes in messenger ribonucleic acid encoding luteinizing hormone receptor, cytochrome P450-side chain cleavage, and aromatase are associated with recruitment and selection of bovine ovarian follicles. Biol Reprod. 1997 May 1, 1997;56(5):1158-68.
[31] Braw-Tal R, Roth Z. Gene expression for LH receptor, 17α-hydroxylase and StAR in the theca interna of preantral and early antral follicles in the bovine ovary. Reproduction. 2005 April 1, 2005;129(4):453-61.

[32] Ginther OJ, Beg MA, Donadeu FX, Bergfelt DR. Mechanism of follicle deviation in monovular farm species. Anim Reprod Sci. 2003;78(3–4):239-57.
[33] Ireland JJ, Roche JF. Development of Nonovulatory Antral Follicles in Heifers: Changes in Steroids in Follicular Fluid and Receptors for Gonadotr opins. Endocrinology. 1983 January 1, 1983;112(1):150-6.
[34] Ireland JJ, Roche JF. Development of Antral Follicles in Cattle after Prostaglandin-Induced Luteolysis: Changes in Serum Hormones, Steroids in Follicular Fluid, and Gonadotropin Receptors. Endocrinology. 1982 December 1, 1982;111(6):2077-86.
[35] Fortune JE. Ovarian follicular growth and development in mammals. Biol Reprod. 1994 February 1, 1994;50(2):225-32.
[36] Mihm M, Austin EJ, Good TEM, Ireland JLH, Knight PG, Roche JF, et al. Identification of Potential Intrafollicular Factors Involved in Selection of Dominant Follicles in Heifers. Biol Reprod. 2000 September 1, 2000;63(3):811-9.
[37] Fortune JE, Quirk SM. REGULATION OF STEROIDOGENESIS IN BOVINE PREOVULATORY FOLLICLES. J Anim Sci. 1988 January 1, 1988;66(Supplement 2):1-8.
[38] Crowe MA, Enright WJ, Boland MP, Roche JF. Follicular growth and serum follicle-stimulating hormone (FSH) responses to recombinant bovine FSH in GnRH-immunized anoestrous heifers. Anim Sci. 2001;73:115-22.
[39] Crowe MA, Kelly P, Driancourt MA, Boland MP, Roche JF. Effects of Follicle-Stimulating Hormone With and Without Luteinizing Hormone on Serum Hormone Concentrations, Follicle Growth, and Intrafollicular Estradiol and Aromatase Activity in Gonadotropin-Releasing Hormone-Immunized Heifers. Biol Reprod. 2001 January 1, 2001;64(1):368-74.
[40] Dorrington JH, Moon YS, Armstrong DT. Estradiol-17beta biosynthesis in cultured granulosa cells from hypophysectomised immature rats; stimulation by follicle-stimulating hormone. Endocrinology. 1975;97:1328–31.
[41] Ireland JJ. Control of follicular growth and development. J Reprod Fertil Suppl. 1987;34:39-54.
[42] Rinderknecht E, Humbel RE. The amino acid sequence of human insulin-like growth factor I and its structural homology with proinsulin. J Biol Chem. 1978 April 25, 1978;253(8):2769-76.
[43] Rinderknecht E, Humbel RE. Primary structure of human insulin-like growth factor II. FEBS Lett. 1978;89(2):283-6.
[44] Spicer LJ, Echternkamp SE. The ovarian insulin and insulin-like growth factor system with an emphasis on domestic animals. Domest Anim Endocrinol. 1995;12(3):223-45.
[45] Hammond JM, Mondschein JS, Samaras SE, Smith SA, Hagen DR. The ovarian insulin-like growth factor system. J Reprod Fertil Suppl. 1991;43:199-208.
[46] Rivera GM, Fortune JE. Proteolysis of Insulin-Like Growth Factor Binding Proteins -4 and -5 in Bovine Follicular Fluid: Implications for Ovarian Follicular Selection and Dominance. Endocrinology. 2003 July 1, 2003;144(7):2977-87.
[47] Canty MJ, Boland MP, Evans ACO, Crowe MA. Alterations in follicular IGFBP mRNA expression and follicular fluid IGFBP concentrations during the first follicle wave in beef heifers. Anim Reprod Sci. 2006;93(3–4):199-217.

