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Modulation of uterine function by endocrine and paracrine factors in ruminants

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Abstract

Uterine adenogenesis in the neonate is critical as uterine glands are essential for pregnancy in adult ruminants. The uterus is stimulated by estrogens (E2) and progesterone (P4) that prepare it to respond to biochemical signals from the conceptus (embryo/fetus and placenta). Interferon tau (IFNT) is responsible for pregnancy recognition and modification of uterine gene expression including sensitivity to placental lactogen and placental growth hormone that stimulate development and gene expression by epithelial cells of uterine glands. P4 is permissive for most actions of IFNT. Novel genes are expressed by uterine luminal and superficial glandular epithelia in response to P4 and IFNT as those cells are in direct contact with conceptus trophectoderm. But, uterine glandular epithelium and stromal cells respond to P4 and IFNT by expressing classical interferon stimulated genes. Uterine receptivity to implantation requires loss of expression of receptors for P4 and E2 by uterine epithelia. P4 stimulates P4 receptor-positive stromal cells to express fibroblast growth factor 10 (FGF10) and hepatocyte growth factor (HGF) that act via their respective receptors on uterine epithelia and trophectoderm to regulate cellular functions and gene expression. FGF10 and IFNT are hypothesized to activate complementary cell signaling pathways that modulate expression of genes for implantation, modify phenotype of uterine stromal cells, silence expression of genes for P4 and E2 receptors, 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. Those actions are essential for a successful outcome of pregnancy.

Keywords: conceptus, growth factors, placental hormones, pregnancy, uterus.

Uterine adenogenesis: a post-natal event affecting uterine function in adult females

The uterus supports growth and development of the conceptus (embryo/fetus and extra-embryonic membranes) in all mammals. In particular, uterine glands secrete and transport molecules into the uterine lumen, i.e., histotroph, that include nutrients such as amino acids and glucose, as well as growth factors, cytokines, lymphokines, fatty acids, transport proteins for vitamins and minerals and enzymes essential for survival and development of the conceptus. Results from studies of the ovine uterine gland knockout (UGKO) ewe model demonstrate that functional uterine glands are essential for ewes to experience normal estrous cycles and to support conceptus development beyond the early peri-implantation period of pregnancy (Spencer *et al*., 2004). Uterine glands are also essential for pregnancy in mice (Dunlap *et al*., 2011) and in humans during the first two months of gestation (Burton *et al*., 2007).

Uterine adenogenesis in ewe lambs involves differentiation and development of endometrial glands, development of endometrial folds, organization of intercaruncular endometrial stroma and growth of endometrial caruncular areas and myometrium (Bartol *et al*., 1988; Spencer and Bazer, 2004; Bartol *et al*., 2006). Uterine adenogenesis begins between post-natal days (PND) 0 and 7 and by PND 56 the caruncular and intercaruncular endometrial areas are histoarchitecturally mature. However, maturation of the uterus continues through puberty (Kennedy *et al*., 1974) and successive pregnancies as the uterine glands undergo extensive hyperplasia and hypertrophy to meet demands of the developing fetus for uterine histotroph (Bazer, 1975). The development and functional cycle of uterine glands parallel those of the mammary gland during mammogenesis, lactogenesis and involution. This suggests that the phenotypes of both uterine glands and mammary glands are subject to effects of genetic variation, parity, and epigenetic factors.

Uterine morphogenesis is governed by a variety of hormones and growth factors that effect cellular and molecular events that include interactions between epithelium and stroma for establishment of normal uterine histoarchitecture (Spencer and Bazer, 2004; Bartol *et al*., 2006). In the neonatal ovine uterus, fibroblast growth factor 7 (FGF-7), FGF-10, hepatocyte growth factor (HGF), insulin-like growth factors 1 (IGF1) and (IGF2), and the activin-follistatin system are candidate regulatory molecules for uterine adenogenesis (Spencer and Bazer, 2004). Each of these stromal-derived growth factors has receptors that are expressed by uterine epithelia.

