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Role of growth factors from fertilization to conception in farm animals: A comprehensive review

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Abstract

Growth factors are polypeptide signaling molecules that regulate fundamental biological processes including cell proliferation, differentiation, survival, and migration. In the reproductive context of farm animals encompassing cattle, sheep, goats, pigs, and horses, growth factors orchestrate the intricate sequence of events from gamete maturation and fertilization through early embryonic development to successful implantation and conceptus establishment. The insulin-like growth factors (IGFs), epidermal growth factor (EGF), fibroblast growth factors (FGFs), transforming growth factors (TGFs), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) have each been identified as essential mediators in these reproductive processes. Their expression within the oocyte, cumulus cells, follicular fluid, oviduct, uterus, and developing embryo underscores their paracrine and autocrine roles. This review synthesizes current knowledge of major growth factor families and their receptors, their spatiotemporal expression patterns, and their functional contributions across the reproductive continuum in farm animals. Understanding these molecular regulators provides mechanistic insight into reproductive efficiency and offers avenues for improving assisted reproductive technologies (ART), embryo culture systems, and fertility outcomes in livestock production.

Keywords: Growth factors, farm animals, fertilization, embryo development, implantation, IGF, EGF, FGF, TGF- β , VEGF, conception, livestock reproduction

Introduction

Reproduction in farm animals is a highly coordinated biological process that begins with gametogenesis and culminates in the establishment of a viable pregnancy. The economic importance of reproductive efficiency in livestock including cattle, sheep, goats, pigs, and horses is immense, as it directly impacts productivity, profitability, and food security. Despite decades of advances in reproductive management and assisted reproductive technologies, reproductive failure rates remain notably high across species, primarily due to early embryonic mortality and impaired conceptus-maternal communication (Diskin and Morris, 2008) [10]. At the molecular level, reproduction is governed by a complex interplay of hormones, cytokines, and growth factors. Among these, growth factors have emerged as critical autocrine and paracrine modulators of virtually every stage of the reproductive process from the maturation of oocytes within follicles to the implantation of the blastocyst in the uterine wall (Lonergan and Fair, 2008) [30]. Growth factors are typically low molecular weight polypeptides that bind to specific cell-surface receptors, initiating intracellular signaling cascades that regulate gene expression, cell cycle progression, metabolism, and survival.

In the context of farm animal reproduction, several growth factor families have received substantial attention: the insulin-like growth factors (IGF-1 and IGF-2), epidermal growth factor (EGF) family, fibroblast growth factors (FGFs), transforming growth factor-beta (TGF- β) superfamily, vascular endothelial growth factor (VEGF), and colony-stimulating factors. These molecules are expressed not only in endocrine organs but also locally within reproductive tissues viz-follicular fluid, oviductal epithelium, uterine endometrium, trophectoderm, and the inner cell mass of developing embryos emphasizing their paracrine and autocrine significance (Watson et al., 1999) [48].

This review aims to provide a comprehensive synthesis of the roles played by major growth factor families throughout the reproductive continuum in farm animals, from folliculogenesis and oocyte maturation through fertilization, early embryonic development, and implantation/conceptus elongation. Special emphasis is placed on identifying growth factor expression patterns, receptor distribution, downstream signaling, and functional evidence from *in vitro* and *in vivo* studies.

1. Growth Factors in Folliculogenesis and Oocyte Maturation

1.1 Insulin-like Growth Factors (IGF System)

The IGF system, comprising IGF-1, IGF-2, their receptors (IGF-1R, IGF-2R), and a family of six binding proteins (IGFBPs 1-6), is among the most extensively characterized growth factor systems in farm animal reproduction. IGF-1 is produced by granulosa and theca cells in response to gonadotropins and plays a pivotal role in folliculogenesis. In cattle, IGF-1 promotes granulosa cell proliferation, steroidogenesis, and LH receptor upregulation, thereby facilitating follicle selection and dominant follicle emergence (Lucy, 2001)^[33]. Concentrations of IGF-1 in bovine follicular fluid are significantly higher in dominant compared to subordinate follicles, and exogenous IGF-1 supplementation enhances oocyte developmental competence *in vitro* (Ginther et al., 2001)^[16].