[48] Lucy MC. The bovine dominant ovarian follicle. J Anim Sci. 2007 March 1, 2007;85(13 suppl):E89-E99.
[49] Knight PG, Glister C. TGF-beta superfamily members and ovarian follicle development. Reproduction. 2006 Aug;132(2):191-206.
[50] Knight PG, Glister C. Local roles of TGF-beta superfamily members in the control of ovarian follicle development. Anim Reprod Sci. 2003 Oct 15;78(3-4):165-83.
[51] Phillips DJ, de Kretser DM. Follistatin: A Multifunctional Regulatory Protein. Front Neuroendocrinol. 1998;19(4):287-322.
[52] Findlay JK, Drummond AE, Dyson ML, Baillie AJ, Robertson DM, Ethier JF. Recruitment and development of the follicle; the roles of the transforming growth factor-β superfamily. Mol Cell Endocrinol. 2002;191(1):35-43.
[53] Wiltbank M, Lopez H, Sartori R, Sangsritavong S, Gümen A. Changes in reproductive physiology of lactating dairy cows due to elevated steroid metabolism. Theriogenology. 2006;65(1):17-29.
[54] Vailes LD, Washburn SP, Britt JH. Effects of various steroid milieus or physiological states on sexual behavior of Holstein cows. J Anim Sci. 1992 July 1, 1992;70(7):2094-103.
[55] Stevenson JS. A review of oestrous behaviour and detection in dairy cows. In: Diskin, MG (Ed) Proc BSAS Occasional Publication No 26, Fertility in the High-Producing Dairy Cow, vol 1, pp 43–62; 2001; 2001. p. 43-62.
[56] Diskin MG. HeatWatch: a telemetric system for heat detection in cattle. Vet Q. 2008;30: 37-48.
[57] Lopez H, Satter LD, Wiltbank MC. Relationship between level of milk production and estrous behavior of lactating dairy cows. Anim Reprod Sci. 2004;81(3–4):209-23.
[58] O'Farrell KJ. Fertility management in the dairy herd. Irish veterinary journal. 1980;34:160-9.
[59] Stevenson JS, Lamb GC, Kobayashi Y, Hoffman DP. Luteolysis During Two Stages of the Estrous Cycle: Subsequent Endocrine Profiles Associated with Radiotelemetrically Detected Estrus in Heifers. J Dairy Sci. 1998;81(11):2897-903.
[60] Dransfield MBG, Nebel RL, Pearson RE, Warnick LD. Timing of Insemination for Dairy Cows Identified in Estrus by a Radiotelemetric Estrus Detection System. J Dairy Sci. 1998;81(7):1874-82.
[61] Hansel W. Luteotrophic and luteolytic mechanisms in bovine corpora lutea. J Reprod Fertil. 1966:33–48.
[62] Alila HW, Hansel W. Origin of different cell types in the bovine corpus luteum as characterized by specific monoclonal antibodies. Biol Reprod. 1984 December 1, 1984;31(5):1015-25.
[63] Stronge AJH, Sreenan JM, Diskin MG, Mee JF, Kenny DA, Morris DG. Post-insemination milk progesterone concentration and embryo survival in dairy cows. Theriogenology. 2005;64(5):1212-24.
[64] Starbuck GR, Darwash AO, Mann GE, Lamming GE. The detection and treatment of post insemination progesteroneinsufficieny in dairy cows. In: Diskin MG, editor. Fertility in the High Producing Dairy Cow BSAS Occasional Pulication No2; 2001; 2001. p. 447-50.

[65] McNeill RE, Sreenan JM, Diskin MG, Cairns MT, Fitzpatrick R, Smith TJ, et al. Effect of systemic progesterone concentration on the expression of progesterone-responsive genes in the bovine endometrium during the early luteal phase. Reprod Fertil Dev. 2006;18(5):573-83.

