Published in final edited form as:

Adv Anat Embryol Cell Biol. 2015 ; 216: 189–213. doi:10.1007/978-3-319-15856-3_10.

Implantation and Establishment of Pregnancy in Human and Nonhuman Primates

Ren-Wei Su and Asgerally T. Fazleabas

Department of Obstetrics, Gynecology and Reproductive Biology, Michigan State University, Grand Rapids, MI, 49503, USA

Asgerally T. Fazleabas: asgi@hc.msu.edu

Abstract

Implantation and the establishment of pregnancy are critical for the propagation of the species, but yet remain the limiting steps in human and primate reproduction. Successful implantation requires a competent blastocyst and a receptive endometrium during a specific window of time during the menstrual cycle to initiate the bilateral communication required for the establishment of a successful pregnancy. This chapter provides an overview of these processes and discusses the molecular mechanisms associated with implantation of the blastocyst and decidualization of the uterus in primates.

10.1 Introduction

Reproduction is absolutely essential for the propagation of every species from generation to generation. In most mammalian species, a zygote is formed in vivo following fertilization of an egg by a sperm. After the egg is successfully fertilized in the fallopian tube, it travels through the fallopian tube toward the uterus, during which time the fertilized egg divides and develops into a multicellular structure termed a blastocyst. It then adheres itself to the endometrium, which is the initial step in the process of implantation (Wilcox et al. 1999).

Implantation and the establishment of pregnancy are critical for human reproduction. Implantation failure is responsible for significant pregnancy loss in the human (Koot and Macklon 2013; Koot et al. 2012; Norwitz et al. 2001). Understanding the mechanisms associated with the implantation process and other events during early pregnancy will significantly improve the success of assisted reproductive technologies (ART).

10.2 Implantation

In humans, as well as other nonhuman primates, implantation is one of the most interesting biological events and marks the first biological interaction of the blastocyst with the uterus during the establishment of pregnancy. In humans, one in every six couples is subfertile, and 25 % of those are classified as unexplained infertility. ART offers many subfertile couples effective treatment, but implantation failure remains the rate-limiting step: only around 25 %

of transferred blastocysts will successfully implant (Edwards 2006). Both a competent blastocyst and a receptive endometrium are key components required for successful implantation of the blastocyst (Cha et al. 2012).

10.2.1 Window of Implantation

Driven by estrogen and progesterone, the two primary steroid hormones produced by the ovaries, the human endometrium undergoes cyclic changes in morphology and function during the menstrual cycle (Cha et al. 2012). However, during the menstrual cycle, the uterus is only receptive to the blastocyst for implantation for a short window of time. In humans, implantation occurs during the mid-secretory phase, between cycle days (CD) 20 and 24, or 6–10 days after ovulation (Blesa et al. 2014; Donaghy and Lessey 2007; Psychoyos 1973), which is a temporally framed period called the window of implantation (WOI). During the WOI, the endometrium which has been primed by estrogen and progesterone is characterized by changes that are collectively termed endometrial receptivity (Lessey 2011). During the past decades, intensive morphological, histological, and molecular studies have defined the “signature” of the WOI in many species (Cheong et al. 2013; Diaz-Gimeno et al. 2014; Lessey 2011).

10.2.1.1 Morphological and Histological Characteristics—*Histological dating* of the endometrium has been performed for over 60 years following the Noyes criteria (Noyes et al. 1950). Using these established criteria, histological features of the receptive endometrium include the glands becoming more irregular with a papillary or sawtooth appearance, movement of vacuoles to a supranuclear position of epithelial cells with the possibility of the contents being visible within the uterine lumen, the uterine stroma becoming looser and more edematous, and decidualization of the uterine stroma (Diaz-Gimeno et al. 2013).

Pinopods or *uterodomes* are the hairlike microvilli of epithelial cells which transiently fuse to form a single flowerlike membrane projection which appears only on the luminal surface of endometrial epithelial cells during the WOI (Nikas 1999; Nikas and Aghajanova 2002). Pinopods found in human endometria are proposed as a marker of uterine receptivity to implantation (Gordon 1975; Psychoyos 1986). Pinopods can be separated into developing pinopods, fully developed pinopods, and regressing pinopods according to their morphology (Nikas and Aghajanova 2002). Pinopods have also been observed in uteri of baboons (Nikas 1999). The association of pinopods with endometrial receptivity has been correlated with implantation outcomes in a clinical study: all patients with abundant pinopods (>50% of endometrial surface) became pregnant, while pregnancy rates were lower than 50 % in the patients with moderate numbers of pinopods group (20–50 %), and none of the patients with few pinopods (<20 %) were pregnant (Nikas and Aghajanova 2002). Other evidence that supports a correlation between numbers of pinopods and uterine receptivity to implantation is the expression of potential molecular markers of receptivity on the pinopods (Aplin et al. 1996; Nardo et al. 2003).

Epithelial plaques are an early endometrial response in primates to implantation of the blastocyst and the initiation of pregnancy. The epithelial plaque reaction is a morphological

transformation of epithelia lining the uterine lumen and necks of the uterine glands characterized by the hypertrophy, hyperplasia, and rounded acinar multicellular pad (Enders 1991). The presence of epithelial plaques is common among primates, and it has been described in several Old and New World Monkeys such as rhesus monkeys (Enders 1991; Ramsey et al. 1976), baboons (Enders et al. 1997; Fazleabas et al. 1999b), green monkeys (Owiti et al. 1986), cynomolgus monkeys (Enders et al. 1996), and dusky leaf monkeys (Burton 1980), whereas this type of structural change has not been reported for humans and great apes. The epithelial plaque reaction of the endometrium has been observed as early as 1 day after implantation in primary implantation sites of rhesus monkeys and baboons (Enders et al. 1983; Tarara et al. 1987). The epithelial plaque reaction induced by chorionic gonadotropin affects the entire luminal surface of the endometrium in baboons compared to a reaction restricted to the site of implantation in pregnant baboons (Fazleabas et al. 1999a). Additionally, there are few reports of spontaneous epithelial plaque reactions in the secretory phase of the menstrual cycle in nonpregnant primates (Kaspereit et al. 2004). The absence of epithelial plaques is associated with infertility in the bonnet monkey (Rosario et al. 2005).

10.2.1.2 Molecular Characteristics—*Steroid hormone nuclear receptors* in humans and other primates, both estrogen (ESR1) and progesterone receptors (PGR), decline in uterine epithelial cells at the time of implantation while persisting in the stromal compartment of the uterus (Brenner et al. 1990). The mechanism responsible for this downregulation of PGR is progesterone dependent in the macaque (Dorofeyeva 1975).

Mucin 1 (MUC1) is a highly glycosylated polymorphic mucin-like protein. In the human endometrium, MUC1 is produced and secreted by the epithelium as a large and extended transmembrane glycoprotein, which continues to be expressed in the luteal phase and peri-implantation period of pregnancy in a progesterone-dependent manner (Hey et al. 1994). In baboons, however, MUC1 displayed strong surface expression on days 5–8 postovulation or following treatment with estrogen and progesterone, and its expression decreases in the late secretory phase (Hild-Petito et al. 1996).

Integrins are transmembrane glycoproteins with alpha and beta subunits which mediate cell-to-cell and cell-to-extracellular matrix (ECM) adhesion as heterodimers. Three integrins were discovered that have unique expression patterns which correlate with the WOI in women: $\alpha 1\beta 1$, $\alpha 4\beta 1$, and $\alpha v\beta 3$ (Lessey 2002). The localization of $\alpha v\beta 3$ on the pinopods on the apical surface of the luminal epithelium at the time of uterine receptivity suggests a role for this integrin in initializing implantation (Aplin et al. 1996; Lessey 2002).

Osteopontin (OPN, also known as secreted phosphoprotein 1, SPPI) is a glycoprotein produced by endometrial epithelia and secreted into the uterine lumen at the time of implantation where it binds to the $\alpha v\beta 3$ integrin present on the surface of uterine luminal epithelia (Apparao et al. 2001). OPN is also the only common differentially expressed gene from five microarray studies that identified the genomic signature of endometrial receptivity to implantation of the blastocyst (Mirkin et al. 2005).

Heparin-binding epidermal growth factor-like growth factor (HB-EGF) is expressed in a cycle-dependent manner by luminal epithelial cells of the human endometrium in response

to both estrogen and progesterone (Lessey et al. 2002). HB-EGF is expressed by the uterine luminal epithelium when fully developed pinopods are localized to the surface of pinopods during the menstrual cycle which suggests its role in the ability of the endometrium to interact with the blastocyst during implantation (Stavreus-Evers et al. 2002).

Transcriptomics signature Since the beginning of the twenty-first century, a number of studies have been performed to identify the global transcriptomic signature of the endometrium during the WOI of natural menstrual cycles (Borthwick et al. 2003; Carson et al. 2002; Kao et al. 2002; Mirkin et al. 2005; Riesewijk et al. 2003) and controlled ovarian stimulated menstrual cycles (Horcajadas et al. 2005; Mirkin et al. 2004). The results offer an opportunity to develop a database of endometrial genes expressed uniquely during the WOI, even though there are significant variations among the studies due to differences in experimental design, sample collection, data analyses, and statistical methods (Horcajadas et al. 2007). Based on the transcriptomic signature elucidated from these studies, a customized endometrial receptivity array (ERA) that contains 238 endometrial receptivity-related genes was created as a genome-based diagnostic tool for assessing human endometrial receptivity to implantation (Diaz-Gimeno et al. 2011). This ERA is superior in accuracy and reproducibility to the traditional histological dating method as a diagnostic tool for endometrial receptivity (Diaz-Gimeno et al. 2013) and offers a chance for clinicians to personalize the time of transfer of a blastocyst(s) during ART procedures (Diaz-Gimeno et al. 2014).

10.2.2 Process of Implantation

Histological examination of human uteri during early pregnancy revealed distinct patterns of blastocyst adherence to the endometrial surface and underlying stroma: the process of implantation could be classified into three stages: apposition, adhesion, and invasion (Hertig et al. 1956; Lindenberg 1991).

10.2.2.1 Apposition and Attachment—Apposition is the very first connection between the blastocyst and the endometrium, during which the human blastocyst finds a location at which to implant, guided by the maternal endometrium. At this stage the blastocyst is able to be dislodged from the uterine surface by flushing the uterine lumen without damage to the blastocyst (Bischof and Campana 1996; Sharma and Kumar 2012). The attachment phase is much stronger and initiates a physical connection between the blastocyst and the endometrium. During attachment, direct contact occurs between the endometrial epithelium and the trophoblast, and the blastocyst cannot be dislodged (Bischof and Campana 1996; Sharma and Kumar 2012; Valles and Dominguez 2006).

