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The Effect of Insulin-Like Growth Factor System on Embryo Growth and Development

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Abstract: Insulin like growth factors (IGF-I and IGF-II) are expressed in embryos and reproductive tracts of several species including cow, sheep and swine. They are mitogenic and have endocrine, paracrine and autocrine function infusing cell division, blastocyst formation, implantation and embryo growth. Increase in embryo growth will probably result with a higher implantation rates leading to consequent increases in the number of live offspring. In this review, insulin, IGFs, their receptors and their physiology and function in embryonic growth development were concerned.

Key words: Development, embryo, growth, IGF, IGFBP, insulin

INTRODUCTION

Insulin synthesized in the pancreas within the beta cells (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. The receptors for insulin have been shown in embryos of rabbit, mouse, rat, cow and sheep (Mattson *et al*., 1988; Harvey *et al*., 1995; Kaye and Harvey, 1995; Santos *et al*., 2004) and the beneficial effect of insulin on development of preimplantation embryos in mice (Gardner and Kaye, 1991), rats (Hertogh *et al*., 1991), pigs (Lewis *et al*., 1992) and cattle (Matsui *et al*., 1995) have been reported.

The amino acid sequences of insulin and insulin-like growth factors (IGF-I and IGF-II), from all vertebrate groups, are currently known and there is a high degree of similarity for each hormone among the different vertebrates (Reinecke and Collet, 1998). Because, insulin, IGF-I and II have been derived from a common ancestral molecule through a series of gene duplications and point mutations.

Insulin like Growth Factors (IGFs) are normally expressed in various tissues and reproductive organs (Table 1) of many species (Carlsson *et al*., 1993; Spicer, 1995; Daliri *et al*., 1999; Kowalik *et al*., 1999; Watson *et al*., 1999; Wang *et al*., 2000; Jin and Wang, 2001; Pushpakumara *et al*., 2002; Hastie *et al*., 2004; Daftary and Gore, 2005; Hastie and Haresign, 2008; Zakaria *et al*., 2009). Also, oviductal and endometrial secretions contain IGF-I and IGF-II in many species including pig, cow and sheep (Letche *et al*., 1989; Simmen *et al*., 1989; Geisert *et al*., 1991; Ko *et al*., 1991; Wiseman *et al*., 1992; Makarevich and Sirotkin, 1997).

Endocrine IGF-I has been associated with several reproductive traits, such as age at first calving (Yilmaz *et al*., 2006; Brickell *et al*., 2007), conception rate to first service (Patton *et al*., 2007), twin ovulations (Echternkamp *et al*., 2004), and pre-implantation embryo development (Velazquez *et al*., 2005). Insulin-like growth factor-II is essential for normal placental and fetal growth, but not post-natal growth (DeChiara *et al*., 1990). Excess IGF-II is, however, detrimental to the embryo or fetus as it can lead to over-stimulation of IGF-1R, resulting in somatic overgrowth, cardiac and skeletal abnormalities and perinatal death (Lau *et al*., 1994).

Increase in the number of live newborn is dependant upon the optimal uterine environment concerted with of optimal physiology mediated by hormones and growth factors. The aim of this review is to outline the impact of insulin and insulin like growth factors on embryo growth and development.

Insulin and its role in embryonic development: Insulin is composed of 51 amino acids. 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.

Insulin signals through the receptor embedded in the plasma membrane. Its presence in embryos of mouse, rat, cow and sheep have been reported (Harvey *et al*., 1995; Kaye and Harvey,1995) and the stimulatory effect of insulin on cow (Zhang *et al*., 1991), rat (Zhang and Armstrong,1990) and pig (Lewis *et al*., 1992) embryos have been mentioned. Dose response studies provided evidence that the insulin receptor mediated the stimulatory actions of insulin. Insulin receptor is composed of two extracellular α-subunits and two transmembrane β-subunits linked by disulfide bonds. Binding of insulin to the α-subunit induces a conformationalchangeresulting in the autophosphorylation of a number of tyrosine residues present in the β-subunit (Van Obberghen *et al*., 2001). Insulin receptor functions just like an enzyme transferring the phosphate groups from ATP to tyrosine residues on intracellular proteins which in turn alters their activity, thereby generating a biological response (Lizcano and Alessi, 2002).

Table 1: Insulin-like growth factor ligand and receptor expression in reproductive organs of bovine, ovine and swine

	Bovine			Ovine			Swine		
Liands and receptors	Ovary	Oviduct	Uterus	Ovary	Oviduct	Uterus	Ovary	Oviduct	Uterus
IGF-I	+	+	+	+	+	+	+	+	+
IGF-II	+	+	+	+	+	+	+	+	+
IGF-IR	+	+	+	+	+	+	+	+	+
IGF-IIR	-	-	-	+	-	-	+	-	-

+: Indicates the presence of expression, references in text above; -: Indicates that the data is not present, references in text above

Insulin promotes growth of pre-implantation embryos in several species (Susa *et al*., 1984; Kane *et al*., 1997). Insulin response arose during compaction (Harvey and Kaye, 1988) and persisted in both trophectoderm and inner cell mass lineages of the blastocyst (Harvey and Kaye, 1991). The number of cells within bovine (Zhang *et al*., 1991) and murine (Gardner and Kaye, 1991) blastocysts is increased by culturing in medium supplemented with insulin. However, insulin did not stimulate cell proliferation in trophectoderm, as it did in the inner cell mass (Harvey and Kaye, 1991). The resistance of trophectoderm proliferation to insulin suggests that the receptors in these cells are coupled to a different set of signaling pathways from those in the inner cell mass. Apical and basolateral membranes of trophectoderm cells and the inner cell mass membranes seemed to express both insulin and IGF-1 receptors. Therefore, it is controversial whether insulin is capable of inducing mitogenic effects through its own receptor, or whether the growth-promoting effects of insulin result from its weak interaction with the IGF-I receptor or occur within insulin/IGF-I receptor hybrids (Sweet *et al*.,1987; Soos *et al*., 1993).

Insulin-like growth factors and their role in embryo development: Insulin and IGF-I, II act endocrine as well as paracrine/autocrine manner mediated by, two type of receptors (IGF-IR, IGF-IIR) and six IGF binding proteins (IGFBPs) (Jones and Clemmons, 1995; Pavelic *et al*., 2007). Mature IGF-I and IGF-II consist of A, B, C, and D-domains. The A- and B-domains of IGFs are homologous to those of insulin. Unlike in the case of insulin, the C-domain is not cleaved off in mature IGFs. Insulin-like growth factors contain an additional D-domain, which is not present in insulin (Le-Roith *et al*., 2001).

