Reproductive Health

REVIEW

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Epidemiology, etiology and treatment of female vaginal injury

Di Zhang[1] and Hua Li[1*]

Abstract

The preservation of vaginal anatomical structure and physiological function is critical for women's health and should not be ignored. Vaginal injuries have a negative impact on women's quality of life. Vaginal delivery is the most common cause of vaginal injuries, 53-79% of women suffer from perineal and vaginal lacerations during labor. The incident of vaginal atrophy caused by decreased estrogen in menopausal women is growing, reaching 39%. The primary medical treatment of menopause-related vaginal atrophy is estrogen, which has a recognized therapeutic effect. Severe obstetric lacerations and trauma-related vaginal damage must be identified promptly and treated surgically. Radiotherapy-induced vaginal stenosis and adhesion could be treated with a vaginal dilator, however, there is a lack of consensus on therapy plans. Furthermore, surgical closure of genitourinary fistulas arise from the tumor or vaginal delivery is technically challenging. Stem cells have been proven to be effective in treating vaginal atrophy in animal models. Traditional treatments for Mayer-Rokitansky-Küster-Hauser syndrome, which is caused by a congenital anomaly of vaginal development, include vaginal dilation and vaginoplasty with autologous tissue. However, due to poor compliance and surgical complications, tissue engineering technology has received considerable attention for vaginal reconstruction because of its preferred characteristics. Nonetheless, the biological therapy of stem cell and tissue engineering technology still faces severe challenges, without application for clinical translation. Therefore, for women with vaginal injuries, the choice of treatment should be guided by the etiology and symptom severity. Stem cell therapy and tissue engineering technology show promising application prospects for vaginal injury repair and reconstruction, in addition to medical and surgical treatments. However, it is necessary to conduct additional preclinical animals and clinical trials in order to provide reliable references for future clinical practice.

Keywords Vaginal injury, Epidemiology, Etiology, Stem cell therapy, Tissue engineering technology

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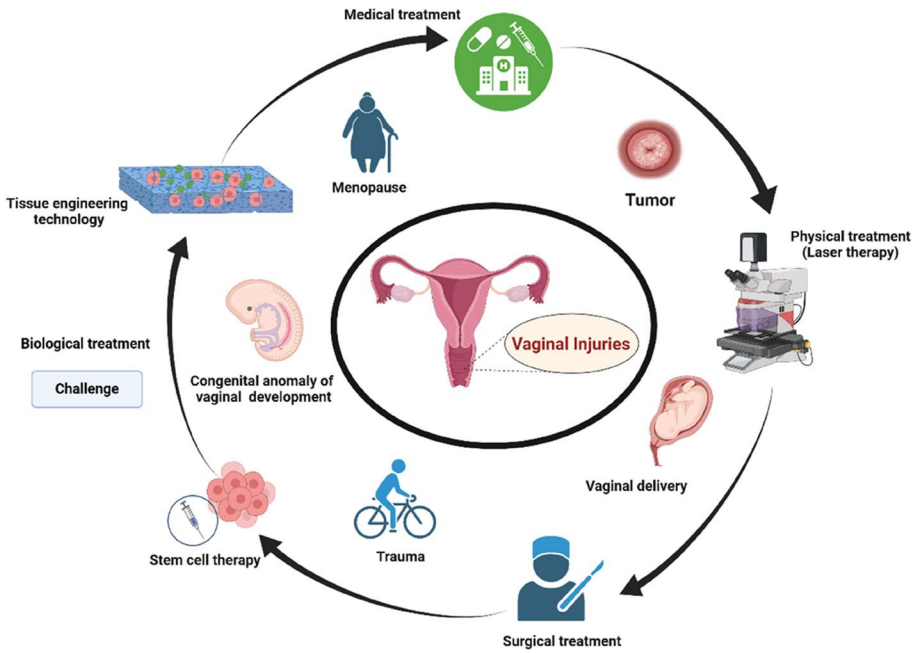
Graphical Abstract



1. The etiologies of vaginal injuries include vaginal delivery, trauma, tumor, congenital anomaly of vaginal development and menopause.

2. Therapies vary depending on the underlying cause. Biological treatments for vaginal injuries, such as stem cell and tissue engineering technology, nevertheless face challenges because of limited research.

3. This review may provide leads for further exploration and application of various treatment methods for vaginal injuries.

Introduction

The vagina is an essential part of the female internal genitalia, with important functions, i.e., sexual intercourse [1], and is a channel for menstrual blood discharge [2] and childbirth [3]. Furthermore, the vagina can prevent potentially invasive microorganisms, acting as a barrier to defense against genital tract infection [4]. The integrity of the vaginal wall and its pelvic floor support structure are indispensable for the anatomical position of organs and for maintaining pelvic floor function [5, 6]. Therefore, the vagina is a crucial reproductive organ for women's health.

Women of various ages may sustain vaginal injuries due to different causes. Abnormal genital development, particularly congenital anomalies of vaginal development such as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, affects the women's quality of life and sexual life [7], thus clinicians should not disregard the psychosexual impact of vagina aplasia. Vaginal delivery is the main way of female delivery, childbearing age women experience vaginal lacerations to varied degrees following vaginal delivery [8]. Because of hormone deficiency and aging, menopausal women suffer from vulvovaginal atrophy (VVA), which affects women's daily lives as well as intimate relationships between couples [9]. Thus, vaginal health is critical for improving women's physical, emotional and mental well-being.

Today, more and more researchers are focusing on vaginal injuries and functional anatomy recovery. There are numerous treatment options for vaginal injuries depending on their etiologies. However, vaginal injury repair faces a lot of challenges due to differing therapeutic effects and complications. This paper primarily reviews the research progress on epidemiology, etiologies, and treatment methods of vaginal injuries in recent years, and looks forward to provide more references for treatment selections.

Vaginal anatomy and embryogenesis origin

According to reports, the original hypothesis of uterovaginal embryogenesis was proposed by Müller in 1830, and the vagina had two origins: the cephalic part originated in the mesodermal Müllerian ducts, and the tailed part originated in the endodermal urogenital sinus [10]. The vagina is a naturally open cavity that extends from the vulva to the cervix of uterus in an upward and backward direction, forming a 90° angle with the uterus [6, 10]. The length of anterior vaginal wall is 6 to 7.5 cm, while the length of posterior vaginal wall is approximately 9 cm. The vagina is surrounded by closed levator ani muscle tissue in front of the rectum and behind the bladder and urethra. The posterior wall links to the anal canal via the perineal body [10].