In pigs, the IGF system regulates follicular growth and atresia. IGF-1 promotes survival of granulosa cells by activating the PI3K-Akt signaling pathway, while IGFBP-3 and IGFBP-5 modulate bioavailability of free IGF-1 in follicular microenvironments (Mazerbourg et al., 2003)^[35]. Studies in sheep have demonstrated that IGF-1 acts synergistically with FSH to promote granulosa cell differentiation and estradiol secretion during the antral phase of follicular development (Monget and Monniaux, 1995)^[37]. In horses, intra-follicular IGF-1 is positively correlated with estradiol concentrations and follicle diameter, supporting its role in pre-ovulatory follicle development (Donadeu and Watson, 2007)^[11].

1.2 Epidermal Growth Factor (EGF) Family

The EGF family, including EGF, transforming growth factor- α (TGF- α), amphiregulin (AREG), epiregulin (EREG), and betacellulin (BTC), signal through the ErbB family of receptor tyrosine kinases (ErbB1-4). In the ovary, EGF-like factors are crucial mediators of the LH surge response and cumulus-oocyte complex (COC) expansion. LH stimulates granulosa cells to produce AREG, EREG, and BTC, which in turn activate ErbB receptors on cumulus cells to trigger meiotic resumption and cumulus expansion (Park et al., 2004)^[39].

In bovine and porcine systems, supplementation of oocyte maturation media with EGF significantly improves *in vitro* maturation (IVM) rates, embryo cleavage, and blastocyst development (Lonergan et al., 1994; Prochazka et al., 2003)^[31, 40]. EGF promotes cumulus expansion through induction of hyaluronan synthase 2 (HAS2) and cyclooxygenase-2 (COX-2) expression, which are essential for the production of the cumulus extracellular matrix. In sheep, EGF receptor signaling in the COC is required for the acquisition of oocyte developmental competence (Gilchrist and Thompson, 2007)^[15]. Amphiregulin and epiregulin have more recently been shown to have specific roles in mediating the LH signal to the

oocyte in cattle and pigs, representing a paracrine relay system within the follicle (Shimada et al., 2006)^[41].

1.3 Fibroblast Growth Factors (FGFs)

The FGF family encompasses 22 members (FGF1-22) that signal through four receptor tyrosine kinases (FGFR1-4). Within the ovarian follicle, FGF2 (basic FGF), FGF7, FGF8, FGF10, and FGF17 have been identified as important regulators. FGF2 is expressed in granulosa cells, theca cells, and oocytes of cattle and pigs and promotes granulosa cell proliferation while inhibiting apoptosis (Berisha et al., 2004). FGF2 also stimulates angiogenesis in the theca layer, supporting follicular vascularization and nutrient delivery. Studies in cattle have demonstrated that FGF10 and FGF17, produced by the oocyte, act on granulosa and cumulus cells expressing FGFR2-IIIb to regulate glucose metabolism, glycolysis, and pentose phosphate pathway activity in cumulus cells (Sugiura et al., 2007)^[44]. This metabolic support from oocyte-secreted FGFs is critical for oocyte developmental competence. FGF8, also oocyte-derived, has been shown to promote cumulus cell survival and improve oocyte quality in cattle and mice (Buratini et al., 2007)^[6]. In pigs, FGF7 (keratinocyte growth factor, KGF) is expressed by theca cells and acts on granulosa cells through FGFR2-IIIb to promote cell survival and steroidogenesis (Valve et al., 1997)^[40].

1.4 Transforming Growth Factor-Beta (TGF- β) Superfamily

The TGF- β superfamily is a large group of dimeric proteins including TGF- β 1, - β 2, - β 3, activins, inhibins, bone morphogenetic proteins (BMPs), and growth differentiation factors (GDFs). In the follicle, BMPs and GDFs are particularly important. BMP-15 and GDF-9 are oocyte-secreted factors that play non-redundant roles in granulosa cell proliferation, differentiation, and cumulus expansion in sheep, cattle, and pigs (Juengel and McNatty, 2005)^[20]. Mutations in BMP-15 and GDF-9 in sheep (Booroola and Inverdale breeds) are associated with ovulation rate phenotypes ranging from infertility to high prolificacy, highlighting the essential nature of these factors in folliculogenesis (McNatty et al., 2004)^[36]. In pigs and cattle, BMP-6 produced by oocytes and granulosa cells suppresses FSH-stimulated progesterone production and modulates the transition from mitosis to meiosis in granulosa cells (Brankin et al., 2005)^[5]. Activins, particularly activin A, stimulate FSH receptor expression and granulosa cell responsiveness to gonadotropins in cattle and pigs. Conversely, inhibins produced by granulosa cells act endocrinologically to suppress FSH secretion from the pituitary (Findlay, 1993)^[12].

