REPRODUCTIVE BIOLOGY

REVIEW

Interferons and progesterone for establishment and maintenance of pregnancy: interactions among novel cell signaling pathways[1]

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SUMMARY

Type I and/or type II interferons (IFNs) are important in establishing uterine receptivity to implantation in mammals. Gene expression effected by IFNs may be induced, stimulated or inhibited, but most are IFN-stimulated genes (ISGs). Effects of IFNs range from pregnancy recognition signaling in ruminants by IFN tau (IFNT) to effects on cellular functions of the uterus and uterine vasculature. For most, if not all, actions of IFNs on the uterus, progesterone (P_4) is permissive to ISG expression, with genes being induced by IFN or induced by P_4 and stimulated by IFN. Uterine receptivity to implantation is P_4-dependent; however, implantation events are preceded by loss of expression of progesterone (PGR) and estrogen (ESR1) receptors by uterine epithelia. Thus, P_4 likely stimulates PGR-positive stromal cells to express one or more progestamedins, e.g., fibroblast growth factors-

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7 and -10, and/or hepatocyte growth factor, that act *via* their respective receptors on uterine epithelia and trophectoderm to regulate expression of ISGs. FGF10 appears to be the most important progestamedin in sheep uteri during pregnancy. Sequential effects of P_4 to induce and IFNs to stimulate gene expression suggest that P_4 and IFNs activate complimentary cell signaling pathways to modulate expression of genes for attachment of trophectoderm to uterine lumenal and superficial glandular epithelia (LE/sGE), modify phenotype of uterine stromal cells, silence PGR and ESR1 genes, signal pregnancy recognition, suppress genes for immune recognition, alter membrane permeability to enhance conceptus-maternal exchange of factors, increase endometrial vascularity and activate genes for transport of nutrients into the uterine lumen. In ewes, IFNT abrogrates the uterine luteolytic mechanism and stimulates expression of classical ISGs by GE and stromal cells, whereas LE/sGE express P_4-induced and IFNT-stimulated genes important for uterine receptivity to implantation and conceptus development. These include wingless-type MMTV (mouse mammary tumor virus) integration site family member 7A (*WNT7A*) induced by IFNT, as well as galectin, proteases, protease inhibitors, transporters for glucose and amino acids, gastrin releasing polypeptide, insulin-like growth factor binding protein 1 and a hypoxia inducible factor. The specific functions of IFNs and ISGs induced in primates, pigs and other mammals during pregnancy are not known, but likely are important in establishment of pregnancy. Understanding the roles of IFNs and ISGs in uterine receptivity for implantation is necessary to develop strategies to enhance reproductive health and fertility in humans and domestic animals. *Reproductive Biology 2008* ***8*** *3:179-211.*

Key words: interferons, progesterone, pregnancy, interferon-stimulate genes, progestamedins, fertility, reproductive health

INTRODUCTION

Type I and/or type II interferons (IFNs) appear to be important in establishing uterine receptivity to implantation in most mammals as they affect expression of many genes [151, 152]. These IFN-stimulated genes (ISGs) are expressed

in a specific temporal and spatial (cell-specific) manner. For most, if not all actions of IFNs on the uterus, progesterone (P_4) is permissive to expression of ISGs. In most cases, P_4 induces and IFN stimulates expression of many ISGs, but IFN may stimulate expression of some ISGs directly with P_4 being permissive. There is a paradox with respect to actions of P_4 on uterine receptivity to implantation. That is, receptivity is P_4-dependent, but implantation is preceded by loss of expression of progesterone (PGR) and estrogen (ESR1) receptors by uterine epithelia in all animals studied [142, 148, 151, 152]. The P_4-induced down-regulation of PGR in uterine luminal (LE), superficial glandular (sGE) and glandular (GE) epithelia of ewes is a prerequisite for expression of ISGs. Thus, P_4 likely acts on PGR-positive stromal cells to increase expression of progestamedins that include fibroblast growth factors-7 (FGF7) and -10 (FGF10) and hepatocyte growth factor (HGF) that may exert paracrine effects on uterine epithelia and conceptus trophectoderm that express their respective receptors, *FGFR2IIIb* and MET (protooncogene *MET;* [24, 25, 81-83, 142, 148, 151]). In ewes, FGF10 appears to be the progestamedin responsive to P_4 [136]. In sheep, classical ISGs e.g., interferon stimulated gene 15, Mx (Mouse Myxovirus Resistance 1) and 2',5' oligoadenylate synthase induced by IFNT are limited to uterine GE and stromal cells because uterine LE/sGE express interferon regulatory factor 2 (IRF2; [28]) which is a potent inhibitor of gene transcription that silences expression of genes such as ESR1 and signal transducer and activator of transcription factor 1 (STAT1; [121, 154, 155]). Because ovine uterine LE/sGE lack PGR and STAT1, IFNT is unable to affect gene transcription through the Janus activated kinases (JAKs) and tyrosine kinase 2 (TYK2) cell signaling pathway and P_4 is unable to activate gene transcription through nuclear PGR. Rather, both P_4-induced progestamedins and IFNT can stimulate gene expression in uterine LE/sGE through activation of phosphoinositide 3-kinase (PI3K)/ mitogen activated protein kinase (MAPK) cell signaling pathways (see fig. 1; [71, 107, 114, 121, 131, 156]).

Uterine receptivity to implantation involves changes in expression of genes for attachment of trophectoderm to uterine LE/sGE, modification of uterine stromal cell phenotype, silencing PGR and ESR1 genes in uterine epithelia, signaling for pregnancy recognition, suppression of genes

