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# **PELVIC ORGAN PROLAPSE— ASPECTS OF ETIOLOGY, SYMPTOMATOLOGY AND OUTCOME AFTER SURGERY**

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*To Science  
and  
to Women's Health*



# ABSTRACT

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The objective of this thesis was to increase the understanding of symptoms related to pelvic support defects, to study the influence of non-obstetric risk factors for pelvic organ prolapse, to describe short-term natural history in women with symptomatic prolapse and to evaluate outcome after surgery.

In a cross-sectional survey investigation of the age-specific prevalence of prolapse in Stockholm 8,000 women, 30-79 years of age, were randomly selected from the Swedish Population Register. All women were mailed a validated 5-item questionnaire for identification of symptomatic prolapse and 454 (8.3%) women gave self-reports that were consistent with symptomatic prolapse.

Two hundred and six women, randomly selected among the 454 women whose self-reports were consistent with POP, and 206 randomly selected women among the 5035 whose questionnaire answers did not indicate presence of POP, were invited to a standardized gynaecological examination. Two hundred eighty women, 160/206 women classified as having symptomatic prolapse and 120/206 as not having symptomatic prolapse were examined according to POP-Q by two gynecologists blinded to symptom reports. Anatomical findings were correlated to symptom reports (*Paper I*). Pelvic floor related symptoms could not predict the anatomical location of the prolapse. The feeling of a vaginal bulge was significantly associated with prolapse but a non-compartment specific symptom, stress urinary incontinence had a stronger association with posterior wall prolapse and no convincingly associations between bowel symptoms and prolapse were observed.

To investigate possible risk factors for symptomatic prolapse (*Paper II*) a 72-item questionnaire was mailed to all 454 cases classified in the initial survey investigation as having symptomatic prolapse and 405 control subjects. All of the 280 women who had undergone gynecological examination were included. Age, parity and family history of prolapse were the dominating risk factors but significant independent associations were found with conditions suggestive of deficient connective tissues (varicose veins, hernia, hemorrhoids) and non-obstetric strain on the pelvic floor (overweight/obesity, heavy lifts, and constipation) implying that individual predisposition and lifestyle may also play an important role.

To study short term natural history of prolapse (*Paper III*), a cohort consisting of the 160 examined women whose scores had been indicative of symptomatic prolapse and the 120 examined control women were followed up after 5 years with the same 5-item questionnaire and invited for reexamination according to POP-Q. Most symptomatic women reported a reduction of the key symptom "vaginal bulging" (64%; 95%CI 56-72%). Among the control women symptomatic prolapse developed in 2%. For the re-examined women, (n=188) few had an anatomical progression, asymptomatic women fared worse than the women classified with symptomatic prolapse.

Finally, in a prospective study (*Paper IV*) of women who underwent vaginal reconstructive surgery for pelvic organ prolapse (n=185) during a 3-year period, anatomical and functional outcome was evaluated 1, 3 and 5 years postoperatively. Anatomical recurrences in operated compartment were 40.0% and prolapse in new compartment was 8.6%. Anterior compartment was most prone for recurrence. Urinary incontinence remained at the same level at one-year follow up. De novo urge occurred in 22.6% and de novo stress incontinence 6.0%. An improvement was seen in difficulty emptying bowel one year after surgery (54%). Patients were primarily cured from mechanical symptoms.

**Key words:** pelvic organ prolapse; risk factors; urinary incontinence; cross sectional study; pelvic reconstructive surgery; natural history of prolapse;



# LIST OF PUBLICATIONS

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This thesis is based upon the following papers, which will be referred to by their Roman numerals:

- I Miedel A, Tegerstedt G, Maehle-Schmidt M, Nyrén O, Hammarström M  
**Symptoms and Pelvic Support Defects in Specific Compartments**  
*Obstet Gynecol 2008;112; 853-8*
- II Miedel A, Tegerstedt G, Maehle-Schmidt M, Nyrén O, Hammarström M  
**Non-obstetric risk factors for symptomatic pelvic organ prolapse- a population-based cross-sectional study in Sweden**  
*Obstet Gynecol 2009, In press*
- III Miedel A, Ek M, Tegerstedt G, Maehle-Schmidt M, Nyrén O, Hammarström M  
**Short-term natural history in women with symptoms indicative of pelvic organ prolapse –a prospective study**  
*In manuscript*
- IV Miedel A, Tegerstedt G, Mörlin B, Hammarström M  
**A 5-year prospective follow-up study of vaginal surgery for pelvic organ prolapse**  
*Int Urogynecol J 2008; 19;1593-1601*





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# LIST OF ABBREVIATIONS

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POP	Pelvic Organ Prolapse
POP-Q	Pelvic Organ Prolapse Quantification
SUI	Stress Urinary Incontinence
UUI	Urge Urinary Incontinence
UI	Urinary Incontinence
OR	Odds Ratio
POR	Prevalence Odds ratio
CI	Confidence Interval
BMI	Body Mass Index
PFMT	Pelvic Floor Muscle Training
QOL	Quality of Life
SF 36	The 36-item Medical Outcomes Study Short-Form Health Survey
ICS	International Continence Society
NIH	National Institute of Health



# INTRODUCTION

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Pelvic organ prolapse (POP) is a poorly understood condition that affects millions of women worldwide. It is a disease with low morbidity and it affects primarily quality of life.

Despite the apparent prevalence and the fact that pelvic organ prolapse is one of the most common indications for gynecological surgery little information exists regarding epidemiology, risk factors and natural history<sup>1</sup>.

Research has been hampered by the lack of definition of pelvic organ prolapse. For most practitioners, pelvic organ prolapse is something they recognize when they see it and conversely recognize its absence, but they cannot define the point at which a patient goes from normal support to pelvic organ prolapse. A definition of pelvic organ prolapse should preferably not only include an anatomic description but also an evaluation of the symptoms associated with the prolapse. But how the degree of support relates to symptoms has not been well characterized or absolutely established<sup>2 3</sup>.

Women with prolapse may present with a variety of complaints such as bladder, bowel and sexual dysfunction. Given the poor understanding of symptoms related to pelvic organ prolapse it is frequently difficult to counsel patients regarding which of their symptoms will improve with treatment. Surgical outcomes have focused more on goals and outcomes identified by surgeons rather than on patients' expectations and satisfaction<sup>4</sup>

The current body of evidence points to direct and indirect pelvic floor trauma during childbirth and advancing age as major risk factors but the fact that the majority of parous women do not develop severe prolapse raises the question of the influence of other factors.

Complex environmental factors may also hasten the development or worsening of pelvic organ prolapse.

Some degree of pelvic organ prolapse is observed in most parous women but we know little about the natural history of prolapse. We are unable to answer clinical questions such as how often women develop clinically significant prolapse, what the risk is of minor prolapse to worsen or whether prolapse may regress.



# BACKGROUND

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## EPIDEMIOLOGY

The prevalence and incidence of pelvic organ prolapse (POP) depends on the definition and the studied population. <sup>1</sup> Most available work derives from clinical populations or surgical registries <sup>5</sup> and many women with POP are managed conservatively or are never presented for evaluation. Thus, surgically managed patients that are described in the literature do not represent the full spectrum of disease in the population.

Few studies have attempted to describe and document the normal distribution of genital support in a general female population.

In a general gynecological population, using Baden Walker classification, some form of prolapse was found in 31 % of women aged 20 to 59 years <sup>6</sup>. Prolapse was observed in 44% of all parous women and in 6% of nonparous women. Using the Pelvic organ prolapse quantification system (POP-Q) for describing pelvic support in a general gynecological population, women aged 18 to 82 years, most women were found to have stage I or II support <sup>7</sup>. A few years later the same authors published data from a cross sectional study of 1,004 women seen for annual gynecological examination and found consistent results and only 7% having the leading edge of the prolapse at or beyond the hymenal remnants<sup>8</sup>. Some reservations were made about the findings because the population was more heavily weighted towards Hispanic and black patients and overrepresented by low-income subjects and therefore not an accurate representation of the general US population.

In a more narrow age range (45-55 years) 241 women were examined in a study of the effect of soya bean beverage on menopausal symptoms, most women exhibited stage 0, 73% and only 4% stage II<sup>9</sup>.

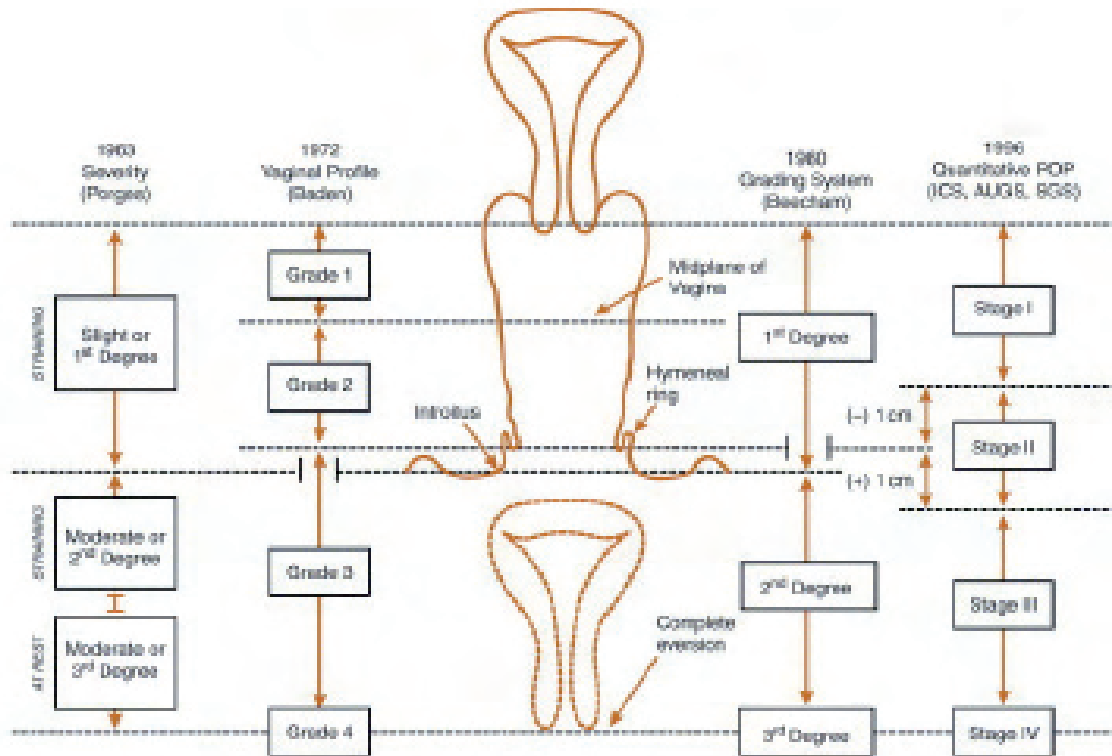
Using postal questionnaire for assessing the prevalence of symptomatic POP in women without known pelvic floor disorders, symptomatic prolapse has been estimated in 4.0-11.4 %.<sup>10-14</sup>