Ovariectomy of ewe lambs at birth does not affect uterine adenogenesis at PND 14 (Bartol *et al*., 1988), but does result in reduced uterine weight after

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PND 28 (Kennedy *et al*., 1974). Ovariectomy of ewe lambs on PND 7 reduces uterine weight by almost 50% and numbers of branched uterine glands as compared to control ewes on PND 56 which indicates effects of ovarian-derived factors on coiling and branching morphogenesis of uterine glands (Carpenter *et al*., 2003). The coordinate activities of the activin-inhibin-follistatin system in the ovary and uterus may be important in ewes with both an intrinsic high ovulation rate and enhanced uterine capacity to maintain large litters.

Treatment of neonatal ewes with an estrogen receptor alpha ESR1 antagonist from birth to PND 56 does not affect weight and length of uterine horns, but significantly reduces ductal gland invaginations and number of endometrial glands, as well as coiling and branching of those uterine glands (Carpenter *et al*., 2003). Prolactin (PRL) and its receptor (PRLR) also have primary roles in ovine uterine adenogenesis as concentrations of PRL in blood are high on PND 1, reach a maximum on PND 14, and then decline to PND 56 (Bazer and Spencer, 2004). Induction of hyperprolactinemia in ewes lambs using recombinant ovine PRL from birth to PND 56 increases the number of uterine glands by over 60% (Carpenter *et al*., 2003). Similarly, in adult ewes, intrauterine administration of placental lactogen (CSH1), a member of the prolactin/growth hormone (GH1) family that activates the PRLR (Gertler and Djiane, 2002) stimulates proliferation of uterine glandular epithelium GE, particularly GE in coiled and branched glands within the stratum spongiosum of the endometrium (Bazer and Spencer, 2004). On the other hand, neonatal ewes treated with bromocryptine, an inhibitor of PRL secretion, from birth to PND 56 had 35% fewer uterine glands. In adult ewes, uterine gland hyperplasia and hypertrophy occur during pregnancy in response to placental GH1 and CSH1 which increases secretion of histotroph that supports growth and development of the conceptus. Thus, PRL and CSH1, acting via PRLR in GE, stimulate uterine development and function in ewes and may be useful hormones to increase uterine capacity in adult ewes.

Knowledge of the basic mechanisms regulating uterine adenogenesis is necessary to develop strategies to increase uterine capacity, litter size and neonatal survival, as well as ameliorate certain types of infertility. Of equal importance is the recognition that one must not expose the neonatal female to anabolic steroids that can disrupt uterine adenogenesis so that the adult female is unable to experience normal estrous cycles or pregnancy.

Hormones of the estrous cycle and pregnancy

Estrous cycle and luteolysis

Ruminant species ovulate spontaneously and have recurring estrous cycles ranging from 17 to 21 days (Bazer *et al*., 2011). Ewes have been studied in greatest detail with respect to endocrine regulation of the estrous cycle and pregnancy; however, the basic mechanisms for luteolysis and maternal recognition of pregnancy are considered to be very similar for ewes, cows and goats.

In ewes, day 0 of the estrous cycle is the day of onset of sexual receptivity for mating. Estrus lasts about 30 h and ovulation occurs about 30 h after onset of estrus in response to an estrogen-induced ovulatory surge of luteinizing hormone (LH). Metestrus, days 1 to 4 of the estrous cycle, is characterized by formation of the corpus luteum under the influence of LH and its secretion of P4. Diestrus, days 4 to 14 of the estrous cycle, is when the corpus luteum (CL) reaches maximum size and secretion of P4. Near the end of diestrus progesterone receptors PGR are down-regulated in uterine lumenal (LE), superficial glandular (sGE) and glandular (GE) epithelia by progesterone (P4) which allows increased expression of ESR1 and oxytocin receptor (OXTR) necessary for oxytocin (OXT)-induced secretion of luteolytic pulses of prostaglandin F2α (PGF) and luteolysis. The onset of proestrus begins when the CL has regressed and the ovarian follicles begin producing significant amounts of E2.

