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Review

An Update on Experimental Therapeutic Strategies for Thin Endometrium

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Abstract: Infertility caused by a thin endometrium remains a significant challenge in assisted reproduction and is often associated with a low success rate after treatment with assisted reproductive technology. There is a lack of consensus in the field concerning both its diagnostic criteria and clinical management. The currently available treatment options are few with limited efficacy. Recent advances in cell therapy and bioengineering have, however, shown promising results for the treatment of a thin endometrium. Notably, these novel interventions have demonstrated the ability to increase endometrial thickness, restore endometrial function, and improve reproductive outcomes. In this comprehensive review, we focus on a critical evaluation of these emerging therapeutic strategies for a thin endometrium including platelet-rich plasma, exosomes derived from stem cells, and bioengineering-based techniques. By synthesizing the findings from available clinical trials, we highlight the promising outcomes achieved so far and underscore the importance of robust clinical trials in assessing the safety and efficacy of these interventions in the future. Continued research efforts to unravel the intricate mechanisms involved in endometrial repair and regeneration will also be essential to enhance our understanding of this multifactorial condition and to identify novel treatment targets for future therapeutic interventions.

Keywords: infertility; thin endometrium; platelet-rich plasma; stem cell therapy; bioengineering

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1. Introduction

Infertility caused by a thin endometrium represents a challenging condition to treat and is frequently associated with a low success rate and impaired reproductive outcomes using assisted reproductive technologies (ART) [1,2]. An endometrial thickness (EMT) of at least 7 mm is generally regarded as more suitable for successful embryo implantation in an ART program [3]. There is, however, no consensus on the threshold of EMT that should be applied for the diagnosis of a thin endometrium [4–6]. The etiology of thin endometria is complex, diverse, and often unknown (Figure 1), making it challenging to treat these patients and to study the underlying pathological mechanisms. Proposed causes of a thin endometrium include Asherman's syndrome and previous intrauterine surgery including sharp curettage, radiation to the pelvis, genetics, impaired uterine blood flow, and acute or chronic endometrial infection. Moreover, it is linked to the use of medications such as clomiphene citrate as well as low estrogen levels or impaired estrogen signaling as a result of dysfunctional estrogen receptors [7–11]. A recent single-cell RNA sequencing study suggested that cellular senescence in the stroma and epithelium together with collagen overdeposition around the blood vessel is involved in endometrial thinness [12]. Furthermore, results from a cumulative in silico study that included five RNA sequencing datasets on a thin endometrium revealed dysfunctional intercellular communication and metabolic signaling pathways in the thin endometrium [13].

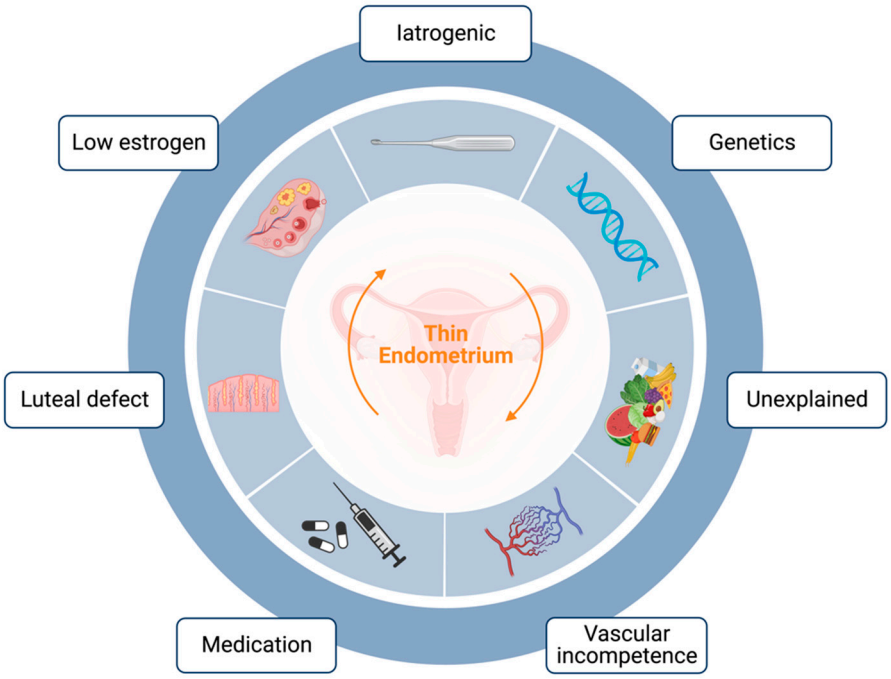

Figure 1. Schematic image of representative etiologies of thin endometrium (created using Biorender).

