Prolapsus Uteri in Pelvic Floor Disorders

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Received, 18 December 2000; accepted, 17 January 2001.

Abstract: Prolapsus uteri in pelvic floor disorders are common in elderly women. The etiology is unclear and more likely to be multifactorial. Abnormal connective tissues may be a key factor in the development of pelvic floor disorders, possibly due to an intrinsic abnormality in collagen synthesis, such as abnormal collagen, an imbalance between synthesis and degradation, or an imbalance between collagen types. In addition, the marked reduction in elastin gene transcripts and elastin production in patients with prolapsus uteri could lead to a paucity of ligament elastic fibers, and this may contribute to the loss of supportive function in the uterus. Further studies in this field will aid in clarifying the mechanisms of the development of prolapsus uteri.

Key words: prolapsus uteri, collagen, elastin, ligament fibroblasts

INTRODUCTION

Pelvic supportive tissues contain prominent blood vessels, nerves, and fibrous connective tissues that can be thought of as mesenteries supplying the genital tract bilaterally. Endopelvic ligaments and fascia are a more mesh-like group of collagen fibers interlaced with elastin fibers, smooth muscle, and vascular structures1). Their composition reflects their combined functions as neurovascular conduits and supportive structures2). Although much has been written about the causes of pelvic floor disorders, the scientific data to confirm theories as being correct are not yet available. There has long been controversy between the fascialists, who believe that genital prolapse is a disorder of connective tissue, and the antifascialists3). DeLancey4) demonstrated that damage to the upper suspensory fibers of the paracolpium (level I) causes a different type of prolapse from that caused by damage to the mid-level supports of the vagina (level II). Defects in the support provided by the level II vaginal supports (pubocervical and rectovaginal fasciae) result in cystocele and rectocele, and the loss of the upper suspensory fibers of the paracolpium and parametrium (level III) is responsible for the development of vaginal and uterine prolapse. These defects usually occur in varying combinations, and this variation may be responsible for the diversity of clinical problems encountered in the overall spectrum of pelvic organ prolapse5). Prolapsus uteri in pelvic floor disorders are common in elderly women. It is as yet unclear why women develop genital prolapse and how factors lead to the failure of surgical repair.

The purpose of this article is to review current knowledge of prolapsus uteri in pelvic floor disorders.

Terminology of Pelvic Organ Prolapse and Pelvic Floor Dysfunction

Pelvic organ prolapse has conventionally been classified by the degrees of descensus of uteri as follows: descensus uteri, prolapsus uteri partialis (or incompletes), and prolapsus uteri totalis (or completes) (Fig. 1). In addition, prolapsus uteri cum elongatio colli, with elongation of the cervix, are frequently observed not only in elderly or parous women, but also in comparatively young (30-40 years old) or nulliparous women. Descensus vaginae and prolapsus vaginae are frequently generated with proceeding or advance of prolapsus uteri. Prolapsus vaginae are often accompanied by cystocele (cystocele vaginalis in the case of prolapse of the vagina anterior) or rectocele (rectocele vaginalis in the case of prolapse of the vagina posterior).

A standard system of terminology was approved by the International Continence Society in October, 1995, the American Urogynecologic Society in January, 1996, and the Society of Gynecologic Surgeons in March, 1996, to describe female pelvic organ prolapse and pelvic floor dysfunction9). An objective site-specific system for describing, quantitating, and staging pelvic support in women is included. The points and measurements are presented in Fig. 2. The position of points Aa, Ba, Ap, Bp, C, and (if applicable) D with reference to the hymen, and the length of points gh, pb, and tvl should be...
Fig. 1. Diagrammatic representation of pelvic organ prolapse.

Fig. 2. Points for pelvic organ support quantitation.

Fig. 3. Three-by-three grid for recording quantitative descriptions of pelvic organ support.

Stage 0: No prolapse is demonstrated. Points Aa, Ap, Ba, and Bp are all at $-3$ cm and the quantitation value is $< -1$ cm. Stage I: The quantitation value is $< -1$ cm but $\leq +1$ cm. Stage II: The quantitation value is $\geq -1$ cm but $\leq +1$ cm. Stage III: The quantitation value is $> +1$ cm but $< [+tv] - 2$ cm. Stage IV: The quantitation value is $\geq +[tv] - 2$ cm. In most instances, the leading edge of a stage IV prolapse will be the cervix or vaginal cuff scar. This system of nomenclature has been developed to enhance both clinical and academic communications regarding individual patients and populations of patients.

