Unveiling the depths of pelvic organ prolapse: From risk factors to therapeutic methods (Review)

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Abstract. Pelvic organ prolapse (POP) is a condition where one or more pelvic organs (such as the uterus, bladder and rectum) descend from their normal anatomical positions into the vagina, primarily due to the weakening of the pelvic floor support structures. While not life-threatening, POP can substantially diminish the patient's quality of life and lead to serious social and psychological complications. Researchers have explored novel directions regarding the etiology, mechanism and treatment of POP. However, existing literature on the subject often lacks comprehensive and systematic overviews. To address this gap and enhance researchers' understanding of POP, the present study reviewed the risk factors and molecular mechanisms of POP [including matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs, transforming growth factor β, advanced glycation end products (AGEs)/receptor for AGE, phosphoinositide 3-kinase/protein kinase B, fibulin, lysyl oxidase-like 1, homeobox A11, collagen α-1 (XVIII) chain, Wnt signaling pathways and estrogen receptor α], as well as therapeutic approaches, such as lifestyle interventions, physical methods, pharmacotherapy, stem cell transplantation and surgical techniques. The present review aims to provide new insights for future research and contribute to the advancement of diagnosis and treatment strategies for POP.

Contents

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Abbreviations: AGE, advanced glycation end product; AKT, protein kinase B; COL18A1, collagen α-1 (XVIII) chain; ERα, estrogen receptor α; ECM, extracellular matrix; HOXA11, homeobox A11; GWAS, genome-wide association study; LOXL1, lysyl oxidase-like 1; MMPs, matrix metalloproteinases; POP, pelvic organ prolapse; PARP1, poly (ADP-ribose) polymerase 1; PI3K, phosphoinositide 3-kinase; PFD, pelvic floor dysfunction; PFMT, pelvic floor muscle training; RAGE, receptor for AGE; SNP, single nucleotide polymorphism; TIMPs, tissue inhibitors of MMPs; TGF-β, transforming growth factor β; USL, uterosacral ligament; VWFs, vaginal wall fibroblasts

Key words: pelvic organ prolapse, molecular mechanisms, risk factors, treatment methods

1. Introduction

Pelvic organ prolapse (POP) is a condition characterized by the downward displacement of the uterus and adjacent organs, such as the bladder and rectum, due to the weakening of pelvic floor support and reduced structural tension. This condition manifests clinically as uterine, urethral, bladder and rectal prolapse and bulging of the anterior and posterior vaginal walls. It is often associated with stress urinary incontinence (1). Although POP can affect adult women across all age groups, the exact prevalence remains uncertain.

Epidemiological data reveal a significant discrepancy between prevalence rates determined by prolapse symptoms and those based on clinical examination, largely because numerous women with POP have no obvious clinical symptoms. A prospective cohort study involving 259 perimenopausal women found an incidence rate of 26% at 1 year after menopause, rising to 40% after 3 years (2). Furthermore, 30-76% of adult women are first diagnosed with vaginal or uterine prolapse during routine gynecological exams, with 3-6% of these cases showing prolapse that reaches or exceeds the hymen, although only ~3% report subjective symptoms (3). Research indicates that 13% of women in the US will require

surgical intervention for POP, with most surgeries occurring between the ages of 70 and 79 years. By 2050, the number of women affected by POP will further increase (4). While several women with POP are asymptomatic, others may experience swelling, discomfort, sexual dysfunction and psychological distress in severe cases (5-7). Therefore, POP has emerged as a significant health and social problem, posing substantial risks to the well-being and quality of life of adult women (8,9).

The present study reviews the risk factors, molecular pathogenesis pathways [including matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs), transforming growth factor β (TGF-β), advanced glycation end products (AGEs)/receptor for AGE (AGE/RAGE), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), the fibulin family, lysyl oxidase-like 1 (LOXL1), homeobox A11 (HOXA11), collagen α-1 (XVIII) chain (COL18A1), Wnt signaling pathways and estrogen receptor α (ERα)] and the therapeutic approaches of POP, aiming to enhance clinicians' understanding of the progression of POP and to support effective interventions and treatments.

2. Physiological structure and disease stratification

Physiological structure. The pelvic floor is anatomically composed of muscles, ligaments and fascia that provide crucial support to the reproductive organs, the rectum and the bladder. The bony pelvis, comprising the sacrum and two innominate bones, forms the skeletal framework that stabilizes and encircles the pelvic floor (10). The pelvic fascia, levator muscles and ligaments work in unison to support the pelvic organs. Dysfunction in these structures has been shown to disrupt their support points, leading to the descent of pelvic organs and subsequent symptoms and pathologies (11,12). A considerable body of research has emphasized that the molecular alterations in connective tissue play a significant role in the development of POP. The connective tissue of the pelvic floor, including ligaments and fascia, is primarily made up of extracellular matrix (ECM) components such as collagen, elastin and other fibrous elements (13-15). The network of cross-linked collagen and elastin fibers enables the pelvic organs to maintain their shape and position, providing a buffering capacity to withstand external pressure, thereby preserving pelvic organ function (13).

Staging of POP. The International Urogynecological Association/International Continence Society categorizes the stages of POP into five levels, ranging from 0 to 4: Stage 0 signifies no prolapse; stage 1 indicates that the most distal prolapse is 1 cm above the hymen; stage 2 is characterized by the most distal prolapse being 1 cm above to 1 cm below the hymen; stage 3 occurs when the most distal portion of the vagina extends beyond the hymenal plane by >1 cm, but the prolapse remains at least 2 cm shorter than the total vaginal length; and stage 4 is defined by complete prolapse or prolapse extending to within 2 cm of the total length of the lower genital tract (16).

3. Risk factors for POP

The etiology of POP is multifaceted, influenced by a combination of factors rather than a singular cause. Current research identifies key risk factors as lifestyle, age, pregnancy and parity, mode of delivery, estrogen levels, obesity, intra-abdominal pressure, history of pelvic surgery and genetic predispositions (Fig. 1).

Lifestyle. Epidemiological and observational studies have identified an association between POP and various lifestyle factors, including alcohol consumption (17), coffee intake (18), smoking (19), physical activity (20), labor (21) and hypertension (22,23). However, the association between these risk factors and POP remain unclear, with scientific studies often yielding inconsistent or contradictory conclusions (24). To investigate the relationship between lifestyle factors, metabolic factors and socioeconomic status with POP, Liu *et al* (25) conducted a two-sample Mendelian randomization study utilizing pooled data from the largest existing genome-wide association study (GWAS). Their findings suggest a positive association between genetically predicted coffee consumption, strenuous physical activity, high-density lipoprotein cholesterol and POP (25). Additionally, a cross-sectional study involving 76 women with significant levator ani deficiency found that 51 had symptomatic POP, while 25 did not. Severe levator ani deficiency is associated with a higher incidence of symptomatic POP, particularly among older women and smokers (26).

