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Regulation of Follicular Growth and Development in Sheep

Review Article

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ABSTRACT

This manuscript reviews the present knowledge related to folliculogenesis in sheep. Folliculogenesis starts with formation of primordial follicles before birth, present as a pool containing a certain number of follicles. By the attainment of puberty, a group of follicles from that pool starts to grow, a process known as primordial follicle activation or recruitment. The number of growing primordial follicles directly affects the number of available oocytes for fertilization. Many studies, especially in rodents, have been performed to understand the mechanisms that control the primordial follicle growth. Therefore, many autocrine, paracrine, intacrin factors from oocyte, granulasa and surrounding stroma have been identified. These regulating factors depend on species, age, physiological condition of the gonad and the environment. Also, interactions between these regulating factors have been observed and some discrepancies among results were found. The factors regulating primordial follicle activation probably act in concert with gonadotropins and regulate follicle growth and atresia before the antrum formation. Although many studies have been performed to understand the mechanisms controlling preantral follicle growth, no precise key points have been identified. The majority of the factors that affect primordial follicle transition have not yet been studied in sheep, while many studies have been performed to understand the controlling mechanisms of follicular growth through the antral the stages. Therefore new experimental studies are needed to understand the controlling mechanisms of preantral follicle growth.

KEY WORDS atresia, follicle, growth, ovary, sheep.

INTRODUCTION

Sheep ovary is a unique endocrine and gametogenic organ responsible for the synthesis of an appropriate number of developmentally competent oocytes through the folliculogenesis (Sidis *et al.* 1998). Folliculogenesis starts with the formation of primordial follicles, which are formed before birth and comprised of small, non growing, functionally immature oocytes, surrounded by a single layer of flattened pre-granulosa cells (Dissen *et al.* 2009). The ovary of a lamb contains about 230000 ± 120000 quiescent primordial follicles and only 250-1500 will start to grow in a process referred as follicle activation (Wandji *et al.* 1996; Fair, 2003). Thus, primordial follicles serve as a reservoir for cyclic recruitment of follicles and oocytes (Kim, 2012). Initiation of folliculogenesis through the induction of primordial follicles development has an important role in determining the fertility and reproductive fitness. Therefore, many studies have been performed to understand the mechanisms that control the primordial follicle activation. Most of the studies have been performed on while a limited number of studies were conducted in sheep. It has been observed that many many factors derived from oocytes, granulosa and somatic cells are involved in the control mechanisms, although results differ among species, age, physiological condition of the gonad and the environment. From the primary stage, these factors act in concert with gonadotropines and regulate the balance between survival

and apoptotic factors modulating whether a follicle continues to grow or undergo atresia. Presently, it is not possible to identify the key points determining whether a follicle will continue to develop or be diverted into atresia during the preantral stage. Therefore, intensive researches are required to identify the key points in sheep as well as in other mono-ovular species. Presently, plenty of knowledge is available to control the antral follicle growth and ovulation in sheep and in cattle. Therefore, the aim of this review is to evaluate the available knowledge of folliculogenesis, with a particular attention for primordial follicle growth in sheep.

Factors regulating the growth of primordil follicles

The activation or growth of primordial follicles is manifested by the differentiation of the flattened granulosa cells into cuboidal morphology, resulting in formation of larger primary follicles (Figure 1c). Granulosa cells proliferation and oocyte growth begin at this point and it is independent of gonadotropic effect (Wandji *et al.* 1992a; Mc Natty *et al.* 1999; Campbell *et al.* 2000; Fortune *et al.* 2000). Several autocrine, paracrine ad intracrine factors from oocyte, granulosa and stroma, as well as factors present in blood (*e.g.* insulin), were found to take part in the primordial follicles activation. Sheep pregranulosa cells secrete kit ligand (KL) under the influence of circulating insulin, leukemia inhibitory factor (LIF) from granulosa cells, bone morphogenetic protein (BMP), basic fibroblast growth factor (bFGF) and growth differentiation factor-9 (GDF-9) from the oocyte. Kit ligand secreted from granulosa causes a decrease the synthesis of BMP and the activity of forkhead transcription factor (FOXO3a) from the oocyte. Leukemia inhibitory factor produced from pregranulosa cells has autocrine and paracrine effect on granulosa and on oocyte to increase the secretion of KL and to decrease the activity of FOXO3a respectively. The secretion of mullearian inhibiting substance (MIS) from granulosa decreases, under the influence of circulating insulin, bFGF and LIF. Circulation insulin causes decrease in BMP synthesis from the stroma, increases the mitosis of granulosa cells and inhibits the activity of FOXO3a from the oocyte. Inactivation of FOXO3a is necessary for the transition of primordial follicle into primary stage. In the presence of KL, LIF and inactive FOXO3a, primordial follicles enter the early primary stage. Follicular growth before antrum formation (a-d) is not dependant on gonadotropines. By initiation of antrum formation (e-f), the dependency to gonadotropins, especially to FSH, increases (Figure 1).

