

Unexpected Significant Uterine Pathological Findings at Vaginal Hysterectomy Despite Unremarkable Preoperative Workup

Yossi Mizrahi MD, Samer Tannus MD, Jacob Bar MD, Ron Sagiv MD, Tally Levy MD, Alexander Condrea MD and Shimon Ginath MD

Department of Obstetrics and Gynecology, Wolfson Medical Center, Holon, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Several studies have addressed the issue of undetected uterine pathology in women undergoing hysterectomy for pelvic organ prolapse (POP). However, these studies differ largely with respect to the incidence of malignancy found, study population, and preoperative evaluation.

Objectives: To assess the risk of unexpected pre-malignant and malignant uterine pathological findings after vaginal hysterectomy for POP repair, in a single medical center in Israel.

Methods: A retrospective study was performed of all patients who underwent vaginal hysterectomy due to symptomatic POP between January 1990 and April 2015 in a single tertiary medical center. Selected clinical and pathological data were retrieved from the computerized medical records. All specimens were routinely sent for histopathological assessment. All women were managed according to a uniform protocol that required the presence of a preoperative normal Pap smear, and included preoperative transvaginal sonography and endometrial biopsy when indicated. Patients in whom premalignant or malignant lesions were found preoperatively were not included in the study.

Results: The study comprised 667 patients. The overall rate of malignant or significant premalignant pathologies (6 cases) was 0.89%, including one (0.14%) case of endometrial carcinoma. All premalignant and malignant pathologies were found only in post-menopausal patients. The rate of significant endometrial pathological lesions found in asymptomatic post-menopausal women was only 0.35%.

Conclusions: The rate of preoperatively undetected abnormal histopathological findings in patients who undergo vaginal hysterectomy due to POP is very low, and therefore more extensive preoperative evaluation is not warranted in them.

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shown to achieve comparable success rates and was associated with shorter operative time, less blood loss, quicker recovery, and fewer urinary symptoms [2-7]. As a consequence, the number of hysterectomies for POP in the United States declined by 39.4%, from 122,495 in 2002 to 74,230 in 2010 [8]. However, one argument of those who are reluctant to preserve the uterus in POP surgery is the risk of missing an undetected malignancy.

Several previous studies have addressed the issue of undetected uterine pathology in women undergoing hysterectomy for POP. The incidence of malignancy in these women ranged from 0 to 0.8% [9-16]. However, these studies differ largely with respect to inclusion and exclusion criteria and preoperative evaluation. Therefore, the aim of this study was to assess the risk of incidental premalignant and malignant uterine pathology at the time of vaginal hysterectomy for POP, following a strict preoperative evaluation protocol.

PATIENTS AND METHODS

We performed a retrospective cohort study of all patients who underwent vaginal hysterectomy due to symptomatic POP in a single tertiary medical center in Israel between January 1990 and April 2015. Cases were identified using the *International Classification of Disease, Ninth Revision (ICD9)* codes [17]. Data regarding demographic characteristics, medical history, symptoms, preoperative evaluation, intraoperative findings, and pathology findings were retrieved from the computerized medical records. All specimens were routinely sent for histopathological assessment. The study was approved by the local institutional review board.

According to our local protocol, all pre-menopausal women with abnormal uterine bleeding (AUB), defined as intermenstrual bleeding or menorrhagia, underwent endometrial biopsy prior to surgery. All menopausal women underwent preoperative transvaginal sonography (TVS). Endometrial biopsy was performed pre-operatively in all menopausal women with a history of post-menopausal bleeding (PMB) or if endometrium thickness was more than 5 mm on TVS. Endometrial biopsy was performed using the Pipelle® endometrial sampling device (Cooper Surgical, CT, USA). In addition, women were required to present a normal Pap smear test performed within 1 year of

Pelvic organ prolapse (POP) is a common health problem with significant negative effects on women's quality of life. The lifetime risk of surgery for POP in the general female population is 19% [1]. Recently, there has been great interest in uterine-sparing procedures for POP. Uterine preservation was

surgery. Cases with preoperative diagnosis of malignant or pre-malignant pathology were excluded from this study. This restriction included cases of endometrial carcinoma or endometrial hyperplasia with or without atypia as well as cervical dysplasia or carcinoma.

