Epidemiology and Etiology of Pelvic Organ Prolapse

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Learning Objectives

- This chapter aims to provide to the reader the actual knowledge on epidemiological data based on different classification systems, different definitions, and the concomitance of symptoms related to POP with or without functional disorders.
- This chapter also illustrates the evidence of risk factors and pathophysiological mechanisms based on the most recent literature, making the reader aware regarding all the multifactorial elements related to POP.

45.1 Definition and Classification

Prolapse (Latin: Prolapsus—"a slipping forth") refers to a falling, slipping, or downward displacement of a part or organ. Pelvic organ refers most commonly to the uterus and/or the different vaginal compartments and their neighboring organs such as bladder, rectum, or bowel. Different sites of female genital prolapse are described according to the organ involved. The anterior compartment prolapse is characterized by herniation of anterior vaginal wall often associated with descent of the bladder (also called cystocele). Hernia of the posterior vaginal segment, or posterior compartment prolapse, is often associated with descent of the rectum (or rectocele). Apical compartment prolapse (uterine prolapse, vaginal vault prolapse) is characterized by the descent of the apex of the vagina into the lower vagina, to the hymen, or beyond the vaginal introitus. The apex can be either the uterus and cervix, cervix alone, or vaginal vault, depending upon whether the woman has undergone hysterectomy. Apical prolapse is often associated with enterocele, the herniation of the intestines to or through the vaginal wall. The uterine procidentia is instead, the herniation of all three compartments through the vaginal introitus. Division of the vagina into separate compartments is somewhat arbitrary, because the vagina is a continuous organ, and prolapse of one compartment is often associated with prolapse of another [1]. About 50% of parous women are affected. Prolapse of pelvic organ (POPs) can cause pelvic, urinary, bowel, and sexual symptoms [2].

A system of three integrated levels of vaginal support has been described by DeLancey [3]. All levels of vaginal support are connected through a continuous endopelvic fascia support network:

- *Level 1*—Uterosacral/cardinal ligament complex, which suspends the uterus and upper vagina to the sacrum and lateral pelvic side wall. Level 1 support represents vertical fibers of the paracolpium that are a continuation of the uterosacral/cardinal ligament complex which inserts variably into the cervix and vagina. Loss of level 1 support contributes to the prolapse of the uterus and/or vaginal apex.
- *Level 2*—Paravaginal attachments along the length of the vagina to the superior fascia of the levator ani muscle and the arcus tendineus fascia pelvis (also referred to as the "white line"). Loss of level 2 support contributes to anterior vaginal wall prolapse (cystocele).

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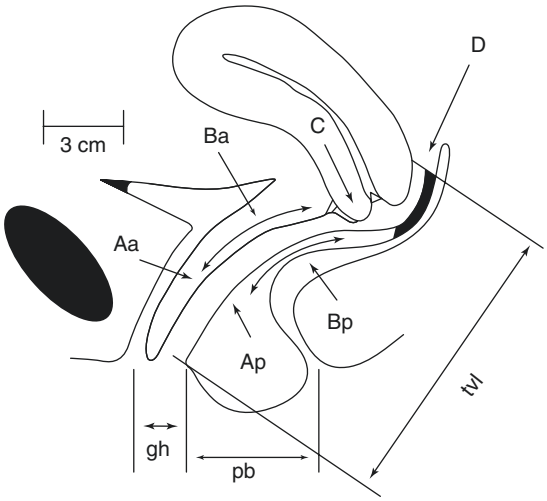
– *Level 3*—Perineal body, perineal membrane, and superficial and deep perineal muscles, which support the distal one third of the vagina. Anteriorly, loss of level 3 support can result in urethral hypermobility. Posteriorly, loss of level 3 support can result in a distal rectocele or perineal descent [4, 5].

A second classification system was introduced in 1996, the Pelvic Organ Prolapse Quantification (POP-Q) system, and it has become the standard classification system [6]. The POP-Q system is the POP classification system of choice of the International Continence Society (ICS), the American Urogynecologic Society (AUGS), and the Society of Gynecologic Surgeons (SGS) [6]. The American College of Obstetricians and Gynecologists has also recommended its use [7]. It has proven interobserver and intraobserver reliability [8] and is the system used most commonly in the medical literature [9]. The POP-Q is an objective, site-specific system for describing and staging POP in women [10]. In the POP-Q system, the topography of the vagina is described using six points (two on the anterior vaginal wall, two on the superior vagina, and two on the posterior vaginal wall) and several other measurements [10]. Taken together, these measurements can be used to produce a sagittal diagram of the prolapse and a detailed description of vaginal anatomy. For the purposes of simple clinical communication or grouping patients for research purposes, an ordinal staging system using the POP-Q measurements was developed:

