Genitourinary Tract in Women with Marfan Syndrome

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Pelvic organ prolapse and urinary stress incontinence in women are multifactorial in etiology. The etiologic factors associated with these two conditions are thought to have considerable overlap. Stress incontinence is associated with hypermobility of the bladder neck as well as intrinsic sphincter weakness with most patients having overlap of these two components. Hypermobility of the bladder neck can be elicited on physical examination with the presence of cystourethrocele.

The denervation of the pelvic floor and physical trauma which occurs with childbirth is thought to contribute to these conditions but individual predisposition also has a considerable effect. The strength and resilience of the connective tissue of the pelvis is thought to have a major influence on the occurrence of pelvic organ prolapse and stress incontinence.

A constitutional predisposition to stress incontinence and pelvic organ prolapse has been sought by studying joint hypermobility and collagen. Joint hypermobility has been associated with pelvic organ prolapse [1, 2]. Ehlers-Danlos syndrome, a connective tissue disorder involving collagen, has been studied in association with gynecologic disorders and while incontinence was a frequent complaint, joint hypermobility was not correlated with pelvic floor prolapse [3, 4]. Weaker collagen cross linking [5], reduced overall collagen production [6, 7] and changes in the ratios of collagen types [8] have all been studied in relation to stress incontinence or prolapse and suggest an etiologic role for reduced overall fascial strength as a predisposing factor for stress incontinence and prolapse.

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Collagen and fibrillin are essential components of connective tissue. Marfan syndrome is an autosomal dominant hereditary condition which results from mutations in the FBN1 gene which encodes fibrillin-1 on chromosome 15q21.1. Fibrillin-1 is an extracellular matrix component found in non-collagenous microfibrils in virtually every tissue. Microfibrils contribute to the formation of elastic fibers as well as serving an anchoring function in non-elastic tissue.

Marfan syndrome was first described more than 100 years ago [9] and remains a clinical diagnosis which can be confirmed by demonstrating a mutation in the FBN1 gene. Two of the three main systems (ocular, cardiovascular, skeletal) must be affected to make the diagnosis [10]. If a first degree relative is classically affected, involvement of one system is sufficient to make the diagnosis. Marfan syndrome affects approximately 1 in 5000 population world-wide and 25 % of cases are a result of a new mutation [11]. There are many overlapping syndromes affecting these systems which are related to defects in specific domains of the fibrillin gene or other mutations affecting microfibrils.

Medline literature search for Marfan syndrome, fibrillin, prolapse and incontinence did not reveal any studies of these urogynecological disorders in women with Marfan syndrome despite the frequent mention of connective tissue disorders as etiologic features of pelvic organ prolapse and stress incontinence. One study on pelvic organ prolapse in women less than 35 years of age found an increased number of women with neurological, autoimmune and congenital diseases but included no cases of Marfan syndrome or Ehlers-Danlos syndrome. The association of medical diseases with prolapse may also have been related to the treatment of these disorders (e.g. corticosteroids) or to the university hospital setting predisposing to an increased number of referrals of young women with underlying medical conditions [12].

A postal survey was undertaken with 240 questionnaires sent to addresses obtained from the Marfan Association in the United Kingdom. Surveys were sent to both men and women and asked questions eliciting presence of diseases involving the renal, urinary and reproductive systems (unpublished data, Anne Child). Responses were received from 42 females who had a mean age of 41 years (range 14–63). Eleven women were age 50 years or above. There were 14 positive responses to the question regarding stress incontinence. This corresponds to a 33 % crude prevalence rate of stress incontinence in this group. Due to the embarrassing nature of urinary incontinence, we suspect the prevalence rate of the postal survey to be an underestimate of the true rate of incontinence.

An observational study by Jabs showed a prevalence of pelvic organ prolapse and stress incontinence in a population of women with Marfan syndrome. The association between pelvic organ prolapse, stress incontinence and joint hypermobility in women with Marfan syndrome was also studied and found not to be correlated.