The vaginal wall has four layers. The epithelial layer is consisted of non-keratinized, stratified, squamous epithelial cell [6], playing a role in maintaining an acidic environment and providing immune barriers for women [11, 12]. The lamina propria is a dense connective tissue layer comprised of collagen and elastic fibers, abundant in blood vessels and lymphatics. The muscularis, surrounded by connective tissue, is made up of circular and longitudinal smooth muscle cells, when combined with the lamina propria, can provide the support strength to pelvic organs [6]. Adventitia (serosa) is the loose connective tissue layer composed of collagen and elastic fibers, blood vessels, lymphatic vessels and nerves, and it can separate the vaginal muscularis from paravaginal tissue [6, 10]. The vaginal blood supply is adequate, mainly provided by the cervicovaginal artery and the vaginal artery of internal iliac arterial branches, meanwhile, the vagina has abundant venous plexuses [6], and it is easily bleeding and producing hematoma following vaginal injuries.

The epidemiology and etiologies of vaginal injuries

The etiologies of vaginal injuries are listed in Fig. 1 and include vaginal delivery, trauma, tumor, congenital anomaly of vaginal development and menopause. The epidemiology and etiologies of vaginal injuries are presented in Table 1.

Vaginal delivery

Delivery injury is the most common cause of genital tract injuries in women of child-bearing age [13]. Lacerations are common in women undergoing vaginal deliveries, affecting 53–79% of women [8, 14–16]. The majority of vaginal delivery women experienced first-degree (perineal skin and vaginal mucosa laceration) and second-degree (perineal muscle laceration without anal sphincter complex damage) perineal lacerations [8, 15, 16]. Perineal lacerations always involve the vaginal wall, specifically the vaginal posterior and lateral walls [8]. It has been reported that risk factors for an increase in vaginal lacerations during birth include parity, operative vaginal delivery, gestational age, nationality, and so on [16–18]. Lacerations can result in perineal pain, bleeding, and

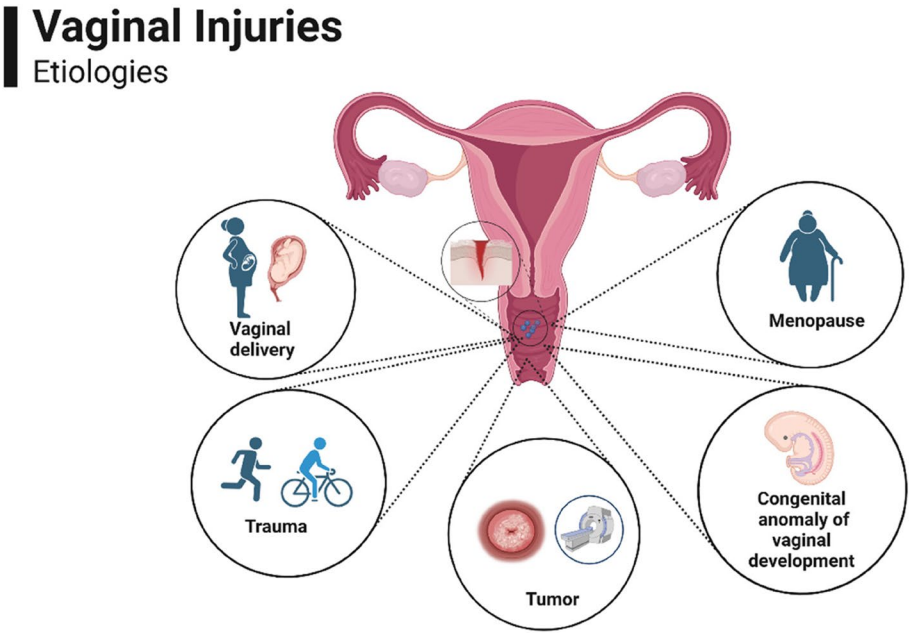


Fig. 1 The etiologies of vaginal injuries. (Created with BioRender.com)

Table 1 Summary of epidemiology and etiologies of vaginal injuries

Etiology	Typical disease	Incidence rate	Impact
Vaginal delivery	Obstetric laceration	53–79% in vaginal delivery women	Perineal pain, bleeding, hematoma formation and infection; Urinary and fecal incontinence; Sexual dysfunction.
	Obstetric RVF	0.02%–0.4%	Impact physical, social and mental health; Limit daily activities.
Trauma	Non-obstetric VVT(straddle injuries, sexual assault and abuse)	3.7%	Vaginal lacerations and abrasions; Vulvar hematoma and pain; Dysuria; Psychological problems.
Tumor	Radical hysterectomy	/	Reduction in vaginal length (3 cm); Dyspareunia, orgasm difficulty and sexual dissatisfaction.
		VVF 0.3%–2.61%	Depression and anxiety; Secondary surgery and readmission; Delay adjuvant therapy.
	Pelvic radiotherapy	VS 2.5%–88%	Vaginal dryness, bleeding and pain; Vaginal fibrosis, adhesion and obliteration; Affect sexual life.
		Vaginal necrosis 3%–6%	Fistula formation, perforation, even death.
Congenital anomaly of vaginal development	MRKH syndrome	1/5000 in live female births	No vagina; Primary amenorrhea; Affect sexual life; Vaginoplasty complications.
Menopause	VA	39% in postmenopausal women	Vaginal itching, dryness and dyspareunia; Affect QOL; POP.

RVF rectovaginal fistula, *VVT* vulvovaginal trauma, *VVF* vesicovaginal fistula, *VS* vaginal stenosis, *MRKH* Mayer-Rokitansky-Küster-Hauser, *VA* vaginal atrophy, *QOL* quality of life, *POP* pelvic organ prolapse

hematoma formation [18], infection [19], urinary and fecal incontinence [20], and even sexual dysfunction [21].

