



## Review

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# Fibroblast growth factors and endometrial decidualization: models, mechanisms, and related pathologies

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**Abstract:** The onset of pregnancy is marked by the formation of a zygote, while the culmination of gestation is manifested by the delivery of a fetus. Meanwhile, a successful pregnancy entails a meticulously coordinated sequence of events from embryo implantation to sustained decidualization of the uterus to placental development and childbirth. The decidual reaction, a pivotal process occurring within the endometrium during pregnancy, is finely regulated by sex steroids and cytokines. Notably, fibroblast growth factors (FGFs), particularly FGF2, play a critical role in this physiological cascade. Dysregulated FGF expression may trigger inadequate decidualization, precipitating a spectrum of adverse pregnancy outcomes, including preeclampsia, recurrent implantation failure, and miscarriage. Furthermore, the human decidua, distinct from most mammalian species and similar to great apes, undergoes regular cycles of formation and shedding, independent of the presence of the embryo in the endometrium. This process is also tightly controlled by various FGFs. In this review, we comprehensively compare diverse research decidualization models, delineate the trend of endometrial FGFs during the menstrual cycle, and provide a synopsis of endometrial diseases triggered by FGF dysregulation.

**Key words:** Fibroblast growth factor (FGF); Decidualization; Pregnancy; Adverse pregnancy outcome

## 1 Introduction

The transition from oviparity to viviparity is an important evolutionary leap, which profoundly alters the reproductive process: embryos are no longer expelled from the mother's body but instead remain inside it, where they can receive the nutrients essential for development. However, the embryo may be recognized as foreign and invasive by the host body (the mother); thus a delicate balance between nutrition and ensuring the safety of the mother during pregnancy is necessary. As a result, viviparous animals have evolved a unique organ to house embryos—the uterus. Decidualization is a major remodeling event in the uterus

and is critical for the regulation of embryo implantation and placentation. In most mammalian species, endometrial decidualization is initiated upon embryo implantation. However, in humans and several other species, this physiological process occurs both during embryo implantation and during the menstrual cycle (Emera et al., 2012; Evans et al., 2016). Once decidualization commences, endometrial stromal cells undergo irreversible differentiation, with the spatiotemporal progression of this process tightly controlled by various morphogens and cytokines, including members of the fibroblast growth factor (FGF) family (Bhurke et al., 2016; Murata et al., 2022).

The FGF family includes structurally related polypeptides that play essential roles in embryonic development and postnatal homeostasis of cellular function. In mammals, it comprises 22 members, FGF1–FGF23, with FGF15 being the mouse ortholog of human FGF19. In addition to FGF11–FGF14 (also known as FGF homolog factors), other members perform their biological functions by activating FGF

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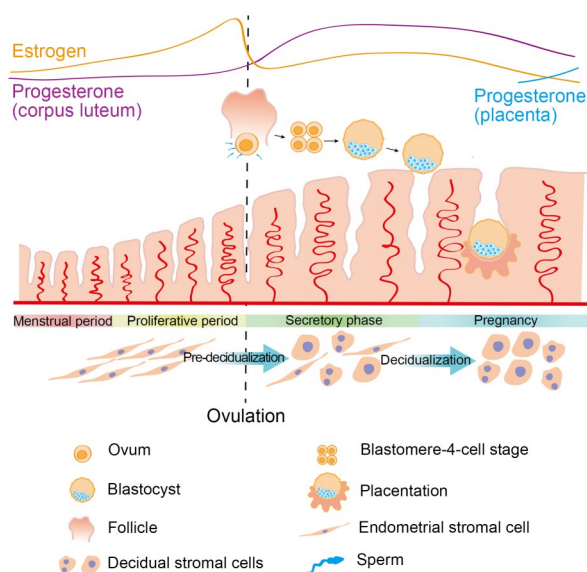
receptors (FGFRs) in a paracrine or endocrine manner (Zhang et al., 2006; Fang et al., 2022). To date, a total of four main subtypes have been identified, namely, FGFR1–FGFR4. After ligands bind to FGFRs, they dimerize and activate subsequent signaling pathways, including the phospholipase C $\gamma$  (PLC $\gamma$ ), Ras–mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT) pathways (Li et al., 2016). FGF-FGFR signaling participates in the regulation of the decidualization process, with various FGF and FGFR subtypes exhibiting different temporal and spatial expression patterns (Figuroa et al., 2019). Moreover, dysregulation of FGF-FGFR signaling can contribute to pathological conditions, which can result in adverse pregnancy outcomes.

In this review, we briefly summarize the current knowledge regarding models of decidualization and discuss the biological and pathological mechanisms and recent developments related to the regulation of decidualization by FGFs.

## 2 Decidualization of the endometrium

Decidualization is a vital event for the successful establishment and maintenance of pregnancy. In this process, under stimulation by sex hormone signals, endometrial stromal cells undergo DNA replication but not cytokinesis, which leads to multinucleation and polyploid cell formation (Qi et al., 2015; Tong et al., 2022). These changes occur throughout the entire endometrium, as an important step for embryo implantation, subsequent placenta formation, and the survival of the conceptus. From an evolutionary perspective, the decidua plays a unique function, preventing the embryo from being ignored by the mother's immune response and protecting the mother from excessive invasion by the placenta (Chavan et al., 2017). The initiation of the decidual process is dependent on the progesterone signaling pathway. It is accelerated by functional molecules, including corticotropin-releasing hormone (CRH), activin A, interleukin-11 (IL-11), matrix metalloproteinases (MMPs), and prostaglandin E $_2$ , and inhibited by inflammatory cytokines, including IL-1, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and macrophage colony-stimulating factor (M-CSF) (Salamonsen and Jones, 2003).