The IGF peptides (IGF-I and -II) mediate their effects through IGF-IR receptor, which is structurally related to the insulin receptor and binds both IGF-I and IGF-II with high affinity and insulin with lower affinity. Insulin-like growth factors-IIR receptor, also known as the mannose-6-phosphate receptor, binds IGF-II with high affinity but will not bind IGF-I or insulin (Fig. 1).

The expression of IGF-I, II and their receptor proteins (IGF-1R and IGF-IIR) have been detected in ovary, oviducts and uterus of bovine (Table 1) (Daliri *et al*., 1999; Armstrong *et al*., 2000; Llewellyn *et al*., 2007; Sudo *et al*., 2007; Winger *et al*., 1997; Fenwick *et al*., 2008a, b), ovine (Teissier *et al*., 1994; Stevenson and Wathes , 1996; Taylor *et al*., 2001; Hastie *et al*., 2004; van Lier *et al*., 2006) and swine (Simmen *et al*., 1992; Liu *et al*., 2000).

The presence of IGF ligands and receptors in pre-implantation embryos from the different species, including sheep, have also been mentioned (Watson *et al*.,1994, 1999; Lonergan *et al*., 2000; Lighten *et al*., 1997; Wang *et al*.,2009).

It has been reported that, Addition of IGF-I, IGF-II to the culture of bovine embryos significantly accelerated embryonic development, especially the change from the expanded blastocyst to hatched blastocyst stages (Neira *et al*., 2010). In bovine, addition of IGF-I and II to the *in vitro* maturation or culture media increased embryo development (Bonilla *et al*., 2011). The similar result obtained from rabbit, When rabbit embryos incubated with IGF-I progressed to the blastocyst stage (Herrler and Beier, 1994). In mouse embryo culture, when IGF-II expression was reduced by the presence of antisense IGF-II oligonucleotides, the rate of embryo development was inhibited. This effect was abolished by the addition of IGF-II to the culture medium (Rappolee *et al*., 1992).

Also, insulin-like growth factors are important for the development and functional maturation of the Central Nervous System (CNS), skeletal tissues, and reproductive organs. In mice, knock out of the IGF-I gene causes infertility (Baker *et al*., 1996), underdevelopment of muscle tissue (Powellbraxton *et al*., 1993), significant decrease in auditory neuron number and increase in apoptosis of cochlear neurons (Camarero *et al*., 2001).

Insulin-like growth factor-I (GF-1) and its impact on embryo development: Insulin-like growth factr-1 (GF-I) is a single-chain polypeptide with a molecular mass of 7649 Da and shares 43% amino acid sequence homology with insulin. This peptide is produced in organs of reproductive significance such as hypothalamus, ovaries, oviducts, and uterus (Spicer, 1995; Watson *et al*., 1999; Daftary and Gore, 2005). The IGF-1 exerts its effect by binding to high-affinity membrane receptors. The IGF-I receptor (IGF-IR) binds to IGF-I with the highest affinity and there is a 60% homology between IGF-1R and the insulin receptor (DeMeyts and Whittaker, 2002). The IGF-IR has two α-subunits and two β-subunits linked by disulfide bonds (Fig. 1). The α-chains are located extracellularly while the β-subunit spans the membrane

and is responsible for intracellular signal transduction upon ligand stimulation. Both of the subunits (α and β) are synthesized from a single mRNA precursor. The α-subunit contains a cysteine-rich ligand-binding site. The precursor is glycosylated, proteolytically cleaved, and cross-linked by cysteine bonds to form a functional transmembrane αβ-chain. The b-subunit has tyrosine kinase activity. Insulin and IGF-1 can cross-activate the receptors, due to the exhibition of high sequence and structural similarity, when they added together at high concentrations in cell culture studies. Recent genetic studies in Xenopus and zebrafish suggest that the structure and function of the IGF-IR is evolutionarily conserved (Pera *et al*., 2001; Richard-Parpaillon *et al*., 2002; Eivers *et al*., 2004; Schlueter *et al*., 2006, 2007). Using antisense Morpholino Oligonucleotide (MO)-based target gene knockdown approach and by specific inhibiting IGF-1R-mediated signaling using a dominant-negative IGF-IR fusion protein, Schlueter *et al.* (2007) have shown that IGF-IRs in zebra fish are required for embryo viability and proper growth.

Most of the IGF-I measured in blood is produced by the liver (Pfaffl *et al*., 1998; Yakar *et al*., 1999; Fenwick *et al*., 2008a, b). Endocrine IGF-I has been associated with several reproductive traits, such as age at first calving (Liu *et al*., 1993; Baker *et al*., 1996; Zhou *et al*., 1997; Kadakia *et al*., 2001; Yilmaz *et al.*, 2006; Brickell *et al*., 2007), conception rate to first service (Patton *et al*., 2007), twin ovulations (Echternkamp *et al*., 2004) and preimplantation embryo development (Velazquez *et al*., 2005).

Locally produced IGF-I in ovary has various actions including enhancement of cell proliferation, aromatase activity, and progesterone biosynthesis (Adashi *et al*., 1985; Kamada *et al*., 1992; Savion *et al*., 1981). Supplementation of bovine embryo culture with IGF1 has been reported to increase rate of blastocyst development, embryo survival as well as reducing the effects of heat shock on embryos (Bonilla *et al*., 2011).

Insulin-like growth factor-II (IGF-II) and embryo development: Insulin-like growth factor-II (IGF-II) is a single chain polypeptide. Mature IGF-II is a 7.5 kDa protein (Liu *et al*., 1993). It binds to the IGF-IR and with the highest affinity to type IGF-II receptors (IGF-IIR). IGF-IIR is a polypeptide hormone and sharing approximately 70% sequence identity with IGF-IR. But, IGF-IIR is also acts as a mannose-6-phosphate (M6P) receptor. Therefore, it is structurally and functionally distinct from the IGF-IR. The IGF-IIR/ M6P are a monomeric transmembrane protein with an extracellular domain composed of 15 cysteine-rich repeats. Mammalian IGF-IIR/ M6P has about 100 times higher affinity for IGF-II than IGF-I. Knockout of the IGF-IIR gene or loss of the imprinted IGFIIR results in fetal overgrowth and perinatal lethality (Lau *et al*., 1994; Wylie *et al*., 2003).