Additionally, vaginal delivery can also cause severe damage to the reproductive tract, resulting in genitourinary fistulas that significantly reduce women's quality of life. Long-term compressing of the fetal head on the vagina and its surrounding tissues after vaginal birth causes widespread ischemic tissue injury and necrosis, which leads to the formation of vesicovaginal fistula (VVF) and rectovaginal fistula (RVF) [22].VVF is an abnormal connection formed between bladder and vagina that results in urine flowing out of the vagina [23]. In developing countries, VVF is a common complication mainly due to prolonged labor during the delivery or obstructed labor [24].RVF leads to discharge of feces in the vagina because of the connection between rectum and vagina [25]. Birth injury is the main cause of RVF, and the incidence of RVF associated with childbirth varies from 0.2 to 4 cases per 1000 deliveries (0.02% to 0.4%) [26]. Severe perineal laceration and episiotomy injury to the anal sphincter can also result in the occurrence of RVF [25, 27]. Despite having a low frequency, obstetric fistulas negatively impacts on women's physical, social and mental health, limiting women's daily activities [23, 27, 28].

Trauma

Trauma is the common cause of genital vaginal wall injuries in women. Compared to obstetric perineal-vaginal lacerations, non-obstetric vulvovaginal trauma (VVT) is extremely rare, with a rate of only 3.7%, which may be underestimated by researchers [29]. Straddle injuries are the most common type of unintentional genital injuries in children and adolescents [13], and occur when they fall in a straddle position and the urogenital area strikes the surface of a hard object. Straddle injuries can result in compression injuries to the vulvar soft tissues, as well as various degrees of vaginal lacerations and abrasions, pain and bleeding, vulvar hematoma, and dysuria [13, 29, 30]. Sexual assault and abuse can also result in vaginal lacerations and acute blood loss, which should be diagnosed and treated as soon as possible [31]. Although genital injuries alone are rarely deadly, they can lead to chronic discomfort, painful intercourse, fistula formation, infertility, and even psychological problems. Therefore, early identification of the location and severity of genital trauma, as well as timely treatment, can help to minimize damage [13, 29].

Tumor

Tumor-induced vaginal injuries are classified into two types: surgery results in vaginal injuries such as changes in length and function, and radiation therapy results in changes in vaginal structure and function.

Vaginal length shortening occurs primarily in hysterectomy patients. The vaginal length of cervical cancer survivors were reduced by about 3 cm after radical hysterectomy of cancer [32]. Transvaginal hysterectomy for prolapse reduced vaginal length by roughly 1.7 cm, which is less than radical hysterectomy [33]. Shortening vaginal length can affect women's sex lives. Jensen et al. [34] reported that radical hysterectomy for early stage cervical carcinoma had an impact on women's sexual intercourse, including dyspareunia, orgasm difficulty and sexual dissatisfaction because of decreased vaginal size.

Radiotherapy is an important part of the treatment of gynecologic malignancies, and brachytherapy (BT) is closed to the tumor tissue and treats cervical, endometrial, vaginal and vulvar cancers, especially cervical cancers at stage IB and above [35]. The proximal vagina is the primary site of endovaginal brachytherapy-related toxicities [36], which lead to vaginal fibrosis and atrophy [32, 37]. Women suffer from vaginal dryness, bleeding, pain [38, 39], vaginal stenosis (VS), decreased sexual activity and sexual dysfunction following radiotherapy [37, 40]. Vaginal stenosis (VS) is an obstruction of the vaginal canal formed by vaginal scar tissue. The overall incidence of radiotherapy-induced VS ranges from 2.5% to 88% [41]. The incidence of VS after radiotherapy are almost 50% in endometrial cancer women [42] and 60% in cervical cancer women [43]. The incidence of VS varies depending on tumor type, radiotherapy modality and dose, hormone levels, use of dilators, and so on [41]. If vaginal fibrosis and adhesion further worsen, radiotherapy may result in full vaginal obliteration, affecting women's quality of life and sexual function [44]. Severe vaginal necrosis occurs primarily in the late stage of radiotherapy injury, with an incidence of 3% to 6%, and can result in serious complications such as necrosis-associated bladder or rectal fistula, perforation, or even death [45].

Excessive electrocoagulation and lateral thermal spread during laparoscopic radical hysterectomy can also cause vaginal and urinary tissue injuries, leading to fistula formation [46]. The incidence of VVF after radical hysterectomy varies from 0.3% to 2.61% [46–50]. Therefore, in order to reduce the risk of genitourinary fistulas, a thorough examination and diagnosis of urinary injuries should be performed before the end of operation [51]. Although genitourinary fistulas are rare, they can result in depression, anxiety and a decline in women's mental health [23], as well as an increase in secondary surgery and readmission rate [52]. Furthermore, genitourinary fistulas may cause patients to delay adjuvant therapy, affecting women's short-term survival [53].

Congenital anomaly of vaginal development

In addition to acquired diseases including trauma and cancer, the absence of the normal vagina primarily arises from congenital vaginal aplasia, especially MRKH syndrome [54]. MRKH syndrome is a female congenital disease with Müllerian duct aplasia, marked by agenesis or aplasia of uterus and vagina's upper part, and a 46,XX chromosome karyotype in women [55]. The prevalence of MRKH syndrome is approximately 1/5000 in live female births [56]. In most cases, MRKH syndrome is diagnosed with primary amenorrhea, which places a psychological burden on young women and affects their sex lives [57]. Complications from vaginoplasty for vaginal agenesis can lead to a variety of vaginal injuries, including graft rejection or necrosis [58], VS, fistula formation [59], prolapse, and reoperation [60]. Transverse and longitudinal vaginal septum can also result in hematocolpos, if not diagnosed and treated promptly, women may experience long-term severe pelvic pain and late fertility problems [61].

Menopause

Menopause is a natural process that all women go through as their estrogen levels decline. Menopausal women are frequently accompanied with urinary symptoms and pelvic organ prolapse (POP) as a result of estrogen decline [62, 63]. Women with anterior vaginal prolapse, the most common type of POP, have altered vaginal thickness, mechanical properties, and structural composition [64–66]. Zhu et al [66] used single-cell RNA sequencing to show the cellular composition of the vaginal wall in women with POP. They detected that fibroblasts and smooth muscle cells were the most abundant, the morphology of the vaginal wall was changed at every layer and muscularis showed atrophy in POP women. Yu et al [67] also revealed changes in the overall structure of the vaginal wall caused by a bilateral ovariectomized rat model, such as thinning of the vaginal epithelial layer and adventitia layer, sparsely deposited collagen in the lamina propria, and disordered and reduced smooth muscle, all of which contributed to a reduction in vaginal support and POP development.

