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Scaffold-based tissue engineering approaches in treating infertility

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ABSTRACT

Tissue engineering and the use of scaffolds have shown high therapeutic potentialities about male and female infertility. Nowadays, many couples are suffering from infertility problems. There are different causes for infertility including chemotherapy (for male and female), uterine injuries, and intrauterine adhesions. Extra-cellular matrix in tissue engineering provides a supportive medium for blood or lymphatic vessels making it a suitable substrate for cell implantation and growth. Dominant successes in this branch have been in use of patient-derived primary cells, these cells loaded in scaffolds and used to generate tissue for re-implantation. However, this method has limitations, because of the invasive nature of cell collection, also the cells patient-derived may be not healthy and become the source of disease. Therefore, use of stem cells, including embryonic stem (ES) cells, bone marrow mesenchymal stem cells (BM-MSCs) and umbilical cord-derived mesenchymal stem cells (UC-MSCs) have been considered. Cell/scaffold systems have a substantial role in fertility organs or agents repair or regeneration. This review summarizes the novel scaffold-based tissue engineering approaches to treat infertility.

1. Introduction

Infertility threatens individual s' psychological and physical stability and even social stability of specially young couples [1]. Although infertility is not considered a vital disease, but effect of this problem on all aspects of their personal and social lives is clearly seen. For couples suffering from infertility, mental problems such as depression, anxiety, lack of self-confidence and dissatisfaction with their lives are expected [2]. Infertile couples are exposed to different physical and emotional problems that naturally affect their marital and social status. Infertility can also leave effect on the relationship between infertile patients and their spouses, friends and colleagues [3,4]. Many structural abnormalities in male and female reproductive system can be affected by diseases, trauma and some of special therapies particularly cancer therapies which ultimately contribute to infertility. On the other hand, regenerative medicine and the use of scaffolds to treat these abnormalities have recently been taken as promising approaches to treat infertile young couples. The utilized scaffolds for this subject must be characterized as: biodegradable and biocompatible, inter-connectivity, macro porous 3D structure for cell culture, and also have appropriate mechanical properties for closely mimicking the natural Extra-Cellular Matrix (ECM) [5,6]. For transportation of food and waste materials and for cellular communication processes, the existence of interconnectivity is vital. For cell migration, adhesion, proliferation and metabolism, scaffolds must have suitable mechanical properties, and furthermore, for resistance and stability of the gels, mechanical properties play key roles [7–13]. Atala et al. [14], expanded and seeded the urothelial and muscle cells biopsies, obtained from end-stage bladder disease patients, on a scaffold to generate bladder constructs. The bladders were then implanted into the patients to rehabilitate normal bowel function. This method of therapies eliminated rejection risk of organ transplantation. The ability to collect cells from patient to produce healthy cells, reduces significantly the risk of immune responses to the implantation, therefore the need to use immunosuppressive drugs and the resultant infection probability is reduced [15]. However, there are several challenges in front of regenerative medicine that are needed to be solved in

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Table 1
Paracrine effects of stem cells in regenerative medicine.

Paracrine effect	Outcome	References
Cytoprotective effect	• MSCs represent cytoprotective and anti-apoptotic actions through the release of soluble active mediators	[19,20]
Provasculogenic effects	• MSCs represent a source of pro angiogenic and pro arteriogenic factors	[21,22]
Anti-inflammatory effect	• MSCs present anti-inflammatory effects by secretion of trophic factors	[23–26]
Endogenous regeneration	• MSCs transplantation active resident cardiac progenitor cells	[27,28]
Antifibrotic effect	• ESCs and MSCs transplantation decrease fibrosis in the most organs	[29–31]
Metabolism	• MSCs transplantation attenuates cardiac metabolic remodeling	[32,33].

MSC: mesenchymal stem cell, ESC: embryonic stem cell.

order to achieve successful treatment.

2. Regenerative medicine

Due to the congenital defects, trauma, and diseases, humans and animals lose tissues and organs. It should be noted that, for many reasons, human body, in many cases, cannot do regenerative processes [16]. Despite the presence of many stem cells in many body tissues, in most cases these cells are inactive [17]. Stem cells mediate therapeutic mechanisms by anti-apoptotic and pro-meiotic, generally paracrine effects [18] (Table 1).