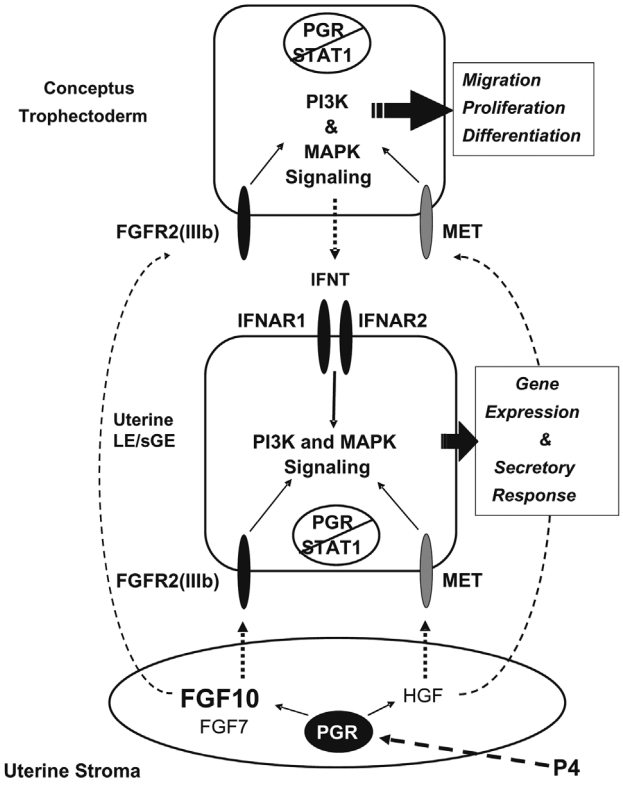

Figure 1. Hypothesis on the roles of progesterone (P_4), progestamedins (FGF7, FGF10 and HGF) and interferon tau (IFNT) on gene expression and secretory functions of ovine uterine lumenal and superficial glandular epithelia (LE/sGE) that lack both progesterone receptor (PGR) and signal transducer and activator of transcription 1 (STAT1). Ovine uterine LE/sGE lack detectable PGR and STAT1, indicating that P_4 and IFNT use non-classical signaling pathways to regulate expression of P_4-induced and IFNT-stimulated genes. The stroma remains PGR-positive. Results from our laboratory indicate that P_4 increases production primarily of stromal-derived FGF10 and very low levels of HGF that can act on uterine LE/sGE and conceptus trophectoderm cells that express FGFR2(IIIb) and MET receptors for FGF10 and HGF, respectively, to activate mitogen activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) cell signaling. Progestamedins and type I IFNs activate the PI3K and AKT1 signaling pathways in other cell types [see 14]. Our unpublished results [J-Y Kim, G. Song, T.E. Spencer and F.W. Bazer] indicate that IFNT activates p38 MAPK and PI3K-AKT1-FRAP1(mTOR) signaling pathways and that promoter/enhancer regions of novel P_4-induced and IFNT-stimulated genes expressed in uterine LE/sGE have binding sites for transcription factors activated by MAPK and PI3K signaling pathways.

for immune recognition of the conceptus (embryo/fetus and associated membranes), alterations in membrane permeability to enhance conceptus-maternal exchange of factors, increased vascularity of the endometrium and activation of genes for transport of nutrients into the uterine lumen [40, 58, 151, 152]. In sheep, effects of IFNT are pleiotrophic in that it signals pregnancy recognition by abrograting the uterine luteolytic mechanism, stimulates expression of classical ISGs by GE and stromal cells, and stimulates expression of P_4-induced and IFNT-stimulated genes by LE/sGE that lack both PGR and STAT1 [148, 151, 152]. The known P_4-induced and IFNT-stimulated genes expressed by ovine uterine LE/sGE are listed in Table 1. Understanding demonstrated and potential pleiotrophic effects of

Table 1. Progesterone-induced and interferon tau-stimulated genes expressed by ovine uterine lumenal and superficial glandular epithelia

Gene	**Function of Gene Product**	**Reference**
HIF2A	transcription factor: induces VEGF (angiogenesis) and SLC2A1 (glucose transport)	146
SLC2A1	facilitative glucose transporter	50
SLC5A11	sodium-dependent glucose transporter	50
SLC7A2B	solute carrier family 7 (cationic amino acid transporter, y+ system), member 2, arginine transporter	footnote
SLC1A5	solute carrier family 1 (neutral amino acid transporter), member 5, glutamine transporter	footnote
CTSL	cathepsin L, cysteine proteinase affecting protein catabolism	144
CST3	cystatin C, proteinase inhibitor	145
LGALS15	galectin 15; lectin: stimulates migration and adhesion of trophectoderm cells	39, 135
GRP	gastrin releasing polypeptide: affects morphogenesis, migration and adhesion of cells, and angiogenesis	147
IGFBP1	insulin-like growth factor binding protein 1: modulation of mitogenesis	136
WNT7A	secreted morphogen: cell fate and patterning	62

Footnote: Unpublished results (H. Gao, G. Wu, T.E. Spencer, G.A. Johnson and F.W. Bazer)

IFNT and other IFNs, as well as ISGs in uterine receptivity for implantation is required for development of strategies to enhance reproductive health and fertility in humans and animals (see fig. 2).

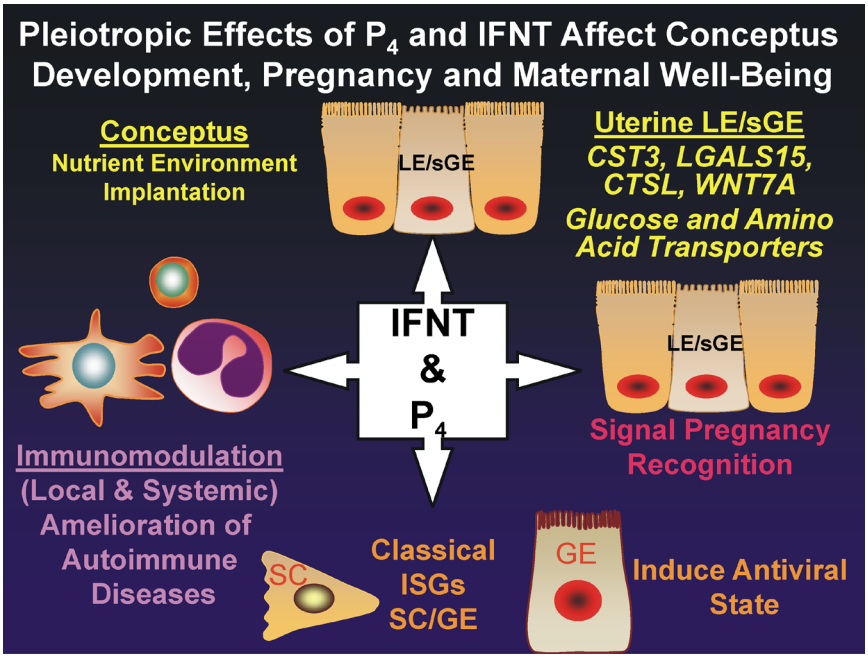

Figure 2. The effects of progesterone (P_4) and interferon tau (IFNT) are pleiotrophic in that they are required for signaling pregnancy recognition by abrograting the uterine luteolytic mechanism, stimulating expression of classical interferon stimulated genes (ISGs) by uterine luminal (LE), superficial glandular (sGE), and glandular (GE) epithelia, and stromal cells (SC), stimulating expression of P_4-induced and IFNT-stimulated genes by uterine LE/sGE that lack both PGR and STAT1 [148, 151, 152] and acting systemically to modulate the maternal immune system [11].