[66] Parr MH, Mullen MP, Crowe MA, Roche JF, Lonergan P, Evans ACO, et al. The repeatability of embryo survival, and the relationship between plasma progesterone in the early luteal phase and embryo survival in dairy heifers. J Dairy Sci. 2012;In press.

[67] Clemente M, de La Fuente J, Fair T, Al Naib A, Gutierrez-Adan A, Roche JF, et al. Progesterone and conceptus elongation in cattle: a direct effect on the embryo or an indirect effect via the endometrium? Reproduction. 2009 September 1, 2009;138(3):507-17.

[68] Spencer TE, Johnson GA, Bazer FW, Burghardt RC, Palmarini M. Pregnancy recognition and conceptus implantation in domestic ruminants: roles of progesterone, interferons and endogenous retroviruses. Reprod Fertil Dev. 2006;19(1):65-78.

[69] Simmons RM, Erikson DW, Kim J, Burghardt RC, Bazer FW, Johnson GA, et al. Insulin-Like Growth Factor Binding Protein-1 in the Ruminant Uterus: Potential Endometrial Marker and Regulator of Conceptus Elongation. Endocrinology. 2009 September 1, 2009;150(9):4295-305.

[70] Forde N, Carter F, Fair T, Crowe MA, Evans ACO, Spencer TE, et al. Progesterone-regulated changes in endometrial gene expression contribute to advanced conceptus development in cattle. Biol Reprod. 2009 October 2009;81(4):784-94.

[71] Forde N, Beltman ME, Duffy GB, Duffy P, Mehta JP, O'Gaora P, et al. Changes in the endometrial transcriptome during the bovine estrous cycle: effect of low circulating progesterone and consequences for conceptus elongation. Biol Reprod. 2011 Sep 29(Feb;84(2)):266-78.

[72] Forde N, Spencer TE, Bazer FW, Song G, Roche JF, Lonergan P. Effect of pregnancy and progesterone concentration on expression of genes encoding for transporters or secreted proteins in the bovine endometrium. Physiol Genomics. 2010 March 1, 2010;41(1):53-62.

[73] Satterfield MC, Gao H, Li X, Wu G, Johnson GA, Spencer TE, et al. Select Nutrients and Their Associated Transporters Are Increased in the Ovine Uterus Following Early Progesterone Administration. Biol Reprod. 2010 January 1, 2010;82(1):224-31.

[74] Carter F, Forde N, Duffy P, Wade M, Fair T, Crowe MA, et al. Effect of increasing progesterone concentration from Day 3 of pregnancy on subsequent embryo survival and development in beef heifers. Reprod Fertil Dev. 2008;20(3):368-75.

[75] Kimmins S, Maclaren LA. Oestrous Cycle and Pregnancy Effects on the Distribution of Oestrogen and Progesterone Receptors in Bovine Endometrium. Placenta. 2001;22(8–9):742-8.

[76] Spencer TE, Sandra O, Wolf E. Genes involved in conceptus–endometrial interactions in ruminants: insights from reductionism and thoughts on holistic approaches. Reproduction. 2008 February 1, 2008;135(2):165-79.

[77] Lamothe P, Bousquet D, Guay P. Cyclic variation of F prostaglandins in the uterine fluids of the cow. J Reprod Fertil. 1977 July 1, 1977;50(2):381-2.

[78] Baird DT, Land RB, Scaramuzzi RJ, Wheeler AG. Endocrine changes associated with luteal regression in the ewe; the secretion of ovarian oestradiol, progesterone and androstenedione and uterine prostaglandin F2 alpha throughout the oestrous cycle. J Endocrinol. 1976 May 1, 1976;69(2):275-86.

[79] Kindahl H, Edqvist LE, Granstrom E, Bane A. The release of prostaglandin F2alpha as reflected by 15-keto-13,14-dihydroprostaglandin F2alpha in the peripheral circulation during normal luteolysis in heifers. Prostaglandins. 1976 May;11(5):871-8.

[80] Nett TM, Staigmiller RB, Akbar AM, Diekman MA, Ellinwood WE, Niswender GD. Secretion of Prostaglandin F2α in Cycling and Pregnant Ewes. J Anim Sci. 1976 April 1, 1976;42(4):876-80.