In most tissues such as heart, skin, and uterine, after they are damaged, the scar tissue is replaced, which do not usually exert the desired performance and are un-functional. Therefore, scientists and clinicians have suggested the transplantation of differentiated cells or stem cells to regenerate damaged tissues. For this aim, reliable resources of tissues and organs are needed to build or improve the therapeutic approaches and in some cases, create new tissues. To create new tissues and organs, and to promote the damaged or diseased tissues and organs reconstruction, regenerative medicine is greatly beneficial however, after transplantation process, the use of regenerative medicine has been limited by different factors such as poor cell survival, distribution, and integration. A cell delivery system utilizing the least aggressive and biodegradable properties of the material is needed, eliminate these limitations [34]. In this technology, an extracellular matrix or highly porous scaffold is used to replace the mammalian cells to guide tissue growth and regeneration in a three dimensional environment, mimicking natural ECM. Scaffolding approaches should be able to create three dimensional hierarchical porous structures with permeable and diffusive properties to achieve the desired mechanical structure and mass transfer.

3. Infertility

As defined by World Health Organization (WHO), if pregnancy won't happen after 12 months of regular intercourse it is clinically dubbed as infertility. Infertility has diverse consequences that include social problems and mental suffering [35]. Despite the willingness to have children, about 9% of couples are childless, Due to the delay in childbearing, a quarter of couples cannot have the optimal size for their families, while only half of them seek treatment [36]. In recent years, efforts have increased sharply to treat infertility among young couples. As the result, treatment methods are also developing day by day. Infertility in couples may have different causes and maybe resulted from a problem regarding male and female pregnancy involving factors or a combination of both. For male infertility there are some problems, including the production or function of subnormal sperm, sperm delivery problems, overexposure to specific environmental factors, cancer-related damages and for female infertility these include ovulation disorders, uterine or cervical abnormalities, fallopian tube harm or blockage, endometriosis, primary ovarian insufficiency, pelvic adhesions, and cancer and its treatment.

Due to very large advances made in the field of regenerative medicine and scaffold-based therapies, seems to use of scaffolds for treatment of infertility related abnormalities is also very promising.

4. Female infertility

Fallopian tubes, uterus, and vagina are constituent components of female reproductive system. Any problem in these organs can cause infertility problems or pregnancy complications.

4.1. Tissue engineering application in uterine disorders treating

4.1.1. Scaffold-based tissue engineering approaches in treating intrauterine adhesion & Asherman syndrome

The intrauterine adhesion was initially reported by Heinrich Fritsch in 1894 and the full description of Asherman's Syndrome (AS) was presented by Joseph Schmanner, 54 years later. One of the reasons causing partial or complete endometrial dysfunction with fertility impairment and menstrual pattern, is adhesion in the uterine cavity. Asherman syndrome occurs due to endometrial lesion and major luminal epithelial cells loss. By replacing fibrous tissue with stroma, the endometrium becomes significantly thin and losses its response to estrogen and progesterone. The main reasons for this disorder include miscarriage curettage, caesarean section, infection, uterine artery and embolization [37,38]. Intravenous or intrauterine administration of stem cells is currently utilized for partial uterus repair in endometrium regeneration. However, one of the major limitations is cell death by necrosis or apoptosis on the initial days post-transplantation. Scaffolds are among the best approaches to overcome this limitation. These 3 Dimentional (3D) environments create an effective approaches to increase cell retention and survival [39]. Lijun Ding et al. [40] in a study, were successful to partially regenerate and reconstruct the rat uterus through the transplantation of Bone Marrow Mesenchymal Stem Cells (BM-MSCs) on collagen scaffolds. Collagen is the most important extra cellular matrix material and, Collagen scaffolds are very popular due to their unique characteristics [41,42]. Some of scaffolds and their properties are presented in Table 2.