Conventional therapies, including estradiol or combined hormonal therapy [14], growth hormone [15], Granulocyte colony-stimulating factor (G-CSF) [16,17], sildenafil citrate [18], and several vasoactive substances [19] such as aspirin, pentoxifylline, tocopherol, and L-Arginine have shown limited and inconsistent efficacy regarding an increase in EMT increase and restoration of endometrial function [20,21]. Consequently, there is a growing demand for novel adjuvant therapies. In recent years, cell-based therapy and other innovative treatment options have emerged as promising strategies in various medical fields [22–24]. Considering the encouraging results in numerous experimental studies, these novel approaches may hold great potential as treatment options for thin endometria.

In this review, we aim to summarize and critically discuss the recent progress and application of emerging novel therapeutic strategies for a thin endometrium. We will explore the potential of cell therapy and regenerative medicine as promising strategies to restore endometrial thickness and function. By shedding light on the latest advancements, this review seeks to pave the way for more effective and personalized treatment options for individuals with a thin endometrium, ultimately improving the pregnancy outcome after ART treatment.

2. Experimental Therapeutic Strategies

2.1. Platelet-Rich Plasma

Platelet-rich plasma (PRP) is an autologous plasma-based concentration of platelets, offering a host of therapeutic advantages [25]. Its autologous nature significantly reduces the risk of immune rejection, pathogen transmission, and cancer development, making it an attractive treatment option [26–28]. Rich in growth factors (GFs) and cytokines, PRP has demonstrated pro-regenerative properties, particularly in healing injured tissues. Recently, there has been growing interest in its potential for treating endometrial disorders, such as thin endometria [29].

In 2018, Molina et al. [30] administrated PRP through intrauterine infusions to 19 patients with refractory thin endometria undergoing IVF. After the second PRP injection, the endometrial thickness in each patient exceeded 9 mm. Notably, this resulted in an impressive 73.7% positive pregnancy test rate and 26.2% live births. Later in the same year, the first randomized controlled trial [31] reported significantly higher rates of implantation and clinical pregnancy rates in the PRP group (27.94% vs. 11.67%; 44.12% vs. 20%; $p < 0.05$,

respectively), along with improved endometrial thickness (p = 0.001). Subsequently, an increasing number of prospective clinical studies [32–38] further support these findings, showing that intrauterine infusion of PRP effectively thickened the endometrial lining and improved clinical pregnancy outcomes to different extents (Table 1). Although growing evidence indicates that PRP treatment is beneficial for treating thin endometria, the positive effects only manifest for certain parameters. For instance, one study in South Korea [33] enrolled 24 women who had a history of two or more failed IVF cycles and a refractory thin endometrium and who found no statistical significance in the endometrial thickness increase in frozen embryo transfer (FET) cycles. Another study in 2020 [39] analyzed 24 IVF cycles performed in patients with an EMT below 5 mm during preparation for FET. Similarly, no difference in EMT was observed after PRP infusion. It should be noted that the experimental conditions, PRP preparation protocol, infusion dosages, eligibility criteria, etc., vary across different studies. In the future, it is important to standardize PRP treatment protocols and report on essential outcome parameters such as live birth. It has been proposed that the abundant growth factors, concentrated peptides, and cytokines in PRP may improve endometrial thickness and receptivity by promoting cell proliferation and vascularization and by decreasing inflammation [40]. However, a recently published ESHRE good practice recommendation on recurrent implantation failure noted that the use of intrauterine PRP infusions is not deemed to be supported by the existing evidence [41]. Given the complex composition of PRP, further in-depth investigations are needed to uncover its exact mechanism of action. To establish the effectiveness and safety of PRP therapy and determine whether it should be further explored as an adjuvant therapy for a thin endometrium, there is a pressing need for more robust evidence generated through well-designed studies.