Insulin-like growth factor-II is expressed in ovary, oviduct and uterus of human, bovine and sheep (Watson *et al*., 1999; Wang *et al*., 2000; Jin and Wang, 2001; Hastie *et al*., 2004; Hastie and Haresign, 2008; Zakaria *et al*., 2009). In mice, use of homologous recombination technology proved conclusively that IGF-II was required for normal embryonic development, as IGF-II null mice were 60% smaller than their wild-type littermates (DeChiara *et al*., 1990, 1991). IGF-II has been reported to be essential for normal placental and fetal growth, but not post-natal growth (DeChiara *et al*., 1990). Excess IGF-II is, however, detrimental to the embryo or fetus as it can lead to over-stimulation of IGF-1R, resulting in somatic overgrowth, cardiac and skeletal abnormalities and perinatal death (Lau *et al*., 1994).

The effect of IGF-binding proteins and their functional role: There are a family of secreted proteins, named as Insulin-like Growth Factors Binding Proteins (IGFBPs) that specifically bind IGF-I and IGF-II with affinities that are equal to or greater than those of the IGF-IR (Fig. 1). There are six well characterized mammalian IGFBPs, designated IGFBP-1 to -6 (Allan *et al*., 2001). Most IGFBPs, including IGFBP-2 to -6, are expressed in peripheral tissues and most mammalian cells express more than one form of IGFBPs (Duan and Xu, 2005; Firth and Baxter, 2002; Jogie-Brahim *et al*., 2009; Jones and Clemmons, 1995; Yamada and Lee, 2009). Insulin-like growth factors binding proteins function as carrier proteins in the circulation and regulate IGF turnover, transport, and half-life of circulating IGFs (Jones and Clemmons, 1995). The affinity of IGFBPs for IGFs is controlled by phosphorylation, glycosylation and specific proteolysis (Clemmons, 1998). The IGF/IGFBP complexes help to prevent potential hypoglycemic effect of circulating IGFs by preventing possible cross-binding of IGFs with the insulin receptor (Rajaram *et al*., 1997). In addition to functioning as carrier proteins, IGFBPs also have their own receptors mediating IGF-independent actions. Cell surface receptors for IGFBP-1 (Jones *et al*., 1993), IGFBP-2 (Rauschnabel *et al*., 1999), IGFBP-3 (Oh *et al*., 1993), IGFBP-5 (Andress, 1995, 1998), IGFBP-6 (Bach *et al*., 1992) and a low-affinity IGFBP, namely IGFBP-7 and 8 bearing structural homology to the classic IGFBPs was recently described (Oh *et al*., 1996; Kim *et al*., 1997) although, to date, none of these proteins have been cloned.

Insulin-like growth factor binding proteins shares a common domain structure arrangement. They all have a highly conserved N-terminal domain (N-domain) and C-terminal domain (C-domain), and a variable central domain (L-domain). The N- and C-domain contain multiple conserved cysteine residues, which form intra-

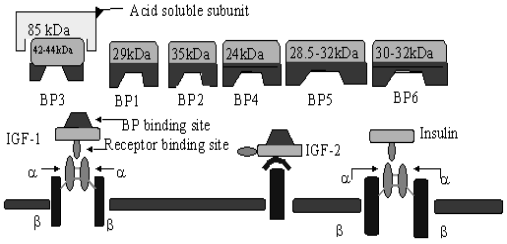

Fig. 1: The IGF system consist of three different parts, two ligands (IGF-I, IGF-II), which are structurally related to insulin, two receptors and six binding proteins. Insulin like Growth Factor-I and II are complexed with the family of binding proteins (IGFBP's) in serum, amniotic and other body fluids. These binding proteins modulate the autocrine and paracrine action of the ligands. They inhibit the mitogenic effect of IGFs (IGF1 and IGF-2) by limiting peptide access to specific cell surface receptors (Modified from Fig. 1 of Monget and Monniaux, 1995).

domain disulfide bonds within the N-domain and C-domain, thereby defining their overall globular structure.

The highly variable L-domain is considered as a flexible linker region connecting the N- and C- domain (Chelius *et al*., 2001; Forbes *et al*., 1998; Neumann and Bach, 1999). The N-domain contains the high affinity IGF-binding site, but the C-domain also contributes to IGF binding to some degree (Brinkman *et al*., 1991; Clemmons, 2001; Hobba *et al*., 1998; Zeslawski *et al*., 2001). The C-domain of an IGFBP often mediates its interactions with other proteins. For instance, both IGFBP-3 and IGFBP-5 bind to the acid-labile subunit (ALS) through their C-domains (Firth and Baxter, 2002; Guler *et al*., 1987). This ternary complex (IGF-IGFBP-ALS) greatly increases the half-life of IGFs in circulation.

The central L-domain is the least conserved and often contains sites for post-translational regulations (Clemmons, 2001; Firth and Baxter, 2002). The post-translational regulations (such as phosphorylation, glycosylation and proteolysis) influence the affinity of IGFBPs to IGFs and regulate IGF availability.

Insulin-like binding protein-1 (IGFBP-1) is a 25-34 kDa protein and isolated in two forms. Placental form was originally isolated from human placenta as protein 12 and it is growth hormone independent. Amniyotic form is 28 kDa protein isolated from human amiyotic fluid. Both forms have the same amino acid sequence at the N-terminal (Koistinen *et al*., 1986). Amniyotic form of IGFBP-1 binds to both IGF-I and IGF-II with high affinity. Using the zebra fish model, it was hypothesed that elevated IGFBP-1 mediates hypoxia-induced embryonic growth retardation and developmental delay by binding to and inhibiting the activities of IGFs using loss- and gain of function approaches. Knockdown of IGFBP-1 using antisense oligonucleotides (MOs) significantly alleviated the hypoxia-induced growth retardation and developmental delay. Over-expression of IGFBP-1 caused growth and developmental retardation under normoxia. Furthermore, re-introduction of IGFBP-1 to the IGFBP-1 knocked down embryos restored the hypoxic effects on embryonic growth and development (Kajimura *et al*., 2005).

Insulin-like binding protein-2 (IGFBP-2) is a 32-34 kDa protein present in fetal tissue,serum lymph, amniyotic fluid, follicular fluid and cerebrospinal fluid (Mondschein *et al*., 1990; Schoen *et al*., 1992). IGFBP-2 preferently binds to IGF-II.

Insulin-like binding protein-3 (IGFBP-3) is a 53 kDa protein binds to IGF-1 and II with high affinity. It can function either as inhibitor or activator of IGF-1 stimulated DNA synthesis. Molecular weight of IGFBP-3 depends on glycosylation degree (Russell and Van Wyk, 1995). Glycosylated IGFBP-3 is able to bind to cell surface by a weak non-covalent sugar-sugar interaction. Free IGFBP-3 has 3 to 10-fold higher affinity to ligand than cell surface-associated IGBP-3 (McCusker and Clemmons, 1992). The concentration of IGFBP-3, in blood, is 40-fold higher than IGFBP-1 and also has higher affinity to IGF-I. Therefore, the majority of IGF-I, in circulation, is bond to IGFBP-3.