Estrogen insufficiency can also cause vaginal atrophy (VA) in postmenopausal women, with an incidence of 39%, which is accompanied by vaginal itching, dryness, and dyspareunia [63, 68, 69]. VA, sometimes also known as VVA, has a negative effect on women's sexual health and quality of life, over half of them have never received treatment because they may be embarrassed to seek medical attention [68]. As a result, in order to further diagnose and treat VA, clinicians should give it enough attention. In the meantime, clinical practice should

include measures of the pH value and vaginal maturation index in addition to symptom assessment [69].

Treatments of vaginal injuries

The treatment methods of vaginal injuries vary depending on the etiology, and include medical treatment, physical treatment, surgical treatment and biological treatment.

Medical treatment

The main medications used to treat vaginal injuries are estrogen, hyaluronic acid, and growth factor, and the mechanisms involved in each treatment are detailed in Fig. 2.

Estrogen

Estrogen regulates vaginal physiology predominantly through the estrogen receptor alpha (ERα) [70, 71]. Estrogen therapy is beneficial for VA and stress urinary incontinence (SUI), and it improves the vaginal wound healing of POP and other vaginal surgeries including urinary incontinence and vaginal fistula surgery [63, 72], thus it is widely utilized nowadays.

Estrogen can reduce wound size and inflammation [73, 74] expedite epithelialization and increase vaginal wall thickness, promote angiogenesis and collagen synthesis, enhance vaginal tissue strength, and maintain vaginal tissue integrity. The positive effects of estrogen therapy on vaginal wound healing are essential for maintaining pelvic organ position and preventing POP recurrence [72]. Local estrogen therapy plays a role in improving vaginal microcirculation in VVA women [75], and is the most effective therapy for non-mild VVA [70]. Estrogen can dilate blood vessels, increase vaginal blood flow, and improve vaginal lubrication through NOS and VIP pathways [76] (Fig. 2). The vaginal application of estrogen after radiotherapy promotes the regeneration of vaginal epithelium, which may be more remarkable when estrogen is given in women more than 3 months after radiotherapy [77]. It is worth noting that radiation-induced alterations in vaginal morphology diminish the efficacy of vaginal estrogen treatment because pelvic radiotherapy decreases the expression of vaginal estrogen receptors [44, 78]. Due to the risk of recurrence and side events in different tumors, there is limited evidence supporting the use of local and systemic estrogen therapy in women with gynecologic tumors [44].

Hyaluronic acid

Hyaluronic acid (HA), a basic component of extracellular matrix (ECM), is an effective vaginal pharmaceutical agent with moisturizing and lubricating properties. It may be appropriate for women with VA who have contraindications to estrogen treatment, as well as for other diseases that affect vaginal symptoms and signs. HA can effectively alleviate symptoms such as vaginal pain, itching, burning, dryness, and bleeding [79]. Liu et al [80] demonstrated that local injection of HA vaginal gel effectively relieved symptoms of VA in a postmenopausal rat model while also enhancing vaginal epithelium repair. Furthermore, higher expression of P-AKT and VEGF in

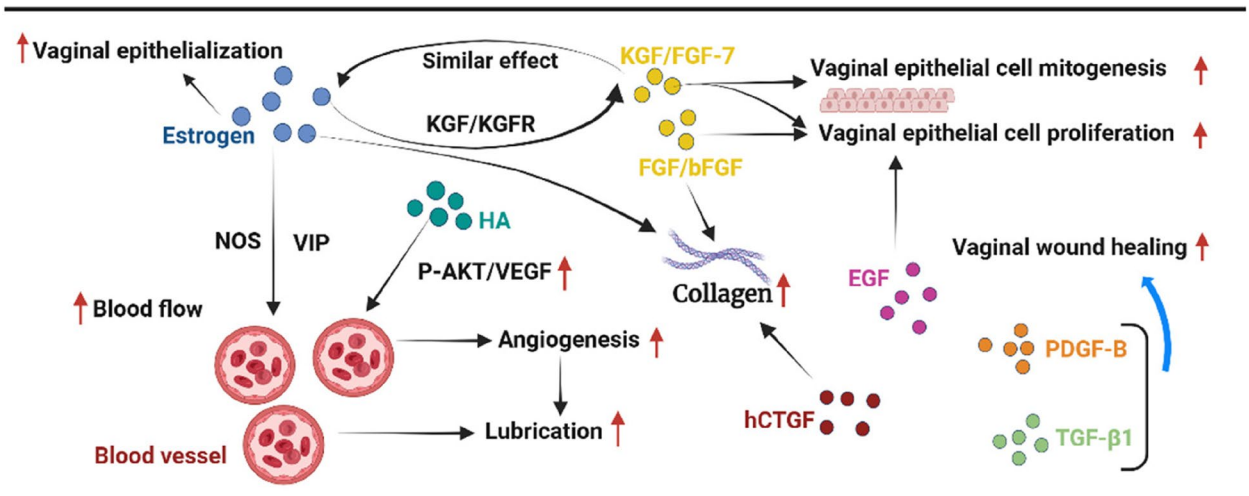


Fig. 2 Medical treatments of vaginal injuries. *NOS* nitric oxide synthase, *VIP* vasoactive intestinal polypeptide, *FGF* fibroblast growth factor, *bFGF* basic fibroblast growth factor, *KGF* keratinocyte growth factor (also named as FGF-7), *KGFR* keratinocyte growth factor receptor, *HA* hyaluronic acid, *P-AKT* phosphorylated protein kinase B, *VEGF* vascular endothelial growth factor, *EGF* epidermal growth factor, *PDGF-B* platelet-derived growth factor-B, *TGF-β1* transforming growth factor beta1, h*CTGF* human connective tissue growth factor. (Created with BioRender.com)

vaginal tissue suggested that HA may treat vaginal injuries by promoting angiogenesis (Fig. 2).