The apposition and attachment of the trophoblast to the endometrial epithelium is unique in that it occurs via respective apical cell membranes of the endometrium (Lindenberg 1991). On the blastocyst, the inner cell mass (ICM) usually faces the endometrium. Nevertheless, the area of the blastocyst at which apposition occurs is not dependent on the orientation of the ICM. Instead, the ICM migrates along the inside face of the trophoblast to align itself to the side of apposition. In short, the entire surface of the blastocyst has the potential to form

the apposition and attachment site to the endometrium (Sharma and Kumar 2012; Vinatier and Monnier 1990).

There is significant communication between the blastocyst and the endometrium during apposition and attachment phases of implantation which is mediated by receptor-ligand interactions. For example, L-selectin is a protein expressed on the surface of trophoblast cells, and an in vitro model of implantation provided evidence to support the hypothesis that L-selectin mediates apposition of the blastocyst to the uterine epithelium by interacting with its carbohydrate ligands (Genbacev et al. 2003). MUC1 was later identified as a major scaffold for L-selectin to bind to the surface of the endometrium (Carson et al. 2006). Another example of receptor-ligand pairing that mediates blastocyst-endometrial communication is integrin $\alpha v \beta 3$ and its ligand OPN which are both spatially and temporally expressed on the surface of endometrial epithelium when attachment occurs (Apparao et al. 2001; Lessey 2002). The integrin heterodimer $\alpha v \beta 3$ is also present on the surface of human trophoblast cells; therefore, it is likely that integrin $\alpha v \beta 3$ and its ligand OPN participate in trophoblast endometrial recognition during attachment (Reddy and Mangale 2003).

10.2.2.2 Invasion—Invasion of the uterine endometrium by the blastocyst is a process during which trophoblast cells penetrate the endometrial epithelium and invade into the endometrial stroma to reach maternal blood vessels. In humans and nonhuman primates, as attachment is established, trophoblast cells penetrate the endometrial epithelium and reach the matrix layer under the epithelial cells, known as the basement membrane (BM), via intercellular gaps between neighboring endometrial epithelial cells without destroying them (Carson et al. 2000). This is defined as interstitial implantation (Bischof and Campana 1996).

The formation of invadopodia, the thin folds of trophoblast cells between the adjacent endometrial epithelial cells, leads to degradation of the basement membrane and extracellular matrix (ECM), allowing trophoblast cells to reach the endometrial stromal compartment (Giudice 1999). The activated gelatinases (metalloproteinases, MMPs) play a primary role in degrading matrices during this process, and different types of integrins guide the invading trophoblast through different layers of cells and matrices within the endometrium (Bischof and Campana 1996).

The process of invasion in humans and nonhuman primates is followed by syncytialization, during which the protrusions of trophoblast cells that migrate into the endometrium continue to proliferate, differentiate, and fuse to become a new type of cell: syncytiotrophoblasts (STB). The rest of the trophoblast cells, surrounding the inner cell mass, are referred to as cytotrophoblasts (CTB). STB cells invade the endometrium to guide the entire blastocyst as it invades into the endometrium. In humans, the blastocyst is completely embedded within the endometrial stroma at 8 days after ovulation and the entry site is covered by fibrin, over which the endometrial epithelial cells grow and embed the blastocyst in the endometrium (Bischof and Campana 1996). In nonhuman primates such as gibbons, gorillas, and chimpanzees, implantation is also invasive, like humans, whereas in baboons and macaques, implantation is superficial (Carter and Pijnenborg 2011; Houston 1969).

In STB, fluid-filled spaces, known as lacunae, separated by trabeculae appear, transforming the STB into a spongelike material (Bischof and Campana 1996). Eventually, the STBs come into contact with maternal blood vessels, and maternal blood is trapped within the lacunae, forming a basic oxygen and nutrition transfer unit for the developing conceptus (embryo/fetus and placenta). The CTBs grow into the trabeculae of STB to form the primary chorionic villi which are considered to represent the initiation of placentation (Dockery et al. 2000).

10.3 Decidualization

10.3.1 Decidua

The word decidua is from the Latin “de” which means down and “cadere” which means to fall and is so named since the uterine decidua is shed after parturition. The decidua is classified into three different types in the human uterus during pregnancy relative to the developing conceptus: the region of the decidua directly beneath the site of implantation forms the decidua basalis; the region that overlies the developing conceptus and separates it from the uterine cavity is the decidua capsularis; and the rest of decidua is the decidua vera or decidua parietalis (Pritchard et al. 1985). Both the decidua basalis and the decidua capsularis can be invaded by trophoblast cells and chorionic villi of the conceptus, but only the decidua basalis supports the formation of the discoid placenta in middle and late pregnancy while the rest of the tissue undergoes degeneration later in pregnancy (Pritchard et al. 1985). The decidua in great apes resembles that of humans, whereas Old World monkeys such as baboons and macaques do not have the decidua capsularis due to their superficial implantation (Carter and Pijnenborg 2011).

10.3.2 Functions of Decidua

The main cell type of the decidua is decidualized endometrial stromal cells, which can provide nutritional support for the implanting blastocyst. Apart from the decidual stromal cell, other cell types within the decidual tissue include hematopoietic cells, macrophages, an abundance of uterine natural killer (uNK) cells, and monocytes (Dunn et al. 2003). Associated with these cells are uterine glands and small blood vessels, including spiral arteries, which support the maternal blood supply to the growing conceptus. Functionally the decidua plays a central role in the establishment and maintenance of pregnancy.

10.3.2.1 Controlled Trophoblast Invasion—Implantation and placentation in the human involves deep invasion of trophoblast cells into the maternal uterine architecture. The decidua is the compartment of the uterus with which trophoblast cells interact with during invasion. The decidua forms a dense cellular matrix that, on the one hand, generates a local microenvironment to promote trophoblast attachment and invasion and, on the other hand, limits the extent of aggressive invasion of trophoblast cells (Gellersen et al. 2007; Gellersen and Brosens 2014).

The extracellular matrix formed by decidual cells is the target of trophoblast invasion. Recent studies showed that decidual cells actively engage in the process of invasion by encapsulating the blastocyst (Gellersen and Brosens 2014). Trophoblast invasion requires

proteolytic degradation and remodeling of the decidual extracellular matrix. Matrix metalloproteinases (MMPs) secreted by trophoblast cells are able to degrade the extracellular matrix of the decidua (Librach et al. 1991; Shimonovitz et al. 1994). Based on recent studies, decidualized stromal cells also produce MMPs, and the capacity of MMP secretion of these cells is comparable to that of trophoblast cells (Anacker et al. 2011; Weimar et al. 2013). In in vitro culture models, decidualized human endometrial stromal cells (HESCs) surrounding the blastocyst migrate away to accommodate the outgrowth of the trophoblast (Grewal et al. 2010; Grewal et al. 2008). Furthermore, elastin microfibril interfacer 1, a connective tissue glycoprotein produced by the decidua, can attract migrating extravillous trophoblast cells (Spessotto et al. 2006).

Alternatively, decidual cells and their microenvironment play a role to limit over-invasion of the trophoblast to protect the endometrium from invasive damage. Conditioned medium from human decidual cells inhibits growth of cultured BeWo choriocarcinoma cells as well as invasion of trophoblast cells (Graham and Lala 1991; Lewis et al. 1993). The actions of MMPs are inhibited by tissue inhibitors of metalloproteinase (TIMPs). In humans, TIMPs abolish trophoblast invasion (Librach et al. 1991). *TIMP-3* mRNA expression is upregulated in decidualized endometrial stromal cells by progesterone treatment both in vivo and in vitro (Higuchi et al. 1995), whereas endometrial *TIMP-1* and *TIMP-2* mRNA expression is not dependent on the stage of the menstrual cycle. Additionally, decidual cells secrete transforming growth factor- β (TGF- β) to inhibit the production of MMPs by trophoblast cells (Graham et al. 1992).

10.3.2.2 Protection of the Conceptus from Maternal Immune Rejection—The decidua also plays an integral role in ensuring immune tolerance toward the semi-allogeneic fetal-placental unit and protects the conceptus from the mother's immune system. The physiological mechanisms are mediated by immune cells, particularly uterine natural killer (uNK) cells and regulatory T cells (Tregs), which increase in their numbers during early pregnancy (Fu et al. 2013; Tilburgs et al. 2008; Xiong et al. 2010).

The uterine NK cells are often considered to be cytotoxic, killing virally infected cells and cancer cells (Biron 2010). However, this killing function is lost in the uterus during pregnancy: the uNK cells play a supportive role. Differentiating resident stromal cells, but not trophoblast cells, have been demonstrated to play a critical role in the recruitment of CD56^{bright}/CD16[−] uNK cells at the maternal-conceptus interface (Rieger et al. 2004; Vassiliadou and Bulmer 1998). uNK cells promote immune tolerance and successful pregnancy by dampening inflammatory Th17 cells via IFN- γ (Fu et al. 2013). The uNK cells can also inhibit the function of T cells by expressing immunomodulatory molecules such as galectin-1 and glycodelin A (Koopman et al. 2003). Galectin-1 is known as an inhibitor of T-cell proliferation and survival, and it promotes apoptosis of activated T cells in the decidua (Kopcow et al. 2008). Glycodelin A inhibits T-cell activation through its ability to interact with the tyrosine phosphatase receptor CD45 on the T-cell surface (Rachmilewitz et al. 2003; SundarRaj et al. 2008). The uNK cell-mediated T-cell regulatory response is lost in patients who experience recurrent spontaneous abortions (RSA) due to extensive local inflammation (Fu et al. 2013).

Tregs are CD4⁺CD25⁺ T cells, which suppress the activity of other immune cell types and are involved in downregulating immune responses (Campbell and Koch 2011). Tregs produce immunosuppressive cytokines such as IL-10 for exerting immune tolerance (Hara et al. 2001). Tregs are essential for the maintenance of pregnancy. The decrease in these cells and its product IL-10 in the decidua is associated with RSA which involves an inflammatory response and is accompanied by an increase in Th17 cells (Plevyak et al. 2002; Sasaki et al. 2004). Since IL-10 signaling in Tregs is required for suppression of Th17 cell-mediated inflammation (Chaudhry et al. 2011), it is plausible that Tregs regulate immune tolerance in decidua during early pregnancy by suppressing Th17 cell-mediated inflammation via its product IL-10.

Besides immune cells, decidualized stromal cells are able to induce apoptosis of activated T cells by inducing expression of Fas ligand (FasL) (Kayisli et al. 2003). Thus, the decidua acts as a gatekeeper that controls immune tolerance during pregnancy by blocking T cells that would otherwise attack the developing conceptus.

