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Review Article

Epidemiology and matrix metalloproteinases associated with pelvic organ prolapse: narrative review of the literature

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ABSTRACT

Pelvic organ prolapse carries a risk of recurrence and leads to several disorders which bother the patient and alter her quality of life and her self-esteem. The objective of this review is to provide an overview of the published literature on the epidemiology and matrix metalloproteinases involved in the development of pelvic organ prolapse. We carried out online searches in electronic databases: Hinari, Google scholar, Pubmed and Embase; and manual searches of the references of each selected article to identify more studies not captured by the online search. Studies on adult women published in English and French over the past 25 years were collected. We excluded animal studies, those published multiple times, duplicates, letters, commentaries, editorial notes, congress report, clinical practice guidelines, case reports, studies of comorbidities (cervical cancer, fistulas, pregnancy), and those evaluating paraclinical examinations and treatment. A total of 153 articles were read and 84 studies were retained, including 33 on the prevalence of genital prolapse, 24 on its epidemiological and physiopathological risk factors, 7 on the recurrence of genital prolapse and its risk factors, 20 on the matrix metalloproteinases associated with pelvic organ prolapse and their regulatory factors. The identification of the epidemiology and matrix metalloproteinases associated with pelvic organ prolapse appears important for improving its treatment through appropriate advice and measures.

Keywords: Epidemiology, Matrix metalloproteinases, Pelvic organ prolapse

INTRODUCTION

Pelvic organ prolapse is defined as an permanent or strained protrusion into or outside the vaginal canal, vulvar opening, pelvic organs such as the uterus, bladder, rectum and small intestine.[1,2] Although genital prolapse is not fatal, it has a significant impact on the quality of life of patients and leads to serious social problems including loss of self-esteem.[1-3]

Pelvic organ prolapse constitutes a reason for consultation and surgical interventions that are increasing in both gynecological and urological units.[4] Taking into account various factors, notably the increase in life expectancy, the number of patients suffering from pelvic organ prolapse will double in the coming decades.[4] Economically, the direct cost of treating pelvic organ prolapse is very high, exceeding $1 billion per year in the USA with nearly 200,000 surgical interventions.[4]

According to the WHO, pelvic organ prolapse affects approximately 50% of women who have given birth and its lifetime prevalence varies from 20 to 50%. Which is one of the most common reasons for gynecological surgery.[1-4] Previous studies have estimated that a woman's lifetime risk of having at least one surgery for pelvic organ

prolapse and urinary incontinence is 11.1 %, with a 10-year reoperation rate of 17%.[2]

Pelvic organ prolapse is a disease of the endopelvic ligaments and fascia characterized by the reduction of collagen content.[5,6] The cause of pelvic organ prolapse is multifactorial and involves alterations of the extracellular matrix of connective tissues of genetic origin in cases of Ehlers-Danlos syndrome, Marfan syndrome, Recklinghausen syndrome or acquired in case of any situation of the imbalance between matrix metalloproteinases (elevated) and their tissue inhibitors (decreased), oxidative stress and exaggerated cellular apoptosis in connective tissues.[2,5,7-14] These connective tissue abnormalities can be caused by several factors predisposing to pelvic organ prolapse known in the literature.[15]

The female urogenital system is supported by the pelvic muscles, pelvic ligaments, pelvic fascia and the bony pelvis.[15-17] Mechanical stability of the genitourinary tract depends on intact and functional collagen fibers, which support the bladder neck, urethra, and pelvic organs. Hence the loss of collagen is the basis of the instability of these pathways, a source of pelvic organ prolapse.[30] The pelvic ligaments and fascia are made up of connective tissues which contain collagen and matrix metalloproteinases (=MMP).[18,19]

MMPs are endopeptidases that have fixed the zinc atom and are controlled by the transcription of their genes, their production in inactive zymogen form and the co-secretion of their tissue inhibitors of metalloproteinases (TIMP).[20-22] They are involved in the degradation of collagen.[8,22-24] Further research in this direction has demonstrated that increased degradation of collagen causing its reduced content predisposes a person to pelvic organ prolapse by decreasing the mechanical strength of the ligaments.[16,18,24-29] They are divided into 6 groups according to domain organization, substrate specificity and structural differences, including collagenases (matrix metalloproteinase-1=MMP-1) and gelatinases (matrix metalloproteinase-2=MMP -2 and matrix metalloproteinase-9=MMP-9) are involved in the disassembly of collagen, from its reduced content in pelvic connective tissues to the base of the pelvic organ prolapse.[16,18,24-29]

