Minireview

Progesterone and Placental Hormone Actions on the Uterus: Insights from Domestic Animals

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ABSTRACT

Progesterone is unequivocally required for maternal support of conceptus (embryo/fetus and associated extraembryonic membranes) survival and development. In cyclic sheep, progesterone is paradoxically involved in suppressing and then initiating development of the endometrial luteolytic mechanism. In cyclic and pregnant sheep, progesterone negatively autoregulates progesterone receptor (PR) gene expression in the endometrial luminal (LE) and superficial glandular epithelium (GE). In cyclic sheep, PR loss is closely followed by increases in epithelial estrogen receptor (ERα) and then oxytocin receptor (OTR) expression, allowing oxytocin to induce uterine release of luteolytic prostaglandin F2α (PGF2α) pulses. In pregnant sheep, the conceptus produces interferon τ (IFNτ) that acts on the endometrium to inhibit transcription of the ERα gene and thus development of the endometrial luteolytic mechanism. After Day 13 of pregnancy, the endometrial epithelia do not express the PR, whereas the stroma and myometrium remain PR positive. The absence of PR in the endometrial GE is required for onset of differentiated function of the glands during pregnancy. The sequential, overlapping actions of progesterone, IFNτ, placental lactogen (PL), and growth hormone (GH) comprise a hormonal servomechanism that regulates endometrial gland morphogenesis and terminal differentiated function during gestation. In pigs, estrogen, the pregnancy-recognition signal, increases fibroblast growth factor 7 (FGF-7) expression in the endometrial LE that, in turn, stimulates proliferation and differentiated functions of the trophectoderm, which expresses the receptor for FGF-7. Strategic manipulation of these physiological mechanisms may offer therapeutic schemes to improve uterine capacity, conceptus survival, and reproductive health of domestic animals and humans.

INTRODUCTION

Conceptus (embryo/fetus and associated extraembryonic membranes) growth and development in mammals unequivocally requires progesterone and placental hormone actions on the uterus that regulate endometrial differentiation and function, pregnancy recognition signaling, uterine receptivity for blastocyst implantation, and conceptus-uterine interactions (for review, see [1–5]). This review summarizes current information on the biology of progesterone and placental hormone actions on the uterus, with particular emphasis on domestic animals (sheep and pig).

PROGESTERONE ACTIONS ON THE UTERUS

Regulation of the Endometrial Luteolytic Mechanism

Domestic animals are spontaneous ovulators that undergo uterine-dependent estrous cycles until establishment of pregnancy (for reviews, see [4, 6–9]). The estrous cycle is dependent on the uterus, because it is the source of the luteolysin, prostaglandin F2 alpha (PGF2α). During the estrous cycle, the endometrium releases oxytocin-induced luteolytic pulses of PGF that result in functional and structural regression of the ovarian corpus luteum (CL), termed luteolysis. In sheep, the source of luteolytic PGF2α pulses is the endometrial luminal epithelium (LE) and superficial ductal glandular epithelium (sGE) [10] because they express the oxytocin receptors (OTR) [6] and are the only uterine cell types that express cyclooxygenase 2 (COX-2), a rate-limiting enzyme in the synthesis of prostaglandins [11, 12]. As illustrated in Figure 1, the luteolytic mechanism that develops in the endometrial LE and sGE requires sequential effects of progesterone, estrogen, and oxytocin, acting through their respective receptors [4, 7–9]. At estrus (Day 0), estrogen levels peak from an ovulatory Graafian follicle and stimulate increased uterine estrogen receptor alpha (ERα), progesterone receptor (PR), and OTR expression [13, 14]. During early diestrus, progesterone from the newly formed CL stimulates accumulation of phospholipids in LE and sGE that can liberate arachidonic acid for synthesis and secretion of PGF2α. During diestrus, progesterone levels increase and act via PR to block expression of ERα and OTR in the endometrial LE and sGE [15]. Therefore, ERα and OTR expression is not detected between Days 5 and 11 of the cycle, i.e., during most of diestrus. The precise molecular mechanism whereby progesterone suppresses ERα gene transcription is unknown. However, the effects
of progesterone on OTR gene expression may be indirect through suppression of ERα. The rat OTR gene contains palindromic ER response elements (EREs) that mediate estrogen effects [16], whereas the ovine OTR promoter DNA contains several Sp1 elements that also mediate responsiveness to liganded EREs [17]. Continuous exposure of the uterus to progesterone for 8–10 days down-regulates expression of PR in endometrial LE and sGE after Days 11 and 12 [18], allowing for rapid increases in expression of EREs on Day 13 followed by OTR on Day 14 in LE and sGE [19, 20]. Progesterone-negative autoregulation of PR expression may involve PR-mediated decreases in PR gene transcription [21, 22]. Oxytocin, secreted beginning on Day 9 of the estrous cycle and pregnancy from the posterior pituitary and/or CL, then induces release of luteolytic PGF2α, pulses from the endometrial LE and sGE on Days 14–16 [6]. The CL undergoes regression, allowing for the sheep to return to estrus and complete the 17-day estrous cycle.