Table 1. Clinical trials of PRP in thin endometria.

Reference	Study Design	PRP Injection Protocol	Control Group (n)	Intervention Group (n)	Outcome
Molina et al., 2018 [30]	Prospective interventional study	1 mL PRP infusion on HRT day 10, repeated after 72 h	/	19	EMT increased; CPR 73.7%, LBR 26.3%
Eftekhar et al., 2018 [31]	RCT	0.5–1 mL PRP infusion on cd13, repeated after 48 h if EMT still <7 mm	43	40	EMT; IR increased; CPR/cycle increased (32.5 vs. 14.0%); OPR/cycle increased (27.0 vs. 14.0%)
Chang et al., 2019 [32]	Prospective cohort study	0.5–1 mL PRP infusion on cd10, repeated every 3 days until EMT > 7 mm	30	34	EMT, IR, and CPR increased ($p < 0.05$)
Kim et al., 2019 [33]	Prospective interventional study	0.7–1 mL PRP infusion from cd10, repeated 2 or 3 times until EMT > 7 mm	/	22	EMT increased (0.6 mm); IR 12.7%, CPR 30%, OPR/LBR 20%
Kusumi et al., 2020 [34]	Prospective cohort compared with the prior cycle	1 mL PRP infusion on cd10 and cd12	/	36	EMT increased; CPR 15.6%
Russell et al., 2022 [35]	Retrospective cohort compared with the prior cycle	0.5–0.75 mL PRP infusion several times between cd10 and 15 until EMT > 7 mm	/	85	EMT, CPR (37 vs. 20%); LBR (19% vs. 2%) increased

Table 1. *Cont.*

Reference	Study Design	PRP Injection Protocol	Control Group (n)	Intervention Group (n)	Outcome
Agarwal et al., 2020 [36]	Cross-sectional study	Hysteroscopic subendometrial injection with 4 mL PRP (1 mL per wall) 7–10 days after injecting leuprolide during the previous cycle	/	32	EMT increased; CPR, ORP, and LBR increased
Frantz N et al., 2020 [39]	Retrospective study	0.5 mL PRP intrauterine infusion after 14 to 17 days of oral estradiol valerate, repeated 2–3 times every second day	/	21 (24 IVF cycles)	EMT did not increase; CPR (66.7%), LBR (54%, 13 cycles)
Dogra et al., 2022 [37]	Prospective interventional study	0.5–1 mL PRP infusion on HRT day 8, repeated 2–3 times every 48 h until EMT > 7 mm	/	20	EMT increased; IR, CPR, and LBR increased significantly in a fresh group
Gangaraju et al., 2023 [38]	Prospective interventional study	0.8 mL lyophilized PRP infusion 2–3 days before FET	/	9	EMT increased; positive pregnancy outcomes in 8/9

PRP = platelet-rich plasma; HRT = hormone replacement therapy; RCT = randomized controlled trial; cd = cycle day; EMT = endometrial thickness; IR = implantation rate; h = hour; CPR = clinical pregnancy rate; OPR = ongoing pregnancy rate; LBR = live birth rate; and FET = frozen-thawed embryo transfer.

2.2. Stem Cell Therapy

During the last decades, stem cell therapy has rapidly evolved and been applied in the treatment of various diseases. Stem cells possess unique characteristics, such as high self-renewal capacity and the ability to differentiate into multiple cell types. Stem cell therapy has emerged as a promising frontier in reproductive medicine giving its potential to restore endometrial function for patients with a thin endometrium [42,43]. As summarized in Table 2, various types of stem cells have been tested in the treatment of thin endometrium in several pilot clinical trials, demonstrating that stem cell therapy has significant potential in the recovery of endometrial function, including improvements in endometrial receptivity, implantation rates, pregnancy rates, and live birth rates.