The identification of the epidemiology and matrix metalloproteinases associated with pelvic organ prolapse therefore appears important for improving the management of pelvic organ prolapse in order to provide appropriate advice and measures. An overview of the literature on the epidemiology and matrix metalloproteinases associated with genital prolapse would aid in the development of a risk model to identify women at low and high risk. The objective of this narrative review is to provide an overview of the published literature on the epidemiology and matrix metalloproteinases involved in the development of pelvic organ prolapse.

Material and methods

Data sources

These are four electronic databases: Hinari, Google scholar, Pubmed and Embase which constitute our data sources where studies evaluating the epidemiology and/or the correlation between matrix metalloproteinases in women with and without pelvic organ prolapse from 1996 to 2021 or over the last 25 years. The search terms (MeSH) were "epidemiology", "risk factors", "associated factors" and "matrix metalloproteinases" or "matrix metalloproteinases" or "MMP" in combination with "genital prolapse" or "GP" or "PG" or "prolapse pelvic organs" or "POP" and "systematic review". We included only human studies and also checked the reference list of any articles or studies collected to ensure/preserve the sensitivity of the search procedure.

Data selection

We made a first selection of available studies by title, followed by a second selection by abstracts. In case of disagreement, the third selection was made based on the full text review. If the full text was not available, the authors were contacted to obtain the article.

Inclusion criteria

We included human cross-sectional, case-control and cohort community and hospital studies on the epidemiology and matrix metalloproteinases associated with pelvic organ prolapse, conducted in Western developed countries and in non-developed African countries, Asian and South American.

Exclusion criteria

We excluded animal studies, multiple published studies, duplicates, letters, commentaries, editorial notes, congress report, clinical practice guidelines, case reports, studies of comorbidities (cervical cancer, fistulas, pregnancy) and those evaluating paraclinical examinations and treatment.

We also performed a manual search of the references of each selected article to identify more studies not captured by the online search, but potentially relevant to this review.

Data extraction

Two reviewers independently selected studies from the literature and then extracted relevant data. Discussion until consensus was reached was used to resolve disagreements between the two reviewers. We extracted information on epidemiology (prevalence-frequency, epidemiological and pathophysiological risk factors, staging of pelvic organ prolapse e according to the pelvic organ prolapse quantification system[30]) and matrix metalloproteinases (MMP-1, MMP-2 and MMP-9) associated with genital

prolapse. We did not perform meta-analysis of data but rather a narrative review or review.

Ethical considerations

As this work is based on previously published studies, no ethical approval or informed consent is required.

Results

From our electronic sources, we initially identified 1579 potentially eligible articles, but many were excluded after title and abstract screening because they were duplicates or animal studies or not relevant. After evaluating the full texts of 153 articles on pelvic organ prolapse, we retained 55 eligible studies including 19 on the prevalence of genital prolapse, 14 on its epidemiological and physiopathological risk factors, 5 on the recurrence of genital prolapse and its risk factors, 15 on matrix metalloproteinases associated with pelvic organ prolapse and their regulatory factors, 69 studies were excluded because they were recommendations for clinical practice, studies evaluating paraclinical examinations and treatment, studies of morbid associations, and congress reports (Figure 1).