A woman's lifetime risk of undergoing surgery for pelvic organ prolapse by age 80 years is about 7% <sup>15</sup> and the peak incidence of such surgery is age 60-69 years. An estimated 30 % of patients with surgically treated prolapse or incontinence will have two or more surgical procedures <sup>16</sup>.

## CLASSIFICATION

Early attempts at devising a system for classifying pelvic organ prolapse have used simplistic descriptions describing prolapse as either complete or incomplete. In attempts to classify the severity of pelvic organ prolapse there has been disagreements regarding which pelvic landmarks should be used as reference points. The Beecham system was introduced in 1980 and proposed a grading system for prolapse in three degrees defined separately for rectocele, cystocele, uterus, vaginal apex and enterocele without straining <sup>17</sup>. This system used the introitus as reference. The most widespread system has been the Baden-Walker <sup>18</sup> which has been gradually developed and modified. This system uses the hymen as the reference point and also stressed the importance of maximizing the prolapse. However still the definitions (“normal”, “halfway to”, “halfway past” or “maximum descent”) are subject to variable interpretations by different examiners.

None of these grading systems have been adequately validated with respect to reproducibility<sup>2</sup>. The shortcomings of classification systems have hindered communication about findings in individual patients and groups of patients. In a review of the literature 1993 only 12.7% used a formal grading system<sup>19</sup>.



**Figure 1.** Comparison of ordinal classifications of pelvic organ prolapse 1963-1998. Theofrastous JP, Swift SE The clinical evaluation of pelvic floor dysfunction; *Obstet Gynecol Clin North Am* 1998;25:783-804. Copyright with permission from Elsevier.

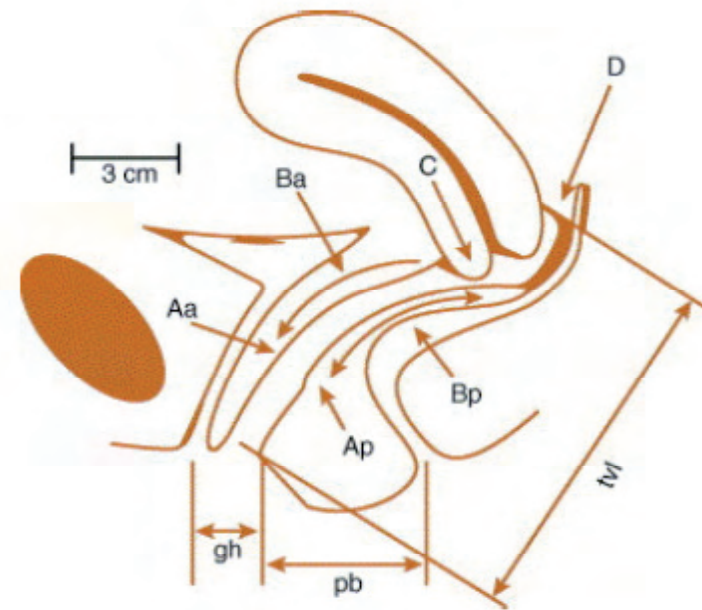
In recognition of the need for an objective, accepted, validated system for describing POP, the International Continence Society established an international, multidisciplinary, terminology standardization committee for prolapse in 1993. The committee published a document describing the pelvic organ prolapse quantification system (POP-Q) that was reviewed and adopted by the members of the International Continence Society (ICS), American Urogynecological Society and the Society of Gynecologic Surgeons in 1996.<sup>2</sup>

The POP-Q system measures nine locations on the vagina and on the perineum, six defined anatomic points in centimeters on the vagina with the plane of hymen as the reference point, additionally the total vaginal length, genital hiatus and the perineal body in centimeters. Negative numbers are assigned to structures that have not prolapsed beyond the hymenal ring and positive numbers to structures that protrude beyond the hymenal ring.

The six anatomic points on the vagina are used to assign an ordinal stage of prolapse (stage 0-IV in relation to the hymen).

Absence of prolapse is defined as stage 0.





**Figure 2.**

**Table 1 International Continence Society Stages of Pelvic Organ Prolapse Determined by Pelvic Organ Prolapse Quantification System Measurements**

<b>Stage 0</b>	No prolapse; anterior and posterior points are all -3 and C (cervix) or D (posterior fornix) is between -TVL (total vaginal length) and $-(TVL - 2)$ cm
<b>Stage I</b>	The criteria for stage 0 are not met and the most distal prolapse is $> 1$ cm above the level of the hymen ( $< -1$ cm).
<b>Stage II</b>	The most distal prolapse is between 1 cm above and 1 cm below the hymeneal ring (at least one point is -1, 0, or +1).
<b>Stage III</b>	The most distal prolapse is $> 1$ cm below the hymeneal ring but no further than 2 cm less than TVL.
<b>Stage IV</b>	Represents complete vault eversion the most distal prolapse protrudes to at least $(TVL - 2)$ cm

POP-Q is the first classification system to undergo extensive testing and has been shown to have excellent intra- and inter-examiner reliability in four studies involving 240 subjects<sup>20</sup> but normative data of POP-Q on larger groups in the population are sparse.

The POP-Q was introduced in 1996 but in a review of the literature in 2002, still a non-standardized staging system or no staging system were cited in 54.1% of studies and the use of POP-Q was only 29.1 %<sup>21</sup>.

At present the POP-Q system is the only validated prolapse grading system and is considered to be a major advance in studying prolapse as it allows groups of researchers to report findings in a standardized fashion.

## SYMPTOMS

Comprising three compartments, the anterior compartment containing the bladder and urethra, the middle compartment containing the uterus and cervix, and the posterior compartment containing the anus and rectum, the pelvic floor has a variety of pathology that can present with non specific and overlapping symptoms. Understanding the variation in pelvic organ support and how the degree of support relates to symptoms is essential in defining the disease state of pelvic organ prolapse.

In the report from 1996 standardizing terminology and description of pelvic organ prolapse, clinicians and researchers were encouraged to also describe functional symptoms in four areas assumed to be related to POP. In 2001 the National Institutes of Health identified the associations of specific symptoms with physical findings of prolapse as high priority research<sup>3</sup>.

Most of the studies evaluating symptoms of pelvic organ prolapse with physical findings are primarily based on women seeking care for urogynecological problems.

### Mechanical symptoms

Mechanical or local symptoms are well-known symptoms of POP and have been described in history for a long time<sup>22</sup>. The symptom most strongly correlated with the presence of advanced pelvic organ prolapse is “seeing” or “feeling” a vaginal bulge<sup>23-25</sup> but the correlation between this symptom and the physical findings of prolapse is at best moderate<sup>24</sup>. The hymen seems to be an important cutoff point for symptom development and most women with stage III or IV are symptomatic. Vaginal bulging is the only bothersome symptom that appears to be consistently linked to worsening of POP<sup>23,24</sup>.

Other local symptoms such as vaginal heaviness, vaginal pressure and discomfort have shown only weak correlations with examination findings<sup>23,26</sup>.

Pelvic pain and low back pain have also been listed in gynecologic textbooks as a symptom of pelvic organ prolapse but have no support in the literature<sup>27</sup>.

### Urinary symptoms

Lower urinary tract symptoms, including incontinence frequently co-exists with pelvic organ prolapse<sup>28</sup>. The prevalence of any urinary incontinence increase with advancing age, but shows a prevalence peak in midlife and then a steady increase among the elderly population. Stress urinary incontinence has been observed to be more frequent between 25-49 years of age and thereafter decrease in contrast to mixed urinary incontinence which increases with advancing age<sup>29,30</sup>.

In a review of the literature<sup>31</sup> frequencies of stress urinary incontinence (SUI) in patients with POP range between 13-83% in different studies. SUI particularly co-exist with POP when the prolapse is mild<sup>32</sup>. The common concurrence of POP and stress urinary incontinence and observed similar risk factors such as vaginal delivery suggests shared etiology<sup>33 34,35</sup>.

In contrast women with advanced prolapse are less likely to have stress urinary incontinence<sup>36</sup> and more likely to manually reduce prolapse to void. In a study of women with anterior wall prolapse, urethral obstruction occurred in 58% of the women with grade 3 and 4 anterior wall prolapse compared with 4% in women with grade 1 and 2<sup>37</sup>.

Women with severe prolapse have been reported to develop SUI in 11-22 % of cases after surgical correction of prolapse<sup>38,39</sup> so called masked, latent or occult stress urinary incontinence<sup>40</sup>. Some

investigators advocate that a positive barrier test indicates the need for concomitant anti-incontinence surgery but the selection to prophylactic anti-incontinence procedure is still an area for debate. It is suggested that the barrier test overestimates the risk of incontinence postoperatively<sup>31</sup>.