10.3.3 Decidualization

Decidualization is the differentiation of elongated fibroblast-like mesenchymal cells in the uterine stroma to rounded epithelioid-like cells during the menstrual cycle and pregnancy. This process is one of the most critical and remarkable events that occurs within the endometrium of human and nonhuman primates during pregnancy (Kim et al. 1999a). This morphological change in humans is initiated in the luteal phase and begins with stromal cells surrounding the spiral arteries in the upper two-thirds of the endometrium regardless of the presence or absence of a conceptus (Ramathal et al. 2010). This initial change is referred to as predecidualization.

Once implantation of the blastocyst occurs, the reaction persists and spreads beyond the perivascular regions and becomes the decidua of pregnancy. The decidual reaction continues throughout pregnancy. Not only do the decidual cells increase in size throughout pregnancy, but the percentage of stromal cells in the decidua increases progressively from 9.8 % in early pregnancy to 57.8 % at term (Wewer et al. 1985). In contrast, baboons and macaques do not undergo a predecidual reaction during the menstrual cycle (Enders 1991; Kim et al. 1999a; Ramsey et al. 1976). However, the stromal cells undergo extensive modification following the establishment of pregnancy to form the decidua in baboons and macaques (Enders 1991). This decidualization process is slower in the baboon compared to the human, but earlier than that seen in the macaque (Carter et al. 2015). Decidualization of HESCs as well as baboon uterine stromal cells can be induced in vitro in the presence of hormones and cyclic adenosine monophosphate (cAMP) (Kim et al. 1998). Additionally, human uterine fibroblast (HuF) cells obtained from full-term decidua (maternal side of placenta) are able to differentiate morphologically and biochemically in vitro (Richards et al. 1995). HuF cells are used extensively to study decidual function due to the fact that these cells are readily available in larger numbers than those from endometrial biopsies (Afshar et al. 2012; Richards et al. 1995; Strakova et al. 2000).

Ultrastructural studies of human decidual cells indicate characteristics of epithelioid cells: progressive enlargement, rounding of the nucleus, increased number and complexity of

nucleoli, expansion of the rough endoplasmic reticulum and Golgi complex, cytoplasmic accumulation of glycogen and lipid droplets, and dense membrane-bound secretory granules (Wynn 1974). In between these cells, adherens junctions, but not true desmosomes, are found and the arrangement of gap junctions in these cells may be helpful for trophoblast invasion (Lawn et al. 1971). Extracellular matrix (ECM) proteins produced by decidualized stromal cells include decorin, laminin, type IV collagen, fibronectin, and heparin sulfate proteoglycans (Gellersen et al. 2007).

The characteristics of decidual cells described previously are also characteristics of secretory cells (Kim et al. 1999a). The major secretory products of decidual cells are prolactin (PRL) and insulin-like growth factor binding protein-1 (IGFBP1), which have been used widely as marker genes for decidualization (Gellersen et al. 2007). Other secretory molecules from decidual cells include interleukin-11 (IL-11), epidermal growth factor (EGF), heparin-binding epidermal growth factor (HB-EGF), LEFTY2, activin A, and neuropeptides (Dimitriadis et al. 2005). In the past decades, microarray studies have been used to identify transcriptional changes during differentiation of stromal cells to decidual cells. Based on results of those studies, decidualization has been described as a process of sequential reprogramming of functionally related changes including ECM organization, cell adhesion, cytoskeletal organization, signal transduction, metabolism, stress responses, cell cycle progression, differentiation, and apoptosis (Gellersen et al. 2007).

10.3.4 Molecular Mechanisms

The decidualization process encompasses changes that commence in response to the actions of progesterone. Circulating concentrations of progesterone increase during the secretory phase of the menstrual cycle and remain elevated during pregnancy. Progesterone acts by binding and activating its nuclear receptor, PGR. In the stromal compartment of the human endometrium, PGR-A is the dominant isoform (Chen et al. 2009). It is highly expressed in stromal cells throughout the menstrual cycle and in pregnancy, whereas its expression in epithelial cells decreases after ovulation (Chen et al. 2009). Progesterone regulates the expression of IGFBP1 and decidual PRL via PGR-A (Christian et al. 2002a; Gao et al. 2000). Silencing of downstream progesterone-regulated genes and PGR co-regulators such as *HOXA10*, *KLF9*, and *FKBP52* leads to decrease in expression of markers of decidualization, *PRL* and *IGFBP1*, in HESC cells (Lu et al. 2008; Pabona et al. 2010; Yang et al. 2012). However, decidualization of the superficial layer of the endometrium is only apparent in vivo approximately 10 days after the increase in circulating concentrations of progesterone (de Ziegler et al. 1998). The induction of decidualization of HESC in vitro with progesterone or progesterone and estradiol is relatively slow (Brar et al. 1997). The addition of cAMP rapidly accelerates decidualization of HSEC cells (Brosens et al. 1999).

The concentration of cAMP is higher in endometrial biopsies taken during the secretory phase compared with proliferative phase of the menstrual cycle (Bergamini et al. 1985) and reaches a peak in the late-secretory phase in response of prostaglandin E2 (PGE2) (Tanaka et al. 1993). In pregnancy, human chorionic gonadotropin (hCG) further enhances concentrations of cAMP and decidualization of endometrial stromal cells (Tang and Gurpide 1993). In cultured HESCs, cAMP alone increases the expression of *PRL*, but for only a few

days (Brosens et al. 1999). Further induction and stabilization of PRL, a decidualization marker requires the presence of both cAMP and progesterone (Brosens et al. 1999). The effect of cAMP during in vitro decidualization can be blocked with a PKA inhibitor (Brar et al. 1997). Thus, cooperation of progesterone and cAMP is necessary and sufficient for decidualization. Progesterone, via PGR-A, together with cAMP and genes under regulation of progesterone/cAMP, such as *HOX10*, *FOXO1*, *BMP2*, and *WNT4*, comprise a critical network for decidualization of endometrial stromal cells (Li et al. 2007, 2013; Lu et al. 2008; Takano et al. 2007; Vasquez et al. 2015).

Based on in vivo studies in the baboon, the process of decidualization can be separated into two distinct phases. The first phase is manifested by the expression of alpha smooth muscle actin (α -SMA) in the differentiation of endometrial stromal cells, which is regulated by chorionic gonadotropin (CG) and progesterone (Christensen et al. 1995). This change in cytoskeletal reorganization is associated with binding of decidual integrins to the ECM, which also undergoes extensive remodeling in response to CG (Fazleabas et al. 1997a). The second phase of decidualization requires the presence of a conceptus and is manifested by the downregulation of expression of α -SMA and the induction of IGFBP1 (Kim et al. 1999a).

Results from high-throughput analysis revealed that genes and proteins involved with the cell cycle, apoptosis, transcription and translation, metabolism, inflammatory response, cell structure remodeling, and paracrine signaling are differently regulated during decidualization of human endometrial cells (Brar et al. 2001; Popovici et al. 2000). MicroRNAs also play a role during decidualization (Estella et al. 2012; Qian et al. 2009). As a result of differentiation, decidual cells acquire unique biochemical and cellular properties that enable them to support implantation of the blastocyst. Therefore, the decidualization of stromal fibroblasts within the human endometrium is a requirement for successful pregnancy.

10.4 Endometrial Response to Blastocyst/Conceptus Signals

In humans, the presence of a blastocyst/conceptus alters the endometrial phenotype compared to the normal menstrual cycle in the mid-secretory phase. This altered phenotype of endometrium during the cycle of conception includes the persistent increase of stromal edema, predecidual formation, and the absence of leukocytic infiltration compared to the normal menstrual cycle (Hertig 1964; Karow et al. 1971; Wentz et al. 1986). These observations suggest the importance of embryonic signals for the development of uterine receptivity to facilitate implantation.

10.4.1 Endometrial Response to Chorionic Gonadotropin (CG)

Chorionic gonadotropin (CG), the major embryonic signal in the primate, is a glycoprotein hormone synthesized and secreted by the trophoblast cells. The CG β mRNA is detected as early as the 6–8 cell stage of the human embryo, but measureable levels of CG protein are present in culture medium of the late blastocyst (Srisuparp et al. 2001). In vivo, CG is first detectable in maternal serum during the window of implantation and increases rapidly along with the establishment and progress of early pregnancy (Alfthan and Stenman 1996). In

primates, CG acts as a luteinizing hormone (LH) superagonist, extending the lifespan of the corpus luteum to sustain progesterone production to support the pregnancy. In baboons, pregnancy-associated serum CG activity is detectable by day 15 of gestation, peaks at day 27, and returned to baseline values by day 51. Lower levels of CG are associated with spontaneous abortion (Fortman et al. 1993). Besides the ovarian response to CG, the endometrium also responds to embryonic CG, since LH/CG receptor is expressed in the primate endometrium (Reshef et al. 1990; Cameo et al. 2006). In vivo studies in the baboon from our laboratory showed that CG alters the morphology and biochemical activity of the endometrium (Banerjee and Fazleabas 2011; Fazleabas et al. 1999a; Hausermann et al. 1998). Transcriptomics analysis identified genes influenced by CG in the baboon and identified pathways that are involved in embryo attachment, extracellular matrix remodeling, and modulation of the immune response around the implanting blastocyst (Banerjee and Fazleabas 2010; Sherwin et al. 2007).

10.4.1.1 Epithelial Response—Our laboratory has utilized the baboon as a nonhuman primate model to investigate endometrial responses to embryonic CG. CG was infused into the uterine cavity of cycling baboons from day 6 to day 10 postovulation to mimic normal blastocyst transit (Fazleabas et al. 1999a; Jones and Fazleabas 2001). As a result of CG treatment, an epithelial plaque reaction was observed in the luminal epithelium (Fig. 10.1) (Fazleabas et al. 1999a; Jones and Fazleabas 2001). Endometrial glandular structures in response to CG infusion resemble those observed in the pregnant baboon at the same age of gestation. Glandular secretions including glycodeclin, a major secretory protein of uterine glands during the secretory phase and pregnancy, also increase in response to CG (Fig. 10.1) (Fazleabas et al. 1997a, b; Hausermann et al. 1998).