Thus, progesterone is paradoxically involved first in suppressing and then inducing development of the endometrial luteolytic mechanism during the estrous cycle. The timing of PR down-regulation by progesterone appears to determine when the luteolytic mechanism develops in the endometrium. This hypothesis is strongly supported by the finding that exogenous progesterone administration during metestrus decreased the interestrus interval in sheep and cattle [23, 24]. Further, treatment of cyclic sheep with RU486, a PR antagonist, during the early luteal phase extended the interestrus interval [25]. PR antagonists prevent progesterone-negative autoregulation of PR gene expression, thereby extending the period of PR expression [26].

**Antiluteolytic Effects of Interferon Tau**

Maternal recognition of pregnancy in ruminants (sheep, cattle, goats) requires that the conceptus elongate from a spherical to a tubular and then filamentous form to produce interferon tau (IFNτ), which is the signal that prevents development of the endometrial luteolytic mechanism [4, 7, 8, 27]. This antiluteolytic effect of IFNτ results in the maintenance of functional CL and, hence, secretion of progesterone that is essential to maintain a uterine environment that supports events critical to successful development of the conceptus to term.

During maternal recognition of pregnancy, the monocellular nuclees of the conceptus trophoderm synthesizes and secretes IFNτ between Days 10 and 21–25 with maximal production on Days 14–16 [27, 28]. IFNτ appears to be the sole factor produced by the conceptus that prevents development of the endometrial luteolytic mechanism [28]. IFNτ does not act to stabilize the PR expression in the endometrial epithelium during pregnancy [14, 18]. Rather, IFNτ acts in a paracrine fashion on endometrial LE and sGE to suppress transcription of ERα and OTR genes [29, 30], thereby abrogating development of the endometrial luteolytic mechanism. Indeed, the increases in ERα and OTR gene expression detected in LE and GE on Days 11–17 postestrus in cyclic sheep do not occur in pregnant sheep [14] or in cyclic sheep infused with IFNτ [31]. By inhibiting increases in OTR expression, IFNτ prevents endometrial production of luteolytic pulses of PGF2α. However, IFNτ does not inhibit basal production of PGF2α, which is higher in pregnant than cyclic sheep, and the conceptus and IFNτ do not affect COX-2 expression in the endometrial epithelium of early pregnant sheep [11, 12]. Available evidence strongly supports the idea that antiestrogenic actions of IFNτ prevent increases in epithelial ERα and PR expression by directly inhibiting transcription of the ERα gene and maintaining secretion of progesterone by the CL [30].

IFNτ is a novel member of the Type I IFN family that acts differentially on the endometrial LE, GE, and stroma to regulate expression of a number of IFN-stimulated genes (ISGs) that are hypothesized to play roles in endometrial differentiation and conceptus implantation [4, 32, 33]. The actions of IFNτ to signal pregnancy recognition [34] and induce or increase expression of a number of ISGs, including ISG17 [35] and 2′,5′-oligoadenylate synthetase (OAS) [36], is dependent on the effects of progesterone. The Type I IFN receptor subunits, IFNAR1 and IFNAR2, are expressed in all endometrial cell types, with highest expression in endometrial LE [37]. However, the majority of ISGs are induced or increased in response to the conceptus or

![Diagram of Hormonal Regulation](https://academic.oup.com/biolreprod/article-abstract/71/1/2/2667066)