Recurring estrous cycles in ruminants are dependent on uterine LE/sGE for production of luteolytic PGF. During diestrus, P4 increases phospholipid stores, as well as prostaglandin synthase 2 (PTGS2) in uterine epithelia which is necessary for mobilization of arachidonic acid from phospholipids by phospholipase A2. Arachidonic acid is converted by PTGS2 to prostanoids that lead to secretion of luteolytic pulses of PGF. Importantly, exposure of the uterus to P4 for 10 to 12 days down-regulates PGR which, in turn, allows ESR1 and OXTR expression by uterine LE/sGE initially and then GE and stromal cells. Following up-regulation of ESR1 and OXTR in uterine LE/sGE, E2 induces phospholipase A2 to mobilize arachidonic acid for conversion to PGF while pulsatile release of OXT from CL and posterior pituitary act via OXTR in uterine LE/sGE and GE to induce pulsatile release of luteolyic PGF that culminates in regression of CL on day 16.

Pregnancy

The antiluteolytic signal for maternal recognition of pregnancy in ruminants is IFNT (Bazer *et al*., 2009, 2010, 2011, 2012). IFNT, acting via its receptors on uterine LE/sGE, abrogates the uterine luteolytic mechanism for maternal recognition of pregnancy signaling. IFNT is secreted by conceptus trophectoderm as it transitions morphologically from spherical to tubular and filamentous forms during the peri-implantation period.

All Type I IFNs, including IFNT, bind a common receptor composed of two subunits, IFNAR1 and IFNAR2, to induce cell signaling via the classical Janus activated kinases (JAKs) and signal transducer

and activator of transcription (STAT1) pathway. This cell signaling pathway appears to account for actions of IFNT on uterine GE and stromal cells of ewes. However, uterine LE/sGE lack both PGR and STAT1. Therefore, P4-induces and IFNT further stimulates expression of many genes critical to conceptus development due to actions of P4 and IFNT being mediated through combined effects of a progestamedin(s), e.g., FGF10 in sheep, and IFNT acting via a non-classical cell signaling pathway(s) that may involve mitogen activated protein kinase (MAPK) or phosphatidylinositol 3-kinase, to induce gene expression and uterine receptivity to implantation (Plantanias, 2005). Unlike uterine stromal cells and GE, the uterine LE/sGE of sheep expresses interferon regulatory factor 2 (IRF2) in response to IFNT. IRF2 restricts expression of novel non-classical IFNT-stimulated genes in uterine LE/sGE that are in direct contact with conceptus trophectoderm. These novel genes support conceptus growth and development whereas uterine GE and stromal cells, that do not express IRF2, express classical interferon stimulated genes such as interferon stimulated gene 15 (ISG15) and 3', 5' oligoadenylate synthase (OAS).

It is equally important to appreciate that silencing ESR1 expression by IFNT prevents E2 from acting via ESR1 to induce PGR in uterine epithelia. The absence of PGR in uterine epithelia permits expression of a unique set of P4-induced and IFNT-stimulated genes in ovine uterine LE/sGE during pregnancy. Thus, uterine receptivity to implantation is P4-dependent, but it is preceded by loss of expression of PGR and ESR1 by uterine epithelia which allows P4 to act via PGR-positive stromal cells to increase expression of a progestamedin(s), such as FGF10, that exerts paracrine effects on uterine epithelia and conceptus trophectoderm that express FGFR2IIIb.

Progesterone, IFNT and Progestamedins

IFNT exerts multiple effects on the uterus that are required for establishment and maintenance of pregnancy (Bazer *et al*., 2009, 2010, 2011, 2012). P4 is permissive to actions of IFNT and other hormones secreted by the trophectoderm/chorion on uterine epithelia. The paradox is that cessation of expression of PGR and ESR1 by uterine epithelia is a prerequisite for uterine receptivity to implantation, as well as expression of genes by uterine LE/sGE and GE that encode for secretory proteins and membrane transporters of nutrients into the uterine lumen that are required for conceptus development. These genes may be induced by P4 alone, IFNT alone or induced by P4 and further stimulated by IFNT in uterine LE/sGE. Down-regulation of PGR in uterine LE results in loss of MUC1 (mucin 1, cell surface associated) which is a prerequisite for attachment of conceptus trophectoderm to uterine LE for initiation of implantation (Johnson *et al*., 2001; Carson *et al*., 2002). Silencing expression of PGR in uterine epithelia is preceded by P4 actions via PGR-positive uterine stromal cells to induce expression of one or more progestamedins, e.g., FGF7, FGF10 and HGF in the ovine uterus. These growth factors can exert paracrine effects on uterine LE/sGE, GE and conceptus trophectoderm that express FGFR2IIIb and MET; however, FGF10 appears to be the primary progestamedin expressed by uterine stromal cells in ewes (Chen *et al*., 2000a, b; Satterfield *et al*., 2008).