Several in vitro studies also support the role of CG in inducing changes in endometrial epithelial cells in the baboon and human. Prostaglandin E₂ (PGE₂) induces cAMP in endometrial stromal cells to promote their predecidualization response during the secretory phase (Tanaka et al. 1993). According to results from our and other laboratories, treatment of both human and baboon endometrial epithelial cells with CG induces expression of cyclooxygenase-2 (COX2, coded by *PTGS2*) and prostaglandin E synthase (PGES), two enzymes that control the synthesis of PGE₂ (Banerjee et al. 2009; Zhou et al. 1999), as well as the production of PGE₂ (Srisuparp et al. 2003). The response of endometrial epithelial cells to CG and the downstream PGE₂ production occurs through the CG receptor LHCGR, a seven transmembrane G protein-coupled receptor, and the inositol phosphate-dependent mitogen-activated protein kinases (MAPK) pathway (Banerjee et al. 2009). Interestingly, treatment with CG failed to induce production of cAMP in endometrial epithelial cells, but leads to a release of PGE₂ which induces cAMP production in stromal cells (Srisuparp et al. 2003; Tanaka et al. 1993), suggesting the role of epithelial cells mediating the stromal response to embryonic CG. The mechanism by which this response is initiated is summarized in Fig. 10.1a. Furthermore, CG downregulates expression of its receptor in baboon endometrial epithelium, but upregulates LHCGR in stromal cells surrounding spiral arteries (Cameo et al. 2006), indicating a shift in the endometrial response to CG from epithelium to stroma which is driven by CG itself.

10.4.1.2 Stromal Response—In the baboon model, the first detectable molecular response to CG in uterine stromal cells is an increase in the expression of α -SMA in the subepithelial region in early gestation after implantation and after CG infusion, indicating that remodeling of the stromal cell cytoskeleton is necessary for decidualization of endometrial stromal cells (Fazleabas et al. 1999a; Jones and Fazleabas 2001; Strakova et al. 2005). This stimulation has been attributed to binding of ECM proteins to integrin heterodimers on stromal cells (Fazleabas et al. 1997a). The remodeling of the cytoskeleton of stromal cells is essential for their differentiation. In vivo, in the absence of α -SMA, endometrial stromal cells in baboons are not able to predecidualize until induced by CG signaling from the implanting blastocyst or infusion of CG into the uterine lumen (Enders 1991; Kim et al. 1999a; Ramsey et al. 1976). However, these stromal cells can be induced to decidualize by cAMP and steroid hormones since they induce expression of α -SMA during in vitro culture (Kim et al. 1998). Furthermore, disruption of actin filaments by cytochalasin D sensitizes the cultured baboon endometrial stromal cells response to inducers of decidualization characterized by expression of IGFBP1 within 24 h after treatment (Kim et al. 1999b) compared to 6 days under standard conditions (Kim et al. 1998). Stromal cells isolated from the endometrium primed by embryonic or infused CG in vivo exhibit the decidualization response in vitro as rapidly as cytochalasin D-sensitized stromal cells (Kim et al. 1999b), indicating the importance of CG to initiate decidualization of endometrial stromal cells. Expression of the decidualization marker IGFBP1 is also regulated by the conceptus and CG (Fazleabas et al. 1997b). In early gestation (day 28), LHCGR is expressed by stromal cells around spiral arteries where decidualization is initiated, indicating that those cells are a direct target of CG to induce initiation of decidualization (Cameo et al. 2006). Responses of endometrial stromal cells to CG during decidualization are summarized in Fig. 10.1b.

Full differentiation of endometrial stromal cells requires a decrease in abundance of α -SMA to allow for an increase in the expression of IGFBP1. In vivo, α -SMA disappears between days 32 and 40 of pregnancy, which is the time when expression of IGFBP1 is detectable (Christensen et al. 1995; Strakova et al. 2005; Tarantino et al. 1992). In vitro, an increase in IGFBP1 is associated with the decrease in expression of α -SMA (Kim et al. 1998, 1999b). This decrease in α -SMA is also associated with a decrease in expression of LHCGR in later stages of gestation (days 40–50) and at the completion of in vitro decidualization (Cameo et al. 2006). Collectively, the embryonic signal CG first induces expression of α -SMA to promote remodeling of the cytoskeleton of stromal cells and differentiation of endometrial stromal cells around spiral arteries via its membrane receptor. Subsequently the decrease in CG signaling appears to be necessary for the completion of decidualization. Our recent studies demonstrated that NOTCH1, a membrane receptor of Notch signaling, may mediate CG-regulated decidualization (Afshar et al. 2012; Su et al. 2015).

10.4.2 NOTCH1 Acts Downstream of Chorionic Gonadotropin (CG)

CG is believed to rescue the endometrium from its apoptosis cascade, which usually occurs at the end of each menstrual cycle, and direct it toward a decidualization response. CG inhibits this apoptotic fate of endometrial cells (Lovely et al. 2005) and, with ovarian

hormones, differentiates them into the decidualized phenotype (Jasinska et al. 2006). CG prevents apoptosis by inducing anti-apoptosis genes like BCL-2 (Jasinska et al. 2006).

Notch signaling is a highly conserved pathway across most multicellular organisms. It plays an important role in cell-cell communication and mediates cell fates such as proliferation, differentiation, and apoptosis (Rizzo et al. 2008). Notch signaling is associated with four transmembrane receptors (Notch 1–4) and five transmembrane ligands of the jagged/delta-like families (Afshar et al. 2012). Activation of Notch signaling is generally initiated by interactions between adjacent cells expressing receptor and ligand. This results in a series of receptor-mediated cleavage events and the release of the Notch intracellular domain (NICD) which translocates to the nucleus where it binds and activates the Notch family transcription factor, recombination signal binding protein $J\kappa$ (RBP- $J\kappa$). RBP- $J\kappa$ then initiates the expression of Notch target genes, such as the “hairy enhancer of split” (Hes) and Hes-related (Hey) transcription factor families (Su et al. 2015).

Notch signaling mediates cellular processes that are essential for successful decidualization. Expression of NOTCH1 and its target α -SMA are both induced by CG in baboon endometrial stromal cells in vivo. Silencing of NOTCH1 in human uterine fibroblast (HuF) cells cultured in vitro leads to the impairment of decidualization, suggesting that NOTCH1- α -SMA mediates CG function in rescuing endometrial stromal cells from apoptosis and differentiating them to decidual cells (Afshar et al. 2012). In vivo CG infusion upregulates expression of both NOTCH1 and α -SMA in human endometrium, which further supports our findings from studies of the baboon model (M.R. Strug and A.T. Fazleabas, unpublished data). Furthermore, activation of Notch signaling is regulated by progesterone which indicates a significant interaction between the CG-Notch pathway and progesterone signaling during decidualization (Afshar et al. 2012). Additional studies have shown that silencing NOTCH1 in HuF cells inhibits decidualization only during the initiation of the differentiation process. To inhibit decidualization of HuF cells in vitro, NOTCH1 must be silenced before the induction of decidualization, whereas silencing NOTCH1 three days after induction of decidualization does not inhibit the expression of decidualization markers (Su et al. 2015). Furthermore, comparative microarray analysis indicated that Forkhead box protein O1 (FOXO1) is a downstream target of NOTCH1 during in vitro decidualization, since FOXO1 and its specific target genes are downregulated when NOTCH1 is silenced during in vitro decidualization (Su et al. 2015). FOXO1 is one of the earliest genes induced during decidualization (Brar et al. 2001; Christian et al. 2002b). A number of in vitro experiments conclusively demonstrated the importance of FOXO1 for the induction of decidualization (Buzzio et al. 2006; Grinius et al. 2006; Labied et al. 2006). Overexpression of FOXO1 in human endometrial stromal cells can induce expression of IGFBP1 and PRL independent of cAMP and hormones induced in vitro decidualization (Buzzio et al. 2006; Christian et al. 2002b; Kim et al. 2005; Takano et al. 2007). A recent study demonstrated that FOXO1 is functionally required for the binding of PGR to genomic targets during decidualization (Vasquez et al. 2015). These results demonstrate that NOTCH1 acts downstream of CG and plays a critical role during the decidualization response of endometrial stromal cells by regulating the expression of its targets, α -SMA and FOXO1 (Fig. 10.1b).

On the other hand, NOTCH1 is downregulated at the completion of decidualization (Afshar et al. 2012) similar to α -SMA and LHCGR expression, which is necessary for the induction of IGFBP1 (Cameo et al. 2006; Kim et al. 1998). Results of our most recent studies indicated that constitutively active Notch signaling by over-expressing the NOTCH1 intracellular domain (N1ICD) prevents HuF cells from undergoing decidualization (R. Su and A.T. Fazleabas, unpublished data). The necessity for the decrease in NOTCH1 expression for the completion of decidualization may be because decidualization depends on cAMP stimulation, sustained PKA activity, and CREB activation (Gellersen and Brosens 2014; Kusama et al. 2014), but N1ICD sequesters nuclear CREB and inhibits cAMP/PKA mediated signaling (Hallaq et al. 2015).

In summary, NOTCH1 initially mediates a survival signal in the uterine endometrium in response to CG from the implanting blastocyst together with progesterone, so that menstrual sloughing is averted. Subsequently, NOTCH1 downregulation may be critical for the complete transition of stromal fibroblasts to decidual cells, which is essential for the establishment of a successful pregnancy.

10.4.3 Endometrial Response to Interleukin-1 β

Implantation has been characterized as an inflammatory response, and IL-1 β is a key regulator of this response (Fazleabas et al. 2004). Cytotrophoblast cells isolated from first trimester placentae release more IL-1 β than those from second and third trimester in culture (Librach et al. 1994), and co-culture of cytotrophoblast cells with HuF cells induces them to decidualize (Jasinska et al. 2004). Numerous studies have provided evidence of the importance of IL-1 β as an embryonic signal that affects endometrial responses in primates.

Our laboratory previously reported that IL-1 β induces expression of COX2 and PGE2 synthesis in human and baboon endometrial stromal cells (Strakova et al. 2000), which is believed to subsequently increase cAMP in stromal cells and induce decidualization (Fazleabas et al. 2004). Indeed, induced expression of the decidualization marker IGFBP1 by IL-1 β in the presence of steroid hormones is blocked by COX-2 inhibitor in human and baboon endometrial stromal cells (Strakova et al. 2000). Induction of IGFBP1 expression by cAMP with steroid hormones is not affected by inhibition of COX-2 which supports the inference that cAMP acts downstream of IL-1 β -COX2-PGE2 signaling during decidualization. Interestingly, cAMP prevents decidualization induced by IL-1 β which suggests a negative cross-talk between IL- β - and cAMP-induced decidualization responses (Strakova et al. 2000, 2002).