HA could improve vaginal health in women who experience vaginal injuries from cancer and radiotherapy. It promotes vaginal epithelial regeneration, enhances vaginal elasticity and lubrication, and reduces vaginal adhesions and obliterations. Given its safety and absence of contraindications, HA is used to repair tissue injuries [44]. Laliscia et al [81] discovered that local therapy with HA was helpful in reducing vaginal toxicities in endometrial cancer patients undergoing postoperative vaginal BT and was recommended to be administered from the start of BT until at least two weeks after completion. Delia et al [82] also demonstrated that vaginal use of HA suppositories decreased radiotherapy-induced vaginal discomfort and facilitated the repair of vaginal mucosa in patients with cervical cancer, potentially assisting women in completing radiation therapy. More high-quality clinical research on the usefulness of HA for vaginal injuries is necessary in the future.

Growth factor

Numerous studies have been conducted on the positive effects of growth factors on vaginal wound healing, with fibroblast growth factor (FGF) being the most extensively studied at present. Vaginal wound healing involves modulating ECM metabolism. Basic fibroblast growth factor (bFGF) promotes cell proliferation, stem cell differentiate into fibroblast and collagen production, nonetheless, better POP animal models are needed to demonstrate bFGF's therapeutic impact in enhancing vaginal wound healing [83]. Interestingly, multiple clinical investigations indicated that FGF/bFGF had an influence on neovaginal epithelialization in women having vaginoplasty for MRKH syndrome and played a major role in the regeneration of vaginal tissue when combined with biomaterials [84, 85]. Keratinocyte growth factor (KGF) is a member of the FGF family, commonly known as FGF-7. It is produced by mesenchymal cells and has a mitogenic effect on uterine and vaginal epithelial cells [86, 87]. KGF has been shown to enhance vaginal epithelial cell proliferation, thicken the epithelial layer in neonatal mice, and generate long-term impacts on the vaginal epithelium [86]. KGF and estrogen have similar effects in treating VA, possible due to the interaction between estrogen and KGF receptors and changes in intracellular ER-α distribution. Based on the murine model, KGF may be a possible alternative treatment for VA compared with estrogen because it has no systemic negative effects [88]. Similarly, epidermal growth factor (EGF), an essential mediator of estrogen activity, promotes cell growth in the reproductive tract in a manner similar to estrogen [89]. Transforming growth factor beta1(TGF-β1) is a significant mediator of wound repair in skin tissue, and is also involved in vaginal wound repair process [90]. Transforming growth factor alpha (TGF-α) regulates the development and morphogenesis of Müllerian ducts and urogenital sinus, potentially contributing to reproductive tract disorders [91]. Meanwhile, platelet-derived growth factor-B (PDGF-B) was found to be significantly associated with vaginal wound closure [92]. In vitro, recombinant human connective tissue growth factor (hCTGF) can influence the expression of collagen I and III and induce ADSC differentiation, making it potentially beneficial in the POP therapy [93] (Fig. 2). More clinical trials are required to conduct and confirm the safety and efficacy of growth factors in vaginal injury repair, as the majority of existing studies are carried out on animals.

Physical treatment

When patients do not benefit from local estrogen treatment or have contraindications to horm one therapy, laser may be an effective alternative treatment for VVA. Acute thermo-ablative damage and proliferation are the two stages of the CO2 laser system. The laser is used to promote the synthesis of collagen and ECM in the injury site, increase the elasticity of the vaginal wall, and relieves vaginal discomfort symptom [94]. Similarly, Samuels et al [95] discovered that fractional CO2 laser treatment can improve symptoms of VVA in postmenopausal women, increase the submucosal vascularization, collagen and elastic fiber content in the vagina, and is better tolerated by women. CO2 laser treatment could also improve vaginal discomfort in cancer and radiotherapy patients. In a prospective research, Perrone et al [96] discovered that intravaginal non-ablative CO2 laser therapy increased the vaginal length and improved vaginal health index in genital cancer women after pelvic radiotherapy. Quick et al [97] performed fractional CO2 laser therapy on gynecologic cancer patients with sexual dysfunction and discovered that women's sexual function improved after treatment, and CO2 laser therapy was relatively safe without serious side effect. However, study sample sizes for vaginal injuries followed by laser treatment were small, and larger future studies with long-term follow-up are needed to demonstrate effectiveness.

Surgical treatment

In addition to superficial and hemostatic lacerations, vaginal wall lacerations caused by vaginal delivery should be sutured to avoid persistent bleeding or anatomical malformation. The apex of the vaginal laceration should be identified. Interrupted or continuous sutures are positioned 1 cm above the apex to close the vaginal mucosa and the underlying fascia, ultimately achieving the hemostasis and restoring vaginal anatomic structure [98, 99].

Non-obstetric VVT could lead to vulvovaginal hematoma formation. When vulvovaginal injury occurs, the decision to operate or not should be dependent on the severity of the trauma, the size of the hematoma, and bleeding. If the hematoma continues to grow, it should be surgically removed, bleeding vessels must be ligated, and sutures should be used to heal vulvovaginal tissues, avoiding necrosis and secondary infections of tissues [13, 100]. If the hematoma is restricted to a small anatomical area and there is no active bleeding, substantial enlargement, or dysuria, ice packs may be used as a conservative treatment [13, 101, 102].

Radiotherapy-induced vaginal stenosis or adhesion could be treated with vaginal dilation using a vaginal dilator, which works by expanding the vaginal tissue, stimulating the growth of vaginal epithelium, and preventing fibrosis and elastic degeneration [41]. Vaginal dilator therapy (VDT) is beneficial to maintain vaginal length and improve sexual function after radiation therapy [103]. However, there is no consensus on the type of vaginal dilator, initiation timing after radiotherapy, the duration of usage, or the method of application [44]. Bakker et al [104] considered that the use of vaginal dilators should begin 4 weeks after radiotherapy and last 9 to 12 months to prevent vaginal adhesion and shortening, and that plastic dilator sets were the best appropriate option for VDT. In another study, vaginal dilator was used at the beginning of radiotherapy or 4 weeks after radiotherapy for 3 months to relieve patients' vaginal dryness [105]. Matos et al [106] believed that the method of vaginal dilation should be personalized and utilized with lubricants indefinitely, depending on the need of patients. Unfortunately, women undergoing radiotherapy have poor adherence to vaginal dilators, which is related to psychological burden such as embarrassment, anxiety, pain and fear of vaginal injury [107]. Long-term intervention trials are required to further understand standardized vaginal dilation techniques and find effective and optimal vaginal dilation treatments [108]. Additionally, vaginal anatomical defects caused by vaginal stenosis after radiation therapy can be restored by forming a vaginal pouch with absorbable sutures, achieving vaginal reconstruction [109].

