**REVIEW**

# The role of extracellular matrix on unfavorable maternal–fetal interface: focusing on the function of collagen in human fertility

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## Abstract

Extracellular matrix (ECM) is characterized as widespread, abundant, and pluripotent. Among ECM members, collagen is widely accepted as one of the most prominent components for its essential structural property that can provide a scaffold for other components of ECM and the rich biological functions, which has been extensively used in tissue engineering. Emerging evidence has shown that the balance of ECM degradation and remodeling is vital to regulations of maternal–fetal interface including menstrual cycling, decidualization, embryo implantation and pregnancy maintenance. Moreover, disorders in these events may eventually lead to failure of pregnancy. Although the improvement of assisted conception and embryo culture technologies bring hope to many infertile couples, some unfavorable outcomes, such as recurrent implantation failure (RIF), recurrent pregnancy loss (RPL) or recurrent miscarriage (RM), keep troubling the clinicians and patients. Recently, in vitro three-dimensional (3D) model mimicking the microenvironment of the maternal–fetal interface is developed to investigate the physiological and pathological conditions of conception and pregnancy. The progress of this technology is based on clarifying the role of ECM in the endometrium and the interaction between endometrium and conceptus. Focusing on collagen, the present review summarized the degradation and regulation of ECM and its role in normal menstruation, endometrium receptivity and unsatisfying events occurring in infertility treatments, as well as the application in therapeutic approaches to improve pregnancy outcomes. More investigations about ECM focusing on the maternal–fetal interface interaction with mesenchymal stem cells or local immunoregulation may inspire new thoughts and advancements in the clinical application of infertility treatments.

**Keywords:** Collagen, Extracellular matrix (ECM), Matrix metalloproteinases (MMPs), Endometrium, Maternal–fetal interface, Infertility

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**Graphical abstract**
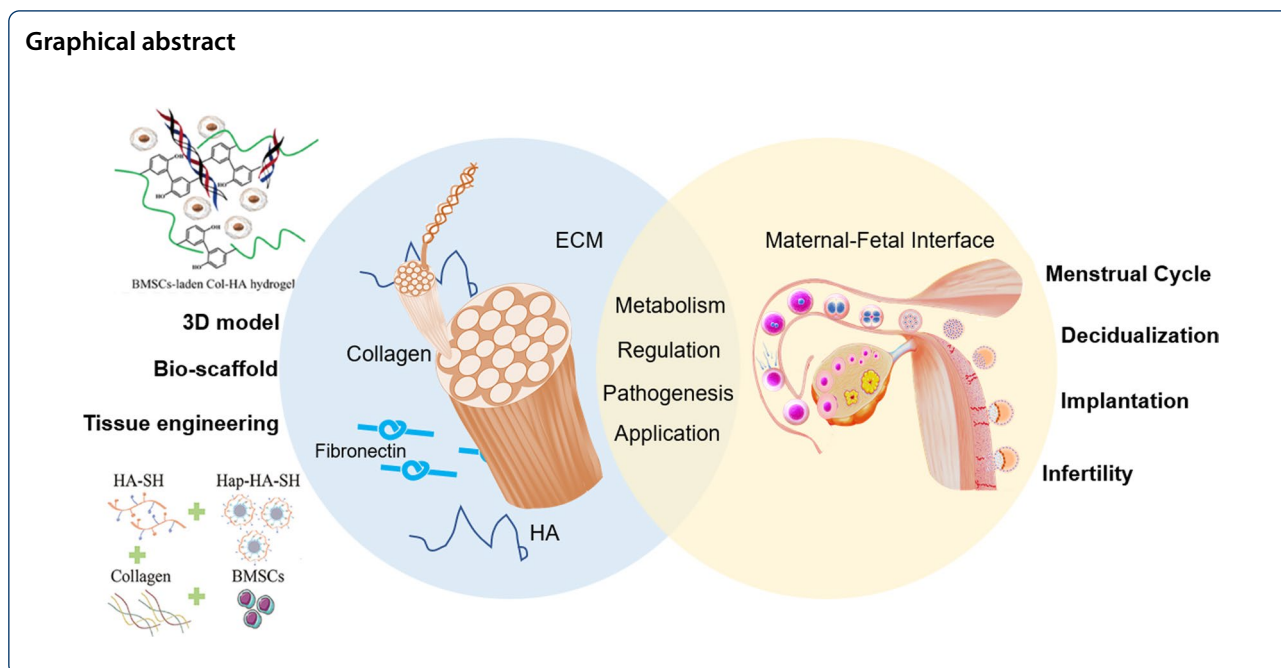


## 1 Introduction

The extracellular matrix (ECM) is a stereoscopic structure that distributes all around the human body but with unique composition in every organ tissue. Not only supporting mechanical integrity as a tissue scaffold, ECM also provides a living environment for different types of cells and dynamically controls the tissue homeostasis by matrix-cell signaling, regulating the cell survival, proliferation, migration, and differentiation [1–3]. Collagen, the crucial component of ECM, is an important natural renewable resource in nature, which has been used in leather manufacturing for thousands of years. Approximately 29 types of collagen molecules have been identified and studied, and a variety of multi-functional biomaterials have been prepared using collagen. Generally, collagen could be classified into non-fibrillar and fibrillar (e.g., collagen I, III, V) forms, and the latter mainly plays architectural and mechanical functions like providing skin tensile strength and ligament traction. The abundant biological functions of collagen may also include anchoring, tissue-tissue adhesion, ossification and synaptic formation [4, 5]. In the human body, it composes 75% of the dry weight of skin, more than 90% of tendon and corneal tissue and about 80% of organic bone tissue [5]. ECM is also composed of glycoproteins and proteoglycans. Glycoproteins might function as connectors between ECM with cells, like fibronectin, while proteoglycans are responsible for tissue hydrating [6, 7]. Functioning as hydrating ECM, hyaluronic acid (HA), a non-sulfated glycosaminoglycan polymer, naturally presents in many mammalian tissues and intercellular substances [8, 9]. It has a variety of physiological effects such as natural moisturizing effect, lubricating joints to protect cartilage, promoting wound healing and so on [10, 11]. For good biocompatibility and biodegradability, the application of ECM in regenerative medicine has been gradually expanded.

For the world community, the number and structure of the population have always been related to the stability of human society. At present, the global fertility rate continues to decline. It is expected that the world's population will reach the highest peak of 9.7 billion by 2064, then it will fall to 8.8 billion by 2100, and the world's working-age population has decreased significantly, which will also have a serious negative impact on the global economy [12]. It is essential to restore steady population growth as soon as possible and to correct the deviation in the age structure, the most important of which is to increase fertility and birth rates. For a successful pregnancy, not only "seed", but also "soil" is a critical determinant. As the soil for incubating a new life, the endometrium undergoes continuous and dynamic changes, equipping to be receptive for an embryo and adjusting for embryo development. In clinical practice of assisted reproductive technology (ART), there are a certain group of patients that could not achieve satisfying outcomes possibly explained by the unfavorable endometrium or decidua, including recurrent implantation failure (RIF), recurrent pregnancy loss (RPL) or recurrent miscarriage (RM), etc. [13–15]. These remain as knotty problems for reproductive

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clinicians especially when embryos of good quality were acquired and no chromosome anomalies could be diagnosed. Although viewpoints, like endometrium unresponsiveness, asynchrony between endometrium and embryos growth, natural selection of maternal–fetal interface or chronic inflammation-related unreceptivity, are widely accepted, the mechanism in-depth behind the unfavorable pathological endometrium are complex and not yet to be clearly understood.