2.2.1. BMDSCs

Bone-marrow-derived stem cells (BMDSCs) are multipotent stem cells that can differentiate into different functional cells. Due to their easy acquisition in adult bone marrow, these cells have emerged as an important candidate for stem cell therapy in various diseases [44–46]. In 2011, Nagori et al. [47] reported a successful pregnancy in a patient with refractory intrauterine adhesions through the autologous transplantation of BMDSCs. Later in 2013, Zhao et al. [48] transplanted autologous BMDSCs into the uterine cavity under ultrasound guidance in a woman with severe intrauterine adhesions, resulting in a spontaneous pregnancy after three months. Moreover, Singh et al. reported that autologous transplantation of BMDSCs significantly increased endometrial thickness at 3, 6, and 9 months compared to pre-treatment thickness in six patients with refractory intrauterine adhesions. Menstruation was also restored in five out of six patients [49]. In 2016, a cohort study [50] demonstrated that compared to a hormonal replacement group,

the transplantation of autologous peripheral blood CD133+ BMDSCs through the spiral arterioles via catheterization not only increased the average endometrial thickness from 4.3 mm to 6.7 mm but also boosted the mature vessel density. The above findings suggest that BMDSCs hold great promise for the restoration of injured endometrial tissue including upregulation of regenerative and receptivity markers and improved reproductive outcomes. Evidence from numerous animal studies has also supported the conclusion that the transplantation of BMDSCs is beneficial in enhancing endometrial thickness, modulating regenerative markers, and contributing to the repair of an injured endometrium [51–54]. However, it is worth noting that MSC function declines with age, which could lead to suboptimal outcomes connected to cellular senescence [55]. Further research is necessary to fully understand the mechanisms underlying the promising outcomes and to validate the efficacy and safety of BMSC transplantation in RCTs with a larger sample size.

2.2.2. ADSCs

Adipose-derived stem cells (ADSCs) are another abundant and easily accessible stem cell source that are available in large quantities and have the benefit of allowing for isolation and production using a minimally invasive lipectomy procedure [56]. These cells have been tested in repairing injured endometrium in a few clinical trials. In 2019, one study [57] recruited 25 women with thin endometria (EMT < 5 mm) who had embryo implantation failure at least three times. After subendometrial injection of ADSCs, the EMT increased in 80% (20/25) of patients, leading to 13 pregnancies and 9 healthy live births. Another pilot study in 2020 [58] examined the effectiveness of restoring functional endometrium in patients with severe Asherman's syndrome (intrauterine adhesions) using autologous adipose-derived stromal vascular fraction (AD-SVF) containing adipose stem cells (ASCs). Five out of six infertile women with severe intrauterine adhesions achieved increased endometrial thickness along with an increased volume of menstrual bleeding. One of the five women who underwent ART treatment and transferred an embryo became pregnant but spontaneously miscarried at nine weeks. Recently, a phase I ongoing registered clinical trial (ChiCTR2000035126) aimed to enroll 30 patients with thin endometria and evaluate the efficacy and safety of autologous transplantation of adipose-tissue-derived stromal vascular fractions. A follow-up at 3 months was to be conducted to quantify endometrial thickness, menstrual volume and duration, the incidence and severity of adverse events, and early pregnancy outcomes. A 2-year telephone follow-up was to be used to monitor late pregnancy outcomes and the offspring's condition. The detailed protocol of the trial including adverse events monitoring was published in 2022 [59]. This study may provide further insight into the safety and efficacy of the treatment. A well-designed RCT with enough power is, however, required to get unbiased evidence on the safety and efficacy of the treatment compared to standard care. ADSCs' immunomodulatory, proliferating, and multi-differentiating characteristics make them an important and efficient candidate for cell therapy in treating thin endometria.