2. Growth Factors in Fertilization

2.1 Sperm Function and Capacitation

While growth factors are primarily studied in the context of oocyte and embryo biology, emerging evidence indicates their roles in sperm function. IGF-1 receptors have been identified on spermatozoa of cattle, pigs, and horses, and IGF-1 has been shown to enhance sperm motility, capacitation, and acrosome reaction *in vitro* (Henricks et al., 1994). IGF-1 treatment of bovine spermatozoa activates protein tyrosine phosphorylation pathways associated with capacitation, potentially improving fertilization rates.

EGF and EGF receptor (EGFR) signaling have also been implicated in sperm biology. EGFR is present on bull and boar spermatozoa, and EGF stimulates sperm motility and

capacitation-associated events in vitro (Lax et al., 1994). The oviductal secretion of EGF-like factors creates a microenvironment conducive to sperm function during the peri-fertilization period. VEGF has been detected in seminal plasma of bulls and stallions and may contribute to spermatogenesis and sperm function, though the precise mechanisms remain incompletely characterized (Korpelainen et al., 1998)^[24].

2.2 Oviductal Growth Factor Environment

The oviduct provides a specialized microenvironment for fertilization and early embryo development, and oviductal epithelial cells actively secrete a range of growth factors. In cattle, EGF, IGF-1, FGF2, and TGF- β have been identified in oviductal fluid and/or secreted by oviductal epithelial cells in culture (Kolle et al., 2000). EGF supplementation to oviductal cell co-culture systems improves bovine embryo development, suggesting a functional role for oviductal EGF during fertilization and early cleavage (Gandolfi et al., 1992). In pigs, the oviduct secretes significant amounts of IGF-1, EGF, and FGF2 during the peri-ovulatory period, and these concentrations change dynamically through the estrous cycle, suggesting hormonal regulation of oviductal growth factor production (Flores et al., 2003). The oviductal secretome in mares contains multiple growth factors including EGF, IGF-1, and FGF2, and these factors likely contribute to the high fertility rates observed in horses compared to other livestock species (Killian, 2004)^[22].

3. Growth Factors in Early Embryonic Development

3.1 Autocrine Growth Factor Signaling in the Embryo

Early preimplantation embryos are capable of both producing and responding to growth factors, establishing autocrine signaling loops that regulate cleavage, compaction, and blastocyst formation. In cattle, transcripts for IGF-1, IGF-1R, EGF, EGFR, TGF- α , and FGF2 are detectable by reverse transcription PCR from the zygote through blastocyst stage (Watson et al., 1999; Lonergan and Fair, 2008)^[30, 48]. The presence of growth factor receptors on preimplantation embryos provides the molecular basis for their responsiveness to exogenous growth factor supplementation.

IGF-1 and IGF-2 have been shown to promote bovine blastocyst development, increase inner cell mass (ICM) cell number, and reduce apoptosis in trophectoderm and ICM cells (Byrne et al., 2002)^[7]. The signaling pathway primarily involves IGF-1R activation of the PI3K-Akt-mTOR axis, which promotes protein synthesis and cell survival, and the Ras-MAPK pathway, which stimulates cell proliferation. In pigs, IGF-1 supplementation to culture media significantly improves blastocyst development rates and total cell number, and IGF-2 is expressed by porcine embryos from the 4-cell stage onward (Lighten et al., 1998)^[28].

3.2 EGF Family in Embryo Development

EGF and TGF- α promote bovine and ovine embryo development in vitro. Supplementation of embryo culture media with EGF (10-100 ng/mL) improves cleavage rates, blastocyst yield, and blastocyst quality in cattle (Lonergan et al., 1994)^[31] and sheep (Tervit et al., 1972 — modified conditions)^[45]. EGF activates EGFR on embryonic cells, triggering MAPK signaling that promotes trophectoderm differentiation and blastocyst expansion. AREG, EREG, and BTC, the paracrine mediators of LH action in the follicle, are also expressed by preimplantation bovine embryos, suggesting continued EGF-family signaling after fertilization.