Growing evidence has shown that ECM plays a crucial role in the physiological regulation of implantation and pregnancy. Moreover, the dysregulation of ECM is also related to the unfavorable maternal–fetal interface and the pathogenesis of a variety of related diseases, which is becoming a popular research focus. Major components of ECM on maternal–fetal interface include collagen families, fibrillin, fibulin, elastin, tenascin C, fibronectin, laminin, hyaluronan and heparan sulfate, building up local interstitial fibers, stroma, vessels, basement membranes or decidual cells on endometrium and placenta. Most of them are under dynamic regulation along with menstrual cycling and pregnancy maintenance [16]. In recent years, advanced in vitro models highly simulating in vivo micro-physiological environment, called organ-on-chips (OOC), are developed for studying human physiological and pathological processes as well as therapeutic strategies against the background of scientific ethics and sampling difficulties [17]. Investigating the mechanism of the unfavorable maternal–fetal interface in infertility focusing on ECM lay the foundation for fetal-maternal OOC (FM-OOC) engineering progression. In turn, in vitro models are crucial to verify the associated speculations and possible treatments on infertile endometrium. This review, focusing on collagen, aims to summarize the degradation and regulation of ECM and the potential role of ECM on infertile endometrium or decidua, and the application of ECM as biomaterials, expecting to provide a better comprehension of micromechanism of the unfavorable outcomes in infertility treatment.

## 2 Degradation and regulation of the ECM
### 2.1 Degradation
Collagen, the abundant and crucial component of ECM, can affect the important biological function and stability of ECM. There are many different types of collagen and corresponding communication receptors in the maternal–fetal interface, including collagen type I, III, IV [18]. Collagen and other ECM components hydrolysis can regulate the assembly of ECM, correct the excess expression of proteins in ECM and reshape its structure, and play the role of releasing biologically active fragments and growth factors in the process of growth, morphological change,
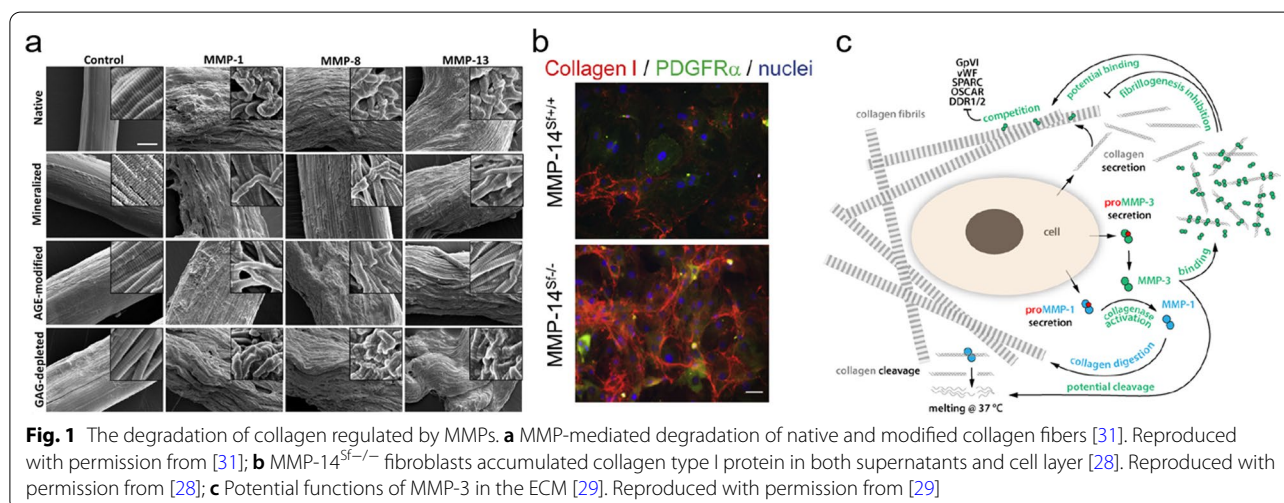
tissue repair and pathological change [19]. Matrix metalloproteinases (MMPs), A Disintegrin and Metalloproteinase (ADAM) and A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS) are zinc-dependent endopeptidases that play a critical role in the destruction of extracellular matrix proteins [20]. Under normal physiological conditions, MMPs, ADAM and ADAMTS gene expression aids in the maintenance of homeostasis.

ADAMs belong to the family of transmembrane and secretory proteins with important roles in regulating cellular phenotypes through effects on cell adhesion, migration, proteolysis and signaling [20]. It has been shown to be participated in a variety of biological processes, such as the process of sperm maturation, sperm adhesion and migration in the uterus, osteoarthritis, tumors and the occurrence of inflammatory reactions (21). ADAMTS shares some common structural features with ADAM, which is the family of secretory proteins. It tends to integrate into the extracellular matrix or is free in the blood plasma, which may favor its biological function [22]. There are amounts evidence indicate that ADAMTS plays a role in the degradation of the extracellular matrix, the adhesion of cells to the matrix and the reconstitution of tissues and organs, thereby regulating ovulation, embryonic development, connective tissue diseases, tumors and other physiological and pathological processes [23]. However, MMPs are considered to be the main enzymes that degrade ECM, also known as matrixins [24]. They were first mentioned in 1949 [25] and were first identified as a collagen hydrolase by Gross, J. and Lapiere, CM in 1962 [26]. As shown in Table 1, they are commonly classified on the basis of their substrates and the organization of their structural domains into collagenases (Fig. 1a), gelatinases, stromelysins, matrilysins, membrane-type (MT) MMPs, and other MMPs [27]. With the attention to collagen, it is necessary to describe the regulation of MMPs on it more widely. As shown in Fig. 1b, c, except for the collagenase family, it was found that MMP-14 and MMP-3 also played an important role in collagen degradation [28, 29] (Fig. 1b, c). For sustaining homeostatic ECM conditions, MMPs, ADAMs and ADAMTS are regulated via their expression, the processing of their zymogens to active them and via endogenous tissue inhibitors of matrix metalloproteinases (TIMPs) [30]. Here, we focus on the significance of the balance of MMPs and TIMPs for ECM proteins hydrolysis metabolism.