IFNT and P4 stimulate expression of genes during the peri-implantation period of pregnancy in ewes. In uterine LE/sGE, IFNT alone induces WNT7A, while P4 alone induces expression of endogenous Jaagsiekte retrovirus, MET, GLYCAM1, and MUC1, as well as PRLR in GE (see Bazer *et al*., 2009, 2010, 2011, 2012). In addition, P4 and CSH1 induce expression of serine protease inhibitor (SERPIN; also known as uterine milk proteins), stanniocalcins (STC1) and secreted phosphoprotein 1 (SPP1) in uterine GE.

Genes induced by P4 and further stimulated by IFNT in uterine LE/sGE include: 1) morphogens (gastrin releasing peptide, GRP; interferon regulatory factor 6, IRF6); 2) proteases (cathepsin L, CTSL); 3) protease inhibitors (cystatin C, CST3); 4) mediators of cell migration and adhesion (SPP1; galectin 15, LGALS15; periostin, POSTN; insulin-like growth factor binding protein 1, IGFBP1); 5) hypoxia inducible factors (HIF1A and HIF2A) that stimulate angiogenesis and erythropoiesis; 6) hydroxysteroid dehydrogenase 11B (HSD11B1) that mediates corticosterone metabolism and expression of glucocorticoid receptors (GCCR); 7) synthesis of prostaglandins (PTGS2); and 8) IRF2 a potent repressor of transcription (see Bazer *et al*., 2009, 2010, 2011). The uterine LE/sGE in closest proximity to or adhered to conceptus trophectoderm express these unique genes because IFNT induces expression of IRF2 in uterine LE/sGE to silence expression of ESR1, STAT1, STAT2 and IRF9. The uterine LE/sGE likely responds to P4 via a uterine stromal cell-derived progestamedin, particularly FGF10; therefore, effects of IFNT are mediated via a JAK/STAT-independent cell signaling pathway. P4 stimulates expression of both HGF and FGF10 by ovine uterine stromal cells. Recent reviews provide insight into the roles of proteins encoded by genes expressed by ovine uterine LE/sGE that are induced by IFNT, P4 or the combined actions of P4 and IFNT (Bazer *et al*., 2009, 2010, 2011, 2012).

Studies using an ovine model of early administration of exogenous P4 at 36 h after onset of estrus, i.e., about 6 h post-ovulation, revealed that P4-accelerated conceptus development was associated with advanced expression of uterine genes that favored survival, growth and development of the conceptus (Satterfield *et al*., 2006, 2007, 2008; Carter *et al*., 2008). The early increase in circulating concentrations of P4: 1) advanced time of down-regulation of PGR in uterine epithelia and onset of secretion and abundance of IFNT

in uterine flushings; 2) increased abundance of secreted proteins such as LGALS15, CTSL, GRP, STC1/2, and IGFBP1 by uterine LE/sGE; 3) increased expression of FGF10 and MET mRNA that may affect both uterine epithelia and conceptus trophectoderm; 4) decreased tight-junction associated proteins in uterine LE that may facilitate paracellular trafficking and/or transport of stromal and serum-derived molecules (Satterfield *et al*., 2007); 5) increased total recoverable glucose, aspartic acid, asparagine, serine, and alanine, glutamine and beta-alanine, citrulline, arginine, and lysine in the uterine lumen on day 9; 6) increased steady-state levels of SLC2A1 and SLC5A1 mRNAs and proteins in uterine LE/sGE for glucose transport; and 7) increased steady-state levels of SLC7A2 mRNA in uterine LE/sGE for transport of cationic amino acids, particularly arginine (see Satterfield *et al*., 2008, 2010).

