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Review

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

Xueni ZHANG[1], Yidi MO[1], Chunbin LU[1], Zhijian SU[1,2,3]✉, Xiaokun LI[4]✉

[1]*Department of Developmental Biology and Regenerative Medicine, Jinan University, Guangzhou 510632, China*
[2]*Guangdong Provincial Key Laboratory of Bioengineering Medicine, Department of Cell Biology, Jinan University, Guangzhou 510632, China*
[3]*National Engineering Research Center of Genetic Medicine, Jinan University, Guangzhou 510632, China*
[4]*State Key Laboratory for Macromolecule Drugs and Large-scale Preparation, Wenzhou Medical University, Wenzhou 325035, China*

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 factor (FGF), particularly FGF-2, assumes 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 failures, 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 embryo presence in the endometrium. This process is also tightly controlled by various FGFs. In this review, we comprehensively compare diverse research decidualization models, delineate the regulatory mechanisms of FGFs in decidualization, and provide a synopsis of endometrial diseases triggered by FGF dysregulation.

Key words: Fibroblast growth factor; Decidualization; Pregnancy; Adverse pregnancy outcomes

1 Introduction

The transition from oviparity to viviparity was an important evolutionary leap, which profoundly altered the reproductive process: embryos were no longer expelled from the mother's body but instead remained inside it, where they could 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 (ESCs) undergo irreversible differentiation, with the spatiotemporal progression of this process tightly controlled by various morphogens and cytokines, including members of the FGF family (Murata *et al*., 2022; Bhurke *et al*., 2016).

✉ Zhijian SU, tjnuszj@jnu.edu.cn
Xiaokun LI, xiaokunli@wmu.edu.cn
Zhijian SU, https://orcid.org/0000-0001-6261-1294
Xiaokun LI, https://orcid.org/0000-0002-6556-6262

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The fibroblast growth factor (FGF) family includes structurally related polypeptides that play essential roles in embryonic development and the postnatal homoeostasis 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 receptors (FGFRs) in a paracrine or endocrine manner (Fang *et al*., 2022; Zhang *et al*., 2006). To date, a total of four FGFR subtypes have been identified, namely, FGFR1, FGFR2, FGFR3, and FGFR4. After ligands bind to FGFRs, they dimerize and activate subsequent signaling pathways, including the phospholipase Cγ (PLCγ), Ras–mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase–Akt (PI3K-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 (Figueroa *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 protects 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 interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), 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 phase 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).

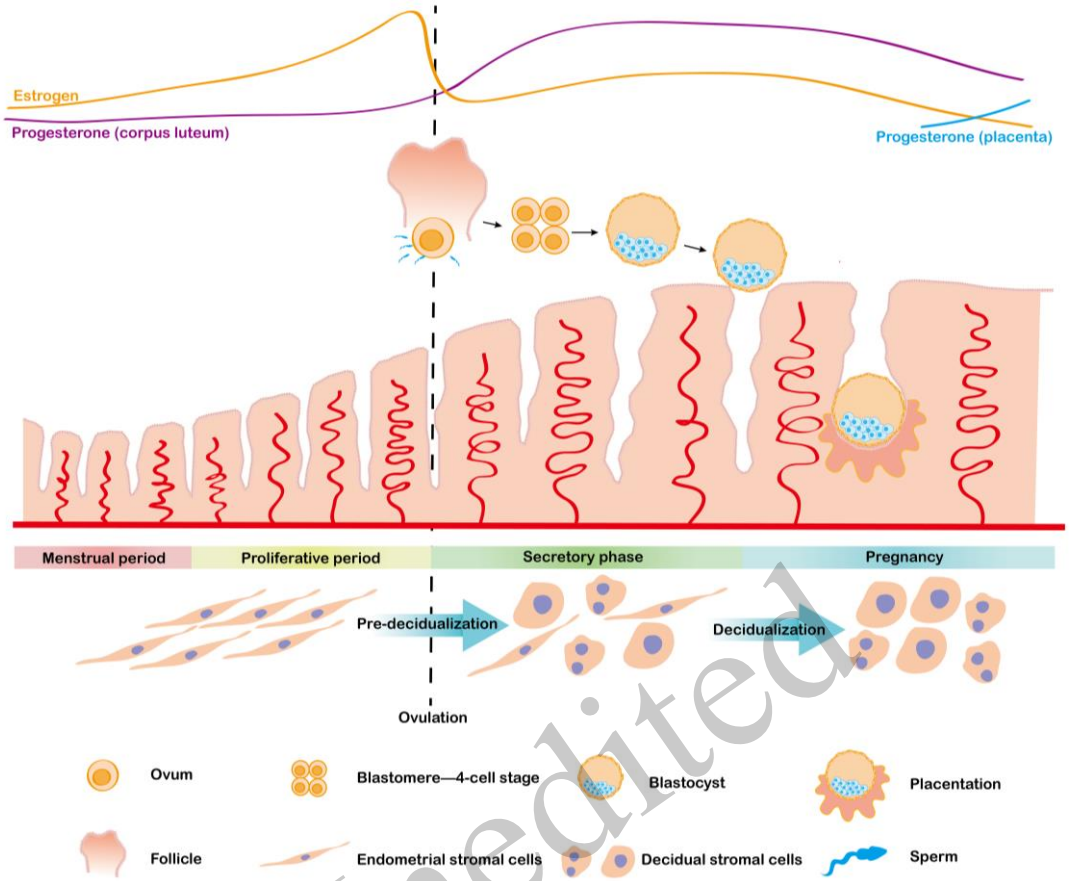

Fig. 1 Changes in hormone levels and endometrial stromal cells during implantation

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 (Duncan, 2021; Jukic *et al*., 2013).

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 days 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 AMP (cAMP) can significantly shorten the time required to induce human endometrial cell decidualization (Tang *et al*., 2021; Kajihara *et al*., 2013; Li, 2011). Therefore, estradiol and progesterone with/without cAMP is the most frequently used combination used to

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

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

Cell type	Factor(s) used to induce decidualization	Induction in vitro (days)	Marker	Reference
PhESCs	1 μmol/L MPA and 0.5 mmol/L cAMP	4	IGFBP-1, dPRL, morphology	(Pan-Castillo *et al*., 2018)
PhESCs	3×10^{-10} mol/L estradiol and 5×10^{-8} mol/L progesterone	13	*Prl*, *Igfbp-1*, PRL, IGFBP-1	(Wu *et al*., 2017)
PhESCs	1 μmol/L progesterone and 30 nmol/L estradiol	9	PRL, morphology	(Estella *et al*., 2012)
PhESCs	0.5 mmol/L 8-Br-cAMP and 1 μmol/L MPA	5	PRL, morphology	(Estella *et al*., 2012)
PhESCs	Start with 1 μg/mL insulin and 1 nmol/L estradiol, then treat with 0.5 mmol/L 8-Br-cAMP	4-5	*Prl* , dPRL	(Gellersen *et al*., 2010)
PhESCs	0.5 mmol/L cAMP	5	PRL	(Jones *et al*., 2002)
PhESCs	10^{-8} mol/L estradiol and 10^{-7} mol/L progesterone	10	PRL	(Jones *et al*., 2002)
PhESCs	0.1 mg/mL 8-Br-cAMP and 1 mmol/L progesterone	1, 2, 4, 8	*Prl*, *Igfbp-1*, PRL, IGFBP-1	(Gibson *et al*., 2016)
PhESCs	200 pg/mL estradiol, 100 ng/mL progesterone and 0.5 mmol/L 8-Br-cAMP	10	*Prl*, *Igfbp-1*	(Tanaka *et al*., 2003)
PhESCs	10 nmol/L estradiol and 1 μmol/L progesterone	10	*Prl*, *Igfbp-1*	(Popovici *et al*., 2000)
PhESCs	1 mmol/L 8-Br-cAMP	2	*Prl*, *Igfbp-1*	(Popovici *et al*., 2000)
PhESCs	500 μmol/L db-cAMP and 1 mmol/L progesterone	2	*Prl*, *Igfbp-1*	(Kusama *et al*., 2021)
CRL-4003 cells	0.5 mmol/L 8-Br-cAMP and 1 mmol/L MPA	4, 8	*Prl*, *Igfbp-1*	(Rytkönen *et al*., 2019)
CRL-4003 cells	10 nmol/L estradiol, 1 μmol/L MPA and 0.5 mmol/L db- cAMP	3	*Prl*, *Igfbp-1*	(Jiang *et al*., 2015)
CRL-4003 cells	0.5 mmol/L 8-Br-cAMP, 10 nmol/L estradiol and 1 μmol/L progesterone	3, 6	*Prl*, *Igfbp-1*	(Li *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; **IGFBP-1**: insulin-like growth factor binding protein 1; **dPRL**: decidual Prolactin; ***Prl***: prolactin gene; ***Igfbp-1***: insulin-like growth factor binding protein 1 gene; **PRL**: prolactin.