The primary outcome was the incidence of undetected malignancy or significant pre-malignant pathology, defined as endometrial hyperplasia with atypia, endometrial carcinoma, cervical intraepithelial neoplasia (CIN) grade 2–3, or cervical carcinoma.

Data were analyzed using SPSS software, version 23 (IBM Corp, Armonk, NY, USA). The incidence of the various pathological findings was compared using the chi square test. A *P*-value of < 0.05 was considered statistically significant.

RESULTS

A total of 667 patients underwent vaginal hysterectomy for POP with no known malignant or pre-malignant pathology preoperatively, and were included in the study. Mean age was 65.4 ± 10.2 years (range 35–90), and median number of vaginal deliveries was 3 (interquartile range 2–3). Overall, 179 patients (26.8%) had stage I to II uterine prolapse and the remaining 488 (73.2%) had stage III to IV, according to the POP-Q system [18]. Fifty-nine patients (8.9%) were pre-menopausal, with a mean age of 47.0 ± 4.8. Among them, 16 (27.1%) had a history of AUB and 608 (91.1%) were menopausal, with a mean age of 67.2 ± 8.7. Among them, 17 (2.8%) patients used hormonal replacement therapy, and 41 (6.7%) had a history of PMB.

Table 1 describes the operative procedures performed. Table 2 describes the histopathology findings of the patients. Table 3 describes the incidence of premalignant and malignant endometrial pathologies among menopausal patients, with and without PMB. None of the pre-menopausal women had pre-malignant or malignant pathology, including 16 patients who underwent endometrial biopsy due to AUB. The difference

Table 1. Additional procedures performed at the time of vaginal hysterectomy for pelvic organ prolapse repair

Procedures	n (%)
Colporrhaphy	637 (95.5%)
Anterior	246 (36.8%)
Posterior	33 (4.9%)
Anterior and posterior	358 (53.6%)
Vaginal vault suspension	22 (3.2%)
Sacrospinous fixation	9 (1.3%)
Sacrocolpopexy	13 (1.9%)
Procedures for incontinence	221 (33.1%)
Midurethral sling	180 (27.0%)
Raz bladder neck suspension	41 (6.1%)
Bilateral salpingo-oophorectomy	73 (10.9%)

between the incidence of pre-malignant and malignant pathological findings between pre-menopausal and menopausal patients did not reach statistical significance.

There was one case of malignancy. This was a stage 1A, grade 1 endometrial carcinoma, found in a 65 year old woman with no history of hormonal replacement therapy. Preoperative TVS demonstrated an endometrial thickness of 3 mm. She did not undergo endometrial biopsy since she had no history of PMB and endometrial thickness on TVS was less than 5 mm. She underwent vaginal hysterectomy, bilateral salpingo-oophorectomy (BSO), and anterior and posterior colporrhaphy. No further treatment was required. She is now 84 years old with no recurrence of the disease.

The overall incidence of malignant or significant pre-malignant pathologies (6 cases) was therefore 0.89%. Since none of these cases was found in the pre-menopausal group, the incidence of malignant or significant pre-malignant pathologies in the post-menopausal group was 0.98%. Significant endometrial pathology occurred in asymptomatic post-menopausal women at a rate of 0.35% (Table 3).