Collagen distribution can also be regulated by TIMP-MMP balance [32]. TIMPs are endogenous protease inhibitors, which together with several other zinc-dependent metallopeptidase families regulate MMPs, forming a very tight 1:1 stoichiometric inhibitory complex. After secretion, they can interact with various

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**Table 1** Classification of MMPs and main substrates of the principal members

| Classification | Member | Main ECM substrates |
|---|---|---|
| Collagenases | MMP-1 | Collagen-I, II, III; gelatin; aggrecan; nidogen; perlecan |
| | MMP-8 | Collagen-I, II, III; gelatin; aggrecan; elastin; fibronectin |
| | MMP-13 | Collagen-I, II, III, IV; gelatin; aggrecan; laminin; fibronectin |
| | MMP-18 | Collagen-I, II, III; gelatin; |
| Gelatinases | MMP-2 | Collagen-IV, V; gelatin; aggrecan; laminin; fibronectin |
| | MMP-9 | Collagen-IV, V, VII, X; gelatin; elastin |
| Stromelysins | MMP-3 | Collagen-II, IV, IX, X; gelatin; laminin; fibronectin |
| | MMP-10 | Collagen-III, IV, V; gelatin; elastin; laminin; fibronectin |
| Matrilysins | MMP-7 | IV, X; gelatin; aggrecan; elastin; enactin |
| | MMP-26 | IV; gelatin; fibrinogen; fibronectin; vitronectin |
| Membrane-type | MMP-14, -15, -16, -17 | Gelatin; aggrecan; elastin; fibrin; fibronectin; laminin; nidogen; vitronectin |
| Other MMPs | MMP-12, -19, -20,-22, -27 | Gelatin; aggrecan; fibronectin; laminin; nidogen; |



**Fig. 1** The degradation of collagen regulated by MMPs. **a** MMP-mediated degradation of native and modified collagen fibers [31]. Reproduced with permission from [31]; **b** MMP-14$^{Sf-/-}$ fibroblasts accumulated collagen type I protein in both supernatants and cell layer [28]. Reproduced with permission from [28]; **c** Potential functions of MMP-3 in the ECM [29]. Reproduced with permission from [29]

membrane-anchored or secreted MMPs [33]. The TIMP family (TIMP 1–4), has similar but not identical protease inhibitory profiles, possesses broad, overlapping specificity and selectively inhibits different MMPs, ADAMs and ADAMTS [33]. MMPs play an important role in activating biologically active proteins (such as cytokines, chemokines and cell surface proteins). Therefore, regulating these physiological processes through TIMPs can also affect matrix turnover under many conditions, resulting in ECM deposition [34].

Regulation of collagen by MMPs play a significant role in many physiological processes, such as bone remodeling, angiogenesis and inflammation, and MMPs secreted by endometrial cells are involved in physiological processes such as the menstrual cycle, endometrial remodeling, endometrial vascular formation, decidualization, embryo implantation, trophoblast invasion and migration [35]. In the endometrium, MMP-11 expression is

regulated by sex steroid hormones and is related to the degradation and remodeling of normal endometrium [36]. Decreased MMP-2 expression in the endometrium leads to collagen deposition in the interstitial and perineal regions [37]. Both MMP-2 and MMP-9 play an integral role in human embryo implantation and are the main rate-limiting enzymes in ECM remodeling during implantation [38]. MMPs (MMP-14 and ADAM-10) are also present in exosomes secreted by the endometrium, and hormones that regulate uterine receptivity can also regulate the composition of MMPs in exosomes [39, 40]. Expression of MMP-3 and MMP-10 in endometriosis is significantly increased [41]. Altered MMP expression is also critical to the physiology of the reproductive system, and these molecules play a key role in ECM remodeling based on fine-tuning between MMP activation and inhibition during embryo implantation [38]. Therefore, the MMPs secreted by the endometrium at different periods

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**Fig. 2** The regulation of collagen deposition. **a** The lack of p-Erk1/2 decreased MMP-1 synthesis, which promoted collagen III accumulation and scar formation [64]. Reproduced with permission from [64]; **b** an ERK- and Ets-1-dependent pathway is involved in Lipo-PGE1-inhibited collagen production [65]. Reproduced with permission from [65]. **c** Wound healing potential effectuated by EGFR conjugated hydrogel [57]. Reproduced with permission from [57]

play a crucial role in maintaining a healthy environment in the uterus.

When the expression of MMPs is disordered, the collagen degradation process of the endometrium will be affected, leading to the occurrence of uterine pathological processes. Excess deposition of collagen may block the growth of smooth muscle, leading to inadequate spiral artery remodeling, which contributes to the pathogenesis of preeclampsia [42]. In the mouse model of diabetes, over collagen deposition was found in the decidua and impaired decidua and implantation were detected [42, 43]. There is sufficient evidence that MMPs and TIMPs also play an important role in the pathogenesis of endometriosis [44], RIF [45–47], RPL [48] and other related diseases. We will elaborate on this point in this review.

### 2.2 Regulation
Collagen degradation and remodeling play an important role in the physiological cycle of the endometrium. The expression and activity of MMPs, the most important protease in its metabolism, are also strictly regulated by various metabolic pathways and cellular signal molecules [49]. The MMPs and TIMPs are considered to play an important role in degradation of ECM, showing that the expression level and activity alteration of MMPs/TIMPs will further regulate the balance of ECM. For example, tumor necrosis factor (TNF)- α and relaxin-2 (a peptide hormone) can up-regulate the expression of MMPs and down-regulate the expression of TIMP-1 [50], then the MMP-TIMP imbalance can cause a disordered degradation of collagen type IV alpha1 [32]. When ERK 1/2 signaling pathway is inhibited, the transcription of MMPs is down-regulated [51], and activation of ERK 1/2 also exhibited crucial effect on collagen deposition [52] (Fig. 2a, b). RD1 can up-regulate MMP-10 and activate its activity in combination with MMP-1 [53]. Nuclear factor κB (NFκB) and signal translator and activator of transcription-3 (Stat-3) can regulate the transcription of