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 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 comparing the expression levels of differentially expressed genes, the IVD model was found to be unreliable, requiring further optimization regarding gene expression (Wang *et al*., 2020).

Table 2 Approaches for inducing decidualization and markers for evaluating decidualization in mice and mouse 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 *et al*., 2017)
NPD	Kunming mice (6-8 weeks)	Mating with fertile males to induce pregnancy	*Prl8a2*, morphology of the uterus	(Gong *et al*., 2019)
NPD	CD1 mice (8-10 weeks)	Mating with fertile males	*Prl8a2*	(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	*Bmp2, Bmp8a, Fkbp5, Hand2*	(Mcconaha *et al*., 2011)
AD	Kunming mice (adult)	Induction of pseudopregnancy, infusion of 50 μL 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 μL of sesame oil	*Prl8a2*	(Jin *et al*., 2022)
AD	C57BL/6 mice (8 weeks)	Continuous subcutaneous injection of 2 ng/μL estradiol and 0.2 ng/μL progesterone after ovariectomy, injection of 20 μL of sesame into the uterine horn	*Prl8a2, Alpl, Igfbp1*, morphological analysis by HE staining	(Zhang *et al*., 2022)
PmESCs	C57Bl/6 mice (8-12 weeks)	1 μmol/L MPA and 0.5 mmol/L 8-Br-cAMP	*Prl8a2*, morphology	(De Clercq *et al*., 2017)
PmESCs	ICR mice (4 weeks)	0.1 nmol/L estradiol and 100 nmol/L progesterone	Morphology, *D/tprp*, *Prl*	(Kimura *et al*., 2001)
PmESCs	CD-1 mice (adult)	10 nmol/L estradiol and 1 μmol/L progesterone	*D/tprp*	(Ding *et al*., 2018)
PmESCs	Kunming mice (adult)	1 μmol/L progesterone and 10 nmol/L estradiol	*D/tprp*	(Guo *et al*., 2014; Li *et al*., 2014)
PmESCs	ICR mice (8-10 weeks)	10 nmol/L estradiol and 1 μmol/L progesterone	*D/tprp*	(Tsai *et al*., 2013)
PmESCs	CD1 mice (8-10 weeks)	10 nmol/L estradiol and 1 μmol/L progesterone	*D/tprp, Abpl, E2f8*	(Fu *et al*., 2019)

NPD: natural pregnancy decidualization; **AD**: artificial decidualization; **PmESCs**: mouse morphogenetic primary endometrial cells; **HE**: hematoxylin-eosin**; MPA**; medroxyprogesterone acetate: **8-Br-cAMP**: 8-bromo-cAMP; ***Prl8a2***: prolactin 8a2 gene; ***Bmp2***: bone 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; ***Igfbp-1***: 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 (PR) bind to progesterone in the cytoplasm, activating the cAMP/PKA signaling pathway (Fu *et al*., 2019; Li *et al*., 2014; Tsai *et al*., 2013; 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; Fu *et al*., 2019; Mikihiro *et al*., 2015; Wang *et al*., 2020; Yu *et al*., 2020). cAMP is a critical molecule promoting the decidualization of human endometrial stromal cells; it can increase the expression of Forkhead box O1 (FOXO1) in decidual cells. This cell-specific core transcription factor is located downstream of the phosphoinositide-3 kinase (PI3K)/AKT signaling pathway and participates in cell proliferation, apoptosis, differentiation, and processes involving antioxidative stress and DNA damage (Cho *et al*., 2011; Mikihiro *et al*., 2015; Wang *et al*., 2020; Yu *et al*., 2020). Subsequently, FOXO1 increases the expression of multiple decidualization-related genes, including *Igfbp-1* and decorin (DCN) (Halari *et al*., 2020; Nakamura *et al*., 2013; 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 *Igfbp-1*, *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 AKT signaling pathway results in FOXO1 phosphorylation, impairing the decidualization process (Fabi *et al*., 2017; Yin *et al*., 2012). During decidualization, cAMP contributes to the inactivation of AKT in endometrial stromal cells via reducing the levels of protein phosphatase 2A (PP2A) inhibitors, among which cancerous inhibitor of protein phosphatase 2A (CIP2A) is particularly significant. The ETS family of transcription factors acts as a crucial intermediary 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 SRC kinase and in turn promoting the decidual transformation of human endometrial stromal cells (Nagashima *et al*., 2008). The mammalian target of rapamycin (mTOR), extracellular signal-regulated kinase (ERK) and neurogenic locus notch homolog (NOTCH) protein 1 signaling pathways also participate in decidualization. Activating the mammalian target of rapamycin 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 (Fabi *et al*., 2017; Mak *et al*., 2002; Nagashima *et al*., 2008; 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-β (TGF-β), bone morphogenetic protein (BMP), FGF, and Notch signaling, contributing to the establishment and maintenance of pregnancy (Li *et al*., 2022).