Progesterone also affects uterine function, embryonic survival and conceptus development in cattle. A 3-fold increase in circulating concentrations of P4 increased recovery rates of blastocysts and a 2.3-fold increase in blastocyst size on day 13 of pregnancy (Lonergan *et al*., 2007; Carter *et al*., 2008), as well as increasing the frequency of elongated conceptuses on day 16 of pregnancy (Carter *et al*., 2008). These effects of P4 on conceptus development appear to be mediated via the endometrium and are not direct effects on the conceptus (Clemente *et al*., 2009). As for ewes, early P4 treatment advanced down-regulation of PGR (Okuma *et al*., 2010) and increased expression of genes associated with nutrient transport such as SLC5A1 (sodium-dependent glucose transporter), nutrient availability such as DGAT2 (diacylglycerol–o- acetyltransferase for synthesis of triglycerides), MSTN (myostatin or growth/differentiation factor 8) that affects embryonic development and muscle mass, FABP (fatty acid binding protein) and CRYGS (crystalline gamma-s for development of the lens in the eye; Forde *et al*., 2009). Forde *et al*. (2010) also found that high concentrations of P4 in blood are associated with an increase in expression of CTGF (connective tissue growth factor), LPL (lipoprotein lipase), and SLC5A1 mRNAs in cattle. These results indicate that P4 modifies the uterine environment by modifying the composition of histotroph to advance and enhance conceptus development (Ford *et al*., 2011).

Effects of IFNT on uterine glandular epithelium and stromal cells

Classical interferon stimulated genes (ISG) are expressed by maternal immune cells, uterine GE and uterine SC that do not express IRF2. Therefore, those cells respond to IFNT via the classical JAK/STAT cell signaling pathway. Endometrial proteins induced by IFNT, including B2M (β_2-microglobulin) in sheep (Vallet *et al*., 1991) and 12 and 28 kDa ubiquitin-like proteins in cattle (Perry *et al*., 1999), may be important markers of gene expression in response to early activation of transcription factors that bind interferon stimulated response elements (ISRE) on target genes. Detailed studies of genes induced by IFNT include ISG15 (Perry *et al*., 1999), OAS (Short *et al*., 1991) and Mx (mouse myovirus resistance 1; Ott *et al*., 1998) and genes inhibited by IFNT (ESR1 and OXTR) are necessary to elucidate intracellular cell signaling mechanisms responsible for preventing secretion of luteolytic PGF by uterine LE/sGE.

In ewes, classical ISGs (e.g., ISG15, Mx and OAS) are induced by IFNT only in uterine GE, stroma and immune cells that do not express IRF2. Because ovine uterine LE/sGE lack PGR and STAT1, IFNT is unable to affect transcription of classical ISG through the classical JAK-STAT1 cell signaling pathway. However, IFNT may activate gene transcription through alternate cell signaling pathways such as MAPK and PI3K to effect gene expression in uterine LE/sGE (Plantanias, 2005).

Endocrine and paracrine hormones of pregnancy

In sheep, establishment and maintenance of pregnancy requires integration of endocrine and paracrine signals from the ovary, conceptus, and uterus (Spencer and Bazer, 2004). Superficial implantation, placentation and placental growth occur between days 15 and 60 of pregnancy as the uterus grows and remodels to accommodate development and growth of the conceptus in the last trimester of pregnancy. In addition, caruncles and cotyledons develop and interdigitate to form placentomes which increase in vascularity and intercaruncular endometrial glands grow substantially during pregnancy to secrete increasing amounts of histotroph that is transported across the areolae of the chorioallantois and into the fetal-placental circulation. From the fetal-placental circulation, components of histotroph are cleared via the kidney and urachus into the allantoic fluid, a nutrient reservoir, and then reabsorbed into the vasculature of placenta to again enter the fetal circulation.

Extensive endometrial gland hyperplasia and hypertrophy occurs during each pregnancy in ewes (Wimsatt 1950; Stewart *et al*., 2000). In sheep, superficial implantation and placentation begins on days 15-16, but is not completed until days 50-60 of pregnancy (Guillomot, 1995). During this period, the uterus grows and remodels substantially to accommodate rapid growth of the conceptus in the latter one-half to one-third of pregnancy. In addition to development of the placentomes, there is an increase uterine vascularity and the uterine increase in length (4-fold) and width (10-fold) and degree of branching during the last half of pregnancy (Wimsatt, 1950). During gestation, endometrial gland hyperplasia occurs between days 15 and 50 followed by hypertrophy to increase surface area (Stewart *et al*., 2000) that allows

for maximal production of histotroph after day 60, e.g., SERPIN and SPP1 (Spencer and Bazer, 2004). Indeed, the capacity of the endometrial glands to secreted and/or transport components of histotroph is well correlated with fetal growth, indicating the importance of histotrophic nutrition and the role of placental areolae to transport histotroph into the fetal circulation.