The remodeling of the cytoskeleton of stromal cells is essential to the differentiation of stromal cells (Kim et al. 1998). Cytoskeleton changes can be induced by the disruption of the ECM (Fazleabas et al. 1997a). In baboon endometrial stromal cells, IL-1 β induces expression and synthesis of MMP3, which can degrade the ECM (Strakova et al. 2003). This induction of MMP3 is regulated via the MAPK pathway and is critical for decidualization. Inhibition of MMP3, using doxycycline or specific MMP-3 inhibitor N-isobutyl-N-(4-methoxyphenylsulfonyl) glycyl hydroxamic acid (NNGE), suppresses the induction of decidualization by IL-1 β and hormones (relaxin, estradiol-17 β , and medroxyprogesterone acetate) (Strakova et al. 2003). The expression of MMP3 and degradation of ECM may

contribute to the decrease in expression of the cytoskeleton protein α -SMA that is induced by IL-1 β and hormones during decidualization (Strakova et al. 2000). Additionally, expression of IGFBP1 can be induced in stromal cells close to the apical surface by in vivo infusion of IL-1 β in the presence of CG which further supports a role for IL-1 β from the blastocyst in regulating decidualization of endometrial stromal cells during implantation (Strakova et al. 2005). The postulated roles of IL-1 β during decidualization are summarized in Fig. 10.1.

10.5 Summary

Successful implantation and decidualization are necessary for providing required maternal support and protection of the developing conceptus. Human reproduction is highly inefficient compared to other primates. In women the average chance of pregnancy is only 15 % per cycle during their reproductive lifespan (Hjollund et al. 2000). In ART, only around 25 % of transferred embryos will successfully implant (Edwards 2006). Understanding the processes and mechanisms required for implantation and the establishment of pregnancy can help improve outcomes of ART. In support of results of studies on the role of CG in modulating the receptive endometrium as discussed in Sect. 10.4, intrauterine injection of CG before embryo transfer significantly improves implantation and pregnancy rates following ART (Mansour et al. 2011). Thus, an understanding of endometrial response to embryonic cells in primates may provide insight into improving pregnancy rates in women who are infertile.

References

- Afshar Y, Miele L, Fazleabas AT. Notch1 is regulated by chorionic gonadotropin and progesterone in endometrial stromal cells and modulates decidualization in primates. *Endocrinology*. 2012; 153:2884–2896. [PubMed: 22535768]
- Alfthan H, Stenman UH. Pathophysiological importance of various molecular forms of human choriogonadotropin. *Mol Cell Endocrinol*. 1996; 125:107–120. [PubMed: 9027349]
- Anacker J, Segerer SE, Hagemann C, Feix S, Kapp M, Bausch R, et al. Human decidua and invasive trophoblasts are rich sources of nearly all human matrix metalloproteinases. *Mol Hum Reprod*. 2011; 17:637–652. [PubMed: 21565864]
- Aplin JD, Spanswick C, Behzad F, Kimber SJ, Vicovac L. Integrins beta 5, beta 3 and alpha v are apically distributed in endometrial epithelium. *Mol Hum Reprod*. 1996; 2:527–534. [PubMed: 9239663]
- Apparao KB, Murray MJ, Fritz MA, Meyer WR, Chambers AF, Truong PR, et al. Osteopontin and its receptor alphavbeta(3) integrin are coexpressed in the human endometrium during the menstrual cycle but regulated differentially. *J Clin Endocrinol Metab*. 2001; 86:4991–5000. [PubMed: 11600576]
- Banerjee P, Fazleabas AT. Endometrial responses to embryonic signals in the primate. *Int J Dev Biol*. 2010; 54:295–302. [PubMed: 19876822]
- Banerjee P, Fazleabas AT. Extragonadal actions of chorionic gonadotropin. *Rev Endocr Metab Disord*. 2011; 12:323–332. [PubMed: 21845366]
- Banerjee P, Sapru K, Strakova Z, Fazleabas AT. Chorionic gonadotropin regulates prostaglandin E synthase via a phosphatidylinositol 3-kinase-extracellular regulatory kinase pathway in a human endometrial epithelial cell line: implications for endometrial responses for embryo implantation. *Endocrinology*. 2009; 150:4326–4337. [PubMed: 19556419]

- Bergamini CM, Pansini F, Bettocchi S Jr, Segala V, Dallochio F, Bagni B, et al. Hormonal sensitivity of adenylate cyclase from human endometrium: modulation by estradiol. *J Steroid Biochem.* 1985; 22:299–303. [PubMed: 2985871]
- Biron CA. Expansion, maintenance, and memory in NK and T cells during viral infections: responding to pressures for defense and regulation. *PLoS Pathog.* 2010; 6:e1000816. [PubMed: 20361055]
- Bischof P, Campana A. A model for implantation of the human blastocyst and early placentation. *Hum Reprod Update.* 1996; 2:262–270. [PubMed: 9079419]
- Blesa D, Ruiz-Alonso M, Simon C. Clinical management of endometrial receptivity. *Semin Reprod Med.* 2014; 32:410–413. [PubMed: 24959823]
- Borthwick JM, Charnock-Jones DS, Tom BD, Hull ML, Teirney R, Phillips SC, et al. Determination of the transcript profile of human endometrium. *Mol Hum Reprod.* 2003; 9:19–33. [PubMed: 12529417]
- Brar AK, Frank GR, Kessler CA, Cedars MI, Handwerger S. Progesterone-dependent decidualization of the human endometrium is mediated by cAMP. *Endocrine.* 1997; 6:301–307. [PubMed: 9368687]
- Brar AK, Handwerger S, Kessler CA, Aronow BJ. Gene induction and categorical reprogramming during in vitro human endometrial fibroblast decidualization. *Physiol Genomics.* 2001; 7:135–148. [PubMed: 11773600]
- Brenner RM, West NB, McClellan MC. Estrogen and progestin receptors in the reproductive tract of male and female primates. *Biol Reprod.* 1990; 42:11–19. [PubMed: 2178696]
- Brosens JJ, Hayashi N, White JO. Progesterone receptor regulates decidual prolactin expression in differentiating human endometrial stromal cells. *Endocrinology.* 1999; 140:4809–4820. [PubMed: 10499541]
- Burton GJ. Early placentation in the dusky leaf monkey (*Presbytis obscura*). *Placenta.* 1980; 1:187–195. [PubMed: 7443640]
- Buzzio OL, Lu Z, Miller CD, Unterman TG, Kim JJ. FOXO1A differentially regulates genes of decidualization. *Endocrinology.* 2006; 147:3870–3876. [PubMed: 16690806]
- Cameo P, Szmidt M, Strakova Z, Mavrogianis P, Sharpe-Timms KL, Fazleabas AT. Decidualization regulates the expression of the endometrial chorionic gonadotropin receptor in the primate. *Biol Reprod.* 2006; 75:681–689. [PubMed: 16837644]
- Campbell DJ, Koch MA. Phenotypical and functional specialization of FOXP3+ regulatory T cells. *Nat Rev Immunol.* 2011; 11:119–130. [PubMed: 21267013]
- Carson DD, Bagchi I, Dey SK, Enders AC, Fazleabas AT, Lessey BA, et al. Embryo implantation. *Dev Biol.* 2000; 223:217–237. [PubMed: 10882512]
- Carson DD, Lagow E, Thathiah A, Al-Shami R, Farach-Carson MC, Vernon M, et al. Changes in gene expression during the early to mid-luteal (receptive phase) transition in human endometrium detected by high-density microarray screening. *Mol Hum Reprod.* 2002; 8:871–879. [PubMed: 12200466]
- Carson DD, Julian J, Lessey BA, Prakobphol A, Fisher SJ. MUC1 is a scaffold for selectin ligands in the human uterus. *Front Biosci.* 2006; 11:2903–2908. [PubMed: 16720361]
- Carter AM, Pijnenborg R. Evolution of invasive placentation with special reference to non-human primates. *Best Pract Res Clin Obstet Gynaecol.* 2011; 25:249–257. [PubMed: 21056010]
- Carter AM, Enders AC, Pijnenborg R. The role of invasive trophoblast in implantation and placentation of primates. *Philos Trans R Soc Lond B Biol Sci.* 2015; 370:20140070. [PubMed: 25602074]
- Cha J, Sun X, Dey SK. Mechanisms of implantation: strategies for successful pregnancy. *Nat Med.* 2012; 18:1754–1767. [PubMed: 23223073]
- Chaudhry A, Samstein RM, Treuting P, Liang Y, Pils MC, Heinrich JM, et al. Interleukin-10 signaling in regulatory T cells is required for suppression of Th17 cell-mediated inflammation. *Immunity.* 2011; 34:566–578. [PubMed: 21511185]
- Chen JJ, Hannan NJ, Mak Y, Nicholls PK, Zhang J, Rainczuk A, et al. Proteomic characterization of midproliferative and midsecretory human endometrium. *J Proteome Res.* 2009; 8:2032–2044. [PubMed: 19714818]