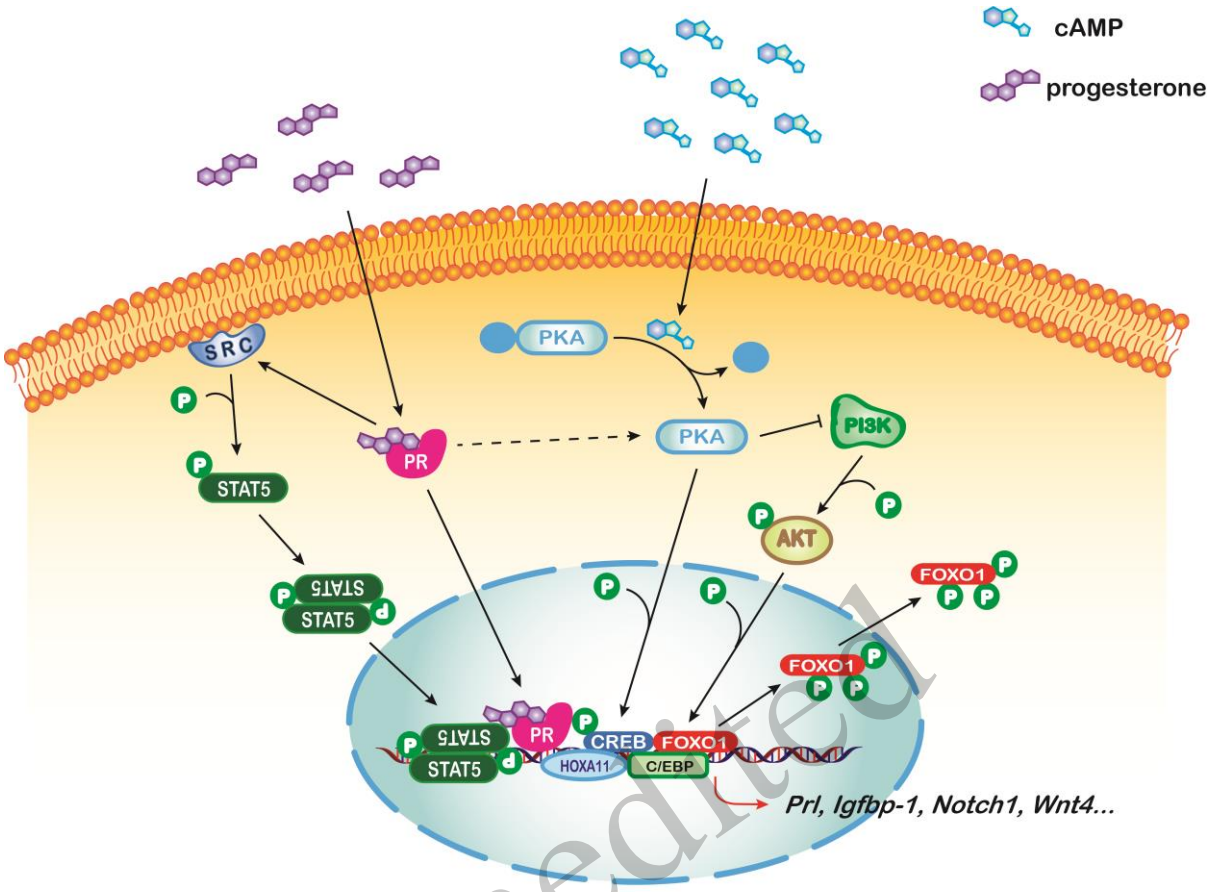

Fig. 2 Molecular mechanism of decidualization in human endometrial stromal cells

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 coregulates the expression of decidualization-related genes. The activation of PI3K/AKT pathway can result in the phosphorylation of the transcription factor FOXO1 and promote its nuclear export. cAMP; cyclic adenosine monophosphate; *Igfbp-1*: insulin-like growth factor binding protein 1 gene; *Prl*: prolactin gene; *Notch1*: neurogenic locus notch homolog protein 1 gene; *Wnt4*: Wingless-type MMTV integration site family member 4 gene; PR: progesterone receptor; SRC: Rous sarcoma oncogene cellular homolog; STAT5: signal transducer and activator of transcription 5; PKA: protein kinase A; PI3K: phosphoinositide 3 kinase; CREB: cAMP response element-binding protein; C/EBP: CCAAT-enhancer-binding proteins; HOXA11: homeobox A11; FOXO1: Forkhead box O1; AKT: AKT8 virus oncogene cellular homolog, also called protein kinase B.

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.

5.1 Humans

The human uterine cycle is divided into the following three phases: proliferative, secretory, and menstruation phase (Murray *et al*., 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 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 (Afshar *et al*., 2012; Fujimoto *et al*., 1996; Mori *et al*., 2017; Strassmann, 1996; 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*., 1996; 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 (Ding *et al*., 2018; Lim *et al*., 2017; Strassmann, 1996). FGF2 was 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 mainly expressed in the glandular epithelium, which gradually decreases after menopause (Hague *et al*., 2002). Paiva's research group reported that FGF2 expression increased throughout the menstrual cycle and was highest in the endometrium in the secretory phase and first trimester of human pregnancy (Paiva *et al*., 2011). 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), interleukin-6 (IL-6), interleukin-8 (IL-8), and monocyte chemotactic protein-1 (MCP1), 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*., 2019). Murata and colleages treated human ESCs with MPA and revealed that MPA did not affect FGF2 expression; however, FGF9 was found to be significantly downregulated after 3 days of treatment. They also showed that progesterone inhibited angiopoietin 2 (ANGPT2) production by inducing heart and neural crest derivative expressed 2 (HAND2) to inhibit FGF9, thereby attenuating FGF9 production in hESCs (Murata *et al*., 2019). 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 CREB1 modulate the expression of Shp2 by binding to the PTPN11 promoter, mediating FGF and IGF1 signaling to control cell proliferation (Zhou *et al*., 2024; Cheng *et al*., 2022). FGF7 stimulates the expression of *Igfbp-1* and *Prl* through the ERK and 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 reaches a peak 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 tests were used for statistical analysis, $\alpha = 0.05$) (Fig. 3a)

(Sutton *et al*., 2018).

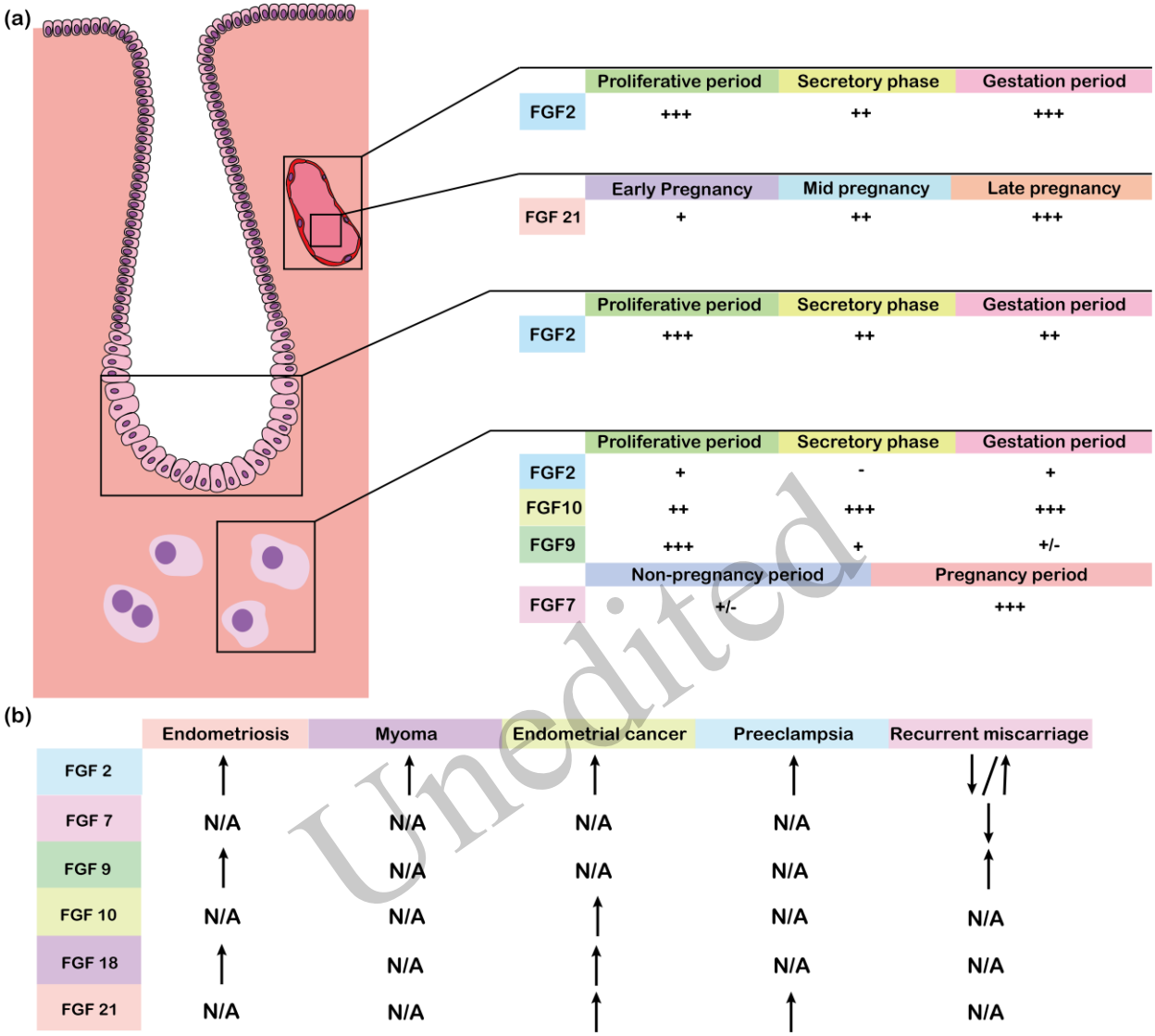

Fig. 3 Expression of FGFs in the context of a normal menstrual cycle, pregnancy, and disease

(a) The spatiotemporal expression patterns of FGF2, 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) 1) endothelial cells; 2) the serum; 3) the glandular epithelium; 4) endometrial stromal cells. The expression levels of FGFs during proliferation, secretion, and pregnancy are shown. The number of "+" symbols signifies the expression level. (b) The trend of changes in FGF2, FGF7, FGF9, FGF18, and FGF21 expression in various endometrial diseases is shown compared with those in healthy endometrium. "↑" Indicates an increase in expression levels in disease compared to healthy endometrium, "↓" indicates a decrease in expression levels in disease compared to healthy endometrium, and N/A indicates not applicable.

