



Bioengineering Using Scaffolds Restores Endometrium Function in Infertility: A Review

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Abstract

In women of reproductive age, there is often an injury to the endometrium such as endometrial damage or Asherman's Syndrome (AS), Intrauterine Adhesions (IAU), or endometrial scar formation such as cesarean section, myomectomy, curettage which can cause infertility. To overcome these problems, a uterine tissue engineering strategy emerged using scaffold biomaterials. In this journal, natural and synthetic scaffold materials and cell sheets are used, mostly natural materials, the target species are humans, *rattus norvegicus*, and rabbit, while the largest target tissue is the endometrium. In vitro culture and transplanted in vivo. Endometrial regeneration and pregnancy were studied in two in vitro and in vivo clinical trials employing scaffold tissue engineering technologies. Thus, uterine generation with tissue engineering technology has become a strategy for treating patients with uterine disorders to restore uterine function and structure to restore fertility. The purpose of this article paper is to give an overview and point of view on uterine biotechnology, specifically tissue engineering using scaffold biomaterials for infertility treatment.

Introduction

The survival of the species lies in the reproductive systems and organs [1]. The uterus is a reproductive organ that plays a very important role, the uterus consists of 3 layers, namely the perimetrium, myometrium, and endometrium [1]. For blastocyst implantation, embryonic growth, and fetal nourishment, the uterus supplies an interior environment. Infertility, miscarriage, uterine injury, and recurrent miscarriage can all be caused

by structural and functional uterine problems or diseases such as severe uterine trauma induced by cesarean section, myomectomy, curettage, or hysteroscopic incision of the uterine septum [2,3,4]. A significant impact is infertility where the incidence is 14% in couples of reproductive age [5].

The endometrium is the uterus's deepest layer. It is necessary for embryo implantation and pregnancy maintenance to have a good intrauterine environment [6]. About 6% of women



undergoing infertility therapy have a malfunctioning uterus, which supports several biological functions that are critical to reproduction [2]. There are several forms of ailments that can be overcome. Anomalies in uterine function and structure cannot be remedied by conventional means, but bioengineering of the entire or part of the uterus, which can be done by engineering uterine tissue using scaffold biomaterials, can overcome them.

Scaffold biomaterials are efficient regeneration and construction of organs and tissues and provide a 3D structure that allows tissue growth and differentiation. Tissue engineering, which tries to manufacture biological tissues and organs to treat diverse illnesses that cause structural and functional abnormalities, is emerging as an appealing option for treating functional disorders of the uterus. Biological tissue and supporting cells will be implanted on the scaffold, allowing migratory proliferating and differentiating cells, resulting in tissue and organ regeneration [7].

The purpose of this review paper is to give an overview and point of view on uterine biotechnology, specifically tissue engineering using scaffold biomaterials for infertility treatment.

Research method

Tissue engineering endometrial biotechnology using scaffold on endometrial damage, literature review and overall search through Google Scholar and Pubmed. The literature search was carried out from the beginning of 19-21 June 2021. With the following keyword searches (“Scaffold” or (“Tissue engineering”) and (“Uterus”) or (“endometrium”). The search was limited to studies published from 2021 to 2016. Electronic database searches were completed along with reference lists and citation hand searching. The selection of studies used criteria to identify studies that met the requirements (1) Scaffold, (2) Natural Biomaterials, (3) Synthetic Biomaterials, (4) Cell Sheet, (5) Stem cells (6) Uterus, (7) Endometrium, and (8) Uterine Infertility, (9) Asherman syndrome, (10) Intrauterine adhesions. Exclusion criteria were (1) Cancer and, (2) Endometriosis.

Table 1: Study of Endometrium Tissue Engineering using scaffold biomaterials in Infertility.