**FIG. 1.** Schematic illustrating hormonal regulation of the endometrial luteolytic mechanism and antiluteolytic effects of the conceptus on the endometrium in the ovine uterus. During estrus and metestrus, oxytocin receptors are present on the uterine luminal epithelium and superficial ductal glandular epithelium because estrogen levels are high and increase expression of estrogen receptor alpha and OTR. The progesterone receptor is present, but low systemic levels of progesterone result in insufficient numbers of activated PR to suppress ERα and OTR synthesis. During early diestrus, endometrial ERα and estrogen are low, but progesterone levels begin to increase with formation of the CL. Progesterone acts through the PR to suppress ERα and OTR synthesis for 8–10 days. Continuous exposure of the endometrium to progesterone eventually down-regulates PR gene expression in the endometrial luminal epithelium by Days 11 to 12 of the estrous cycle. The loss of PR terminates the progesterone block to ERα and OTR formation. Thus, ERα appears on Days 11 and 12 postestrus, which is closely followed by OTR on Days 13 and 14. The increase in OTR expression is facilitated by increasing secretion of estrogen by ovarian follicles. In both cyclic and pregnant sheep, oxytocin is released from the posterior pituitary and corpus luteum beginning on Day 9. In cyclic sheep, OT binds to OTR on the endometrial epithelium and increases release of luteolytic pulses of prostaglandin F2α to regress the CL through a COX-2 pathway. In pregnant sheep, interferon tau is synthesized and secreted by the elongating conceptus beginning on Day 10 of pregnancy. IFNτ binds to Type I IFN receptors on the endometrial LE and inhibits transcription of the ERα gene through a signaling pathway involving IFN regulatory factor 2. These actions of IFNτ on the ERα gene prevent OTR formation, thereby maintaining the CL and progesterone production. E, Estrogen; ERα, estrogen receptor alpha; IFNτ, interferon τ; IRF-2, interferon regulatory factor two; OT, oxytocin; OTR, oxytocin receptor; P, progesterone; PGF2α, prostaglandin F2α; PR, progesterone receptor.
Progesterone-Regulated Genes in the Uterus

Progesterone, the hormone of pregnancy, plays a pivotal and indisputable role in the establishment and maintenance of pregnancy in mammals. In all mammalian uteri, PR are expressed in the endometrial epithelium and stroma during the early luteal phase, allowing direct regulation of a number of genes by progesterone via activation of the PR. However, continuous exposure of the endometrium to progesterone negatively autoregulates PR expression in the endometrial epithelium. Indeed, expression of PR protein is not detectable in endometrial LE and GE in sheep after Days 11 and 13 of pregnancy, respectively [14]. Further, PR expression is only detected in stroma and myometrium throughout most of gestation in the ovine uterus (Fig. 2). The paradigm of loss of PR in uterine epithelia immediately before implantation is common to sheep [14], cattle [42], pigs [43], western spotted skunks [44], baboons [45], rhesus monkeys [46], humans [47], and mice [48]. Thus, regulation of endometrial epithelial function during the peri-implantation period must be directed by specific factors produced by PR-positive stromal cells in response to progesterone [49]. In sheep, endometrial stromal cells express both fibroblast growth factor 10 (FGF-10) and hepatocyte growth factor (HGF) while endometrial epithelium and trophoderm express their respective receptors, FGF receptor 2 (FGFR2) and c-met (FGFR2) [50, 51]. The tunica intima of uterine blood vessels in sheep also expresses FGF-7, which acts via FGFR2 [52]. Mechanisms regulating these stromal-derived growth factors are not known.

A number of genes in the rodent, human, and primate uterus are directly regulated by progesterone, including transcription factors (osteoblast-specific factor 2), growth factors (epidermal growth factor), binding proteins (insulin-like growth factor one binding protein), homeobox genes (Hoxa-10 and Hoxa-11), morphogens (Indian hedgehog), enzymes (leukocyte- and epidermal-12/15 lipoxygenases and histidine decarboxylase), protease inhibitors (p12 serine protease inhibitor and cytotoxic lymphocyte activator 2β), peptide hormones (proenkephalin and calcitonin), biogenic amines (histamine), and adhesion proteins (immune responsive gene 1 or Irgl1) [reviewed in [1, 3, 5]]. The presence and function of these progesterone-regulated genes in the uterus of domestic animals should be investigated.