Kit ligand and its receptor

Kit ligand (KL) is a multifunctional growth factor that belongs to the cytokine family. It is also known as stem cell factor (SCF) because of its ability to influence stem cell growth and differentiation. Kit ligand receptor (c-Kit) is a transmembrane tyrosine kinase receptor expressed in sheep oocyte (Clark *et al.* 1996). The stimulatory roles of KL and c-Kit in primordial follicles activation have been confirmed in neonatal mice after the treatment with a neutralizing c-Kit antibody (Yoshida *et al.* 1997). It was concluded that the KL/c-Kit interaction is important for primordial follicles activation, particularly during the first 5 days after the birth. Parrott and Skinner (1999) observed that the addition of recombinant human KL to rat ovaries organ cultures stimulated the transition of undeveloped primordial follicles to early primary stage and an increase of the number of primary follicles, while in porcine, Magamage *et al.* (2011) reported that KL does not promote primordial follicle activation, but promotes follicle viability. In human, Carlsson *et al.* (2006) reported that receptor KL/c-Kit signaling system is likely to control the survival of primordial follicles rather than their activation. In sheep, the presence of KL factor (but not KL mRNA) in granulosa cells of primordial follicles has been observed by Tisdall *et al.* (1999), as early as day 90 of gestation. This indicates that KL is synthesized in a distant site, in soluble form and then comes to granulosa cells. Although, the expression of KL and c-Kit protein in sheep ovary has been reported (Clark *et al.* 1996; Tisdall *et al.* 1999), but the contribution of KL and its receptor in sheep primordial follicle activation has not been studied yet. Leukaemia inhibitory factor (LIF) is a 43 kDa poly functional glycoprotein that belongs to cytokine family. Its name came from its ability to induce the terminal differentiation of myeloid leukemic cells. In culture condition, human granulosa cells can produce LIF (Coskun *et al.* 1998; Arici *et al.* 1997). In humans, the presence of LIF receptors has been shown in the oocytes of antral stage follicles and in early stage embryos (Van Eijk *et al.* 1996). It exerts an important role on follicular growth, oocyte maturation in a wide variety of cultured cell types including somatic and follicular cells (Demeestere *et al.* 2005). In rats, the immunocytochemical localization of LIF protein has been shown in the granulosa cells of primordial and primary follicles (Nilsson *et al.* 2002). It was also mentioned that LIF is absent or present at very low levels in the oocytes of these follicles. In ovarian culture, LIF promotes the transition of primordial follicles to primary stage in rat (Nilsson *et al.* 2002) and in goats (Da Nóbrega *et al.* 2012). It has been reported that LIF does not affect sheep and caprine preantral follicle growth in culture (Luz *et al.* 2012a; Luz *et al.* 2012b). In sheep, the effect of LIF on primordial follicle growth remains to be elucidated.

Anti-mullerian hormone (AMH)

Anti-mullerian hormone (AMH) or mullerian inhibiting substance (MIS) is a homodimeric disulfide linked glyco-

protein that belongs to transforming growth factor-β superfamily. In males, it is synthesized as a 140 kD protein by Sertoli cells from the time of fetal sex differentiation to puberty (Josso *et al.* 2001). It causes the regression of mullerian duct during the differentiation of the male reproductive tract. In females, it is synthesized by granulosa cells from the time of birth to the end of ovarian activity. It signals through two related but distinct receptors, both are serine / threonine protein kinases with a single transmembrane domain, called type II and type I. The type II receptor has been cloned in 1994 and it is expressed solely in AMH target organs. Engagement of the type I receptor BMPR-IB and downstream effector smad1 by AMH has been reported (Josso *et al.* 2001).