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a variety of MMPs and its disorder may induce collagen deposition [54, 55]. Epidermal growth factor receptor (EGFR) can promote the expression of MMP-7 by forming a positive feedback loop [56], and EGFR hydrogels can also cause collagen deposition in tissue engineering to promote wound healing [57] (Fig. 2c). The expression level and activity of MMPs and TIMPs in the endometrium are also regulated by a variety of factors secreted by the uterus, which will further regulate the degradation and remodeling of ECM in the endometrium. Studies have shown that MMPs can be regulated by hormones during the menstrual cycle, for example, estrogen can enhance the inhibitory effect of progesterone on the synthesis and release of MMPs by up-regulating the production of progesterone receptors [58]. Inflammatory factors also participate in the regulation of MMPs. 17b-estradiol can up-regulate the expression of IL-33 and promote the expression of MMP-9 in the stromal cells of endometriosis through the estrogen receptor pathway [59]. In human endometrial stromal cells (HESCs), ATP can cause the nuclear translocation of phosphorylated ERK 1/2 to up-regulate the expression of MMP-2, -3, -10, -24 [60]. During the late luteal phase, increased TGFβ1 expression promotes the expression of MMP-2, -9, -11 mRNA, and can activate the activity of MMP-2 [61]. Activin A can promote the expression of proMMP-2, -3, -7, and -9 in the endometrium and initiate the activity of MMP-2, while inhibin A is an effective inhibitor of proMMP-2, which can antagonize the effect of activin A on MMPs [62]. Basigin-2, also known as CD147, expressed in the endometrium, can promote the expression of MMP-1, -2, -3. It has also been found that in mice, EGF, bFGF, and TGF beta can increase the expression of MMPs and reduce the expression of TIMPs in the uterine metamorphosis [63]. In general, as shown in Table 2, in the complex physiological environment of the endometrium, MMPs are jointly regulated by a variety of hormones and inflammatory factors in the uterus, and then regulate collagen degradation and remodeling, which plays a vital role in the function of the endometrium.
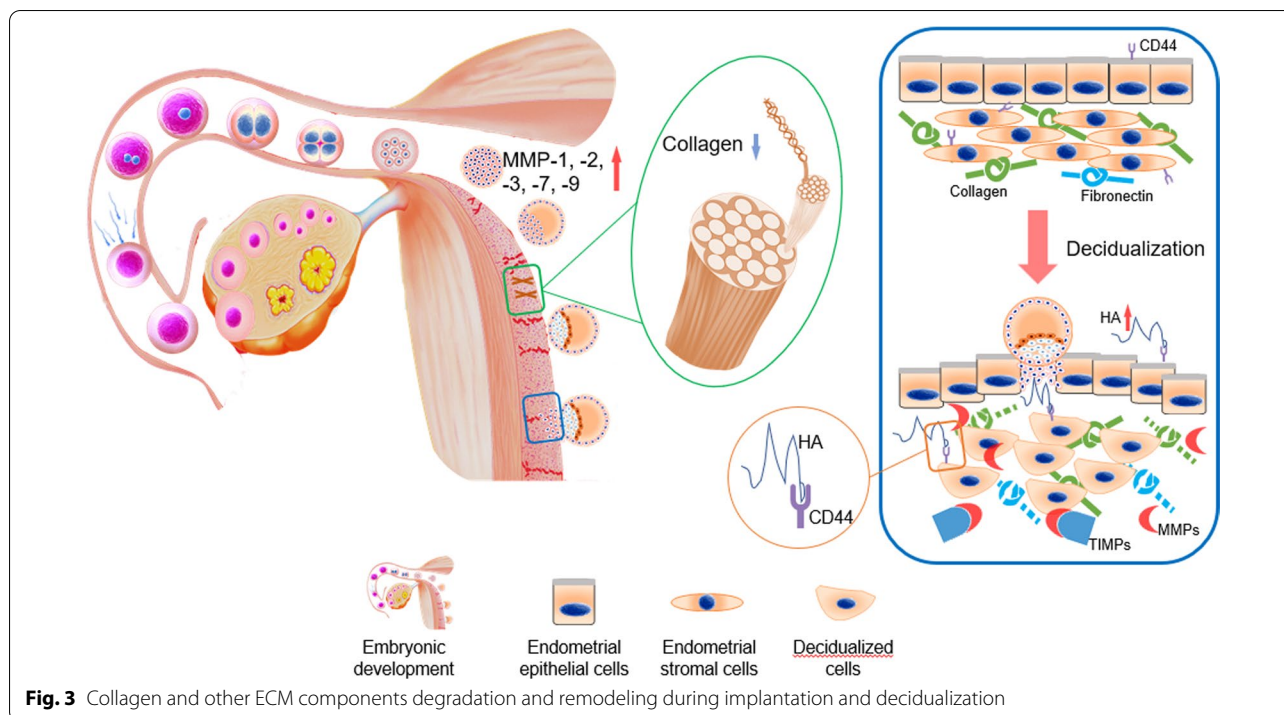
## 3 ECM in physiological activity
### 3.1 Alterations of ECM in normal menstruation
Normally, endometrium continuously undergoes cyclic dynamic changes including shedding, repairing, regenerating and remodeling, and the rhythmicity is essential for human fertility and pregnancy. The orchestration of level changes of estrogen and progesterone regulate the tissue morphological transformation from menstrual phase, proliferative phase, secretory phase and decidualization [66, 67], accompanied with the balanced turnover of degradation and reconstruction of extracellular matrix at the molecular level (Fig. 3) [68]. Endometrial basal lamina, which is a special form of ECM and mainly composed of collagen and laminin, is responsible for angiogenesis and vessel permeability, and defect of the basal lamina may lead to fragile vascularity and breakthrough bleeding [69]. During normal menstruation, factors that induce vascular breakdown may include MMP and plasminogen activators. MMP-1 (collagenase) was one of the MMPs detected in the perimenstrual period and menstrual period, which degrades COL I-III, VII and X, suggesting that collagenase may be related to the degradation of the endometrium during the menstrual period [69, 70]. Furthermore, 3D engineered endometrial stroma was cultured to mimic normal menstruation, and significantly increased collagenase activity was found after steroid withdrawal [71]. After shedding off, the endometrium rapidly starts to regenerate. One of the unique characteristics of the endometrium is scar-free

**Table 2** The regulation mechanism of main members of MMPs

| Molecular | Members of MMPs | Regulation mechanism |
|---|---|---|
| TNF-α | A variety of MMPs | Up-regulate the expression of MMPs and down-regulate the expression of TIMP-1 |
| ERK 1/2 | A variety of MMPs | Up-regulate the transcription of MMPs |
| RD1 | MMP-10 | Up-regulate the expression of MMP-10 and activate its activity in combination with MMP-1 |
| NFκB | A variety of MMPs | Up-regulate the transcription of MMPs |
| EGFR | MMP-7 | Forming a positive feedback loop |
| Estrogen | A variety of MMPs | Promote the release of MMPs |
| 17b-estradiol | MMP-9 | By up-regulate the expression of IL-33 |
| ATP | MMP-2, -3, -10, -24 | Cause the nuclear translocation of phosphorylated ERK 1/2 |
| TGFβ1 | MMP-2, -9, -11 | Promotes the expression of MMPs mRNA; Activate the activity of MMP-2 |
| Activin A | MMP-2, -3, -7, -9 | Promote the expression of MMPs |
| CD 147 | MMP-1, -2, -3 | Up-regulate the expression of MMPs |
| EGF, bFGF | A variety of MMPs | Increase the expression of MMPs and reduce the expression of TIMPs |