In porcine embryos, EGF supplementation (10 ng/mL) during IVF and early embryo culture significantly improves blastocyst development and hatching rates, and increases the expression of trophinin, an adhesion molecule important for early embryo-endometrium interaction (Prochazka et al., 2003)^[40]. Heparin-binding EGF (HB-EGF), a member of the EGF family expressed by the uterine endometrium, has been identified as a critical signaling molecule in bovine embryo-endometrium cross-talk, and its receptor (EGFR/ErbB1) is expressed on bovine blastocysts (Wang et al., 2012)^[47].

3.3 FGF Signaling in Embryo Development

FGF signaling, particularly through FGF4 and FGF2, plays critical roles in the maintenance of the ICM and trophectoderm lineage specification in preimplantation embryos. In bovine embryos, FGF4 is expressed from the 8-cell stage and signals through FGFR2 to promote trophectoderm (TE) differentiation, while FGFR1 expression in the ICM supports pluripotency maintenance (Kuijk et al., 2012)^[25]. FGF2 has been shown to improve bovine blastocyst quality and viability when added to culture media, and co-culture with FGF2-secreting cells enhances embryo development rates (Lim et al., 2013)^[29].

In porcine embryos, FGF4 is a key signal for TE proliferation during early embryo elongation, which is a prerequisite for implantation in pigs. Exogenous FGF2 supplementation to porcine embryo culture media improves blastocyst development and ICM quality (Ozawa et al., 2006)^[38]. In sheep, FGF10 has been identified as a uterine-derived signal that promotes trophectoderm survival and elongation during the peri-implantation period (Chen et al., 2013)^[8].

3.4 TGF- β Superfamily in Early Embryo Development

TGF- β 1, TGF- β 2, and TGF- β 3 are expressed in bovine preimplantation embryos and in the oviduct and uterus. TGF- β 1 supplementation to bovine embryo culture systems has been reported to improve blastocyst development and quality, potentially through antiapoptotic mechanisms in the ICM (Larson et al., 1992)^[26]. Activins (dimers of inhibin β subunits) have also been detected in bovine and porcine preimplantation embryos and appear to promote early embryo development in vitro.

BMP4 produced by the trophectoderm of bovine and porcine embryos signals to the ICM through BMPR2 and ACVR2 to regulate ICM cell number and early lineage segregation. In the bovine embryo, BMP4 promotes TE differentiation at the blastocyst stage, while Nodal/activin signaling supports epiblast specification (Berg et al., 2011)^[2]. GDF9 and BMP15, the oocyte-secreted factors, continue to be expressed in the early embryo and may contribute to embryo-maternal signaling during the pre-implantation period (Juengel and McNatty, 2005)^[20].

3.5 VEGF and Angiogenic Factors

VEGF and its receptors (VEGFR-1/Flt-1 and VEGFR-2/KDR) are expressed in bovine, porcine, and ovine preimplantation embryos. In cattle, VEGF expression is detected from the morula stage onward and peaks at the blastocyst stage, where it is particularly prominent in the TE cells (Loureiro et al., 2009)^[32]. While the conceptus at the pre-implantation stage is avascular, VEGF produced by the embryo may act through VEGFR-1 in an autocrine manner to promote TE cell survival and migration, processes that are critical for implantation.

In pigs, VEGF is expressed by the trophoblast of elongating conceptuses and stimulates uterine endometrial angiogenesis in preparation for placentation (Welch et al., 1990) [49]. VEGF produced by the bovine trophoblast promotes endometrial vascularization during the period of implantation, facilitating nutrient exchange at the developing placenta. Angiopoietins (Ang-1 and Ang-2) and their Tie-2 receptor are co-expressed with VEGF in the trophoblast and endometrium and cooperate with VEGF to regulate vascular remodeling during the peri-implantation period (Maisonpierre et al., 1997) [34].