Age. Age is a significant risk factor for POP, with its incidence rising as individuals age. A study by Patel *et al* (27) observed that in menopausal women, the incidence of POP increases by ~40% with each decade of age. In the United States of America, an epidemiological study revealed that the prevalence of POP is 26.5% among women aged 40-59, 36.8% in those aged 60-79 and 49.7% in women aged ≥80 years (28). Beyond the influence of smoking, Rostaminia *et al* (26) noted that women with noticeable levator ani muscle defects but without POP are, on average, 18 years younger than those with POP and apparent muscle defects. These results underscore age as a key factor in the development of POP.

Pregnancy and parity. Pregnancy and childbirth also constitute major risk factors for POP. Approximately two-thirds of first-time mothers experience pelvic floor dysfunction (PFD) symptoms within a year postpartum (29). Patel *et al* (27) reported that the risk of POP is 4 times higher in women who have given birth once compared with nulliparous women, and this risk escalates to 8.4 times after 2 deliveries. As pregnancy progresses, the increasing size and weight of the uterus places greater strain on the pelvic floor support structures. Although the body initially compensates for this strain, the continued growth of the fetus during the mid to late stages of pregnancy can overwhelm these compensatory mechanisms, leading to damage to the pelvic floor muscles (30,31).

Mode of delivery. Vaginal delivery is recognized as the risk factor most closely associated with POP, likely due to the damage inflicted on the connective tissues of the pelvic floor, muscles and nerves during childbirth (32-34). Compared with controls, vaginal delivery increases the likelihood of developing POP by 4 to 11 times (35). This association may, in part, be attributed to injury to the levator ani muscle (36). A longitudinal study of postpartum PFD, which followed participants

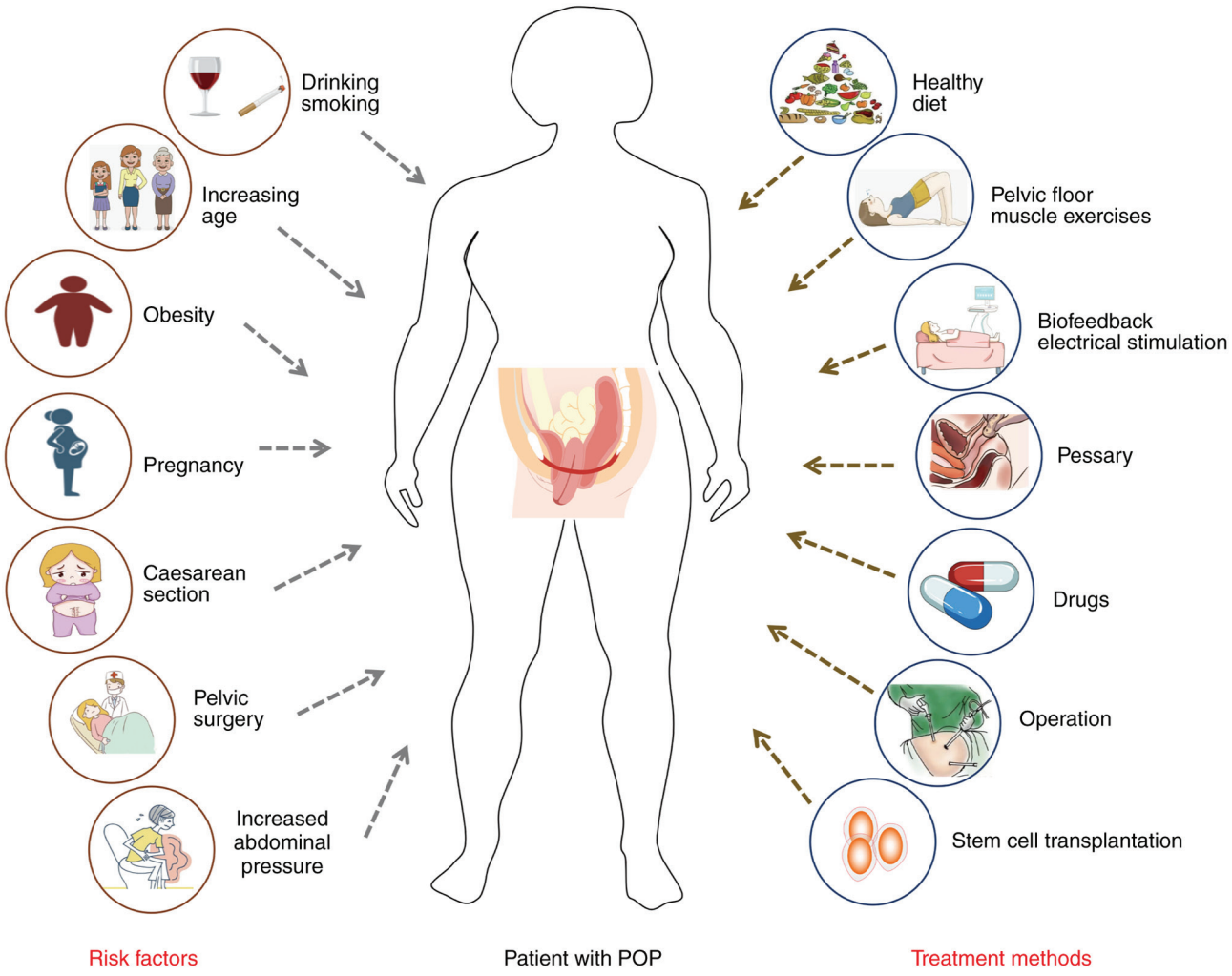

Figure 1. Risk factors and treatment of female POP. There are a number of risk factors for female POP, including lifestyle habits (drinking and smoking), age, obesity, pregnancy and parity, caesarean section, history of gynecological surgery, and increased abdominal pressure. Current treatments include diet control, exercise, pelvic floor muscle exercises, biofeedback electrical stimulation of the uterus, drugs, surgery and stem cell transplantation. POP, pelvic organ prolapse.

5-10 years after their first childbirth and conducted annual evaluations for up to 9 years, found that the incidence of POP increases following vaginal delivery but not cesarean section (37). A prospective cohort study further demonstrated that women aged <60 years are at the highest risk of POP due to vaginal delivery (38), while cesarean section and nulliparity may act as protective factors (39). In the absence of subsequent vaginal deliveries, cesarean section provides protection against POP, whereas instrumental deliveries heighten the risk (40,41).

Estrogen levels. ERs are extensively distributed throughout the pelvic floor tissues, including the cardinal ligaments, uterosacral ligaments, levator ani muscles, posterior vaginal fornix and vaginal wall. After menopause, systemic estrogen levels decline significantly, leading to a marked reduction in serum estrogen and ER content within the pelvic floor ligaments (42-44). This estrogen-deficient environment causes alterations in collagen composition and strength, as well as atrophy and degeneration of pelvic floor tissues, making it increasingly difficult to maintain the pelvic organs in their proper anatomical positions, thus contributing to prolapse (44,45). Postmenopausal women with POP exhibit significantly decreased serum estrogen concentrations and pelvic floor ligament ER levels compared with their non-POP counterparts (46). Additionally, a notable 1.5-2.5-fold reduction in ERα levels has been observed in postmenopausal women with POP compared with those in the group without POP, while premenopausal women with POP show increased ERβ levels compared with those without POP (47).