**Fig. 3** Collagen and other ECM components degradation and remodeling during implantation and decidualization
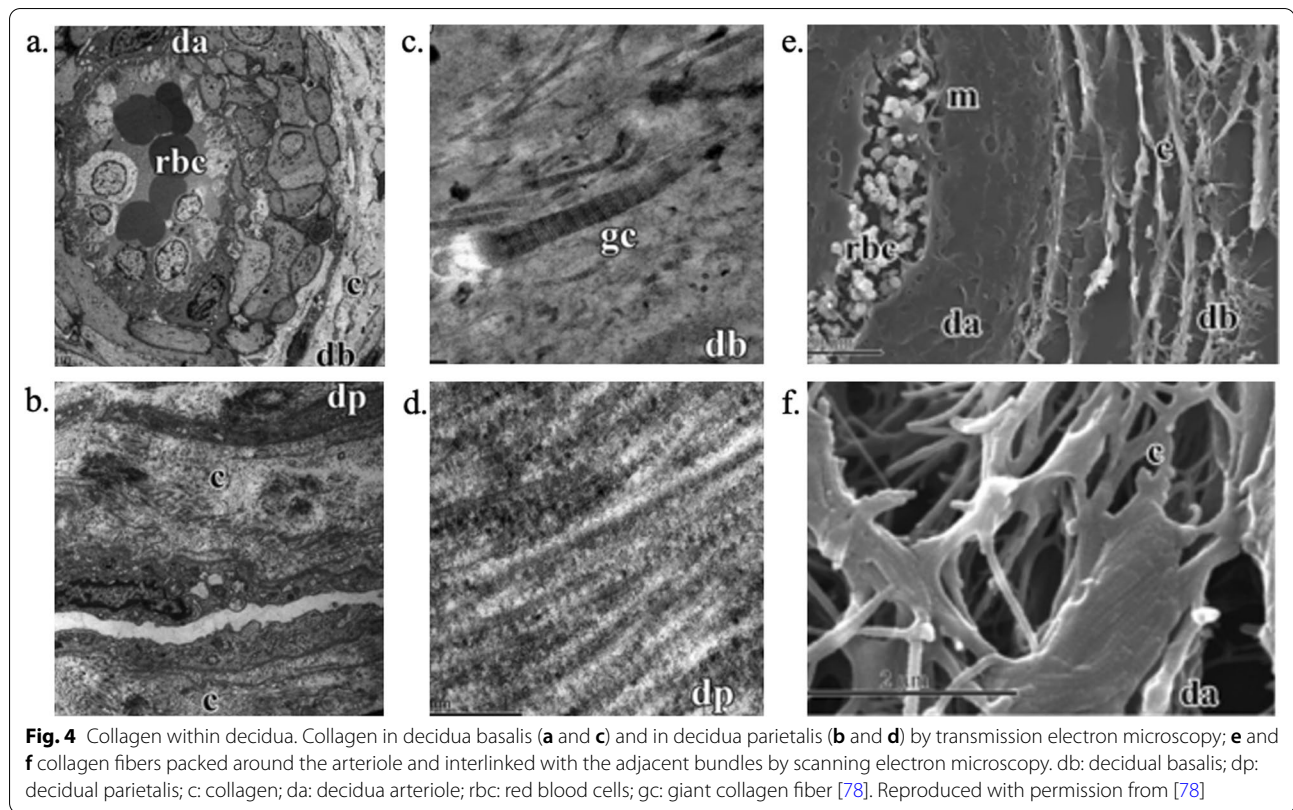
healing even undergoing physiological self-damage for up to 400 cycles. Eremichev R et al. attributed this feature to the suppressive effect on fibrogenesis of soluble components of menstrual discharge serum (MDS), displayed by the decreased production of COL I in endometrial stromal cells, even though MDS was abundant of TGF-β1, which facilitated the transition from stromal cells to myofibroblasts [72].

## 3.2 ECM remodeling on endometrium preparing for embryo implantation

To be prepared for embryo implantation, human endometrial stromal cells undergo structural and functional differentiation regulated by the increased level of progesterone, transiting from fibroblast-like cells into epithelial-like decidua cells. This process is termed decidualization and occurs about 6 days after ovulation, proceeding to the window of implantation [73]. In this stage, decidual cells are surrounded by ECM abundant of basement membrane-like proteins including collagen IV and laminin and produce anti-fibrinolytic agents like plasminogen activator inhibitor type-1 (PAI-1) to maintain endometrial homeostasis, which also attributes to the down-regulation of MMPs [67]. In the decidual stroma, collagen types I, III, and VI were detected with more intense staining compared to the endometrial stroma, and collagen type IV firstly appeared around the spiral arteries in the decidualising sheath, which indicated that collagen IV participated in the remodeling of arteries [74]. To be receptive,

the polarization of endometrial epithelial cells decreases to a lower degree with the intercellular spaces widen and intercalated by ECM components. It was detected on in vivo receptive endometrium that the α6 subunit of hemidesmosomal α6/β4-integrin, which was the receptor of laminin-322, lateralizes under hormone stimulation. Also, microvilli are lacking and glycocalyx is thin in receptive endometrium epithelium for easier implantation [75]. Subsequently, trophoblast adhesion and migration occur. Hannan et al. found ECM including collagen is under the regulation of endometrium chemokines like CX3CL1 and CCL14. With chemokine treatment, gene expressions of some collagens such COL5A1, COL16A1, COL6A3 and COL7A1 were upregulated and trophoblast adhesion to fibronectin was enhanced [76]. Both decidual stromal cells and trophoblast cells can secrete a certain amount of fibronectin, which is considered as a platform to mediate trophoblast migration [74]. Fibulin is also responsive to progesterone during the secretory phase and plays an essential role in cell migration and adhesion together with other ECM components [77]. For successful invasion, collagens are unevenly arranged in the embryo-maternal interface. It was revealed with decidua biopsies from patients terminating the pregnancy in the first trimester that collagen fibrils were thicker and discontinuous around decidua cells and trophoblast, while distributing uniformly in decidua parietalis (Fig. 4) [78]. Expression levels of MMPs such as MMP-2, -3, -9 in the decidua are associated with invasion of trophoblast cells

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**Fig. 4** Collagen within decidua. Collagen in decidua basalis (**a** and **c**) and in decidua parietalis (**b** and **d**) by transmission electron microscopy; **e** and **f** collagen fibers packed around the arteriole and interlinked with the adjacent bundles by scanning electron microscopy. db: decidual basalis; dp: decidual parietalis; c: collagen; da: decidua arteriole; rbc: red blood cells; gc: giant collagen fiber [78]. Reproduced with permission from [78]

[79]. MMP-9 expressed by trophoblast cells in embryos and TIMP-3 expressed by maternal uterine cells are the main enzymes involved in the invasion of endometrial trophoblasts, and are important participants in the process of embryo implantation and development [80, 81]. Furthermore, the stiffness of ECM in the interface is vital to limit the aggressive trophoblast invasion [73].

## 4 ECM in infertility

### 4.1 Thin and unresponsive endometrium

Endometrial thickness (EMT) assessed by transvaginal ultrasonography is one of the regular measures before embryo transplantation for in vitro fertilization (IVF) prognosis evaluation. On some occasions, clinicians and patients may be disappointed by the sustained thin endometrium, possibly caused by traumatic uterine cavity procedures like curettage or just being idiopathic. There might be some iatrogenic reasons like the effect of clomiphene, which is anti-estrogenic, and prolonged use of progesterone [82–84]. Although not certainly leading to implantation failure or unfavored outcomes, thin endometrium was reported in many studies to associate with various obstetrical and perinatal complications including miscarriages, ectopic pregnancy, preterm birth or low birth weight [85]. It is strongly recommended that frozen or fresh IVF-ET cycles should be counseled when

EMT < 7 or 8 mm to avoid the negative impact on outcomes [86]. The mechanism of thin endometrium leading to an unsatisfying prognosis has not yet been well addressed. It was hypothesized that with thinning of the endometrium surface, the implanted embryo was much closer to the high vascularity in the basal layer and thus exposed to detrimental reactive oxygen species [13, 82]. Miwa et al. compared the pathophysiologic features of thin endometrium to normal samples and found that arterial resistance was significantly higher in the thin endometrium of the mid-luteal phase. In addition, the area of glandular epithelial cells, the number of blood vessels, and the expression of vascular endothelial growth factor (VEGF) were all decreased in the thin endometrium [87]. The signaling, processing and up-taking of VEGF, which regulates endothelial cells activity and angiogenesis, was thought to be modulated by the stiffness of ECM [88]. As the neovascular network forms with signals from stimuli like VEGF, collagen undergoes active remodeling to facilitate the migration of endothelial cells from parent blood vessels. Secretion of collagen is upregulated during cell migration through ECM and collagen fibrils are pulled toward the sprouting orientation of the endothelial tip cells [89]. In vitro experiment demonstrated that in the presence of proangiogenic agents including VEGF, human uterine microvascular