Collagen scaffolds mimic the functions of the target tissue and provide the critical factors needed to modulating cell dynamic behavior and intercellular communication [46,47]. In other study [40], isolated rat BM-MSCs were seeded on the collagen scaffolds and were transplanted to the rat uterus, damaged with resection segment of 1.5 cm in length and 0.5 cm in width from the horn of the uterus. The results showed higher pregnancy rate in collagen/BM-MSCs group (77.8%) when compared to collagen/PBS (33.3%), and spontaneous repair group (25%). The collagen/BM-MSCs group also showed increased in the presentation of the blood vessel von Willebrand factor (marker vWF), higher vessels formation and effective endometrium regeneration. With increased angiogenesis caused by principle Fibroblast Growth Factor (bFGF) and secretion of Vascular [34] Endothelial Growth Factor (VEGF), regeneration of uterus by collagen/BM-MSCs happens. Vascularity accelerates tissue regeneration process by improving oxygen, Nutrient, and hormones availability. Moreover, BM-MSCs by paracrine effect and producing the Transform of Growth Factor1 (TGFb1) probably promotes tissue repair that results into a regenerative microenvironment. In addition, TGFb1 has a positive

Table 2
Properties of biomaterials as a scaffold.

Scaffold type	Advantages	Limitations	Reference
Collagen scaffold	Biocompatible Biodegradable Cell adhesion (because of RGD motifs) Cohesive and high porosity Quickly integration with new tissue matrix	No inherent rigidity Potential for antigenicity through telopeptides	[41,42]
Alginate scaffold	Biocompatible Biodegradable Used in the form of hydrogel Ability to create permanent gel	Difficulty of alginate purification from substances that cause cytotoxicity and apoptosis in the final sample	[43]
Silk scaffold	Biocompatible Biodegradable Water based processing	Low quality (restricted length) Fast degradation Limited permanent for revascularization	[44]
Nanofiber scaffold	Mimic natural extra cellular matrix fibers	Most of production methods are not ideally for large scale production	[45]

impact on uterine regeneration by reducing apoptosis, and decreasing inflammatory and immune responses [48–51]. However, there is insufficient data on the molecular mechanisms for endometrium regeneration in Asherman Syndrome (AS), but; some of the factors involved in this mechanism are investigated. ΔNp63 is known as a component of p53 group with a regulatory action. ΔNp63 is significantly adjusted in residual epithelial cells of the impaired endometrium in AS. Findings have suggested that the transplantation of biodegradable collagen scaffolds, that loaded with high density autologous Bone Marrow Mononuclear Cells (BMNCs) into the uterine lining of AS patients, down-regulates ΔNp63 expression resulting in normalized stemness alterations and restored endometrial regeneration To avoid clinical risks of in vitro cultured BMSCs and allogeneic sources, the autologous BMNCs were chosen as the seeding cells for clinical therapy in the present investigation. After the therapy, patients had longer and heavier menstrual cycle than usual and all these five patients showed considerable recovery in the endometrial thickness and blood flow. This research was the first clinical trial on conducted on the transplantation of collagen scaffold with stem cells that was performed in 2016 on five females. All patients exhibited the restoration of endometrial regeneration and spontaneous pregnancy following one or two successful IVF rounds and after BMNCs-seeded collagen scaffold transplantation [52]. In 2018, allogeneic cell therapy using umbilical cord MSCs-seeded collagen scaffolds in patients with recurrent Intrauterine Adhesion (IUA) also showed highest improvements in endometrial thickness and pregnancy rate [53]. Additionally, this therapeutic method caused 40% improvement in infertility complications in these patients. Due to the biocompatibility and biodegradability properties of collagen, such as biomaterials, collagen scaffolds in combination with growth factors are utilized in tissue engineering. Xin'an Li et al. [54] in a study, by blending a collagen-binding domain to the native basic Fibroblast Growth Factor (bFGF) N-terminal, designed a targeting delivery system by collagen-based bFGF. Collagen/bFGF group with higher Alpha-Smooth Muscle Actin (alpha-SMA) areas, and neovascularization played an important role in increasing the thickness of the endometrium. This work was carried out with collagen remodeling and complete degradation of scaffold endometrial cells and muscle fibers were replaced. In another research a collagen-binding Vascular Endothelial Growth Factor (VEGF) was investigated for uterine repair. VEGF is a potent agent for endothelial cell-related subjects such as proliferation, migration and tubular formation, and angiogenesis [55]. Collagen/VEGF was directly injected into the scarred rat uterus after full-thickness injuries. After the implantation, the increased levels of uterine wall regeneration, presence of glands, presence of smooth muscle cells, and vascular growth were observed. These results are encouraging to restore mammal's fertility, but seemingly, these strategies are beneficial for larger animal models.