The frequency of women with pelvic organ prolapse who complain of urge urinary incontinence ranges between 21-73% in different studies<sup>31</sup>. POP and urge urinary incontinence do not share risk factors in the same way. Detrusor overactivity is a common finding in neurological diseases but the majority of women with urge urinary incontinence have idiopathic overactivity with no obvious neurogenic cause<sup>41</sup>. Detrusor instability however has been claimed to be more common in women with advanced anterior wall prolapse<sup>37</sup> and improvement of urge urinary incontinence after prolapse surgery has been reported<sup>42,43</sup> however confirmatory data are lacking.

The need to manually reduce the prolapse to void is a more specific symptom for prolapse than prolonged flow, change in position or difficult voiding but is an uncommon symptom in less advanced prolapse (<10%)<sup>26</sup>.

Hardly any studies have addressed the question of lower urinary tract symptoms and defects in the posterior compartment but studies in recent years of women with referred prolapse have found no differential effect of anterior versus posterior prolapse on urinary symptoms<sup>23,25</sup>.

In the Cochrane meta-analysis on the impact of POP surgery on continence the conclusion was that the data was “limited and inconclusive”<sup>44</sup>, approximately 10% of women developed new incontinence symptoms postoperatively.

### **Bowel symptoms**

Most associations between bowel symptoms and the presence and severity of pelvic organ prolapse are weak<sup>45</sup>. Difficulty emptying the rectum, splinting and digiting is the defecatory symptom most consistently linked to posterior wall prolapse<sup>25,46,47</sup>. The need for digital assistance is estimated to be experienced by approximately one-third of the women with posterior wall prolapse.<sup>46,48</sup>

The symptom of digital assistance for fecal evacuation has shown to be equally common in stage II posterior wall prolapse as in POP-Q stage III-IV suggesting that a more advanced posterior wall prolapse does not necessarily cause a marked increase in symptomatology<sup>26,45,49</sup>.

Many women with posterior wall prolapse do not even have that symptom and some women without prolapse also use manual pressure to accomplish defecation<sup>45,50</sup>. Rectal evacuation disorders can also lead to excessive straining during defecation which may predispose to changes in pelvic floor neurological function and abnormalities of pudendal nerve function<sup>51</sup>.

Repair of a posterior wall prolapse, even if anatomically corrected, do not always solve and may contribute to functional problem, either producing bowel symptoms or aggravating disorders present<sup>52</sup>. This has, however been considered to be a result of inappropriate surgical technique of levator plication. The shift towards discrete fascial repair have contrary shown upon an improvement of both bowel and sexual symptoms<sup>53-55</sup>. Thus despite the weak relationship between bowel symptoms and POP, the literature supports the improvement of certain bowel symptoms such as feeling of incomplete emptying, splinting and straining after a posterior repair<sup>55-57</sup>.

Anal incontinence is not considered to be a symptom of prolapse but sometimes co-exist<sup>1</sup>. Fecal incontinence has been reported in 7-30% of women with urinary incontinence and/or pelvic organ

prolapse<sup>33,58</sup>. All three disorders share common risk factors such as neuropathic and muscular injury to the pelvic floor after vaginal delivery and the effects of ageing<sup>1,33</sup>.

### **Sexual symptoms**

Women's sexuality and sexual function involves many dimensions, such as general physical and mental well-being, quality of partnership, partner's age and health<sup>59</sup>. Prevalence estimates of sexual dysfunction in community based studies vary considerably<sup>60</sup>. Surveys of middle-aged and elderly women have demonstrated high prevalence of sexual dysfunction<sup>61</sup>. In these age groups the prevalence of pelvic floor disorders is also high.

The impact of prolapse on sexual function has received little attention. Inconsistencies in the ways in which female sexual dysfunction have been measured, have also made it difficult to establish whether the differences reported between populations are real or the product of the different methods used<sup>62</sup>.

A recently published paper concluded that sexual function was worse in women with symptomatic prolapse but not in women with asymptomatic prolapse. They found that women with anatomic prolapse (stage III–IV) were more likely to report infrequent orgasm but they were not at increased risk of other sexual problems. Another observation was that women with stage II support were not more likely to report any sexual complaint than women with stage 0 support<sup>63</sup>.

An increasing number of papers have raised the issue of female sexual dysfunction in women undergoing urogynecological surgery but conflicting data have been reported. Sexual life can be improved<sup>64,65</sup>, unchanged or worsened<sup>66 67</sup>.

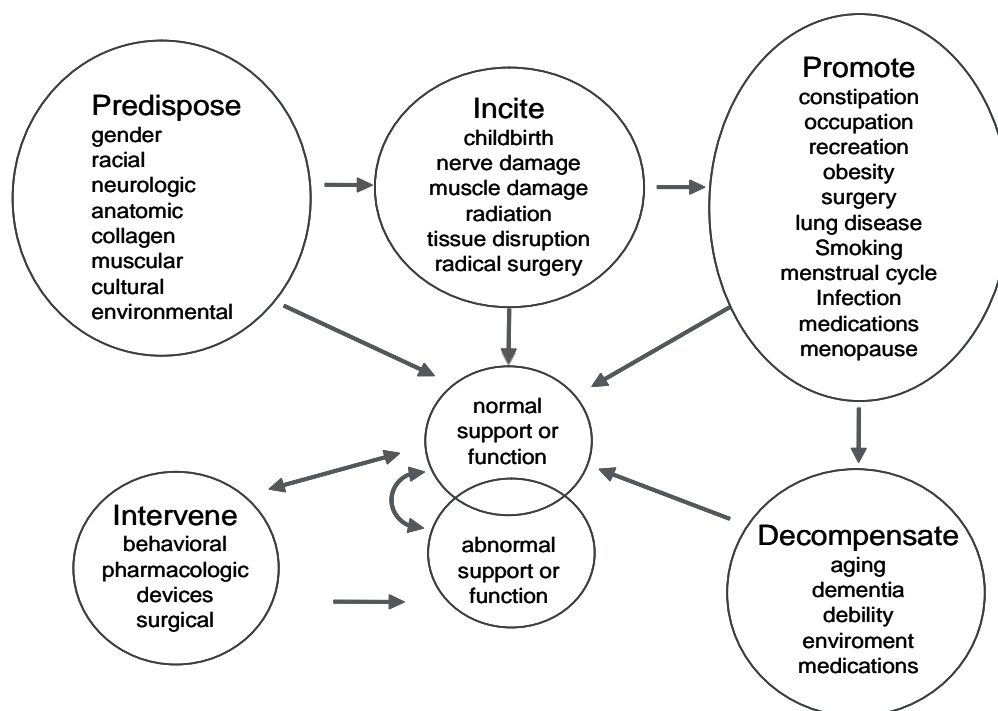
The most studied single sexual dysfunction is dyspareunia. Several studies report prevalences of dyspareunia after posterior colporrhaphy of 21-27 % but this has been blamed on levator ani plication<sup>64 52,68</sup>. Improvement or lower rates of dyspareunia have been reported with site specific repair or midline plication procedures<sup>53,69</sup>.

### **RISK FACTORS**

The cause of the pelvic organ prolapse is likely to be multifactorial, attributable to a combination of risk factors, varying from individual to individual.<sup>70</sup> Epidemiological studies point to advancing age and in particular vaginal delivery as the strongest risk factors<sup>71</sup>. However the specific aspects of parturition are not well defined and to control for the many variables that comprise the complex event of parturition is difficult<sup>72</sup>.

The fact that the majority of parous women do not develop severe prolapse raises the question about the influence of non-obstetric factors but most of them are supported by limited epidemiologic and clinical evidence<sup>72-75</sup>. Each of these risk factors individually fails to fully explain the genesis and progression of POP.

A useful approach to consider putative risk factors for POP was suggested in 1998 by Bump and Norton dividing them into three categories: *predisposing* (family history, race and ethnicity, variations of anatomy and collagen synthesis and structure), *inciting* (vaginal delivery through its effect on nerve damage, muscle damage, and tissue disruption), and *promoting* (other possible risk factors including lifestyle)<sup>72</sup>.



**Figure 3.** Model for the development of pelvic floor dysfunction in women. Adapted from Bump RC, Norton PA Epidemiology and natural history of pelvic floor dysfunction. *Obstet Gynecol Clin North Am* 1998;25:723-46. Copyright with permission from Elsevier.

In the following section I will discuss some of the non obstetric risk factors for POP that was addressed in Paper II.

## Predisposing

### *Family history*

Genetic factors undoubtedly play a role in the etiology of POP but the relative contribution of genetic predisposition and environmental factors is insufficiently understood. A positive family history of POP among first degree relatives has support in several studies<sup>14</sup>. In a case-control study of women undergoing surgery for POP, a two- to threefold risk increase was reported for women with sisters or mother reporting a history of the condition<sup>76</sup>. In a cohort of younger women (45 years or less) undergoing surgery for POP, 30 % reported at least one first degree relative with POP<sup>77</sup>. More recent work determined that the risk of POP among sisters of young women (younger than 55 years) with stage III and IV POP to be five times higher than in the general population<sup>78</sup>. Both maternal and paternal transmissions have been noted in family trees<sup>78,79</sup>. Epidemiological evidence of genetic inheritance of both urinary incontinence and POP have also been shown in a large Twin Registry study but the authors concluded that the influence of environmental factors was substantial<sup>80</sup>.