Insulin-like binding protein-4 (IGFBP-4) was isolated in two forms with different molecular weight (29kDa and 24 kDa) from ovine blood plasma. It blocks the effect of exogenously added IGF-I to the cells (Russell and Van Wyk., 1995). Although a large number of *in vitro* studies have shown IGFBP-4 to be an inhibitory IGFBP, knockout of the IGFBP-4 gene in mice reduces, rather than increases, prenatal growth (Ning *et al*., 2008).

Insulin-like binding protein-5 is a 23 kDa protein and originally purified from human osteoblast derived culture. It is present in endocrine tissues.

Insulin-like binding protein-6 is a 23 kDa protein was originally isolated form human cerebrospinal fluid). Relatively little is currently known about its role and regulation. IGFBP-6 is O-glycosylated and its glycosylated form exhibits much greater resistance to proteolysis than its nonglycosylated counterpart (Neumann *et al*., 1998). IGFBP-6 is distinct in its preferential affinity for IGF-II relative to IGF-I, which, unlike any other IGFBP, is 20- to 100-fold higher (Neumann and Bach, 1999). IGFBP-6 functions to inhibit the actions of IGFII, with inhibition thought to result from the formation of high-affinity IGF-IGFBP complexes that prevent IGF-II from binding to the IGF receptors (Neumann and Bach, 1999). Several hormones, including a number of growth factors, have been shown to regulate IGFBP-6, but the manner in which they act appears to be very cell-specific, and the mechanisms at this time are not fully understood (Neumann and Bach, 1999).Insulin-like binding protein-7 together with IGFBP-8 show a low

affinity to IGFs. IGFBP-8 is probably connective tissue growth factor (Kim *et al*., 1997).

CONCLUSION

Insulin-like growth factors and their receptor are expressed in embryos and in reproductive organs of farm animal. Although there are many published reports concerning importance of IGF system and their receptors in blastocyst formation, implantation and embryo growth, there is not enough information about the exact physiologic regulation and function of some components of the IGFs system (such as GFBPs). The regulation of IGF system is complicated.

REFERENCES

Adashi, E.Y., C.E. Resnick, J.D. Ercole, M.E. Svoboda and J.J. Van-Wyk, 1985. Insulin-like growth factor as intraovarian regulators of granulosa cells. Endocrinol. Rev., 6(3): 400-420.

Allan, G.J., D.J. Flint and K. Patel, 2001. Insulin-like growth factor axis during embryonic development. Reproduction, 122: 31-39.

Andress, D.L., 1998. Insulin-like growth factor-binding protein-5 (IGFBP-5) stimulates phosphorylation of the IGFBP-5 receptor. Am. J. Physiol., 274: E744-E750.

Andress, D.L., 1995. Heparin modulates the binding of Insulin-like Growth Factor (IGF) binding protein-5 to a membrane protein in Osteoblastic cells. J. Biol. Chem., 270: 28289-28296.

Armstrong, D.G., C.G. Gutierrez, G. Baxter, A.L. Glazyrin, G.E. Mann, K.J. Woad, C.O. Hogg and R. Webb, 2000. Expression of MRNA encoding IGF-I, IGF-II and type 1 IGF receptor in bovine ovarian follicles. J. Endocrinol., 165(1): 101-113.

Bach, L.A., N.R. Thotakura and M.M. Rechler, 1992. Human insulin-like binding protein-6 is O-glycosylated. Biochem. Biophys. Res. Commun., 186: 301-307.

Baker, J., M.P. Hardy, J. Zhou, C. Bondy, F. Lupu, A.R. Bellve and A. Efstratiadis, 1996. Effects of an IGF1 gene null mutation on mouse reproduction. Mol. Endocrinol., 10: 903-918.

Brickell, J.S., N. Bourne, Z. Cheng and D.C. Wathes, 2007. Influence of plasma IGF-1 concentrations and body weight at 6 months on age at first calving in dairy heifers on commercial farms. Reprod. Domest. Anim. Suppl., 2(42): 118.

Brinkman, A., D.J. Kortleve, E.C. Zwarthoff and S.L. Drop, 1991. Mutations in the Cterminal part of Insulin-like Growth-factor (IGF)-binding protein-1 result in dimer formation and loss of IGF-binding capacity. Mol. Endocrinol., 5: 987-994.

Bonilla, A.Q.S., L.J. Oliveira, M. Ozawa, E.M. Newsom, M.C. Lucy and P.J. Hansen, 2011. Developmental changes in thermoprotective actions of insulin-like growth factor-1 on the preimplantation bovine embryo. Mol. Cell. Endocrinol., 332: 170-179.

Camarero, G., C. Avendano, C. Fernandez-Moreno, A. Villar, J. Contreras, F. De Pablo, J.G. Pichel and I. Varela-Nieto, 2001. Delayed inner ear maturation and neuronal loss in postnatal IGF-1-deficient mice. J. Neurosci., 21: 7630-7641.

Carlsson, B., T. Hillensjo, A. Nilsson, J. Tornell and H. Billig, 1993. Expression of insulin-like growth factor-I (IGF-I) in the rat fallopian tube: Possible autocrine and paracrine action of fallopian tube-derived IGF-I on the fallopian tube and on the preimplantation embryo, Endocrinol., 33: 2031-2039.

Chelius, D., M.A. Baldwin, X. Lu and E.M. Spencer, 2001. Expression, purification and characterization of the structure and disulfide linkages of insulin-like growthfactor-binding protein-4. J. Endocrinol., 168: 283-296.

Clemmons, D.R., 2001. Use of mutagenesis to probe IGF-binding protein structure/function relationships. Endocr. Rev., 22: 800-817.

Clemmons, D.R., 1998. Role of insulin-like growth factor binding proteins in controlling IGF actions. Mol. Cell. Endocrinol., 140: 19-24.

Daftary, S.S. and A.C. Gore, 2005. IGF-1 in the brain as a regulator of reproductive neuroendocrine function. Exp. Biol. Med., 230: 292-306.

Daliri, M., K.B.C. Appa Rao, G. Kaur, S. Garg, S. Patil and S.M. Totey, 1999. Expression of growth factor ligand and receptor genes in preimplantation stage water buffalo (Bubalus bubalis) embryos and oviduct epithelial cells. J. Reprod. Fertil., 117: 61-70.

