IGF-1 in Reproductive system of female, a Review

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Insulin-Like Growth Factor-I (IGF-I) in Reproductive System of Female - A Review

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Abstract

Insulin-like Growth Factor-I is a peptide with a molecular weight of 7649 Da. The IGF system is a complex molecule that can act autocrine, paracrine and endocrine which can be produced in the uterus, oviduct, ovaries, hypothalamus, and liver. Basically, IGF consists of six IGF-binding proteins (IGFBP 1 to 6) and two growth factors are IGF-I and IGF-II, two cell surface receptors (IGF-IR and IGF mannose-6-phosphate receptor (M-6-PR)) and nine related IGFBP proteins (IGFBP-rPS). IGFs are involved in cell proliferation, growth, differentiation and survival of cells as well as in metabolic regulation protein, glucose, and fat. Unlike insulin, the circulation of IGFs in complex plasma with a group of IGF specific binding proteins (IGFBPs). In the circulatory system more than 99% of IGFs are bound and means less than 1% in free. IGF-I plays a role in the female reproductive system, especially in the ovaries to stimulate development and growth of follicles (preantral follicles to antral follicles), stimulate the onset of puberty, maintain estrous cycles until can get pregnant, and during the postpartum period.

Keywords: Insulin-like Growth Factor–I; endocrine; paracrine; autocrine; female reproductive system.

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1. Introduction

Insulin-like Growth Factor-I is a peptide composed of 70 amino acids with a molecular weight of 7649 Da. Similar to Insulin, IGF-I has chains A and B which are connected by disulfide chains [1]. Of the 70 IGF-I amino acids, 12 amino acids analogous to pro-insulin C peptide, 21 homologous amino acids with A chain insulin, and 29 homologous amino acids with B chain insulin, while 8 other amino acids do not have the same function as insulin [2]. The IGF system is a complex molecule acting autocrine, paracrine and endocrine [3]. Endocrine action of IGF-I is demonstrated by the secretion of IGF-I by the liver and distributed through the circulatory system and reaches the target tissue and stimulating Growth hormone (GH) secretion from the pituitary. Except in liver, IGF-I is also secreted by several other body tissues (uterus, oviducts, ovaries, and hypothalamus) and role by paracrine-autocrine mechanism. The role of endocrine IGF-I is shown when the gene that encodes the secreting of IGF-I is removed will cause a decrease in IGF-I concentration by 75% in the circulatory system and will affect development and growth [4]. In this paper we review some of the literature related to Insulin-like Growth Factor-I (IGF-I) in the reproductive system of female animals.

2. Insulin-like Growth Factor–I (IGF-I)

2.1. Insulin-Like Growth Factor-I molecular structure

IGF-I and insulin have about 50% the same amino acid composition [5]. IGF-I has about 48% of amino acid sequences that are homologous with pro-insulin [6]. About 60-70% of the A and B domains of IGF-I and insulin are composed of the same amino acids [7]. The difference in shape and structure between IGF-I and insulin can be seen in Figure 1.

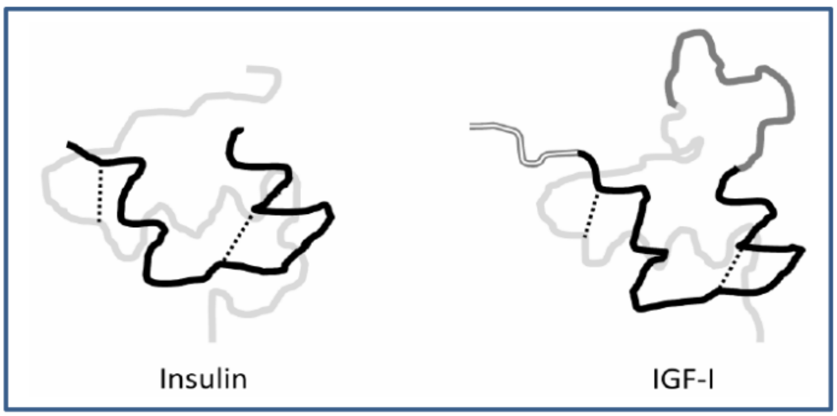

Figure 1: Structure of IGF-I and Insulin. Insulin consists of part A (black) connected to part B (gray) by a cysteine pathway (dotted line). Whereas IGF-I besides having parts A and B also have part C (dark gray) which is located between parts B and A and part D (open line) as the end [3]