Endogenous Jaagsiekte sheep endogenous retroviruses (enJSRVs). The ovine genome contains 15–20 copies of endogenous betaretroviruses that are highly related to two oncogenic exogenous betaretroviruses, JSRV and enzootic nasal tumor virus (ENTV) [52]. Expression of endogenous JSRVs (enJSRVs) in sheep is limited to epithelia of the oviduct, uterus, cervix, and vagina [53, 54]. The enJSRV RNAs are among the most abundant RNAs in the endometrium, and their expression increased by 15-fold between Days 1 and 13 of the estrous cycle or early pregnancy [54]. Uterine expression of enJSRV RNAs is restricted to the endometrial LE and GE, which suggests physiological roles in regulating conceptus-endometrial interactions, production of IFNγ, and placental differentiation and development [52].

The enJSRVs are the only known genes in the endometrium of the ovine uterus directly increased by progesterone via the PR. Progesterone, acting via PR, increases transcription of enJSRV genes in vivo and transcriptional activity of several enJSRV long terminal repeats (LTRs) in vitro [54]. Further, JSRV capsid and envelope proteins are expressed by endometrial LE and GE and detected in binucleate cells of conceptus trophoderm that forms syncyta with endometrial LE. Indeed, steady-state levels of enJSRV RNAs in LE and GE increase rapidly between Days 1 and 13 in cyclic and pregnant sheep and then decrease to low levels by Day 15 in cyclic sheep and by Day

![Image](https://academic.oup.com/biolreprod/article-abstract/71/1/2/2667066/1670066)
Mucin glycoproteins. In both humans and rodents, the expression pattern of the mucin glycoproteins (MUC) MUC1 and MUC4 on uterine LE may control accessibility of trophodectoderm integrin receptors to their ligands by sterically blocking cell-cell and cell-extracellular matrix (ECM) adhesion and access of conceptus trophodectoderm to uterine LE [1, 55, 57]. The implantation adhesion cascade in rodents and sheep is initiated following down-regulation of MUC1, which is coincidental with loss of PR from uterine epithelium [56, 57]. This pattern of MUC1 expression contrasts with that in rabbits and humans, in which there is an overall increase in MUC1 expression during the receptive phase under the influence of progesterone; however, MUC1 is locally reduced at implantation sites, perhaps due to paracrine signals from blastocysts [1].

Extracellular matrix and cell adhesion molecules. Integrins play a dominant role in interactions with ECM to transduce cellular signals in uterine epithelial cells and conceptus trophodectoderm [55]. The endometrium exhibits both constitutive and cycle-dependent expression of integrins and appears to be the only tissue known to exhibit hormone-dependent integrin expression. Three integrins are considered markers of uterine receptivity for implantation in humans, which occurs when the uterus is under the influence of progesterone. The timing of αvβ3 expression correlates with embryo attachment and disappearance of the α4 integrin subunit [58]. The presence of both αβ3 and αβ1 on the apical surface of uterine LE suggests a role for these integrins in trophodectoderm-LE interactions during implantation [58]. In sheep, αv(4,5) and βv(3,5) integrin subunit expression occurs in endometrium of both cyclic and pregnant sheep and conceptus trophodectoderm [59]. These integrin subunits are detected at the apical surfaces of the LE and GE and on conceptus trophodectoderm; expression of these integrins is constitutive and not influenced by pregnancy or presence of the conceptus. In the sheep, receptivity to implantation does not appear to involve changes in temporal or spatial patterns of integrin expression but rather may depend on expression of ECM proteins, such as osteopontin (OPN), which are ligands for heterodimers of these integrins [59]. In species such as pig, mouse, and humans, interactions between specific integrins and ECM proteins frame the putative window of implantation [1, 55, 60]. In pigs, progesterone increases expression of αβ1 and αβ1 during the peri-implantation period, which may in part define the implantation window in that species [55, 61].

Uterine Gland Secretions

In the sheep, continuous exposure of the uterus to progesterone induces expression of proteins in the endometrial glandular epithelium (GE) that are secreted into the uterine lumen. The two best characterized GE secretory products are the ovine uterine milk proteins (UTMP), also termed ovine uterine serpins, and OPN. UTMPs are members of the serpin family of serine protease inhibitors [62] and serve as excellent markers for endometrial secretory capacity during pregnancy in sheep [63–65]. In pregnant sheep, UTMP mRNA expression is restricted to GE and not LE or sGE. UTMP mRNA expression is tightly regulated, appearing in GE between Days 15 and 17, and then increasing in abundance during gestation in a manner that parallels fetal growth and development [63, 65].