### *Connective tissue*

To date biochemical studies of the vagina and its supportive tissue in the pathogenesis of pelvic organ prolapse are limited<sup>81,82</sup>. It has been speculated that the vagina and supportive tissues in patients with prolapse have a decrease in collagen content. A change in collagen subtypes, collagen ratios, collagen morphology has also been suggested but results are conflicting<sup>83,73</sup>. In many studies the specimens have not been defined histologically making comparisons between studies difficult. It is not clear whether observed changes are cause or effect of prolapse<sup>73</sup>. Current research suggests however that the vagina and its supportive tissues actively remodel in response to different environmental stimuli such as pregnancy, menopause, the administration of hormones and pelvic organ prolapse and that the metabolism of collagen and elastin is altered within prolapsed tissue<sup>82</sup>.

A clinical marker- suggesting connective tissue abnormality as a predisposing factor for pelvic relaxation -has been addressed in a study of joint hypermobility. Joint hypermobility is a common finding in conditions of known connective tissue abnormalities such as Ehler-Danlos syndrome. Women with joint hypermobility were found to have significantly higher prevalence of genital prolapse compared to women with normal mobility <sup>84</sup>.

More operations for abdominal hernias have also been found in a study of young women with prolapse compared to the controls <sup>77</sup>.

## **Inciting**

### *Parity*

Increasing vaginal parity is the major inciting factor for development of POP in women younger than 60 years.<sup>8,71,85</sup> The link is well established in epidemiological and clinical cohort studies<sup>73,86</sup>. Compared with nulliparous individuals, the relative risk of developing prolapse was 8.4 for a woman who had delivered two children and 10.9 for someone with four or more children <sup>71</sup>. The association observed for pelvic organ prolapse and childbirth is stronger than the association observed for childbirth with urinary or fecal incontinence <sup>71</sup>.

The insult during labor may include nerve damage, muscular damage and direct tissue disruption. An increase in pudendal nerve terminal motor latency have been found in women after vaginal delivery, particularly a first vaginal delivery, when comparing post partum values with antepartum values<sup>87</sup>. More recent studies have through magnetic resonance imaging (MRI) been able to demonstrate injuries of the levator ani muscle in women after vaginal birth <sup>88</sup>. The association of levator ani injury with prolapse is suggested to be one plausible birth-related factor in the pathophysiology of prolapse <sup>89,90</sup>. Women with prolapse have been diagnosed with a higher proportion of major levator ani muscle defects on MRI compared to age-, race-, and hysterectomy-matched controls <sup>89</sup>. Caesarean section seems to protect against prolapse development <sup>86,91,92</sup> but nulliparity does not provide absolute protection.<sup>74</sup>

To date the understanding of the specific birth injuries and how they influence the development of pelvic organ prolapse is still not well understood <sup>93</sup> but two facts remain– POP occurs temporally distant from the vaginal childbirth and most women who bear children do not develop POP.

### *Previous Gynecologic Surgery*

Previous gynecological surgery identified as a risk factor for pelvic organ prolapse is not surprising <sup>94</sup>. Subjects who have undergone surgery to correct POP should be viewed as already having the underlying processes or defects that lead to this disorder.

The role of prior hysterectomy on the subsequent development of POP is less clear. POP is one of the most common indications for hysterectomy <sup>74</sup>. The risk of prolapse following hysterectomy is 5.5 times higher in women whose initial hysterectomy was for genital prolapse as opposed to other reasons <sup>71</sup>. It has further been claimed that subtotal hysterectomy with preservation of the cervix and its pelvic attachments through the cardinal-uterosacral ligaments would prevent the development of subsequent prolapse. However, a recent meta-analysis of observational and randomized studies found a trend of more women having prolapse after subtotal than after total hysterectomy <sup>95</sup>.

## **Promoting**

### *BMI*

Increasing body-mass index as a risk factor for POP has support in the literature <sup>71 6,85,96</sup> and is even quoted as an established risk factor <sup>1</sup> but published data do still conflict <sup>76 13,77</sup>. Several studies have addressed BMI and the risk of POP in postmenopausal women in the Women's Health Initiative

(WHI) trial. Analyzing all women included in the hormone trial, BMI greater than 30 kg/m<sup>2</sup> gave a 40-75% increased the risk of POP<sup>74</sup>. In a secondary study including only women with an intact uterus high BMI was found to be associated with progression of POP over a 5 year period<sup>97</sup>. Other studies of the women in selected groups from the WHI trial have failed to find an association.<sup>98</sup>

Furthermore a BMI greater than 26 kg/m<sup>2</sup> has been identified as a risk factor for undergoing POP surgery compared to controls<sup>91</sup>.

The differences in findings between BMI and POP are not completely understood and may reflect differences in studied populations.

#### *Chronic pulmonary disease and smoking*

Chronic pulmonary disease as a risk factor for POP has been implicated largely because of the association with stress urinary incontinence<sup>99</sup> and on the assumption that increased abdominal pressure puts excessive strain on supporting structures and the pudendal nerve and its branches<sup>73</sup>. In one case-control study of younger women who underwent surgery for prolapse asthma was a more frequent observation<sup>77</sup> but the most cited report on surgically managed urinary incontinence and prolapse<sup>15</sup> found women operated on for urinary incontinence alone to be more likely to have chronic lung disease compared to those operated on only for POP suggesting a difference the two groups.

The association between smoking and POP has shown mixed results. Women in the WHI study who smoked had lower risks (OR 0.81) for uterine prolapse<sup>74</sup> whereas no associations have been found in other studies<sup>76,85</sup>

#### *Bowel habits*

The role of bowel habits as a risk factor for the development of POP is not clear. Constipation and chronic straining have been proposed as risk factors<sup>100</sup>. Chronic straining may cause neurologic, muscular and other anatomic damage to the pelvic floor and its connective tissue resulting in the elongation of the levator muscles, perineal descent and pelvic organ prolapse. Studies of women with chronic constipation who had strained at stool over a prolonged period have demonstrated changes in pelvic floor neurological function.<sup>51,101</sup> In a retrospective case-control study constipation and straining at stool as a young adult was significantly more common in women with POP compared to the controls<sup>46</sup>.

Perineal descent and POP, especially posterior wall prolapse may on the other hand contribute to constipation symptoms primarily in outlet symptoms, such as perineal or vaginal splinting, the sensation of incomplete emptying and the need to strain. A vicious cycle can result in which straining leads to more damage followed by more staining etc<sup>102</sup>. Likewise POP, chronic constipation increases with age<sup>103</sup>.

#### *Socioeconomic status*

Heavy lifting increases the intra-abdominal pressure and certain occupations involving heavy physical work have been found to be associated with a higher prevalence of POP<sup>14</sup>.

For instance in a cross-sectional study of 1,004 women presenting for routine gynecological care a significant association between POP-Q stage  $\geq$  II in laborers/factory workers versus other job categories was observed<sup>104</sup>. In a population of assistant nurses in Denmark<sup>105</sup> heavy lifting at work was associated with a 60% increased risk for POP surgery compared to the overall female population but no adjustments were made for parity and nursing assistants could possibly be more familiar with surgical treatment options. In an Italian case-control study of women planned for POP surgery housewives were found to have a three times higher risk of POP compared to professional managerial women<sup>76</sup>. The authors speculated that housework could be considered as more heavy physical work.

Another study, although small, suggesting forces transmitted to the pelvic floor to be a risk factor for the development of POP, looked at nulliparous women in the US military academy, and the effect of paratrooper training on pelvic support before and after a summer training. They found paratrooper training to significantly increase the risk for development of stage II prolapse<sup>106</sup>.

Level of education and background knowledge of available treatment options are other factors that can influence care seeking for POP and hospital based data<sup>104</sup>.

## **Decompensating**

### *Age*

Aging is a complex process and the increase in prolapse may be the result of the combination of physiological aging, hypoestrogenism and increased age-related degenerative and organic diseases<sup>70</sup>.

The literature has previously been consistent in that the risk of prolapse increases with advancing age<sup>6,94</sup> but a few studies have rather found a knee around menopause among non-care seeking women on the age-prevalence curve for stage II prolapse whereas stage III prolapse continued to increase after 50 years.<sup>7,12</sup> Age as a risk factor for POP has even been questioned in a recent observational study of 971 women<sup>107</sup>. The authors found anterior and posterior wall prolapse to be positively associated with age up to the sixth decade but negatively associated above this age.

Two other population based studies found a relatively stable prevalence of POP throughout the age groups but prolapse status were not confirmed by examination<sup>5,13</sup>.

## **NATURAL HISTORY**

The natural history of prolapse is an unknown issue. Two prospective studies have addressed pelvic support over time in postmenopausal women with an intact uterus participating in the WHI trial. Spontaneous regression of grade 1 (Baden Walker), which might be considered as artificial, was common but regression of grade 2 to 3 was also observed<sup>115</sup>. In the other study<sup>116</sup> the women were examined according to POP-Q. Changes in vaginal descent were registered in centimeters. The authors concluded that prolapse can progress and regress in older women although in their study population the progression rate was slightly higher in contrast with the other study. Regression of POP has also been reported postpartum, attributed to the resolution of pregnancy and childbirth<sup>117</sup>. To further confirm the certainty of these findings more studies are required.

## **TREATMENT**

Management of pelvic organ prolapse is an important component of gynecological care. Options available for treatment include conservative management, mechanical devices and surgery. The majority of interventions are based on relative indications. Treatment of prolapse depends on the severity of the prolapse, symptoms, the woman's general health and the surgeon's preference of approach.

Conservative management, such as giving lifestyle advice and pelvic floor muscle training (PFMT) are often used in cases of mild to moderate prolapse. Pelvic floor muscle training is designed to increase the strength and endurance of the pelvic muscles, thereby improving support to the pelvic organs. Ideally, PFMT will decrease symptoms and prevent prolapse from worsening. PFMT can be particularly beneficial in women whose symptoms do not match their physical findings-severe symptoms with mild prolapse. PFMT could also perhaps be an effective contribution to maximize surgical outcome, but even if there is evidence of effectiveness in treatment of urinary incontinence, the evidence is not sufficient to judge the value of pelvic floor muscle training in the treatment of



pelvic organ prolapse<sup>108</sup>. Large better quality randomized controlled trials are still required. Mechanical devices for treating prolapse have been used since the beginning of recorded history<sup>22</sup>. This treatment is often reserved for patients with symptomatic prolapse who decline surgery, who are poor surgical candidates because of medical co-morbidities, or who need temporary relief of prolapse. Unfortunately most available data for pessary use are restricted to case reports of pessary complications<sup>1</sup>.