4. Growth Factors in Implantation and Conceptus Elongation

4.1 Uterine Growth Factor Expression During the Peri-implantation Period

The uterine endometrium undergoes dramatic changes in gene expression during the peri-implantation period in preparation for conceptus attachment and implantation. In cattle, sheep, pigs, and horses, the uterine epithelium and stromal cells produce a variety of growth factors under the influence of progesterone and conceptus-derived signals (Spencer et al., 2004) [43]. These growth factors are secreted into the uterine lumen as components of histotroph — the complex mixture of secretions that nourishes the pre-attachment conceptus.

EGF, FGF2, FGF7 (KGF), FGF10, IGF-1, IGF-2, HB-EGF, and FGF1 have all been identified as components of ovine and bovine histotroph during the peri-implantation period (Spencer et al., 2004) [43]. In sheep, progesterone stimulates uterine expression of FGF7 and FGF10 beginning on day 10 of pregnancy, and conceptus-derived IFN- τ further modulates uterine growth factor expression to create an optimal environment for trophoblast elongation and implantation (Bazer et al., 2012) [1].

4.2 Conceptus Elongation in Ruminants and Pigs

In ruminants (cattle and sheep) and pigs, the blastocyst undergoes a dramatic process of elongation prior to implantation, transforming from a spherical blastocyst (1-2 mm diameter) into a filamentous conceptus (up to 20 cm in cattle, 100 cm in pigs) within a few days. This rapid elongation is a critical period during which substantial embryonic losses occur, and growth factors are essential drivers of this process (Bazer et al., 2012) [1].

In sheep, IGF-1 and IGF-2 produced by the uterus and conceptus trophoblast stimulate trophoblast cell migration and proliferation during elongation. Exogenous IGF-1 infusion into the uterine lumen of ewes accelerates conceptus elongation, while neutralization of IGF-1 with specific antibodies impairs elongation (Bazer et al., 2012) [1]. FGF2 and FGF10 produced by uterine glands stimulate trophoblast cell proliferation via the FGFR2-IIIb receptor and are essential for conceptus elongation in sheep (Chen et al., 2013) [8].

In pigs, FGF4 secreted by the trophoblast and FGF7 secreted by the endometrium cooperate to promote trophoblast elongation via paracrine and autocrine mechanisms (Ka et al., 2007) [21]. VEGF produced by the porcine trophoblast promotes endometrial vascularization concurrent with elongation, preparing the uterus for placentation. HGF (hepatocyte growth factor) secreted by porcine endometrial stromal cells acts on trophoblast cells expressing the c-Met receptor to promote cell migration and invasion during elongation (Bhatt et al., 2004) [4].

4.3 Implantation and Trophoblast Attachment

Implantation in farm animals involves a series of molecular interactions between trophoblast cells and uterine epithelial cells, culminating in the physical attachment of the conceptus to the endometrium. In cattle and sheep (synepitheliochorial placentation) and pigs (epitheliochorial placentation), implantation is non-invasive, but still requires precise molecular signaling for successful attachment (Wooding and Fowden, 2006) [50]. Growth factors are key mediators of both the preparation of the endometrial attachment site and the trophoblast cell changes required for adhesion.

HB-EGF, produced by uterine epithelial cells in response to progesterone and conceptus signals, acts on EGFR/ErbB1 expressed on the trophoblast to stimulate trophoblast cell differentiation and adhesion in cattle (Wang et al., 2012) [47]. In sheep, EGF and HB-EGF stimulate expression of integrins (α v, β 3) on trophoblast cells, which are adhesion molecules required for trophoblast attachment to the endometrium. FGF2 and FGF10 signaling through FGFR2 promotes trophoblast cell spreading and migration required for placenta formation in ruminants (Bazer et al., 2012) [1]. In pigs, the transition from blastocyst to elongated conceptus is associated with upregulation of VEGF and HGF in the trophoblast, which promote endometrial vascular remodeling and stromal cell decidualization respectively (Ka et al., 2007) [21]. PDGF (platelet-derived growth factor) and its receptors (PDGFR α , PDGFR β) are expressed in the bovine and ovine placenta and likely contribute to placental stromal cell differentiation and vasculogenesis during early placentation (Wooding and Fowden, 2006) [50].