INTERFERONS AND UTERINE RECEPTIVITY

Conceptus trophectoderm must signal pregnancy recognition to maintain a functional corpus luteum (CL) for production of P_4 that is permissive to actions of IFNs, growth factors and cytokines responsible for uterine receptivity to implantation [41, 143, 151]. In primates, chorionic gonadotrophin (CG) is the luteotrophic signal that acts directly *via* receptors for luteinizing hormone

to maintain structural and functional integrity of the CL [41]. In ruminants and pigs, antiluteolytic hormones for pregnancy recognition are IFNT and estradiol, respectively. IFNT silences expression of ESR1 and oxytocin receptor (OXTR) to prevent oxytocin-induced release of luteolytic pulses of prostaglandin $F_{2\alpha}$ (PGF) for CL maintenance [151]. In pigs, estradiol, likely in combination with prolactin, exerts antiluteolytic effects on uterine epithelia to prevent endocrine release of luteolytic PGF [10]. However, pig conceptus trophectoderm also expresses both type I (interferon delta, IFND) and type II (interferon gamma, IFNG) interferons [22].

Although IFNT is the only known IFN to act as the pregnancy recognition signal, IFNs appear to affect uterine receptivity, decidualization and placental growth and development in primates, ruminants, pigs and rodents [8, 63, 119, 124, 151]. The IFN family includes multiple type I IFNs and one type II IFN (IFN gamma, IFNG; [118, 128]). Type I IFNs that share high structural homology include interferons alpha (IFNA; 13 subtypes), beta (IFNB), delta (IFND), tau (IFNT), and omega (IFNW1). IFNT is unique to ruminants and IFND is unique to pigs [91, 127, 128] and perhaps horses [157]. IFNT shares highest identity to IFN omega with respect to biological activities and induction of ISGs in endometria and human cell lines [127, 128].

All type I IFNs bind a common receptor composed of two subunits, IFNAR1 and IFNAR2, to induce cell signaling *via* the Janus activated kinases (JAKs) and tyrosine kinase 2 (TYK2) pathways, respectively [32, 131, 153]. Signaling by type II IFNG involves activation of the JAK family with JAK1 and JAK2 constitutively associated with IFNGR1 and IFNGR2 subunits of type II IFNR, respectively. IFNG stimulates autophosphorylation and subsequent tyrosine phosphorylation and homodimerization of STAT1. STAT1 homodimers translocate to the nucleus and bind GAS elements in promoter regions of IFNG-regulated genes to initiate transcription [94]. There is evidence that IFNs are expressed by human placentae (IFNA, IFNB, IFNG), decidua (IFNA, IFNB and IFNG) and fetal membranes (IFNA, IFNG), as well as conceptus trophectoderm of sheep (IFNT), pig (IFND and IFNG) and rodent uteri and/or conceptuses (IFNA, IFNB; [1, 11, 16, 23, 91]). These IFNs have classical antiviral, antiproliferative and immunosuppressive effects, as well as unique biological activities.

IFNT: PREGNANCY RECOGNITION AND UTERINE RECEPTIVITY TO IMPLANTATION IN RUMINANTS

Pregnancy Recognition Signaling by IFNT. IFNT, the pregnancy recognition signal in ruminants, suppresses transcription of *ESR1* and, therefore, estrogen-induced expression of the oxytocin receptor (*OXTR)* gene in uterine LE/sGE to abrogate development of the endometrial luteolytic mechanism that is dependent on oxytocin-induced luteolytic pulses of PGF [148, 151]. However, basal production of PGF is higher in pregnant than cyclic ewes due to continued expression of prostaglandin endoperoxide synthase 2. Further, IFNT inhibits *ESR1* expression to prevent estrogens from inducing *PGR* in endometrial epithelia as the absence of PGR in uterine epithelia is required for expression of P_4-induced and IFNT-stimulated genes in ovine uterine LE/sGE [see 58, 152].

Uterine Receptivity to Implantation. Implantation of blastocysts of ruminants involves: 1) hatching from the zona pellucida; 2) contact with uterine LE/sGE and orientation of the blastocyst; 3) apposition between trophectoderm and uterine LE/sGE; 4) adhesion of trophectoderm to uterine LE/sGE; and 5) limited endometrial invasion [60]. Initiation of implantation in sheep on Days 12 and 13 coincides with loss of PGR from uterine epithelia, but not stromal or myometrial cells, and reduced expression of anti-adhesive genes, such as *MUC1* from uterine LE to allow contact with trophectoderm for initiation of implantation [148, 151]. As uterine receptivity and implantation occur after uterine LE/sGE cease expressing PGR, P_4-regulated LE/sGE and GE functions are likely directed by progestamedins [148, 151], particularly FGF10 in sheep [13]. The P_4-induced and IFNT-stimulated genes expressed by ovine uterine LE/sGE important during the period of uterine receptivity to implantation and conceptus development are listed in Table 1.

Galectin 15 is secreted into the uterine lumen where it binds integrins on cell surfaces to stimulate trophectoderm cell attachment and migration *in vitro* [39]. Cathepsins degrade extracellular matrix, catabolize intracellular proteins, process prohormones, and regulate uterine receptivity for implantation

and trophoblast invasion in many species, including humans [6, 132, 133]. Cathepsin L and its inhibitor, cystatin C, are coordinately expressed by ovine uterine LE/sGE and conceptus trophectoderm during pregnancy [144, 145], probably to modify their glycocalyx [132] and/or secreted extracellular matrix proteins during apposition and adhesion phases of implantation.

WNT7A, an IFNT-stimulated gene unique to ovine endometrial LE, may mediate trophoblast-epithelial interactions critical for uterine receptivity to implantation [62]. The WNT family of genes (19 in human) encode highly conserved secreted glycoproteins that regulate cell and tissue growth and differentiation during embryonic development [123] and coordinate uterine-conceptus interactions during implantation in mice [35, 68, 110, 111] and perhaps humans [84, 159]. *WNT7A*, a LE-specific gene in all mammals studied, stimulates ovine trophectoderm cell proliferation by activating the canonical WNT signaling pathway which is proposed to coordinate conceptus-endometrial interactions required for implantation in mice and humans [62].