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-Citrinovitz *et al*., 2015). In rhesus monkeys (*Macaca mulatta*), uterine cells are able to synthesize FGF1 and FGF2. FGF1 is mainly localized 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 mediates the synthesis of these two factors distinctly (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 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 (Yang *et al*., 2023; Liu *et al*., 2022; Paria *et al*., 2001; Sahin Ersoy *et al*., 2017). 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 ≤ 4, and 19% had a score of 0 (maximal score = 6) (Dambaeva *et al*., 2021). These findings suggest that most people with RIF experience impaired decidualization (Dambaeva *et al*., 2021; Lash and Ernerudh, 2015). The causes of RIF are complicated and include 1) abnormal ciliogenesis of decidual stromal cells; 2) inactivation of TGF-β signaling in decidual cells (Hassan *et al*., 2022); 3) downregulation of the circadian clock gene *Bmal1* (Lv *et al*., 2019); and 4) homeostatic imbalance of decidual macrophages (dMφs). The number of CD86+ macrophages (M1) is significantly increased and the number of CD163+ 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 (Garrido-Gómez *et al*., 2022; Sahu *et al*., 2019). Recent studies have highlighted that the dysregulation of *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 ESC decidualization and the uterine microenvironment (Garrido-Gomez *et al*., 2020).

7 Fibroblast growth factor and endometrial diseases

The endometrium, an important part of the female reproductive system, comprises glands, vessels, the epithelium, and the stroma (Zhu *et al*., 2023). Fibroblast growth factors play a critical role in the regulation of endometrial physiology and pathology. In normal and ectopic human endometrium, 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 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 ERK1/2 signaling pathway (Yu *et al*., 2021; Ferriani *et al*., 1993). 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 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 FGF1, FGF2 and FGF9 expression 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 a key predisposing factor of 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 to 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 (Bodner-Adler *et al*., 2016; Li *et al*., 2020; Afrin *et al*., 2023; Helmke *et al*., 2011; Li *et al*., 2014; Soufla *et al*., 2008).

In humans, abnormal FGF signaling has been associated with endometrial cancer. Most FGFs carry out their 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 tissue 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 $\alpha = 0.05$ (the Mann–Whitney U test was used for comparisons between groups, the 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 the 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 (the Shapiro–Wilk test was employed to verify data normality, the 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) (Buell-Acosta *et al*., 2022; Stepan *et al*., 2013). 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 for 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 figures preparation. Xueni ZHANG and Zhijian SU drafted the manuscript. All authors 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 conflict of interest.

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

References

Afrin S, El Sabah M, Manzoor A, Miyashita-Ishiwata M, Reschke L, Borahay MA. 2023. Adipocyte coculture induces a pro-inflammatory, fibrotic, angiogenic, and proliferative microenvironment in uterine leiomyoma cells. *Biochim Biophys*

Acta Mol Basis Dis. 1869(1):166564.
https://doi.org/10.1016/j.bbadis.2022.166564

Afshar Y, Miele L,Fazleabas AT, 2012. Notch1 is regulated by chorionic gonadotropin and progesterone in endometrial stromal cells and modulates decidualization in primates. *Endocrinology*, **153**(6):2884-96.
https://doi.org/10.1210/en.2011-2122

Baerwald AR, Adams GP,Pierson RA, 2012. Ovarian antral folliculogenesis during the human menstrual cycle: a review. *Hum Reprod Update*, **18**(1):73-91.
https://doi.org/10.1093/humupd/dmr039

Buell-Acosta JD, Garces MF, Parada-Baños AJ, *et al*., 2022. Maternal Fibroblast Growth Factor 21 Levels Decrease during Early Pregnancy in Normotensive Pregnant Women but Are Higher in Preeclamptic Women-A Longitudinal Study. *Cells*, **11**(14).
https://doi.org/10.3390/cells11142251

Bhurke AS, Bagchi IC, Bagchi MK. 2016. Progesterone-Regulated Endometrial Factors Controlling Implantation. *Am J Reprod Immunol*. 75(3):237-45.
https://doi.org/10.1111/aji.12473

Bodner-Adler B, Mayerhofer K, Czerwenka K, *et al*.,2016. The role of fibroblast growth factor 2 in patients with uterine smooth muscle tumors: an immunohistochemical study. *Eur J Obstet Gynecol Reprod Biol*. 207:62-67.
https://doi.org/10.1016/j.ejogrb.2016.10.028

Borahay MA, Al-Hendy A, Kilic GS, Boehning D. 2015. Signaling Pathways in Leiomyoma: Understanding Pathobiology and Implications for Therapy. *Mol Med*. 13;21(1):242-56.
https://doi.org/10.2119/molmed.2014.00053

Chavan AR, Griffith OW,Wagner GP, 2017. The inflammation paradox in the evolution of mammalian pregnancy: turning a foe into a friend. *Curr Opin Genet Dev*, **47**:24-32.
https://doi.org/10.1016/j.gde.2017.08.004

Cho JH, Yoon MS, Koo JB, *et al*., 2011. The progesterone receptor as a transcription factor regulates phospholipase D1 expression through independent activation of protein kinase A and Ras during 8-Br-cAMP-induced decidualization in human endometrial stromal cells. *Biochem J*, **436**(1):181-91.
https://doi.org/10.1042/bj20101614

Cheng J, Liang J, Li Y, *et al*., 2022. Shp2 in uterine stromal cells critically regulates on time embryo implantation and stromal decidualization by multiple pathways during early pregnancy. *PLoS Genet*. 13;18(1):e1010018.
https://doi.org/10.1371/journal.pgen.1010018\

Cheng J, Sha Z, Li J, Li B, Luo X, Zhang Z, Zhou Y, Chen S, Wang Y. 2023. Progress on the Role of Estrogen and Progesterone Signaling in Mouse Embryo Implantation and Decidualization. *Reprod Sci*. 30(6):1746-1757.
https://doi.org/10.1007/s43032-023-01169-0

Chung D, Gao F, Jegga AG, Das SK. 2015. Estrogen mediated epithelial proliferation in the uterus is directed by stromal Fgf10 and Bmp8a. *Mol Cell Endocrinol*. 15;400:48-60.
https://doi.org/10.1016/j.mce.2014.11.002

Conrad KP, Rabaglino MB, Post Uiterweer ED. 2017. Emerging role for dysregulated decidualization in the genesis of preeclampsia. *Placenta*. 60:119-129.
https://doi.org/10.1016/j.placenta.2017.06.005

Dambaeva S, Bilal M, Schneiderman S, *et al*., 2021. Decidualization score identifies an endometrial dysregulation in samples from women with recurrent pregnancy losses and unexplained infertility. *F S Rep*, **2**(1):95-103.
https://doi.org/10.1016/j.xfre.2020.12.004

De Clercq K, Hennes A,Vriens J, 2017. Isolation of Mouse Endometrial Epithelial and Stromal Cells for In Vitro Decidualization. *J Vis Exp*, (121).
https://doi.org/10.3791/55168

Dey SK, Lim H, Das SK, *et al*., 2004. Molecular cues to implantation. *Endocr Rev*, **25**(3):341-73.
https://doi.org/10.1210/er.2003-0020

Ding J, Yin T, Yan N, *et al*., 2019. FasL on decidual macrophages mediates trophoblast apoptosis: A potential cause of recurrent miscarriage. *Int J Mol Med*, **43**(6):2376-2386.
https://doi.org/10.3892/ijmm.2019.4146

Ding NZ, Qi QR, Gu XW, *et al*., 2018. De novo synthesis of sphingolipids is essential for decidualization in mice. *Theriogenology*, **106**:227-236.
https://doi.org/10.1016/j.theriogenology.2017.09.036

Ding J, Tan X, Song K, *et al*., 2018. Bushen Huoxue Recipe Alleviates Implantation Loss in Mice by Enhancing Estrogen-Progesterone Signals and Promoting Decidual Angiogenesis Through FGF2 During Early Pregnancy. *Front Pharmacol*. 15; 9:437.
https://doi.org/10.3389/fphar.2018.00437\

Duncan WC. 2021. The inadequate corpus luteum. *Reprod Fertil*. 26;2(1):C1-C7.
https://doi.org/10.1530/RAF-20-0044

Emera D, Romero R,Wagner G, 2012. The evolution of menstruation: a new model for genetic assimilation: explaining molecular origins of maternal responses to fetal invasiveness. *Bioessays*, **34**(1):26-35.
https://doi.org/10.1002/bies.201100099