The study involved recruitment of female subjects from the clinical genetics practice of Anne Child. Female patients, 18 years of age or older, who could be contacted were invited to participate. Seventy-five names of adult female patients with Marfan syndrome were obtained from the records of Dr. Child. Four patients were deceased and 12 patients were unable to be contacted by any means leaving 59 patients available for recruitment. Of the 25 women who agreed to participate,

Table 20.1 Effect of parity

	Nulliparous	Parous
Stress/mixed incontinence (18)	7	11
Prolapse (9)	3	6
Total study group (25)	10	15

14 patients underwent interview, questionnaire and examination. An additional 11 were interviewed by telephone and completed the questionnaire. Information collected included: age, obstetrical history, gynecological history, medical complications associated with Marfan syndrome, medical conditions unrelated to Marfan syndrome, and medications. Symptoms of urinary incontinence, pelvic organ prolapse and bowel dysfunction were elicited. A standardized urinary symptom questionnaire was used to document bladder function, type of incontinence and effects on quality of life [13]. Physical examination determined joint hypermobility using the method described by Beighton [14] which allocates a score of 0–9 with a score of 4 or more indicating hypermobility. Pelvic examination was carried out with pelvic organ prolapse staging recorded according to the International Continence Society guidelines in the left lateral position at maximum Valsalva maneuver.

Of the 25 women with Marfan syndrome recruited to the study, the mean age was 43 years (range 22–59 years). Ten women were postmenopausal of whom eight were using hormone replacement therapy. Ten women were nulliparous. Four women had undergone abdominal hysterectomy, 1 had undergone vaginal hysterectomy. A history of urinary incontinence was elicited in 22/25 (88 %) of patients, of whom 13/25 (52 %) considered the problem significant. Five had undergone surgical treatment for stress incontinence and 1 had medical treatment of urge incontinence. Of the women with a history of incontinence, 18/25 (72 %) had a history of stress incontinence (pure or mixed) and 10/25 (40 %) felt that stress incontinence interfered with their life. Twenty-four percent of women had undergone treatment for stress incontinence. Women with stress incontinence were older than women without stress incontinence (47.6 vs. 31 years, $p=0.004$). Seven of the 18 women with stress incontinence were nulliparous (Table 20.1). Parity was not associated with stress incontinence in this population.

Nine women had Stage II prolapse on examination, one patient had undergone Manchester repair on history and one additional patient had symptomatic prolapse but was not available for examination and had not undergone treatment therefore 11/25 (44 %) of the total group had history or evidence of prolapse. Six women (24 %) had undergone surgical treatment of prolapse. The average age of women with prolapse on examination was similar to women without prolapse (47.2 vs. 42.6 years, $p=0.3$). Nine (64 %) of the women examined had Stage II prolapse (descent to –1, 0 or +1 cm from the hymenal ring). Seven women had anterior wall prolapse, all of whom had stress incontinence and two were symptomatic with a genital bulging sensation. Three had Stage II posterior wall descent, two of which complained of incomplete evacuation and the third had fecal soiling. Three of the 9 women with prolapse were nulliparous and parity was not associated with the finding of prolapse (Table 20.1).

Table 20.2 Examination – hypermobility and prolapse

N = 14	Prolapse	No prolapse
Hypermobility	5	3
No hypermobility	4	2

Three of the 6 women with Stage II anterior descent (cystocele/cystourethrocele) had undergone previous anterior repair for prolapse or stress incontinence and now had recurrent prolapse. One of the 2 women with Stage II posterior wall descent (rectocele) had previously undergone a vaginal prolapse repair. The patient with anterior and posterior prolapse had previously undergone anterior and posterior repair. Of note is that of the 5 women with previous surgical repair of prolapse, all now had findings of recurrent Stage II prolapse.

Eight of the 14 women examined had evidence of joint hypermobility with a score of 4 or more out of 9. Of the 9 women with Stage II prolapse, 5 occurred in the hypermobile group and 4 occurred in the group without hypermobility (Table 20.2). Eleven of the 14 women examined complained of stress incontinence of whom 6 were in the hypermobile group while 5 were not. Prolapse and stress incontinence were not significantly associated with hypermobility.

The etiology of pelvic organ prolapse and stress incontinence is not yet fully understood. Individual variation has a significant impact as patients presumed to be at high risk are commonly seen with no stress incontinence and no evidence of prolapse, while nulliparous women at low risk are sometimes found to have these conditions. This is presumed to be due to variation in pelvic floor muscle and connective tissue. Marfan syndrome affects strength and elasticity of connective tissue. An abstract by Carley and Schaffer at the American Urogynecologic Society Meeting 1998 presented interview data on 12 women with Marfan syndrome and found a rate of urinary incontinence of 42 % and pelvic organ prolapse of 33 %. There is no other published article defining the incidence of these disorders in women with Marfan syndrome.