The hypoxia-inducible (HIF) gene family includes three alpha (*HIF1A*, *HIF2A*, and *HIF3A*) and three beta (*HIF1B* [also known as aryl hydrocarbon receptor nuclear translocator], *HIF2B*, and *HIF3B*) subunits. Increases in *HIF1A* expression in response to hypoxia increases erythropoiesis, glycolysis and angiogenesis to counteract oxygen deficiency and *HIF2A* is expressed predominantly in highly vascularized tissues such as heart, lung, and placenta [37, 139]. Over 200 genes respond to HIF, including *erythropoietin* (*EPO)*, *CBP/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 2* (*CITED2*), *vascular endothelial growth factor* (*VEGF*), *GLUT1/SLC2A1*, and *insulin-like growth factor 2* (*IGF2*). Mice with lacking *Hif1a*, *Hif2a* or *Hif1b (Arnt)* die at mid-gestation due to vascular defects in the embryo and placenta [5, 31, 74, 89, 101, 117, 140]. In peri-implantation mouse uteri, P_4 increases *Hif1a* in uterine LE/sGE and estrogen increases *Hif2a* in uterine stroma [31]. *HIF1A* and *HIF2A* are P_4-induced and IFNT-stimulated genes in LE/sGE and *CITED2* and *VEGF* are expressed in ovine endometria and conceptus trophectoderm [146]. Thus, HIF2A may mediate actions of P_4 and IFNT to establish uterine receptivity to implantation and conceptus development in sheep [146].

Gastrin-releasing peptide (GRP), a mammalian homologue of bombesin from the amphibian *Bombina bombina*, induces gastrin secretion by porcine gastric tissue [105, 116]. GRP is also expressed in the hypothalamus, anterior pituitary, gastrointestinal tract, lung, and pancreas [116], as well as in uteri of sheep, cattle and humans [17-19, 47, 48, 54-56, 141, 167-170, 174, 175]. *GRP* mRNA is expressed in uteri of cyclic and pregnant ewes and GRP-derived peptides have been detected in the uterine lumen and in allantoic fluid [48, 55, 168, 170, 174]. The cell-specific location of GRP receptors in ovine uteri is not known, but kidneys of fetal and adult sheep express GRP receptors [36] and they are present in human uterine myometrium, subsets of secretory cells in endometrial glands and subsets of endometrial blood vessels [44, 167]. GRP is a potent mitogen for cancer cells [116] and exerts effects on cell morphogenesis, migration, and adhesion, as well as angiogenesis [104, 116]. These biological actions of GRP likely affect peri-implantation growth and development of conceptuses in ruminants [59, 149].

GRP expression is greater in endometria of Day 14 pregnant compared to Day 14 cyclic ewes and its expression is stimulated by IFNT in ewes treated with P_4, but not by P_4 alone [169]. Further, estrogen and/or estrogen with P_4 decrease *GRP* mRNA levels in endometria of long-term ovariectomized ewes [169]. Our laboratory determined that: 1) *GRP* is an IFNT-stimulated gene in LE/sGE; 2) changes in GRP expression are coordinate with growth and development of the blastocyst into a filamentous conceptus; 3) up-regulation of *GRP* expression occurs in response to early P_4 administration to pregnant ewes that advanced formation of filamentous conceptuses [147].

The insulin-like growth factor (IGF) family consists of IGF1, IGF2, and their receptors IGF1R and IGF2R, as well as seven IGF binding proteins (IGFBPs 1-7) which modulate IGF activity and bioavailability [42, 65, 113, 160]. IGF1 and IGF2 have mitogenic and differentiative properties that may influence embryonic and placental development in humans, rodents, and domestic animals [73, 162, 163]. In humans, the IGF1R binds IGF1 and IGF2 with high and moderate affinities, respectively [160]. IGFBPs can enhance or inhibit activity of IGFs [30, 76]. IGFBPs 1-6

bind IGFs with high affinity, but are released by actions of proteases to act on adjacent cells expressing IGF1R. IGFBP proteases include matrix metalloproteinases, kallikreins, cathepsins, pregnancy associated plasma protein A, calpain and other serine proteases [65]. Thus, activities of IGFs are affected by availability of receptors, abundance of IGFBPs and activities of specific proteases that influence local concentrations of IGF. In pigs, proteolytic cleavage of IGFBPs to yield free IGF occurs in association with elongation of the conceptus [95]. In the cow, *IGFBP1-5* are expressed in endometria during the peri-implantation period of pregnancy [86] and blastocyst development can be stimulated by exogenous GH that increases IGF1 [158].

Expression of *IGF1* in ovine uteri is predominantly in endometrial stromal cells and not affected by early P_4 although *IGF1* mRNA levels decreased in stromal cells between Days 9 and 12 of pregnancy [136]. In contrast, *IGF2* mRNA levels were unaffected by day of pregnancy or early P_4 treatment. The presence of *IGF1* and *IGF2* mRNA in uterine stromal cells during pregnancy suggests an epitheliomesenchymal role(s) in ovine endometria *via* IGF1R in uterine LE and GE [57, 136]. Results from studies of mice and humans suggest that IGF1 regulates effects of estrogen on proliferation of endometrial epithelia [57, 134]. The induction of *IGF2* mRNA in uterine LE/sGE of ewes treated with both P_4 and RU486 suggests that P_4 suppresses *IGF2* expression in uterine epithelia [136]. Nevertheless, IGF1 and IGF2 in ovine and bovine uterine luminal histotroph may regulate blastocyst growth and development [86-88]. Both ovine and bovine pre-implantation embryos [163], as well as Day 15 elongated bovine conceptuses express *IGF1R* [137] which may allow IGF1 to stimulate proliferation and inhibit apoptosis [77]. In ewes, total IGF1 in the uterine lumen is 50% lower in early P_4-treated ewes on Day 9, but not on Day 12, which suggests that: 1) Day 9 is a critical period when developing blastocysts have unrestricted access to free IGF prior to up-regulation of epithelial *IGFBP1* and *IGFBP3* between Days 9 and 12; and 2) the reduction in total IGF1 protein in the uterine lumen is due to its rapid utilization by blastocysts [136]. Indeed, blastocysts recovered from early P_4-treated ewes were larger than those from CO-treated ewes on Day 9

[135]. Access of blastocysts to IGF1 in the uterine lumen may be limited due to increases in *IGFBP1* and *IGFBP3* in uterine LE/sGE between Days 9 and 12 of pregnancy. IGF2 can stimulate ovine trophectoderm cell migration [87] which may be critical for blastocyst elongation and formation of a filamentous conceptus [149]. Thus, interactions between IGFBP1, IGFBP3, IGF1 and IGF2 in the uterine lumen likely influence endometrial functions, as well as blastocyst growth and development.