Estella C, Herrer I, Moreno-Moya JM, *et al*., 2012. miRNA signature and Dicer requirement during human endometrial stromal decidualization in vitro. *PloS one*, **7**(7):e41080. https://doi.org/10.1371/journal.pone.0041080

Evans J, Salamonsen LA, Winship A, *et al*., 2016. Fertile ground: human endometrial programming and lessons in health and disease. *Nat Rev Endocrinol*, **12**(11):654-667. https://doi.org/10.1038/nrendo.2016.116

Fabi F, Grenier K, Parent S, *et al*., 2017. Regulation of the PI3K/Akt pathway during decidualization of endometrial stromal cells. *PloS one*, **12**(5):e0177387. https://doi.org/10.1371/journal.pone.0177387

Flannery CA, Fleming AG, Choe GH, *et al*., 2016. Endometrial Cancer-Associated FGF18 Expression Is Reduced by Bazedoxifene in Human Endometrial Stromal Cells In Vitro and in Murine Endometrium. *Endocrinology*, **157**(10):3699-3708. https://doi.org/10.1210/en.2016-1233

Fu T, Zheng HT, Zhang HY, *et al*., 2019. Oncostatin M expression in the mouse uterus during early pregnancy promotes embryo implantation and decidualization. *FEBS Lett*, **593**(15):2040-2050. https://doi.org/10.1002/1873-3468.13468

Fujimoto J, Hori M, Ichigo S, *et al*., 1996. Ability of Ovarian Steroids to Regulate the Expression of the Fibroblast Growth Factor Family in Fibroblasts Derived from Uterine Endometrium. *J Biomed Sci*, **3**(4):280-285. https://doi.org/10.1007/bf02253708

Fujimoto J, Hori M, Ichigo S, *et al*., 1996. Expression of basic fibroblast growth factor and its mRNA in uterine endometrium during the menstrual cycle. *Gynecol Endocrinol*, **10**(3):193-7. https://doi.org/10.3109/09513599609027988

Fang Z, Tian Y, Sui C, Guo Y, Hu X, Lai Y, Liao Z, Li J, Feng G, Jin L, Qian K. 2022. Single-Cell Transcriptomics of Proliferative Phase Endometrium: Systems Analysis of Cell-Cell Communication Network Using CellChat. *Front Cell Dev Biol*. 22;10:919731. https://doi.org/10.3389/fcell.2022.919731

Figueroa V, Rodríguez MS, Lanari C, Lamb CA. 2019. Nuclear action of FGF members in endocrine-related tissues and cancer: Interplay with steroid receptor pathways. *Steroids*. 152:108492. https://doi.org/10.1016/j.steroids.2019.108492

Garrido-Gómez T, Castillo-Marco N, Cordero T, *et al*., 2022. Decidualization resistance in the origin of preeclampsia. *Am J Obstet Gynecol*, **226**(2s):S886-s894. https://doi.org/10.1016/j.ajog.2020.09.039

Garrido-Gomez T, Quiñonero A, Dominguez F, *et al*., 2020. Preeclampsia: a defect in decidualization is associated with deficiency of Annexin A2. *Am J Obstet Gynecol*, **222**(4):376.e1-376.e17. https://doi.org/10.1016/j.ajog.2019.11.1250

Gellersen B, Reimann K, Samalecos A, *et al*., 2010. Invasiveness of human endometrial stromal cells is promoted by decidualization and by trophoblast-derived signals. *Hum Reprod*, **25**(4):862-73. https://doi.org/10.1093/humrep/dep468

Gibson DA, Simitsidellis I, Cousins FL, *et al*., 2016. Intracrine Androgens Enhance Decidualization and Modulate Expression of Human Endometrial Receptivity Genes. *Sci Rep*, **6**:19970. https://doi.org/10.1038/srep19970

Gong H, Wu W, Xu J, *et al*., 2019. Flutamide ameliorates uterine decidualization and angiogenesis in the mouse hyperandrogenemia model during mid-pregnancy. *PloS one*, **14**(5):e0217095. https://doi.org/10.1371/journal.pone.0217095

Guo B, Tian XC, Li DD, *et al*., 2014. Expression, regulation and function of Egr1 during implantation and decidualization in mice. *Cell Cycle*, **13**(16):2626-40. https://doi.org/10.4161/15384101.2014.943581

Hague S, Manek S, Oehler MK, *et al*., 2002. Tamoxifen induction of angiogenic factor expression in endometrium. *Br J Cancer*, **86**(5):761-7. https://doi.org/10.1038/sj.bjc.6600157

Halari CD, Nandi P, Jeyarajah MJ, Renaud SJ, Lala PK. 2020. Decorin production by the human decidua: role in decidual cell maturation. *Mol Hum Reprod*. 26(10):784-796. https://doi.org/10.1093/molehr/gaaa058

Hassan E, Kojima R, Ozawa F, *et al*., 2022. Abnormal ciliogenesis in decidual stromal cells in recurrent miscarriage. *J Reprod Immunol*, **150**:103486. https://doi.org/10.1016/j.jri.2022.103486

Helmke BM, Markowski DN, Müller MH, *et al*., 2011. HMGA proteins regulate the expression of FGF2 in uterine fibroids. *Mol Hum Reprod*, **17**(2):135-42. https://doi.org/10.1093/molehr/gaq083

Jagodzińska A, Chudecka-Głaz A, Michalczyk K, *et al*., 2023. The Diagnostic Role of FGF 21 in Endometrial Cancer and Other Pathologies of the Uterine Corpus. *Diagnostics (Basel)*, **13**(3):399. https://doi.org/10.3390/diagnostics13030399

Jiang Y, Liao Y, He H, *et al*., 2015. FoxM1 Directs STAT3 Expression Essential for Human Endometrial Stromal Decidualization.

Sci Rep, **5**:13735.
https://doi.org/10.1038/srep13735

Jin ZY, Liu CK, Hong YQ, *et al*., 2022. BHPF exposure impairs mouse and human decidualization. *Environ Pollut*, **304**:119222.
https://doi.org/10.1016/j.envpol.2022.119222

Jones RL, Salamonsen LA,Findlay JK, 2002. Activin A promotes human endometrial stromal cell decidualization in vitro. *J Clin Endocrinol Metab*, **87**(8):4001-4.
https://doi.org/10.1210/jcem.87.8.8880

Jukic AM, Baird DD, Weinberg CR, *et al*., 2013. Length of human pregnancy and contributors to its natural variation. *Hum Reprod*, **28**(10):2848-55.
https://doi.org/10.1093/humrep/det297

Kajihara T, Brosens JJ,Ishihara O, 2013. The role of FOXO1 in the decidual transformation of the endometrium and early pregnancy. *Med Mol Morphol*, **46**(2):61-8.
https://doi.org/10.1007/s00795-013-0018-z

Kimura F, Takakura K, Takebayashi K, *et al*., 2001. Messenger ribonucleic acid for the mouse decidual prolactin is present and induced during in vitro decidualization of endometrial stromal cells. *Gynecol Endocrinol*, **15**(6):426-32.
https://doi.org/10.1080/gye.15.6.426.432

Kusama K, Yamauchi N, Yoshida K, *et al*., 2021. Senolytic treatment modulates decidualization in human endometrial stromal cells. *Biochem Biophys Res Commun*, **571**:174-180.
https://doi.org/10.1016/j.bbrc.2021.07.075

Kato N, Iwase A, Ishida C, *et al*., 2019. Upregulation of Fibroblast Growth Factors Caused by Heart and Neural Crest Derivatives Expressed 2 Suppression in Endometriotic Cells: A Possible Therapeutic Target in Endometriosis. *Reprod Sci*. 26(7):979-987.
https://doi.org/10.1177/1933719118802053

Lash GE,Ernerudh J, 2015. Decidual cytokines and pregnancy complications: focus on spontaneous miscarriage. *J Reprod Immunol*, **108**:83-9.
https://doi.org/10.1016/j.jri.2015.02.003

Li Ran, 2011. The promotion effect of cAMP on decidualization process in vitro of stromal cells in eutopic endometrium of patients with endometriosis. *Maternal and Child Health Care of China*, **26**(07):1092-1094.
https://api.semanticscholar.org/CorpusID:86922407

Li DD, Gao YJ, Tian XC, *et al*., 2014. Differential expression and regulation of Tdo2 during mouse decidualization. *J Endocrinol*, **220**(1):73-83.
https://doi.org/10.1530/joe-13-0429