Surgery can successfully repair VVF with a urinary continence rate of 87.09% [28]. Conservative treatment for VVF consists primarily of an indwelling catheter, which is more successful when the fistula is less than 4 mm [110]. RVF is rarely self-healing, and surgical repair has a success rate of about 55%, with the key to success being a proper diagnosis and surgery plan [111]. Fistula surgery is technically difficult, and closing the pelvic fistula does not ensure control of urination or defecation because fistulas may cause damage to bowel and bladder tissue [112].

The first-line treatment for MRKH syndrome is vaginal dilation, whereas the second-line treatment is surgical development of a neovagina. If vaginal dilatation fails or patient does not comply with treatment, surgery will be a choice [113, 114]. The most traditional approach to vaginal reconstruction in women with congenital absence of the vagina is to create a neovagina using vaginoplasty between bladder and rectum, with grafts such as skin [115], buccal mucosa [116], peritoneum [117], and bowel [118]. The choice of grafts greatly influences the outcome of surgery, however, autologous tissue may not be the optimal choice for vaginoplasty because of side effects and complications. Ideal vaginal reconstruction requires the rehabilitation of vaginal morphology and function, as well as the regeneration of smooth muscle and nerve tissue. Tissue engineering technology provides new therapy possibilities for vaginal reconstruction [54]. However, vaginal repair with new grafted tissues will be a significant challenge for clinicians in the future [119]. Figure 3 summarizes various surgical treatment methods for vaginal injuries.

Biological treatment

Stem cell therapy

Stem cell therapy has been used to improve the biological function of damaged tissue in medical fields due to its paracrine activity and targeted differentiation potential [120, 121]. Mesenchymal stem cells (MSCs) become the seed cells for vaginal reconstruction [54]. MSCs can differentiate into endothelial-like cells and smooth muscle cells in vitro, both of which are essential components in vaginal reconstruction and vascularization, and participate in the repair process of vaginal injury [122]. To present, the most common MSCs used for vaginal injury repair are bone marrow derived mesenchymal stem cell (BMDSC), adipose derived mesenchymal stem cell (ADMSC), and human umbilical cord mesenchymal stem cell (HUMSC). These investigations on vaginal repair and reconstruction with MSCs have mainly focused on animal models. Kasap et al [123] used the rat oophorectomy menopause model and discovered that injection of ADMSC and BMDSC into the below vaginal mucosa increased the thickness of the vaginal epithelium and improved vaginal atrophy, with ADMSC being more effective than BMDSC. Mao et al [124] detected that mRNA levels of angiogenic factors (bFGF/VEGF) were significantly increased in the vaginal wall of ovariectomized rats injected with HUMSCs, implying that paracrine effects of HUMSCs may repair the vaginal

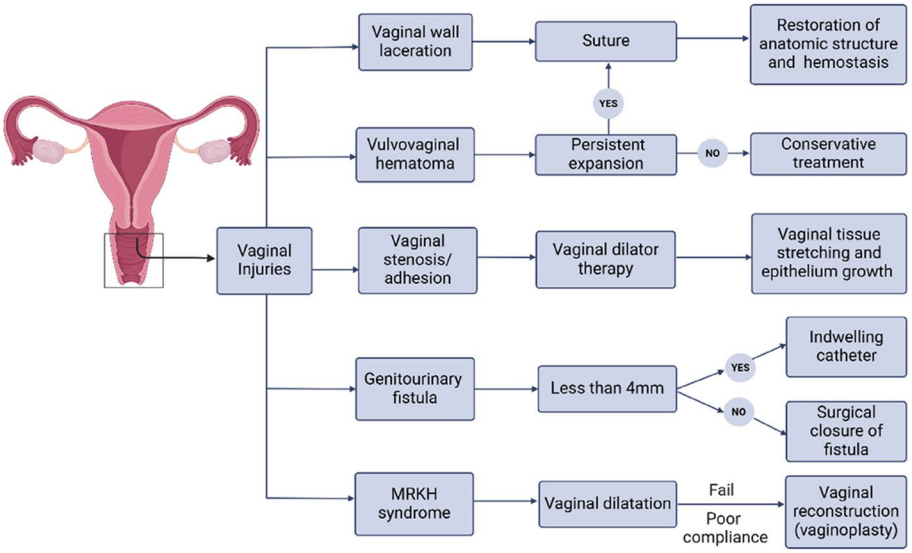


Fig. 3 Surgical treatments for vaginal injuries**.** *MRKH* syndrome Mayer-Rokitansky-Küster-Hauser syndrome.(Created with BioRender.com)

wall's fibromuscular structure. In a similar oophorectomy menopause model of rhesus macaques, Zhang et al [120] demonstrated that injecting HUMSCs into the vaginal wall can repair vaginal tissue by promoting ECM growth, neovascularization, and smooth muscle content increase, as well as improving the vagina wall's biomechanical property. Figure 4 summarizes the role of MSCs in vaginal injury repair in the animal model. Although MSCs have the capacity to heal poor vagina tissue, the mechanism remains to be fully understood. Stem cell therapy,