2.2. Insulin-Like Growth Factor-I system and functions

The IGF system is a complex molecule acting autocrine, paracrine and endocrine. Basically, IGF consists of six IGF-binding proteins (IGFBP 1 to 6) and two growth factors are IGF-I and IGF-II, two cell surface receptors and nine related IGFBP proteins (IGFBP-rPS). Functions of IGF-IR are a biological target for IGF-I [3].

Function of IGFs are involved in cell proliferation, growth, differentiation and cell survival, protein regulation, glucose, and metabolism of fat. In general function of IGF is presented in Figure 2.

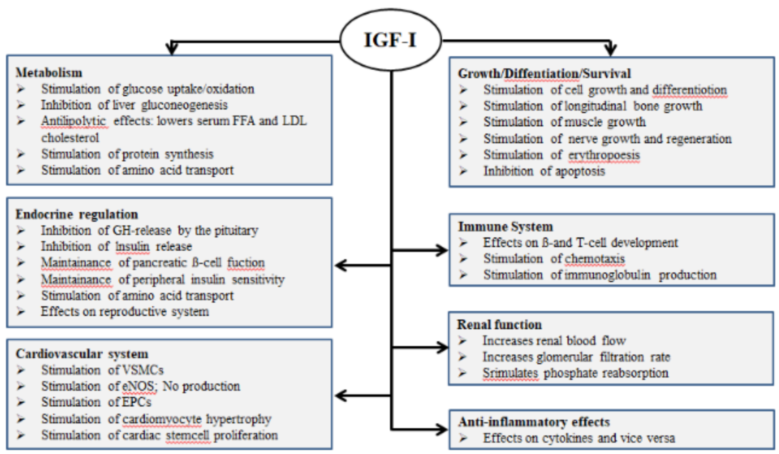

Figure 2: The general function of IGF-I (Modification of Schaid and his colleagues [8])

3. The Role of Insulin-Like Growth Factor-I (IGF-I) in Reproductive System of Female

3.1. Endocrine Action versus Paracrine-Autocrine Insulin-Like Growth Factor-I

The endocrine role of IGF-I is very important especially in the ovaries. This is evidenced by the administration of IGF-I exogenous to stimulate the growth and development of follicles and secretion of the hormone estradiol in sheep [9]. The peripheral concentration of IGF-I can regulate the reproductive mechanism by binding to its receptors. IGF-I receptor expression in cattle can be shown in the ovaries, oviducts, uterine cornua, and conceptus. In addition, in the brain are also expressed receptors of IGF-I and role to the release of LH. In general, the relationship between IGF-I endocrine and activity of reproductive is a causal relationship. The role of IGF-I endocrine mainly occurs in activity of ovarian while the role of paracrine-autocrine occurs in the oviduct and uterus [4].

3.2. Role of Insulin-Like Growth Factor-I during Puberty

Age of puberty in female cattle is a feature/sign that can be used as one of the most important production parameters to see the ability/level of productivity of livestock both dairy and beef cattle [4]. Puberty in cows is characterized by the first ovulation that follows estrus and the normal corpus luteum development [10]. The main endocrine factors at the onset of puberty are characterized by an increase in LH release during the peripubertal period, which increases follicular development in the ovary followed by an increase in estradiol production so as to induce estrus and preovulatory surge in gonadotropin. Nevertheless, the hormonal mechanism is greatly influenced by body size and metabolic status [11].

Besides weight, IGF-I concentration in blood serum is also influenced by breeds. Further it was explained that nutrition also greatly influences the concentration of IGF-I before puberty. Heifer who gets good quality feed will reach puberty earlier than those who get restricted feeding. Restrictions on feeding are related to low IGF-I concentrations in the blood resulting in a low ability of the ovaries to produce estradiol preovulatory thereby inhibiting LH surge stimulation [4].