Studies on anti-mullerian hormone gene knockout mice (AMKO) have revealed that AMH, in addition to its role in primordial follicle recruitment, plays a role in fine-tuning the sensitivity of growing follicles to FSH. Despite a lower serum FSH concentration, ovaries of 4-month-old AMHKO mice contain more growing follicles than do ovaries of their wild-type littermates (Durlinger *et al.* 1999). This was confirmed by *in vitro* studies, which have shown that the addition of AMH to cultures of newborn mouse ovaries partially inhibited the initiation of follicle growth (Durlinger *et al.* 2002) and AMH attenuated the growth of medium-sized and large preantral follicles cultured in the presence of FSH (Durlinger *et al.* 2001).

The pattern of AMH expression in sheep is similar to that observed in mice (Durlinger *et al.* 2002) and humans (Weenen *et al.* 2004). Immunohistochemical studies, in sheep, have shown that only granulosa cells express AMH and its expression is influenced by animal age and by the degree of follicular development (Bézard *et al.* 1988). In contrast to mice, AMH does not affect the rate of primordial follicle recruitment but it appears to regulate the rate at which follicles progress through the gonadotropin-responsive phase, during which it is maximally expressed. Active immunization of sheep against AMH have also been reported to cause a decline in the population of gonadotropin-responsive preantral, a decline in the number of small antral follicles, increases in both the number of gonadotropin-dependent antral follicles and ovulation rate (Campbell *et al.* 2012).

Growth differentiating factor-9 (GDF-9)

Growth differentiation factor-9 (GDF-9) is a member of TGF-beta superfamily proteins. The active mature peptide is 135 amino acids long (Bodensteiner *et al.* 1999). It has a similar amino acid sequence to bone morphogenic proteins (BMPs) and its three dimensional structure is predicted to be also similar to BMPs structure (Mc Pherron and Lee, 1993). Growth differentiation factor-9 has been identified in the oocyte of sheep (Bodensteiner *et al.* 1999; Feary *et al.* 2007) and mice (Mc Grath *et al.* 1995; Dong *et al.* 1996) in all stages of follicular development.

In sheep, the gene coding GDF-9 protein is located on chromosome 5 (Sadighi *et al.* 2002) spanning about 2.5 kilo bases (kb). A mutation, in GDF-9 gene, has been found that causes increased ovulation rate in sheep (Feary *et al.* 2007). *In vitro* studies, in cattle (Tang *et al.* 2012) and goat (Martins *et al.* 2008), have shown the positive effect of GDF-9 in primordial follicle activation while, there are no reports in sheep. The potential role of GDF-9 in the primordial-primary follicle transition in sheep will need to be elucidated.

In GDF-9 deficient mice, oocyte growth and zona pellucida formation proceed normally, but other aspects of oocyte differentiation are compromised. Deletion of the GDF-9 gene, in mice, blocked folliculogenesis at the primary stage. Addition of GDF-9 to cultured preantral and primordial follicles from rats (Elvin *et al.* 1999; Hayashi *et al.* 1999; Vitt *et al.* 2000; Orisaka *et al.* 2006) and goats (Martins *et al.* 2008) increased follicular growth.

Growth Differentiation Factor-9 promotes granulosa cell proliferation as reflected by increases in thymidine incorporation (Vitt *et al.* 2000). Injection of GDF-9 gene fragments to the ovaries of 2-month-old pre-pubertal gilts resulted in an increase in the number of primary, secondary and tertiary follicles with a concomitant decrease in the number of primordial follicles (Shimizu *et al.* 2004).

Studies in humans have shown that addition of GDF-9 to the culture of ovarian follicles, within slices of ovarian cortical tissue, increased the proportion of growing primordial follicles. Therefore, more follicles went to primary stage of development (Hreinsson *et al.* 2002; Kedem *at al.* 2011).