DeChiara, T.M., E.J. Robertson and A. Efstratiadis, 1991. Parental imprinting of the mouse insulin-like growth factor II gene. Cell., 64: 849-859.

DeChiara T.M., A. Efstratiadis and E.J. Robertson, 1990. A growth-deficiency phenotype in heterozygous mice carrying an insulin-like growth factor II gene disrupted by targeting. Nature, 345: 78-80.

DeMeyts, P. and J. Whittaker, 2002. Structural biology of insulin and IGF1 receptors: Implications for drug design. Nat. Rev. Drug Discov., 1: 769-783.

Duan, C.M. and Q.J. Xu, 2005. Roles of insulin-like growth factor (IGF)-binding proteins in regulating IGF actions. Gen. Comp. Endocrinol., 142: 44-52.

Echternkamp, S.E., J. Roberts, D.D. Lunstra, T. Wise and L.J. Spicer, 2004. Ovarian follicular development in cattle selected for twin ovulations and births. J. Anim. Sci., 82: 459-71.

Eivers, E., K. McCarthy, C. Glynn, C.M. Nolan and L. Byrnes, 2004. Insulin-like growth factor (IGF) signaling is required for early dorso-anterior development of the zebrafish embryo. Int. J. Dev. Biol., 48: 1131-1140.

Fenwick, M.A., S. Llewellyn, R. Fitzpatrick, D.A. Kenny, J.J. Murphy, J. Patton and D.C. Wathes, 2008a. Negative energy balance in dairy cows is associated with specific changes in IGF binding protein expression in the oviduct. Reproduction, 135: 63-75.

Fenwick, M.A., R. Fitzpatrick, D.A. Kenny, M.G. Diskin, J. Patton, J.J. Murphy and D.C. Wathes, 2008b. Interrelationships between Negative Energy Balance (NEB) and IGF regulation in liver of lactating dairy cows. Domest. Anim. Endocrinol., 34: 31-44.

Firth, S.M. and R.C. Baxter, 2002. Cellular actions of the insulin-like growth factorbinding proteins. Endocr. Rev., 23: 824-854.

Forbes, B.E., D. Turner, S.J. Hodge, K.A. McNeil, G. Forsberg and J.C. Wallace, 1998. Localization of an insulin-like growth factor (IGF)-binding site of bovine IGF binding protein-2 using disulfide mapping and deletion mutation analysis of the C-terminal domain. J. Biol. Chem., 273: 4647-4652.

Gardner, H.G. and P.L. Kaye, 1991. Insulin increases cell numbers and morphological development in mouse pre-implantation embryos in vitro. Reproduction Fertility Devel., 3: 79-91.

Geisert, R.D., C.Y. Lee, F.A. Simmen, M.T. Zavy, A.E. Fliss, F.W. Bazer and R.C. Simmen, 1991. Expression of messenger RNAs encoding insulin-like growth factor-1, -II, and insulin-like growth factor binding protein-2 in bovine endometrium during the estrous cycle and early pregnancy. Biol. Reproduction, 45: 975-983.

Guler, H.P., J. Zapf and E.R. Froesch, 1987. Short-term metabolic effects of recombinant human insulin-like growth factor-I in healthy adults. N. Engl. J. Med., 317: 137-140.

Harvey, M.B., K.J. Leco, M.Y. Arcellana-Panlilo, X. Zhang, D.R. Edwards and G.A. Schultz, 1995. Roles of growth factors during peri-implantation development. Hum. Reprod., 10(3): 712-718.

Harvey, M.B. and P.L. Kaye, 1991. Mouse blastocysts respond metabolically to short-term stimulation by insulin and IGF-1 through the insulin receptor. Mol. Reprod. Devel., 29: 253-258.

Harvey, M.B. and P.L. Kaye, 1988. Insulin stimulates protein synthesis in compacted mouse embryos. Endocrinol., 122: 1182-1184.

Hastie, P.M. and W. Haresign, 2008. Modulating peripheral gonadotrophin levels affects follicular expression of mRNAs encoding insulin-like growth factors and receptors in sheep. Anim. Reprod. Sci., 109: 110-123.

Hastie, P.M., O.M. Onagbesan and W. Haresign, 2004. Co-expression of messenger ribonucleic acids encoding IGF-I, IGFII, type I and II IGF-receptors and IGF binding proteins (IGFBP-1 to 6) during follicular development in the ovary of seasonally anoestrous ewes. Anim. Reprod. Sci., 84: 93-105.

Herrler, A. and H.M. Beier, 1994. Influence of IGF-I on blastocyst formation in the rabbit. J. Reprod. Fertil., Abstract Series 13: Abstract WI.

Hertogh, R.D., I. Vanderheyden, S. Pampfer, D. Robin, E. Dufrasne and J. Delcourt, 1991. Stimulatory and inhibitory effects of glucose and insulin on rat blastocyst development *in vitro*. Diabetes, 40: 641-647.

Hobba, G.D., A. Lothgren, E. Holmberg, B.E. Forbes, G.L. Francis and J.C. Wallace, 1998. Alanine screening mutagenesis establishes tyrosine 60 of bovine insulin-like growth factor-binding protein-2 as a determinant of insulin-like growth factor binding. J. Biol. Chem., 273: 19691-19698.

Jin, H.Y. and Z.N. Wang, 2001. Insulin-like growth factor sand their receptors in human fallopian tube in reproductive-age women. Fertil Steril, 75:1037-1038.

Jogie-Brahim, S., D. Feldman and Y. Oh, 2009. Unraveling insulin-like growth factor binding protein-3 actions in human disease. Endocr. Rev., 30: 417-437.

Jones, J.I. and D.R. Clemmons, 1995. Insulin-like growth factors and their binding proteins: Biological actions. Endocr. Rev., 16(1): 3-34.

Jones, J.I., A. Gockerman W.H. Jr. Busby, G. Wright and D.R. Clemmons, 1993. Insulin-like growth factor binding protein 1 stimulates cell migration and binds to the alpha 5 beta 1 integrin by means of its Arg-Gly-Aspsequence Proc. Natl. Acad. Sci., USA, 90: 10553-10557.

Kadakia, R., J.A. Arraztoa, C. Bondy and J. Zhou, 2001. Granulosa cell proliferation is impaired in the Igf1 null ovary. Growth Horm. IGF Res., 11: 220-224.

Kajimura, S., K. Aida and C.M. Duan, 2005. Insulin-like growth factor-binding protein-1 (IGFBP-1) mediates hypoxia-induced embryonic growth and developmental retardation. Proc. Natl. Acad. Sci., USA. 102: 1240-1245.