4.4 Growth Factors and Conceptus Survival

A critical function of growth factors during the peri-implantation period is the promotion of conceptus survival through suppression of apoptosis and enhancement of proliferative activity in trophoblast and embryonic disc cells. GM-CSF (granulocyte-macrophage colony-stimulating factor) is expressed by uterine endometrial cells in cattle, sheep, and pigs and acts on the trophoblast expressing CSF2R (GM-CSFR) to promote cell survival and reduce apoptosis (Imakawa et al., 2006) [19]. Supplementation of bovine embryo culture media with GM-CSF significantly increases blastocyst cell number and reduces the proportion of apoptotic cells (Sjoblom et al., 2005) [42].

Leukemia inhibitory factor (LIF) and its receptor (LIFR/gp130) system, while primarily characterized in rodent implantation, has been identified in bovine and porcine uterine tissue and may contribute to conceptus survival and implantation in these species (Bhatt et al., 2004) [4]. LIF produced by the bovine endometrium promotes trophoblast cell survival through Jak-STAT3 signaling and may facilitate the conceptus-maternal dialogue required for successful implantation.

5. Species-Specific Considerations

5.1 Cattle

In cattle, the pre-attachment conceptus must produce interferon-tau (IFN- τ) between days 14 and 21 of pregnancy to signal maternal recognition of pregnancy and prevent luteolysis. Growth factors, particularly FGFs and IGFs from the uterine glands, are essential supports for the elongating conceptus during this critical window. Studies using intrauterine infusion of growth factors in dairy cows have demonstrated that IGF-1 and FGF2 can improve conceptus elongation and pregnancy rates, particularly in high-

producing dairy cows that experience systemic IGF-1 deficiency during the transition period (Lucy, 2001)^[33].

The negative energy balance experienced by high-yielding dairy cows in early lactation dramatically reduces plasma IGF-1 concentrations and impairs follicular development, oocyte quality, and early embryo development, contributing to the well-documented decline in reproductive efficiency in modern dairy cattle (Diskin and Morris, 2008)^[10]. Strategies to supplement exogenous IGF-1 or improve the endogenous IGF-1 status of transition dairy cows represent promising approaches to mitigating reproductive failure.

5.2 Sheep and Goats

In small ruminants, BMP-15 and GDF-9 from oocytes and their receptors on granulosa cells are critical determinants of ovulation rate and litter size. Naturally occurring mutations in BMP-15 in the Inverdale and Hanna breeds of sheep lead to hyperprolificacy in heterozygous ewes and infertility in homozygous ewes (Davis et al., 1999)^[9], demonstrating the gene-dosage sensitivity of growth factor signaling in folliculogenesis. Similarly, activin signaling through the endogenous activin system modulates FSH secretion and ovarian responsiveness in sheep and goats, affecting prolificacy.

Uterine FGF7 and FGF10 expression during the peri-implantation period is regulated by progesterone and IFN- τ in sheep, creating a growth factor-rich histotroph environment that supports conceptus elongation. FGF receptor signaling is critical for trophoblast survival and proliferation during the rapid elongation phase (days 11-17) in sheep, a period during which the conceptus grows from approximately 1 mm to several centimeters in length (Bazer et al., 2012)^[11].

5.3 Pigs

Porcine reproduction presents unique features relevant to growth factor biology: litter-bearing species with synchronous elongation of up to 20+ blastocysts, epitheliochorial non-invasive placentation, and a need for estrogens from the trophoblast (rather than IFN- τ) for maternal recognition of pregnancy. Conceptus elongation in pigs occurs between days 10-14 and is among the most rapid in any mammalian species, with individual conceptuses growing from ~2 mm spheres to >100 cm filamentous threads within 24-48 hours (Ka et al., 2007)^[21].

FGF4 plays a particularly prominent role in porcine trophoblast elongation, stimulating both autocrine growth of trophoblast cells and paracrine induction of uterine FGF7 production. The abundant FGF signaling milieu in the porcine uterus during early pregnancy, combined with estrogen from the trophoblast and progesterone-stimulated uterine secretions, creates the growth factor environment required for conceptus elongation. Understanding these species-specific features of porcine growth factor signaling provides mechanistic targets for improving piglet numbers and litter uniformity.