OPN is an acidic phosphorylated glycoprotein component of the ECM detected in epithelia and in secretions of many tissues, including the uterus [59]. OPN binds to integrin heterodimers (αvβ1, αvβ3, αvβ5, αvβ6, αvβ8, α4β1, α5β1, and α8β1) via its Arg-Gly-Asp sequence and to α4β1 and α9β1 by other sequences to promote cell adhesion, spreading, and migration [59, 66]. OPN increases in uterine flushings from pregnant sheep during the peri-implantation period (Days 11–17) when adherence and attachment of conceptuses to uterine LE occurs [67, 68]. Secreted OPN then binds integrin heterodimers expressed by trophodectoderm and uterus to 1) stimulate changes in morphology of conceptus extraembryonic placental membranes and 2) induce adhesion between LE and trophodectoderm essential for implantation and placentaion [59]. Although OPN mRNA increases only in GE of pregnant sheep, OPN protein is localized on the apical aspect of the endometrial LE, GE, and conceptus trophodectoderm and continues to be present at the uterine-placental interface. The OPN gene is expressed in GE throughout gestation and OPN abundance parallels fetal growth and development [69].

Continuous administration of progesterone to sheep induces UTMP and OPN expression by ovine endometrium [26, 64, 70]. As revealed by Ingr and coworkers [71], treatment of ovariectomized sheep with progesterone for 6 days induced very little UTMP mRNA and protein in the endometrium, whereas treatment with progesterone for 14 or 30 days greatly enhanced UTMP expression. The protracted nature of this progesterone effect is not typical of genes regulated by progesterone through PR in a classic transcriptional manner involving receptor interaction with ligand, homodimerization, and DNA binding and transactivation. Recent studies strongly support the hypothesis that the loss of PR gene expression in GE is required for progesterone induction of UTMP and OPN gene expression [26, 64]. Spencer and colleagues [64] found that administration of estrogen with progesterone induced PR expression in endometrial GE and concomitantly ablated effects of progesterone alone to induce UTMP and OPN mRNA expression in GE. Similarly, administration of the PR antagonist ZK136,317 along with progesterone ablated effects of progesterone alone to induce OPN mRNA expression in GE [26]. In that study, the ZK antiprogestin prevented progesterone from down-regulating PR expression. The contention that loss of epithelial PR is required for endometrial GE function during pregnancy is also supported by studies of PR gene expression in endometrium from cyclic and pregnant sheep [13, 14]. During early pregnancy, PR expression is detectable in LE and GE on Day 11, but PR are undetectable in LE and sGE from Days 13 to 19 and are present only in stromal cells and myometrium after Day 25 of gestation in sheep (Fig. 2).

Why does progesterone negatively autoregulate expression of the PR gene? Loss of PR by GE appears to be required for GE morphogenesis and differentiated function as well as to prevent inhibition of these events by progesterone [72, 73]. In uterine LE of mice, progesterone inhibits estrogen-induced cyclin D1 and cyclin-dependent kinase 4 (cdk4) nuclear translocation, cyclin E- and cyclin A-cdk2 kinase activation, and cell proliferation [73]. Therefore, ligation of PR likely inhibits epithelial morphogenesis due to negative effects on progression through the cell cycle. It
follows that the absence of the PR after Day 15 in GE of sheep uteri is essential for the endometrial glands to undergo a pregnancy-dependent program of hyperplasia from Days 16 to 50 followed by hypertrophy from Days 50 to term [65, 74]. Interestingly, the PR gene is also not expressed in the lobuloalveolar epithelium of the mammary gland during lactation [75]. It is tempting to speculate that the absence of PR is required for secretory epithelia to initiate and maintain expression of genes encoding secretory proteins. Available evidence suggests that disruption of epithelial morphogenesis that involves dysfunction of PR gene expression in the endometrial glands could compromise blastocyst survival and growth during early pregnancy [2, 76].

PLACENTAL HORMONE ACTIONS ON THE UTERUS

In domestic animals, the placenta produces a variety of steroid and protein hormones that act in a paracrine manner on the endometrium to elicit changes in gene expression that support conceptus growth and development. This section of the review describes effects of placental lactogens (PL) and growth hormone (GH) in sheep and placental estrogens in pigs on endometrial support of conceptus growth.