DISCUSSION

In this 25-year cohort study, we assessed the incidence of undetected uterine pathology in women undergoing vaginal hyster-

Table 2. Unexpected premalignant and malignant pathological findings in women undergoing vaginal hysterectomy for pelvic organ prolapse

Pathology	Menopausal patients* (N=608)
Endometrium, n (%)	
Simple hyperplasia without atypia	9 (1.4%)
Simple hyperplasia with atypia	1 (0.1%)
Complex hyperplasia without atypia	0
Complex hyperplasia with atypia	1 (0.1%)
Endometrial carcinoma	1 (0.1%)
Cervix, n (%)	
Cervical or endocervical polyp	10 (1.6%)
CIN2	2 (0.3%)
CIN3	1 (0.1%)
Cervical carcinoma	0

CIN = cervical intraepithelial neoplasia

*Among the 59 pre-menopausal women there were no cases of malignant or premalignant pathological findings

Table 3. Pre-malignant and malignant endometrial pathological findings in post-menopausal women undergoing vaginal hysterectomy for pelvic organ prolapse

	No PMB N=567	PMB N=41
Simple hyperplasia without atypia	8	1
Simple hyperplasia with atypia	1	0
Complex hyperplasia with atypia	0	1
Endometrial carcinoma	1	0
Significant endometrial pathology	2 (0.35%)	1 (2.4%)

PMB = post-menopausal bleeding

ectomy for pelvic organ prolapse. No significant pathologies were found in pre-menopausal women. An incidence of almost one percent (0.98%) was found among menopausal women, despite normal preoperative evaluation. All menopausal women had a preoperative TVS examination and a subsequent endometrial biopsy if endometrial thickness was more than 5 mm on TVS, or if the patient had a history of PMB. Interestingly, among menopausal women with no PMB, 9 had endometrial hyperplasia and one had endometrial carcinoma undiagnosed by preoperative TVS. This result can be explained by the fact that endometrial thickness was shown to be a poor screening tool for endometrial carcinoma and atypical endometrial hyperplasia in asymptomatic post-menopausal women [19]. Furthermore, three patients were found to have CIN grade 2–3, despite having a normal Pap smear within 1 year. This finding can be attributed to the low sensitivity of the Pap smear [20].

The risk of missing an undetected uterine pathology in women undergoing hysterectomy for POP repair was assessed in several previous studies [9-16]. However, non-uniformity in study design and different preoperative evaluation protocols make it difficult to draw conclusions. Three large well-designed studies reported the exact preoperative evaluation and pathology findings [9,10,14]. Preoperative endometrial biopsy was performed in all patients with abnormal or post-menopausal bleeding in these studies. Their results, along with ours, are summarized in Table 4. Frick and colleagues [9] found that the total incidence of significant premalignant and malignant pathologies was slightly higher. This result can be explained by different preoperative evaluations. In that study, preoperative TVS was not performed. When combining the results of these four studies together, the overall incidence of malignancy was 0.37%, and the incidence of significant premalignant pathologies was 0.6%. Given these findings, 267 hysterectomies would be required to detect one case of existing malignancy, whereas 103 hysterectomies would be required to detect one case of existing malignancy or significant premalignant pathology. Of

note, Ramm et al. [14] did not report cervical pathologies. Thus, the incidence of significant pathologies may be a little higher.

Most studies, including ours, did not demonstrate any cases of malignancy in pre-menopausal women [9,11,13,14,16]. Although differences in the rates of malignancy in our department did not reach statistical significance, there is a trend toward fewer pathological findings in pre-menopausal patients. It can be concluded that the risk of missing a concurrent malignancy in pre-menopausal women undergoing a uterine-sparing procedure is minimal. In post-menopausal patients with negative strict preoperative evaluation, a risk for significant uterine pathology exists, but is very low. Clinicians should also take into consideration, when performing a uterine-sparing procedure, that endometrial carcinoma is characterized by early diagnosis and good prognosis.

The most frequent endometrial pathology found in post-menopausal patients without uterine bleeding was simple endometrial hyperplasia without atypia (1.5%), a condition that does not usually require further treatment [21]. The risk of endometrial carcinoma was 0.37%. This risk is similar to the risk of incidental uterine sarcoma in women undergoing hysterectomy or myomectomy for the treatment of fibroids as reported by the U.S. Food and Drug Administration [22]. In view of the low rate of malignancy, we conclude that more extended preoperative evaluation in such patients is not mandatory. In women presenting with post-menopausal bleeding and negative endometrial evaluation the risk of change in the final post-operative diagnosis to pre-malignant or malignant condition is minimal. Thus, proper evaluation of the endometrium prior to surgery for POP can minimize incidental findings of significant uterine pathology in such cases.