Bone morphogenetic protein-15 (BMP-15)

Bone morphogenetic protein-15 (BMP-15) is an oocyte-derived growth factor and a member of transforming growth factor-β superfamily. It has high similarity to GDF-9 thus; it is also named as GDF-9B. According to a suggestion, both BMP-15 and GDF-9 have similar actions in sheep (Juengel *et al.* 2004), while *in vitro* studies show that GDF9 and BMP15 have distinct effects on reproductive physiology in a specie-specific manner (Vitt *et al.* 2002). The presence of a regulatory feedback system between oocyte BMP-15/GDF-9 and KL secreted from granulosa cells could maintain the appropriate expression level of BMP-15 and GDF-9 in the oocyte, which is essential for their physiological functions (Otsuka and Shimasaki, 2002). According to a report, in sheep, BMP-15 mRNA is not detected in oocytes of primordial follicles. It is expressed only in the oocytes of growing primary follicles (Dube *et al.* 1998; Laitinen *et al.* 1998).

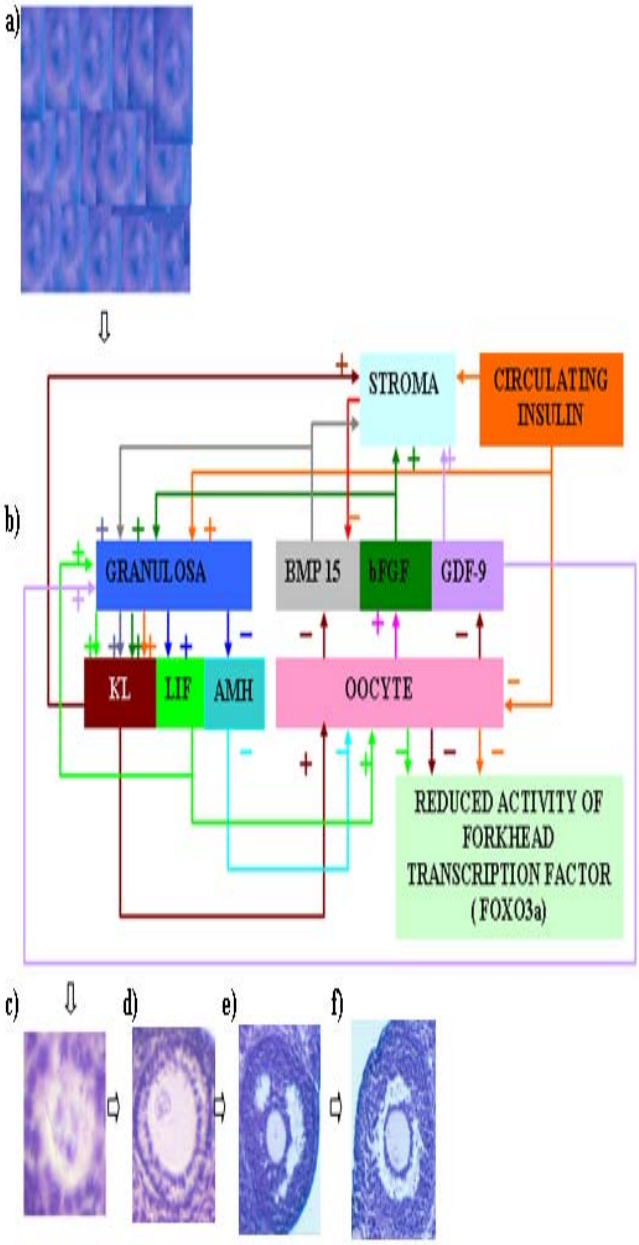

Figure 1 Schematic representation of folliculogenesis. a) Primordial follicles (oocytes surrounded by flattened granulosa cells). b) Local and circulating factors involved in the activation of primordial follicles. c) Primary follicle. d) Secondary follicle. e) Early antral follicle. f) Antral follicle. (Illustrations were obtained from Çiftci, 2004)

It was concluded that the expression BMP increases in relation to follicle growth (Otsuka *et al.* 2000). But, according to an *in vitro* study, mRNA expressions for GDF-9 and BMP-15 were detected in oocytes cultured for 15 days together with cortical slices of 5- to 6-month-old lamb. Along the 15 days of culture, the mean percentage of primordial follicles decreased, while the number of primary follicles increased (Mery *et al.* 2007). These two different results present some controversy. Thus, it is not quite clear whether BMP mRNA expression is present in the oocytes of sheep primordial follicles. Bone Morphogenetic Protein-15 stimulates KL expression in granulosa cells (Otsuka and Shimasaki, 2002). Interestingly, KL inhibits BMP-15 expression in the oocytes. Thus, BMP-15 and KL form a negative feedback loop between the oocyte and surrounding granulosa cells; when the oocyte produces BMP-15 this stimulates granulosa cells to produce KL that in turn signals back to the oocyte via c-kit to inhibit further oocyte BMP-15 expression (Figure 1). Therefore, BMP-15 might be involved in activating primordial follicles.