- Cheong Y, Boomsma C, Heijnen C, Macklon N. Uterine secretomics: a window on the maternal-embryo interface. *Fertil Steril*. 2013; 99:1093–1099. [PubMed: 23433513]
- Christensen S, Verhage HG, Nowak G, de Lanerolle P, Fleming S, Bell SC, et al. Smooth muscle myosin II and alpha smooth muscle actin expression in the baboon (*Papio anubis*) uterus is associated with glandular secretory activity and stromal cell transformation. *Biol Reprod*. 1995; 53:598–608. [PubMed: 7578684]
- Christian M, Pohnke Y, Kempf R, Gellersen B, Brosens JJ. Functional association of PR and CCAAT/enhancer-binding protein beta isoforms: promoter-dependent cooperation between PR-B and liver-enriched inhibitory protein, or liver-enriched activatory protein and PR-A in human endometrial stromal cells. *Mol Endocrinol*. 2002a; 16:141–154. [PubMed: 11773445]
- Christian M, Zhang X, Schneider-Merck T, Unterman TG, Gellersen B, White JO, et al. Cyclic AMP-induced forkhead transcription factor, FKHR, cooperates with CCAAT/enhancer-binding protein beta in differentiating human endometrial stromal cells. *J Biol Chem*. 2002b; 277:20825–20832. [PubMed: 11893744]
- de Ziegler D, Fanchin R, de Moustier B, Bulletti C. The hormonal control of endometrial receptivity: estrogen (E2) and progesterone. *J Reprod Immunol*. 1998; 39:149–166. [PubMed: 9786459]
- Diaz-Gimeno P, Horcajadas JA, Martinez-Conejero JA, Esteban FJ, Alama P, Pellicer A, et al. A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature. *Fertil Steril*. 2011; 95:50–60. 60.e51–15. [PubMed: 20619403]
- Diaz-Gimeno P, Ruiz-Alonso M, Blesa D, Bosch N, Martinez-Conejero JA, Alama P, et al. The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity. *Fertil Steril*. 2013; 99:508–517. [PubMed: 23102856]
- Diaz-Gimeno P, Ruiz-Alonso M, Blesa D, Simon C. Transcriptomics of the human endometrium. *Int J Dev Biol*. 2014; 58:127–137. [PubMed: 25023678]
- Dimitriadis E, White CA, Jones RL, Salamonsen LA. Cytokines, chemokines and growth factors in endometrium related to implantation. *Hum Reprod Update*. 2005; 11:613–630. [PubMed: 16006437]
- Dockery P, Bermingham J, Jenkins D. Structure-function relations in the human placenta. *Biochem Soc Trans*. 2000; 28:202–208. [PubMed: 10816128]
- Donaghy M, Lessey BA. Uterine receptivity: alterations associated with benign gynecological disease. *Semin Reprod Med*. 2007; 25:461–475. [PubMed: 17960531]
- Dorofeyeva LV. Obtaining of measles virus haemagglutinin from strain L-16 grown in primary cell cultures. *Acta Virol*. 1975; 19:497. [PubMed: 1998]
- Dunn CL, Kelly RW, Critchley HO. Decidualization of the human endometrial stromal cell: an enigmatic transformation. *Reprod Biomed Online*. 2003; 7:151–161. [PubMed: 14567882]
- Edwards RG. Human implantation: the last barrier in assisted reproduction technologies? *Reprod Biomed Online*. 2006; 13:887–904. [PubMed: 17169215]
- Enders AC. Current topic: structural responses of the primate endometrium to implantation. *Placenta*. 1991; 12:309–325. [PubMed: 1946242]
- Enders AC, Hendrickx AG, Schlafke S. Implantation in the rhesus monkey: initial penetration of endometrium. *Am J Anat*. 1983; 167:275–298. [PubMed: 6881070]
- Enders AC, Lantz KC, Schlafke S. Preference of invasive cytotrophoblast for maternal vessels in early implantation in the macaque. *Acta Anat (Basel)*. 1996; 155:145–162. [PubMed: 8870783]
- Enders AC, Lantz KC, Peterson PE, Hendrickx AG. From blastocyst to placenta: the morphology of implantation in the baboon. *Hum Reprod Update*. 1997; 3:561–573. [PubMed: 9584946]
- Estella C, Herrero I, Moreno-Moya JM, Quinonero A, Martinez S, Pellicer A, et al. miRNA signature and Dicer requirement during human endometrial stromal decidualization in vitro. *PLoS One*. 2012; 7:e41080. [PubMed: 22911744]
- Fazleabas AT, Bell SC, Fleming S, Sun J, Lessey BA. Distribution of integrins and the extracellular matrix proteins in the baboon endometrium during the menstrual cycle and early pregnancy. *Biol Reprod*. 1997a; 56:348–356. [PubMed: 9116133]

- Fazleabas AT, Donnelly KM, Hild-Petito S, Hausermann HM, Verhage HG. Secretory proteins of the baboon (*Papio anubis*) endometrium: regulation during the menstrual cycle and early pregnancy. *Hum Reprod Update*. 1997b; 3:553–559. [PubMed: 9584945]
- Fazleabas AT, Donnelly KM, Srinivasan S, Fortman JD, Miller JB. Modulation of the baboon (*Papio anubis*) uterine endometrium by chorionic gonadotrophin during the period of uterine receptivity. *Proc Natl Acad Sci U S A*. 1999a; 96:2543–2548. [PubMed: 10051679]
- Fazleabas AT, Kim JJ, Srinivasan S, Donnelly KM, Brudney A, Jaffe RC. Implantation in the baboon: endometrial responses. *Semin Reprod Endocrinol*. 1999b; 17:257–265. [PubMed: 10797944]
- Fazleabas AT, Kim JJ, Strakova Z. Implantation: embryonic signals and the modulation of the uterine environment—a review. *Placenta*. 2004; 25(Suppl A):S26–S31. [PubMed: 15033303]
- Fortman JD, Herring JM, Miller JB, Hess DL, Verhage HG, Fazleabas AT. Chorionic gonadotropin, estradiol, and progesterone levels in baboons (*Papio anubis*) during early pregnancy and spontaneous abortion. *Biol Reprod*. 1993; 49:737–742. [PubMed: 8218636]
- Fu B, Li X, Sun R, Tong X, Ling B, Tian Z, et al. Natural killer cells promote immune tolerance by regulating inflammatory TH17 cells at the human maternal-fetal interface. *Proc Natl Acad Sci U S A*. 2013; 110:E231–E240. [PubMed: 23271808]
- Gao J, Mazella J, Tang M, Tseng L. Ligand-activated progesterone receptor isoform hPR-A is a stronger transactivator than hPR-B for the expression of IGFBP-1 (insulin-like growth factor binding protein-1) in human endometrial stromal cells. *Mol Endocrinol*. 2000; 14:1954–1961. [PubMed: 11117526]
- Gellersen B, Brosens JJ. Cyclic decidualization of the human endometrium in reproductive health and failure. *Endocr Rev*. 2014; 35:851–905. [PubMed: 25141152]
- Gellersen B, Brosens IA, Brosens JJ. Decidualization of the human endometrium: mechanisms, functions, and clinical perspectives. *Semin Reprod Med*. 2007; 25:445–453. [PubMed: 17960529]
- Genbacev OD, Prakobphol A, Foulk RA, Krtolica AR, Ilic D, Singer MS, et al. Trophoblast L-selectin-mediated adhesion at the maternal-fetal interface. *Science*. 2003; 299:405–408. [PubMed: 12532021]
- Giudice LC. Potential biochemical markers of uterine receptivity. *Hum Reprod*. 1999; 14(Suppl 2):3–16. [PubMed: 10690796]
- Gordon M. Cyclic changes in the fine structure of the epithelial cells of human endometrium. *Int Rev Cytol*. 1975; 42:127–172. [PubMed: 172466]
- Graham CH, Lala PK. Mechanism of control of trophoblast invasion in situ. *J Cell Physiol*. 1991; 148:228–234. [PubMed: 1652588]
- Graham CH, Lysiak JJ, McCrae KR, Lala PK. Localization of transforming growth factor-beta at the human fetal-maternal interface: role in trophoblast growth and differentiation. *Biol Reprod*. 1992; 46:561–572. [PubMed: 1374270]
- Grewal S, Carver JG, Ridley AJ, Mardon HJ. Implantation of the human embryo requires Rac1-dependent endometrial stromal cell migration. *Proc Natl Acad Sci U S A*. 2008; 105:16189–16194. [PubMed: 18838676]
- Grewal S, Carver J, Ridley AJ, Mardon HJ. Human endometrial stromal cell rho GTPases have opposing roles in regulating focal adhesion turnover and embryo invasion in vitro. *Biol Reprod*. 2010; 83:75–82. [PubMed: 20357266]
- Grinius L, Kessler C, Schroeder J, Handwerger S. Forkhead transcription factor FOXO1A is critical for induction of human decidualization. *J Endocrinol*. 2006; 189:179–187. [PubMed: 16614392]
- Hallaq R, Volpicelli F, Cuchillo-Ibanez I, Hooper C, Mizuno K, Uwanogho D, et al. The Notch intracellular domain represses CRE-dependent transcription. *Cell Signal*. 2015; 27:621–629. [PubMed: 25479589]
- Hara M, Kingsley CI, Niimi M, Read S, Turvey SE, Bushell AR, et al. IL-10 is required for regulatory T cells to mediate tolerance to alloantigens in vivo. *J Immunol*. 2001; 166:3789–3796. [PubMed: 11238621]
- Hausermann HM, Donnelly KM, Bell SC, Verhage HG, Fazleabas AT. Regulation of the glycosylated beta-lactoglobulin homolog, glycodelin [placental protein 14:(PP14)] in the baboon (*Papio anubis*) uterus. *J Clin Endocrinol Metab*. 1998; 83:1226–1233. [PubMed: 9543146]

- Hertig AT. Gestational hyperplasia of endometrium; a morphologic correlation ova, endometrium, and corpora lutea during early pregnancy. *Lab Invest.* 1964; 13:1153–1191. [PubMed: 14212348]
- Hertig AT, Rock J, Adams EC. A description of 34 human ova within the first 17 days of development. *Am J Anat.* 1956; 98:435–493. [PubMed: 13362122]
- Hey NA, Graham RA, Seif MW, Aplin JD. The polymorphic epithelial mucin MUC1 in human endometrium is regulated with maximal expression in the implantation phase. *J Clin Endocrinol Metab.* 1994; 78:337–342. [PubMed: 8106621]
- Higuchi T, Kanzaki H, Nakayama H, Fujimoto M, Hatayama H, Kojima K, et al. Induction of tissue inhibitor of metalloproteinase 3 gene expression during in vitro decidualization of human endometrial stromal cells. *Endocrinology.* 1995; 136:4973–4981. [PubMed: 7588231]
- Hild-Petito S, Fazleabas AT, Julian J, Carson DD. Mucin (Muc-1) expression is differentially regulated in uterine luminal and glandular epithelia of the baboon (*Papio anubis*). *Biol Reprod.* 1996; 54:939–947. [PubMed: 8722612]
- Hjollund NH, Jensen TK, Bonde JP, Henriksen TB, Andersson AM, Kolstad HA, et al. Spontaneous abortion and physical strain around implantation: a follow-up study of first-pregnancy planners. *Epidemiology.* 2000; 11:18–23. [PubMed: 10615838]
- Horcajadas JA, Riesewijk A, Polman J, van Os R, Pellicer A, Mosselman S, et al. Effect of controlled ovarian hyperstimulation in IVF on endometrial gene expression profiles. *Mol Hum Reprod.* 2005; 11:195–205. [PubMed: 15695772]
- Horcajadas JA, Pellicer A, Simon C. Wide genomic analysis of human endometrial receptivity: new times, new opportunities. *Hum Reprod Update.* 2007; 13:77–86. [PubMed: 16960016]
- Houston ML. The villous period of placentogenesis in the baboon (*Papio sp.*). *Am J Anat.* 1969; 126:1–15. [PubMed: 4982041]
- Jasinska A, Han V, Fazleabas AT, Kim JJ. Induction of insulin-like growth factor binding protein-1 expression in baboon endometrial stromal cells by cells of trophoblast origin. *J Soc Gynecol Investig.* 2004; 11:399–405.
- Jasinska A, Strakova Z, Szmidi M, Fazleabas AT. Human chorionic gonadotropin and decidualization in vitro inhibits cytochalasin-D-induced apoptosis in cultured endometrial stromal fibroblasts. *Endocrinology.* 2006; 147:4112–4121. [PubMed: 16740972]
- Jones CJ, Fazleabas AT. Ultrastructure of epithelial plaque formation and stromal cell transformation by post-ovulatory chorionic gonadotrophin treatment in the baboon (*Papio anubis*). *Hum Reprod.* 2001; 16:2680–2690. [PubMed: 11726596]
- Kao LC, Tulac S, Lobo S, Imani B, Yang JP, Germeyer A, et al. Global gene profiling in human endometrium during the window of implantation. *Endocrinology.* 2002; 143:2119–2138. [PubMed: 12021176]
- Karow WG, Gentry WC, Skeels RF, Payne SA. Endometrial biopsy in the luteal phase of the cycle of conception. *Fertil Steril.* 1971; 22:482–495. [PubMed: 5110231]
- Kaspereit J, Friderichs-Gromoll S, Buse E, Habermann G, Vogel F. Spontaneous epithelial plaques in the uterus of a non-pregnant cynomolgus monkey (*Macaca fascicularis*). *Exp Toxicol Pathol.* 2004; 56:9–12. [PubMed: 15581270]
- Kayisli UA, Selam B, Guzeloglu-Kayisli O, Demir R, Arici A. Human chorionic gonadotropin contributes to maternal immunotolerance and endometrial apoptosis by regulating Fas-Fas ligand system. *J Immunol.* 2003; 171:2305–2313. [PubMed: 12928375]
- Kim JJ, Jaffe RC, Fazleabas AT. Comparative studies on the in vitro decidualization process in the baboon (*Papio anubis*) and human. *Biol Reprod.* 1998; 59:160–168. [PubMed: 9675007]
- Kim JJ, Jaffe RC, Fazleabas AT. Blastocyst invasion and the stromal response in primates. *Hum Reprod.* 1999a; 14(Suppl 2):45–55. [PubMed: 10690800]
- Kim JJ, Jaffe RC, Fazleabas AT. Insulin-like growth factor binding protein-1 expression in baboon endometrial stromal cells: regulation by filamentous actin and requirement for de novo protein synthesis. *Endocrinology.* 1999b; 140:997–1004. [PubMed: 9927334]
- Kim JJ, Buzzio OL, Li S, Lu Z. Role of FOXO1A in the regulation of insulin-like growth factor-binding protein-1 in human endometrial cells: interaction with progesterone receptor. *Biol Reprod.* 2005; 73:833–839. [PubMed: 15987820]