Kamada, S., T. Kubota, M. Taguchi, W.R. Ho, S. Sakamoto and T. Aso, 1992. Effects of insulin-like growth factor-II on proliferation and differentiation of ovarian granulosa cells. Horm. Res., 37: 141-149.

Kane, M.T., P.M. Morgan and C. Coonan, 1997. Peptide growth factors and preimplantation development. Hum. Reprod. Update, 3: 137-157.

Kaye, P.l. and M.B. Harvey, 1995. The role of growth factors in preimplantation development. Prog. Growth Factor Res., 6(1): 1-24.

Kim, H.S., S.R. Nagalla, Y. Oh, E. Wilson, C.T. Roberts and R.G. Rosenfeld, 1997. Identification of a familiy of low-affinity insulin-like growth factor binding proteins (IGFBPs): Characterization of connective tissue growth factor as a member of the IGFBP superfamily. Porc. Natl. Acad. Sci., 94: 12981-12986.

Ko, Y., C.Y. Lee, T.L. Ott, M.A. Davis, R.C. Simmen, F.W. Bazer and F.A. Simmen, 1991. Insulin-like growth factors in sheep uterine fluids: Concentrations and relationship to ovinetro-phoblast protein-1 production during early pregnancy. Biol. Reprod., 45: 135-142.

Koistinen, R., N. Kalkkinen, M.L. Huhtala, M. Seppala, H. Bohn and E.M. Rutanan, 1986. Placental protein 12 is a decidual protein that binds somatomedin and has an identical N-terminal amino acid sequence with somatomedin-binding protein from human amniotic fluid. Endocrinol., 118: 1375-1378.

Kowalik, A., H.C. Liu, Z.Y. He, C. Mele, L. Barmat and Z. Rosenwaks, 1999. Expression of the insulin-like growth factor-1 gene and its receptor in preimplantation mouse embryos; Is it a marker of embryo viability? Mol. Hum. Reprod., 5: 861-865.

Lau, M.M., C.E. Stewart, Z. Liu, H. Bhatt, P. Rotwein and C.L. Stewart, 1994. Loss of the imprinted IGF-2/cation-independent mannose 6-phosphaterece ptorre sultsin fetalover-growth and perinatalle thality. Genes. Dev., 8: 2953-2963.

Le Roith, D., C. Bondy, S. Yakar, J.L. Liu and A. Butler, 2001. The somatomedin hypothesis. Endocr. Rev., 22: 53-74.

Letche, R., R.C. Simmen, F.W. Bazer and F.A. Simmen, 1989. Insulin-like growth factor-Iexpression during early conceptus development in the pig. Biol. Reprod., 41: 1143-1151.

Lewis, A.M., P.L. Kaye, R. Lising and R.D. Cameron, 1992. Stimulation of porcine synthesis and expansion of pig blastocysts by insulin *in vitro*. Reprod. Fertil. Dev., 4: 119-123.

Lighten, A.D.,K.Hardy, R.M.L. Winston and G.E. Mootr, 1997.Expressionof mRNAfor the insulin-like growthfactors and their receptors in human preimplantation embryos. Mol. Reprod. Dev., 47: 134-139.

Liu, J., A.T. Koenigsfeld, T.C. Cantley, C.K. Boyd, Y. Kobayashi and M.C. Lucy, 2000. Growth and the Initiation of steroidogenesis in porcine follicles are associated with unique patterns of gene expression for individual components of the ovarian insulin-like growth factor system. Biol. Reprod., 63: 942-952.

Liu, F., B.K. Baker, D.R. Powell and R.L. Hintz, 1993. Characterization of proinsulin-like growth factor-II E-region immunoreactivity in serum and other biological fluids. J. Clini. Endocrinol., Metabolism, 76: 1095-1100.

Llewellyn, S., R. Fitzpatrick, D.A. Kenny, J.J. Murphy, R.J.Scaramuzzi and D.C. Wathes, 2007. Effect of negative energy balance on the insulin-like growth factor system in pre-recruitment ovarian follicles of post partum dairy cows. Reprod., 133(3): 627-639.

Lizcano, J.M. and D.R. Alessi, 2002. The insulin signaling pathway. Curr. Biol., 12: 236-238.

Lonergan, P., A. Gutiérrez-Adán, B. Pintado, T. Fair, F. Ward, J.D. Fuente, and M. Boland, 2000. Relationship between time of first cleavage and the expression of IGF-I growth factor, its receptor, and two housekeeping genes in bovine two-cell embryos and blastocysts produced in vitro. Mol. Reprod. Dev., 57: 146-152.

Matsui, M., Y. Takahashi, M. Hishinuma and H. Kanagawa, 1995. Stimulatory effects of insulin on the development of bovine embryos fertilized *in vitro*. J. Veter. Med. Sci., 57: 331-336.

Makarevich, A.V. and A.V. Sirotkin, 1997. Theinvolve mentof the GH / IGF-I axis in the regulation of secretory activity by bovine oviduct epithelial cells. Anim. Reprod. Sci., 48:197-207.

Mattson, B.A., I.Y. Rosenblum, R.M. Smith and S. Heyner, 1988. Autoradiographic evidence for insulin and insulin-like growth factor binding to early mouse embryos. Diabetes, 37: 585-589.

McCusker, R.H. and D.R. Clemmons, 1992. The Insulin-Like Growth Factor Binding Proteins: Structure and Biological Functions. In: Schofield, P.N. (Ed.), The Insulin-Like Growth Factors: Structure and Biological Functions. Oxfort University Press, Oxford, pp: 110-149.

Mondschein, J.S., S.A. Smith and J.M. Hammond, 1990. Production of Insulin-like Growth Factors Binding Proteins (IGFBPs) by porcine ganulosa cells: Identification of GFBP-2 and -3 and regulation by hormones and growth factors. Endocrinol., 127: 2298-2306.

Monget, P. and D. Monniaux, 1995. Growth factors and the control of folliculogenesis. J. Reprod. Fertil. Suppl., 49: 321-333.

Neira, J.A., D. Tainturier, M.A. Pen and J. Martal, 2010. Effect of the association of IGF-I, IGF-II, bFGF, TGF-β1, GM-CSF,and LIF on the development of bovine embryos produced *in vitro*. Theriogenol., 73: 595-604.

Neumann, G.M. and L.A. Bach, 1999. The N-terminal disulfide linkages of human insulin-like growth factor-binding protein-6 (hIGFBP-6) and hIGFBP-1 are different as determined by mass spectrometry. J. Biol. Chem., 274: 14587-14594.