Uterine Gland Morphogenesis in the Ovine Uterus During Pregnancy

In sheep, establishment and maintenance of pregnancy requires integration of endocrine and paracrine signals from the ovary, conceptus, and uterus [4]. Maintenance of pregnancy requires reciprocal communication between the conceptus and endometrium during implantation and syncytiotrophoblastic placentation. In sheep, superficial implantation and placentation begins on Days 15 and 16, but is not completed until Days 50–60 of pregnancy [74, 77]. During this period, the uterus grows and remodels substantially to accommodate rapid conceptus development and growth in the latter two thirds of pregnancy. In addition to placentomal development in the caruncular areas of the endometrium and changes in uterine vascularity, the intercaruncular endometrial glands grow substantially in length (4-fold) and width (10-fold) and establish additional side branchings during pregnancy [74]. During gestation, endometrial gland hyperplasia occurs between Days 15 and 50 followed by hypertrophy to increase surface area that allows for maximal production of histotroph after Day 60 [65]. These uterine glands synthesize, secrete, or transport a variety of enzymes, growth factors, cytokines, lymphokines, hormones, transport proteins, and other substances, collectively termed histotroph [1, 2, 78]. Secretions from the endometrial epithelium influence conceptus survival, growth, and development in all mammals [2, 5, 76]. During pregnancy in other mammals (cow, goat, pig, horse, primates), the uterine glands undergo a similar morphogenetic pattern of development [2].

Hormonal Servomechanism Regulating Uterine Gland Morphogenesis and Differentiated Function in the Ovine Uterus

In the rabbit and pig, interactions between lactogenic hormones and ovarian steroids have been proposed to constitute a servomechanism that regulates endometrial function [79, 80]. Interactions between prolactin (PRL) and progesterone increase endometrial proliferation and uteroglobin secretion in long-term ovariectomized rabbits by increasing the concentration of endometrial PR and uterine responsiveness to progesterone [81, 82]. This mechanism does not appear to be present in the ovine uterus because neither PL nor GH affected endometrial PR or ERα gene expression [64].

The servomechanism proposed to regulate endometrial gland proliferation and function during pregnancy in sheep is illustrated in Figure 3. The pregnant ovine uterus is exposed sequentially to estrogen, progesterone, IFNγ, PL, and placental GH. These hormones appear to regulate endometrial gland morphogenesis and differentiated secretory function in the ovine uterus [64, 83]. The placentas of a number of species, including rodents, humans, nonhuman primates, and sheep, secrete hormones structurally related to pituitary GH and PRL that are termed PLs [84, 85]. Ovine PL is produced by binucleate cells of the conceptus trophectoderm beginning on Day 16 of pregnancy, which is concomitant with the initiation of expression of UTMP and increases in OPN by GE [65, 67, 68]. In maternal serum, PL can be detected as early as Day 50 and peaks between Days 120 to 130 of gestation [84]. A homodimer of the PRL receptor (PRLR) as well as a heterodimer of PRLR and GH receptor (GHR) transduces signals by ovine PL [85]. In the ovine uterus, PL binding sites are specific to GE expressing PRLR [65, 83]. Temporal changes in conceptus production of PL are correlated with endometrial gland morphogenesis and increased production of UTMP and OPN by the GE during pregnancy [65, 67–69]. The ovine placenta also expresses GH between Days 35 and 70 of gestation [86], which is correlated with onset of GE hypertrophy and maximal increases in UTMP and OPN gene expression by GE. These results suggest that members of the lactogenic and somatogenic hormone family play key roles in stimulating endometrial gland morphogenesis and differentiated function during pregnancy to facilitate conceptus growth and development.