In humans, decidualization occurs spontaneously and periodically in the absence of pregnancy. Unlike in decidualization during embryo implantation, decidual cells that underlie the surface epithelium and surround the terminal spiral arteries begin to appear during the mid- to late-secretory phases of the menstrual cycle. In addition to a decrease in the progesterone concentration, inflammatory events are triggered in the decidualizing endometrium, resulting in partial tissue destruction and bleeding (Fig. 1) (Muter and Brosens, 2018).



**Fig. 1** Changes in hormone levels and endometrial stromal cells during implantation. During the menstrual cycle, the endometrium undergoes corresponding periodic changes. In the proliferative phase, estradiol levels continue to rise and the endometrium thickens. From the 14th day of the cycle, estradiol concentrations decrease rapidly and progesterone production increases. At this time, the follicle matures and ruptures, and secondary oocytes are released, marking the end of the proliferative phase and the onset of the secretory phase. With the formation of the corpus luteum, progesterone is continuously secreted, and endometrial stromal cells begin to pre-decidualize in preparation for embryo implantation (Baerwald et al., 2012; Conrad et al., 2017; Meng et al., 2023). On the 7th day after ovulation, the whole endometrium enters a brief period of pre-decidualization that allows the embedding of the embryo. After embryo implantation, the corpus luteum develops into the pregnant corpus luteum that continuously secretes progesterone, while endometrial stromal cells rapidly decidualize. Thereafter, the placenta gradually takes over the secretion of progesterone from the pregnant corpus luteum, while endometrial stromal cells continue to decidualize until the fetus is delivered (Jukic et al., 2013; Duncan, 2021).

### 3 Established models of decidualization

The decidualization of endometrial stromal cells is initialized by estradiol and progesterone, with the latter being the core driver of this event (Okada et al., 2018). Early in vitro studies often used the combination of estradiol and progesterone to induce decidualization in proliferating human endometrial cells and analyzed the prolactin (PRL) concentration to evaluate the differentiation of endometrial stromal cells. Typically, 10–20 d are required to induce decidualization by this method, especially in human cell lines (Tang et al., 2021). Subsequent studies have indicated that progesterone and cyclic adenosine monophosphate (cAMP) can significantly shorten the time required to induce human endometrial cell decidualization (Ran and Song, 2011; Kajihara et al., 2013; Tang et al., 2021). Therefore, estradiol and progesterone with/without cAMP are most frequently used in combination to induce decidualization (Table 1). The genes

*PRL* and insulin-like growth factor-binding protein 1 (*IGFBP1*) are used as markers of differentiation. During the process of decidualization, the expression levels of these two genes are generally increased by thousands and tens of thousands of times, respectively. Correspondingly, the concentrations of PRL and IGFBP1 gradually increase in the medium (Wu et al., 2017; Liu et al., 2020).

Mouse has been an important model animal for studying decidualization. Three types of mouse models of decidualization have been developed: (1) the natural pregnancy decidualization (NPD) model, wherein, on the 5th day of pregnancy, mouse blastocysts begin to be implanted in the endometrium and decidualization begins to occur in the contact area under blastocyst stimulation (Zhao et al., 2017); (2) the artificial decidualization (AD) model, which involves first treating mice with hormones and then artificially inducing the decidualization of mouse endometrium by mechanically stimulating the uterus or implanting embryonic

**Table 1 Approaches for inducing decidualization and markers for evaluating decidualization in human cells**

Cell type	Factor used to induce decidualization	Induction in vitro (d)	Marker	Reference
PhESCs	1 μmol/L MPA and 0.5 mmol/L cAMP	4	IGFBP1, dPRL, morphology	Pan-Castillo et al., 2018
PhESCs	3×10 <sup>-10</sup> mol/L estradiol and 5×10 <sup>-8</sup> mol/L progesterone	13	<i>PRL</i> , <i>IGFBP1</i> , <i>PRL</i> , IGFBP1	Wu et al., 2017
PhESCs	1 μmol/L progesterone and 30 nmol/L estradiol	9	<i>PRL</i> , morphology	Estella et al., 2012
PhESCs	0.5 mmol/L 8-Br-cAMP and 1 μmol/L MPA	5	<i>PRL</i> , morphology	Estella et al., 2012
PhESCs	Start with 1 μg/mL insulin and 1 nmol/L estradiol, and then treat with 0.5 mmol/L 8-Br-cAMP	4, 5	<i>PRL</i> , dPRL	Gellersen et al., 2010
PhESCs	0.5 mmol/L cAMP	5	<i>PRL</i>	Jones et al., 2002
PhESCs	1×10 <sup>-8</sup> mol/L estradiol and 1×10 <sup>-7</sup> mol/L progesterone	10	<i>PRL</i>	Jones et al., 2002
PhESCs	0.1 mg/mL 8-Br-cAMP and 1 mmol/L progesterone	1, 2, 4, 8	<i>PRL</i> , <i>IGFBP1</i> , <i>PRL</i> , IGFBP1	Gibson et al., 2016
PhESCs	200 pg/mL estradiol, 100 ng/mL progesterone, and 0.5 mmol/L 8-Br-cAMP	10	<i>PRL</i> , <i>IGFBP1</i>	Tanaka et al., 2003
PhESCs	10 nmol/L estradiol and 1 μmol/L progesterone	10	<i>PRL</i> , <i>IGFBP1</i>	Popovici et al., 2000
PhESCs	1 mmol/L 8-Br-cAMP	2	<i>PRL</i> , <i>IGFBP1</i>	Popovici et al., 2000
PhESCs	500 μmol/L db-cAMP and 1 mmol/L progesterone	2	<i>PRL</i> , <i>IGFBP1</i>	Kusama et al., 2021
CRL-4003	0.5 mmol/L 8-Br-cAMP and 1 mmol/L MPA	4, 8	<i>PRL</i> , <i>IGFBP1</i>	Rytkönen et al., 2019
CRL-4003	10 nmol/L estradiol, 1 μmol/L MPA, and 0.5 mmol/L db-cAMP	3	<i>PRL</i> , <i>IGFBP1</i>	Jiang et al., 2015
CRL-4003	0.5 mmol/L 8-Br-cAMP, 10 nmol/L estradiol, and 1 μmol/L progesterone	3, 6	<i>PRL</i> , <i>IGFBP1</i>	Li Y et al., 2017