Species to be targeted	Tissue to be targeted	Material for scaffolds	Cells were used	In vitro cell culture time	In vivo experiments	Test for pregnancy	Reference
Rattus Norvegicus	Endometrium	Hydrogel	MSCs generated from human bone marrow	3 days	7-day period	7 days after transplantation	Liu et al, 2019 [8]
Rattus Norvegicus	Endometrium	Collagen	MSCs obtained from human umbilical cord	3 days	60-day period	60 days after the transplant	Xin et al, 2019 [9]
Rabbit	Full thickness	Polyglycolic acid/Polylactide-co-glycolide PGA/PLGA	Endometrial and myometrial cells from rabbits	-	6 month period	6 months after transplant	Magalhaes et al, 2020 [10]
Rattus Norvegicus	Full thickness	Collagen	No (leukemia inhibitory factor [LIF])	-	12 week period	8 weeks after the transplant	Xue et al, 2019 [11]
Human	Endometrium	Collagen	MSCs obtained from human umbilical cord blood	-	3 months	10/26 Patients have gotten pregnant	Cao et al, 2018 [12]
Mouse	Endometrium	Hyaluronic acid (HA) Hydrogel/fibrinogen/thrombin	Mouse endometrial stromal cells	24 hours	14-day period	14 days after the transplant	Kim et al 2019 [13]
Rattus Norvegicus	Endometrium	Cell sheet	Rat endometrial cells	-	4 weeks	6 weeks after the transplant	Kuramoto et al, 2018 [14]
Rattus Norvegicus	Endometrium	Heparin- modified poloxamer	Mouse endometrial epithelial cells	4 hours.	7-day period	90-day period after the transplant	Xu et al, 2017 [15]
Rattus Norvegicus	Endometrium	Hydrogel-gelatin	Human induced MSC	24 hours	15 days	1 month post transplantation	Wanqing et al, 2020 [2]

Bioengineering scaffold for the endometrium

This journal uses natural scaffold materials, synthetic materials, and cell sheets, mostly using natural materials, namely hydrogel-collagen (8,9,11,12,13,16), synthetic materials (10,15), and cell sheets (14) target species. are human, rattus norvegicus and rabbit. While the largest target tissue is the endometrium. In vitro culture and in vivo transplantation Endometrial regeneration and pregnancy were studied in two in vitro and in vivo clinical trials employing scaffold tissue engineering technologies. Natural scaffold biomaterials to treat or treat patients with endometrial damage or Asherman Syndrome (AS), Intrauterine Adhesions (IAU), or endometrial scar formation that can cause infertility.

Natural materials

Liu et al study with the US case using MSC Sec, through cy-

tokine arrays, variables that may contribute to endometrial and endothelial cell proliferation and migration as a result of MSC-Sec were studied. A number of cytokines have been associated to tissue regeneration in MSC-Sec. In an In vitro MSC-Sec study, bioactive assays of MSC-derived in endothelial, epithelial, and stromal cell cultures were carried out showing that the ability of HUVECs to form cells was elevated in the MSC-Sec- compared to the untreated group IMDM. Furthermore, when compared to the control, the rate of proliferation of HUVEC treated with MSC-Sec was substantially faster. MSC Sec promotes endothelial cell proliferation and endometrial epithelial cell development. Patients with intrauterine adhesions have been found to have compromised myometrial and endometrial vasculature. Thus, AS prognostic factors include endometrial vasculature. Thus increased endothelial cell proliferation contributes to the restoration of the endometrium. Endometrial glands are made up primarily of epithelial cells, which produce and secrete

chemicals necessary for the embryo's survival and growth. As a result, infertility is common in patients with AS who have epithelial cell damage. Epithelial and endothelial cells can both proliferate after MSC-Sec is applied to the endometrium. Then an in vitro cell-based test administered MSC-Sec/gel into the rat uterus and surrounded the endometrium for 7 days. The MSC Sec gel group produced considerably more fetuses after these female mice mated with male mice after a week and a half. It can be concluded that MSC-Sec/gel therapy contributed to the fertility recovery of the mice.