4.1.2. Scaffold-based tissue engineering approaches in treating thin endometrium

The uterus is comprised of three inner, middle and outer layers, endometrium is the inner lining and contains two layers including the stratum basalis and stratum functional, respectively as the first and the second layers. Stratum basalis provides regenerative niches including endometrial-intrinsic progenitors/stem cells [56–58]. The second layer is dynamic changes happen in response to the monthly flux of hormones that guide menstrual cycle. One of the very important parameters on the time of embryo transfer on IVF outcome is the impact of endometrial thickness. When endometrial thickness is less than about 6–7 mm, the egg cannot nest. Therefore, endometrial thickness is vital in the quality of egg nests and pregnancy rate will be improved with the increased endometrial thickness [59]. In some patients, low serum estrogen levels are also associated with thin endometrium that can be improved by the administration of estrogen tablets, patches, or injections. However, in some other cases with normal estrogen levels, thin endometrial lining may be the result of previous uterine infection or post-intrauterine surgery uterus lining damages. It seems that endometrial regeneration can be effective in these cases. Stem cells have the ability to build every tissue in the human body, hence they great potential for future therapeutic uses in tissue regeneration and tissue repair. Especially in the case of the endometrium, which is a prime example of regeneration in the human body, which is shed and regenerated more than 400 times in women of childbearing age [39,60,61]. In 2013 Use of rat bone marrow mesenchymal stem cells for regeneration of thin endometrium in rat, bone marrow mesenchymal stem cells are a major type of multi-potent mesenchymal stem cells that are capable of differentiating into lineages of cells (mesenchymal stem cells can be differentiated into endothelial cells in vitro) after these studies. In 2018, umbilical cord-MSCs combined with collagen scaffold entered the clinical phase to treat thin endometrium (Fig. 1).

4.2. Scaffold-based tissue engineering approaches in treating ovulation disorders

One of the key organs in women's reproductive system is ovary. Ovulation disorders are of the reason for the infertility of about 25% of couples. Ovarian preservation is a vital practice in patients with pediatric cancer undergoing chemotherapy and/or pelvic radiotherapy. For this reason, engineered ovarian tissues and in vitro oocyte culture systems in order to in vivo implantation have received much attention and many efforts have been made in this regard. In recent years, cryopreservation and transplantation of ovarian tissue to restore the fertility in cancer patients, seems to be one of the most deep concerns [62]. Ovarian metastasis possibility is low in some cancers; however, in the other types such as leukemia this probability is higher. Breast cancer is also considered to have moderate risk [63,64]. Hence, it must be noted that for these patients, the transplantation of ovarian tissue