The energy substrate for mammalian conceptuses switches from pyruvate to glucose at the blastocyst stage which is coordinate with increases in expression of uterine glucose transport proteins [33, 126, 178]. In ovine uteri, total recoverable glucose increases 12-fold between Days 10 and 15 of pregnancy coincident with increases in expression of the glucose transporters *SLC2A1* and *SLC5A11* in ovine uterine LE/sGE and SLC2A3 in conceptus trophectoderm [50]. Similarly, expression of the cationic amino acid transporter, y+ system, member 2 (*SLC7A2B*) increases coincidentally with increases in total recoverable arginine between Days 10 and 15 of pregnancy [50, 67].

Glucose, a major nutrient for conceptuses and cells of the uterus [112], is delivered into the uterine lumen by glucose transporters [97, 115] as neither conceptuses nor uterine endometrium can carry-out gluconeogenesis. Transport of glucose from the maternal circulation into the uterine lumen is essential for pregnancy [138] as it can enhance trophoblast cell growth and proliferation by activating the glutamine:fructose-6-phosphate amidotransferase (GFAT)-mediated FK506 binding protein 12-rapamycin associated protein 1 (FRAP1, formerly mTOR) signaling pathway [164]. Accordingly, total glucose in uterine lumenal fluid increased 6-fold between Days 10 and 15 of gestation in ewes [49] in association with rapid growth and development of blastocysts from spherical, to tubular and filamentous conceptuses [43].

Transport of glucose across the plasma membrane can be mediated by facilitative transporters such as solute carriers SLC2A and/or sodium-dependent transporters such as sodium/glucose cotransporters SLC5A [171]. Sodium-dependent glucose transporters are necessary to transport glucose against electrochemical gradients, e.g., from endometrium

into the uterine lumen [51]. Our laboratory investigated effects of the estrous cycle, pregnancy, P_4 and IFNT on expression of both facilitative (*SLC2A1*, *SLC2A3* and *SLC2A4)* and sodium-dependent (*SLC5A1* and *SLC5A11*) glucose transporters in ovine uterine endometria between Days 10 to 16 of the estrous cycle and Days 10 and 20 of pregnancy, as well as in conceptuses from Days 10 to 20 of pregnancy [50]. SLC2A1 and SLC5A1 mRNAs and proteins were most abundant in uterine LE/sGE, whereas *SLC2A4* was present in stromal cells and GE. *SLC5A11* mRNA was most abundant in endometrial GE. *SLC2A1, SLC2A3* and *SLC2A4, SLC5A1* and *SLC5A11* were expressed in trophectoderm and endoderm of conceptuses, and *SLC2A1, SLC5A1* and *SLC5A11* mRNAs were more abundant in endometria from pregnant than cyclic ewes. Progesterone increased *SLC2A1, SLC5A11* and *SLC2A4* mRNAs in LE/sGE and *SLC5A1* in GE of uteri from ovariectomized ewes. Further, P_4 induced and IFNT stimulated expression of *SLC2A1* and *SLC5A11* indicating differential expression of facilitative and sodium-dependent glucose transporters in ovine uteri and conceptuses for transport and uptake of glucose during the peri-implantation period of pregnancy [50].

Cationic amino acid transporters transport amino acids such as arginine that is essential for fetal-placental growth and development [173], including synthesis of nitric oxide (NO) and polyamines [172]. NO is a major regulator of angiogenesis [106] and utero-placental-fetal blood flows which affect delivery of nutrients and oxygen from mother to fetus [14] and polyamines are essential for DNA and protein synthesis, and proliferation and differentiation of cells [70]. Further, arginine regulates metabolic pathways critical for nutrient utilization and protein deposition through FKBP12-rapamycin complex-associated protein 1 (FRAP1) and NO signaling pathways [75, 102, 103]. Our laboratory reported that arginine increased 10-fold in uterine flushings between Days 10 and 15 of pregnancy, i.e., the peri-implantation period [49] and hypothesized that arginine transport into the uterine lumen is especially important for ruminants and pigs that establish synepitheliochorial and epitheliochorial placentae, respectively after conceptuses undergo rapid elongation during a protracted peri-implantation period [60].

Transport of L-arginine is primarily by the Na^+-independent System y^+ for cationic amino acids that has low affinity, but high capacity in cells, and designated SLC7A1, SLC7A2, and SLC7A3. System y^+ (*SLC7A1*, *2,* and *3*) cationic amino acid transporters in uteri of cyclic and pregnant ewes and conceptuses were characterized to determine effects of pregnancy, P_4 and IFNT on their expression [H. Gao, G. Wu, T.E. Spencer and F.W. Bazer, unpublished results]. *SLC7A1* mRNA was most abundant in endometrial LE/sGE on Day 16 of the estrous cycle and Days 16 to 20 of pregnancy, whereas *SLC7A2* mRNA was most abundant in LE and mid- to deep GE on Days 14 to 20 of gestation, but *SLC7A3* levels were not affected by day or pregnancy status. *SLC7A1, SLC7A2* and *SLC7A 3* mRNAs were expressed in both trophectoderm and endoderm of conceptuses. Long-term treatment of ovariectomized ewes with P_4 stimulated *SLC7A1* in LE and GE, and IFNT tended to increase *SLC7A1* abundance in LE. However, *SLC7A2* mRNA was clearly induced by P_4 and stimulated by IFNT in endometrial LE/sGE. These results indicate coordinate changes in *SLC7A1, SLC7A2* and *SLC7A3* expression in uterine endometria and conceptuses to affect transport of arginine critical to conceptus growth, development and survival.