Basic fibroblast growth factor (bFGF)

Basic fibroblast growth factor (bFGF) is a single chain polypeptide composed of 146 amino acids. It is expressed by the oocytes of primordial follicles and the granulosa cells of developing follicles (Van Wezel *et al.* 1995; Yamamoto *et al.* 1997; Nilsson *et al.* 2001). Receptors for bFGF are found on granulosa cells (Shikone *et al.* 1992; Wandji *et al.* 1992b). Therefore, oocyte-derived bFGF is thought to signal to surrounding granulosa and stromal cells to promote the primordial to primary follicle transition (Nilsson *et al.* 2001). According to the result of a study, both KL and bFGF must be active for optimal promotion of the changes that occur in oocytes, granulosa cells, and stroma when primordial follicles start to develop (Nilsson and Skinner, 2004).

In rat ovarian culture, the ability of bFGF treatment to increase primordial follicle transition was blocked by an anti-c-kit receptor antibody. Also, the ability of KL treatment to increase primordial follicle transition was blocked by a bFGF neutralizing antibody (Nilsson and Skinner, 2004). In a study, pre-pubertal rat ovaries were cultured in the presence of bFGF and it was reported that the number of primordial follicles was decreased, while there was a corresponding increase the number of developing follicles (Nilsson *et al.* 2001).

Studies, concerning the effect of bFGF on primordial follicle growth, are generally focused on rodents. No particular results, indicating the effect of bFGF on sheep primordial follicle activation, are presently available.

Insulin

Insulin synthesized in the pancreas within the β-cells of the islets of Langerhans as a 6 kDa endocrine protein composed of two peptide chains referred to as the A and B held together by disulfide bonds. Its amino acid sequence varies among species, but certain segments of the molecule are highly conserved, including the positions of the three disulfide bonds, at the both ends of the A chain and at the C-terminal residues of the B chain. Its receptor expression has been shown in the oocyte of human primordial follicle and in the stromal cells surrounding oocyte by the avidin / bio-

tin immunoperoxidase techniques. With the increase in the size of the follicles, the immunostaining of the oocyte and follicular elements intensifies, while the staining intensity of the stromal cells surrounding growing follicles reduces (Samoto *et al.* 1993).

It was thought that insulin in circulation may promote primordial follicle activation. However, there is no report indicating the effect of insulin on primordial follicle activation in sheep. In other animals, such as rat, it was reported that the transition of primordial follicle to primary stage was increased after the addition of insulin to ovary culture as compared to control group, while insulin like growth factor-1 (IGF) did not cause any change (Kezele *et al.* 2002). It has also been reported that addition of insulin to LIF-supplemented rat ovarian culture enhanced the stimulatory action of LIF on primordial follicle activation (Nilsson *et al*. 2002). This shows that, effect of insulin on primordial follicle activation depends on animal species and also the availability of another factor.