3.3. Role of Insulin-Like Growth Factor-I during the estrus cycle

After puberty, the cow must maintain its estrous cycle until become pregnant. This proves that IGF-I can affect activity of follicular and luteal. From the endocrine side, IGF-I greatly influences the estrus cycle and is highly dependent on the availability of nutrients. This is evidenced by the gradual limitation of feed which can reduce the concentration of peripheral IGF-I in cows that are in cycle can even cause ovulation failure [4]. Blood plasma derived from animals that are treated with food restriction gives a less effect in stimulating the proliferation of granulosa cells in vitro when compared to blood plasma from cyclic heifers [12]. The concentration of IGF-I progressively increases during the follicular growth wave until it reaches the dominant follicle until ovulation and will subsequently re-cycle [4]. Failure of ovulation can occur during feed restriction, this is thought to be related to the lack of IGF-I concentrations in follicular fluid in the ovaries [13], although there is no specific corelation between changes in IGF-I concentration, LH and FSH secretion with weak ovarian function as a result of feeding restrictions in heifers [4]. This shows that to be able to reach ovulation requires IGF-I concentrations circulating in sufficient quantities.

Spicer and his colleagues [12] reported that limiting food intake could reduce follicular size without affecting the concentration of IGF-I in plasma and follicles fluid of cycle cows. It was further explained that the concentration of IGF-I in blood serum was not related to variations in the number of follicles during growth of follicular wave in dairy cows lactating. However, what gives a direct influence on activity of ovarian is how much concentration of IGF-I is found/circulates in the ovary. IGF-I concentrations in fluid follicle can be lower, equal, or higher than IGF-I concentrations in peripheral blood, although there is a correlation between them. In some cases for example, in a short-term state of fasting the concentration of IGF-I secreted from the liver significantly decreases not affect the concentration of IGF-I intrafollicular. Whereas in conditions pathological such as ovarian cystic, concentrations of IGF-I intrafollicular can be lower than concentrations of IGF-I serum [4].

In connection with function of luteal, cells luteal in cows express IGF-I mRNA [14] and protein [15]. Giving IGF-I with a system microdialysis can stimulate in vitro production of progesterone [15]. In post puberty cows that under conditions of negative energy balance (NEB) IGF-I concentrations in blood plasma are lower, corpus luteum is small, and lower concentrations of progesterone in corpus luteum compared to heifers in conditions of positive energy balance (PEB) [16]. However, when the concentration of IGF-I is restored by administration of bovine somatoropin (bST), the weight or progesterone concentration in the corpus luteum is not affected [17]. Therefore, the intraovarian IGF system may become more important than the system endocrine in function of luteal.

Based on several researchs, throughout the estrous cycle IGF-I secretion pattern in cattle varies. Velazquez and his colleagues [4] notifyed that throughout the period preovulatory there was an increase in the concentration of IGF-I in circulation in dairy and beef cows. It was further explained that the IGF-I concentration in plasma remained relatively stable throughout the estrous cycle. Spicer and his colleagues [12] explained that IGF-I concentrations in circulation were not significant variations in crossbred cattle. Bishop and his colleagues [18] reported that IGF-I concentrations in blood might represent status of nutrition and the potency for estrous cycles normal.

3.3.1. Influence of Insulin-Like Growth Factor-I on preantral follicles

Vendola and his colleagues [19] reported that the IGF-I and its receptors can mediate the transition of primordial to primary follicles, this is evidenced by hormonal treatment can increase the number of follicles primary, together with a threefold increase concentration of IGF-I and five times the IGFR-I mRNA in oocytes primordial follicles. Fortune and his colleagues [20] explained that the initial stages of follicular development in cows are regulated by IGF concentrations in the follicular microenvironment, although administration of IGF-I did not encaurage the transition of follicles primordial to primary during ovarian culture. Armstrong and his colleagues [21] reported that the system of IGF was not the initiation of growth in primordial follicles, but was the subsequent growth process. In cows, IGFBP-2 and IGFBP-3 are detected in preantral follicles. IGFBP-2 and IGFBP-3 can bind to IGF from circulating or adjacent follicles antral and access regulate to receptors of IGFR-I in oocyte and preantral follicular cells granulosa.