PhESCs: primary human endometrial stromal cells; CRL-4003: immortalized human endometrial stromal cell line; MPA: medroxyprogesterone acetate; cAMP: cyclic adenosine monophosphate; 8-Br-cAMP: 8-bromo-cAMP; db-cAMP: dibutyryl-cAMP; IGFBP1: insulin-like growth factor-binding protein 1; PRL: prolactin; dPRL: decidual PRL.

mimics, with injection of sesame oil into the uterine horn being the most commonly used stimulation method (Peterse et al., 2018; Meng et al., 2019); and (3) the in vitro decidualization (IVD) model, which involves extracting endometrial cells from mice and inducing decidualization in vitro, followed by the administration of estradiol and progesterone to induce decidualization (Song et al., 2022). Notably, the mouse uterus cannot enter a receptive state and the embryo cannot be implanted after ovariectomy and upon treatment with progesterone only (Dey et al., 2004; Cheng et al.,

2023). In addition, in vitro, cAMP cannot significantly promote the full decidualization of mouse endometrial stromal cells, unlike what has been observed in human cell models (Wang et al., 2020). To date, three mouse models of decidualization, namely, the NPD, AD, and IVD models, have been well established and applied in various studies (Table 2). After the expression levels of differentially expressed genes were compared, the IVD model was found to be unreliable, requiring further optimization of gene expression (Wang et al., 2020).

**Table 2 Approaches for inducing decidualization and markers for evaluating decidualization in mouse models and cells**

Model/cell type	Mouse species and age	Induction approach	Marker	Reference
NPD	Kunming mice (6–8 weeks)	Mating with fertile males to induce pregnancy	Morphology of the uterus	Li XY et al., 2017
NPD	Kunming mice (6–8 weeks)	Mating with fertile males to induce pregnancy	<i>Prl8a2</i> , morphology of the uterus	Gong et al., 2019
NPD	CD1 mice (8–10 weeks)	Mating with fertile males	<i>Prl8a2</i>	Jin et al., 2022
AD	CD1 mice (9–12 weeks)	Mating with vasectomized males, transfer of blastocyst-sized concanavalin A-coated agarose beads into the uterine lumen	<i>Bmp2</i> , <i>Bmp8a</i> , <i>Fkbp5</i> , <i>Hand2</i>	McConaha et al., 2011
AD	Kunming mice (adult)	Induction of pseudopregnancy, infusion of 50 $\mu$ L sesame oil into the uterine horn	Weight of the uterine horn and histological examination of uterine sections	Teng et al., 2004
AD	CD1 mice (8–10 weeks)	Induction of pseudopregnancy, unilateral intrauterine injection of 10 $\mu$ L sesame oil	<i>Prl8a2</i>	Jin et al., 2022
AD	C57BL/6 mice (8 weeks)	Continuous subcutaneous injection of 2 ng/ $\mu$ L estradiol and 0.2 ng/ $\mu$ L progesterone after ovariectomy, injection of 20 $\mu$ L sesame into the uterine horn	<i>Prl8a2</i> , <i>Alpl</i> , <i>Igfbp1</i> , morphological analysis by HE staining	Zhang et al., 2022
PmESCs	C57BL/6 mice (8–12 weeks)	1 $\mu$ mol/L MPA and 0.5 mmol/L 8-Br-cAMP	<i>Prl8a2</i> , morphology	de Clercq et al., 2017
PmESCs	ICR mice (4 weeks)	0.1 nmol/L estradiol and 100 nmol/L progesterone	Morphology, <i>D/tprp</i> , <i>Prl</i>	Kimura et al., 2001
PmESCs	CD-1 mice (adult)	10 nmol/L estradiol and 1 $\mu$ mol/L progesterone	<i>D/tprp</i>	Ding NZ et al., 2018
PmESCs	Kunming mice (adult)	1 $\mu$ mol/L progesterone and 10 nmol/L estradiol	<i>D/tprp</i>	Guo et al., 2014; Li DD et al., 2014
PmESCs	ICR mice (8–10 weeks)	10 nmol/L estradiol and 1 $\mu$ mol/L progesterone	<i>D/tprp</i>	Tsai et al., 2013
PmESCs	CD1 mice (8–10 weeks)	10 nmol/L estradiol and 1 $\mu$ mol/L progesterone	<i>D/tprp</i> , <i>Abpl</i> , <i>E2f8</i>	Fu et al., 2019

NPD: natural pregnancy decidualization; AD: artificial decidualization; PmESCs: primary mouse endometrial stromal cells; HE: hematoxylin-eosin; MPA: medroxyprogesterone acetate; 8-Br-cAMP: 8-bromo-cyclic adenosine monophosphate; *Prl8a2*: prolactin 8a2 gene; *Bmp2*: bone morphogenetic protein 2 gene; *Bmp8a*: bone morphogenetic protein 8A gene; *Fkbp5*: FK506 (tacrolimus)-binding protein 5 gene; *Hand2*: heart and neural crest derivatives-expressed 2 gene; *Alpl*: alkaline phosphatase gene; *Prl*: prolactin gene; *Igfbp1*: insulin-like growth factor-binding protein 1 gene; *D/tprp*: decidual/trophoblast prolactin-related protein-encoding gene; *Abpl*: amine oxidase copper-containing 1 gene; *E2f8*: E2F transcription factor 8 gene.