Surgical treatment for prolapse can be categorized into reconstructive and obliterative techniques. Obliterative procedures are usually reserved for women who are elderly, medically compromised and no longer sexually active. The advantages of obliterative surgery in these populations are shorter operative time, decreased perioperative morbidity and a low recurrence risk. Reconstructive surgery for prolapse, on the other hand, aims to correct the prolapsed vagina while maintaining (or improving) vaginal sexual function and relieving any associated pelvic symptoms. Surgery can be undertaken by either abdominal or vaginal route. Still the preferred route for most prolapse surgery is vaginal<sup>109</sup>. The wide variety of surgical treatments available for prolapse indicates the lack of consensus regarding the optimal surgical treatment<sup>44</sup>. Depending on the extent and location of prolapse, vaginal surgery usually involves a combination of repairs. Anterior and posterior colporrhaphy, dating back to the early 19<sup>th</sup> century, is among the most frequently and still primarily, performed operations in gynecological surgery<sup>110</sup>. In Scandinavia the Manchester repair has been the traditional choice comprising anterior and posterior colporrhaphy, perineorrhaphy and amputation of the uterine cervix<sup>68</sup>.

Traditional teaching has held that all defects should be repaired at one setting but troublesome complications such as dyspareunia and de novo stress urinary incontinence have resulted in a shift in treatment towards more selective compartment repairs and avoidance of prophylactic repair in other compartments<sup>111</sup>.

The high rate of anatomical recurrence in prolapse surgery is well-known and especially recurrent anterior wall prolapse<sup>112,113</sup>.

During recent decades this has led to an alteration of surgical approach such as site-specific repair, paravaginal repair and the introduction of biological and synthetic prostheses.

Expert opinion varies widely regarding the usefulness of graft augmentation in repair of POP<sup>44</sup>.

## QUALITY OF LIFE

It has become increasingly obvious that women with POP seek treatment to improve their quality of life and there is a growing recognition that instruments for measuring quality of life are essential for evaluating women with pelvic floor disorders. Until recently there has been a lack of validated condition-specific questionnaires but today several quality of life instruments for pelvic floor dysfunction have been developed and validated<sup>114</sup>. None has yet been validated in the Swedish language.



# AIMS

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The overall objective of this thesis was to study associations between pelvic floor related symptoms and pelvic support defects, non-obstetric risk factors for symptomatic pelvic organ prolapse, the short-term natural history of prolapse and to evaluate outcome after surgery

The specific aims were

1. To investigate whether the nature of the anatomical defects in pelvic organ prolapse correlates with the character of the symptoms. (Paper I)
2. To identify possible non-obstetric risk factors for symptomatic pelvic organ prolapse in a general female population. (Paper II)
3. To investigate the possible further development of symptoms and anatomic changes in women with symptoms indicative of pelvic organ prolapse and in a control group of women without such symptoms (Paper III)
4. To evaluate anatomic, functional, short- and long-term outcome of vaginal surgery for pelvic organ prolapse. (Paper IV)



# SUBJECTS AND METHODS

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Sweden has a high quality population-based register which provides unique opportunities to conduct epidemiological studies <sup>118</sup> Papers I-III were based on a random sample of women in Stockholm, selected from the Swedish population-based register.

## PAPER I-III

### Study populations and research design

This cross sectional study started in February 2002 when 8,000 women, 30-79 years of age and residents of Stockholm, randomly selected from the computerized and continuously updated Swedish Population Register, were asked to answer a postal validated five-item questionnaire for identification of symptomatic prolapse <sup>119</sup> (*Appendix 1*). Five thousand four hundred eighty nine women (69%) provided adequate answers and 454 (8.3%; 95% CI 7.3-9.1) provided self reports consistent with symptomatic prolapse <sup>12</sup>.

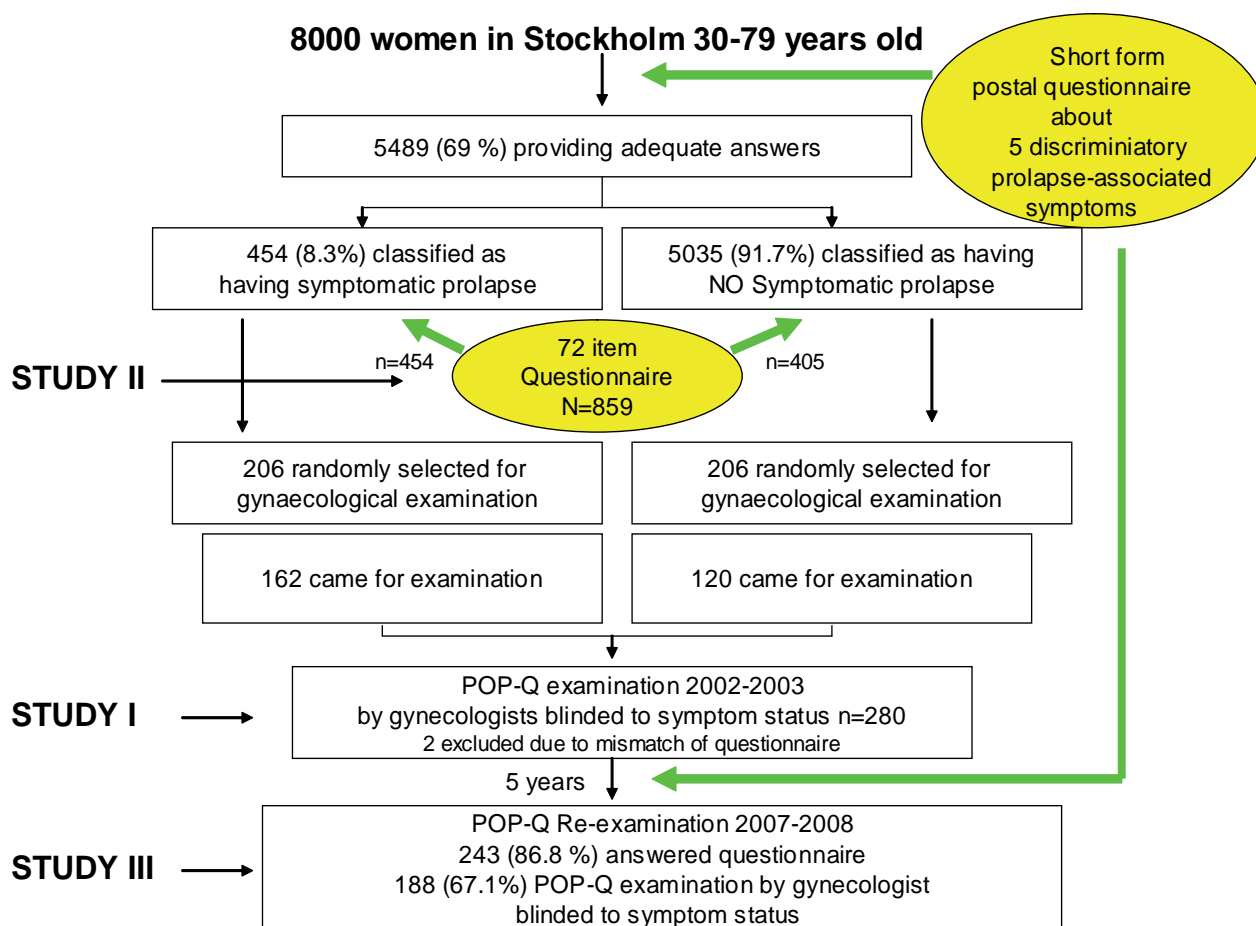
To validate the presumed POP status, 206 randomly selected cases from the 454 women with symptomatic prolapse and 206 women randomly selected from the 5035 without symptomatic prolapse were invited to undergo a gynaecological examination according to pelvic organ quantification (POP-Q). The intention was to examine approximately 400 women, 200 test- positive for symptomatic prolapse and 200 test-negative. As it was important that not too much time had elapsed between the initial questionnaire had been answered, the sampling commenced before all questionnaires had been returned. A fixed proportion was sampled from each wave of response following the first mailing and two reminders - equal numbers of prolapse-positive and prolapse-negative women. This resulted in the unusual value of 412 women; 206 women from each group. Among the women who provided self-reports consistent with POP, 162 women came for examination as did 120 women of those whose questionnaire answers did not indicate the presence of POP. In total 282 women underwent a gynecological examination according to POP-Q at Södersjukhuset, Stockholm between March 2002 and February 2003.

To investigate possible risk factors for symptomatic prolapse all 454 cases classified in the initial survey investigation as having symptomatic prolapse (of whom 162 had undergone gynecological examination in the validation substudy) and 405 control subjects were mailed a 72-item questionnaire (*Appendix 2*). The 405 controls had been randomly selected among the 5035 women whose responses in the initial survey investigation did not meet our criteria for symptomatic prolapse and included the 206 women selected for the validation substudy.

The data collection of possible risk factors was concluded in August 2003.

A detailed analysis of obstetric risk factors has been published elsewhere <sup>86</sup>.

After approximately 5 years the 280 examined women were mailed the same validated five-item questionnaire supplemented with questions about body weight, height, any changes in obstetric, gynecological or medical history and bowel habits. They were also invited to a renewed pelvic examination.