Obesity. A previous study indicated that a higher body mass index significantly increases the likelihood of developing POP (25). Obesity exacerbates the strain on pelvic floor tissues, resulting in continuous damage to pelvic floor muscles, nerves and other structures due to prolonged mechanical stress and traction (48,49). A study comparing 358 obese women with non-obese women of the same age found a higher prevalence of POP in the obese group (91 vs. 22%) (50).

Increased abdominal pressure. Increased abdominal pressure is another well-established risk factor for POP, often arising from conditions such as obesity, chronic cough or persistent constipation. Sustained elevation in abdominal pressure directly strains the pelvic floor muscles, ligaments and other

tissues, while chronic mechanical stress disrupts the cellular microenvironment, leading to an imbalance in cellular homeostasis and accelerating the progression of POP (51-53). Chronic constipation, in particular, maintains elevated tension in the rectus abdominis and anal sphincter, perpetuating high abdominal pressure. This ongoing pressure is a primary driver in promoting or exacerbating reproductive tract prolapse. A study investigating the prevalence and risk factors of symptomatic POP in rural China included 25,864 rural women from February 2014 to March 2016. The results showed that 20.84% of women with POP had a history of constipation for >1 year (19). Therefore, chronic constipation is also one of the risk factors for POP in women (54,55).

History of pelvic surgery. A history of pelvic surgery heightens the risk of developing POP. Gynecological surgeries, such as total hysterectomy, pelvic mass removal and radical pelvic organ resection, can damage the supporting structures of the pelvic floor, including muscles, connective tissue and ligaments, thereby inducing POP (37). A number of studies show that vaginal vault prolapse often manifests 2-13 years post-hysterectomy. The procedure not only removes the uterus but also severs the ligaments, blood vessels and nerves essential for maintaining pelvic floor function, thus compromising the pelvic floor support system (56). A cohort study involving 160,000 women post-hysterectomy found a 3.2% risk of POP, compared with only 2% in the control group (32). Another retrospective study indicated that POP could develop within 20 years following a hysterectomy (57).

Genetic factors. Clinically, uterine prolapse can occasionally be observed in young nulliparous women, or even in those without any sexual history. A study by Buchsbaum *et al* (58) found that the degree of POP after menopause is similar between women who have given birth and their biological sisters who have not, highlighting genetics as an important risk factor for POP. Jack *et al* (59) investigated 10 female patients under the age of 55 with a positive family history of POP and discovered that POP in these families exhibited an incomplete penetrance inheritance pattern, with both parents potentially passing on the trait. The risk of POP in such families is substantially higher than in the general population. Another study utilizing the Swedish Twin Registry, which included all known same-sex female twins born between 1926 and 1958, indicated that genetic factors contribute to the development of stress urinary incontinence and POP, although environmental factors are also influential (60). Evidence-based research has shown that women with a family history of POP have a 2.3-2.7 times higher risk of developing the condition and a 1.4 times greater risk of POP recurrence compared with those without such a history (30). A GWAS conducted by Allen-Brady *et al* (61) identified six single nucleotide polymorphisms (SNPs) significantly associated with POP in participants from high-risk families, located at 4q21 (rs1455311), 8q24 (rs1036819), 9q22 (rs430794), 15q11 (rs8027714), 20p13 (rs1810636) and 21q22 (rs2236479). Additionally, numerous studies have demonstrated that gene loci related to pelvic floor tissue components, such as collagen-, elastin- and ECM-related genes, are implicated in the pathogenesis of POP (62-64).

Other factors. Furthermore, studies involving subjectively reported and objectively measured POP in ethnically diverse cohorts have shown that Latino and white women are 4-5 times more likely to develop symptomatic prolapse, as measured according to the POP classification system, compared with African American women (65). These results suggest that race is also a factor influencing the occurrence of POP.

4. Molecular biological mechanisms of POP

The supporting structures of female pelvic organs primarily consist of connective tissues, including pelvic floor nerves, muscles, ligaments and fascia (1). Fibroblasts within these connective tissues secrete significant amounts of ECM, composed of structural proteins (such as collagen and elastin), matrix adhesion molecules (fibronectin and laminin) and proteoglycans (13,14). Recent research into the pathogenesis of POP has largely focused on the signaling molecules involved in collagen and elastin biosynthesis, as well as ECM metabolic processes (Fig. 2). The relevant molecular mechanisms underlying the occurrence and progression of POP are detailed in Table I.

MMPs/TIMPs. MMPs are enzymes responsible for degrading ECM proteins, while TIMPs act as their inhibitors. An imbalance between MMPs and TIMPs can lead to collagen metabolism disorders, playing a pivotal role in the development of POP (66). Studies have demonstrated a significant upregulation of MMP1 and MMP9 expression in the uterosacral ligament (USL) and vaginal mucosa tissues of patients with POP (67-69). Evidence indicates that an imbalance between MMPs and TIMPs can impair pelvic connective tissue quality, contributing to POP pathogenesis (70,71). It has been reported that collagen content in the pelvic floor support structures of patients with POP is not significantly decreased compared with that in individuals without POP. Instead, accelerated collagen degradation appears to be a key factor in the pathophysiology of POP (64). In a study by Hu *et al* (72), anterior vaginal wall tissue from 97 patients with POP and 35 controls was analyzed, revealing significantly increased mRNA and protein expression of MMP-1 and MMP-8 in patients with POP compared with controls. Additionally, a marked reduction in the mRNA and protein levels of type I and type III collagen, as well as TIMP-1, was observed in the POP group (72). Zhu *et al* (73) further investigated USL tissues from 35 patients with POP and 20 controls, finding that MMP2 and MMP9 protein and mRNA levels are significantly increased in the POP group, while TIMP1 and TIMP2 levels are markedly lower. Moreover, the study revealed that in patients with POP, the mRNA and protein levels of collagen I and ERα are considerably reduced, whereas the mRNA levels of Bax and Bad, as well as caspase-3 protein expression, are significantly higher compared with controls (73). These results suggested that POP is associated with ECM remodeling in USL tissue, characterized by decreased collagen production, increased collagen degradation and increased cellular apoptosis (73).

TGF-β. TGF-β is a multifunctional cytokine that plays a critical role as both a proliferation inhibitor and mitogen for mesenchymal-derived cells. It is a key molecule in fibrotic

Table I. Molecular mechanism of pelvic organ prolapse.