- Koopman LA, Kopcow HD, Rybalov B, Boyson JE, Orange JS, Schatz F, et al. Human decidual natural killer cells are a unique NK cell subset with immunomodulatory potential. *J Exp Med*. 2003; 198:1201–1212. [PubMed: 14568979]
- Koot YE, Macklon NS. Embryo implantation: biology, evaluation, and enhancement. *Curr Opin Obstet Gynecol*. 2013; 25:274–279. [PubMed: 23787799]
- Koot YE, Teklenburg G, Salker MS, Brosens JJ, Macklon NS. Molecular aspects of implantation failure. *Biochim Biophys Acta*. 2012; 1822:1943–1950. [PubMed: 22683339]
- Kopcow HD, Rosetti F, Leung Y, Allan DS, Kutok JL, Strominger JL. T cell apoptosis at the maternal-fetal interface in early human pregnancy, involvement of galectin-1. *Proc Natl Acad Sci U S A*. 2008; 105:18472–18477. [PubMed: 19011096]
- Kusama K, Yoshie M, Tamura K, Nakayama T, Nishi H, Isaka K, et al. The role of exchange protein directly activated by cyclic AMP 2-mediated calreticulin expression in the decidualization of human endometrial stromal cells. *Endocrinology*. 2014; 155:240–248. [PubMed: 24169561]
- Labied S, Kajihara T, Madureira PA, Fusi L, Jones MC, Higham JM, et al. Progestins regulate the expression and activity of the forkhead transcription factor FOXO1 in differentiating human endometrium. *Mol Endocrinol*. 2006; 20:35–44. [PubMed: 16123151]
- Lawn AM, Wilson EW, Finn CA. The ultrastructure of human decidual and predecidual cells. *J Reprod Fertil*. 1971; 26:85–90. [PubMed: 5091297]
- Lessey BA. Adhesion molecules and implantation. *J Reprod Immunol*. 2002; 55:101–112. [PubMed: 12062825]
- Lessey BA. Assessment of endometrial receptivity. *Fertil Steril*. 2011; 96:522–529. [PubMed: 21880273]
- Lessey BA, Gui Y, Apparao KB, Young SL, Mulholland J. Regulated expression of heparin-binding EGF-like growth factor (HB-EGF) in the human endometrium: a potential paracrine role during implantation. *Mol Reprod Dev*. 2002; 62:446–455. [PubMed: 12112577]
- Lewis MP, Morlese JF, Sullivan MH, Elder MG. Evidence for decidua-trophoblast interactions in early human pregnancy. *Hum Reprod*. 1993; 8:965–968. [PubMed: 8345092]
- Li Q, Kannan A, Wang W, Demayo FJ, Taylor RN, Bagchi MK, et al. Bone morphogenetic protein 2 functions via a conserved signaling pathway involving Wnt4 to regulate uterine decidualization in the mouse and the human. *J Biol Chem*. 2007; 282:31725–31732. [PubMed: 17711857]
- Li Q, Kannan A, Das A, Demayo FJ, Hornsby PJ, Young SL, et al. WNT4 acts downstream of BMP2 and functions via beta-catenin signaling pathway to regulate human endometrial stromal cell differentiation. *Endocrinology*. 2013; 154:446–457. [PubMed: 23142810]
- Librach CL, Werb Z, Fitzgerald ML, Chiu K, Corwin NM, Esteves RA, et al. 92-kD type IV collagenase mediates invasion of human cytotrophoblasts. *J Cell Biol*. 1991; 113:437–449. [PubMed: 1849141]
- Librach CL, Feigenbaum SL, Bass KE, Cui TY, Verastas N, Sadovsky Y, et al. Interleukin-1 beta regulates human cytotrophoblast metalloproteinase activity and invasion in vitro. *J Biol Chem*. 1994; 269:17125–17131. [PubMed: 8006017]
- Lindenberg S. Experimental studies on the initial trophoblast endometrial interaction. *Dan Med Bull*. 1991; 38:371–380. [PubMed: 1802622]
- Lovely LP, Fazleabas AT, Fritz MA, McAdams DG, Lessey BA. Prevention of endometrial apoptosis: randomized prospective comparison of human chorionic gonadotropin versus progesterone treatment in the luteal phase. *J Clin Endocrinol Metab*. 2005; 90:2351–2356. [PubMed: 15671112]
- Lu Z, Hardt J, Kim JJ. Global analysis of genes regulated by HOXA10 in decidualization reveals a role in cell proliferation. *Mol Hum Reprod*. 2008; 14:357–366. [PubMed: 18456676]
- Mansour R, Tawab N, Kamal O, El-Faissal Y, Serour A, Aboulghar M, et al. Intrauterine injection of human chorionic gonadotropin before embryo transfer significantly improves the implantation and pregnancy rates in in vitro fertilization/intracytoplasmic sperm injection: a prospective randomized study. *Fertil Steril*. 2011; 96:1370–1374. e1371. [PubMed: 22047664]
- Mirkin S, Nikas G, Hsiu JG, Diaz J, Oehninger S. Gene expression profiles and structural/functional features of the peri-implantation endometrium in natural and gonadotropin-stimulated cycles. *J Clin Endocrinol Metab*. 2004; 89:5742–5752. [PubMed: 15531538]

- Mirkin S, Arslan M, Churikov D, Corica A, Diaz JJ, Williams S, et al. In search of candidate genes critically expressed in the human endometrium during the window of implantation. *Hum Reprod.* 2005; 20:2104–2117. [PubMed: 15878921]
- Nardo LG, Nikas G, Makrigiannakis A, Sinatra F, Nardo F. Synchronous expression of pinopodes and alpha v beta 3 and alpha 4 beta 1 integrins in the endometrial surface epithelium of normally menstruating women during the implantation window. *J Reprod Med.* 2003; 48:355–361. [PubMed: 12815909]
- Nikas G. Cell-surface morphological events relevant to human implantation. *Hum Reprod.* 1999; 14(Suppl 2):37–44. [PubMed: 10690799]
- Nikas G, Aghajanova L. Endometrial pinopodes: some more understanding on human implantation? *Reprod Biomed Online.* 2002; 4(Suppl 3):18–23.
- Norwitz ER, Schust DJ, Fisher SJ. Implantation and the survival of early pregnancy. *N Engl J Med.* 2001; 345:1400–1408. [PubMed: 11794174]
- Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. *Fertil Steril.* 1950; 1:3–25.
- Owiti GE, Cukierski M, Tarara RP, Enders AC, Hendrickx AG. Early placentation in the African green monkey (*Cercopithecus aethiops*). *Acta Anat (Basel).* 1986; 127:184–194. [PubMed: 3788465]
- Pabona JM, Zeng Z, Simmen FA, Simmen RC. Functional differentiation of uterine stromal cells involves cross-regulation between bone morphogenetic protein 2 and Kruppel-like factor (KLF) family members KLF9 and KLF13. *Endocrinology.* 2010; 151:3396–3406. [PubMed: 20410205]
- Plevyak M, Hanna N, Mayer S, Murphy S, Pinar H, Fast L, et al. Deficiency of decidual IL-10 in first trimester missed abortion: a lack of correlation with the decidual immune cell profile. *Am J Reprod Immunol.* 2002; 47:242–250. [PubMed: 12069391]
- Popovici RM, Kao LC, Giudice LC. Discovery of new inducible genes in in vitro decidualized human endometrial stromal cells using microarray technology. *Endocrinology.* 2000; 141:3510–3513. [PubMed: 10965925]
- Pritchard, JA.; MacDonald, PC.; Gant, NF., editors. *Williams obstetrics.* 17. Vol. Chapter 6. Appleton & Lange; Norwalk: 1985. The placenta and fetal membranes; p. 97–117.
- Psychoyos A. Hormonal control of ovoid implantation. *Vitam Horm.* 1973; 31:201–256. [PubMed: 4620375]
- Psychoyos A. Uterine receptivity for nidation. *Ann N Y Acad Sci.* 1986; 476:36–42. [PubMed: 3541745]
- Qian K, Hu L, Chen H, Li H, Liu N, Li Y, et al. Hsa-miR-222 is involved in differentiation of endometrial stromal cells in vitro. *Endocrinology.* 2009; 150:4734–4743. [PubMed: 19589872]
- Rachmilewitz J, Borovsky Z, Riely GJ, Miller R, Tykocinski ML. Negative regulation of T cell activation by placental protein 14 is mediated by the tyrosine phosphatase receptor CD45. *J Biol Chem.* 2003; 278:14059–14065. [PubMed: 12556471]
- Ramathal CY, Bagchi IC, Taylor RN, Bagchi MK. Endometrial decidualization: of mice and men. *Semin Reprod Med.* 2010; 28:17–26. [PubMed: 20104425]
- Ramsey EM, Houston ML, Harris JW. Interactions of the trophoblast and maternal tissues in three closely related primate species. *Am J Obstet Gynecol.* 1976; 124:647–652. [PubMed: 816200]
- Reddy KV, Mangale SS. Integrin receptors: the dynamic modulators of endometrial function. *Tissue Cell.* 2003; 35:260–273. [PubMed: 12921709]
- Reshef E, Lei ZM, Rao CV, Pridham DD, Chegini N, Luborsky JL. The presence of gonadotropin receptors in nonpregnant human uterus, human placenta, fetal membranes, and decidua. *J Clin Endocrinol Metab.* 1990; 70:421–430. [PubMed: 1688865]
- Richards RG, Brar AK, Frank GR, Hartman SM, Jikihara H. Fibroblast cells from term human decidua closely resemble endometrial stromal cells: induction of prolactin and insulin-like growth factor binding protein-1 expression. *Biol Reprod.* 1995; 52:609–615. [PubMed: 7756454]
- Rieger L, Honig A, Sutterlin M, Kapp M, Dietl J, Ruck P, et al. Antigen-presenting cells in human endometrium during the menstrual cycle compared to early pregnancy. *J Soc Gynecol Investig.* 2004; 11:488–493.
- Rieseewijk A, Martin J, van Os R, Horcajadas JA, Polman J, Pellicer A, et al. Gene expression profiling of human endometrial receptivity on days LH + 2 versus LH + 7 by microarray technology. *Mol Hum Reprod.* 2003; 9:253–264. [PubMed: 12728018]