– *Stage 0*—No prolapse.
– *Stage I*—The requirements for stage 0 are not met, but the most distal portion of the prolapse is >1 cm distal to the level of the hymenal plane.
– *Stage II*—The most distal portion of the prolapse is between ≤1 cm proximal to the hymenal plane and ≥1 cm distal to the hymenal plane.
– *Stage III*—The most distal portion of the prolapse is between >1 cm distal to the hymenal plane, but no further than 2 cm less than the total vaginal length in. In other words, the maximum prolapse is more than 1 cm outside the hymenal plane, but it is 2 cm less than the maximum possible protrusion.
– *Stage IV*—Eversion of the total length of the vagina.



COMPARTMENT	POP-Q SITE	PROLAPSED ORGAN	VAGINAL WALL SITE
Anterior	Aa	Urethra (urethrocele)	Distal anterior vaginal wall
	Ab	Bladder (cystocele)	Proximal and distal anterior vaginal wall
Middle	C	Cervix	Cervix
	D	Small bowel (enterocele)	Uterosacral scar
Posterior	Ap	Small bowel (enterocele)	Proximal posterior vaginal wall
	Bp	Rectum (rectocele)	Proximal and distal posterior vaginal wall
		Perineal body	Perineal body

A simplified version of the POP-Q system, which was developed by an international group of investigators, has been proposed [11, 12]. Like the standard POP-Q examination, the Simple POPQ (S-POPQ) measures the anterior, posterior, and up to two measurements of the apex, including both the cervix and posterior cul-de-sac. The S-POPQ records the ordinal stage of the four measurements by estimating the distances involved.

While not recommended by leading societies, the Baden-Walker Halfway Scoring System is another commonly used POP staging system. The degree, or grade, of each prolapsed structure is described individually (e.g., grade 1 anterior vaginal wall prolapse or grade 3 uterine prolapse). The grade/degree is defined as the extent of prolapse for each structure noted on examination while the patient is strain-

ing. Because there are no clear demarcations among the cut-off stages, the Baden-Walker system lacks the precision and reproducibility of the POP-Q system. The system has five degrees/grades [13].

45.2 Prevalence and Incidence

Pelvic organ prolapse is one of the most frequent disorders connected with age that makes women visit their gynecologist. The worldwide prevalence of POP has recently been reported to be around 9% [14]. If the diagnosis is based on clinical evaluation, the prevalence ranges from 41% to 56% as compared to 3–7% when the diagnosis is based on symptoms or complaints from women [15, 16]. In a study done in the United States, the prevalence of POP was lower in African American women 1.9% as compared to Caucasian women 2.8% and Hispanic women 5.1% [17]. The difference in prevalence of POP between Africans residing in the United States and those living in Africa could be explained by a comparatively higher number of deliveries, difficult access to skilled delivery attendance, and heavier physical workload among African living in sub-Saharan Africa. In the United States, this problem may affect even 24% of the women's population, whereby the percentage depends mainly on age. Among women between 20 and 39 years of age, it concerns 10% of the population, whereas it involves up to 50% of women in their 80s [18]. With regard to the aging process of the society, this problem will involve a higher rate of the total women's population. One estimates that in 2050 it will concern over 30% of women over 20 years old [19]. In the United States, the incidence of women submitted to surgical procedures connected with one of the types of prolapse is 11.8%, which constitutes the most common indication for surgical procedure. There are approximately 300,000 POP surgeries each year in the United States [20, 21]. In developed countries, approximately 20% of surgical procedures among women are carried out due to pelvic organ prolapse [22–24]. It is also worth mentioning that the problem is probably more frequent, because only 10% of the population struggling with pelvic organ prolapse in their everyday life seeks help from a gynecologist and the majority never ask for it [25]. Population-based studies report an 11–19% lifetime risk in women undergoing surgery for prolapse or incontinence [26, 27].

The exact prevalence of POP is difficult to ascertain, for several reasons: (1) different classification systems have been used for diagnosis; (2) studies vary by whether the rate of prolapse reported is for women who are symptomatic or asymptomatic; and (3) it is unknown how many women with POP do not seek medical attention. The distinction between symptomatic and asymptomatic POP is clinically relevant, since treatment is generally indicated only for women with symptoms. However, there are few high-quality data regarding the prevalence of symptomatic POP.