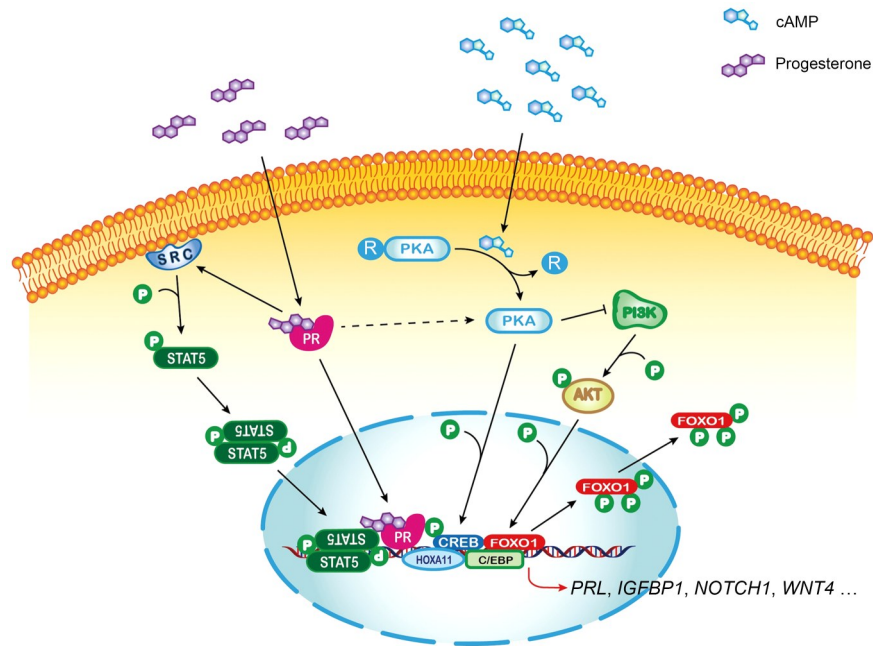
#### 4 Signal transduction during decidualization

Decidualization is a precise and complex phenomenon. During decidualization of the human uterus, progesterone receptors (PRs) bind to progesterone in the cytoplasm, activating the cAMP/protein kinase A (PKA) signaling pathway (Tsai et al., 2013; Li MJ et al., 2014; Fu et al., 2019; Wang et al., 2020; Yu et al., 2020). Then, the progesterone complex is transferred to the nucleus where it interacts with various transcription factors to regulate the expression of decidualization-related genes (Cho et al., 2011; Yoshie et al., 2015; Fu et al., 2019; Wang et al., 2020; Yu et al., 2020). cAMP is a critical molecule promoting the decidualization of human endometrial stromal cells (hESCs); it can increase the expression of forkhead box O1 (FOXO1) in decidual cells. This cell-specific core transcription factor is located downstream of the PI3K/AKT signaling pathway and participates in cell proliferation, apoptosis, differentiation, and processes involving antioxidative stress and DNA damage (Cho et al., 2011; Yoshie et al., 2015; Wang et al., 2020; Yu et al., 2020). Subsequently, FOXO1 increases the expression of multiple decidualization-related genes, including *IGFBP1* and decorin (*DCN*) (Nakamura et al., 2013; Halari et al., 2020; Yu et al., 2022), and interacts with homeobox A11 (*HOXA11*) to activate *PRL* gene expression (Nnamani et al., 2016). Additionally, FOXO1 and PR can regulate the expression of interferon regulatory factor member 4 (IRF4), thereby upregulating the expression of the decidual markers *IGFBP1*, *PRL*, and *WNT4* (Vasquez et al., 2015). After activation, FOXO1 is phosphorylated and exported from the nucleus. In normal decidual cells, the PI3K/AKT pathway is inhibited. The activation of the AKT signaling pathway results in FOXO1 phosphorylation, impairing the decidualization process (Yin et al., 2012; Fabi et al., 2017). During decidualization, cAMP contributes to the inactivation of AKT in endometrial stromal cells by reducing the levels of protein phosphatase 2A (PP2A) inhibitors, among which the cancerous inhibitor of protein phosphatase 2A (CIP2A) is particularly significant. The E26 transformation-specific (ETS) transcription factors act as crucial intermediaries linking cAMP signaling to the modulation of CIP2A expression (Zhao et al., 2023). Signal transducer and activator of transcription 5 (STAT5), a core transcription factor, also mediates the regulation of decidualization (Fig. 2) by (1) increasing the expression of the

*Prl* gene in response to cAMP/medroxyprogesterone acetate (MPA) induction (Mak et al., 2002) and (2) being activated via the phosphorylation of tyrosine 694 by Rous sarcoma oncogene cellular homolog (SRC) kinase and in turn promoting the decidual transformation of hESCs (Nagashima et al., 2008). The mechanistic target of rapamycin (mTOR), extracellular signal-regulated kinase (ERK), and neurogenic locus notch homolog protein 1 (NOTCH1) signaling pathways also participate in decidualization. Activating mTOR complex 1 (mTORC1) signaling contributes significantly to uterine decidual cell senescence early in pregnancy, which leads to preterm birth and fetal death (Nagashima et al., 2008). The abnormal activation of ERK dysregulates the expression of decidualization-related genes (Mak et al., 2002; Nagashima et al., 2008; Fabi et al., 2017; Tang et al., 2022). During the implantation window in primates, the transmembrane protein NOTCH1 plays an important role in the transition of stromal fibroblasts to decidual cells. With the progression of decidualization, the expression of NOTCH1 gradually decreases (Afshar et al., 2012). Recent studies have suggested that ciliated cells in the decidua play a crucial role in pregnancy. Primary cilia, similar to antennas, can serve as signal connectors for various pathways, including transforming growth factor- $\beta$  (TGF- $\beta$ ), bone morphogenetic protein (BMP), FGF, and Notch signaling, contributing to the establishment and maintenance of pregnancy (Li et al., 2022).