Molecules	Mechanism	Impact	(Refs.)
MMPs/TIMPs	In the tissues of the uterosacral ligament and vaginal mucosa, increased expression of MMPs and decreased expression of TIMPs led to an increase in ECM, thereby inhibiting the synthesis of collagen fibers and promoting their degradation.	Aggravating the progression of POP.	(67-73)
TGF-β	In sacral ligament tissue, the reduction of TGF-β1 expression led to an increase in ECM, thereby inhibiting the synthesis of collagen fibers.	Aggravating disease progression in POP patients with hysterectomy.	(76,77)
AGE/RAGE	In the vaginal tissue of patients with POP, increased AGE levels regulated the p38 MAPK and NF-κB pathways, inhibited vaginal fibroblast proliferation and reduced the expression of collagen I. Increased AGEs also promoted fibroblast apoptosis by inhibiting the miR-4429/PTEN/PI3K/AKT pathway.	Aggravating the progression of POP.	(81-85)
PI3K/AKT	Mechanical strain activated the PI3K/AKT pathway in human uterosacral ligament fibroblasts, thereby promoting cell apoptosis and senescence and reducing the production of collagen I.	Aggravating the progression of POP.	(86)
Fibulin	Decreased expression of Fibulin-3/5 promoted the upregulation of MMP-9 expression and increased elastic fiber dissolution.	Promoting the occurrence or aggravation of POP.	(88-93)
LOXL1	In the vagina, LOXL1 deficiency affected MMPs, TIMPs and ECM components, thereby promoting disordered arrangement of collagen fiber bundles.	Promoting the occurrence or aggravation of POP.	(96,97)
HOXA11	In the uterosacral ligament, reduced expression of HOXA11 led to decreased expression of collagen I and III and increased activation of MMP2 and MMP9, and weakened the connective tissue.	Promoting the occurrence or aggravation of POP.	(102,103)
miRNAs	In vaginal fibroblasts from patients with POP, elevated levels of miRNA-19-3p promoted the activation of the AKT/mTOR/p70S6K pathway, which in turn promoted autophagy and apoptosis in vaginal fibroblasts. Elevated levels of miRNA-19-3p also targeted IGF-1, thereby inhibiting the secretion of collagen I by vaginal fibroblasts.	Aggravating the progression of POP.	(104,105)
Wnt	In vaginal wall fibroblasts, FZD3 promoted fibroblast viability and ECM degradation, and inhibited apoptosis by activating the Wnt pathway.	Mitigating the progression of POP.	(107,108)
ERα	In uterosacral ligament fibroblasts, β-estradiol treatment promoted the expression of ERα, PARP1 and Bcl-2, thereby reducing apoptosis.	Mitigating the progression of POP.	(110)
Others	The expression levels of heparinases and COL18A1 gene were increased in the uterosacral ligament connective tissue of patients with POP, but the specific mechanism was unclear.	Aggravating the progression of POP.	(111,112)

MMP, matrix metalloproteinase; TIMP, tissue inhibitors of MMP; ECM, extracellular matrix; TGF-β, transforming growth factor β; AGE, advanced glycation end product; RAGE, receptor for AGE; PI3K, phosphoinositide 3-kinase; AKT, kinase B; LOXL1, lysyl oxidase-like 1; IGF-1, insulin-like growth factor-1; FZD3, frizzled 3; ERα, estrogen receptor α; PARP1, poly (ADP-ribose) polymerase 1; COL18A1, collagen α-1 (XVIII) chain; miRNA/miR, microRNA.

diseases and is involved in the pathogenesis of pelvic organ disorders (74,75). Qi *et al* (76) found that the expression levels of connective tissue growth factor and TGF-β1, both closely linked to collagen synthesis, were significantly reduced in the pubocervical fascia tissue of patients with POP. Liu *et al* (77) extended this research by investigating the role of TGF-β1 in the pathological processes of POP, particularly focusing on the metabolic change in ECM within the USL in patients with POP. This study involved 60 individuals (30 with POP and 30 without POP) who had undergone hysterectomy for benign