**Figure 4.** Outline of the study design and subject accrual

*Paper I – A cross-sectional investigation within a population based sample*

Of the 412 women invited for gynaecological examination, 282 (68.4%) chose to participate. Two women were excluded due to uncertainty if they were the persons who had answered the initial questionnaire. The mean age of the women was 53.4 (range 29-79; SD 13.5) and the mean parity was 1.8 (range 0-5). Seventeen women had previously undergone prolapse surgery and 13 reported previous surgery for incontinence. The women who chose not to participate tended to be somewhat younger (52.3; range 29-79) and to have less previous gynaecological surgery but the differences were generally small.

After the examination the 72-item questionnaire was mailed to all of the 280 women and 246 (88%) provided adequate answers about bowel symptoms.

Twelve symptoms were analysed in relation to objectively observable defects in the three different compartments. The 12 symptoms included the five symptoms in the short-form questionnaire supplemented with a question on stress urinary incontinence and six bowel symptoms from the 72-item questionnaire.

*Paper II- A case control study within a population based cross-sectional study.*

The 72-item postal questionnaire was sent to 859 women—454 cases classified in the initial survey investigation as having symptomatic prolapse and 405 control subjects. In total 655 (76.2%) returned completed questionnaires. Presuming that symptoms and recall might differ among women who had undergone pelvic surgery- 97 women were excluded due to prior surgery for prolapse, incontinence or hysterectomy.

Thus 558 women – 273 cases with self-reported symptomatic POP and 285 controls were included in this analysis of non-obstetric risk factors for POP.

The mean age of the controls was lower compared to the cases (49.1; [range 29-79; SD 13.5] vs 53.3; [range 29-79; SD 12.3]) as was the mean parity (1.4 [median 1; range 0-5] vs 2.1 [median 1; range 0-5]). The cesarean section rate was low in both groups (8.6% and 13.0%)

#### *Paper III- A prospective cohort study*

This prospective cohort consisted of the 280 women (160 whose scores had been indicative of symptomatic prolapse and 120 whose answers indicated absence of POP) who had completed the five-item questionnaire and had undergone a pelvic examination according to POP-Q in 2002-2003. Twenty-eight women (10%) actively declined re-examination. Women who had undergone surgery for prolapse or incontinence during the follow up period were not excluded.

The mean age at enrollment among women with and without symptomatic prolapse was 56.1 years (SD12.5; range 31-79) and 51.5 (SD14.2; range 30-79), respectively. During follow-up, 21 women with symptomatic prolapse underwent surgery for prolapse and /or incontinence and two control women underwent surgery for incontinence

The development of symptoms was based on the 243 (87%) women who answered the follow up questionnaire – 141 (88%) of women with symptomatic prolapse and 102 (85%) of asymptomatic control women.

The development of POP-Q stage was based on the 188 women (67%) who completed the follow up examination between November 2007 and June 2008– 116 (72%) with symptomatic prolapse and 72 (60%) control women. Among the symptomatic women 17 of them had undergone surgery for prolapse and /or incontinence and three had undergone hysterectomy during follow up. Among the control women two had undergone surgery for incontinence.

Six of the parous women reported additional deliveries during follow up (four symptomatic and two asymptomatic).

The mean follow up time between examinations was 5.6 years (SD 0.3; range 4.8-6.2).

## **Questionnaires**

### *Five-item questionnaire*

The five specific mechanical and urinary symptoms asked for are shown in **Appendix 1**.

The questionnaire also included questions about age, parity, previous operations for pelvic organ disorders and the presence of stress urinary incontinence.

A combination of five reported symptoms had in a previous study shown to accurately predict the presence of observable pelvic organ prolapse with a specificity of 94.2% and a sensitivity of 66.5% applying POP-Q as the gold standard in a nonconsulting female population<sup>119</sup>. The question “Do you have a sensation of tissue protrusion (vaginal bulge) from the vagina?” carried almost all of the predictive ability of the questions. The additional four questions added only marginally to its discriminative ability.

### *72-item questionnaire*

This questionnaire addressed selected factors from the risk factor model – *predisposing factors* (family history of prolapse or other conditions signaling weak connective tissue), *inciting factors* (obstetric history, previous gynecological surgery), *promoting factors* (overweight/obesity, chronic pulmonary disease, smoking, bowel habits, socioeconomic status, life-style factors such as dietary intake and physical activity) and finally *decompensating factors* (age).

The participants were asked also about the frequency of pelvic floor muscle training (PFMT), if any, at time of interview as well as 10 and 20 years earlier.

The specific questions are shown in *Appendix 2*.

#### *Follow up questionnaire*

This questionnaire consisted of the same questions from the five-item validated short-form questionnaire supplemented with selected questions from the 72-item questionnaire about body weight, height, any changes in obstetric, gynecological or medical history and bowel habits.

#### Clinical Examination

##### *Paper I*

The patients were examined at the department of Gynaecology and Obstetrics at Södersjukhuset between March 2002 and February 2003. Two gynaecologists (AM and GT) performed all the examinations.

The pelvic floor anatomy was defined in conformity with standards recommended by the ICS, the pelvic organ quantification system, POP-Q<sup>2</sup>. The pelvic examinations were performed in dorsal lithotomy position. The women were asked to empty their bladder before the examination. All nine POP-Q measurements were measured in centimetres to the nearest integer. Each compartment was evaluated separately while the other compartments were retracted with a single-bladed speculum. The prolapse was graded visually at maximum Valsalva manoeuvre from 0 to IV respectively on the anterior wall (point Aa, Ba), superior vagina (point C, D) and posterior wall (point Ap, Bp) of the vagina.

Finally an overall staging was assigned according to the most severely prolapsing compartment. Absence of pelvic organ prolapse was defined as stage 0<sup>2</sup>.

In order to calibrate the POP-Q assessments the two examiners jointly examined the first 10 patients. The interobserver variation was minimal. The examinations were double blind; neither the examiner nor the woman knew if she had been classified as having symptomatic/ asymptomatic prolapse.

##### *Paper III*

One gynecologist (ME) performed all follow-up examinations between November 2007 and June 2008. The pelvic floor anatomy was defined the same way as in paper I. This single examiner had not performed any of the initial examinations. In order to calibrate the POP-Q assessments the first 10 patients were jointly examined together with the previous examiners. The interobserver variation was considered to be minimal.

Anatomical assessment of prolapse over time was classified as unchanged, progression or reduction of POP-Q stage.

#### **Statistical methods**

In Paper I symptoms were cross-tabulated with stage of compartment-specific POP in simple contingency tables. Symptoms were recoded in a dichotomous fashion (absent-present). Univariable associations between compartment abnormalities and symptom prevalence were tested using the Chi-square test or Fisher's exact test as appropriate.

Since prolapse often occurs in two or more compartments simultaneously, we modelled the independent associations of compartment-specific anatomical prolapse with the studied symptoms while controlling for prolapse in other compartments and for age and parity using multiple logistic regression. Each model included individual terms for each prolapse stage (divided into 0, I, II-IV) in each separate location (anterior wall, posterior wall, apical). The reason for combining stages



II-IV was the small numbers of women with advanced stages (III-IV) in the anterior and posterior wall. Small numbers also forced us to analyze apical prolapse in only two categories (0 and >0). Odds ratios (OR), indicating the strength of associations, were given with stage 0 as reference category.

In Paper II possible links between the presence of symptomatic prolapse and the various factors were first studied in simple logistic regression models with and without adjustments for age and parity, using the prevalence odds ratio (POR) and 95% confidence intervals as the measure of association. With a symptomatic prolapse prevalence of 8.3 % the rare disease assumption was considered to be reasonably valid; PORs for moderately strong associations can therefore be considered to be acceptable approximations of relative risks. A stepwise multivariable logistic regression analysis was then performed on the factors identified in trivariable analyses. At the end the variables that were dropped in the stepwise approach were tested again in the resulting model.

In Paper III statistical comparisons of POP-Q stage and reported symptoms were performed using Chi-square test, Fisher's exact test, McNemar's test and the sign test when appropriate. The proportions of women at follow up with improvement or unchanged symptom of vaginal bulging were calculated together with 95% confidence intervals.

The level of significance was 0.05 and all tests were two-sided. No adjustments were made for multiple testing in any of the studies.

## PAPER IV

### Study population

#### *A prospective cohort study*

During a three-year period, between Jan 1998 and Jan 2001, a total of 248 women underwent prolapse surgery at Södersjukhuset in Stockholm. All patients scheduled for operations received information about the study and 185 women agreed to participate. Exclusion criteria included inability to answer questionnaire, dementia or other severe illness. Women with recurrent prolapse were not excluded. The women who chose not to participate were on average the same age (66.2 vs 65.4)

Except for peri- and postoperative morbidity the cohort was evaluated in terms of anatomic and functional outcome, recurrence rate and long-term side effects. Clinical evaluations were performed at two months, one, three and five years postoperatively.

Once the subjects were diagnosed as failure they did not re-enter as new cases but symptoms were recorded at the remaining follow ups.

Of the 185 women, 172 women (93.0%) were evaluated one year after surgery and 151 (81.6%) at three year and 143 (77.3%) at five year follow up. The mean follow up time in the whole group was 53.2 months and 123 women (66.5%) attended all four follow-ups.

Of the 42 women lost to five year follow up their mean follow up time was 20.4 months (SD 13.9). Fourteen had been diagnosed as recurrences and five required reoperation. Thirteen had died during the follow up, with no relation to operation, six women suffered from dementia, two had moved from the region and the rest did not want to participate.

## **Protocols and quality of life questionnaire, SF-36**

### *Protocols*

A predefined protocol was constructed for this study and for the follow-up visits

The protocol prior to surgery was more extensive and included questions about height, weight, smoking, chronic diseases such as diabetes mellitus, chronic lung disease, neurological disease, chronic lower back pain, previous operations, obstetric history, the use of estrogens, use of pessary, mechanical symptoms, urinary symptoms (stress urinary incontinence, urge urinary incontinence, difficulty in bladder emptying, urinary infections ), bowel function (constipation/evactory dysfunction, gas incontinence and fecal incontinence).