Interferon tau activation of the classical JAK-STAT-IRF1 signaling pathway in ovine endometrial stroma and GE *in vivo* and in human 2fTGH cells (human fibrosarcoma cell line) *in vitro* results in expression of many ISGs [see 151, 152]. These include: *beta-2 microglobulin (B2M); bone marrow stromal cell antigen (BST); complement component c1r deficiency (C1R); complement component 1s subcomponent (C1S); cystatin c (CST3); cathepsin L (CTSL); chemokine, CXC motif, ligand 10 (CXCL10); dead H/box 58 (DDX58); guanylate binding proteins (GBP1, GBP2, GBP3, GBP4, GBP5); interferon alpha inducible protein 6 (G1P3); gene associated with retinoid- and interferon-induced mortality 19 (GRIM19); HSXIAPF1; interferon-inducible proteins (IFI27, IFI35); interferon induced with helicase c domain protein 1 (IFIH1); interferon-induced protein with tetratricopeptide repeats (IFIT1, IFIT2, IFIT3, IFIT5);interferon-induced transmembrane proteins (IFITM1, IFITM3); interferon regulatory factors (IRF1, IRF2, IRF6, IRF9); interferon-stimulated gene 15 (ISG15); major histocompatibility complex class I chain-related gene (MIC); homolog of*

myxovirus (influenza virus) resistance 1 and 2 (MX1, MX2); NMYC interactor (NMI); 2',5'oligoadenylate synthetase (OAS1, OAS2, OAS3); phospholipids scrambalase-1 (PLSCR1); prolactin receptor (PRLR); RSAD2; receptor-transporting protein 4 (RTP4); complement component 1 inhibitor (SERPING1); nuclear body protein SP140 (SP140); signal transducer and activator of transcription (STAT1, STAT2); and ubiquitin-activating enzyme e1-like (UBE1L).

Silencing of classical ISGs in uterine LE/sGE during early pregnancy is important for maternal tolerance of the fetal allograft. Major histocompatibility complex (MHC) class I molecules, consisting of an alpha chain and beta2-microglobulin (B2M), regulate immune rejection responses by discriminating self and non-self and are increased by type I IFNs. In the ovine uterus, MHC class I alpha chain and B2M are expressed primarily in endometrial LE/sGE on Days 10 and 12 of the estrous cycle and pregnancy [29]. However, on Days 14 to 20 of pregnancy, increases in MHC class I and B2M expression are restricted to endometrial stromal cells and GE. Accordingly, intrauterine infusion of IFNT increased MHC class I and B2M expression in endometrial stromal cells and GE, but not uterine LE/sGE. During pregnancy, expression of *MHC class I* and *B2M* genes is also limited to uterine stromal cells and GE. Silencing *MHC* class I alpha chain and *B2M* genes in endometrial LE and sGE during pregnancy may be critical in preventing immune rejection of the conceptus allograft. Similar results have been reported from studies of pigs [80].

INTERFERONS AND UTERINE RECEPTIVITY IN PRIMATES

Type I and type II IFNs are produced by human placenta and decidual cells [1-4, 16]. Human extravillous and villous trophoblast produce IFNA and IFNB when cultured in the presence of granulocyte-monocyte colony stimulating factor and platelet derived growth factor followed by infection with Sendai virus, while trophoblast cells produced IFNB in response to double stranded RNA or both IFNA and IFNB in response to Sendai and Newcastle Disease viruses [1, 4]. These IFNs may: 1) regulate proliferation of trophoblast or other cells in the uterus; 2) suppress mitogen-induced

proliferation of T- and B-cells; 3) protect the conceptus from viral infections; 4) regulate cellular differentiation and expression of cell surface antigens; 5) stimulate expression of ε-globin, a component of embryonic hemoglobin; and 6) suppress expression of proto-oncogenes such as EGFR, c-erB2 and c-fms to affect trophoblast growth and differentiation [1, 4].

Many ISGs induced by IFNT in ruminants are among the most upregulated genes in human endometrial stromal cells co-cultured with human trophoblast [124] or treated with human trophoblast conditioned medium [63] and in endometria of baboons, domestic animals, and laboratory animals [8, 9, 13, 15, 20, 26, 27, 66, 85, 93, 99, 100, 108, 125]. These include: *DDX58, GBP1, GBP2, HSXIAPF1, IFIH1, IFIT1, IFIT2, IFIT3, IFIT5, IFI35, IRF1, ISG15, MIC, MX1, MX2, NMI, OAS1, OAS2, OAS3, PLSCR1, PRLR, RSAD2, RTP4, SERPING1, STAT1, STAT2*. During the peri-implantation period of pregnancy, increases in *B2M*, *ISG15*, *GBP1*, *IFI27* and *IRF1* occur in endometria of humans, baboons, domestic animals, and laboratory animals [2-5, 13, 20, 26, 29, 31, 66, 85, 93, 99]. Expression of guanylate binding protein 1 (GBP1), induced by both IFNA and IFNG, is highest during the mid-secretory phase of the menstrual cycle and is most closely associated with temporal changes in IFNG rather than IFNA [93]. Although GBP1, a GTPase, is a marker of uterine receptivity to implantation, its function is not known; however, Mx proteins, also GTPases, are ISGs in most species that may protect against viral infection. Li et al. [99] reported that expression of p27 (cyclin-dependent kinase inhibitor 1b; CDKN1B), which has high homology to interferon regulated gene 1 (IRG1), increases in Ishikawa cells in response to IFNA and that estradiol and IFNA exert synergistic effects to stimulate p27 preceding cell proliferation. The p27 gene is expressed during the window of implantation in humans and is considered essential for normal endometrial proliferation [38]. A shift in endometrial production from PGF to PGE is also associated with implantation in humans with IFNA suppressing P_4-regulated production of basal PGF, but not PGE [109]. Given that ISGs are highly upregulated in human endometrial stromal cells in response to human trophoblast conditioned culture medium, rigorous studies are required to clarify which IFNs are expressed by human trophoblast cells and define temporal and cell-specific expression of ISGs in human uteri

[69, 124]. IFNA from human syncytiotrophoblast [2] and explant cultures of human trophoblast [15] may stimulate transcription of the *CGB* gene without effects on cell proliferation [72]. However, this reported effect of IFNA on CGB production by bladder tumor cell lines must be confirmed using human trophoblast cells.

There are reports of undesirable effects of cytokines on development of human conceptuses. For example, the combined effects of tumor necrosis factor α (TNFA), IFNG and IL1B have been implicated in pregnancy failure, possibly due to loss of blood supply and conceptus death [120]. There is also evidence that CGB has "antiviral" activity, including antiviral lysozyme and antiviral RNases that inhibit HIV-1 by lysing HIV-1 proteins and degrading RNA from HIV-1-infected cells [96].