endothelial cells invaded the collagen matrices and the invasion response was dose-dependent [90]. Up to now, it seems that there is no literature systemically investigating the ECM in the thin or unresponsive endometrium. However, many treatments targeting thin endometrium underline the significance of ECM especially collagen on endometrium thickness maintenance and regeneration. For instance, platelet-rich plasma (PRP), one of the recommended therapies for endometrial infertility, contains abundant proteins, growth factors, cytokines and anti-inflammatory factors that promote endometrium proliferation and angiogenesis. ECM components like fibronectin and vitronectin also exist in platelet granules [91]. PRP treatment is effective on fibrosis inhibition by down-regulation of fibrosis-related factors including collagen type I alpha 1 (COLIA1) [92, 93]. Aghajanova et al. found that expression of members of the MMP family including collagenase was significantly increased by PRP in human endometrial stromal fibroblasts (eSF) [94]. Stem cell therapy is another strategy for thin endometrium. Zhao et al. extracted menstrual mesenchymal stem cells (MenSCs) from thin endometrium to co-culture with endometrial epithelial cells and detected that cell proliferation, migration and invasion were promoted. The expression of MMP3, together with other growth factors, showed to be stimulated, indicating the influence of MenSCs on ECM [95]. Meanwhile, collagen was widely applied as biomaterial carriers for therapeutic components like umbilical cord mesenchymal cells (UC-MSCs) (Fig. 5) and basic fibroblast growth factor (b-FGF) and these binding complexes were demonstrated to significantly improve endometrial thickness and restore the receptivity [96–98]. Xin et al. considered that the increase of endometrial thickness was only attributed to UC-MSCs, and the collagen scaffold itself did not show to significantly promote endometrial regeneration in rat models [97]. Another study found injection of scaffold/UC-MSCs profoundly facilitated collagen degradation with MMP-9 upregulation compared to UC-MSCs only [99]. Furthermore, spatial distribution and the stiffness of the ECM were considered to be capable to determine the fate of stem cell populations and orientate the differentiation axis of epithelial cells [100]. However, studies specifically focusing ECM on endometrial epithelial differentiation are lacking. In summary, ECM are used as the effective components or adjuvants in the treatment of thin or unresponsive endometrium and conversely, the therapy for endometrium might have an impact on ECM remodeling.

### 4.2 Recurrent implantation failure (RIF)
As defined by the European Society of Human Reproduction and Embryology (ESHRE), RIF could be considered when > 3 transfers with high-quality embryos failed or ≥ 10 embryos failed to transfer in multiple transfers. However, there is no consensus on the diagnosis criteria of RIF and the approximate incidence in IVF populations was 10% [101]. Embryos factors causing RIF include chromosomal abnormalities, zone pellucida hardening, culture and transfer techniques [102]. Human zona pellucida (ZP) is an acellular matrix structure composed of 4 glycosylated proteins surrounding the embryo in the pre-implantation stage [103]. It was shown that embryos with thin and fragmented ZP had more significant positive staining of oncofetal fibronectin, which promoted the secretion of MMP2, and supplement of laminin and fibronectin could effectively increase the hatching rate. Thus, it was speculated that resistance to proteolysis of ECM may lead to zona hardening, block the expansion of the blastocyst, and finally cause RIF [104].

With the development of culture techniques and the standardization of embryo assessment and elective single blastocyst transferring, endometrium would be more suspected to be the criminal especially when genetic factors are excluded [14]. Research indicated that RIF was related to the dysregulation of ECM in the endometrium, which may limit the trophoblast invasion. However, certain heterogeneity exists in the results in different studies. Turgut et al. found that endometrial glandular cells, vascular endothelial cells, and stromal cells from the RIF group had lower expression of MMP inducer and the insufficiency indirectly interrupted the remodeling of ECM, thus making the endometrium unreceptive for embryos in RIF [105]. While some researchers observed the expression of MMP-2, MMP-9 and TIMP-3 were significantly downregulated in the endometrium from women with RIF and unexplained infertility [45–47], Inagaki et al. demonstrated that MMP scores were markedly higher in the endometrium from the RIF group than the control group [106]. Researchers found RIF patients may benefit from hyaluronic acid, which is an abundant glycosaminoglycan in the uterine, to achieve an improved implantation rate [107]. HA may function as "glue" to provide sticky matrices for embryo attaching thus reducing implantation failure. However, HA accumulation in the uterine cavity was thought to possibly associate with early embryo loss [9]. Dysregulation of laminin binding might also participate in the implantation failure. The animal experiment demonstrated that injection of laminin-binding protein antibody in the uterine horn led to no or disintegrated embryo implanted. The distribution and regulation of laminin in RIF patients remain to be further investigated [108].

RIF could occur in patients with chronic inflammatory pelvic or uterine environments like endometriosis. Klemmt et al. found in endometriotic stromal
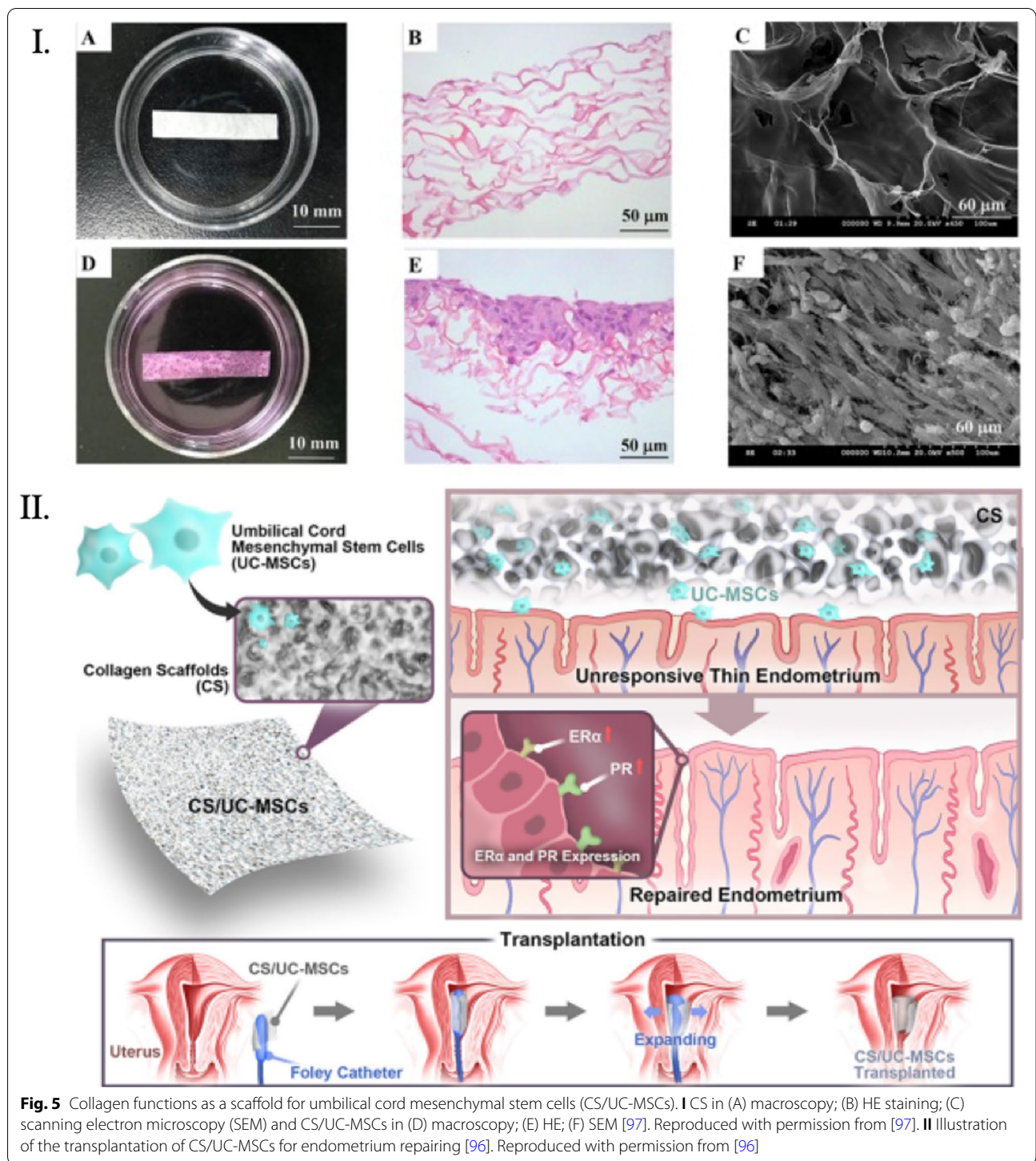
**Fig. 5** Collagen functions as a scaffold for umbilical cord mesenchymal stem cells (CS/UC-MSCs). **I** CS in (A) macroscopy; (B) HE staining; (C) scanning electron microscopy (SEM) and CS/UC-MSCs in (D) macroscopy; (E) HE; (F) SEM [97]. Reproduced with permission from [97]. **II** Illustration of the transplantation of CS/UC-MSCs for endometrium repairing [96]. Reproduced with permission from [96]