Regulation of follicle growth from primary to antral stage

Once a primordial follicle enters the growth phase, it continues to grow until it becomes atretic or proceeds to ovulation. Previously, it was suggested that the entrance of primordial follicles into the growth phase was gonadotropin dependent. This suggestion was not confirmed by experiments in hypophysectomised sheep, because hypophysectomy did not prevent primordial follicles from entering the growth phase. Therefore, gonadotropines may not be essential agents in initiating follicular growth, but a basal level of gonadotropines especially FSH is required for normal development (Mc Neilly and Fraser, 1987). Studies, *in vivo* (Campbell *et al*. 2000) and *in vitro* (Hulshof *et al.* 1995; Gutierrez *et al.* 2000) have revealed that FSH can accelerate the rate of preantral follicle development. But, a role for LH in these early stages of development has not been defined. The sensitivities of preantral follicles to gonadotropines are probably determined by the number of receptors for LH, FSH and possibly prolactin. The development of these receptors depends on the stages of differentiation of the follicle. Granulosa cells of early developing follicles, such as secondary follicles, has FSH receptor expression (Mc Natty *et al*. 2000), but do not have LH receptors until an antrum forms (Armstrong *et al.* 1981; Ireland, 1987). The development of receptors for gonadotropines is influenced by the concentration of locally produced factors (such as BMP-15 and GDF-9) within the follicles. Both GDF-9 and BMP-15 are critical for ongoing preantral follicle development to ovulation, most likely by regulating the proliferative and differentiating functions of adjacent follicular cells. Immunization of sheep against GDF-9 and BMP-15 reduced follicle growth beyond the primary stage. Both GDF-9 and BMP-15 are essential for normal follicular development, including the early and as well as later stages of growth (Mc Natty *et al*. 2007).

Locally produced factors within the ovary, such as member of insulin like growth factor, fibroblast growth factor and epidermal growth factor are all involved in the regulation of preantral follicular growth (Armstrong and Webb, 1997; Webb *et al.* 1999).

Antral follicle growth

Antral follicle growth in sheep is characterized by a much faster growth rate. There are significant increases in the mitosis of granulosa cells (Mc Natty *et al.* 2007). Studies, including hypophysectomy and GnRH-agonist-induced hypogonadotropic hypogonadism (GnRHa), have revealed that antral follicle growth is dependent on the pituitary gonadotropines (Campbell *et al*. 1995). Suppression of FSH secretion and inhibition of pulsatile LH secretion by chronic GnRH agonist treatment stop preovulatory follicle growth. Infusion of pure sheep FSH induced a time-dependent development of preovulatory follicles up to 8 mm diameter, within 72 h of the start of infusion (Picton *et al.* 1990a).

Follicular fluid, in the antral cavity of follicles, is a source of inhibin and cause the specific suppression of FSH, treatment of ewes with follicular fluid at the start of the follicular phase results in the cessation of follicle development (Mc Neilly, 1984; Mc Neilly, 1985; Baird *et al.* 1990).

But, inhibition of pulsatile LH secretion did not prevent preovulatory follicle growth. This confirms that preovulatory follicle growth is not dependent of LH since, infusion of pulsatile LH alone did not cause growth in preovulatory follicles (Picton *et al.* 1990b). However, a basal level of LH is required for FSH induced pre-ovulatory follicle growth, as cessation of basal LH secretion, after the treatment of ewes with LH antiserum, prevented the induction of preovulatory follicle growth induced by FSH (Picton *et al.* 1991).

Although, preovulatory follicle growth, in sheep, is primarily dependent on FSH, the terminal phase of follicular development and differentiation is under the control of LH (Scaramuzzi *et al.* 1993; Campbell *et al.* 1995). As the preovulatory period progresses, the basal level of LH is capable of causing androgen production from theca cells and inducing LH receptors on granulosa cells, thereby causing the secretion of oestradiol that is not dependent on FSH (Webb and England, 1982; Baird, 1983). Thus, the secretion of oestradiol from the preovulatory sheep follicle depends on secretion of LH. Secreted estrogen appears to protect the growing follicle from androgen-induced atresia,

because atretic follicles are characterized by a low follicular fluid estrogen concentration and a decrease in the estrogen/androgen ratio (Filicori, 1999).

Antral follicle selection and dominance

During the follicular phase of the estrus cycle, gondotrophines control follicle growth and development (Hsueh *et al.* 1994; Hussein, 2005; Monniaux *et al.* 1997; Matsuda *et al.* 2012). The growth of small antral follicles is under the control of FSH and it is characterized by highly proliferating granulosa cells. Towards to the time selection occurs, granulosa cells of growing antral follicles progressively lose their capacity to proliferate, while their responsiveness to FSH, measured in term of cAMP (cyclic adenosine monophosphate) response to FSH, increases progressively.