INTERFERONS, ESTROGENS, AND UTERINE RECEPTIVITY TO IMPLANTATION IN PIGS

After hatching from the zona pellucida, pig blastocysts expand and undergo a morphological transition to large spheres of 10 to 15 mm diameter and then tubular (15 mm by 50 mm) and filamentous (l mm by 100-200 mm) forms between Days 10 and 12 of pregnancy and achieve a length of 800 to 1000 mm between Days 12 and 15 of pregnancy [12]. During this peri-implantation period of rapid elongation, the trophectoderm produces significant amounts of estrogen [152], as well as interferons gamma (IFNG) and delta (IFND; [21, 22, 150]).

The pregnancy recognition signal is estrogens produced by conceptus trophectoderm from Days 11 and 12 to Day 15 of pregnancy that directs secretion of PGF away from the uterine vasculature (endocrine secretion) to secretion into the uterine lumen (exocrine secretion) where it is sequestered and metabolized to prevent luteolytic effects on the CL [10, 46]. The conceptus estrogens also modulate uterine gene expression responsible for endometrial remodeling for implantation between Days 13 and 25 of gestation [53]. Secreted phosphoprotein 1 (SPP1) and FGF7 are induced by estrogen in uterine LE to affect trophectoderm and LE adhesion, and signal transduction

and cell migration during the peri-implantation period [52, 82, 83, 166]. The trophectoderm also secretes interleukin-1 beta (IL1B) during this period and estrogen appears to modulate uterine responses to IL1B [129].

Pig conceptus trophectoderm is unique in secreting both type I and type II IFNs during the peri-implantation period. The major species (75% of antiviral activity) is type II IFN gamma (IFNG) and the other (25%) is type I IFN delta (IFND; [21, 22]). Abundant *IFNG* mRNA is detectable in porcine trophectoderm between Days 13 and 20 of pregnancy, whereas *IFND* mRNA is detectable in Day 14 conceptuses only by RT-PCR analysis (fig. 3; adapted from [79]). On Day 15 of pregnancy, immunoreactive IFNG and IFND proteins are co-localized to peri-nuclear membranes typically occupied by endoplasmic reticulum and Golgi apparatus, as well as cytoplasmic vesicles within clusters of trophectoderm cells along the endometrial LE (fig. 3; [21, 22, 79]). This expression is characterized by *de novo* appearance of zona occludens one (ZO1), a marker of epithelial tight junctions, on their basal aspect, suggesting changes in endometrial polarity [21]. In contrast to IFNT being the pregnancy recognition signal in ruminants, pig conceptus IFNs are not known to have antiluteolytic effects that alter length of interestrus intervals or concentrations of progesterone in plasma [21, 22], but they do stimulate PGE_2 secretion [61].

Interactions of estrogen and IFNs regulate cell-type specific expression of multiple genes in the endometrium and highlight the complex interplay between endometrium and conceptus for pregnancy recognition and implantation (fig. 4, adapted from [79, 166]). Table 2 summarizes gene expression in pig uteri in response to intramuscular injections of estrogen and/or intra-uterine injections of pig conceptus secretory proteins containing IFNG and IFND [64, 78, 79, 82, 130, 166]. In pigs, implantation is non-invasive and the placenta is epitheliochorial. Several genes induced in LE by estrogen include *SPP1, FGF7, aldo-keto reducing family 1 member B1 (AKR1B1), cluster of differentiation 24 (CD24), neuromedin beta (NMB), signal transducer* and *activator of transcription 1 (STAT1)* and *IFN regulatory factor 2 (IRF2)*. In pigs, IRF2, a potent inhibitor of transcription of ISGs, is induced in uterine LE by estrogen. These genes likely have roles in establishment of pregnancy that include release of histotroph from uterine

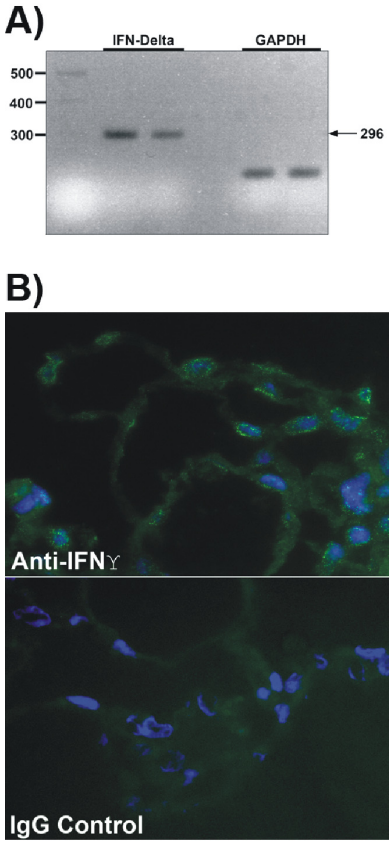

Figure 3. Interferon delta (*IFND*) and interferon gamma (IFNG) are synthesized by pig conceptuses. A) RT-PCR analysis of *IFND* mRNA in total RNA preparation from two Day 14 pig conceptuses. B) *In situ* hybridization analysis of IFNG protein in cryosections of trophectoderm from a Day 13 pig conceptus. Width of each field is 540 μm.

epithelia into the uterine lumen and effects on conceptus trophectoderm to stimulate cell proliferation, attachment and development [64, 78, 79, 82, 166]. In addition, IFND and IFNG may affect blastocyst attachment to LE by inducing labilization and remodeling of uterine epithelia to affect polarity and stimulate production of PGE_2 [21, 22, 61].