For growth of secondary follicular, supplementation of 100 mg/L IGF-I on medium culture effectively to stimulates follicles growth and maintains survival oocyte of goat during in vitro culture. In cattle, IGF-I supplementation can increase diameter of follicular and production of estradiol when follicles preantral are in vitro culture. IGF-I supplementation (1-100 ng/mL) in rat follicle culture stimulates the development of follicles secondary in vitro, both in terms of follicle cell differentiation and proliferation. Ultrastructure of cultured follicles is better in media containing IGF-I compared without IGF-I. It was further explained that in culture conditions the theca cells degenerate without IGF-I, but in the presence of IGF-I ultrastructure normal theca cells are characteristic in the presence of steroid secretion. In addition, oocytes from follicles cultured by IGF-I supplementation contain granules cortical that are distributed along the ooplasm membrane, while those without cortical IGF-I granules are not well distributed [22]. Demeestere and his colleagues [23] reported that after the process of mature oocyte fertilization, embryonic development and the number of blastomer cells increased when the follicle was cultured with IGF-I supplementation.

3.3.2. Influence of Insulin-Like Growth Factor-I on antral follicles

In IGF-I knockout conditions, follicular populations do not arise to be affected until the initial stage antral, but not contain follicles antral and ovulate in the ovaries, moreover after treatment with gonadotrophins exogenous. This indicated that during the development of antral follicles, the IGF have an important role. The administration of IGF-I has a strong and specific effect on in vitro cultured cells granulosa of pig in conditions without serum. It was further reported that IGF-I mainly supported the proliferation of small follicular cells granulosa, while in large follicles antral stimulated secretion of progesterone by cells granulosa in sheep. This shows that stimulates of IGF-I either differentiation or proliferation of cells granulosa, depending on the follicular development stage. In cattle and mice, IGF-I appears to play an important role in small antral follicles to increase their sensitivity to action gonadotropin and transition to follicular development to the next stage. In cattle, IGF-I stimulated of small antral follicles to growth and increases viability of oocyte. In addition, the proliferation and increase secretion of hormone estradiol is stimulated by IGF-I. It was further explained that IGF have a role to an autocrine mechanism in cells theca and paracrine in granulosa cells [22].

IGF-I is known to have a synergistic role with FSH to increase the activity of cells granulosa for proliferation and steroidogenesis. Together with FSH, IGF-I also increases synthesis of LH receptor in cells theca and cells granulosa from follicles antral [22]. The mechanism of the steroidogenesis process in granulosa cells and theca cells is presented in Figure 3. Hastie and Haresign [24] reported that elevated concentrations of IGF-I could modify the regulation of follicular follicogenesis system in ovaries: (1) follicular recruitment for development further, (2) follicles preantral activation and development, (3) maintaining antrum cavities in small antral follicles, and (4) selection of follicles dominant in the follicular wave. The system of IGF in preparing dominant follicles plays role in reducing the FSH availability and increasing the LH availability. The role of IGF-I in follicular growth is presented in Figure 4.

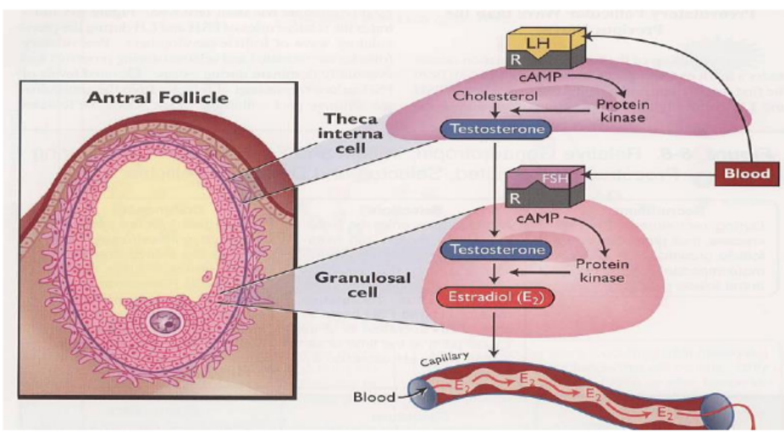

Figure 3: Mechanism of estradiol synthesis by granulosa cells [25].