#### 5 Roles of fibroblast growth factors in endometrial physiology

The intricacies of decidualization, whether in the human or nonhuman endometrium, underscore the pivotal role of pre-decidualization endometrial alterations in shaping subsequent decidual outcomes. To this end, early endometrial aberrations often precipitate adverse decidual consequences prior to the decidualization process itself. Notably, certain pregnancy complications stemming from decidual irregularities manifest prior to decidualization. Herein, we describe the complex involvement and distribution of FGF across diverse endometrial stages in both humans and nonhuman taxa, as well as its regulatory interaction regarding decidualization.



**Fig. 2** Molecular mechanism of decidualization in human endometrial stromal cells. In humans, progesterone is the principal hormone that induces decidualization in endometrial stromal cells. After bypassing the cell membrane, progesterone binds to and activates PRs in the cytoplasm. The progesterone–PR complex directly enters the nucleus and interacts with other transcription factors to regulate the expression of decidualization-related genes. SRC is a downstream target protein of PRs, which can phosphorylate STAT5 after activation. Phosphorylated STAT5 can bind to regulatory sites and regulate gene expression. In addition, the dashed line indicates that the PR pathway may also regulate the decidualization of stromal cells through the cAMP/PKA signaling pathway; cAMP can directly activate PKA. After phosphorylation, PKA activates the transcription factor CREB, interacts with other transcription factors and DNA-binding proteins in the nucleus, and regulates the expression of decidualization-related genes. The activation of the PI3K/AKT pathway can result in the phosphorylation of the transcription factor FOXO1 and promote its nuclear export. AKT: AKT8 virus oncogene cellular homolog, also called protein kinase B; cAMP: cyclic adenosine monophosphate; C/EBP: CCAAT-enhancer-binding protein; CREB: cAMP response element-binding protein; FOXO1: forkhead box O1; HOXA11: homeobox A11; *IGFBP1*: insulin-like growth factor-binding protein 1 gene; *NOTCH1*: neurogenic locus notch homolog protein 1 gene; PI3K: phosphoinositide 3-kinase; PKA: protein kinase A; PR: progesterone receptor; *PRL*: prolactin gene; STAT5: signal transducer and activator of transcription 5; SRC: Rous sarcoma oncogene cellular homolog; *WNT4*: wingless-type MMTV integration site family member 4 gene.

## 5.1 Humans

The human uterine cycle is divided into three phases: the proliferative, secretory, and menstrual phases (Murray and Orr, 2020). In the proliferative phase, endometrial cells multiply under the regulation of estradiol, promoting endometrial hyperplasia and spiral arteriole formation. Next, the endometrial glands begin to secrete various factors, and stromal cells are induced by progesterone to differentiate into secretory decidual stromal cells (Strassmann, 1996). At this point, if embryo implantation does not occur, the corpus luteum gradually degenerates and eventually transforms into the corpus albicans. Moreover, progesterone secretion stops and endometrial shedding occurs (Mak et al., 2002).

Endometrial hyperplasia, whether normal or pathologic, is closely related to angiogenesis. FGF2, as an important angiogenic factor and mitogen, regulates angiogenesis in the endometrium during the human menstrual cycle (Fujimoto et al., 1996a; Strassmann, 1996; Afshar et al., 2012; Mori et al., 2017; Tang et al., 2022; Wang et al., 2022; Zheng et al., 2023). Correspondingly, the expression of FGF2 in the human endometrium in the proliferative phase is significantly greater than that in the secretory phase (Fujimoto et al., 1996b; Sangha et al., 1997). FGF2 has the capacity to promote the proliferation of myometrium and smooth muscle cells, while estradiol does not (Rauk et al., 1995). Therefore, FGF2 is one of the critical functional factors in estradiol-mediated angiogenesis (Strassmann, 1996; Lim et al., 2017; Ding JH et al., 2018). FGF2

has been reported to be expressed in the human endometrial luminal epithelium, blood vessels, and stroma. However, its expression level and location remain highly debated. For example, FGF2 was observed to be highly expressed in the stroma during menstruation and the early proliferative phase (Möller et al., 2001). In the endometrium, FGF2 is expressed mainly in the glandular epithelium, which gradually decreases after menopause (Hague et al., 2002). Paiva et al. (2011) reported that FGF2 expression increased throughout the menstrual cycle and was highest in the endometrium in the secretory phase and the first trimester of human pregnancy. More importantly, in decidual tissue in the first trimester, FGF2 was detected in all cell types, including the glandular epithelium and stroma (Paiva et al., 2011). According to another study, many factors were secreted by biopsied decidual tissue in the first trimester, including granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1), but not FGF2 (Shuya et al., 2011). These inconsistent findings strongly indicate that FGF2 is a valuable marker for regulating uterine physiological processes and detecting related diseases.