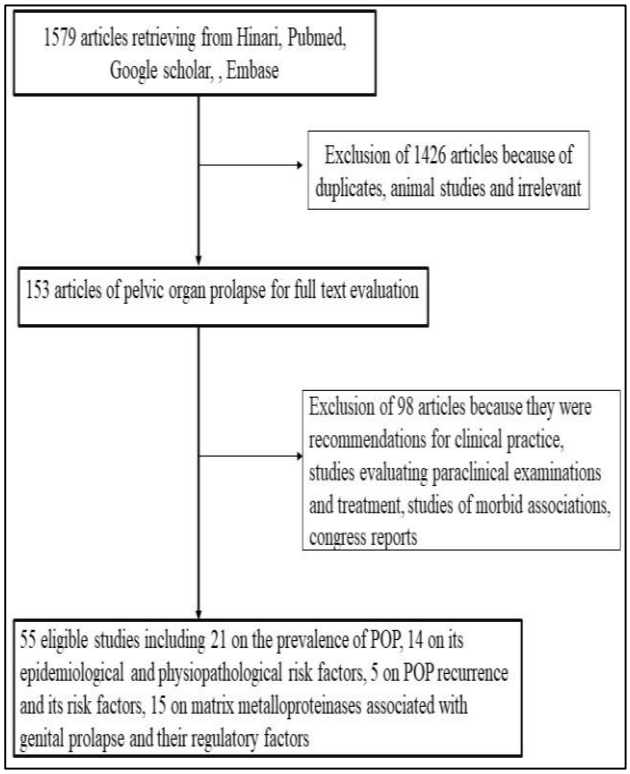

Figure 1: Flowchart of data collection.

DISCUSSION

Pelvic organ prolapse is a major cause of morbidity among women in both high- and low-income countries. The prevalence of pelvic organ prolapse varies from 2.90 to 97.70% worldwide depending on the study methods used. It is estimated from 2.90 to 11.40% when the method used is a symptom questionnaire and from 31.80 to 97.70% when a clinical examination is carried out with the pelvic organ prolapse quantification (POPQ).[31-44] The global prevalence of pelvic organ prolapse has been reported to be around 9.00%, however this figure is estimated to be closer to 20.00% in low-income countries.[45] In sub-Saharan Africa, studies carried out in Ghana, Gambia and Ethiopia and Tanzania have reported prevalence rates varying from 12 to 65.00% while in the democratic Republic of Congo, this prevalence is not known but a hospital study found a frequency of pelvic organ prolapse of 1.15% in Kinshasa in 2019.[46-50]

The risk factors involved in the occurrence of pelvic organ prolapse are known and divided into the following two groups: modifiable risk factors such as obesity, malnutrition, vaginal delivery, parity, smoking, fetal macrosomia, perineal tears, carrying heavy objects, low socio-economic level, anemia and situations of oxidative stress and cellular apoptosis in connective tissues; and non-modifiable risk factors such as age, race including white race, menopause, chronic obstructive pulmonary disease (COPD), spinal curvature abnormalities (thoracic kyphosis, loss of lumbar lordosis), history family and personal pelvic organ prolapse, previous pelvic surgeries (hysterectomy), chronic constipation.[1,12-14,51-54]

These risk factors act on one or both of the following pathogenetic mechanisms of pelvic organ prolapse: the defect of the ligaments, pelvic fascia and levator ani by direct traumatic lesions or by denervation; and increased intra-abdominal forces or pressures (≥ 6 mmHg).[51-53] These two mechanisms lead to the reduction of the collagen content by stimulation of the activity of matrix metalloproteinases at the basis of collagen degradation and by defect of genes or fibroblasts at the basis of the defect in collagen synthesis. This leads to ligamentous alteration in terms of ligamentous hyperlaxity, a source of pelvic organ prolapse.[5,6]

Pelvic organ prolapse appears to be a dynamic disease that can both worsen or regress, especially in the postpartum period.[1,39] It carries a high risk of recurrence after surgical treatment.[1,53] It is the basis of several disorders : urinary, digestive and genital which bother the patient, reduce her quality of life and alter her self-esteem.[1-4,31,35]

Recurrence of pelvic organ prolapse after surgical correction is one of the delicate problems in reconstructive pelvic surgery.[55] Approximately 30.00% of surgeries for pelvic organ prolapse with urinary incontinence in a community study in the USA were performed for recurrent genital prolapse.[55] The prevalence of re-operation for pelvic organ prolapse ranges from 43 to 56% in the USA.[55] Re-operation is totally different from recurrence because many women with recurrent pelvic organ prolapse do not seek or are against its surgical repair. Therefore, the prevalence of recurrent pelvic organ prolapse may be even higher.[55] The recidivism rate is more than 30.00% in

France and 2.00% in the Democratic Republic of Congo.[50,56]

The risk of recurrence of pelvic organ prolapse is linked to young age (<60 years), advanced stage of pelvic organ prolapse (III or IV), surgical technique, surgical route (almost zero risk in the abdominal route), to exposure to high intra-abdominal pressures, to good innervation and good condition of supporting tissues, potentially to serious pelvic tears during childbirth.[55,57]