The prevalence of incontinence in women in the general population is not easily ascertained as the methodologic problems in epidemiologic studies include the sample population chosen, the definition of stress incontinence used and the underreporting of embarrassing conditions. There is also variation between studies which estimate the prevalence of "any incontinence" versus "severe incontinence." This has led to a wide range of estimates for incontinence in the literature from 5 to 51 % [15]. A prevalence of approximately 30 % may be a clinically useful figure with approximately 5 % considered to have "severe" incontinence. In females, stress incontinence accounts for nearly 50 % of symptomatic women with approximately 30 % complaining of mixed symptoms and 20 % complaining of isolated urge incontinence [16]. In the study by Jabs, 88 % of women with Marfan syndrome had experienced urinary incontinence, 72 % had experienced episodes of stress incontinence, 52 % considered stress incontinence a problem and 24 % had undergone previous treatment for stress incontinence. These rates are considerably higher than those quoted for the general population despite the wide range of prevalence found in the literature.

The prevalence of pelvic organ prolapse in the general population is even less well defined than that of urinary incontinence. One study estimates the lifetime risk

of a woman undergoing at least one operation for treatment for prolapse and stress incontinence to be 11.1 % [17]. A study of the prevalence of prolapse in women 20–59 years of age found a prevalence of 30.8 % for any degree of prolapse and 2 % of prolapse that reached the introitus [18]. Age, parity, pelvic floor muscle strength and maximum birth weight were independently associated with prolapse [18]. In one population with Marfan syndrome, 24 % had undergone surgical treatment for prolapse. Of the 14 women examined, 9 (64 %) had Stage II pelvic organ prolapse of whom 5 were recurrent and 3 occurred in nulliparous women.

The high risk of recurrence following operation for prolapse repair in the Marfan population is discouraging. Patients need to be counseled that their risk of recurrence is higher than the general population. Consideration should be given to a trial of conservative therapy for prolapse such vaginal pessary. Anterior repair was used to correct prolapse and stress incontinence in 4 women in this study group. Anterior repair has been shown to be a less effective treatment for stress incontinence in the general population [19, 20] and it should also be avoided in this population with high risk of recurrence. A colposuspension using the strong attachment point of the iliopectineal ligament and permanent suture or a vaginal tape may prove more successful for treatment of stress incontinence.

It appears that there is a higher prevalence of pelvic organ prolapse and stress incontinence in women affected by Marfan syndrome. This agrees with the assumed association of connective tissue disease and these conditions. As prolapse and stress incontinence are multifactorial in origin, it is difficult to determine what, if any, preventive techniques are effective for this high-risk group. Certainly these patients should be counseled to minimize additional theoretical risk factors for these conditions such as constipation, straining at stool, chronic cough, heavy lifting and increased body weight. Pelvic floor exercises with or without the assistance of a physiotherapist, are risk-free and should be encouraged. Elective cesarean delivery cannot be recommended as prophylaxis against prolapse since these patients are at higher surgical risk and prolapse has also been shown to occur in nulliparous women.

Patients with Marfan syndrome are known to have delayed wound healing due to abnormal fibrillin production. The vasculature of Marfan syndrome patients is also fragile which can lead to increased blood loss and hematoma formation [21]. They should be considered at higher risk for incisional hernia and dehiscence. Meticulous surgical technique is required with attention to hemostasis and consideration should be given to using suture material with prolonged delayed absorption (Maxon or PDS) or non-absorbable suture where possible. Suture and staple removal should also be delayed compared with patients with normal wound healing. Antibiotic prophylaxis is required for bacterial endocarditis prevention.

The care of Marfan syndrome patients may be co-ordinated through their family physician but often they are seen more regularly by specialists for complications of Marfan syndrome.

Specialists such as cardiologists, geneticists, ophthalmologists or orthopedic surgeons may be involved depending on the individual patient's health status. Effective treatment for cardiovascular complications of Marfan syndrome has increased the life expectancy for these patients [22]. As a result, Marfan syndrome patients will

more commonly experience diseases that increase in prevalence with age, such as incontinence and pelvic organ prolapse. Physicians caring for these patients should be aware of the diverse manifestations of this disease and request input from a gynecologist or urogynecologist when appropriate.

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