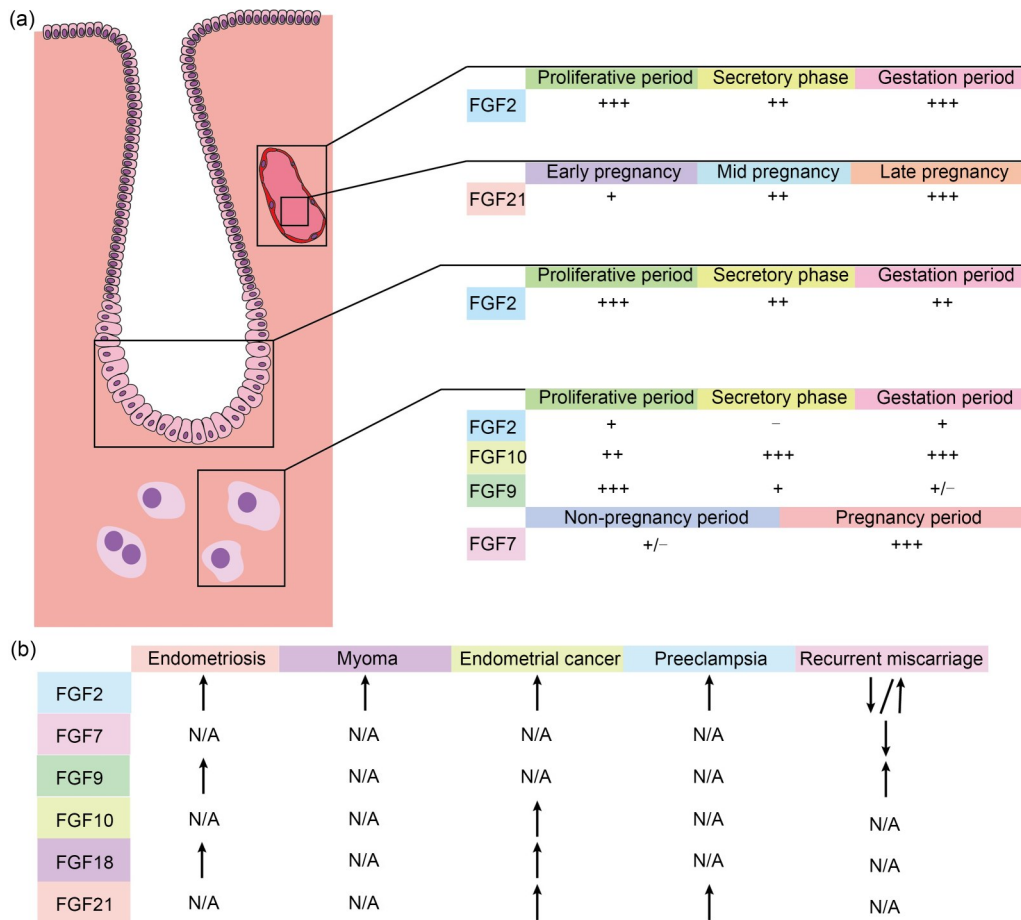
In addition to FGF2, FGF9 and FGF21 also play important roles in normal endometrial remodeling and pregnancy maintenance. FGF9 has been identified as a target of estrogen in the endometrium. It is notably present at high levels in the late proliferative endometrial matrix, stimulating the proliferation of stromal cells, which indicates its involvement in the regulation of endometrial dynamics during the menstrual cycle (Massimiani et al., 2020). Murata et al. (2019) treated hESCs with MPA and revealed that MPA did not affect FGF2 expression; however, FGF9 was significantly downregulated after 3 d of treatment. They also showed that progesterone inhibited angiotensin 2 (ANGPT2) production by inducing heart and neural crest derivatives-expressed protein 2 (HAND2) to inhibit FGF9, thereby attenuating FGF9 production in hESCs. Before ovulation, estrogen stimulates endometrial stromal cells to secrete factors such as FGFs to regulate epithelial cell proliferation. After corpus luteum formation, stromal cells regulate FGFs to send signals to epithelial cells by expressing *Hand2*, thus inhibiting estrogen-mediated proliferation (Wu et al., 2018; Cheng et al., 2022). PR and cAMP response element-binding protein 1 (CREB1) modulate the

expression of Src homology 2 (SH2) domain-containing protein tyrosine phosphatase-2 (SHP2) by binding to the tyrosine-protein phosphatase non-receptor type 11 (*PTPN11*) promoter, mediating FGF and insulin growth factor 1 (IGF1) signaling to control cell proliferation (Cheng et al., 2022; Zhou et al., 2024). FGF7 stimulates the expression of *IGFBP1* and *PRL* through the ERK and c-Jun N-terminal kinase (JNK) signaling pathways in an autocrine manner and induces hESC proliferation (Zhou et al., 2017). It has been confirmed that increased serum FGF21 concentration is associated with obesity-related metabolic complications. In healthy cohorts with overweight or obese women, the expression level of FGF21 in the serum gradually increases with the advancement of pregnancy and peaks in the third trimester. However, this protein is barely expressed in the placenta. These results suggest that the circulating level of FGF21 may be a potential marker of maternal nutrient status during pregnancy (Spearman's correlation or paired Student's *t*-test was used for statistical analysis,  $\alpha=0.05$ ) (Fig. 3a) (Sutton et al., 2018).

## 5.2 Nonhuman mammals

In nonhuman mammals, FGF-FGFR signaling plays vital roles in the functional regulation of the endometrium, similar to humans. In mice, FGF10 and *Bmp8a* act as paracrine mediators in an estrogen-dependent manner during uterine hypertrophy to establish and maintain pregnancy (Chung et al., 2015). In pregnant rats, newly synthesized FGF2 can regulate the proliferation of uterine cells, while circulating progesterone modulates FGF2 production in the uterus (Rider et al., 1997). Inhibiting the activity of PRs in the rat endometrium leads to an increase in FGF2 expression and absorption at the implantation site (Mestre-Citrinovic et al., 2015). In rhesus monkeys (*Macaca mulatta*), uterine cells are able to synthesize FGF1 and FGF2. FGF1 is localized mainly in the nuclei of myometrial cells and epithelial cells, while FGF2 is highly expressed in both the cytoplasm and nucleus of myometrial and vascular cells. Importantly, estradiol distinctly mediates the synthesis of these two factors (Samathanam et al., 1998).