Several study limitations must be acknowledged: its retrospective single-center design and the long study period during which the incidence of endometrial carcinoma might have changed. Moreover, changes in medical management and pathology workup might have occurred over the years. Nevertheless, our preoperative evaluation protocol did not change during the study period.

Table 4. Significant premalignant and malignant uterine findings after hysterectomy for pelvic organ prolapse – summary of previous studies

Study	n	Significant premalignant pathological findings ^a	Malignant pathological findings	Total
Frick et al. [9] (2010)	644	7	2	9 (1.39%)
Ramm et al. [14] (2012) ^b	708	2	5	7 (0.98%)
Wan et al. [10] (2013)	640	2	2 ^c	4 (0.62%)
Mizrachi et al. (present study)	677	5	1	6 (0.88%)
Total	2669	16 (0.6%)	10 (0.37%)	26 (0.97%)

^aSignificant premalignant pathological findings were defined as either atypical endometrial hyperplasia or cervical intraepithelial neoplasia grade 2–3

^bCervical pathological findings were not reported

^cOne case of endometrial carcinoma was omitted since preoperative endometrial biopsy showed complex hyperplasia with atypia

CONCLUSIONS

In conclusion, pre-menopausal women with normal bleeding patterns or with negative endometrial evaluation for AUB are at minimal risk for incidental significant uterine pathology at the time of pelvic reconstructive surgery. In post-menopausal patients with or without bleeding, the risk of significant uterine pathology is low, with a negative endometrial evaluation. This information should be taken into consideration in decision making and patient counselling.

Correspondence

Dr. Y. Mizrachi

Dept. of Obstetrics & Gynecology, Wolfson Medical Center, PO Box 5, Holon 58100, Israel, **Phone:** (972-3) 502-8329, **Fax:** (972-3) 502-8503 **email:** mizrachi.yossi@gmail.com

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Capsule

Disease management in the treatment of patients with chronic heart failure who have universal access to healthcare: a randomized controlled trial

The efficacy of disease management programs in improving the outcome of heart failure patients remains uncertain and may vary across health systems. Katler-Laibovici et al. explored whether a countrywide disease management program is superior to usual care in reducing adverse health outcomes and improving well-being among community-dwelling adult patients with moderate-to-severe chronic heart failure who have universal access to advanced healthcare services and technologies. In this multicenter open-label trial, 1360 patients recruited after hospitalization for heart failure exacerbation (38%) or from the community (62%) were randomly assigned to either disease management or usual care. Disease management, delivered by multi-disciplinary teams, included coordination of care, patient education, monitoring disease symptoms and patient adherence to medication regimen, titration of drug therapy, and home tele-

monitoring of body weight, blood pressure and heart rate. Patients assigned to usual care were treated by primary care practitioners and consultant cardiologists. During the follow-up, 388 patients (56.9%) assigned to disease management and 387 (57.1%) assigned to usual care had a primary endpoint event. The median (range) time elapsed until the primary endpoint event or end of study was 2.0 (0–5.0) years among patients assigned to disease management, and 1.8 (0–5.0) years among patients assigned to usual care (adjusted hazard ratio, 0.908; 95% confidence interval, 0.788–1.047). Hospital admissions were mostly (70%) unrelated to heart failure. Patients assigned to disease management had a better health-related quality of life and a lower depression score during follow-up.

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Eitan Israeli

“The presence of those seeking the truth is infinitely to be preferred to the presence of those who think they’ve found it”

Sir Terence David John Pratchett, (1948–2015), better known as Terry Pratchett, English author of fantasy novels, especially comical works