The expression of CYP19A1 gene encoding the aromatase enzyme, in granulosa cells, increases under the influence of FSH. Therefore, oestradiol secretion from granulosa cells progressively increases. The estrogen synthesizing potential of a preovulatory follicle depends on the amount of androgen substrate produced from theca cells and the ability of granulosa cells to aromatize androgen to oestradiol. Thus, LH is also important factor for estrogen synthesis. A small rise in plasma LH, during the follicular phase, seems necessary for this change (Fortune, 1994).

It was reported that, in the presence of androstenedione, FSH stimulated inhibin production from rat granulosa cells in a dose-dependent manner *in vitro* (Bicsak *et al.* 1986). Therefore, the rate of estradiol and inhibin secretion is dependent on both LH and FSH secretion. Both oestradiol and inhibin modulate FSH secretion by negative feedback on the pituitary gland. The granulosa cells of pre-ovulatory follicles bearing LH receptors will be able to survive in lower serum concentration of FSH, while other follicles become atretic. Thus, the decrease in FSH levels during this time is a key mechanism in follicle selection.

Dominance occurs in the follicular phase when serum concentrations of LH increase and FSH decreases (Sunderland *et al.* 1994). A dominant follicle avoids its own regression by shifting its dependence from FSH to LH (Campbell *et al.* 1995).

Dominance is a process that enables the selected follicle to suppress further growth of other follicles, escape atresia and continue to grow until ovulation or eventual atresia. In sheep, administration of exogenous gonadotropines cause superovulatory response. If the dominant follicle secretes substances that directly inhibit the growth of other follicles, why is there superovulatory response to the administration of exogenous gonadotropines? Thus, it was thought that dominance is probably not operative in sheep. Also co-culture of small follicles with the largest follicles in a closed system did not reduce their incorporation of 3 H thymidine in granulosa cells as compared to small follicles cultured alone (Driancourt *et al.* 1991).

Regulation of follicular atresia

Follicular atresia is a degenerative process characterized by loss of proliferative and steroidogenic activities and loss of sensitivity of follicular cells to gonadotropines (Hsueh *et al.* 1994). Atresia can occur at any stage of follicular development. Big follicles are more susceptible to atresia than the smaller one (Gosden and Spears, 1997; Kaipia and Hsueh, 1997). There is little atresia in primordial follicles and it is also rare in primary follicles (Scaramuzzi *et al.* 1993; Hussein, 2005). When the follicular growth is progressed, the incidence of atresia increases (Figure 2).

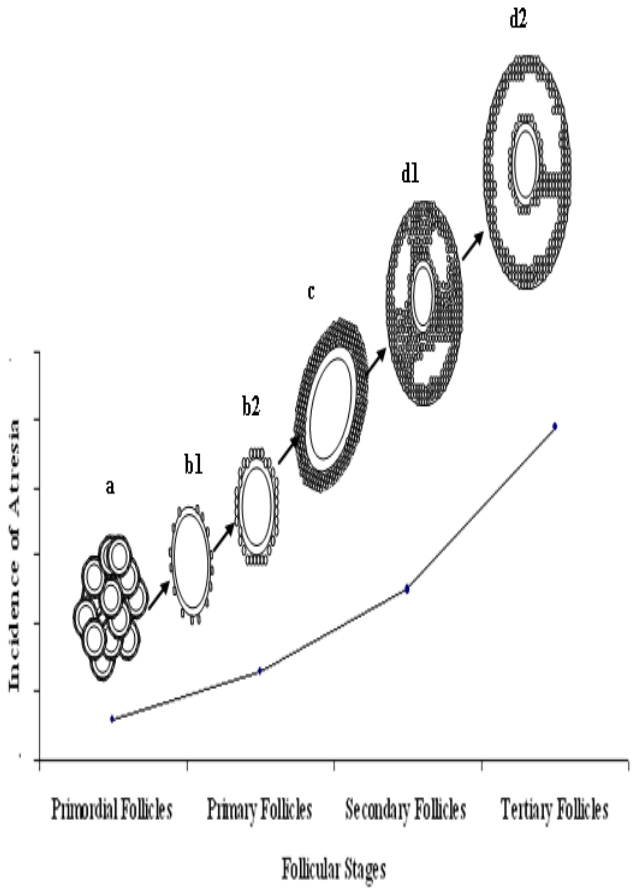

Figure 2 Schematic illustration of incidence of atresia in relation to the stages of follicular development. Atresia can occur at any stage of follicular development. There is little atresia in primordial follicles **(a)** and it is also rare in transitory (**b1**) and primary follicles **(b2)**. The incidence of atresia increases when the follicular growth is progressed from primary, secondary **(c)**, early antral **(d1)** and antral stages **(d2)**. In sheep, most of the atresia occurs when the serum concentration of FSH falls below the level to support the increasing number of developing follicles at preovulatory stage