5.4 Horses

Mares exhibit unique reproductive characteristics including a prolonged luteal phase, the formation of equine chorionic gonadotropin (eCG, also known as PMSG) by the endometrial cups, and diffuse epitheliochorial placentation. The equine preimplantation period involves mobility of the embryo within the uterus for 16-17 days before fixation, during which the conceptus is exposed to uterine secretions rich in growth factors. IGF-1, EGF, FGF2, and TGF- β have been identified

in equine uterine flushings during the pre-fixation period (Killian, 2004)^[22].

The relatively high fertility of horses compared to cattle (approximately 60% vs. 40% per cycle) may partially reflect the more favorable growth factor environment of the equine uterus. VEGF and its receptors are expressed in equine trophoblast and endometrium during early placentation, and VEGF-driven endometrial angiogenesis is critical for the establishment of the epitheliochorial placenta in mares (Wooding and Fowden, 2006)^[50].

6. Growth Factors and Assisted Reproductive Technologies

6.1 In Vitro Maturation (IVM)

The quality of oocytes matured in vitro remains inferior to those matured in vivo, contributing to lower blastocyst development rates, reduced cryotolerance, and lower pregnancy rates from in vitro-produced (IVP) embryos compared to in vivo embryos. Supplementation of IVM media with growth factors is a strategy to improve oocyte developmental competence by replicating the in vivo follicular growth factor environment. EGF (10-100 ng/mL) is the most widely used growth factor supplement in bovine, porcine, and ovine IVM systems, consistently improving maturation rates, cumulus expansion, and subsequent embryo development (Loneragan et al., 1994)^[31].

Combinations of growth factors, including EGF + IGF-1 + FGF2, have been evaluated in cattle and sheep and show additive or synergistic improvements in IVM outcomes (Gilchrist and Thompson, 2007)^[15]. Oocyte-secreted factors GDF9 and BMP15 have been added to bovine IVM systems and improve cumulus cell function, glucose metabolism, and blastocyst development, partially compensating for the loss of oocyte-cumulus communication that occurs in standard IVM protocols (Hussein et al., 2006)^[18].

6.2 In Vitro Culture (IVC) of Embryos

Embryo culture media for farm animal embryos have evolved from simple salt solutions to complex formulations that include growth factors. SOF (synthetic oviduct fluid) medium supplemented with BSA or serum has been the standard for bovine IVC, but defined serum-free systems with growth factor supplementation are increasingly preferred to avoid batch-to-batch variability and potential contamination from serum (Loneragan and Fair, 2008)^[30]. IGF-1 (100 ng/mL) supplementation to bovine IVC media consistently improves blastocyst development rates and blastocyst quality, particularly ICM cell number and total cell number (Byrne et al., 2002)^[7].

GM-CSF supplementation to bovine embryo culture media represents a particularly promising strategy, as it reduces apoptosis in the ICM and TE, improves blastocyst cell allocation, and enhances viability after cryopreservation (Sjoblom et al., 2005)^[42]. In pigs, complex IVC media supplemented with FGF2, LIF, and insulin have improved porcine blastocyst development rates and quality to levels approaching those achieved with co-culture systems (Yoshioka et al., 2003)^[51]. VEGF supplementation to porcine IVC media has been reported to improve blastocyst development and hatching rates, suggesting angiogenic growth factors have embryotrophic functions independent of their angiogenic roles.

6.3 Embryo Transfer and Uterine Preparation

The success of embryo transfer in cattle and other farm animals depends not only on embryo quality but also on the receptivity of the recipient uterus. Growth factors produced by the endometrium in response to progesterone priming are critical determinants of uterine receptivity. Research into improving uterine receptivity through growth factor supplementation has shown that intrauterine infusion of GM-CSF, IGF-1, or EGF around the time of embryo transfer improves pregnancy rates in cattle (Imakawa et al., 2006)^[19]. These growth factors may act by improving endometrial preparation, trophoblast attachment, and conceptus survival during the early post-transfer period.

7. Signaling Pathways and Molecular Mechanisms

Growth factor signaling in reproductive tissues is mediated by a limited number of conserved intracellular signal transduction cascades. Understanding these pathways provides insight into how diverse growth factor signals are integrated and translated into biological outcomes during reproduction.

The MAPK (mitogen-activated protein kinase) cascade, encompassing Raf-MEK-ERK1/2 signaling, is activated by IGF-1R, EGFR, FGFR, and PDGFR and promotes cell proliferation, differentiation, and survival in granulosa cells, cumulus cells, trophoblast, and endometrial cells. ERK1/2 activation by EGF is required for meiotic resumption in bovine and porcine oocytes and for cumulus expansion in response to the LH surge (Park et al., 2004)^[39].