Sequential exposure of the pregnant ovine endometrium to estrogen, progesterone, IFNγ, PL, and placental GH constitutes a servomechanism that activates and maintains endometrial remodeling, secretory function, and uterine growth during gestation [64, 83]. Intrauterine infusions of recombinant ovine PL or GH increased UTMP and OPN expression by uterine GE of progesterone-treated sheep, but only when the sheep were infused sequentially with IFNγ between Days 11 and 21, and then either PL or GH from Days 16 to 29 after onset of estrus [64]. The mechanism whereby effects of IFNγ permit GE to become responsive to PL and GH is not known. IFNγ may induce or up-regulate genes involved in signal transduction, including signal transducers and activators of transcription one (STAT1), STAT2, IRF-1, IRF-9, and 40/42-kDa 2′,5′-OAS [36, 38]. The increase in UTMP expression by endometrial GE was partly attributed to effects of PL and GH to increase the number of endometrial glands because intrauterine infusion of PL and GH into sheep, treated with progesterone and IFNγ, was found to increase endometrial gland hypertrophy, an effect not observed in sheep infused with either PL or GH alone [83]. The ability of PL and GH to elicit similar effects on endometrial glands is not surprising because they are members of a unique hormone family based on genetic, structural, binding, receptor signal transduction, and function studies [85]. In total, these studies suggest that a developmentally programmed sequence of events, mediated by specific paracrine-acting factors at the conceptus-endometrial interface, stimulates both intercaruncular endometrial remodeling and differentiated function to increase pro-
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FIG. 3. Schematic illustrating the current working hypothesis on the hormonal servomechanism regulating uterine gland morphogenesis and function in the ovine endometrium during pregnancy. Interferon tau is produced by the conceptus between Days 11 and 21–25 of pregnancy with maximal production on Days 15 and 16. High levels of endogenous Jaagsiekte sheep retroviruses (enJSRVs) are expressed in the PR-positive endometrial LE and GE in response to increasing progesterone to stimulate trophoblast proliferation and production of IFNt. Continuous exposure of the endometrium to progesterone for 8–10 days negatively autoregulates PR expression, so that LE and GE are PR-negative by Days 11 and 13, respectively. IFNt activates the JAK-STAT pathway in the endometrial glands, which stimulates formation of STAT1 homodimers (or GAF) as well as the transcription factor IFN stimulated gene factor 3 (heterotrimer of STAT1, STAT2, and IRF-9). STAT1 homodimers or GAF transactivate a GAS element in the IRF-1 gene. IRF-1 then binds to IRF-Es and transactivates the UTMP promoter. ISGF3 transactivates ISREs present in the 2',5' oligoadenylate synthetase gene. The 40/46-kDa form of OAS interacts with the intracellular domain of the prolactin receptor, which mediates the actions of ovine PL. Specifically, OAS prevents PRLR signaling to STAT1 and promotes signaling through STAT5. Ovine PL is produced by the conceptus beginning on Days 16 and 17 of pregnancy, which is concomitant with the formation of binucleate cells in the trophoectoderm. The actions of PL are mediated by PRLR homodimers or perhaps heterodimers of PRLR and growth hormone receptor that stimulate formation of STAT5 homodimers. STAT5 dimers bind and transactivate the GAS element in the UTMP promoter. The induction of UTMP gene expression in the GE by IFNt-stimulated IRF-1 is maintained by the actions of PL through STAT5.

A similar servomechanism appears to be present in the uterus of the nonhuman primate. In primates, chorionic gonadotropin (CG) is the pregnancy-recognition signal produced by the trophoblast that acts as LH superagonist on the CL, thereby rescuing the CL from regression and extending production of progesterone. In addition to a role as a luteotropic agent, CG acts directly on the uterus to facilitate the implantation process [87, 88]. In addition to direct effects on the endometrial LE and stroma, CG induces morphologic changes in the endometrial glands in the functionalis and basalis layers. Expression and production of glycodelin, the major progesterone-regulated secretory protein of the endometrium during the secretory phase and pregnancy, is increased by CG. Similar to ovine uterine studies, glycodelin production is inhibited by PR antagonists in baboons due to reexpression of PR and ERα in the endometrial glands [89].