In sheep, atresia in antral stage of follicular growth is characterized by a decreased in aromatase activity and es-

trogen synthesis in response to gondotropines. During the pre-ovulatory follicular development, a basal level of LH is capable of causing androgen production from theca cells and inducing LH receptors on granulose cells, thereby causing the secretion of oestradiol that is not dependent on FSH (Webb and England, 1982; Baird, 1983). The GnRH-antagonist suppression-ovarian autotransplant model has shown that the maintenance of FSH secretion throughout the follicular phase resulted in multiple follicle development and ovulation. In the absence of FSH, LH stimulated pre-ovulatory follicle development. In the absence of both FSH and LH, there were increases in atresia of the ovulatory follicles and anovulation (Campbell *et al.* 1999).

In sheep, as well as in other farm animals, a synergistic relationship has been proposed between the IGF ligands and receptors, and the gonadotropines, in the regulation of follicle growth and atresia (Adashi *et al.* 1988; Hammond *et al.* 1991; Hastie and Haresign, 2008). By using *in situ* hybridization, IGF-I mRNA was found in all major steroidogenic cell types of the sheep ovary, namely the granulosa, theca and luteal cells and, to a lesser extent, the stroma. However, no obvious differences in the levels of IGF-I mRNA expression were observed in ovaries recovered from FSH treated sheep (Leeuwenberg *et al.* 1995). Therefore, the relation between gonadotropines and IGF ligands looks a bit controversial. IGF binding proteins have attached more attention than IGF, in terms of its function in atresia.

The regulatory effects of gondotropines on gene expression for IGF binding proteins (IGFBP-2 to -6) in ovine follicles have been studied by using bovine follicular fluid (bFF) and gonadotropin-releasing hormone antagonist (GnRHa) model systems (Hastie and Haresign, 2010). It was reported that FSH and LH are involved, at least in part, in mediating the proliferative and differentiating changes in intra-follicular IGFBP levels that are observed during follicular growth and atresia. In hypophysectomised ewes, the expression of follicular IGFBPs < 40 kDa was increased during atresia of large follicles (Besnard *et al.* 1996).

Atresia involves granulosa cell apoptosis, which can initiate in mitochondria or cell surface by apoptosis inducing ligands binding to cell surface receptors. This leads to activation of a number of signaling pathways in which caspases are pivotal molecules (Hussein, 2005).

The roles of caspases in apoptosis first became evident when a cell death-related gene, *ced-3*, which is essential for apoptosis in *Caenorhabditis elegans*, was found to be homologous to the mammalian caspases (Yuan *et al.* 1993). Studies in mice, rat, cow, and human ovaries have shown that active caspase-3 causes apoptosis in antral stage follicles (Boone and Tsang, 1998; Matikainen *et al.* 2001; Fenwick and Hurst, 2002; Nicholas *et al.* 2005; Hurst *et al.* 2006). X-linked inhibitor of apoptosis protein (XIAP) has the ability to potently inhibit enzymatic activity of caspases-3, -7, and -9.

It was reported that sheep granulosa and theca cells of antral follicles express XIAP protein. The expression of this protein has been suggested to prevent the activation of caspase-3 by inhibiting its enzymatic activity and thus, regulating follicular atresia in antral follicles (Phillipps *et al.* 2011).

CONCLUSION

The majority of the factors affecting primordial follicle growth, mentioned here, have not been tested in sheep. Although many studies have been performed to understand the basic mechanisms controlling preantral follicle growth, the precise control points have not been indentified yet. Presently, there are plenty of data to control antral follicle growth and ovulation in sheep and cattle. Therefore, new experimental studies are necessary to identify the key points important for the control of prenatral follicle growth in sheep as well as in other mono-ovular mammals.

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