Rates of asymptomatic POP are probably even higher. Several studies have used clinical examination to assess the prevalence of POP in a community-based setting. One study included 497 women who were seen in an outpatient clinic for routine gynecologic care and were assessed using the Pelvic Organ Prolapse Quantification (POP-Q) system. The overall distribution of POP-Q system stages was as follows: stage 0, 6.4%; stage 1, 43.3%; stage 2, 47.7%; and stage 3, 2.6%. No subjects examined had POP-Q system stage 4 prolapse. The distribution of the POP-Q system stages in the population revealed a bell-shaped curve, with most subjects having stage 1 or 2 support. Few subjects had either stage 0 (excellent support) or stage 3 (moderate to severe pelvic support defects) [28].

If we analyze a Sliwa et al. work, we found that the most frequent pelvic disorder reported in their group of patients was the defect connected with both cystocele and rectocele. This may lead to the conclusion that cystocele is the most common type of dysfunction throughout the whole group of women with pelvic organ disorders [24]. Similar results were obtained by Hendrix et al. on a large group where the most frequently observed disorder was also cystocele [29].

45.3 Risk Factors and Pathophysiological Mechanisms

45.3.1 Ethnicity

Several studies showed that Hispanic and European women seem to have a higher risk of developing POP compared to Asian or African women [30–34]. In Zacharin's cadaveric study, pubourethral ligaments, endopelvic fascia, and endopelvic attachment to the obturator fascia were reported to be stronger and thicker in Chinese compared to Caucasian women [35]. A significantly less pelvic organ mobility in Asian women was shown also by Dietz et al. using perineal ultrasound [34]. The reasons for these ethnic discrepancies are still unclear.

45.3.2 Familiarity and Other Genetic Risk Factors

It is generally recognized that POP has an inheritable predisposition. In a case-control study, Chiaffarino et al. showed

that the risk of urogenital prolapse was higher in women with mother or sister reporting this condition: the odds ratios (ORs) were 3.2 (95% CI 1.1–7.6) and 2.4 (95% CI 1.0–5.6), respectively, in comparison with women whose mother or sisters reported no prolapse [36]. The reason why some females with little to no risk factors develop POP while other females with multiple risk factors do not is clearly that some women have a genetic predisposition to prolapse. Analyzing young women with stage III and IV POP, Jack et al. showed that the risk of prolapse among their siblings was five times higher than that of the risk for the general population [37]. The authors concluded that POP has a dominant pattern of inheritance with incomplete penetrance. Buchsbaum et al. found a high concordance in the POP stage between nulliparous women and their parous sisters, thus supporting the hypothesis of a familial basis for this condition [38]. Nevertheless, they highlighted the importance of vaginal delivery that appeared to confer a risk for more advanced prolapse.

Some genetic variants have been found in families with an increased incidence of POP. In the genome-wide association study conducted by Allen-Brady et al., results from association analysis identified five single-nucleotide polymorphisms significantly associated with POP [39]. More recently the same authors performed a genome-wide linkage analysis using a resource of high-risk POP pedigrees and results showed that loci on chromosomes 10q and 17q may predispose to POP development [40].

Further studies investigated the role of specific genetic polymorphisms in increasing the susceptibility to early onset of POP, such as polymorphism in the promoter of LAMC1 gene or of COL1A1 gene [41, 42]. Although results were encouraging, their clinical application cannot be recommended based on current evidence.

Women with genetic disorders of the connective tissue, such as Marfan or Ehlers-Danlos syndrome, have high rates of POP [43–47]. It is well-known that the vaginal wall is composed of connective tissue in its subepithelial layer and adventitia and also vaginal and uterine supportive tissues are mainly made of collagen and elastin. Therefore in these women, the connective tissue disorder may occur also in terms of pelvic organ descent.

Apart from these genetic diseases, numerous data show that women with POP have an abnormal pelvic extracellular matrix metabolism with an increased collagen turnover. Connective tissue remodeling throughout the body is controlled by matrix metalloproteinases (MMP), a family of calcium-dependent zinc-containing endopeptidases. An overexpression of MMP-1 and 2 has been observed in women with prolapse with a concurrent decrease in their inhibitor TIMPs [48, 49]. The consequences are an excessive tendency toward connective tissue degradation and a decrease in the amount of collagen in pelvic tissue that has been reported from women with POP.