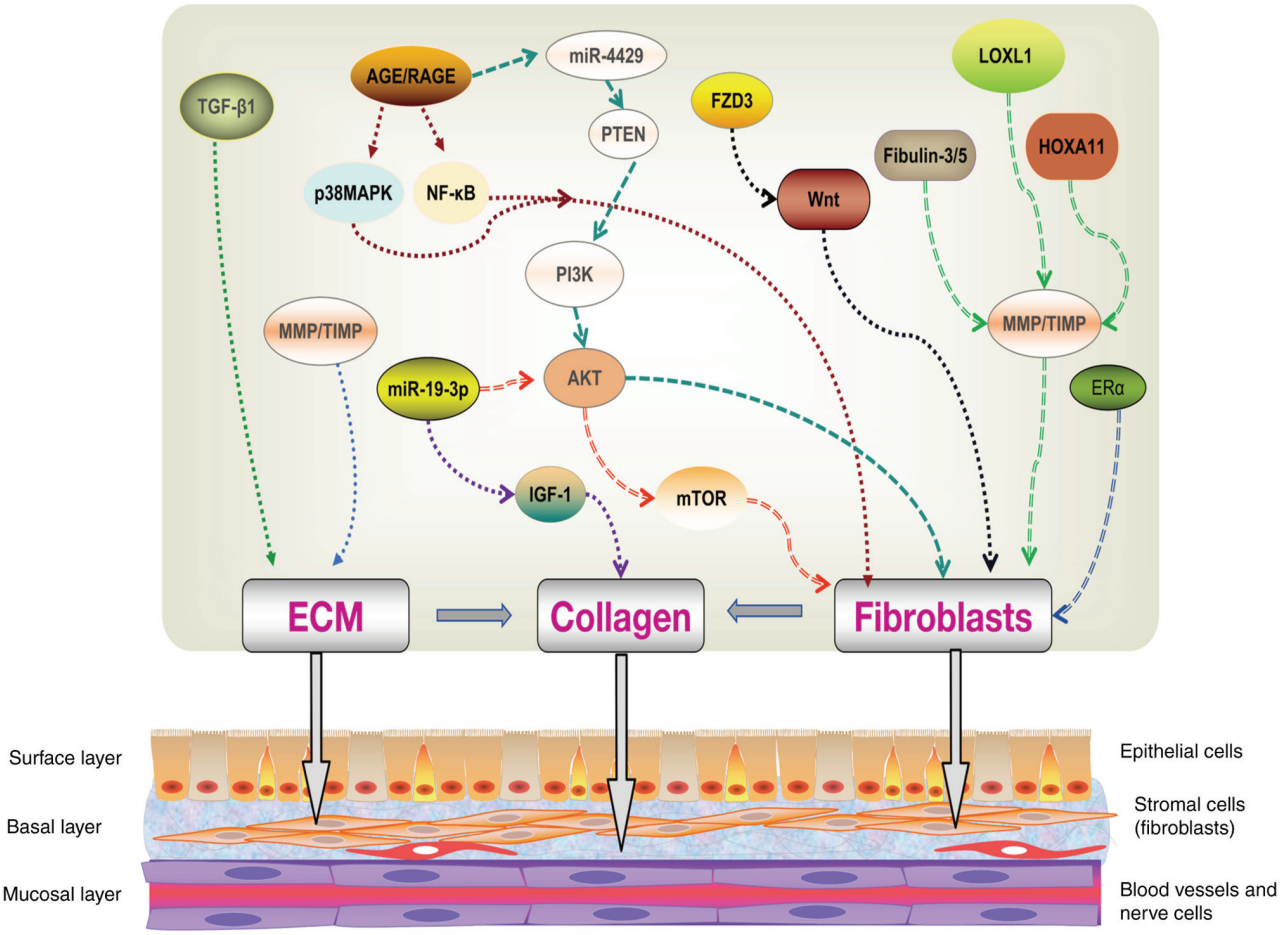

Figure 2. Molecular mechanism of POP. TGF-β1 and MMPs/TIMPs can regulate the occurrence of ECM, thereby affecting the collagen synthesis of POP. AGEs/RAGE can regulate the proliferation of vaginal fibroblasts by regulating the p38 MAPK and NF-κB pathways. AGEs can also affect fibroblast apoptosis by regulating the PTEN/PI3K/AKT pathway by targeting miR-4429. miR-19-3 can affect the apoptosis of fibroblasts by regulating the AKT/mTOR pathway, and can also target IGF-1 to regulate collagen production. FZD3 can affect the viability and apoptosis of fibroblasts by regulating the Wnt pathway. ERα can also affect fibroblast viability and apoptosis, but the downstream mechanisms are unclear. Fibulin-3/5, LOXL1 and HOXA11 can all regulate fibroblasts by regulating MMPs/TIMPs, thereby affecting the synthesis of collagen fibers. POP, pelvic organ prolapse; MMP, matrix metalloproteinase; TIMP, tissue inhibitors of MMP; ECM, extracellular matrix; TGF-β, transforming growth factor β; AGE, advanced glycation end product; RAGE, receptor for AGE; PI3K, phosphoinositide 3-kinase; AKT, kinase B; LOXL1, lysyl oxidase-like 1; IGF-1, insulin-like growth factor-1; FZD3, frizzled 3; ERα, estrogen receptor α; miR, microRNA.

reasons. Compared with the control group, patients with POP exhibited significantly decreased expression levels of collagen, elastin, TIMP-2 and TGF-β1 in their sacral ligament tissue, while MMP-2/9 activity was markedly increased. Statistical analysis revealed that TGF-β1 mRNA expression was inversely correlated with the severity of POP, suggesting that the pathogenic characteristics of POP include reduced ECM protein synthesis and increased degradation in the USL (77). Due to its potential to predict the severity of POP, TGF-β1 should be considered a possible therapeutic target for treating persistent POP.

AGEs/RAGE. AGEs are formed through the non-enzymatic glycation and oxidation of proteins and lipids. AGEs influence collagen metabolism and are implicated in ECM-related diseases, primarily characterized by collagen metabolism disorders (78,79). Chen *et al* (80) studied 44 patients with POP and 46 non-POP women, detecting AGEs and RAGE levels in vaginal tissues. They found that patients with POP exhibited higher protein expression of AGEs and lower levels of type I collagen compared with the controls, although no significant difference in RAGE expression was noted between the two groups. Similar results were observed in vaginal tissue tests conducted on POP rats, where AGEs were inversely correlated with type I collagen content (80). Additionally, sequencing of the complete RAGE gene in 24 patients with POP and 25 controls identified two SNPs (rs184003 and rs55640627) as potential factors contributing to POP (80). Vetuschi *et al* (81) examined the anterior vaginal wall myometrium in 20 patients with POP and 10 control patients undergoing treatment for uterine fibromatosis. In POP samples, the myometrium displayed upregulation of AGE, ERK1/2, Smad-2/3, MMP-3 and collagen III, while the control group showed increased levels of Smad-7 and collagen I. RAGE expression was minimal or absent in both groups. Their findings suggested that AGEs and RAGE may play a significant role in the pathophysiology of POP, although further research is needed to clarify the mechanisms by which the AGEs-RAGE pathway contributes to tissue degeneration and the fragility in POP (81). It has been indicated that AGEs exert cytotoxic effects on human vaginal

wall fibroblasts (VWFs), inhibiting their viability and proliferation while inducing apoptosis (82). Treatment of primary cultured human VWFs derived from POP and non-POP tissues with AGEs revealed that AGEs regulate the RAGE and/or p38 MAPK and NF-κB pathways, thereby inhibiting VWF proliferation and reducing type I collagen levels in patients with POP (83). Sima *et al* (84) further explored AGE-induced apoptosis in human USL fibroblasts, identifying the microRNA (miRNA/miR)-4429/PTEN/PI3K/AKT pathway as a key regulatory mechanism in POP. Their findings suggested that AGEs induce fibroblast apoptosis *via* this pathway (84). Moreover, their latest research demonstrates that quercetin inhibits the AGE-induced downregulation of the miR-4429/PTEN/PI3K/AKT pathway, thereby counteracting AGE-induced fibroblast apoptosis (85).

PI3K/AKT pathway. In the development of POP, factors such as mechanical strain, in addition to the regulatory effects of AGEs on the PI3K/AKT pathway, play a significant role. Li *et al* (86) exposed human USL fibroblasts to mechanical tensile strain at an intensity of 5,333 $\mu\varepsilon$ and a frequency of 0.3 Hz, finding that this strain accelerates cell death and senescence while reducing type I collagen formation by activating the PI3K/AKT-mediated oxidative stress signaling pathway. This process leads to the dysfunction of pelvic support, resulting in the relaxation of the pelvic region and promoting the onset of POP.

Fibulin. The fibulin family, a key component of the basement membrane and elastic fibers, consists of extracellular glycoproteins that facilitate tissue bridging and ECM assembly. The seven members of this family are divided into two subgroups based on their structural regions and size: Fibulin-1, 2 and 6 in the first subgroup and fibulin-3, 4, 5 and 7 in the second subgroup (87). Previous studies have shown that fibulin-3 knockout mice develop elastic fiber abnormalities as they age, such as abdominal wall hernias and POP, with increased MMP activity detected (88). Similarly, fibulin-5 gene knockout mice exhibit reduced elastic fibers, upregulated MMP-9 expression and POP symptoms, which result from the loss of negative feedback control of MMP-9 by fibulin-5, leading to abnormal elastic fiber formation (89,90). Genetic polymorphism analysis by Khadzhieva *et al* (91), involving 210 patients with severe POP and 292 controls, revealed a strong association between POP and high-frequency SNPs in fibulin-5 (SNP rs2018736 and rs12589592). According to Zhao and Zhou (92), it was further observed that although elastin expression levels remain unchanged in patients with POP, defects in elastic fiber remodeling due to reduced LOXL1 and fibulin-5 expression can contribute to POP development. Moreover, fibulin-5 may protect against or aid in the recovery from POP caused by childbirth or elastase deficiency (93).