Li M, Zhang H, Zhao X, *et al*., 2014. SPRY4-mediated ERK1/2 signaling inhibition abolishes 17β-estradiol-induced cell growth in endometrial adenocarcinoma cell. *Gynecol Endocrinol*, **30**(8):600-4.
https://doi.org/10.3109/09513590.2014.912264

Li Q, Kannan A, Demayo FJ, *et al*., 2011. The antiproliferative action of progesterone in uterine epithelium is mediated by Hand2. *Science*, **331**(6019):912-6.
https://doi.org/10.1126/science.1197454

Li X, Shen C, Liu X, *et al*., 2017. Exposure to benzo[a]pyrene impairs decidualization and decidual angiogenesis in mice during early pregnancy. *Environ Pollut*, **222**:523-531.
https://doi.org/10.1016/j.envpol.2016.11.029

Li X, Wang C, Xiao J, *et al*., 2016. Fibroblast growth factors, old kids on the new block. *Semin Cell Dev Biol*, **53**:155-67.
https://doi.org/10.1016/j.semcdb.2015.12.014

Li Y, Kang ZL, Qiao N, *et al*., 2017. Effects of Excess Copper Ions on Decidualization of Human Endometrial Stromal Cells. *Biol Trace Elem Res*, **177**(1):10-15.
https://doi.org/10.1007/s12011-016-0840-y

Liu H, Huang X, Mor G, *et al*., 2020. Epigenetic modifications working in the decidualization and endometrial receptivity. *Cell Mol Life Sci*, **77**(11):2091-2101.
https://doi.org/10.1007/s00018-019-03395-9

Liu M, Deng W, Tang L, *et al*., 2022. Menin directs regionalized decidual transformation through epigenetically setting PTX3 to balance FGF and BMP signaling. *Nat Commun*, **13**(1):1006.
https://doi.org/10.1038/s41467-022-28657-2

Larraín D, Prado J. 2024. New Insights into Molecular Pathogenesis of Uterine Fibroids: From the Lab to a Clinician-Friendly Review. *Leiomyoma - Dilemmas and New Perspectives*.
https://doi.org/10.5772/intechopen.1002969

Li B, Yan YP, Liang C, *et al*., 2022. Primary Cilia Restrain PI3K-AKT Signaling to Orchestrate Human Decidualization. *Int J Mol Sci*. 8;23(24):15573.
https://doi.org/10.3390/ijms232415573

Li Y, Qiang W, Griffin BB, Gao T, Chakravarti D, Bulun S, Kim JJ, Wei JJ. 2020. HMGA2-mediated tumorigenesis through angiogenesis in leiomyoma. *Fertil Steril*. 114(5):1085-1096.
https://doi.org/10.1016/j.fertnstert.2020.05.036

Lim W, Bae H, Bazer FW, Song G. 2017. Stimulatory effects of fibroblast growth factor 2 on proliferation and migration of uterine

luminal epithelial cells during early pregnancy. *Biol Reprod*. 96(1):185-198.
https://doi.org/10.1095/biolreprod.116.142331

Lv S, Wang N, Ma J, *et al*., 2019. Impaired decidualization caused by downregulation of circadian clock gene BMAL1 contributes to human recurrent miscarriage†. *Biol Reprod*, **101**(1):138-147.
https://doi.org/10.1093/biolre/ioz063

Mak IY, Brosens JJ, Christian M, *et al*., 2002. Regulated expression of signal transducer and activator of transcription, Stat5, and its enhancement of PRL expression in human endometrial stromal cells in vitro. *J Clin Endocrinol Metab*, **87**(6):2581-8.
https://doi.org/10.1210/jcem.87.6.8576

Martinez-Fierro ML, Garza-Veloz I, Castañeda-Lopez ME, *et al*., 2022. Evaluation of the Effect of the Fibroblast Growth Factor Type 2 (FGF-2) Administration on Placental Gene Expression in a Murine Model of Preeclampsia Induced by L-NAME. *Int J Mol Sci*, **23**(17).
https://doi.org/10.3390/ijms231710129

Mcconaha ME, Eckstrum K, An J, *et al*., 2011. Microarray assessment of the influence of the conceptus on gene expression in the mouse uterus during decidualization. *Reproduction*, **141**(4):511-27.
https://doi.org/10.1530/rep-10-0358

Mikihiro Y, Kazuya K,Kazuhiro T, 2015. Molecular Mechanisms of Human Endometrial Decidualization Activated by Cyclic Adenosine Monophosphate Signaling Pathways. *Journal of Mammalian Ova Research*, **32**(3):95-102.
https://doi.org/10.1274/jmor.32.95

Möller B, Rasmussen C, Lindblom B, *et al*., 2001. Expression of the angiogenic growth factors VEGF, FGF-2, EGF and their receptors in normal human endometrium during the menstrual cycle. *Mol Hum Reprod*, **7**(1):65-72.
https://doi.org/10.1093/molehr/7.1.65

Mori S, Hatori N, Kawaguchi N, *et al*., 2017. The integrin-binding defective FGF2 mutants potently suppress FGF2 signalling and angiogenesis. *Biosci Rep*, **37**(2).
https://doi.org/10.1042/bsr20170173

Murata H, Tsuzuki T, Kido T, *et al*., 2019. Progestin-induced heart and neural crest derivatives-expressed transcript 2 inhibits angiopoietin 2 via fibroblast growth factor 9 in human endometrial stromal cells. *Reprod Biol*, **19**(1):14-21.
https://doi.org/10.1016/j.repbio.2019.02.005

Muter J,Brosens JJ, 2018. Decidua. Academic Press, Oxford, UK, p. 424-430 (in English).

Massimiani M, Lacconi V, La Civita F, *et al*., 2019. Molecular Signaling Regulating Endometrium-Blastocyst Crosstalk. *Int J Mol Sci*. 18;21(1):23.
https://doi.org/10.3390/ijms21010023

Meng N, Yang Q, He Y, Gu WW, Gu Y, Zhen XX, *et al*., 2019. Decreased NDRG1 expression is associated with pregnancy loss in mice and attenuates the in vitro decidualization of endometrial stromal cells. *Mol Reprod Dev*. 86(9):1210-1223.
https://doi.org/10.1002/mrd.23238

Meng X, Chen C, Qian J, Cui L, Wang S. 2023. Energy metabolism and maternal-fetal tolerance working in decidualization. *Front Immunol*. 19;14:1203719.
https://doi.org/10.3389/fimmu.2023.1203719

Mestre-Citrinovitz AC, Kleff V, Vallejo G, *et al*., 2015. A Suppressive Antagonism Evidences Progesterone and Estrogen Receptor Pathway Interaction with Concomitant Regulation of Hand2, Bmp2 and ERK during Early Decidualization. *PLoS One*. 21;10(4):e0124756.
https://doi.org/10.1371/journal.pone.0124756

Murata H, Tanaka S, Okada H. 2022. The Regulators of Human Endometrial Stromal Cell Decidualization. *Biomolecules*. 10;12(9):1275.
https://doi.org/10.3390/biom12091275

Murray C M, Orr C J. 2020. Hormonal regulation of the menstrual cycle and ovulation. *In*: Christopher S. Kovacs, Cheri L. Deal. (Eds.), Maternal-Fetal and Neonatal Endocrinology. Academic Press, p. 159-167.