45.3.3 Obstetric Factors

Pelvic floor tissue trauma that occurs during childbirth is universally considered the main risk factor for developing POP later in life [50–56]. Pregnancy itself has been widely accepted as a risk factor for pelvic floor dysfunction. This association is strongest for stress urinary incontinence (SUI), whereas for POP it has been less well established. In the study by O'Boyle et al., all 21 nulliparous nonpregnant women had a POP-Q stage 0–I, while out of 21 nulliparous pregnant women, 47.6% had a stage II POP ($p < 0.001$) with POP-Q stage increasing from the first to the third trimester [57].

As confirmed by several studies, a woman's parity is strongly associated with her risk of developing POP. The Women's Health Initiative showed that having one childbirth determined a twofold risk increase for prolapse compared to nulliparity, and each additional childbirth added a 10–20% risk increase [32]. Another case-control study found that in women with a parity of four, the risk for symptomatic POP was 3.3 times higher compared to those with a parity of one [53]. In a population-based study by Rortveit et al., authors found that the risk of prolapse progressively increased from one to three or more vaginal deliveries [31].

The potential protective effect of caesarean section still remains controversial. However, nowadays it has been well demonstrated that elective caesarean section has a protective role on the pelvic floor, and therefore it may decrease the risk of developing POP [36, 50–56, 58–60]. Comparing women who delivered by caesarean section only with vaginal deliveries only, the incidence rate for prolapse surgery was significantly lower in the first group, whereas in the vaginal delivery cohort, it progressively increased reaching its peak about three decades after first childbirth. This interesting result was shown in a register-based cohort study [59] in which authors included 33,167 women having all their pregnancies terminated by caesarean section and an age-matched sample of 63,229 women only having spontaneous births in the decade 1973–1983. Gyhagen et al. reported that the prevalence of POP was not significantly different comparing women who had undergone emergency or elective caesarean section [55].

Controversy remains with regard to the risk of developing POP related to specific obstetrical events and interventions. Several studies found that instrumental delivery significantly increase the risk of prolapse when compared with non-operative vaginal birth, with no differences between forceps and vacuum delivery [60, 61]. On the other hand, a case-control study observed no significant association between instrumental delivery, maternal age, length of delivery, and POP [53]. Similar results were found by Uma et al. with regard to forceps delivery, episiotomy, infant birthweight, and prolonged labor [52].

45.3.4 Age and Hormonal Status

It is well-known that both incidence and prevalence of POP increase with increasing age. Through a large cross-sectional study in menopausal clinics in Italy, members of Progetto Menopausa Italia Study Group showed that in comparison with women aged ≤51 years, the OR of uterine prolapse was 1.3 and 1.7, respectively, for women aged 52–55 and ≥56 years [62]. Similar findings came out from a cross-sectional analysis of American women enrolled in the Women's Health Initiative [32]. The lifetime risk of undergoing a single operation for prolapse or incontinence by age 80 is 11.1% according to Olsen et al. [63]. This surgery is uncommon in people younger than 30 years.

Although it would seem intuitive that the decrease of estrogen levels observed with menopause might predispose to POP, current evidence on this topic is controversial. Some studies support the role of estrogen in the development of pelvic floor disorders. In a cross-sectional study by Lara et al., postmenopausal women with POP were reported to have a lower expression of estrogen receptor α on the vaginal wall and a smaller number of vessels in the lamina propria of the vagina compared to premenopausal controls [64]. On the other hand, according to Trutnovsky et al. the pelvic organ support and levator ani function do not appear to be substantially influenced by hormone deficiency following menopause. The same applies for local or systemic hormone replacement therapy [65].

45.3.5 Socioeconomic Factors

A low socioeconomic status, intended as low educational level and yearly income, is a demographic factor associated with an increased risk of developing POP [66, 67]. Considering the 21,449 non-hysterectomized women around menopause analyzed by the Progetto Menopausa Italia Study Group, the OR of uterine prolapse was 0.8 (95% CI 0.7–0.9) and 0.8 (95% CI 0.6–0.9), respectively, for women with intermediate or high school/university degree compared to women with none/primary education [62].

In a review study on prevalence and risk factors for pelvic floor dysfunction in 16 developing countries, Walker et al. observed that the mean prevalence of POP was 19.7% (range 3.4–56.4%) but risk factors were similar to those in industrialized countries, particularly increased age and parity. In low-income countries additional risk factors for pelvic floor disorders were poor nutrition and heavy work [68].