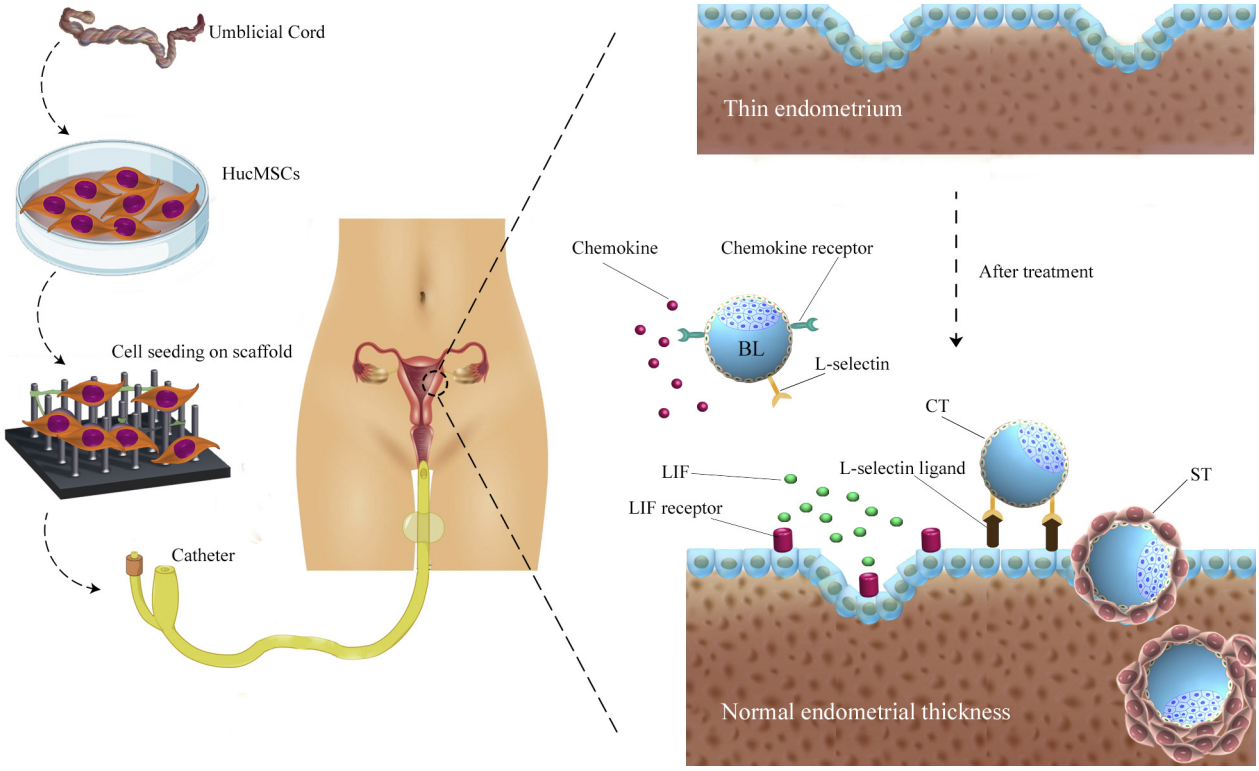

Fig. 1. The use of collagen scaffold/mesenchymal stem cells system. After transplantation of collagen scaffold/mesenchymal stem cells by catheter in uterine, increased endometrial thickness, expression of L-selectin ligand in the human endometrium and improved pregnancy rate are observed.

after disease remission is not advisable. The most highlighted task that artificial ovary must do is to keep isolated follicles in their original three-dimensional nature and therefore, maintenance of intercellular interactions between granulosa cells and oocytes is essential in this regard [65,66]. Alginate hydrogel has good and suitable environment where follicles and OCs are able to survive and grow. Alginate which is extracted from brown algae is a non-cytotoxic natural polymer [67] and has some attractive characteristics for artificial ovary application, such as biodegradability and biocompatibility, easy encapsulation of cells with certain processes such as oxidation and irradiation, finally the entrapped cells are released by biodegradation of alginate hydrogels [68]. For these reasons alginate hydrogel has been used in artificial organs, such as Langerhans island [69], stem cells [70] or hepatocytes [71]. In 2003, Pangas et al. [72] developed an alginate beads-based 3D for growth and development of individual granulosa cell-oocyte complexes (GOCs) in vitro culture system. Ovaries were dissected from 12-day-old female mice. GOCs were initially collected and then encapsulated in alginate beads. The results showed that granulosa cells were proliferated and oocytes growth in volume of alginate beads with spatial arrangement of GOCs. 3D alginate culture system can product more oocytes than the product of the conventional in vitro fertilization. Moreover, Xu et al. [73] in a study, isolated the immature follicles from 16-day-old prepubescent female mice. Single follicles were then pipetted into the middle of each alginate droplet and were cross-linked in calcium chloride. After 8 days of culture, IVF and embryo transfer to pseudo-pregnant female mice were performed Data showed that fertilization operation was successful. Additionally, in other studies, the utilization of biomaterials incorporated with ECM components (such as RGD, collagen (type I and IV) and/or fibronectin) into the polysaccharide-based matrix resulted in the improved growth, differentiation, and oocytes meiotic competence [74–76].