At the follow-up visits the protocol included questions about smoking, use of estrogens, mechanical symptoms, urinary infections, urinary incontinence, bowel function including gas incontinence and fecal incontinence. Dyspareunia was asked about only at follow up visits.

### *SF-36*

Before the five-year follow up visit the women were mailed a general Quality of Life questionnaire, SF-36. The 36-item Medical Outcomes Study Short-Form Health Survey (SF-36) yields an eight scale profile of scores and is a generic measure of health status in opposition to others who targets specific diseases, ages or treatments <sup>120</sup>. Consequently it can be useful to compare general and specific populations. An age matched reference group (n=62) was randomly selected from the Swedish SF-36 database.

## **Clinical evaluation**

The severity of the prolapse was graded according to the Beecham system where the classification was done in three degrees in relation to introitus at rest. No clinical examination was made for type of incontinence.

Anatomic outcome at follow up was determined by vaginal examination. The implementation of the POP-Q system as the standard for describing prolapse resulted in a graduate adaptation and at the five year follow up objective failure was defined according to POP-Q stage  $\geq 2$  at any site. Symptomatic prolapse was defined as symptoms of vaginal bulging.

A single examiner (AM), who had not performed any of the prolapse surgery, completed all the five year follow up examinations and interviews.

## Surgical procedures

Depending on the location of the prolapse surgery involved different types of repairs, all with a vaginal approach. Seventeen gynecologists performed the operations, of which 57 % of the operations were performed by three gynecologists with a special interest in urogynecology.

**Table 2** Surgical procedures among the 185 women who underwent vaginal surgery for pelvic organ prolapse

<i>Surgical procedures</i>	
Manchester procedure	74 (40.0%)
Vaginal hysterectomy	36 (19.5%)
with anterior <i>and</i> posterior colporrhaphy	30
anterior <i>or</i> posterior colporrhaphy	5
Anterior colporrhaphy	7 (3.8%)
Posterior colporrhaphy	36 (19.5%)
Anterior + posterior colporrhaphy	25 (8.7%)
Cervixamputation	2 (1%)
Colpocleisis	4 (2.2%)
IVS	32 (17.3%)

## Peri- and postoperative complications

Definition of peri-and postoperative was hemorrhage requiring blood transfusion or reoperation, deep venous thrombosis or febrile morbidity.

## Statistical methods

Statistical analyses were performed with SPSS 14.0 and odds ratio with 95 percent confidence interval were used to test differences in recurrences between groups.

## ETHICAL CONSIDERATIONS

All four studies included in this thesis were approved by the Regional Ethics Committee of Karolinska Institutet. All women provided informed consent.



# SUMMARY OF THE FINDINGS

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## SYMPTOMS AND PELVIC SUPPORT DEFECTS IN SPECIFIC COMPARTMENT (PAPER I)

Among the 280 examined women the overall POP-Q stages, taking prolapse at any site into consideration (Aa, Ba, Ap, Bp, C and D) were as follows: stage 0 15.7%, stage I 34.0%, stage II 41.8%, stage III 6.8% and stage IV 1.8%. The observed stage distributions by compartment or combination of compartments are exhibited in Table 3

**Table 3** Anatomic Findings by Location and Stage of Prolapse among the 280 women

Stage	Isolated Anterior	Isolated Posterior	Anterior and posterior	Anterior,posterior and apical	Apical or Ant+apical or Post+apical	Tot
0						44 (15.7)
I	3 (1.1)	43 (15.4)	35 (12.5)	6 (2.1)	8 (2.9)	95 (34.0)
II	1 (0.4)	11 (3.9)	70 (25.0)	32 (11.4)	3 (1.1)	117 (41.8)
III		1 (0.4)	7 (2.5)	9 (3.2)	2 (0.7)	19 (6.8)
IV		1 (0.4)		3 (1.1)	1 (0.4)	5 (1.8)

Data are n (%)

As expected, the oversampling of symptomatic women resulted in potentially POP-related symptoms being common in the study group. Mechanical symptoms were reported by 117 (41.8 %) women, 177 (63.2 %) women suffered from any urinary symptom and no less than 205 (73.2 %) had at least one bowel symptom.

### Mechanical symptoms and objectively observed POP

In the simple cross-tabulations isolated prolapse of the anterior wall (with reservation for few observations) and prolapse in more than one compartment were significantly associated with a feeling of a vaginal bulge. Significant associations with aggravation by heavy lifting were confined to multicompartement prolapse. Isolated posterior wall prolapse stage I-IV was not significantly associated with mechanical symptoms when compared to stage 0. Moving stage I to the reference category, the feeling of a vaginal bulge became significant also for posterior wall prolapse.

In the age- and parity-adjusted logistics regression model, mechanical symptoms, particularly a feeling of a vaginal bulge, tended to be associated with prolapse in each of the three compartments, whether in isolation or in combination. Compared with women with no anterior wall prolapse, those who had anterior wall prolapse stage II-IV exhibited a 5.8 fold (95% CI; 2.5-13.3) increased odds of having feeling of a vaginal bulge. The corresponding odds ratio for posterior prolapse was 2.9 (95% CI 0.9-9.2).

### Urinary symptoms and objectively observed POP

In the simple cross-tabulations, prolapse in any compartment, isolated and in combination, compared to stage 0, was statistically significantly associated with stress urinary incontinence

while associations with urge urinary incontinence were found only for women with prolapse that involved more than one compartment. None of the women with stage 0 reported a need for manual reduction of the vaginal wall in order to urinate whereas this was significantly associated with prolapse of all three compartments.

In the age- and parity-adjusted logistics regression model, urge urinary incontinence tended to be associated with prolapse in the anterior and posterior compartment but the association was strongest and stage-dependent only with anterior wall prolapse. Stress urinary incontinence was strongly, stage-dependently and exclusively associated with posterior wall prolapse.

### **Bowel symptoms and objectively observed POP**

In the simple cross-tabulations none of the investigated bowel symptoms showed associations with POP in any compartment except for fecal incontinence and multi- compartment prolapse.

In the age- and parity-adjusted logistics regression model, bowel symptoms were less consistently linked to compartment-specific prolapse, and observed associations lacked clear stage dependency. Posterior wall prolapse of both stage I and stage II-IV was associated with sixfold or more increases in the odds for painful defecation ( $p=0.05$ ), but there was no increasing trend with increasing prolapse stage and the CIs were wide. Apical prolapse stage I-IV was associated with a 2.1-fold increase in the odds of fecal incontinence but was only of borderline statistical significance.

### **Conclusion**

The symptoms investigated in this study among non-patients could not predict the anatomic location of the prolapse. A feeling of a vaginal bulge was found to be specific to prolapse.

**Table 4** Various degrees of compartment-specific anatomical prolapse and mechanical, urinary, and bowel-related symptoms. Associations are expressed as odds ratios and 95% confidence intervals (within brackets). Separate age- and parity-adjusted logistic regression models for each symptom, with adjustments for prolapse in other compartments.

	Anterior wall			Posterior wall			Superior vagina				
	Stage 0	Stage I	Stage II-IV	p-value	Stage 0	Stage I	Stage II-IV	p-value	Stage 0	Stage I-IV	p-value
<b>Mechanical symptoms</b>											
Vaginal bulging	1 (ref)	1.6 (0.7-3.5)	5.8 (2.5-13.3)	p<0.0001	1 (ref)	1.2 (0.4-3.9)	2.9 (0.9-9.2)	p=0.034	1 (ref)	4.2 (2.1-8.5)	p<0.0001
Vaginal discomfort	1 (ref)	0.9 (0.4-2.1)	2.0 (0.8-4.7)	p=0.113	1 (ref)	2.1 (0.5-7.8)	2.7 (0.6-11.0)	p=0.392	1 (ref)	1.3 (0.6-2.8)	p=0.554
Worse upon heavy lifting	1 (ref)	1.6 (0.7-3.5)	3.3 (1.4-7.5)	p=0.015	1 (ref)	5.3 (1.1-26)	4.7 (0.9-24.4)	p=0.118	1 (ref)	1.9 (1.0-3.9)	p=0.068
<b>Urinary symptoms</b>											
Urge incontinence	1 (ref)	1.7 (0.9-3.1)	2.5 (1.2-5.3)	p=0.039	1 (ref)	2.2 (0.9-5.5)	2.1 (0.8-5.9)	p=0.248	1 (ref)	1.0 (0.5-1.8)	p=0.926
Stress incontinence	1 (ref)	1.0 (0.5-1.9)	1.8 (0.9-3.6)	p=0.161	1 (ref)	4.2 (1.6-11)	5.4 (1.9-15.2)	p=0.005	1 (ref)	0.7 (0.4-1.3)	p=0.284
Manual reduction	1 (ref)	4.9 (0.4-62)	17.8 (1.6- 202)	p=0.027	1 (ref)	1.0 (0.1-15)	1.4 (0.1-23.6)	p=0.882	1 (ref)	2.2 (0.5-9.2)	p=0.292
<b>Bowel symptoms</b>											
Constipation	1 (ref)	0.8 (0.3-2.0)	1.5 (0.5-4.3)	p=0.458	1 (ref)	0.9 (0.3-3.0)	1.3 (0.3-5.3)	p=0.633	1 (ref)	0.9 (0.4-2.1)	p=0.827
Hard/lumpy stool	1 (ref)	2.2 (1.1-4.4)	2.0 (0.9-4.2)	p=0.086	1 (ref)	1.1 (0.4-2.8)	1.3 (0.5-3.8)	p=0.786	1 (ref)	0.7 (0.4-1.4)	p=0.292
Difficult evacuation	1 (ref)	2.0 (1.0-4.2)	1.6 (0.7-3.5)	p=0.160	1 (ref)	1.0 (0.4-2.6)	1.2 (0.4-3.4)	p=0.915	1 (ref)	0.8 (0.4-1.7)	p=0.621
Painful defecation	1 (ref)	3.1 (1.2-8.1)	1.5 (0.5-4.4)	p=0.045	1 (ref)	7.6 (1.5-37.7)	6.0 (1.0-36.0)	p=0.041	1 (ref)	0.9 (0.4-2.2)	p=0.801
Flatus incontinence	1 (ref)	1.6 (0.7-3.5)	1.4 (0.6-3.2)	p=0.4960	1 (ref)	1.0 (0.4-2.6)	1.6 (0.5-4.8)	p=0.513	1 (ref)	0.7 (0.3-1.5)	p=0.350
Fecal incontinence	1 (ref)	1.2 (0.4-3.2)	1.3 (0.5-3.7)	p=0.872	1 (ref)	1.7 (0.4-7.8)	2.0 (0.4-9.9)	p=0.705	1 (ref)	2.1 (1.0-4.8)	p=0.060

## NON-OBSTETRIC RISK FACTORS AND SYMPTOMATIC POP (PAPER II)

Age and parity were the dominating risk factors but have been addressed in a previously published paper<sup>12,86</sup>.