Placental Estrogens and Endometrial Growth Factors in the Porcine Uterus

The major hormone produced by the placenta of the pig that acts on the endometrium is estrogen. Pig conceptuses secrete estrogens between Days 10 and 15 of pregnancy, which are essential for establishment of pregnancy [90]. Estrogens, directly or indirectly, alter secretion of PGF2α from the endometrium and thus uterine vasculature to an exocrine direction (toward the uterine lumen). The PGF2α, sequestered in the uterine lumen, is then unavailable to exert a luteolytic effect on the CL. Additionally, an increase in selected histotroph components occurs in the uterine lumen immediately following the release of estrogens from the conceptus on Day 11 of pregnancy [90, 91]. Placental estrogens also act on the endometrial epithelia in a paracrine manner to increase expression of specific growth factors, including insulin-like growth factor one (IGF-I) and fibroblast growth factor seven (FGF-7; also termed keratinocyte growth factor or KGF) that, in turn, act on the trophoectoderm to stimulate cell proliferation and development. IGF-I is a pleiotropic growth factor required for postnatal uterine growth and conceptus growth and development in the mouse (see [92] for review). In the porcine uterus, IGF-I is primarily expressed in the endometrial glands of both cyclic and pregnant pigs [93]. Endometrial IGF-I gene expression increases during early pregnancy and peaks on Days 12 and 13, which is coincidental with production of estrogens by the elongating conceptus [94, 95]. Treatment of either ovariectomized or cyclic gilts with estrogen increases IGF-I expression in the uterus [94]. Type I IGF receptors were detected in the endometrium as well.
as in the embryo, suggesting paracrine and autocrine modes of action of IGF-I in the uterine microenvironment [92].

FGF-7 is an established paracrine mediator of hormone-regulated epithelial growth and differentiation [96]. In all organs studied, FGF-7 was uniquely expressed in cells of mesenchymal origin. Intriguingly, expression of FGF-7 in the porcine uterus is exclusively in LE and particularly abundant between Days 12 and 15 of the estrous cycle and pregnancy [97]. Endometrial FGF-7 mRNA levels were highest on Day 12 in pregnant gilts and Day 15 in cyclic gilts and greater on Day 12 of pregnancy than on Day 12 of the estrous cycle. FGF-7 protein was detected in the uterine flushes of both Day 12 cyclic and pregnant gilts. FGFR2β, the receptor for FGF-7, is expressed in both endometrial epithelia and conceptus trophoderm. Treatment of endometrial explants from Day 9 cyclic gilts with estradiol-17β increased FGF-7 expression [97]. Further, treatment of porcine trophoderm cells with recombinant rat FGF-7 increased their proliferation, phosphorylated FGFR2 IIIb, activated the mitogen-activated protein kinase (MAPK or ERK1/2) cascade, and increased expression of urokinase-type plasminogen activator, a marker for trophoderm cell differentiation [98]. Collectively, these results indicate that estrogen, the pregnancy-recognition signal from the pig conceptus, increases uterine epithelial FGF-7 expression, and in turn, FGF-7 stimulates the proliferation and differentiation of conceptus trophoderm in pigs, which possesses a true epitheliocorial placenta [4, 98, 99].

CONCLUSIONS AND PERSPECTIVE

Progesterone and PR are critical components of uterine physiology and the biology of the estrous cycle and pregnancy in all mammals. In the sexually mature female, progesterone and PR effects during both the estrous cycle and pregnancy must be understood in the context of the temporal and spatial pattern of PR expression. It seems clear that uterine stromal and myometrial cells are always PR positive and may respond to progesterone by producing paracrine factors that regulate proliferation and/or differentiated functions of GE and, to some extent, LE during pregnancy. This poses a number of interesting questions. Why are PR negatively autoregulated in the endometrial epithelium but not stromal and myometrial cells? What is the molecular mechanism by which progesterone down-regulates expression of the PR gene in epithelium but not stroma of the endometrium? What are the mechanisms by which stromal cells regulate epithelial cell functions in reproductive tissues? How do cell signaling pathways activated by growth factors, IFNs, and somatotrophic hormones converge to establish the servomechanism-associated uterine functions that are critical to maintenance of pregnancy in ruminants? Are there other ERVs, like enJSRV, that are regulated by progesterone and PR in the uterus that affect uterine biology and/or conceptus development? We have learned much about effects of progesterone and expression of PR, but there are many unresolved questions about the extent and magnitude of the effects of this key hormone of the estrous/menstrual cycle and pregnancy and its receptor. There exists a clear need to understand convergence of interactions between cell-signaling events mediated by progesterone acting via PR, prostegamedin growth factors acting via their respective receptors, lactogenic hormones acting via PRL-R and GH-R, and IFNγ acting through the Type I IFN receptor that regulate proliferation and differentiated functions of uterine endometrium throughout gestation. Strategic manipulation of the aforementioned physiological mechanisms may offer therapeutic schemes to improve uterine capacity, conceptus survival, and reproductive health in humans and domestic animals.

REFERENCES


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