4.2.1. Scaffold-based tissue engineering approaches in treating premature ovarian failure

Premature Ovarian Failure (POF) is defined as the loss of normal function of ovaries before age 40, this effect can decrease the life quality of these patients. It is usually associated with abnormal sexual hormones, impaired oocyte release and infertility [77]. POF may be one of the side effects of chemotherapy and one of the major concerns of young women with cancer before undergoing chemotherapy, therefore, it is important to find efficient methods for the treatment of POF. The regenerative medicine is one of the methods that has received much attention in recent years. By Intra-ovarian MSCs injection in POF cases, improvement in the ovarian function and fertility in the rodent model was observed [78–80], but in direct cell injection method cell survival and retention be in trouble and it seems that these problems can be solved by scaffold using. In these cases, the use of scaffolds also prolonged cells survival and retention. With the transfer of umbilical cord MSCs-loaded collagen scaffolds into mice dormant ovaries higher improvements in cell attachment, proliferation and differentiation, and consequently efficient entrapment of MSCs into fibrillary networks and also increased long-term retention of MSCs in failed ovaries were achieved [81,82]. Furthermore, for in vitro-activation of primordial follicles, used from transfer of umbilical cord MSCs-loaded collagen scaffold. Application of retrograde injection method for UC-MSCs or collagen/UC-MSCs delivery into the ovary minimized cellular diffusion to other organs. Successful clinical pregnancy was also achieved in women with POF after the transplantation [83].

4.3. Scaffold-based tissue engineering approaches in treating cervix disorders

The most significant issue in natural pregnancy is to maintain anatomical shape of the cervix which crucial in embryo development [84]. Studies have confirmed that early delivery is directly related to cervical laceration. On the other hand, the main cause of infant

Table 3
A summary of the studies with scaffold and stem cells for reproductive system disorders treatment.

Reproductive system disorder	Model of study	Researches	References
Asherman syndrome	• Rat	• Transplantation of collagen scaffold with BM-MSCs promote uterus regeneration	[25]
	• Rat	• Transplantation of collagen scaffold with BM-MSCs improve the level of bFGF, IGF-1, TGFβ1 and VEGF in blood vessels	[63]
	• Human	• Transplantation of collagen scaffold with BM-MNCs promote functional endometrium reconstruction via downregulating ΔNp63 expression	[34]
	• Human	• Transplantation of collagen scaffold with umbilical cord MSCs improves endometrial thickness	[35]
	• Rat	• Transplantation of collagen scaffold with collagen-binding human basic fibroblast growth factor promote Regeneration of uterine horns	[37]
Ovulation disorders	• Mice	• Use of alginate hydrogel for three-dimensional culture of granulosa cell–oocyte complexes	[52]
	• Mice	• Use of alginate hydrogel for IVF and embryo transfer	[53]
Premature ovarian failure	• Rat	• Transplantation of collagen scaffold with MSCs improve function of ovaries	[61,62]
Cervix disorders	• In vitro study	• Use of silk scaffold and human cervical cells for cervical tissue engineering	[66]

BM-MSC: bone marrow mesenchymal stem cell.
IGF-1: insulin-like growth factor 1, TGFβ1: transforming growth factor beta 1.
VEGF: Vascular endothelial growth factor, BM-MNC: bone marrow mononuclear cell.
MSC: mesenchymal stem cell.