LOXL1. LOXL1, a key protein for postnatal elastic fiber deposition, is highly expressed in the mouse reproductive tract, with expression levels diminishing with age. LOXL1 deficiency impairs elastic fiber recruitment to reproductive tissues after delivery, leading to lower urinary tract dysfunction, paraurethral pathology, vaginal wall thinning and POP (94). Liu *et al* (94) compared LOXL1 knockout mice with wild-type mice and found that the former developed varying degrees of POP by the second postpartum day, with some improvement by the 14th postpartum day, but a permanent pelvic floor prolapse persisted. Li *et al* (95) identified disordered collagen fibers in the vaginal tissue of LOXL1 knockout mice, further indicating the presence of aberrant ECM in this tissue. LOXL1 deficiency underlies numerous pathological processes associated with ECM metabolic imbalances. In a different study by Li *et al* (96), LOXL1 deficiency in the vagina was shown to affect key MMPs (MMP2, -9 and -12), TIMPs (TIMP1-4) and mRNA expression levels of ECM components (COL1a1, COL3a1, fibulin-5 and α-SMA). Additionally, a study by Kufaishi *et al* (97) found a significant reduction in the LOXL l and LOXL3 expression in the vaginal wall cells of patients with severe POP, underscoring the crucial role of the LOXL1 gene in maintaining elastic fiber structure and function, with defects in this gene potentially leading to the onset or worsening of POP.

HOXA11. HOXA11 plays a pivotal role in regulating the expression of genes involved in ECM metabolism within reproductive organs, maintaining tissue developmental plasticity in adult mice and humans through its expression in the reproductive tract. The USL, which provides essential support to the upper vagina and uterus, benefits from the ability of HOXA11 to promote fibroblast proliferation in the uterine fundal ligament (98). Disruptions in HOXA11 signaling may hinder the functional development or regeneration of the USL after trauma, leading to compromised biomechanical strength in the USL and, ultimately, uterovaginal prolapse in susceptible women (99,100). A study by Connell *et al* (101) comparing MMP2, MMP9, type III collagen and HOXA11 expression in the USL of patients with POP vs. controls revealed a significant reduction in the HOXA11 and type III collagen expression, alongside a notable increase in the MMP2 levels in patients with POP. Similarly, Ma *et al* (102) found that knocking down HOXA11 in the USL and uterus of mice decreased type I and type III collagen content while increasing MMP2 and MMP9 activation. Zhang *et al* (103) further demonstrated that reduced expression of the human homologous gene HOXA11 and TGF-β1 in the USL of patients with POP contributes to the disorder of ECM, highlighting their role in regulating the downregulation of collagens and MMPs, which leads to POP. These findings suggested that disruptions in the signaling pathways involving HOXA11, collagen and MMPs are key contributors to the onset and progression of POP by compromising connective tissue integrity.

miRNAs. Emerging research also highlights the involvement of certain miRNAs in the development of POP. Yin *et al* (104) found that miR-19-3p is upregulated in the tissues of women with POP, where it induces autophagy and apoptosis *via* the AKT/mTOR/p70S6K pathway. Moreover, miR-19-3p targets insulin-like growth factor-1 to inhibit the secretion of collagen I in vaginal fibroblasts (104). Additionally, miR-30d and miR-181a are overexpressed in women with POP, with their expression inversely correlated with HOXA11 mRNA levels (105). These results suggest that miR-19-3p, miR-30d and miR-181a may be significant players in the pathology of POP, although further research is needed.

Wnt pathway. The reduction in collagen content in pelvic floor tissues is considered to result from increased collagen degradation by collagenase. Changes in the biochemical and ultrastructural properties of collagen fibers are linked to the onset of POP (106). A decrease in fiber quantity leads to the relaxation of supporting structures (such as ligaments and fascia), which eventually contributes to the development of POP (71). The Wnt signaling pathway is known to activate the proliferation and differentiation of myofibroblasts in pelvic floor support tissues, encouraging them to release collagen and synthesize connective tissue. Xie *et al* (107) performed RNA-sequencing on USL samples from women with POP and controls, conducting pathway enrichment analysis on differentially expressed genes. Their findings revealed that the canonical Wnt receptor signaling pathway showed the most significant enrichment (107). Li *et al* (108) isolated VWFs from patients with POP and non-POP individuals and found that the frizzled class receptor 3 promotes VWF activity, enhances ECM degradation and inhibits apoptosis through the Wnt pathway in POP.

ERα. Nakad *et al* (109) analyzed blood samples from 33 women with advanced POP and 33 women without POP to examine the rs2228480 G/A mutation in the ERα gene using PCR technology. Their findings revealed that homozygous ERα rs2228480 G/A mutation is present in 19.2% of women with POP and 0.0% of those without, indicating a potential link between ERα gene mutations and an increased risk of late-stage POP. In a different study, Xie *et al* (110) investigated the effects of β-estradiol on human USL fibroblasts derived from patients with POP and non-POP individuals, finding that estrogen treatment reverses mechanical stress-induced apoptosis and cell death in both groups. This reversal is accompanied by increased protein and mRNA levels of the anti-apoptotic factors poly (ADP-ribose) polymerase 1 (PARP1) and Bcl-2, as well as elevated expression of ERα, the target of PARP1 (110). These studies suggest that ERα may play a significant role in the onset and progression of POP.

Other molecules. One potential mechanism underlying uterine prolapse involves ECM and connective tissue damage in the USL, potentially caused by the presence of heparinase. A study indicated that liver enzymes are more prevalent in the USL connective tissue of women with uterine prolapse compared with those without (111), suggesting that increased heparinase expression may weaken tissue strength and contribute to prolapse.

Li *et al* (112) conducted a candidate gene association study in China involving 48 patients with POP and 8 women without POP, identifying a significant association between three COL18A1 SNPs (rs55690336, rs56335679 and rs1050351) and POP. However, the precise mechanism linking COL18A1 to POP remains unclear and requires further investigation.

Cox *et al* (113), utilizing the Michigan Genomics Initiative (University of Michigan Institutional Review Board project approval no. HUM00161910; approval date, 05.03.2019), performed a GWAS involving 1,329 patients with POP and 16,383 controls, identifying four SNPs (rs12325192, rs9306894, rs1920568 and rs1247943) as potentially increasing susceptibility to prolapse. These SNPs are located near the genes SALL1, GDF7, TBX5 and TBX5 respectively. Despite these findings, the specific mechanisms through which these SNPs contribute to POP remain to be elucidated.

5. Treatment methods for POP

Treatment for POP is generally categorized into non-surgical and surgical approaches. Non-surgical treatments aim to alleviate symptoms, enhance pelvic floor muscle strength and support and prevent severe prolapse, thus avoiding or delaying the need for surgical intervention. Current non-surgical options include conservative lifestyle modifications, pelvic floor muscle training, physical therapy and pharmacotherapy (114-116). Surgical treatment, often considered the final recourse, remains the most critical intervention for POP (Fig. 1). While surgery can effectively address prolapse, potential complications, such as mesh erosion, infection, exposure and postoperative pain, may arise (117-119). Stem cell transplantation holds considerable promise as a treatment for POP, but further research is necessary (120).