Nagashima T, Maruyama T, Uchida H, *et al*., 2008. Activation of SRC kinase and phosphorylation of signal transducer and activator of transcription-5 are required for decidual transformation of human endometrial stromal cells. *Endocrinology*, **149**(3):1227-34.
https://doi.org/10.1210/en.2007-1217

Nakamura M, Takakura M, Fujii R, Maida Y, Bono Y, *et al*., 2013. The PRB-dependent FOXO1/IGFBP-1 axis is essential for progestin to inhibit endometrial epithelial growth. *Cancer Lett*. 336(1):68-75.
https://doi.org/10.1016/j.canlet.2013.04.010

Nnamani MC, Ganguly S, Erkenbrack EM, Lynch VJ, et ai., 2016. A Derived Allosteric Switch Underlies the Evolution of Conditional Cooperativity between HOXA11 and FOXO1. *Cell Rep*. 15(10):2097-2108.
https://doi.org/10.1016/j.celrep.2016.04.088

Okada H, Tsuzuki T,Murata H, 2018. Decidualization of the human endometrium. *Reproductive medicine and biology*, **17**(3):220-227.
https://doi.org/10.1002/rmb2.12088

Orazov MR, Radzinskiy VE, Kostin IN, *et al*., 2021. Endometrial asynchrony in pathogenesis of implantation impairment in women with infertility associated with endometriosis. *Gynecol Endocrinol*, **37**(sup1):1-3.
https://doi.org/10.1080/09513590.2021.2006437

Paiva P, Hannan NJ, Hincks C, *et al*., 2011. Human chorionic gonadotrophin regulates FGF2 and other cytokines produced by human endometrial epithelial cells, providing a mechanism for enhancing endometrial receptivity. *Hum Reprod*, **26**(5):1153-62.
https://doi.org/10.1093/humrep/der027

Pan-Castillo B, Gazze SA, Thomas S, *et al*., 2018. Morphophysical dynamics of human endometrial cells during decidualization. *Nanomedicine*, **14**(7):2235-2245.
https://doi.org/10.1016/j.nano.2018.07.004

Paria BC, Ma W, Tan J, *et al*., 2001. Cellular and molecular responses of the uterus to embryo implantation can be elicited by locally applied growth factors. *Proc Natl Acad Sci U S A*, **98**(3):1047-52.
https://doi.org/10.1073/pnas.98.3.1047

Paul EN, Burns GW, Carpenter TJ, *et al*., 2021. Transcriptome Analyses of Myometrium from Fibroid Patients Reveals Phenotypic Differences Compared to Non-Diseased Myometrium. *Int J Mol Sci*, **22**(7).
https://doi.org/10.3390/ijms22073618

Peterse D, Clercq K, Goossens C, Binda MM, *et al*., 2018. Optimization of Endometrial Decidualization in the Menstruating Mouse Model for Preclinical Endometriosis Research. *Reprod Sci*. 25(11):1577-1588.
https://doi.org/10.1016/j.placenta.2017.06.005

Popovici RM, Kao LC,Giudice LC, 2000. Discovery of new inducible genes in in vitro decidualized human endometrial stromal cells using microarray technology. *Endocrinology*, **141**(9):3510-3.
https://doi.org/10.1210/endo.141.9.7789

Qi QR, Zhao XY, Zuo RJ, Wang TS, Gu XW, Liu JL, Yang ZM. 2015. Involvement of atypical transcription factor E2F8 in the polyploidization during mouse and human decidualization. *Cell Cycle*. 14(12):1842-58.
https://doi.org/10.1080/15384101.2015.1033593

Rauk PN, Surti U, Roberts JM, *et al*., 1995. Mitogenic effect of basic fibroblast growth factor and estradiol on cultured human myometrial and leiomyoma cells. *Am J Obstet Gynecol*, **173**(2):571-7.
https://doi.org/10.1016/0002-9378(95)90284-8

Redman CW, Sargent IL,Staff AC, 2014. IFPA Senior Award Lecture: making sense of pre-eclampsia - two placental causes of preeclampsia? *Placenta*, **35 Suppl**:S20-5.
https://doi.org/10.1016/j.placenta.2013.12.008

Rider V, Carlone DL,Foster RT, 1997. Oestrogen and progesterone control basic fibroblast growth factor mRNA in the rat uterus. *J Endocrinol*, **154**(1):75-84.
https://doi.org/10.1677/joe.0.1540075

Rytkönen KT, Erkenbrack EM, Poutanen M, *et al*., 2019. Decidualization of Human Endometrial Stromal Fibroblasts is a Multiphasic Process Involving Distinct Transcriptional Programs. *Reprod Sci*, **26**(3):323-336.
https://doi.org/10.1177/1933719118802056

Sahin Ersoy G, Zhou Y, İnan H, *et al*., 2017. Cigarette Smoking Affects Uterine Receptivity Markers. *Reprod Sci*, **24**(7):989-995.
https://doi.org/10.1177/1933719117697129

Sahu MB, Deepak V, Gonzales SK, *et al*., 2019. Decidual cells from women with preeclampsia exhibit inadequate decidualization and reduced sFlt1 suppression. *Pregnancy Hypertens*, **15**:64-71.
https://doi.org/10.1016/j.preghy.2018.11.003

Sak ME, Gul T, Evsen MS, *et al*., 2013. Fibroblast growth factor-1 expression in the endometrium of patients with repeated implantation failure after in vitro fertilization. *Eur Rev Med Pharmacol Sci*, **17**(3):398-402.
https://www.europeanreview.org/article/3147

Salamonsen LA,Jones RL, 2003. Endometrial Remodeling. Academic Press, New York, USA, p. 504-512 (in English).

Samathanam CA, Adesanya OO, Zhou J, *et al*., 1998. Fibroblast growth factors 1 and 2 in the primate uterus. *Biol Reprod*, **59**(3):491-6.
https://doi.org/10.1095/biolreprod59.3.491

Sangha RK, Li XF, Shams M, *et al*., 1997. Fibroblast growth factor receptor-1 is a critical component for endometrial remodeling: localization and expression of basic fibroblast growth factor and FGF-R1 in human endometrium during the menstrual cycle and decreased FGF-R1 expression in menorrhagia. *Lab Invest*, **77**(4):389-402.
https://doi.org/10.1121/1.419660

Sevostyanova O, Lisovskaya T, Chistyakova G, *et al*., 2020. Proinflammatory mediators and reproductive failure in women with uterine fibroids. *Gynecol Endocrinol*, **36**(sup1):33-35.
https://doi.org/10.1080/09513590.2020.1816726

Shuya LL, Menkhorst EM, Yap J, *et al*., 2011. Leukemia inhibitory factor enhances endometrial stromal cell decidualization in humans and mice. *PloS one*, **6**(9):e25288.
https://doi.org/10.1371/journal.pone.0025288

Song Z, Li B, Li M, *et al*., 2022. Caveolin-1 Regulation and Function in Mouse Uterus during Early Pregnancy and under Human In Vitro Decidualization. *Int J Mol Sci*, **23**(7).
https://doi.org/10.3390/ijms23073699

Soufla G, Sifakis S,Spandidos DA, 2008. FGF2 transcript levels are positively correlated with EGF and IGF-1 in the malignant endometrium. *Cancer Lett*, **259**(2):146-55.
https://doi.org/10.1016/j.canlet.2007.10.002

Stepan H, Kley K, Hindricks J, *et al*., 2013. Serum levels of the adipokine fibroblast growth factor-21 are increased in preeclampsia. *Cytokine*, **62**(2):322-6. https://doi.org/10.1016/j.cyto.2013.02.019

Strassmann BI, 1996. The evolution of endometrial cycles and menstruation. *Q Rev Biol*, **71**(2):181-220. https://doi.org/10.1086/419369

Sutton EF, Morrison CD, Stephens JM, *et al*., 2018. Fibroblast growth factor 21, adiposity, and macronutrient balance in a healthy, pregnant population with overweight and obesity. *Endocr Res*, **43**(4):275-283. https://doi.org/10.1080/07435800.2018.1473421

Šućurović S, Nikolić T, Brosens JJ, *et al*., 2017. Spatial and Temporal Analyses of FGF9 Expression During Early Pregnancy. *Cell Physiol Biochem*. 42(6):2318-2329. https://doi.org/10.1159/000480004

Tanaka K, Minoura H, Isobe T, *et al*., 2003. Ghrelin is involved in the decidualization of human endometrial stromal cells. *J Clin Endocrinol Metab*, **88**(5):2335-40. https://doi.org/10.1210/jc.2002-021024

Tang Z, Wang L, Huang Z, *et al*., 2022. CD55 is upregulated by cAMP/PKA/AKT and modulates human decidualization via Src and ERK pathway and decidualization-related genes. *Mol Reprod Dev*, **89**(5-6):256-268. https://doi.org/10.1002/mrd.23569

Taniguchi F, Harada T, Sakamoto Y, *et al*., 2003. Activation of mitogen-activated protein kinase pathway by keratinocyte growth factor or fibroblast growth factor-10 promotes cell proliferation in human endometrial carcinoma cells. *J Clin Endocrinol Metab*, **88**(2):773-80. https://doi.org/10.1210/jc.2002-021062