2.2.3. UCMSCs

In contrast to other stem cell sources, umbilical cord mesenchymal stem cells (UCMSCs) stand out as a highly promising cell source for cell therapy due to their abundance, non-controversial nature, painless collection procedure, and rapid self-renewal properties [60]. Particularly noteworthy is the fact that UCMSCs exhibit negligible or undetectable HLA class I expression, indicating the potential for allograft transplantation without the need for immunosuppression [61]. This unique characteristic enhances the appeal of UCMSCs as a viable option for therapeutic applications. In 2018, a phase I clinical trial implanted UCMSCs in biodegradable collagen scaffolds into the uterine cavity of 26 patients with recurrent intrauterine adhesions, resulting in an increase in EMT in all cases from 4.46 ± 0.85 to 5.74 ± 1.2 mm ($p < 0.01$), which is linked to pregnancy in 10 women (38%), 8 of whose pregnancies resulted in live births [62]. Subsequently, another pilot study in 2021 [63] enrolled 16 infertile women with unresponsive thin endometria. UCMSCs

loaded on collagen scaffolds were transplanted into the uterine cavity in two consecutive menstrual cycles. After three months, the EMT increased from 4.08 ± 0.26 mm to 5.87 ± 0.77 mm ($p < 0.001$), resulting in a pregnancy rate of 31% and a live birth rate of 12%. A further histological analysis showed increased micro-vessel density and upregulation of Ki67, estrogen receptor alpha, and progesterone receptors, indicating an improvement in endometrial angiogenesis, proliferation, and response to hormones. The above studies are self-controlled prospective trials; RCT studies with larger sample sizes are needed to verify the efficacy and evaluate the safety compared to standard care. Experimental studies will also be important to clarify the underlying mechanism of action.

2.2.4. Other Stem Cell Sources

Several other sources of stem cells have also been introduced and emerged as potential sources for the treatment of thin endometrium. One such source is menstrual-blood-derived stromal cells (MenSCs), which comprise a mixed population of mesenchymal stem cells and stromal fibroblasts. In 2016, Tan et al. [64] transplanted autologous MenSCs from the menstrual blood of women with intrauterine adhesions back into the uterine cavity. A significant increase in endometrial thickness to 7 mm in five out of seven cases was observed along with successful pregnancies in two out of four women. However, this source of stem cells has certain limitations such as not being applicable for those patients with hypomenorrhea. To explore the endometrial repair mechanism of transplanted MenSCs, one study [65] demonstrated that MenSCs could increase the microvascular density (MVD) of an injured endometrium in a mouse model by activating the ART and ERK pathways; inducing the upregulation of eNOS, VEGFA, VEGFR1, VEGFR2, and Tie2; and promoting cell proliferation, migration, and angiogenesis in vitro. Additionally, uterine-derived cells have been successfully transplanted in a rat model to repair damaged uterine endometrium, leading to promising outcomes [66]. Through transplantation of endometrium-like cells derived from human embryonic stem cell lines (hESCs), researchers demonstrated that these cells could significantly restore the structure and functionality of severely damaged uterine horns in a rat model [67]. Though most of these studies are at a pre-clinical stage, these promising results have encouraged researchers to develop cell-based biomedical approaches for repairing damaged endometria. It is important to note that well-designed clinical trials with proper control groups are crucial to evaluating the real efficacy of those cell-based therapies.

2.2.5. Stem-Cell-Derived Extracellular Vesicles

Stem cells possess the ability to secrete a wide range of regenerative cytokines, and these cellular secretions have been proposed to contribute to the positive therapeutic effects observed in different diseases [68–70]. Extracellular vesicles (EVs) are an important component of these secretions that have cytoprotective, antiapoptotic, and angiogenic effects on injured tissues and can promote progenitor and stem cell homing [71]. Building on this idea, researchers are aiming to develop stem-cell-derived exosome-based therapy that focuses on the EVs that the cells secrete, including exosomes. While the clinical research on EVs is still in an early stage, the results from animal studies are encouraging and highlight the potential of EV-based therapies for thin endometria. In 2020, exosomes derived from adipose mesenchymal stem cells were discovered to be able to preserve normal uterine structure, stimulate endometrial regeneration, support collagen remodeling, and elevate the expression of endometrial receptivity markers including integrin β3, LIF, and VEGF [72]. In another animal study on rabbits, it was demonstrated that exosomes derived from bone marrow stem cells can reverse the EMT process by activating the TGF- β 1/Smad signaling pathway, contributing to the restoration of the endometrium after damage [73]. It is also reported that collected EVs from umbilical-cord-derived MSCs combined with estrogen therapy can promote endometrial growth and reduce fibrotic levels in a rat model of intrauterine adhesions [74]. Furthermore, a recent study showed that exosomes produced by CTF1-modified BMSCs can more potently induce the regeneration of

endometrial and myometrial tissues, by driving neovascularization in a way that improves endometrial receptivity and restores fertility in a rat model of injured endometrium [75].