Pelvic organ prolapse is a collagen disease characterized by loss of mechanical stability of the the genital and urinary tract secondary to loss of integrity of connective tissues supporting the bladder neck, urethra and pelvic organs.[15-17,58] In recent years, several investigators have identified reduced collagen content and increased expression of MMPs in pelvic support structures in women with pelvic organ prolapse.[5,9,16,18,29,58,59] Increased degradation of collagen by MMPs underlies pelvic organ prolapse. The difficulty in quantifying collagen is inherent to its supermolecular structure. In fact, this very stable protein is virtually impossible to solubilize in most physiological buffers.[8,16,23,26,27] The most frequently used biochemical assay to quantify collagen is the hydroxyproline assay. However, this assay, which requires a significant amount of tissue, is an indirect measure of total collagen and is not specific for collagen.[8,16] To overcome these limitations, a group of authors studied collagen metabolism by measuring MMP expression in an easy-to-perform manner.[8,16,18,23,25-27]

Increased combined or isolated expression of MMP-1, MM-2 and MMP-9 is significantly associated with the occurrence and recurrence of pelvic organ prolapse. It has therefore been suggested that increased collagen degradation by MMP-1, MM-2 and MM-9 leads to a decrease in the mechanical strength of the pelvic ligaments, predisposing women to pelvic organ prolapse. This degradation takes place as follows: MMP-1 or collagenase-1 degrades fibrillar or interstitial collagens including type I and transforms them into denatured collagens called “gelatins” which can then be degraded by gelatinases. It is associated with the reduction in the collagen I content in the ligamentous connective tissue.[9,10,16,18,20,21,25-27,29] While MMP-2 or gelatinase A degrades collagens in two steps : by inducing the degradation of interstitial collagens thanks to its weak collagenase-like effect and then by promoting gelatinolysis through the use of the fibronectin-like domain.[20,21,60] MMP-9 can also act as a collagenase and gelatinase.[20,21]

Estrogens and progesterone play an important role in regulating the activity of MMP-1, MMP-2 and MMP-9 involved in the occurrence of pelvic organ prolapse by inhibiting the transcription of their genes underlying the loss of levels of their messenger RNAs, and by stimulating the production of tissue inhibitors of MMP (TIMP) in pelvic fibroblasts. Which blocks pelvic collagenolysis.[5,22,28] Thus, prolonged deprivation of these hormones during menopause leads to the excessive degradation of collagen, the source of pelvic floor weakness and genital prolapse. Hence the prescription of these hormones in menopausal women at risk.[5,10,22,28,29] Obstetric trauma stimulates the activity of MMPs (thanks to inflammatory cytokines: interleukin 1, tumor necrosis factor alpha=TNFα, transforming growth factor beta-1=TGF-β1) to destroy injured local connective tissues, the exaggeration of which is at the basis of pelvic weakness, source of pelvic organ prolapse.[22,61]

Dviri et al, Phillips et al and Jackson et al identified a significant association between reduced collagen content and increased tissue expression of MMPs-1 and -9 in samples of vaginal tissue, round ligaments and uterosacral ligaments collected from women with pelvic organ prolapse compared to controls while the studies by Moalli et al, Chen, Strinic et al and Usta et al found significantly elevated expression of MMP-1 or MMP-9 but not MMP-2 in the group of women with pelvic organ prolapse.[9,10,16,18,24,25,26] On the other hand, Boris et al and Liang et al reported higher expression of MMP-2 but not MMP-1 in the round, uterosacral ligaments of women with pelvic organ prolapse.[27,28] Two recently published reviews show that the combined action of these MMPs is capable of degrading all components of the extracellular matrix, with different specificities for each MMP.[5,62]

CONCLUSION

In this review, we have presented the prevalence of pelvic organ prolapse, its epidemiological and physiopathological risk factors, matrix metalloproteinases-1, -2 and -9 whose expression level is more increased in women suffering from pelvic organ prolapse than in women without prolapse, and the role of these matrix metalloproteinases in the degradation of collagen in the pelvic ligaments at the basis of the reduction in the collagen content, the loss of mechanical resistance of the pelvic ligaments (ligamentous hyperlaxity), source of pelvic organ prolapse. She also exposed the role of estrogen-progestins and the prevention of obstetric trauma in the inhibition of matrix metalloproteinases leading to the prevention of pelvic organ prolapse.

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