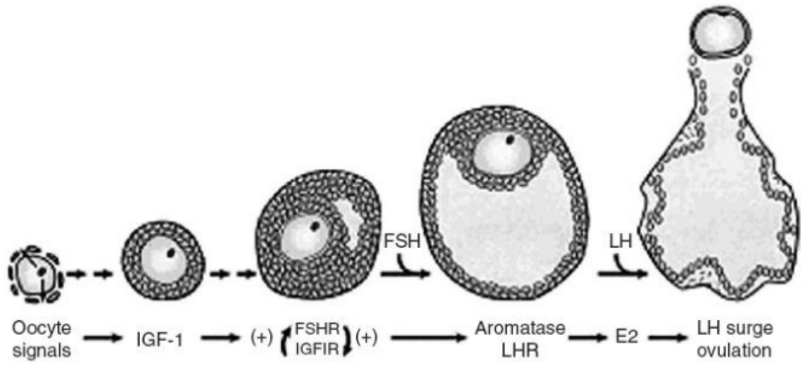

Figure 4: The role of IGF-I in follicles development [26].

3.4. Influence of Insulin-Like Growth Factor-I during pregnancy

After the fertilization process, the embryo must be transported through the oviduct, implantation in the uterus and develop into a healthy fetus until near the end of pregnancy. Endocrine IGF-I plays an important role in influencing the survival of the embryo during the process of transportation to the lumen of organs reproductive, or indirectly through actions on the ovaries, oviducts or uterus. The results showed that IGF-I in vitro embryo production could play a positive role in the development of preimplantation cow embryos. It was further explained that in in vitro embryo culture with IGF-I supplementation during the period of culture the pregnancy rate was higher after transfer to recipients. This is supported by the IGF-I receptors presence in preimplantation embryos. Oviducts, uterus and embryos produce IGF-I and various IGFBPs, so it is likely that the IGF-I availability in the channel is regulated by local factors. In addition, the high IGF receptors expression in the oviduct and uterus indicates that endocrine IGF-I can have an effect indirect through important changes in oviduct and uterine secretion in support of early embryonic survival and changes in local IGFBPs expression patterns can also affect of status metabolic in the oviduct and supports embryonic development during pregnancy [4]. In general, on the 16th day of pregnancy interferon-tau is produce at a concentration sufficient to prevent luteolysis and the mother can accept the embryo [4]. Interferon-tau production by trophoblastic cell of embryos is highly dependent on the pattern secretion of progesterone, mainly at the first week after ovulation and when embryonic development is beginning [27]. Progesterone secretion by luteal cells begins when there is a bond between LH and the receptors on the surface of luteal cells which activates G protein then activates adenylate cyclase to convert ATP to cAMP. cAMP will be activate of protein kinase enzymes and accelerate LDL cholesterol receptors internally, activating the cholesterol esterase enzyme which will break down cholesterol from esters so that cholesterol can enter the mitochondria and the mitochondrial enzymes will convert cholesterol into pregnenolones and then be converted into progesterone enzymatically. In pregnant cows, the concentration of IGF-I in blood plasma is higher than in cows that are not pregnant. The difference increases after conception and statistically significantly increases at 15 weeks after conception. The concentration of IGF-I circulating in the circulatory system will continue to increase at the first and second trimesters and begin to gradually decrease at the beginning of third trimester [4]. This is likely due to decreased IGF-I secretion from the liver as a result of changes in food intake patterns during pregnancy. In the 23rd week of pregnancy the food intake is higher than in the early stages of pregnancy, but from the 26th week onwards it gradually decreases and reaches its lowest point at parturition. The quality feed and changes of hormonal affect the reduction in nutrient intake as a result of pregnancy. In addition, another important factor that can also influence is rumen capacity. For example, at gestational age around day 70 there is a correlation positive between fetal body weight and concentration of IGF-I in blood serum, but after that growth and fetal weight are correlation negative with concentration of IGF-I in blood serum [28]. It was further reported that pregnant cows with female fetuses had higher IGF-I concentrations in serum compared to animals that were pregnant with male fetuses. Whereas pregnant cows with twin fetuses IGF-I concentrations are lower than cows who are pregnant with a single fetus at the last trimester of pregnancy. Other researchers report that the sex of the fetus has no effect on IGF-I concentrations, nor with the number of fetuses IGF-I concentrations in the circulatory system are no different. This proves that the concentration of IGF-I in the circulatory system is more influenced by the amount of nutrient intake. The supplementation of feed at the first and second trimesters of pregnancy can change the concentration of IGF-I in the blood without impacting the live weight and birth weight of the calf [4].