Teng CB, Diao HL, Ma XH, *et al*., 2004. Differential expression and activation of Stat3 during mouse embryo implantation and decidualization. *Mol Reprod Dev*, **69**(1):1-10. https://doi.org/10.1002/mrd.20149

Tong J , Lv S , Yang J ,*et al*. 2022. Decidualization and Related Pregnancy Complications. *Maternal-Fetal Medicine*. 4(1):p 24-35. https://doi.org/10.1097/FM9.0000000000000135

Tsai JH, Schulte M, O'neill K, *et al*., 2013. Glucosamine inhibits decidualization of human endometrial stromal cells and decreases litter sizes in mice. *Biol Reprod*, **89**(1):16. https://doi.org/10.1095/biolreprod.113.108571

Vasquez YM, Mazur EC, Li X, *et al*., 2015. FOXO1 is required for binding of PR on IRF4, novel transcriptional regulator of endometrial stromal decidualization. *Mol Endocrinol*, **29**(3):421-33. https://doi.org/10.1210/me.2014-1292

Wang C, Zhao M, Zhang WQ, *et al*., 2020. Comparative Analysis of Mouse Decidualization Models at the Molecular Level. *Genes (Basel)*, **11**(8). https://doi.org/10.3390/genes11080935

Wang H, Zhang M,Ge L, 2022. Cholesterol: Enhancing FGF2 translocation in unconventional secretion. *J Cell Biol*, **221**(11). https://doi.org/10.1083/jcb.202210007

Wu D, Kimura F, Zheng L, *et al*., 2017. Chronic endometritis modifies decidualization in human endometrial stromal cells. *Reprod Biol Endocrinol*, **15**(1):16. https://doi.org/10.1186/s12958-017-0233-x

Wu X, Blanck A, Olovsson M, *et al*., 2001. Expression of basic fibroblast growth factor (bFGF), FGF receptor 1 and FGF receptor 2 in uterine leiomyomas and myometrium during the menstrual cycle, after menopause and GnRHa treatment. *Acta Obstet Gynecol Scand*, **80**(6):497-504. https://doi.org/10.1034/j.1600-0412.2001.080006497.x

Wu SP, Li R, DeMayo FJ, 2018. Progesterone Receptor Regulation of Uterine Adaptation for Pregnancy. *Trends Endocrinol Metab*. 29(7):481-491. https://doi.org/10.1016/j.tem.2018.04.001

Xu X, Wang J, Guo X, *et al*., 2023. GPR30-mediated non-classic estrogen pathway in mast cells participates in endometriosis pain via the production of FGF2. *Front Immunol*, **14**:1106771. https://doi.org/10.3389/fimmu.2023.1106771

Yan X, Rong M, Zhou Q, *et al*., 2022. DCAF13 is essential for the pathogenesis of preeclampsia through its involvement in endometrial decidualization. *Mol Cell Endocrinol*, **556**:111741. https://doi.org/10.1016/j.mce.2022.111741

Yerlikaya G, Balendran S, Pröstling K, *et al*., 2016. Comprehensive study of angiogenic factors in women with endometriosis compared to women without endometriosis. *Eur J Obstet Gynecol Reprod Biol*, **204**:88-98. https://doi.org/10.1016/j.ejogrb.2016.07.500

Yin X, Pavone ME, Lu Z, *et al*., 2012. Increased activation of the PI3K/AKT pathway compromises decidualization of stromal cells from endometriosis. *J Clin Endocrinol Metab*, **97**(1):E35-43. https://doi.org/10.1210/jc.2011-1527

Yagel S, Goldman-Wohl D S. 2019. Placental implantation and development. *In*: Simcha Yagel, Norman H. Silverman, Ulrich Gembruch. (Eds.), Fetal Cardiology. CRC Press, Boca Raton, p.54-66.

Yang SC, Park M, Hong KH, La H, Park C *et al*..2023. CFP1 governs uterine epigenetic landscapes to intervene in progesterone

responses for uterine physiology and suppression of endometriosis. *Nat Commun*. 14(1):3220. https://doi.org/10.1038/s41467-023-39008-0

Yin Y, Haller ME, Chadchan SB, *et al*., 2021. Signaling through retinoic acid receptors is essential for mammalian uterine receptivity and decidualization. *JCI Insight*. 8;6(17):e150254. https://doi.org/10.1172/jci.insight.150254

Yu SL, Lee SI, Park HW, Lee SK, Kim TH, Kang J, Park SR.2022. SIRT1 suppresses in vitro decidualization of human endometrial stromal cells through the downregulation of forkhead box O1 expression. *Reprod Biol*. 22(3):100672. https://doi.org/10.1016/j.repbio.2022.100672

Yu X, Wang Y, Tan X, Li M.2021. Upregulation of fibroblast growth factor 2 contributes to endometriosis through SPRYs/DUSP6/ERK signaling pathway. *Acta Histochem*. 123(5):151749. https://doi.org/10.1016/j.acthis.2021.151749

Yu HF, Duan CC, Yang ZQ, *et al*., 2020. Malic enzyme 1 is important for uterine decidualization in response to progesterone/cAMP/PKA/HB-EGF pathway. *Faseb j*, **34**(3):3820-3837. https://doi.org/10.1096/fj.201902289R

Zhang X, Ibrahimi OA, Olsen SK, *et al*., 2006. Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. *J Biol Chem*, **281**(23):15694-700. https://doi.org/10.1074/jbc.M601252200

Zhang Y, Zhang Z, Kang N, *et al*., 2022. Generation of a Mouse Artificial Decidualization Model with Ovariectomy for Endometrial Decidualization Research. *Journal of Visualized Experiments*, (185). https://doi.org/10.3791/64278

Zheng W, Zhao S, He H, *et al*., 2023. E2F2 is upregulated by the ERK pathway and regulates decidualization via MCM4. *Gene*, **871**:147400. https://doi.org/10.1016/j.gene.2023.147400

Zhao M, Zhang WQ, Liu JL. 2017. A study on regional differences in decidualization of the mouse uterus. *Reproduction*. 153(5):645-653. https://doi.org/10.1530/REP-16-0486

Zhao L, Yang H, Xuan Y, Luo Z, Lin Q, Zhao J, Ren N, Zhou S, Zhao X. 2015. Increased expression of fibroblast growth factor receptor 1 in endometriosis and its correlation with endometriosis-related dysmenorrhea and recurrence. *Eur J Obstet Gynecol Reprod Biol*. 184:117-24.. https://doi.org/10.1016/j.ejogrb.2014.11.013

Zhao W, Xu C, Peng L, Ma L, Du M. 2023. cAMP/PKA signaling promotes AKT deactivation by reducing CIP2A expression, thereby facilitating decidualization. *Mol Cell Endocrinol*. 571:111946. https://doi.org/10.1016/j.mce.2023.111946

Zhou P, Ouyang L, Jiang T, Tian Y, Deng W, Wang H, Kong S, Lu Z. 2024. Progesterone and cAMP synergistically induce SHP2 expression via PGR and CREB1 during uterine stromal decidualization. *FEBS J*. 291(1):142-157. https://doi.org/10.1111/febs.16966

Zhou WJ, Hou XX, Wang XQ, *et al*., 2017. Fibroblast Growth Factor 7 Regulates Proliferation and Decidualization of Human Endometrial Stromal Cells via ERK and JNK Pathway in an Autocrine Manner. *Reprod Sci*.24(12):1607-1619. https://doi.org/10.1177/1933719117697122

ZJ Tang, HY Guan, L Wang, W Zhang, 2021. Research Progress on Human Endometrium Decidualization In vitro Cell Models. *Reproductive and Developmental Medicine*, 5(2):9. https://doi.org/10.4103/2096-2924.320882

Zhu DL, Tuo XM, Rong Y, *et al*., 2020. Fibroblast growth factor receptor signaling as therapeutic targets in female reproductive system cancers. *J Cancer*, **11**(24):7264-7275. https://doi.org/10.7150/jca.44727

Zhu J, Li Z, Yin F, *et al*., 2023. Fibroblast growth factor 1 ameliorates thin endometrium in rats through activation of the autophagic pathway. *Front Pharmacol*, **14**:1143096. https://doi.org/10.3389/fphar.2023.1143096