In the uterine stroma of mice, *Hand2*, expressed under the effect of progesterone, is able to inhibit the expression of several FGFs and maintain stromal-epithelial communication. The absence of *HAND2* gives rise to the continuous expression of these FGFs, including FGF1, FGF2, FGF9, and FGF18, in the



**Fig. 3** Expression of fibroblast growth factors (FGFs) in the context of a normal menstrual cycle, pregnancy, and disease. (a) Spatiotemporal expression patterns of FGF2, FGF7, FGF9, FGF10, and FGF21 in the context of a normal menstrual cycle or pregnancy. Each table represents a different part of the endometrium, including (from top to bottom) endothelial cells, the serum, the glandular epithelium, and endometrial stromal cells. The expression levels of FGFs during proliferation, secretion, and pregnancy are shown. The number of “+” symbols signifies the expression level and the “-” symbol indicates almost no expression or uncertainty. (b) Trends of changes in FGF2, FGF7, FGF9, FGF10, FGF18, and FGF21 expression in various endometrial diseases are shown compared with those in healthy endometrium. “↑” indicates an increase in expression levels in diseased endometrium compared with healthy endometrium, “↓” indicates a decrease in expression levels in diseased endometrium compared with healthy endometrium, and N/A indicates not applicable.

stroma and epithelial proliferation, which impairs the implantation of embryos (Li et al., 2011; Šućurović et al., 2017; Yin et al., 2021). The in situ hybridization of mouse implantation sites revealed that FGF10 transcripts are localized in the endometrium, while FGF2 transcripts are localized in the antimesometrial site of the uterus. A mechanistic investigation further revealed that the latter affects embryo implantation through crosstalk with the BMP2 signaling pathway (Paria et al., 2001; Sahin Ersoy et al., 2017; Liu et al., 2022; Yang et al., 2023). These results collectively suggest that FGF2 is a marker of endometrial receptivity. Moreover, during placental development, FGF10 is

expressed by decidual cells and cytotrophoblasts in cytotrophoblast columns. This peptide regulates decidual-placental interactions through FGFR-1 signaling (Yagel and Goldman-Wohl, 2019).

## 6 Diseases caused by disordered decidualization

Disordered decidualization can lead to aberrations in implantation and adverse pregnancy outcomes. The most frequent consequences are recurrent implantation failure (RIF) and recurrent miscarriage

(RM). The inability to conceive after multiple embryo transfers without a clear cause is defined as RIF. RM is defined as having three or more consecutive miscarriages before 20 weeks of pregnancy. A study scoring decidualization in women of childbearing age indicated that 76% of women with RIF had a score of  $\leq 4$  and 19% had a score of 0 (maximal score was 6) (Dambaeva et al., 2021). These findings suggest that most people with RIF experience impaired decidualization (Lash and Ernerudh, 2015; Dambaeva et al., 2021). The causes of RIF are complicated and include (1) abnormal cilogenesis of decidual stromal cells; (2) inactivation of TGF- $\beta$  signaling in decidual cells (Hassan et al., 2022); (3) downregulation of the circadian clock gene *BMALL* (Lv et al., 2019); and (4) homeostatic imbalance of decidual macrophages (dM $\phi$ s). The number of CD86<sup>+</sup> macrophages (M1) is significantly increased and the number of CD163<sup>+</sup> macrophages (M2) is decreased in the decidual tissue of RM patients compared with normal decidual tissue (Ding et al., 2019). Endometriosis, which involves disturbances in angiogenesis and apoptosis and renders the eutopic endometrium unable to accept embryos due to asynchronous mesenchymal-epithelial transition and endometrial dystrophy, is a further potential cause of RIF (Orazov et al., 2021).

Preeclampsia (PE) is a disorder of pregnancy that usually occurs after 20 weeks of gestation and manifests as gestational hypertension, proteinuria, and maternal vascular damage. Severe PE can have life-threatening consequences for both the mother and the child (Redman et al., 2014). Insufficient decidualization, which results in aberrations in placental invasion, is a maternal risk factor for PE (Sahu et al., 2019; Garrido-Gómez et al., 2022). Recent studies have highlighted that the dysregulation of DDB1 and CUL4-associated factor 13 (*Dcaf13*) expression leads to the downregulation of *Bmp2* and *Wnt4*, leading to decidualization defects, which in turn are involved in the development of PE (Yan et al., 2022). The downregulation of Annexin A2 also contributes to PE by impairing endometrial stromal cell decidualization and the uterine microenvironment (Garrido-Gomez et al., 2020).

## 7 Fibroblast growth factors and endometrial diseases

The endometrium, an important part of the female reproductive system, comprises glands, vessels,

epithelium, and stroma (Zhu et al., 2023). FGFs play critical roles in the regulation of endometrial physiology and pathology. In normal and ectopic human endometria, both FGF1 and FGF2 are robustly expressed in the epithelial cells of glands but are barely expressed in stromal cells, the myometrium, or endothelial cells. Based on reverse transcription polymerase chain reaction (RT-PCR), FGF2 was expressed in endometrial samples collected from the proliferative and secretory phases, while FGF1 was expressed only in the secretory phase (Ferriani et al., 1993). Moreover, a comparison of 24 patients with primary infertility revealed that FGF1 expression was often lower in endometrial samples from patients with RIF than in those from fertile people (Mann-Whitney *U*-test) (Sak et al., 2013). In contrast, in patients with endometriosis, the expression of FGF2 and FGFR1 in the endometrium is significantly increased by the activation of the ERK1/2 signaling pathway (Ferriani et al., 1993; Yu et al., 2021). Importantly, elevated concentrations of FGF2 in endometriotic lesions are closely related to aggravated endometriosis-related pain in vivo via mast cell-neuron crosstalk (Pearson's correlation analysis was performed to analyze the correlation between FGF2 expression and pain, two-tailed Student's *t*-test was used for comparisons between two groups, and one-way analysis of variance (ANOVA) was employed for comparisons among multiple groups) (Xu et al., 2023). Additionally, in human ectopic endometriotic lesions, FGF9, which is stimulated by estrogen of endometriotic stromal cell origin, regulates the proliferation of endometriotic stromal cells in an autocrine manner (Zhao et al., 2015). Increased expression of FGF1, FGF2, and FGF9 in ectopic endometrial stromal cells was associated with a decrease in HAND2 expression (Kato et al., 2019). FGF18 expression was also found to be significantly increased in the ectopic endometrium in the secretory phase (Yerlikaya et al., 2016). These results suggest that aberrant spatiotemporal expression patterns of FGFs are key predisposing factors for endometrial diseases.