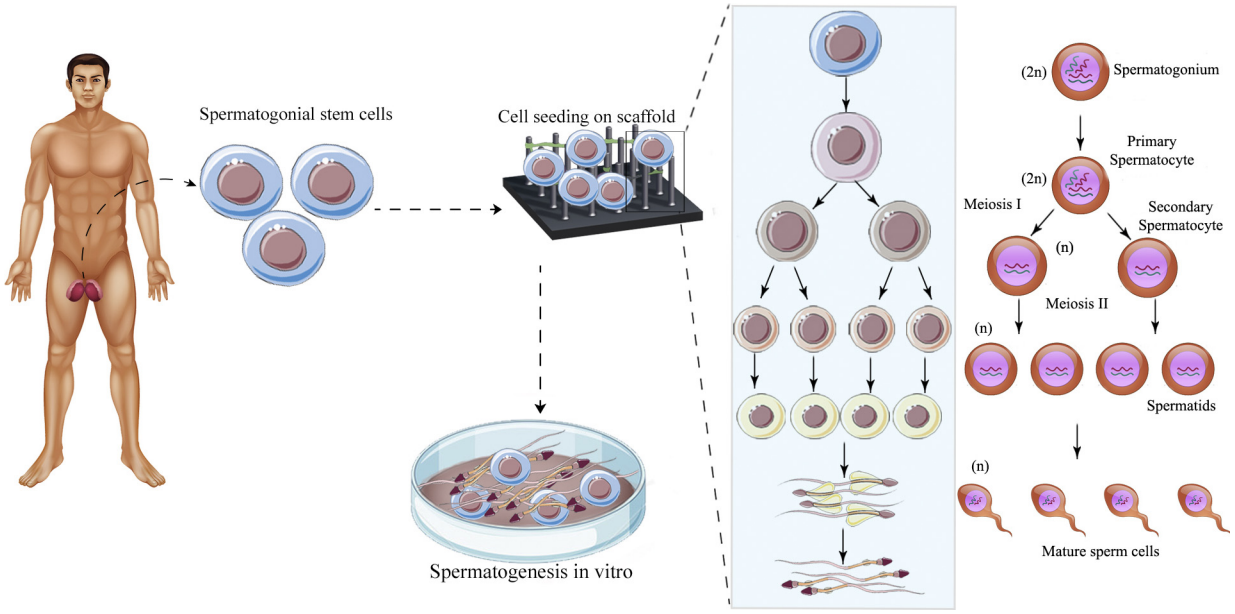

Fig. 2. In vitro spermatogenesis and steps of meiosis and mitosis in spermatogenesis process. Testicular tissue is obtained and germ cells were then produced by the differentiation of cultured spermatogonial stem cells in nano-fiber scaffolds.

mortality and morbidity is preterm birth [85]. House et al. [86] in a study, repaired the collagen-coated porous silk scaffolds for cultivation in a 3D condition Cervical cells were isolated from two premenopausal women undergoing hysterectomy, and an extracellular matrix was synthesized. Silk scaffolds by controlled morphological properties provide a suitable support for cell and tissue growth and can mimic the native tissue. Cervix-like tissue was formed by filling pores of scaffold by proliferated cervical cells. The results showed the feasibility of cervix-like tissues construction by tissue engineering approaches. However, it still needs to be more examined to measure the cervix during pregnancy and labor conditions. A summary of the studies is presented in Table 3.

5. Scaffold-based tissue engineering approaches in treating male infertility

The prevalence of male factor-related infertility is difficult to be estimated, probably because of global under-report. Estimations for male factor-only infertility and male factor contribution in infertility range from 6.4% to 42.4%, and 18.8% to 39%, respectively [87]. Mammalian spermatogenesis can be divided into three steps of cellular events including the proliferative phase (Spermatogonia), the meiotic phase (spermatocytes), and the differentiation phase called spermiogenesis (spermatids), These steps are followed by a series of post-testicular maturation processes that are necessary for fully functional spermatozoa production (motility and fertilization capability) [88]. Procedures such as cancer therapy usually disrupt the sperm production due to the effects of long-term radiation and chemotherapy in premature male that finally cause infertility. That is why, in boys, the cryopreservation of testicular tissue is crucial prior to cytotoxic treatments. By this method, germ cells will be produced using Spermatogonial Stem Cells (SSC) culture and differentiation [89,90]. In the past decade, many researchers have tried to mimic spermatogenesis in vitro (Fig. 2). Synthetic nano-fiber scaffolds, due to high surface/volume ratio, provide broad area for cell growth, differentiation and migration [91]. Additionally, these scaffolds, for the close relationship between Sertoli cells, do not block the paracrine effects. Nano fibrillar surface has positive impact on mouse spermatogonial stem cell-like colony numbers, cell numbers per colony, colony area, survival, proliferation, and implantation in seminiferous tubules [92].

6. Conclusion

The use of scaffolds has demonstrated significant potential in treatment of female and male infertility. Biodegradable scaffolds are suitable for cell delivery systems because, can mimic ECM condition, they provide a suitable environment for cell proliferation and differentiation. These scaffolds are also degraded over time, eliminating the risk of immune response in the body. Recent studies have shown that scaffold/cell systems promote the proliferation of Human Endometrial Stromal Cells (HEDCs) and significantly reduce the necrosis and induction of apoptosis in cells via paracrine effects. In addition, scaffolds and cell culture are used to build some organs of female reproductive system. In vitro spermatogenesis by scaffolds is also a promising concept. These approaches may significantly improve pregnancy outcomes in clinical settings.

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Author contribution to study

Yalda Jahanbani: Provided inputs for the design and wrote the manuscript.

Soudabe Davaran: Participated in literature survey; edited the final version of the manuscript.

Maryam Ghahremani-Nasab: Participated in literature survey.

Leili Aghebati-Maleki: Designed and supervised the study.

Mehdi Yousefi: Designed and supervised the study.

Declaration of competing interest

Authors declare no conflict of interest.

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