Neumann, G.M., J.A. Marinaro, L.A. Bach, 1998. Identification of O-glycosylation sites and partial characterization of carbohydrate structure and disulfide linkages of human insulin-like growth factor binding protein 6. Biochem., 37: 6572-6585.

Ning, Y., A.G.P. Schuller, C.A. Conover and J.E. Pintar, 2008. Insulin-like growth factor (IGF)-binding protein-4 is both a positive and negative regulator of IGF activity *in vivo*. Mol. Endocrinol., 22: 1213-1225.

Oh, Y., S.R. Nagalla, Y. Yamanaka, H-S. Kim, E. Wilson and R.G. Rosenfeld, 1996. Synthesis and characterization of insulin-like growth factor-binding protein (IGFBP)-7. Recombinant human mac25 protein specifically binds IGF-I and -II. J. Biol. Chem., 271: 30322-30325.

Oh, Y., H.L. Muller, H. Pham and R.G. Rosenfeld, 1993. Demonstration of receptors for insulin-like growth factor binding protein 3 on Hs578T human breast cancer cells. J. Biol. Chem., 268: 26045-26048.

Patton, J., D.A. Kenny, S. McNamara, J.F. Mee, F.P. O'Mara, M.G. Diskin and J.J. Murphy, 2007. Relationships among milk production, energy balance, plasma analysts, and reproduction in Holstein-Friesian cows. J. Dairy. Sci., 90: 649-658.

Pavelic, J., T. Matijevic and J. Knezevic, 2007. Biological & physiological aspects of action of insulin-like growth factor peptide family. Ind. J. Med. Res., 125: 511-522.

Pera, E.M., O. Wessely, S.Y. Li and E.M. De Robertis, 2001. Neural and head induction by insulin-like growth factor signals. Dev. Cell., 1: 655-665.

Pfaffl, M., F. Schwarz and H. Sauerwein, 1998. Quantification of insulin-like growth factor-1 (IGF-1) mRNA: modulation of growth intensity by feeding results in inter- and intra-tissue-specific differences of IGF-1 mRNA expression in steers. Exp. Clin. Endocrinol. Diabetes, 106: 514-521.

Powellbraxton, L., P. Hollingshead, C. Warburton, M. Dowd, S. Pittsmeek, D. Dalton, N. Gillett and T.A. Stewart,1993.IGF-I is required for normal embryonic growth in mice. Genes. Dev., 7: 2609-2617.

Pushpakumara, P. G., R. S. Robinson, K.J. Demmers, G.E. Mann, K.D. Sinclair, R. Webb and D.C. Wathes, 2002. Expression of the insulin-like growth factor (IGF) system in the bovine oviductat oestrus and during early pregnancy. Reprod., 123: 859-868.

Rajaram, S., D.J. Baylink and S. Mohan, 1997. Insulin-like growth factor-binding proteins in serum and other biological fluids: Regulation and functions. Endocr. Rev., 18: 801-831.

Rappolee, D.A., K.S. Sturm, O. Behrendtsen, G.A. Schultz, R.A. Pedersen and Z. Werb, 1992. Insulin-like growth factor II acts through an endogenous growth pathway regulated by imprinting in early mouse embryos. Genes. Dev., 6: 939-952.

Rauschnabel, U., E. Koscielniak, M.B. Ranke, B. Schuett and M.W. Elmlinger, 1999. RGD specific binding of IGFBP-2 to alpha 5 beta 1 integrin of ewing sarcoma cells. Growth Horm. IGF Res., 9: 369-374.

Reinecke, M. and C. Collet, 1998. The phylogeny of the insulin-like growth factors. Int. Rev. Cytol., 183: 1-94.

Richard-Parpaillon, L., C. Heligon, F. Chesnel, D. Boujard and A. Philpott, 2002. The IGF pathway regulates head formation by inhibiting Wnt signaling in Xenopus. Dev. Biol., 244: 407-417.

Russell, W.E. and J.J. Van Wyk, 1995. Peptide Growth Factors. In: Groot, L.J. (Ed.), Endocrinology, De W.B. Saunders Company, pp: 12590-2623.

Santos, A.N., S. Tonack, M. Pantaleon, P. Kaye and B. Fischer, 2004. Insulin acts via mitogen-activated protein kinase phosphorylation in rabbit blastocysts. Reprod., 128: 517-526.

Savion, N., G.M. Lui, R. Laherty and D. Gospodarowicz, 1981. Factor controlling proliferation and progesterone production by bovine granulosa cells in serum-free medium. Endocrinol., 109: 409-420.

Schoen, T.J., D.C. Beebe, D.R. Clemmons, G.J. Chader and R.J. Waldbilling, 1992. Local synthesis and developmental regulation of avian vitreal insulin-like growth factor-binding proteins: A model for independent regulation in extravascular and vascular compartments. Endocrinol., 131: 1846-2854.

Schlueter, P.J., G. Peng, M. Westerfield and C. Duan, 2007. Insulin-like growth factor signaling regulates zebrafish embryonic growth and development by promoting cell survival and cell cycle progression. Cell. Death Differ., 14: 1095-1105.

Schlueter, P.J., T. Royer, M.H. Farah, B. Laser, S.J. Chan, D.F. Steiner and C.M. Duan, 2006. Gene duplication and functional divergence of the zebrafish insulin-like growth factor 1 receptors. FASEB J., 20: 1230-1232.

Simmen, F.A., R.C. Simmen, R.D. Geisert, Martinat-Botte, F.W. Bazer and M. Terqui, 1992. Differential expression, during the estrous cycle and pre- and postimplantation conceptus development, of messenger ribonucleic acids encoding components of the pig uterine insulin-like growth factor system. Endocrinol., 130(3): 1547-1556.

Simmen, R.C., F.A. Simmen, Y. Ko and F.W. Bazer, 1989. Differential growth factor content of uterine luminal fluids from large white and prolific Meishan pigs during the estrous cycle and early pregnancy. J. Anim. Sci., 67: 1538-1545.

Soos, M.A., C.E. Field and K. Siddle, 1993: Purified hybrid insulin/insulin-like growth factor-I receptors bind insulin-likegrowth factor-I, but not insulin, with high affinity. Biochem. J., 290: 419-426.

Spicer, L.J. and S.E. Echternkamp, 1995. The ovarian insulin and insulinlike growth factor system with emphasis on domestic animals. Domest. Anim. Endocrinol., 12: 223-245.

Stevenson, K.S. and D.C. Wathes, 1996. Insulin-like growth factors and their binding proteins in the ovine oviduct during the oestrous cycle. J. Reprod. Fertilitty, 108: 31-40.