General treatment. Comprehensive health education and behavioral guidance should be provided to patients with POP, emphasizing weight management, the reduction of high-intensity physical activities (such as lifting and carrying heavy objects), smoking cessation and the timely management of chronic conditions such as cough and constipation (121,122). Postpartum women should initiate rehabilitation promptly and actively manage risk factors to prevent the onset of POP. Lifestyle intervention can help women prevent the occurrence and development of POP to a certain extent and help patients with POP improve symptoms; however, lifestyle intervention cannot fundamentally solve the problem. Individuals with POP are encouraged to see a physical therapist or combine other methods to treat POP.

Physiotherapy

Pelvic floor muscle training (PFMT). PFMT, commonly known as Kegel training, involves instructing patients to consciously perform voluntary contractions of the pelvic floor muscles. This practice strengthens muscle tension and contraction, improving pelvic blood circulation (123). First introduced by American physician Arnold Kegel in 1948, PFMT is a traditional non-surgical treatment and the primary method for pelvic floor rehabilitation. Kegel exercises focus on tightening the anus and vagina (124), and numerous clinical studies have demonstrated that effective Kegel training significantly alleviates POP symptoms (123,125). In a randomized controlled trial involving patients with POP, PFMT was found to be more effective than stress-reducing exercises in improving POP symptoms (5). However, in clinical applications, it has been found that almost half of the patients cannot contract the pelvic floor muscles correctly but contract the abdominal muscles and gluteus maximus incorrectly. This not only fails to improve symptoms but will aggravate the condition as well (112,126,127). Therefore, Kegel training is rarely used independently in clinical practice, and is often used in conjunction with biofeedback and other methods to improve the symptoms of patients with POP.

Biofeedback electrical stimulation. Electrical stimulation, often combined with biofeedback, uses varying energies, frequencies and pulse widths to induce contractions in the pelvic floor muscles (128). During this process, biofeedback mechanisms, such as electromyography and pressure curves, provide real-time information on pelvic floor muscle activity, allowing patients to observe and correct their muscle function for optimal training results (128-130). Pelvic floor biofeedback therapy, which does not require external stimulation, is safe, non-invasive and effectively reactivates pelvic floor muscles and nerves damaged during childbirth, helping to restore vaginal tightness (131). Extensive literature supports the effectiveness of electrical stimulation in improving POP symptoms, enhancing the strength of type I and II pelvic floor fibers, and treating urinary incontinence (129,132). In current clinical practice, biofeedback therapy is often combined with electrical stimulation to treat patients with POP (129). Studies have shown that this combined approach, when paired with lifestyle interventions, is more effective at improving POP symptoms and muscle strength than lifestyle changes or Kegel exercises alone (125,133). Despite the long-standing use of electrical stimulation in pelvic floor rehabilitation, standardized parameters and treatment protocols are still lacking, necessitating further clinical research and exploration. Biofeedback electrical stimulation has the advantages of being non-invasive, highly efficient and safe. However, clinically, there are no unified parameters and standard treatment courses for treatment. Pelvic floor muscle electrical stimulation may cause a small amount of vaginal bleeding (128,129). Therefore, for different patients with POP, more individualized approaches should be considered, and plans should be formulated according to the degree of each disease. Clinical research and exploration still need to be carried out in the future.

Pessary. Vaginal pessaries are a highly effective non-surgical treatment option for POP (134), particularly suitable for individuals who decline surgery, cannot undergo surgical treatment due to medical reasons, wish to preserve fertility or have experienced POP recurrence post-surgery. The choice of pessary type depends on the severity of the prolapse (134,135). Ramsay *et al* (136) demonstrated a high success rate with pessary use in treating POP, reporting an 87.5% success rate for women aged 65-74 years after 1 year of use and an 80.8% success rate for those >75 years old. Proper pessary fitting can significantly alleviate most clinical symptoms of prolapse. In fact, 85% of French gynecologists view the clinical application of pessaries for POP as satisfactory, with 50% considering it the first-line treatment for POP (137). While pessaries effectively improve symptoms and quality of life for patients with POP, long-term use may lead to side effects such as increased vaginal secretions, mucosal ulcers and bleeding (119,138). Sarma *et al* (119) found that 56% of patients experienced complications after prolonged pessary use, with painful bleeding, leucorrhea, odor and erosion being the most common issues. A prospective cohort study following 130 female patients over 1 year revealed that while 70 patients continued to use pessaries, some developed vaginal erosion complications (138). Ongoing research is evaluating new pessary designs, with results from a study involving 15 adults with stage 2-4 POP still pending (139). To mitigate the side effects associated with long-term pessary use, it is recommended that postmenopausal women with vaginal mucosal atrophy receive local estrogen therapy, which can reduce complications (140,141).

Pessary is the first-line treatment for POP. It is a simple, economical and effective treatment method with a high success rate (136,142). Previous hysterectomy, pelvic reconstruction surgery and posterior vaginal wall prolapse are the main factors leading to the failure of pessary treatment (18). However, pessary treatment also has its risks in the form of complications. Although most complications are relatively minor and can be improved by temporary discontinuation of the device, topical estrogen therapy or attention to hygiene. However, when minor complications are not controlled or the patient leaves the pessary in the vagina, more serious complications may occur, such as vesicovaginal fistula (143). Therefore, strengthening guidance and regular follow-up are the main measures to avoid related complications.

Medication. Topical estrogen preparations are effective in improving vaginal mucosal atrophy and may play a role in the treatment of postmenopausal POP (140). Some studies have shown that preoperative use of local estrogen combined with pelvic floor muscle training can reduce the incidence of cystitis within 1 month postoperatively, and oral raloxifene may decrease the need for POP surgery in women aged ≥60 years old (141). According to Vaccaro *et al* (140), administering vaginal estrogen preoperatively for 2-12 weeks restores vaginal cytology to premenopausal levels without increasing the thickness of the vaginal epithelium. However, randomized controlled trials provide limited evidence regarding the effectiveness of estrogen in preventing and treating POP, indicating a need for further research. Additionally, Xie *et al* (144) revealed that Buzhong Yiqi decoction combined with surgery demonstrates significant clinical efficacy in treating rectal prolapse, suggesting that traditional Chinese medicine may offer benefits in the management of POP. Researchers found that Shenqi Wenyang vaginal dilation suppository (145) and Guyuan Shengti decoction (146) combined with biofeedback electrical stimulation treatment can improve the clinical symptoms of patients with POP, and also improve muscle coordination and strengthen the pelvic floor muscles. Traditional Chinese medicine compounds combined with biofeedback electrical stimulation treatment brought a significantly improvement compared with simple traditional Chinese medicine or physical therapy.

Currently, there are no drugs with confirmed efficacy for the treatment of POP. Short-term external use of estrogen drugs can increase the thickness of the vaginal wall and improve inflammation. It is often used clinically as an auxiliary drug for other conservative treatments and before and after surgery, and can improve POP to a certain extent (140,141). However, long-term treatment effects and adverse reactions need to be confirmed by further research. Traditional Chinese medicine has been used in combination with pelvic floor rehabilitation therapy to treat mild POP (145,146). This combination treatment has important efficacy and few side effects, but more clinical research is still needed to establish its therapeutic effects.