Xin et al established that Collagen Scaffold (CS) was created from human umbilical Mesenchymal Stem cells (UC-MSCs) and used to regenerate the endometrium in a later investigation with patients of intrauterine adhesions (IUA) causing infertility. CS provides optimum physical assistance for UC-MSC Proliferation and attachment. UC-MSCs/CS/ have been demonstrated to boost HESC growth and prevent apoptosis in vitro investigations. The levels of VEGF-A, TGF- β 1, and PDGF-BB in the CS/UC-MSC group were greater than in the control group in this study. HESCs proliferate and apoptosis is reduced were linked to the action of CS/UC-MSC, according to these findings. VEGF-A levels were shown to be increased in the uterus after CS/UC-MSC transplantation. The NR and CS groups were compared to TGF- β 1 and PDGF-bb. As a result, CS/UC-MSC transplantation can help to produce an environment conducive to tissue healing in the early phases of endometrial injury. TGF- β 1 increases endometrial proliferation and modulates immunological responses, Because VEGF helps to re-epithelialize and vascularize the endometrium, PDGF promotes stromal cell proliferation through autocrine actions during the proliferative stage. As a result, this growth factor is critical for endometrial regeneration [9]. At 60 days after surgery, a fertility test is performed. The gold standard for demonstrating the function of the regenerated endometrium is gestational capability. The CS/UC-MSC group exhibited a greater conception rate than the CS and NR groups, showing that the functional endometrium was healed after CS/UC-MSC transplantation. Because of their ease of collection, minimal immunogenicity, and high proliferative capacity, cord-derived MSCs (UC-MSCs) have been praised as a feasible source for cell-based therapy. According to various studies, UC-MSCs have also been employed to treat a range of disorders. The most significant obstacle to employing MSCs to improve endometrial repair is their low endometrial persistence and utilization rate [16]. Several studies have also reported the application of UC-MSCs to promote endometrial repair, the main obstacle to treatment with MSCs is their low local persistence and utilization rate in the endometrium [17].

Research Xue et al can provide useful information, they used collagen scaffold Leukemia-inhibitory factor (LIF) in rats with a severe uterine injury that can cause infertility, which was divided into 4 sample groups. The collagen LIF scaffold boosted the number of endometrial cells and neovascularization after two weeks, according to the findings. In addition, the number of endometrial glands in the LIF collagen scaffold group was higher than in the PBS/collagen scaffold group eight weeks following surgery. The percentage of smooth muscle actin positive regions (α -SMA) was likewise significantly larger in the LIF/collagen scaffold than in the PBS/collagen group. LIF also increases the amount of pregnancies and fetuses. They also discovered that in the wounded uterine horn, LIF blocked inflammatory cell infiltration and reduced the manifestation of the cytokine IL-12 pro-inflammatory cytokine IL-12 while regulating the secretion of the anti-inflammatory cytokine IL-10. Because of its immu-

nomodulatory capabilities, LIF enhances uterine regeneration following injury, according to the findings. LIF has been shown in several studies to play a role in the vasculature of the damaged uterus, as well as guaranteeing appropriate capillary density and influencing VEGF expression [11]. The use of LIF helps to restore uterine function. LIF is involved in skeletal muscle activation and regeneration. Because smooth tissue is structurally identical to skeletal muscle, in vivo injection of LIF improves skeletal muscle regeneration. LIF has the ability to improve survival and block bioblast apoptosis, which explains why LIF causes an increase in the number of myoblast cells. According to Hunt et al., LIF appears to play a substantial role in skeletal muscle regeneration by controlling the inflammatory response rather than directly impacting myogenic cells. In this paper, it is demonstrated that LIF, in combination with Scaffold Collagen, may restore uterine shape and function in a uterine injury mouse model.