Uterine fibroids comprise a common condition that leads to reproductive failure in women of childbearing age by triggering abnormalities in the expression of growth factors (Sevostyanova et al., 2020). Among them, FGF1 and FGF2 may play important roles in the transformation of normal human myometrium to leiomyoma and the subsequent development of tumors (Borahay et al., 2015; Larraín and Prado,

2024). The results of a transcriptomic analysis indicated that the FGF/FGFR1 signaling cascade is activated in fibroids (Paul et al., 2021) and regulated by steroid hormones (Wu et al., 2001). A retrospective study found that the concentrations of FGF2 were notably elevated in human leiomyoma tissues compared with the normal myometrium, with a predominant localization in the extracellular matrix (comparisons between groups were performed using the Chi-square test, univariate analysis was performed using the log-rank test, and multivariate analysis was performed using the Cox proportional hazards model) (Bodner-Adler et al., 2016). Furthermore, consistent high-level expression of FGF2 in leiomyoma was positively correlated with the occurrence of endometrial cancer (Soufla et al., 2008; Helmke et al., 2011; Li MJ et al., 2014; Li YN et al., 2020; Bodner-Adler et al., 2016; Afrin et al., 2023).

In humans, abnormal FGF signaling has been associated with endometrial cancer. Most FGFs carry out important physiological functions in female reproductive system cancers through FGFRs (Zhu et al., 2020). FGF7 and FGF10 can stimulate the growth of endometrial carcinoma cells by activating the MAPK pathway in an autocrine or paracrine manner (Taniguchi et al., 2003). FGF21, which belongs to the FGF endocrine subfamily, also functions as a potential biomarker of endometrial cancer. A study on FGF21 and uterine pathological diagnosis involved the collection of endometrial tissues from 223 patients, which were categorized into endometrial cancer, endometrial polyp, fibroid, sarcoma, and normal endometrium groups. The sensitivity and specificity of biomarkers were evaluated using receiver operating characteristic (ROC) analysis, with a predefined significance level of  $\alpha=0.05$  (Mann-Whitney *U*-test was used for comparisons between groups, Kruskal-Wallis and ANOVA-Welch tests were used for comparisons among multiple groups, Student's *t*-test was performed for comparisons between independent groups, and Pearson Chi-squared test and Fisher test were utilized for comparisons of categorical variables) (Jagodzińska et al., 2023). The expression of FGF18, which is regulated by estradiol, was elevated in endometrial adenocarcinoma (Flannery et al., 2016).

FGF21 levels are significantly elevated in the serum of PE patients during pregnancy. According to a nested case-control study, FGFs appear to have a

biphasic regulatory function in PE. An elevated serum FGF21 concentration is a potential marker of PE, but high levels of FGF21 may be beneficial for preventing some of the negative effects of PE (Shapiro-Wilk test was employed to verify data normality, Mann-Whitney *U*-test was used for comparisons between groups, and Spearman's rank correlation method and Bonferroni's correction were applied for univariate analysis) (Stepan et al., 2013; Buell-Acosta et al., 2022). On the other hand, the intravenous injection of FGF2 was found to alleviate gestational hypertension and proteinuria and increase placental weight in a PE rat model (Fig. 3b) (Martinez-Fierro et al., 2022).

## 8 Conclusions and prospects

Decidualization is one of the most critical events within the endometrium during pregnancy. This process involves a series of morphological changes and functional differentiation steps in ESCs. To date, various *in vitro* and *in vivo* animal research models (particularly mouse) have been established. However, the human decidua, unlike the mouse decidua, is routinely formed and shed in the absence of an embryo in the endometrium (Okada et al., 2018). Furthermore, the pattern of gene expression is significantly different between induced and natural decidualization. Future studies are urgently needed to establish a suitable and reliable approach to studying human decidualization.

The process of decidualization is tightly regulated by complex interactions involving transcription factors, cytokines, and hormones. Regarding the mechanisms involved in this process, the FGF/FGFR signaling pathway plays critical roles in physiological and pathological decidualization. This pathway is precisely controlled, and abnormal expression of its components results in disordered decidualization and subsequently triggers serious consequences, such as PE, RIF, and miscarriage. Moreover, it can also cause the impairment of pre-decidualization during the menstrual cycle. Further delineating the fluctuations in FGF expression during human decidualization could ascertain the possibility of a successful gestation by analyzing endometrial biopsy specimens or uterine fluid at a specific stage preceding conception preparation. FGFs, as widely distributed growth factors in the human body, have been extensively employed as drugs to promote wound

repair and beauty. Once the exact roles of FGFs in decidualization and the related signaling pathway are determined, some members of the FGF family may be developed as less harmful contraceptives or embryo implantation-promoting drugs. This prospect undoubtedly represents an exciting opportunity in the field of female reproduction and contraception.

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### Author contributions

Zhijian SU and Xiaokun LI conceived and designed the manuscript. Xueni ZHANG, Yidi MO, Chunbin LU, and Zhijian SU contributed to the data acquisition and figure preparation. Xueni ZHANG and Zhijian SU drafted the manuscript. All authors have read and approved the final manuscript.

### Compliance with ethics guidelines

Xueni ZHANG, Yidi MO, Chunbin LU, Zhijian SU, and Xiaokun LI declare that they have no conflicts of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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