cells, upregulation of the expression of integrin could be observed and ESC derived from peritoneal cavity and ovary showed increased attachment on ECM components including fibronectin and collagen type I and IV [109]. Aberrant integrin expression and increased adhesion to ECM of stromal cells were believed to be involved in the pathogenesis of endometriosis. A similar conclusion was also drawn by Adachi et al.[110]. In patients with endometriosis, one possible explanation of implantation failure was that trophoblast adhesion was weakened via dysregulation of local activin A, which was effective in decreasing the bindings between

trophoblast cells with fibronectin, collagen IV and collagen I [111].

For successful implantation of a semi-heterogeneous embryo, a series of local immune responses occur to build up a tolerant and anti-inflammatory immunological micro-environment. It is advocated that the local immunological dysregulation contributes to the pathology of RIF and immunomodulatory therapy may be effective to improve pregnancy outcomes [112, 113]. ECM may be involved in the immunoregulation of RIF. For instance, Yes-associated protein (YAP) is one of the sensors of mechanical signals from ECM stiffness in bovine endometrial epithelial cells (bEECs). Mechanical activation of YAP could up-regulate the expression of pro-inflammatory factor IL-6 and failure of embryo implantation may occur when activation of YAP is inhibited [114]. Up to the present, how ECM functions with the immune system in RIF remains to be elucidated.

### 4.3  Recurrent pregnancy loss (RPL) and recurrent miscarriage (RM)

Nomenclature and definition of RPL and RM are inconsistent in the research literature, making the comparison and discussion difficult. As recommended by the 2015 ESHRE early pregnancy special interest group, recurrent pregnancy loss is used to describe the repeated demise of pregnancies, which have been confirmed by at least two positive serum or urine b-hCGs, while recurrent miscarriage is used when all pregnancy losses have been confirmed by ultrasound or histology as intrauterine miscarriages [115]. According to this classification, the incidence of RPL is expected to be higher than RM. As reported, RPL occurs in about 2.5% of women attempting to conceive, and RM, commonly defined as the loss of three or more consecutive pregnancies, is experienced by approximately 1% of couples [116–118]. Common causes for early and late pregnancy loss are not entirely the same. Certain cases of recurrent early miscarriages are caused by fetal aneuploidy, although the occurrence is less common than that in sporadic miscarriage. Preimplantation genetic diagnosis is recommended to couples at risk. However, it is considered ineffective to improve the live-birth rate compared to natural conception [117].

Proper decidualization is essential to maintain a stable maternal–fetal interface in pregnancy, and the perturbation of this process was believed to associate with recurrent pregnancy loss [67]. Decidualized endometrial stromal cells were demonstrated to function as a biosensor of implanted embryos. The production of key cytokine regulators of implantation including IL-1β, IL-6, and IL-10 was down-regulated when co-culturing HESC with an arresting embryo [119]. HESC in patients suffering from RM seems to let down the guarding to permit embryos of poor health to implant as long enough to be clinically confirmed but finally destined to miscarriage [120]. Here the regulation of cytokines in the maternal–fetal interface is complicated, and the associated pathway may include ECM turnover. IL-6 could activate MMP-2 and MMP-9 activity in cytotrophoblasts while IL-10 may decrease MMP-9 expression and limit the invasiveness of cultured cytotrophoblasts [48]. For the population of pregnancy loss, MMP expression levels may vary in different samples (i.e., serum, endometrium, or intrauterine fluid) and different studies. However, these findings indicated the possibility of MMP to be a prognostic marker for miscarriage in the future [121, 122]. Although the exact modulation and mechanism of ECM seem to be ambiguous, a conclusion could be drawn that the pathogenesis of RM is associated with aberrant ECM turnover.

Dysregulation of immune function on endometrial cells is another crucial hypothesis in the pathogenesis of unexplained RPL or RM. As mentioned above, the local immune system on endometrium or decidua does not execute the early rejection to embryos of low quality. Uterine or decidual NK cells, dendritic cells and Treg cells are all involved in the immunoregulation of RPL [123]. Jerzak et al. investigated the relationship between T cells and ECM in patients with recurrent spontaneous abortion (RSA). Compared to normal non-pregnant women, phytohemagglutinin (PHA) activated peripheral blood T cells in RSA patients showed more significant adhesion to collagen IV and fibronectin, which are the main components of the human placenta. This adhesion could be decreased by intravenous immunoglobin (IVIG) infusion. It was thought that strengthening adhesion between T cells and ECM including collagen IV contributed to the immunologic mechanism of pregnancy loss. IVIG infusion relieved the situation possibly by inhibiting the cytotoxic activity of T cells to conceptus or by preventing the recruitment of activated T cells from peripheral blood to the placenta [124]. The authors also demonstrated in another study that collagen IV presented the effect of costimulation when cultured with peripheral blood T cells, activating T cells and accelerating their proliferation, leading to apoptosis. This ECM-dependent T cells apoptosis may associate with the successful pregnancy outcomes in women with RSA history [125]. However, the studies were focusing on T cells from peripheral blood, and further investigation on ECM and T cells or other immunological mediators localized on the maternal–fetal interface is expected.