Surgical treatment. Surgical treatment for POP aims to repair defective tissues and restore the anatomy and function of the pelvic floor (117,135). Women with late-stage POP face a higher risk of recurrence following native tissue repair compared with those with early-stage POP; on the other hand, they may experience improved sexual function, particularly in more advanced cases. Due to the elevated risk of recurrence, it is advisable for women with early-stage POP to postpone surgery until the condition progresses (118). In current clinical practice, the selection of a surgical method requires careful consideration of various factors, including the location and severity of the prolapse, patient age, overall health and accompanying symptoms. The advent of new materials, such as biological meshes, has expanded the surgical options available for POP (147). In 2023, Dong *et al* (148) reported a case of transvaginal extraperitoneal uterine mesh fixation for treating POP, with no interlaminar or mesh exposure issues observed during postoperative follow-up. However, previous studies have documented vaginal erosion rates ranging from 11.4-15.6% after transvaginal POP mesh repair (149,150). The incidence of such complications tends to increase significantly over time. For instance, Hokenstad *et al* (57) reported erosion rates of 17% at 1 year, rising to 42% after 7 years. Moreover, the incidence of pain following mesh surgery has been reported to exceed 9.1%.

Traditional surgeries (vaginal hysterectomy, anterior and posterior vaginal wall repair and Manchester operation) mostly involve repeated reinforcement of weak tissues, which may not only distort or damage the anatomical structure and fail to improve the upper vaginal defects, but also cause postoperative vaginal discomfort and pain (151). In previous years, mesh repair has been widely used in the treatment of POP and has achieved good clinical results (120,152). The aim of this treatment is not only to repair defects but also to strengthen the support of the pelvic floor muscles and uterine ligaments. The addition of synthetic mesh to the vagina can effectively improve the cure rate of POP, but its complications cannot be ignored. The most common complications are mesh erosion and infection (153,154). Given these concerns, the development of more advanced and biocompatible graft materials is essential, and further research is needed to evaluate the efficacy and safety of these alternatives to traditional synthetic materials for POP repair.

Stem cell transplantation. Stem cell therapy is emerging as a promising avenue for the treatment of PFDs, although most studies remain in the experimental stage, with limited *in vivo* research. For example, scientists have successfully injected stem cells into the urethral striated muscle of rats with stress urinary incontinence to promote sphincter regeneration (155). Li *et al* (82) demonstrated that umbilical cord-derived mesenchymal stem cells (MSCs) can inhibit the cytotoxic effects of AGEs on the cells of patients with POP by triggering anti-inflammatory responses and activating the PI3K/AKT/PTEN signaling pathway. MSCs can promote new collagen synthesis and have the ability to transform into smooth muscle cells (156), which provides a theoretical basis for repairing the weak vaginal wall of POP. Currently, to the best of our knowledge, there are few studies using stem cells to treat POP. At the same time, the mechanisms underlying stem cell repair of pelvic floor tissue damage remain incompletely understood, and challenges such as stem cell survival, differentiation, ethical considerations, adverse reactions, complex culture requirements and long treatment cycles persist. Thus, further research is needed to support the clinical application of stem cell therapy in POP treatment.

In addition, MSCs combined with tissue engineering technology are regarded as a new approach to POP treatment (157,158). MSCs use their powerful immunomodulatory and paracrine abilities to promote successful implantation, recruitment and integration of mesh. Mesh materials provide a suitable living environment and mechanical support for MSCs. The advantages of the two complement each other, which promotes the biological patch developed by tissue engineering technology. Good biocompatibility, mechanical stability, elasticity and flexibility make it an ideal new therapeutic material (159). However, the current research on MSCs is still in its infancy, the development of new materials also needs to be improved, and further research is needed in the future. MSCs in combination with mesh materials may bring new opportunities for the treatment of POP.

6. Conclusions

PFD have emerged as a prominent concern in obstetrics and gynecology both domestically and internationally. Among these, POP is a particularly common condition that significantly impacts the quality of life, mental health and social interactions of adult women. The development of POP is complex, involving multiple contributing factors rather than a single cause. These risk factors include lifestyle, age, pregnancy parity, mode of delivery, estrogen levels, abdominal pressure, pelvic surgery history and genetic predispositions. Some of these factors act independently, while others interact and collectively influence the progression of POP, underscoring the importance of women being mindful of these elements in daily life.

Research into the pathogenesis of POP remains relatively sparse, with most studies focusing on various molecules or signaling pathways related to fibroblasts, collagen and the ECM, such as MMPs/TIMPs, TGF-β, AGEs/RAGE, PI3K/AKT, the fibulin family, LOXL1, HOXA11, COL18A1, Wnt signaling pathways and ERα. Due to the significant burden this disease places on women, particularly postpartum women, it is crucial to conduct more comprehensive and detailed research. With the advancement of research methodologies and deepening scientific inquiries, it is anticipated that understanding of the molecular biological mechanism driving the development and progression of POP will expand. However, current studies face several limitations. Primarily, much of the research on the molecular mechanisms of POP is confined to isolated proteins and pathways, with insufficient exploration of the upstream and downstream interactions within these pathways, as well as a lack of comprehensive cross-sectional studies of multiple pathways. Additionally, much of the research on how specific molecules and pathways influence POP remains at the level of cell and animal models, lacking verification in clinical settings. Furthermore, while changes in the expression levels of certain molecules (such as TGF-β, ERα and MMPs) have been observed in patients with POP, the research often fails to delve into the underlying mechanisms. Future research should

prioritize in-depth exploration of the interactions among multiple proteins and pathways, while also integrating animal studies with clinical research to uncover the molecular mechanisms of POP more comprehensively in clinical contexts.

For the treatment of POP, clinicians should prioritize non-surgical approaches as the first-line treatment, emphasizing early prevention, timely intervention and prompt recovery. While PFMT has certain limitations, it offers significant and effective benefits when practiced consistently under the guidance of a clinician or rehabilitation therapist. Electrical stimulation biofeedback, a conventional treatment for pelvic floor muscle dysfunction, is particularly valuable for its emphasis on individualized treatment plans. Pessary use remains an essential option for elderly patients who cannot undergo surgery, often serving as the only viable treatment for this population. Pharmacological treatment presents a promising avenue, but further research is needed to identify new therapeutic targets and develop effective drugs. Stem cell transplantation holds considerable therapeutic potential, yet more clinical trials are necessary to establish its efficacy. Surgical treatment, while effective, is associated with complications. The development and use of advanced bionic and biological graft materials as alternatives to traditional synthetic options for POP repair are ongoing, but additional studies are required to assess their safety and effectiveness. The pelvic floor plays a critical role in overall health, and future pelvic floor rehabilitation efforts will likely focus on simple, effective home-based treatments. There is also a growing commitment to leveraging technological advancements to provide sequential, precise and targeted training and treatment, aiming to achieve optimal recovery of pelvic floor function.

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JG and YL contributed to the acquisition, analysis and interpretation of the data and drafted the manuscript. JH contributed to the acquisition and analysis of the data. YW contributed to the conception and design of the study and critically revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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