Before this EV-based therapeutic approach can be tested in human clinical trials, there are still several issues that need to be addressed. For instance, the efficacy and safety of EV therapy in vitro and in vivo should be carefully assessed. It will also be important to know the exact content of these EVs and which components—proteins or nucleic acids—contribute most to the regenerative process. As the field continues to evolve, exploring the therapeutic potential of EVs may open new avenues for innovative and minimally invasive therapies for tissue repair and regeneration.

Table 2. Clinical studies on stem cell therapy as a treatment for thin endometrium.

Reference	Cell Source	Study Design	Administration Protocol	Control Group (n)	Intervention Group (n)	Outcome
Nagori et al., 2011 [47]	Autologous BMDSCs	Case report	0.7 mL BMDSCs infusion on cd2	/	1	OP at 8th week of pregnancy
Zhao et al., 2013 [48]	Autologous BMDSCs	Case report	1×10^7 BMDSCs infusion following hysteroscopic adhesion lysis	/	1	Spontaneous pregnancy after 3 months
Singh et al., 2014 [49]	Autologous BMDSCs	Prospective case series	3 mL SVF sub-endometrial injection. After the exclusion of other causes of secondary amenorrhea	/	6	EMT increased, resume of menstruation in 5 patients
Santamaria et al., 2016 [50]	Autologous CD133+ BMDSCs	Prospective case series	15 mL of saline suspension with selected CD133+ cells infusion; BMDSC delivered into the spiral arterioles via catheterization	/	18	EMT increased; 3 spontaneous pregnancies, 7 pregnancies after 14 EMT
Tan et al., 2016 [64]	Autologous MenSCs	Prospective case series	Instillation of 0.5 mL MenSCs suspension on cd16	/	7	EMT increased; 2/4 CP; one spontaneous pregnancy after the second MenSCs transplantation
Cao et al., 2018 [62]	UC-MSCs	Prospective case series	1×10^7 UC-MSCs on collagen scaffold following hysteroscopic adhesion lysis	/	26	EMT increased; improvement in endometrial proliferation, differentiation, and neovascularization; 10/26 CP, 8/10 LB
Sudoma et al., 2019 [57]	Autologous ADSCs	Prospective case series	A sub-endometrial injection every 5–7 days 3 times	/	25	EMT increased; 13/25 pregnancies, 9/25 live births

Table 2. *Cont.*

Reference	Cell Source	Study Design	Administration Protocol	Control Group (n)	Intervention Group (n)	Outcome
Lee et al., 2020 [58]	Autologous adipose-derived cells	Prospective case series	Transcervical instillation of autologous AD-SVF from adipose tissue	/	6	EMT increased; resume of menstruation in 2/5 patients, 1/5 pregnancies after EMT
Zhang et al., 2021 [63]	UC-MSCs	Self-controlled prospective study	A suspension of 1×10^7/mL (2 mL) UC-MSCs on collagen scaffolds, transplanted into the uterine cavity	/	16	Average EMT increased ($p < 0.001$); 3/15 CP, 2/3 LB

BMDSC = bone-marrow-derived stem cell; MenSCs = menstrual-blood-derived stem cells; UC-MSCs = umbilical cord mesenchymal stem cells; ADSCs = adipose-derived stem cells; RCT = randomized controlled trial; cd = cycle day; EMT = endometrial thickness; OP = ongoing pregnancy; CP = clinical pregnancy; OPR = ongoing pregnancy rate; and LBR = live birth rate.