Recurrent miscarriage is one of the manifestations of antiphospholipid syndrome (APS). Antiphospholipid antibodies (aPL) could induce inflammation at the maternal–fetal interface by recognizing β2-glycoprotein 1 (GP1) expressed by trophoblasts and reducing

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proliferation, migration and invasion of extravillous trophoblasts, finally leading to the impaired of placentation [126]. Simone et al. found polyclonal anti-β2-GP1 antibodies could bind to endometrial endothelial cell membranes. The authors cultured HEEC with polyclonal aPL and demonstrated that aPL significantly reduced the production of VEGF and MMP2, inhibiting angiogenesis [127]. Patients with unexplained RM were reported to significantly increase platelet aggregation. Transmembrane platelet-specific collagen receptor glycoprotein VI (GP6), which is crucial for collagen-initiated signal transduction and platelet activity including activation, adhesion and aggregation. Significantly high occurrence of mutant genotypes of GP6 SNPs was observed in RM and relevant biologic pathways were confirmed including platelet adhesion to exposed collagen, ECM-receptor interaction and collagen binding [128].

In ART, the effect of chronic inflammatory pelvic environment on oocyte is bypassed. Endometrium thus might be the dominant causation of recurrent miscarriage in endometriosis patients with assisted conception [129]. However, studies focusing on the ECM microenvironment or more specifically, collagen on the endometrium in the etiology of pregnancy loss or miscarriage in patients with endometriosis are lacking.

## 5 Application of ECM in IVF-ET

HA is one of the most abundant macromolecules in the female reproductive system. Produced by the cumulus and granulosa cells of ovarian follicles, it is distributed in human fallopian tubes, uterus, endometrium and cervix [130, 131]. Collagen, which could function to provide a scaffold for other ECM components, is used in tissue engineering as a vector for HA. It is shown that collagen plays an important role in tissue repair, which provides a vascular tissue-engineered scaffold for promoting endothelial cell proliferation [132] and achieves the biofunction of basement membrane [133]. However, nothing has been reported for collagen-HA use in reproductive medicine. The expression of HA in the endometrium reaches its peak in the middle and late stages of proliferation and secretion, suggesting its key role in the process of embryo implantation [131]. Studies have shown that elevated endogenous HA concentration could increase embryo implantation rate during IVF-ET [134], animal studies have also clarified that adding HA in embryo transfer fluid concentrated the elevation of embryo implantation rate and promoted embryo development [135]. However, the mechanisms underlying HA facilitating embryo implantation have not been clarified completely, and the knowns were as follows: (a) decidualizing the endometrium by promoting the proliferation of decidual cells when preparing for pregnancy [136]; (b) promoting angiogenesis indirectly and improving adhesion between cells and intercellular matrix [137]; (c) promoting the adhesion of the trophoblast to the endometrium in the early stage of implantation [9], (d) acting as a CD44 mediator for the ligand-receptor relationship between HA and CD44 [138, 139]; It is worth mentioning that HA has now been applied clinically and benefits patients. A recent review also pointed out that adding high concentration of HA (0.5 mg / ml) to the transfer fluid can promote embryo implantation, clinical pregnancy, and promote live birth of embryos at all stages of development [140]. Nevertheless, the latest research has shown that the use of transplantation solution rich in a high concentration of HA in frozen embryo transfer can not significantly improve the clinical pregnancy and live birth rate of embryos [141], suggesting there are some disadvantages in the clinical use of HA.

Although literature on the application of elastin, laminin, and other ECM components in reproductive medicine has not yet been retrieved, they have been used in tissue regeneration and repair. A scaffold material called HeatTro constructed from elastin can increase the proliferation, migration and adhesion of fibroblasts, thereby promoting wound healing [142]. Laminin is often used as a coating for scaffolds, which can significantly promote the proliferation of stem cells [143, 144]. Fibrin sealants are used in embryo transfer to increase the adhesion of the embryo transfer fluid to prevent fluid outflow, which is a common trouble when transferring embryos [145]. This may suggest that laminin could possibly play a similar role as fibrin sealants in IVF-ET. Based on the above-mentioned changes of ECM in the process of embryo implantation and pregnancy maintenance, the improvement of pregnancy outcome benefited from other kinds of ECM can be further studied. Among them, collagen, as a biodegradable material, has great biocompatibility and is widely used in regenerative medicine. Therefore, it has broad prospects to further expand collagen and other ECM components application in reproductive medicine, especially in improving embryo implantation and clinical pregnancy.

## 6 Conclusion and perspective

Collagen, the most important component of ECM, has an irreplaceable role in biological processes. In other words, collagen metabolic disorders are closely related to ECM dysfunction. The dysregulation or instability of ECM is related to the pathogenesis of a variety of diseases, which is becoming a popular research focus in recent years. This review focuses on the ECM in the endometrium or decidua. ECM in the endometrium not only functions as a mechanical scaffold but dynamically turnover with the hormonal stimulation, immunoregulation and

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interaction with the implanted embryo. We conclude that the ECM especially collagen plays an important role in the physiological menstruation, receptivity for embryo implantation and pathogenesis of refractory infertility in assisted conception. Here in this review, we also discussed the application of ECM in IVF outcome improvement. However, most of the present studies focusing on ECM in infertility remain on expression level and mechanism discussion, and heterogeneity still exists in various study results.

Much attention has been given to collagen about the therapeutic potential, transport function as biomaterials and in vitro models for mechanism or treatment investigation. Naturally secreted collagen is mechanically weak and degrades relatively quickly in vivo [146]. Collagen hydrogels also contract to a certain extent after loading cells, so it is difficult to meet different applications in tissue engineering. Chemical crosslinkers are often used in collagen modification to enhance the mechanical strength of the hydrogel to make it injectable, while being able to respond to temperature in situ gelation [147], or by introducing nanoparticles to make collagen hydrogels have better thermal stability and anti-enzymatic degradation [148]. In recent years, collagen, as a biodegradable material, has good biocompatibility and is widely used in regenerative medicine. However, the applications of collagen or other ECM components as therapeutic targets or treatment effectiveness on fertility restore or outcome improvement still should to be further investigated. In future research, how to utilize collagen and other ECM components as biomaterials to investigate the mechanism of infertility or how to apply the research findings in regenerative medicine to infertility treatment may greatly promote the development of reproductive medicine and ART. It is believed that the combination of reproductive medicine with bioengineering would be the bright perspective of fertility reconstruction and preservation.

### Abbreviations

ECM: Extracellular matrix; HA: Hyaluronic acid; ART: Assisted reproductive technology; RIF: Recurrent implantation failure; RPL: Recurrent pregnancy loss; RM: Recurrent miscarriage; MMPs: Matrix metalloproteinases; TIMPs: Metalloproteinase tissue inhibitors; ADAM: A Disintegrin and Metalloproteinase; ADAMTS: A Disintegrin and Metalloproteinase with Thrombospondin Motifs; TNF: Tumor necrosis factor; HESCs: Human endometrial stromal cells; PAI-1: Plasminogen activator inhibitor type-1; EMT: Endometrial thickness; IVF: In vitro fertilization; VEGF: Vascular endothelial growth factor; PRP: Platelet-rich plasma; ZP: Zona pellucida; APS: Antiphospholipid syndrome; aPL: Antiphospholipid antibodies.

### Authors' contributions
R.L. and M.D. contributed to the critical discussion, manuscript drafting and figure design. G.G and M.C. participated in manuscript revising. C.C. and T.W. contributed to literature filtration. Z.H. and Y.S. contributed to the critical discussion and conception. J.G. Y.Z. and X.X. made vital contributions to the conception and structure design of this review. All the authors approved the final version of the manuscript.

### Availability of data and materials
Not applicable.

### Declarations

### Competing interests
The authors declare that they have no competing interests.

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