Cao et al used to establish the efficacy of allogeneic cell therapy for recurrent Intrauterine Adhesion (IUA) patients, cord derived mesenchymal stromal cells (UC-MSCs) were put onto a collagen scaffold. In this clinical experiment, 26 patients were enrolled, and 10 of them became pregnant, with 8 of them having live deliveries with no evident birth abnormalities or placental problems. One patient had a spontaneous abortion in the third trimester of pregnancy, while the other had one at 7 weeks of pregnancy. UC-MSC is a type of noninvasive stem cell that is widely utilized in regenerative medicine. It uses a collagen scaffold to give MSC attachment sites at the site of injury, which aids in endometrial regeneration. The augmentation of various variables in the regenerative environment that directly play a role in endometrial reconstruction may be related to the involvement of UC-MSC scaffold collagen in endometrial regeneration [18].

The healing effect of Hyaluronic Acid Hydrogel (HA) with endometrial stromal cells (EMSCs) was tested in vitro in a uterine model of infertility mice in a study conducted by Kim et al employing a scaffold hydrogel collagen biomaterial MSC produced from bone marrow.

EMSCs were decided on using HA hydrogel and three different dosages of fibrinogen/thrombin. When combined with dEMSC, the HA/fibrin gel demonstrated biocompatibility. Within two weeks of therapy with hydrogel, fibrous tissue had diminished and endometrial thickness had grown. Desmin, CD44, PECAM, and IGF-1, which are important for embryo implantation, are produced and secreted by the regenerated endometrium, indicating that it has a recovery role. The transplanted embryos were implanted successfully, and the implanted embryos' normal development was assessed by various marker localization of the three germ layers. The HA hydrogel enabled live birth in the repaired endometrium. As a result, dEMSCs mixed HA hydrogel could be a novel treatment for endometrial injury and infertility with rapid recovery. HA has also been used in several damaged models, including endometrial regeneration attempts, according to multiple research [19]. There is a link between HA levels and endometrial receptivity to preimplantation embryos. These results reflect the elevated amounts of HA seen in the reshaped tissue [13]. So in this study, they prepared a HA/fibrin hydrogel using an optimized concentration of T to accelerate cross-linking and facilitate efficient delivery of conditioned cells, as it could affect the treatment required. Efficient [13]. To make the best HA/fibrin hydrogel, researchers looked at the influence of varying T concentrations on stiffness. Sufficient

stiffness, since cells can be easily integrated and grafted into the injured endometrium's surface. Because uterine fibroids have a higher amount of altered and disordered collagen, lowering uterine tissue stiffness is considered an alternate therapy option for fibroid treatment [20]. The use of cells with hydrogel prevents the loss of injected cells in the uterus. This is necessary in order for the injected cells to survive in the injured endometrium.

Wanqing et al 3D bioprinted human iPSC-derived MSC scaffolds for uterine endometrial repair. Curettage of the uterus, inflammation that can cause infertility in women of childbearing age. In this study, hiMSC cells were viewed first in vitro and followed by in vivo transplantation. hiMSC was induced using a hydrogen scaffold with a device for 3D bioprinting. The results showed that 3D bioprinting of a hydrogel scaffold containing hiMSC promoted the restoration of histomorphology and regeneration of the endometrium of endometrial cells and endothelial cells, as well as repairing the endometrium as a reception function, specifically, repairing embryo implantation and pregnancy maintenance activities in endometrium that has been wounded or diseased. As a result, a 3D It is possible to use a printed hiMSC hydrogel scaffold. to aid in the restoration of the wounded endometrium's structure and function.

Previous research has revealed that MSCs imprinted on hydrogel scaffolds have greater differentiation capabilities and the potential to generate a favorable milieu in vivo to guide new tissue growth and remodeling [20,21].