Sudo, N., T. Shimizu, C. Kawashima, E. Kaneko, M. Tetsuka and A. Miyamoto, 2007. Insulin-like Growth Factor-i (IGF-I) system during follicle development in the bovine ovary: Relationship among IGF-I, type 1 IGF receptor (IGFR-1) and pregnancy-associated plasma protein-A (PAPP-A). Mol. Cell. Endocrinol., 264(1-2): 197-203.

Susa, J.B., C. Neave, P. Sehgal, D.B. Singer, W.P. Zeller and R. Schwartz, 1984. Chronic hyperinsulinemia in the fetal rhesus monkey. Effects of physiologic hyperinsulinemia on fetal growth and composition. Diabetes, 33: 656-660.

Sweet, L.J., B.D. Morrison and J. Pessin, 1987. Isolation of functional a-b heterodimers from the purified human placentalα2-β2 heterotetrameric insulin receptor concept. Structural basis for high affinity ligand binding. J. Biol. Chem., 262: 6939-6942.

Taylor, K.M., C. Chen, A.G. Gray, F.W. Bazer and T.E. Spencer, 2001. Expression of messenger ribonucleic acids for fibroblast growth factors 7 and 10, hepatocyte growth factor, and insulin-like growth factors and their receptors in the neonatal ovine uterus. Biol. Reprod., 64: 1236-1246.

Teissier, M-P., P. Monget, D. Monniaux and P. Durand. 1994. Changes in insulin-like growth factor-II/mannose-6-phosphate receptor during growth and atresia of ovine ovarian follicles. Biol. Reprod., 50: 111-119.

Van Lier, E., A. Meikle, H. Eriksson and L. Sahlin, 2006. Insulin-like growth factor-I (IGF-I) and thioredoxin are differentially expressed along the reproductive tract oftheeweduring theoestrous cycle and after ovariectomy. Acta Veterinaria Scandinavica, 48(1):5.

Van Obberghen, E., V. Baron, L. Delahaye, B. Emanuelli, N. Filippa, S. Giorgetti-Peraldi, P. Lebrun, I. Mothe-Satney, P. Peraldi, S. Rocchi, D. Sawka-Verhelle, S. Tartare-Dechert and J. Giudicelli, 2001.Surfing the insulin signaling web. Eur. J. Clin. Invest., 31: 966-977.

Velazquez, M.A., M. Newman, M.F. Christie, P.J. Cripps, M.A. Crowe, R.F. Smith and H. Dobson, 2005. The usefulness of a single measurement of insulin-like growth factor-1 as a predictor of embryo yield and pregnancy rates in a bovine MOET program. Theriogenol., 64: 1977-1994.

Wang, L.M., H.L. Feng, Y.M. Zh, M. Cang, H.J. Li, Zh. Yan, P. Zhou, J.X. Wen, S. Bou and D.J. Liu, 2009. Expression of IGF receptors and its ligands in bovine oocytes and preimplantation embryos. Animal Reprod. Sci., 114: 99-108.

Wang, H.S., T.H. Wang and Y.K. Soong, 2000. WanChanges in mRNA expression of insulin-like growth factors and insulin-like growth factor-binding proteins in ovarian granulosa cells after cotreatment with growth hormone in low responders. Chang. Gung. Med. J., 23(11): 662-671.

Watson, A.J., M.E. Westhusin and Q.A. Winger, 1999. IGF paracrine and autocrine interactions between conceptus and oviduct. J. Reprod. Fertil. Suppl., 54: 303-315.

Watson, A.J., P.H. Watson, M. Arcellana-Panlilo, D. Warnes, S.K. Walker, G.A. Schultz, D.T. Armstrong and R.F. Seamark, 1994. A growth factor phenotype map for ovine preimplantation development. Biol. Reprod., 50: 725-733.

Winger, Q.A., P. de los. Rios, V.K.M. Han, T. Davit, D.H. Hill and A.J. Watson, 1997. Bovine oviductal and embryonic insulin-like growth factor binding proteins: possible regulators of "Embryotrophic" insulin-like growth factor circuits'. Bioologiy Reprod., 56: 1415-142.

Wylie, A.A., D.J. Pulford, A.J. McVie-Wylie, R.A. Waterland, H.K. Evans, Y.T. Chen, C.M. Nolan, T.C. Orton and R.L. Jirtle, 2003. Tissue-specific inactivation of murine M6P/IGF2R. Am. J. Pathol., 162: 321-328.

Wiseman, D.L., D.M. Henricks, D.M. Eberhardt and W.C. Bridges, 1992. Identification and content of insulin-like growth factors in porcine oviductal fluid. Biol. Reprod., 47: 126-132.

Yakar, S., J.L. Liu, B. Stannard, A. Butler, D. Accili, B. Saur and D. LeRoith, 1999. Normal growth and development in the absence of hepatic insulin-like growth factor I. Proc. Natl. Acad. Sci. USA., 96: 7324-7329.

Yamada, P.M. and K.W. Lee, 2009. Perspectives in mammalian IGFBP-3 biology: local vs. systemic action. Am. J. Physiol. Cell. Ph., 296: C954-C976.

Yilmaz, A., M.E. Davis and R.C.M. Simmen, 2006. Analyses of female reproductive traits in Angus beef cattle divergently selected for blood serum insulin-like growth factor I concentration. Theriogenol., 65: 1180-1190.

Zakaria, R., M.H. Rajikin, N.S. Yaacob and N.M. Nor, 2009. Immunolocalization of insulin-like growth factors and their receptors in the diabetic mouse oviduct and uterine tissues during the preimplantation period. Acta Histochemica., 111: 52-60.

Zeslawski, W., H.G. Beisel, M. Kamionka, W. Kalus, R.A. Engh, R. Huber, K. Lang and T.A. Holak, 2001. The interaction of insulin-like growth factor-I with the Nterminal domain of IGFBP-5. EMBO J., 20: 3638-3644.

Zhang, L., E.G. Blakewood, R.S. Denniston and R.A. Godke. 1991. The effect of insulin on maturation and development of *in vitro* fertilized bovine oocytes. Theriogenol., 35: 301.

Zhang, X. and D.T. Armstrong, 1990. Presence of amino acids and insulin in a chemically-defined medium improves development of cell rat embryos in vitro and subsequent implantation *in vivo*. Biol. Reprod., 42(4): 662-668.

Zhou, J., T.R. Kumar, M. M. Matzuk and C. Bondy, 1997. Insulin-like growth factor-I regulates gonadotropin responsiveness in the marine ovary. Mol. Endocrinol., 11: 1924-1933.