Frequency of Genital Prolapse

The prevalence of genital prolapse in women is unclear. Previous studies have indicated that prolapsus uteri occur frequently in women over 40 years of age and that the incidence increases with aging; the frequency is higher in parous women than in nulliparous women. Akazawa et al. examined new patients over 60 years of age that were seen in consultation in the Gynecology Department of the Tokyo Metropolitan Tama Geriatric Hospital between 1986 and 1990, and found that of the 675 Japanese patients, 52 (7.7%) had prolapsus uteri, including 13 (1.9%) with cystocele and rectocele. The frequency of prolapsus uteri increases with advancing age (9/145 (6.2%) in the 60’s, 22/289 (7.6%) in the 70’s, and 19/209 (9.1%) in the 80’s). In Iraqi women, however, genital prolapse is more common, and patients with genital prolapse are younger: 47.4% (36/76) of patients are younger than 40 years. In Chinese women in Hong Kong, the medical records of 2,312 consecutive patients admitted for major gynecological surgery for benign conditions at 5 major public teaching hospitals in 1993 indicated 578 cases (25%) as having genital prolapse and or urinary problems. Studies of signs of genital prolapse in a Swedish population of women 20 to 59 years of age showed that of 487 women who answered a questionnaire and accepted an invitation to a gynecologic health examination, the prevalence of any degree of prolapse was 30.8%, but only 2% of all women had prolapse that reached the introitus. In multivariate analyses, age, parity, pelvic floor muscle strength, and, among parous women, the maximum birth weight are significantly and independently associated with the presence of prolapse. A recent review has shown that pelvic...
organ prolapse and pelvic floor dysfunction, including urinary incontinence and anal incontinence, is extremely common, affecting at least one-third of adult women. In contrast, Marchionni et al. demonstrated that on pelvic examination, the incidence of vaginal vault prolapse is 4.4% (20 of 448 patients selected for follow-up study) in Italy. The primary risk factor for vaginal vault prolapse in their study is obesity.

Etiology of Pelvic Floor Disorders

Many risk factors such as childbirth, neuromuscular damage to the pelvic floor, poor health care, estrogen deficiency, chronic intraabdominal pressure from pulmonary disease, heavy lifting, obesity, chronic straining during bowel movements, obstipation, neurologic injury, surgical procedures, and aging may play a role in the development of genital prolapse. However, one woman may develop genital prolapse without having any of these risk factors, while another woman who performs heavy work and has delivered many children never develops prolapse. It is likely that these risk factors play a role only in women who are predisposed to genital prolapse that may be caused by something as simple as poor nutrition or as complex as an autosomal dominant genetic abnormality. The high prevalence of genital prolapse in Iraqi women may be due to high parity, poor health care, untrained delivery operations, and housework resuming just after childbirth. A recent study demonstrated that young (≤ 45 years) women with genital prolapse have had a higher number of deliveries and the babies were heavier than for age-matched control women. In addition, women with prolapses more often have had operations for abdominal hernias and also have more chronic pulmonary disease, e.g., asthma. The incidence of preterm delivery is the same in women with genital prolapse as in controls. The familial incidence of genital prolapse is about 30%. Recently, Baessler and Schuessler showed that a deep pouch of Douglas is frequently present in young nulliparous women and may increase the risk for the development of a posterior vaginal wall prolapse. These findings confirm that there are both acquired and congenital factors that predispose women to genital prolapse.

Role of Connective Tissues in Pelvic Floor Disorders

Collagen

Abnormal connective tissue in the pelvic floor ligaments and fascia may be a key factor in pelvic floor disorders. This may be due to an intrinsic abnormality in collagen synthesis such as abnormal collagen, an imbalance between synthesis and degradation, or an imbalance between collagen types. Ulmsten et al. reported a decreased total collagen content in the rectus fascia of women with stress incontinence and decreased collagen synthesis in skin fibroblasts from women with stress incontinence compared with continent control subjects. Keane et al. have also shown that the nulliparous women with genuine stress incontinence have significantly less collagen in their tissues compared with continent controls. In addition, there is a decreased ratio of type I to type III collagen, and the cross-link content is also significantly reduced in women with genuine stress incontinence. In contrast, there is a recent report that stress urinary incontinence in fertile women is associated with changes in collagen metabolism resulting in an increased concentration of collagen and larger collagen fibrils, and that these alterations should result in a more rigid form of extracellular matrix, suggesting a connective tissue with impaired mechanical function. Studies of fibroblasts derived from the pelvic fascia of women with recurrent genital prolapse indicate an imbalance in collagen types, with excess synthesis of type III collagen. Friedman et al. have suggested that a constitutive and systemic increase in type III collagen gene expression and protein synthesis in patients with inguinal hernias results in reduced collagen fibril assembly in the abdominal wall, eventually leading to the development of herniation. We have also found a marked decrease in collagen synthesis in ligament fibroblasts from elderly women with prolapsus uteri compared with fibroblasts from age-matched control patients.