Synthetic materials

Magalhaes et al used a biodegradable polymer scaffold with superior autologous cells made of Poly DL Lactide Coglycolide (PLGA) and coated polyglycolic acid (PGA) implanted with cells originating from the uterus in their research. Scanning Electron Microscopy (SEM) was used to manufacture PGA/PLGA uterine constructions, and SEM analysis revealed cell adhesion and uterine construction thickness during in vitro testing. Subtotal uterine excision was performed on rabbits, who were then reconstituted using scaffolds seeded with autologous endometrium and myometrial cells. This designed uterus creates cell-seeded tissue, including luminal epithelium/organized glands, stroma, vascularized mucosa, and myometrium, 6 months after implantation, just like the original cell structure. Four out of ten uterine segment samples were repaired and maintained fetal growth through term and until live birth, according to the findings of a research of rabbits with normal pregnancies.

Heparin-modified poloxamer (HP) and Keratinocyte Growth Factor (KGF), both potent epithelial tissue healing factors, were employed by Xu et al. To inhibit intrauterine adhesion, KGF-HP is employed as a support matrix (IUA Hydrogel KGF HP was able to prolong the retention of encapsulated KGF in the uterus of an injured mouse model using in vivo bioluminescence imaging. Furthermore, After receiving KGF-HP Hydrogel, the shape and function of the wounded uterus significantly improved. Not only is endometrial glandular epithelial cell growth and luminal epithelial cell proliferation harmed, but also uterine angiogenesis. Finally, the relatively close relationship between autophagy and EEC proliferation and angiogenesis was first verified following KGF treatment by measuring LC3-II and P62 expression. Overall, KGF-HP appears to be a potential candidate for treating IUA. Cell proliferation and angiogenesis were used to assess the impact of KGF in supporting morphological and functional healing of the wounded uterus. Both endometrial glandular epithe-

lial cells and luminal epithelial cells multiplied after 7 days of treatment with KGF-HP hydrogel solution. Cell proliferation may be connected to the restorative microenvironment by reducing the inflammatory response [22]. Because the uterine wall is rich in capillary networks, angiogenesis, or the new growth of pre-existing blood vessels, is particularly vital for sustaining the nutritional needs of developing or repairing tissues. Angiogenesis is important for supporting the nutritional requirements of developing or repairing tissues because the uterine wall is densely packed with capillaries [23].

Cell sheet

Kuramoto et al. used cell sheet technology to restore functional endometrial tissue as a regenerative medicine treatment for infertility-causing endometrial disorders in women. Cell sheets containing GFP positive rat uterine derived cells were transplanted into resected rat uterine endometrial areas as part of the intervention. Cell sheet that was transferred area was examined histopathological investigation and macroscopic observations, including immunohistochemistry. Cross-breeding was also used to test fertility and assure conception in the rat uterus that had been created. Endometrial regeneration was demonstrated After cell sheet transplantation, GFP-positive tissue engraftment was observed both visually and histologically. As a result, cell sheet transplantation can regenerate endometrial tissue that is equivalent to normal endometrial tissue and can support conception. As a result of this study, we've defined a new technique called cell sheet, which allows us to create neighboring cell sheets with multilayers without the use of scaffolding. This approach is advantageous because the sheet retains the original matrix adhesive extracellular, on the basal surface, such as fibronectin and laminin, allowing the cell sheet to be transplanted without the use of sutures [24].

Thus, there are many clinical trials describing natural and manmade materials, as well as cell sheets without scaffolding. Future analysis should determine the best and most suitable material for uterine biotechnology, its biomaterial properties that support uterine treatment and support pregnancy. So the study of uterine bioengineering relies on a variety of scaffold materials including natural materials, synthetics, and cell sheets of various functional and structural problems of the uterus that can cause infertility.

Conclusion

This paper describes the use of scaffolds for efficient tissue regeneration that allows tissue growth and differentiation, i.e. biological tissue will be implanted on the scaffold and also use supporting cells, in order for migratory cells to proliferate, differentiate, and regenerate tissue.

The emphasis is based on the type of materials used and the characteristics of the available scaffolding. In this journal, uterine regeneration through scaffold-based uterine engineering from natural materials, synthesis, and cell sheets, can regenerate the uterus so that infertility cases can be resolved. However, there are still barriers to making whole uterus biotechnology.

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