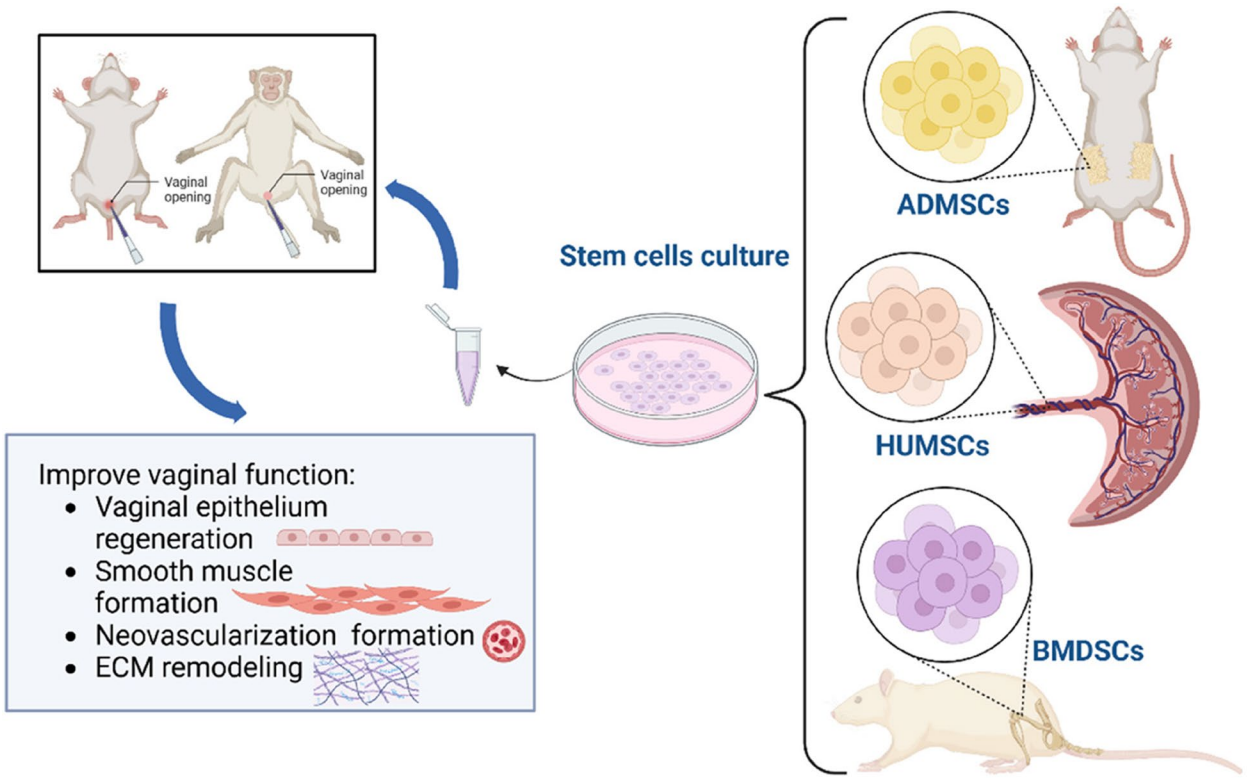


Fig. 4 Stem cell therapy for vaginal injuries. *ADMSCs* adipose derived mesenchymal stem cells, *HUMSCs* human umbilical cord mesenchymal stem cells, *BMDSCs* bone marrow derived mesenchymal stem cells, *ECM* extracellular matrix. (Created with BioRender.com)

Table 2 The applications of biological materials for vaginal injuries

Author and year of publication	Laboratory animal	Site and degree of vaginal injuries	Type of biological materials	Size and placement of biological materials	Therapeutic effect
Xiao et al, in 2023 [134]	Pig	4 cm thickness vaginal apical defects	DBM from pig bladder	4 cm; Placed in the external cervical orifice and the vaginal stump	1.Integrated well with the vagina, achieve the regeneration of vaginal epithelial layers and muscularis. 2.Reconstruct the vaginal anatomy and restore the vaginal function.
Hympánová et al, in 2020 [135]	Sheep	3 cm longitudinal incision in the posterior vaginal wall	1.Ultra-lightweight PP non-degradable textile mesh 2.Electrospun implants (UPy-PC and PU mesh)	3.5 × 3.5 cm; Placed in between vaginal epithelial layer and rectal serosa	1.These three meshes were well adapted for the vagina. 2.Electrospun implants had milder inflammatory response.
Ye et al, in 2020 [136]	Rat	Radiation-induced vaginal injury	3D protein scaffolds with ADSCs	Placed in the site of vaginal injury	A better therapeutic effect on the VS and contracture than simple ADSCs treatment.
Wang et al, in 2019 [93]	Rat	Bilateral oophorectomy	1.ADSCs of rat were treated with recombinant hCTGF 2.ADSCs-seeded APP and ADSCs-seeded ABP	Placed in the vaginal mucosa, and the serosal surface was placed dorsally.	1.hCTGF promoted the expression of collagen I and III and induced ADSCs differentiation. 2. ADSCs -seeded APP and ABP reduced inflammation and improved the biocompatibility in vivo.
Zhang et al, in 2018 [54]	Rat	Vaginal mucosa was stripped	bone marrow MSCs-seeded SIS	Placed in the cervix and vaginal orifice (vaginal reconstruction)	1.The neovagina with SIS+MSCs had more smooth muscle, nerve tissue and angiogenesis than that with SIS only. 2.MSCs promoted neovagina recovery.
Chang et al, in 2017 [137]	Rat	An incision in posterior vaginal wall	Knitted silk fibroin scaffold	1 cm × 0.5 cm; Placed in between vaginal fibromuscular layer and epithelial layer	Good biocompatibility; No severe inflammation; No mesh exposure complication.
Liang et al, in 2017 [138]	Rhesus macaque	Hysterectomy, uterosacral ligaments and paravaginal attachments transection	ECM bioscaffold from urinary bladder matrix	Placed in between the level of uterosacral ligaments (level I support) and paravaginal attachments (level II support), sutured to vagina.	1.Enhance the level I and level II support of vagina. 2.Impair vaginal integrity in a short time.
Zhang et al, in 2017 [139]	Rat	Hysterectomy and proximal vagina was removed by 1 cm	1.AVM from porcine vagina 2. SIS from porcine intestine	Placed in between vaginal stump and retroperitoneal fascia	Compared with SIS, vaginal reconstruction with AVM were closer to normal vagina, and had nice biocompatibility and biomechanical properties.

Table 2 (continued)

Author and year of publication	Laboratory animal	Site and degree of vaginal injuries	Type of biological materials	Size and placement of biological materials	Therapeutic effect
Fan et al, in 2014 [140]	Rabbit	A 2 cm transverse incision in the posterior wall of vagina	1.PP mesh 2.Porcine-derived cUBM	2 cm × 1 cm; Placed in between the fibromuscular layer and epithelium of vagina	1.Compared with cUBM, vaginal PP mesh had greater strength, and erosion. 2. Vaginal cUBM had milder inflammation response, better biocompatibility than PP mesh, and stable mechanical qualities.