2.3. Tissue Bioengineering

Bioengineering approaches have demonstrated promising outcomes in the field of regenerative medicine over recent years. Various biomedical materials and techniques, such as collagen scaffolds, decellularized scaffolds, hydrogels, and microfluidics, have been employed to facilitate tissue repair and regeneration [76,77]. The rapid advancement of biomaterials has also enabled new possibilities for therapeutic strategies in thin endometria. Hydrogels, nanostructured delivery systems, bioactive degradable scaffolds, and other innovations have emerged as promising tools to enhance the survival and function of stem cells [78,79]. In 2021, one study [80] investigated the effects of transplanting UCMSCs, seeded on a human acellular amniotic matrix (AAM), to an endometrial injured site in a rat model. The results showed that endometrial thickness significantly increased, and the expression of vimentin, cytokeratin, and integrin β3 were higher in treated rats compared to untreated rats. The UCMSC–AAM combination might potentiate the endometrial repair effect of UCMSCs. The extracellular matrix is indeed an important component in tissue remodeling. Hydrogel, a highly hydrated collagen-based material, has shown great benefits in facilitating constructive and functional tissue remodeling [81]. One study developed a 3D endometrial-like co-culture system of epithelial and stromal cells using an endometrial extracellular matrix (EndoECM), which could keep cells alive while undergoing significant remodeling. Afterwards, immunocompetent mice were injected with it subcutaneously, and remarkable endometrial regeneration was observed [82]. Furthermore, circulatory systems play a vital role in maintaining homeostasis in tissue remodeling. Microfluidic systems have offered more precise control of fluid flow in a set of micrometer-sized channels [83,84]. Thus, it can create a better microenvironment for a 3D culture of stem cells. In 2017, Gnecco et al. [85] developed a microfluidic model of the human endometrium composed of perivascular stroma and endothelial cells, which could mimic an idealized 28-day menstrual cycle by undergoing temporal hormonal changes and a decidualizing process. In the same year, another microfluidic system termed "EVATAR" was also introduced [86]. By integrating reproductive tract tissues and peripheral organs into a microfluidic platform, the dynamically controlled endocrine models could also mimic the 28-day menstrual cycle. The above advancements in tissue bioengineering may lead to novel therapeutic strategies for the treatment of a thin endometrium. However, it is important to note that the efficacy, safety, and effects on reproductive outcomes and offspring of those novel approaches have not been validated in clinical trials. Further research and mechanistic studies are required in the future.

3. Conclusions and Future Perspectives

Given that there are various etiologies for a thin endometrium including hormonal, molecular, or cellular in nature, the current classical treatments may not be always effective. Despite the current lack of consensus on the diagnosis and effective treatments of thin endometria, an increasing number of promising experimental therapies have been proposed and examined in several pilot clinical trials. By summarizing and analyzing these novel approaches in the therapeutic management of a thin endometrium, we highlighted the importance of functional parameters such as live birth rate and long-term reproductive outcomes, as well as the quality control of those clinical trials. Although cell-based therapies and bioengineering approaches have shown promising results and opened new avenues for the treatment of thin endometrium, the exact mechanisms of these therapies should be investigated in-depth, and robust data are needed to answer several questions. For instance, whether the cellular properties of stem cells can remain stable during the process of proliferation and differentiation in vivo, and whether the process of apoptosis and genetic characteristics are the same as those of normal cells. It will be beneficial to know how to maximize the efficacy of PRP perfusion or cell injection, which is most probably closely related to the concentration, time, frequency, and location of the perfusion and the degree of in vitro culture and differentiation. The development of these innovative therapies lies in the in-depth exploration of endometrial cell heterogeneity; molecular mechanisms for endometrial proliferation, differentiation, and regeneration; and the role of endometrial stem/progenitor cells in endometrial repair and regeneration. We believe that with a deeper understanding of the molecular mechanism that drives endometrial regeneration, precise molecular targets and novel approaches will be discovered in the future. Meanwhile, it is crucial to conduct well-designed randomized controlled trials with defined clinical outcomes to assess the validity, effectiveness, and safety of these novel strategies in humans.

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