3.5. Influence of Insulin-Like Growth Factor-I during postpartum period

The anestrus period after giving birth becomes a very important period because it is related to reproductive efficiency in both beef and dairy cows. One reason is the failure of ovulation not because of the lack development of dominant follicles [29]. Anestrus period after giving birth is shorter in dairy compared with beef cows, one of the factors that influence it is nutrition. The energy balance in the postpartum condition is very important for the resumption of normal cycles and is also closely related to the concentration of IGF-I circulating in the circulatory system. Dry matter intake and feed energy content in the first weeks of lactation are correlation positive with IGF-I concentrations in the blood [4]. Spicer and his colleagues [12] reported that the low IGF-I concentrations in serum were associated with reduced activity of ovarian as a result of NEB during the period of postpartum. Zulu and his colleagues [30] reported that nutritional regulation greatly influences performance of reproductive in cattle during postpartum, this is mediated by the concentration of IGF-I in circulation. It was further explained that the concentration of IGF-I in plasma during the period of postpartum linearly increased until the first day of ovulation, this was closely related to the length of postpartum anestrus. Increasing the concentration of IGF-I 1 ng/ml in circulation reduces 0.13 days of the first interval of ovulation after giving birth. The same is true for dairy cows with follicles ovulation during the first week of postpartum usually showing higher concentrations of IGF-I in the blood compared to animals with ovaries inactive, follicles cystic and corpus luteum persistent. In addition, the reduction in frequency of milking tends to increase IGF-I concentration and is associated with a reduction in the first ovulation interval [4]. The endocrine pattern of IGF-I at the prepartum and postpartum periods is very typical. The concentration of IGF-I in the blood begins to decrease in the last days of pregnancy, reaches its lowest point in the first week post calving, and again begins to increase thereafter. The peripheral IGF-I concentration at postcalving is influenced by breed and production of milk. In beef cattle, plasma IGF-I concentrations increase linearly during the postpartum period, but this is not always the case for all breeds. Whereas in dairy cattle (FH), cows whose milk production is only 5.000-6.000 kg per lactation (305 days) do not experience a decrease in IGF-I concentration during postpartum and the lowest point is reached in the first week of the postpartum and continues to decline as a result of increased production milk 7.000-9.000 kg [4]. Although some researchers report that there is no clear relationship between endocrine of IGF-I and activity reproductive during the period of postpartum with differences in breeds and milk production levels [31].

4. Conclusion

Insulin-like Growth Factor-I is a peptide produced in the ovary, oviduct, uterus, hypothalamus, and liver, that can act autocrine, paracrine, and endocrine. Unlike insulin, IGF circulates in the complex plasma with a group of IGF specific binding proteins, and to be able to functions IGF-I must be mediated by interactions with six types of IGF Binding Protein (IGFBP). IGF-I plays a role in the female reproductive system, especially in the ovaries to stimulate growth and development of follicles, stimulate the onset of puberty, maintain estrous cycles until they can finally become pregnant, and during the postpartum period.

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