- Rizzo P, Miao H, D'Souza G, Osipo C, Song LL, Yun J, et al. Cross-talk between notch and the estrogen receptor in breast cancer suggests novel therapeutic approaches. *Cancer Res.* 2008; 68:5226–5235. [PubMed: 18593923]
- Rosario GX, Modi DN, Sachdeva G, Manjramkar DD, Puri CP. Morphological events in the primate endometrium in the presence of a preimplantation embryo, detected by the serum pre-implantation factor bioassay. *Hum Reprod.* 2005; 20:61–71. [PubMed: 15576397]
- Sasaki Y, Sakai M, Miyazaki S, Higuma S, Shiozaki A, Saito S. Decidual and peripheral blood CD4 + CD25+ regulatory T cells in early pregnancy subjects and spontaneous abortion cases. *Mol Hum Reprod.* 2004; 10:347–353. [PubMed: 14997000]
- Sharma A, Kumar P. Understanding implantation window, a crucial phenomenon. *J Hum Reprod Sci.* 2012; 5:2–6. [PubMed: 22870007]
- Sherwin JR, Sharkey AM, Cameo P, Mavrogianis PM, Catalano RD, Edassery S, et al. Identification of novel genes regulated by chorionic gonadotropin in baboon endometrium during the window of implantation. *Endocrinology.* 2007; 148:618–626. [PubMed: 17110430]
- Shimonovitz S, Hurwitz A, Dushnik M, Anteby E, Geva-Eldar T, Yagel S. Developmental regulation of the expression of 72 and 92 kd type IV collagenases in human trophoblasts: a possible mechanism for control of trophoblast invasion. *Am J Obstet Gynecol.* 1994; 171:832–838. [PubMed: 7522400]
- Spessotto P, Bulla R, Danussi C, Radillo O, Cervi M, Monami G, et al. EMILIN1 represents a major stromal element determining human trophoblast invasion of the uterine wall. *J Cell Sci.* 2006; 119:4574–4584. [PubMed: 17074837]
- Srisuparp S, Strakova Z, Fazleabas AT. The role of chorionic gonadotropin (CG) in blastocyst implantation. *Arch Med Res.* 2001; 32:627–634. [PubMed: 11750740]
- Srisuparp S, Strakova Z, Brudney A, Mukherjee S, Reierstad S, Hunzicker-Dunn M, et al. Signal transduction pathways activated by chorionic gonadotropin in the primate endometrial epithelial cells. *Biol Reprod.* 2003; 68:457–464. [PubMed: 12533408]
- Stavreus-Evers A, Aghajanova L, Brismar H, Eriksson H, Landgren BM, Hovatta O. Co-existence of heparin-binding epidermal growth factor-like growth factor and pinopodes in human endometrium at the time of implantation. *Mol Hum Reprod.* 2002; 8:765–769. [PubMed: 12149409]
- Strakova Z, Srisuparp S, Fazleabas AT. Interleukin-1beta induces the expression of insulin-like growth factor binding protein-1 during decidualization in the primate. *Endocrinology.* 2000; 141:4664–4670. [PubMed: 11108281]
- Strakova Z, Srisuparp S, Fazleabas AT. IL-1beta during in vitro decidualization in primate. *J Reprod Immunol.* 2002; 55:35–47. [PubMed: 12062820]
- Strakova Z, Szmidi M, Srisuparp S, Fazleabas AT. Inhibition of matrix metalloproteinases prevents the synthesis of insulin-like growth factor binding protein-1 during decidualization in the baboon. *Endocrinology.* 2003; 144:5339–5346. [PubMed: 12960035]
- Strakova Z, Mavrogianis P, Meng X, Hastings JM, Jackson KS, Cameo P, et al. In vivo infusion of interleukin-1beta and chorionic gonadotropin induces endometrial changes that mimic early pregnancy events in the baboon. *Endocrinology.* 2005; 146:4097–4104. [PubMed: 15932926]
- Su RW, Strug MR, Joshi NR, Jeong JW, Miele L, Lessey BA, et al. Decreased Notch pathway signaling in the endometrium of women with endometriosis impairs decidualization. *J Clin Endocrinol Metab.* 2015; 100:E433–E442. [PubMed: 25546156]
- SundarRaj S, Mukhopadhyay D, Karande AA. Glycodelin A triggers mitochondrial stress and apoptosis in T cells by a mechanism distinct and independent of TCR signaling. *Mol Immunol.* 2008; 45:2391–2400. [PubMed: 18155767]
- Takano M, Lu Z, Goto T, Fusi L, Higham J, Francis J, et al. Transcriptional cross talk between the forkhead transcription factor forkhead box O1A and the progesterone receptor coordinates cell cycle regulation and differentiation in human endometrial stromal cells. *Mol Endocrinol.* 2007; 21:2334–2349. [PubMed: 17609436]
- Tanaka N, Miyazaki K, Tashiro H, Mizutani H, Okamura H. Changes in adenylyl cyclase activity in human endometrium during the menstrual cycle and in human decidua during pregnancy. *J Reprod Fertil.* 1993; 98:33–39. [PubMed: 8345477]

- Tang B, Gurpide E. Direct effect of gonadotropins on decidualization of human endometrial stroma cells. *J Steroid Biochem Mol Biol*. 1993; 47:115–121. [PubMed: 8274425]
- Tarantino S, Verhage HG, Fazleabas AT. Regulation of insulin-like growth factor-binding proteins in the baboon (*Papio anubis*) uterus during early pregnancy. *Endocrinology*. 1992; 130:2354–2362. [PubMed: 1372242]
- Tarara R, Enders AC, Hendrickx AG, Gulamhusein N, Hodges JK, Hearn JP, et al. Early implantation and embryonic development of the baboon: stages 5, 6 and 7. *Anat Embryol (Berl)*. 1987; 176:267–275. [PubMed: 3631530]
- Tilburgs T, Roelen DL, van der Mast BJ, de Groot-Swings GM, Kleijburg C, Scherjon SA, et al. Evidence for a selective migration of fetus-specific CD4 + CD25bright regulatory T cells from the peripheral blood to the decidua in human pregnancy. *J Immunol*. 2008; 180:5737–5745. [PubMed: 18390759]
- Valles CS, Dominguez F. Embryo-endometrial interaction. *Chang Gung Med J*. 2006; 29:9–14. [PubMed: 16642724]
- Vasquez YM, Mazur EC, Li X, Kommagani R, Jiang L, Chen R, et al. FOXO1 is required for binding of PR on IRF4, novel transcriptional regulator of endometrial stromal decidualization. *Mol Endocrinol*. 2015; 29:421–433. [PubMed: 25584414]
- Vassiliadou N, Bulmer JN. Characterization of tubal and decidual leukocyte populations in ectopic pregnancy: evidence that endometrial granulated lymphocytes are absent from the tubal implantation site. *Fertil Steril*. 1998; 69:760–767. [PubMed: 9548170]
- Vinatier D, Monnier JC. The fetal-maternal interface. Description of its elements from an immunologic perspective. *J Gynecol Obstet Biol Reprod (Paris)*. 1990; 19:691–700. [PubMed: 2258587]
- Weimar CH, Macklon NS, Post Uiterweer ED, Brosens JJ, Gellersen B. The motile and invasive capacity of human endometrial stromal cells: implications for normal and impaired reproductive function. *Hum Reprod Update*. 2013; 19:542–557. [PubMed: 23827985]
- Wentz AC, Herbert CM 3rd, Maxson WS, Hill GA, Pittaway DE. Cycle of conception endometrial biopsy. *Fertil Steril*. 1986; 46:196–199. [PubMed: 3732525]
- Wewer UM, Faber M, Liotta LA, Albrechtsen R. Immunochemical and ultrastructural assessment of the nature of the pericellular basement membrane of human decidual cells. *Lab Invest*. 1985; 53:624–633. [PubMed: 2415774]
- Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. *N Engl J Med*. 1999; 340:1796–1799. [PubMed: 10362823]
- Wynn RM. Ultrastructural development of the human decidua. *Am J Obstet Gynecol*. 1974; 118:652–670. [PubMed: 4813806]
- Xiong H, Zhou C, Qi G. Proportional changes of CD4 + CD25 + Foxp3+ regulatory T cells in maternal peripheral blood during pregnancy and labor at term and preterm. *Clin Invest Med*. 2010; 33:E422. [PubMed: 21134345]
- Yang H, Zhou Y, Edelshain B, Schatz F, Lockwood CJ, Taylor HS. FKBP4 is regulated by HOXA10 during decidualization and in endometriosis. *Reproduction*. 2012; 143:531–538. [PubMed: 22279148]
- Zhou XL, Lei ZM, Rao CV. Treatment of human endometrial gland epithelial cells with chorionic gonadotropin/luteinizing hormone increases the expression of the cyclooxygenase-2 gene. *J Clin Endocrinol Metab*. 1999; 84:3364–3377. [PubMed: 10487712]

Fig. 10.1.

Endometrial responses to the embryonic signal in primates. Epithelial and stromal cells respond to chorionic gonadotropin (*CG*) and interleukin 1 β (*IL-1 β*) during the establishment of pregnancy in the primates. Inserts *A* and *B* reflect the changes in epithelial and stromal cell responses which are described in detail in expanded form in Panels (**a**) and (**b**)