DBM double-sided biomembrane, *PP* polypropylene, *UPy-PC* ureidopyrimidinone-polycarbonate, *PU* polyurethane, *ADSCs* adipose derived mesenchymal stem cells, *VS* vaginal stenosis, *hCTGF* human connective tissue growth factor, *APP* acellular porcine pericardium, *ABP* acellular bovine pericardium, *MSCs* mesenchymal stem cells, *SIS* small intestinal submucosa, *ECM* extracellular matrix, *AVM* acellular vagina matrix, *cUBM* cross-linked urinary bladder matrix

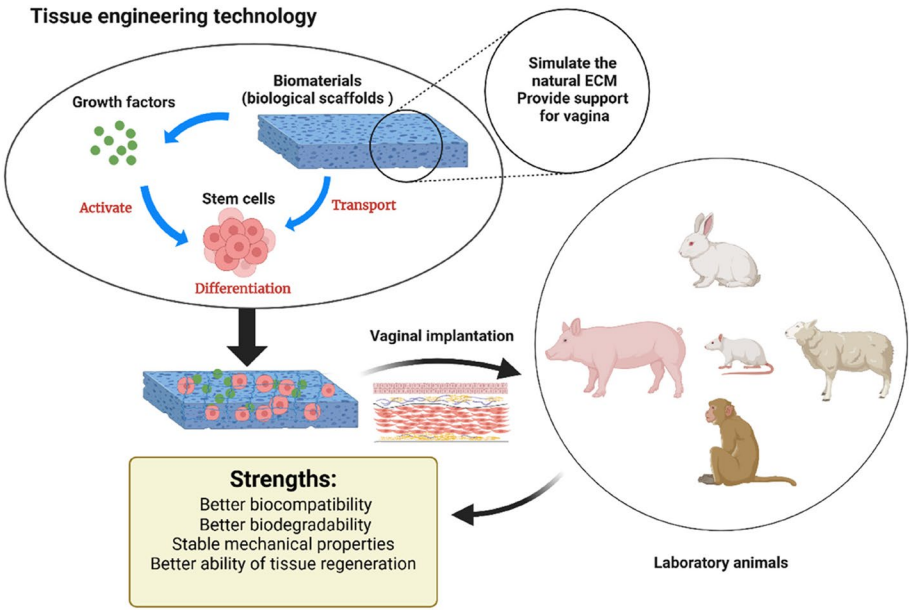


Fig. 5 Tissue engineering technology in the treatment of vaginal injuries. *ECM* extracellular matrix. (created with BioRender.com)

if used on patients, still has certain problems that need to be addressed and improved, including the ethical concerns about cell sources, immune tolerance and rejection between stem cells and the female body, safety, and the assessment of proliferation and differentiation ability after stem cell therapy [125].

Tissue engineering technology

Congenital anomaly of vaginal development, particularly MRKH syndrome, could be treated with vaginoplasty using autologous tissue. However due to a paucity of suitable donor tissue, surgical failures, and complications [119, 126], vaginal reconstruction with tissue grafts remains challenging. Implanted support structures can be used for surgical therapy in women with POP, and nonabsorbable polypropylene (PP) mesh was the most commonly used material in clinical practice [119, 127]. PP mesh can provide mechanical support for the vaginal wall [119], however its clinical application is limited by the non-degradability and complications such as mesh erosion, exposure, chronic pain and infection. The American Food and Drug Administration (FDA) has announced the termination of PP mesh [128].

Tissue engineering technology is a considered therapy option that has been gradually applied to the studies of vaginal injury repair and vaginal reconstruction [54]. Tissue engineering involves using a compound of cells, growth factors/drugs, and biomaterials to treat tissue damage [129]. The role of cells is to accelerate repair, promote the production of connective tissue and regeneration of damaged tissue. Bioactive factors, especially growth factors, could activate stem cells, induce differentiation and promote tissue regeneration. Biomaterials used to repair damaged pelvic floor tissues have a role in providing supportive power for the vagina and transporting cells to damaged tissues [129, 130].

Mammalian tissue healing requires the ECM, and biological scaffolds that mimic the natural ECM have been used to provide a three-dimensional matrix structure for vaginal tissue repair, allowing cells to adhere, proliferate and differentiate [129]. Biological scaffold materials primarily include synthetic and natural materials, produced by decellularization and self-assembly, as well as electrospinning techniques, to restore vaginal function and improve the integrity of vaginal wall by combining vaginal seed cells and/or growth factors [119, 131, 132]. To date, there have been only a few clinical studies using biomaterials for patients with MRKH syndrome and POP, and therapeutic effects are uncertain due to the small number of patients and short follow-up period [84, 85, 133]. The majority of these studies were carried out in large and small animal experiments, as shown in Table 2.

Tissue-engineered biological scaffold materials that lack immunogenicity are more biocompatible and biodegradable than PP mesh, with a certain mechanical quality and good ability to promote tissue regeneration (Fig. 5). Despite the benefits of tissue engineering technology, there are several limits to its clinical translation application, such as cell and growth factor selection and the generation of desirable biological scaffolds [130]. As a result,

more large-scale preclinical animal and clinical research is needed to advance the further development of engineering technology for vaginal injury and reconstruction.

Conclusion and prospect

Different etiologies of vaginal injuries negatively affect women's mental health and quality of life across age groups. Estrogen is the most commonly used medicine for vaginal injuries, particularly vaginal atrophy in postmenopausal women, the therapeutic benefit is obvious, however it has limited application in women with gynecologic tumors, hyaluronic acid or laser therapy may become alternative replacement therapies in the future. Vaginal delivery is the most prevalent cause of vaginal injuries, thus clinical personnel should pay greater attention to labor protection and management, identify the laceration degree, and improve suture techniques, which will be beneficial to reduce postpartum complications. Similarly, trauma-related vaginal injury requires an accurate assessment of the injury site and severity, and timely treatment.

Stem cell therapy shows promise when compared to traditional vaginal injury treatments. Tissue engineering technology, as an advanced scientific research area, brings new expectations to vaginal reconstruction in women with MRKH syndrome due to its superior ability of tissue regeneration. However, most of studies on these new therapies have been limited to cell and animal experiments, with only a few tiny clinical trials. As a result, further research should be made to confirm their therapeutic efficacy and safety in the future.

Acknowledgements
Graphical abstract and figures were created with BioRender.com.

Authors' contributions
D.Z. designed and wrote the manuscript; H.L. designed, supervised and reviewed the manuscript. All authors read and approved the final manuscript.

Funding
This work was supported by Clinical Research Incubation Program (no. CYFH202306).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 16 May 2024 Accepted: 20 April 2025
Published online: 06 May 2025

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