The PI3K-Akt-mTOR pathway is activated by IGF-1, EGF, FGF, and VEGF and promotes protein synthesis, glucose uptake, and cell survival in preimplantation embryos and endometrial cells. In bovine embryos, PI3K-Akt signaling downstream of IGF-1R reduces apoptosis in trophoblast cells and promotes ICM survival (Byrne et al., 2002)^[7]. The JAK-STAT pathway, activated by GM-CSF, LIF, and some EGF family members, regulates gene expression programs involved in trophoblast differentiation, endometrial remodeling, and conceptus-maternal signaling (Imakawa et al., 2006)^[19].

TGF- β superfamily signals through the Smad pathway: ligand binding to type II receptors recruits and transphosphorylates type I receptors (ALK receptors), which then phosphorylate receptor-Smads (R-Smads: Smad1/5/8 for BMPs; Smad2/3 for TGF- β /activins). Phosphorylated R-Smads form complexes with common-Smad4 and translocate to the nucleus to regulate target gene transcription. BMP-Smad1/5/8 signaling is critical for TE differentiation at the blastocyst stage in cattle and pigs, while TGF- β -Smad2/3 signaling regulates endometrial stromal cell decidualization and endometrial remodeling (Berg et al., 2011)^[2].

8. Challenges and Future Perspectives

Despite substantial progress in characterizing growth factor roles in farm animal reproduction, several important challenges and knowledge gaps remain. First, most studies have been conducted in vitro or using a limited number of experimental animals, and the in vivo physiological concentrations, gradients, and temporal dynamics of growth factors in reproductive fluids remain incompletely characterized. Development of sensitive immunoassays and mass spectrometry-based proteomics approaches is needed to map the complete growth factor composition of follicular fluid, oviductal fluid, uterine histotroph, and conceptus secretomes across reproductive stages and species.

Second, the relative contributions of endocrine, paracrine, and autocrine growth factor signaling at different reproductive stages remain to be fully delineated. Systems biology approaches — integrating transcriptomics, proteomics, and metabolomics data with network analysis — hold promise for identifying key growth factor nodes and interaction hubs in the reproductive regulatory network. Third, the application of growth factor knowledge to practical improvements in livestock reproductive management requires translation of research findings into safe, cost-effective, and regulatory-approved interventions. Gene editing approaches to modify growth factor signaling in farm animals offer long-term potential for improving reproductive efficiency, though ethical and regulatory considerations must be addressed.

Future research should also focus on the roles of growth factors in male reproductive biology in farm animals, particularly spermatogenesis, sperm maturation in the epididymis, and seminal plasma composition, areas that have received relatively less attention compared to female reproductive biology. The development of species-specific IVM and IVC systems incorporating physiologically relevant growth factor combinations, and the use of microfluidic technologies to create dynamic growth factor gradients mimicking the in vivo environment, represent promising directions for improving ART outcomes in livestock.

Conclusion

Growth factors are indispensable molecular orchestrators of the reproductive continuum in farm animals, from the earliest events of folliculogenesis through fertilization, early embryo development, conceptus elongation, and implantation. The IGF system, EGF family, FGF family, TGF- β superfamily, VEGF, and GM-CSF each contribute distinct and essential functions at specific reproductive stages, often acting cooperatively through interconnected signaling networks. Their expression by both reproductive tract tissues and by the oocyte, sperm, and developing embryo itself underscores the paracrine, autocrine, and endocrine complexity of reproductive regulation at the molecular level.

Species-specific differences in growth factor biology reflect the diverse reproductive strategies of cattle, sheep, goats, pigs, and horses and have implications for species-tailored approaches to reproductive management. The application of growth factor knowledge to the development of improved IVM and IVC systems, embryo culture media, and uterine preparation protocols represents a significant opportunity to improve reproductive efficiency in livestock production systems. As our understanding of growth factor signaling networks in reproduction deepens, precision reproductive biotechnology guided by molecular biology will increasingly complement traditional reproductive management practices in farm animal production.

Conflict of Interest Statement

The author(s) declare no conflict of interest.

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