During maximal production of histotroph after day 60 by uterine glands, the uterine GE is exposed sequentially to E2, P4, IFNT, CSH1, and placental GH1 that regulate endometrial gland morphogenesis and differentiated functions in the ewe. The binucleate cells of the chorion secrete CSH1 from day 16 of pregnancy which is coordinate with initiation of expression of SERPINS, STC1 and SPP1 that are excellent markers of endometrial GE differentiation and secretory capacity. In maternal serum, CSH1 is detectable by day 50 and peaks between days 120 and 130 of gestation. CSH1 can bind either homodimers of PRLR or heterodimers of PRLR and GHR to transduce cell signaling. In the ovine uterus, PRLR are specifically expressed in GE. Increasing levels of CSH1 are associated with hyperplasia and hypertrophy of uterine GE, as well as their increased production of UTMP, SPP1, STC1 and other components of histotroph that support growth and development of the conceptus (Spencer and Bazer, 2004).

Sequential exposure of the pregnant ovine endometrium to E2, P4, IFNT, CSH1 and GH1 constitutes a "servomechanism" that activates and maintains endometrial remodeling, secretory function and uterine growth during gestation (Spencer and Bazer, 2004). Chronic treatment of ovariectomized ewes with P4 induces expression of SERPINS, STC1 and OPN by GE (Spencer and Bazer, 2004). During early pregnancy, expression of uterine PGR declines to undetectable levels in uterine LE/sGE by day 11 and in GE by days 13 in response to P4 (Spencer and Bazer, 2004). Down-regulation of epithelial PGR is a prerequisite for P4 induction of expression of genes by uterine GE. Treatment with both P4 and E2 increases ESR1 and PGR expression in uterine GE, which markedly inhibits expression of both OPN and SERPIN. These results indicate the requirement for P4 to down-regulate PGR in uterine GE to allow expression of SERPIN and OPN. Intrauterine infusions of recombinant ovine CSH1 or GH1 increased UTMP and OPN expression by uterine GE of P4-treated ewes, but only when the ewes first increased intra-uterine injections of IFNT between days 11 and 21 after onset of estrus and then either CSH1 or GH1 from days 16 to 29 after onset of estrus (Spencer and Bazer, 2004). The increase in UTMP expression by endometrial GE was partly attributed to effects of CSH1 and GH1 to increase branching of the uterine glands. Subsequently, intrauterine infusion of CSH1 and GH1 into ewes treated with P4 and IFNT increased endometrial gland hypertrophy; an effect not observed in ewes infused with either CSH1 or GH1 alone. Thus, a developmentally programmed sequence of events mediated by specific paracrine-acting factors including IFNT, CSH1 and GH1 at the conceptus-endometrial interface stimulates both intercaruncular endometrial remodeling and differentiated function of uterine GE to increase production of histotroph for fetal-placental development and growth during gestation (Spencer and Bazer 2004).

Hormones from the pituitary (PRL), ovary (P4) and placenta (CSH1 and GH1), as well as fetal adrenal (glucocorticoids) and pancreas (insulin) also stimulate mammogenesis, lactogenesis and uterine functions supportive of conceptus development in ruminants (see Guilbault *et al*., 1985; Kann *et al*., 1999).

Summary

This review emphasizes the importance of uterine adenogenesis during the early postnatal period of life of ruminants, as well as the effects of various hormones from the maternal and fetal-placental tissues that affect uterine functions critical to successful establishment and maintenance of pregnancy. The time and cell-specific changes in gene expression in response to P4, IFNT, GH1 and CSH1 are critical to transport and secretion of molecules upon which the conceptus depends for establishment of pregnancy followed by proliferation, differentiation and overall development of fetal and placental tissues during the course of gestation. These results form the basis for developing strategies to increase efficiencies of reproduction by decreasing embryonic/fetal death losses, particularly during the peri-implantation period of pregnancy.

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Conflicts of interest

The authors declare no conflicts of interest.

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