No change in the amount or composition of proteoglycan is observed in women of fertile age with stress urinary incontinence, resulting in a significantly lower proteoglycan/collagen ratio.

Elastin

Elastin fibers apparently play a central role in providing elasticity and resilience to some tissues including skin, large arteries, and certain specialized ligaments. Faulty elastin production in heritable or acquired diseases leads to a loss of elastic recoil, and the resulting impaired integrity of elastic fibers plays a major role in the clinical manifestations of a variety of connective tissue disorders. Little is known about alterations in elastin in prolapsus uteri. Recently, we examined elastin mRNA expression and elastin synthesis in cultured fibroblasts derived from the cardinal ligaments of elderly patients with prolapsus uteri and compared them with those of fibroblasts from age-matched control patients. We found a marked reduction in steady-state elastin gene transcripts and elastin synthesis in quiescent fibroblasts.
derived from prolapsus uteri patients (Fig. 4). The significant decrease in elastin production in the cardinal ligaments may lead to a loss of functional tissue elasticity, a condition that may progress to the development of prolapsus uteri. Furthermore, the maximum stimulation of elastin synthesis by TGF-β1 is significantly less in prolapsus uteri fibroblasts, suggesting that prolapsus uteri fibroblasts have a lower potential for elastin synthesis than control fibroblasts. A down-regulation of elastin mRNA expression and elastin synthesis has been reported in some heritable diseases. Studies of skin fibroblast cultures established from elderly patients have also revealed a marked reduction in elastin mRNA steady-state levels and tropoelastin synthesis, suggesting that reduced elastin production could contribute to the loss of functional elastic fibers associated with innate cutaneous aging. Taken together, the markedly reduced elastin gene expression and elastin production in fibroblasts from elderly women with prolapsus uteri could lead to a paucity of ligament elastic fibers and thus contribute to the loss of supportive function in uterine connective tissues.

Elastin-binding proteins (EBPs)

Extracellular matrix proteins interact directly with cell surface receptors to initiate signal transduction pathways and to regulate several biological processes, especially morphogenesis and differentiation, and pathological situations, e.g. wound healing, atherosclerosis, and tumor progression. Recent evidences suggest the involvement of the 67-kDa EBP in Costello syndrome and Hurler disease. Our recent studies have shown that the expression of EBP is significantly reduced in fibroblasts from patients with prolapse uteri compared with those from control subjects (unpublished data). Furthermore, our findings have suggested that control fibroblasts maintain their normal function by adhering to elastin through reduced expression of the low-molecular-size, low affinity EBP (unpublished data). Changes in the expression and role of EBPs in ligament fibroblasts may be an early key event in the development of prolapsus uteri.

Biological Characteristics of Cardinal Ligament Fibroblasts Derived from Patients with Prolapsus Uteri

During wound healing, the proliferation of fibroblasts from the wounded tissue and the synthesis and remodeling of collagen and elastin appear to be key events. The synthesis and deposition of collagen and elastin depend quantitatively and qualitatively on the stage of cellular growth. Therefore, alterations in collagen synthesis, collagen type, and elastin synthesis in connective tissue disorders may also depend upon the growth stage of ligament fibroblasts. The latency period before the first cell migrates out of a explant and the number of cells migrating from explants does not differ significantly between fibroblasts from patients with prolapsus uteri and fibroblasts from control patients. However, prolapsus uteri fibroblasts respond strongly to serum mitogens, especially to platelet-derived growth factor (PDGF), compared with control fibroblasts, and the high proliferative activity of prolapsus uteri fibroblasts may result from the decreased expression of p53 mRNA and p53 protein followed by a decrease in the amount of p21 protein. Furthermore, elastin significantly suppresses the saturation density of prolapsus uteri fibroblasts. Taken together, the failure of cells to enter quiescence due to the decreases in p53 mRNA and protein levels may lead to a decrease in the synthesis and deposition of elastin and thus may be responsible for the loss of supportive function in uterine connective tissues.

![Graph](image-url)

Fig. 4. Relative levels of elastin mRNA (a) and elastin synthesis in the culture medium (b) and cell layer (c) of fibroblasts derived from prolapsus uteri patients (HPLiF) and control patients (HCLiF).
Finally, surface elastases may break down fibrous elastin to provide a tissue gradient of soluble elastin peptides. A recent study has suggested that the occupancy of the 67-kDa elastin receptor by elastin-derived peptides enhances both the expression and activation of pro-matrix metalloproteinase-2, which degrades insoluble elastin. Further studies aimed at understanding the functional status of extracellular matrix components, their receptors, and matrix metalloproteinases in prolapsus uteri fibroblasts are essential and will aid in clarifying the mechanisms of the development of prolapsus uteri in elderly women.

Acknowledgements: We thank Dr. Margaret Dooley Ohto for reviewing the manuscript.

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