In pigs, as in sheep, expression of IRF2 by uterine LE/sGE restricts expression of most ISGs to endometrial stroma and GE. Classical ISGs increased by IFNs in pig uterine stromal cells, GE and/or endothelium

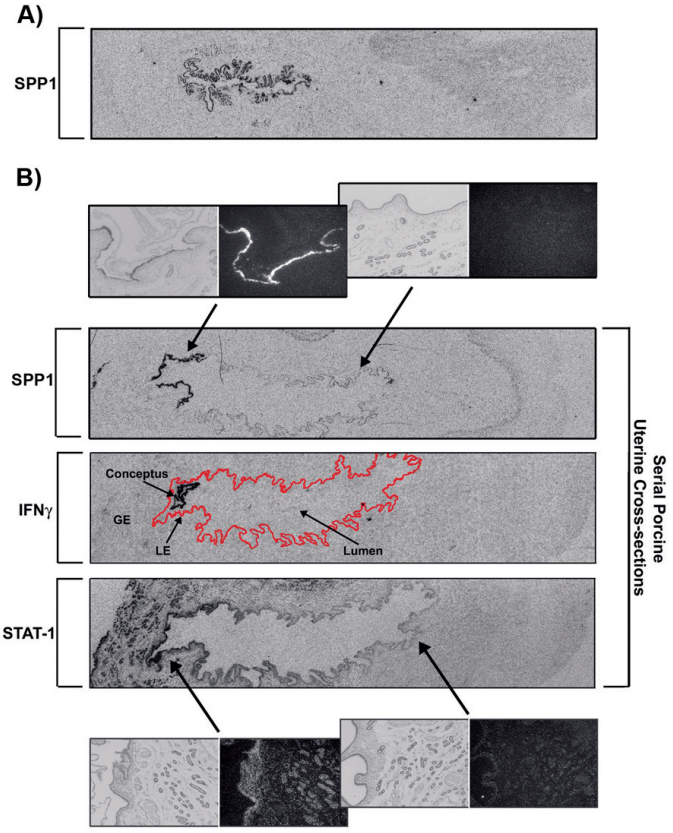

Figure 4. Conceptus estrogens (E_2) induce SPP1 in endometrial luminal epithelium (LE), and conceptus interferons delta and/or gamma induce STAT1 in endometrial stroma and glandular epithelium (GE) during the peri-implantation period of pregnancy in pigs. A) *In situ* hybridization analysis of *SPP1* mRNA in an autoradiographic image (Biomax-MR; Kodak) of an entire cross-section of the uterine wall from a Day 15 cyclic pig treated with E_2 revealed uniform *SPP1* mRNA within the entire LE of Day 15 cyclic pigs. B) Autoradiographic images of entire cross-sections of the uterine wall from Day 15 of pregnancy probed with radiolabeled antisense pig *SPP1* cRNA (top panel), *IFNG* cRNA (middle panel) and *STAT1* cRNA (bottom panel). The LE of the *IFNG* probed tissue is outlined in red for histological reference. Corresponding brightfield and darkfield images from the same sectioned uteri probed with *SPP1* and *STAT1* cRNAs are also shown. Endometrial SPP1 and STAT1 increase in close proximity to paracrine release of E_2, as well as IFND and IFNG from implanting pig conceptuses. Width of each field of autoradiograph images is 20 mm. Width of each field of brightfield and darkfield images is 940 μm.

Table 2. Cell-specific expression of uterine genes in response to conceptus estrogen or IFND and IFNG in pigs [7, 78, 82, 129, 130, 177].

		LE	GE	SC	End
SPP1	E_2	(+)			
	IFN				
FGF7	E_2	(+)			
	IFN				
IRF2	E_2	(+)			
	IFN				
AKR1B1	E_2	(+)			
	IFN				
CD24	E_2	(+)			
	IFN				
NMB	E_2	(+)			
	IFN				
STAT1	E_2	(+)			
	IFN		(+)	(+)	
STAT2	E_2				
	IFN		(+)	(+)	
IRF1	E_2				
	IFN		(+)	(+)	
MX1	E_2				
	IFN		(+)	(+)	
SLA	E_2				
	IFN		(+)	(+)	(+)
B2M	E_2				
	IFN		(+)	(+)	(+)

LE: luminal epithelium; GE: glandular epithelium; SC: stroma; End: endothelium

include STAT1, STAT2, IRF1, MX1, swine leukocyte antigens (SLA) 1-3 and 6-8, and beta 2 microglobulin (B2M; [64, 78-80]). The pregnancy-specific roles of these uterine ISGs remain conjectural, but could: 1) affect decidual/stromal remodeling to protect the fetal semi-allograft from

immune rejection; 2) limit conceptus invasion into the endometrium; and/or 3) stimulate development of uterine vasculature. Because IFNG can initiate endometrial vascular development [7, 177], it is hypothesized that conceptus-derived IFNG in pigs facilitates vascular changes for hematotrophic support of developing conceptuses.

Secretion of both IFND and IFNG is unique to pig conceptuses, but little is known about their interactions. Although type I IFND and type II IFNG each induce expression of largely non-overlapping sets of genes, they may also induce synergistic interactions leading to mutual reinforcement of physiological responses [98]. This synergy has been demonstrated for cooperative induction and maintenance of expression of ISGs such as STAT1 for reinforcement of effects of distinct cell-surface ligands while maintaining their individual specificities for inducing ISGs [34, 122, 174]. Although IFNG may enhance uterine receptivity to implantation in pigs, highly localized and abundant expression of IFNG, TNFA, IL1B and IL1R in the endometrium is associated with arrested conceptus development between Days 15 and 23 of pregnancy [165].

The roles of prostaglandins in the pig uterus during pregnancy remain to be clarified. However, there is evidence that inhibitors of prostaglandin synthesis inhibit establishment and maintenance of pregnancy in pigs [90]. There is also evidence that amounts of PGF and PGE_2 in the uterine lumen are greater in pregnant than cyclic gilts [see 10] and that PGF from the uterus is taken up by the mesometrium and transferred to the uterus in arterial blood by a countercurrent system that exists in the broad ligament of the uterus [92] to be converted to an inactive metabolite [see 45]. There is evidence that PGE_2 synthase, PGF synthase, carbonyl reductase/prostaglandin 9-ketoreductase genes and PGE_2 synthase:PGF synthase ratios are higher in CL of pregnant than cyclic gilts, but not between CL on ovaries ipsilateral and contralateral to the pregnant versus nonpregnant uterine horns [161]. Therefore, it was suggested that compounds from the conceptus are transported within the mesometrium to both ovaries to enhance CL maintenance and function.

It has also been proposed that an integral part of the maternal recognition of pregnancy signaling events are linked to the lipid signaling

system consisting of $PGF_{2\alpha}$, PGE_2 and lysophosphatic acid (LPA) with high expression of PGE_2 synthase in trophoblast and endometrium being responsible for down-regulation of PGF synthase and carbonyl reductase/ prostaglandin 9-ketoreductase in conceptuses in favor of PGE_2 in support of uterine functions and CL maintenance for establishment and maintenance of pregnancy [179]. Expression of LPA3 is also higher during pregnancy and may be another key to establishment and maintenance of pregnancy in the pig. For example, LPA3 is known to be critical for embryo migration and spacing in mice [176] and this is very important for implantation and placentation in pigs.

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