Jobs involving heavy lifting have been reported to increase the risk for POP. In a multicenter cross-sectional study, Woodman et al. showed that the prevalence of severe POP was significantly higher among women who were laborers/factory workers compared to other job categories ($p < 0.001$). They also showed that an annual household income of Dollars 10,000 or less was associated with severe POP [67].

According to Chiaffarino et al., housewives had an OR of urogenital prolapse of 3.1 (95% CI 1.6–8.8) in comparison with professional/managerial women [36].

45.3.6 General Medical Conditions

Through a chronic increase of the pressure on the pelvic floor, obesity may be intuitively associated to global pelvic floor dysfunction and therefore to more severe prolapse [69, 70]. However, this association is not as strong for prolapse as for stress urinary incontinence [71, 72].

According to Swift et al., the OR for developing POP is 2.51 and 2.56 for overweight and obese women, respectively [30]. Similarly, women with a body mass index of more than 26 kg/m^2 are more likely (OR 3.0 95% CI 1.6–5.7) to undergo surgery for prolapse compared to those with a lower value [73].

Kudish et al. evaluated the relationship between change in weight and POP progression/regression in women during a 5-year period [74]. Analyzing 16,608 postmenopausal women with an intact uterus, aged 50–79 years, they observed that the risk of prolapse progression in overweight and obese women as compared with participants with healthy BMIs increased by 32% and 48% for cystocele, by 37% and 58% for rectocele, and by 43% and 69% for uterine prolapse, respectively. The authors also showed that weight loss does not appear to be significantly associated with regression of POP, suggesting that damage to the pelvic floor related to weight gain might be irreversible.

Although not convincingly, chronic obstructive pulmonary disease has been associated with the development of POP causing increased intra-abdominal pressure during chronic cough [75].

The same pathophysiological mechanism might be the basis of an increased risk for prolapse among patients with chronic constipation implying repetitive straining at stool. Spence-Jones et al. reported that the presence of this condition already in the youth was significantly more common in women who then developed uterovaginal prolapse (61% vs. 4%, $p < 0.001$) compared with controls [76]. At the time of consultation, 95% of the women with prolapse were constipated, compared with only 11% of control women. Many of these women also needed to digitate to achieve rectal evacuation.

In a recent study, Rogowski et al. showed that the diagnosis of metabolic syndrome and the presence of elevated triglycerides increased with the overall POP-Q stage and therefore they may be associated with the severity of POP in urogynecological patients [77].

45.3.7 Previous Pelvic Surgery

It is widely accepted that hysterectomy increases the risk for POP, as confirmed by several cross-sectional and retrospective studies. However, considering that prolapse symptoms generally develop many years after this procedure, studies with larger population samples and an adequate long-term follow-up would be required to determine a definite association.

The Oxford-Family Planning Association study on over 17,000 women reported that the incidence of prolapse which required surgical correction following hysterectomy was 3.6 per 1000 person-years of risk [78]. The cumulative risk rises from 1% 3 years after a hysterectomy to 5% 15 years after hysterectomy. The risk of prolapse following hysterectomy is 5.5 times higher (95% CI 3.1–9.7) in women whose initial hysterectomy was for genital prolapse as opposed to other reasons.

In a case-control study, Dällenbach et al. determined that among hysterectomies performed for prolapse, the risk of undergoing a second prolapse repair was particularly increased (8.0 times higher) if preoperative prolapse grade 2 or more was present. Other risk factors included previous POP or urinary incontinence surgery, history of vaginal delivery, and sexual activity [79].

According to Forsgren et al., having a vaginal hysterectomy for reasons other than POP also significantly increase the risk of POP and SUI surgery compared to other modes of hysterectomy [80].

Apart from hysterectomy, previous gynecological surgery in general or rectopexy for rectal prolapse or retropubic colposuspension procedure predisposes to a near 30% risk of subsequent vaginal vault and posterior vaginal prolapse at long-term follow-up [73, 81–83].

Take-Home Messages

POP is a common condition with a prevalence increasing with age but with a great range of reported data in relation to the anatomical finding with or without symptoms. Multiple risk factors and pathophysiological mechanism are involved in the development and/or progression of POP. Some are not preventable, such as ethnicity, familiar or genetic factors, and aging. The increasing awareness and knowledge of other factors such as obstetric, socioeconomic, or the ones related to some medical conditions might be minimized and being an interesting field for future research.

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