### Family history and conditions signaling weak connective tissue

In simple age- and parity models the prevalence of symptomatic prolapse was higher in women whose mothers and/or sisters had undergone surgery for prolapse, compared to women without such family history (POR 3.1; 95%CI 1.7-5.5). A history of conditions suggestive of deficient connective tissues (varicose veins, hernia, hemorrhoids) was also significantly associated with symptomatic prolapse (POR 2.0; 95% CI 1.4-3.0).

### Non-obstetric strain on the pelvic floor (overweight/obesity, heavy lifts, and abnormal bowel habits)

In simple age and parity adjusted models BMI  $\geq 25$ , as well as waist circumference  $\geq 88$ cm, was found to be significantly associated with symptomatic prolapse.

The odds of having symptomatic prolapse were found to fall with increasing duration of the smoking habit. Heavy lifting at work was found to be positively linked to POP.

Subjects currently engaged in physical activity with high impact on the pelvic floor (running, jumping and ball sports) had a lower prevalence of symptomatic prolapse than those reporting low impact exercise (walking, swimming or light physical exercise).

All of the bowel symptoms considered– constipation, problems with hard/lumpy stool, difficult evacuation, pain at defecation, gas and fecal incontinence – showed significant associations with symptomatic prolapse

### Final multivariable logistic regression model

All the variables that were significantly linked to symptomatic prolapse in the simple age- and parity adjusted models were considered, except for incontinence of gas or feces, because these symptoms are more likely to be part of pelvic floor dysfunction rather than a cause of prolapse. Instead, level of education was considered because this factor was *a priori* perceived as potentially linked to the inclination to report prolapse symptoms. Furthermore age at menopause, weight gain ( $<5$  or  $\geq 5$  kg since age 20), weight loss ( $<5$  or  $\geq 5$  kg), the ratio of waist/hip circumference, and asthma/chronic cough were considered– factors for which there were strong *a priori* hypotheses.

Ultimately eight variables turned out to be significant. Age, parity and family history of prolapse were the dominating risk factors although the confidence intervals for PORs were wide. The POR point estimate for age had an apparent threshold of 50-59 years while for parity the odds for symptomatic prolapse tended to increase with increasing parity. This tendency was also observed in relation to increased BMI although the confidence interval included 1 for underweight and obesity, the two categories with the lowest number of subjects. The presence of any condition suggestive of deficient connective tissue was significantly associated with symptomatic prolapse, as was heavy lifting at work although no clear dose-response was confirmed. Smoking duration, remained significantly and inversely related to symptomatic prolapse (POR 0.98 per year of smoking; 95%CI 0.96-0.99). Presence of any abnormal bowel habits conferred twofold increased odds.

The analyses were repeated after restricting to parous women (n=365). The results were essentially unaltered by this restriction.



**Table 5** Multiple logistic regression including variables shown to be significant n=442

Variable	Prevalence odds ratio estimates		
	Point estimate	Confidence limits 95%	p-value
Age			
30-39	ref		
40-49	2.55	1.24-5.24	p=0.0055
50-59	3.52	1.80-6.91	
60-69	2.98	1.40-6.32	
70-79	3.02	1.31-6.92	
Parity			
0	ref		
1	3.47	1.53-7.86	p=0.0013
2	4.71	2.23-9.95	
3	4.40	1.85-10.51	
4-6	6.31	1.75-22.73	
BMI			
Underweight (<19)	0.83	0.24-2.86	p=0.0377
Normal weight (19-25)	ref		
Overweight (26-30)	1.88	1.15-3.08	
Obese (>30)	2.07	0.95-4.50	
Varicer/Hernia/ Hemorrhoids			
no	ref		p=0.0088
yes	1.80	1.16-2.80	
Family history of prolapse			
No	ref		p=0.0005
yes	3.26	1.67-6.35	
Heavy lifting at work			
No	ref		p=0.0135
<10 kg	1.98	1.10-3.59	
≥10kg	1.94	1.15-3.27	
Number of years smoking <sup>1</sup>	0.98	0.96-0.99	p=0.0142
“Normal bowel habits”			
yes	ref		p=0.0008
no <sup>2</sup>	2.13	1.37-3.31	

<sup>1</sup>Continuous variable: each year of smoking decrease OR by 2%.

<sup>2</sup>presence of constipation, hard/lumpy stool and/or difficult evacuation (“yes, often or sometimes”)

## Conclusion

In addition to age, parity and individual predisposition, modifiable risk factors such as BMI, heavy lifting and constipation were associated with symptomatic pelvic organ prolapse.

## SHORT TERM NATURAL HISTORY OF SYMPTOMATIC POP (PAPER III)

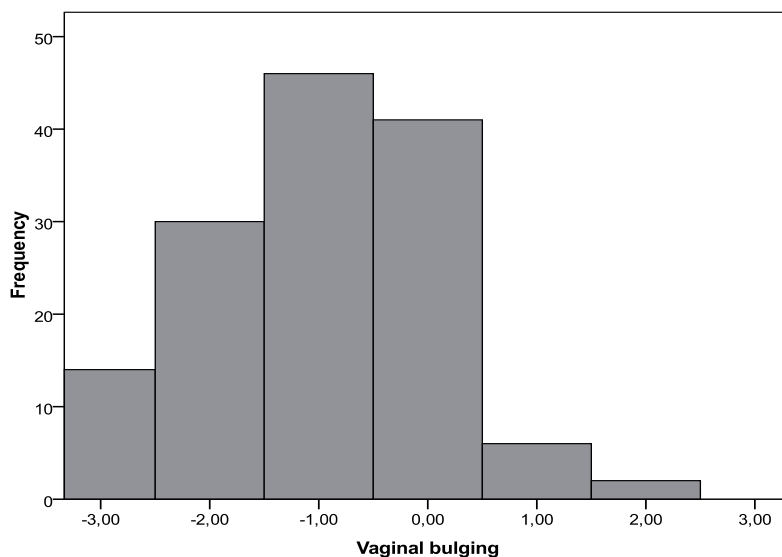
### Development of symptoms

Among women who were initially classified as having symptomatic prolapse, the prevalence of the symptom “feeling of a vaginal bulge” decreased from 61% to 22% ( $p < 0.001$ ), “vaginal discomfort” from 27% to 17% ( $p = 0.041$ ), and “worsening of symptoms with heavy lifting” from 38% to 29% ( $p = 0.088$ , McNemar’s test).

Urinary incontinence at baseline and at follow up was reported to a lesser extent in symptomatic women and control women alike.

For the key symptom “vaginal bulging” individual changes were studied between categories of self-reported frequency using the full resolution of the rating scale (never, infrequently, sometimes, often). This analysis was confined to the 141 women who were initially classified as having symptomatic prolapse and who answered the questionnaire twice. While women with no change constituted 30% (95% confidence interval [CI] 22-37%), more women reported a reduction of symptoms (64%, 95% CI 56-72%) than an increase (6%, 95% CI 2-10%).

A similar analysis among women not fulfilling the criteria for symptomatic prolapse showed that 91% reported no change, while seven (7%) had experienced an increase.



*Figure 5. The frequency distribution of individual changes in the key symptom of vaginal bulging among women classified as symptomatic ( $n = 141$ ). Zero on the x-axis denotes no change,  $-1$  means a change of 1 step in the direction of less symptoms, and  $+1$  represents a 1-step change in the direction of more symptoms.*

### Development of POP-Q stage

Two evaluations of POP-Q stage were performed in a total of 188 women (116 initially classified as having symptomatic prolapse and 72 as having no such prolapse). A majority (84%) of the 116 women who fulfilled our criteria for symptomatic prolapse at entry had POP-Q stages I and II initially. At the five-year follow-up examination the distribution had shifted towards less advanced stages ( $p < 0.0001$ ; sign test), although the majority (66%) still had stage I-II.

A less marked, and statistically non-significant ( $p = 0.743$ ; sign test) shift, was noted among women whose answers in the initial questionnaire were inconsistent with symptomatic prolapse.

The analyses were repeated after combining stage 0 and I. The shift towards less advanced stages remained significant both among women initially classified as having symptomatic prolapse ( $p = 0.007$ ; sign test) and among the 72 who did not fulfill the criteria for symptomatic prolapse at entry ( $p = 0.027$ ; sign test). An additional sensitivity analysis was made among the 116 women initially

classified as having symptomatic prolapse, assuming that operated women would have had POP-Q stage IV at the end of follow-up if the surgical intervention had not occurred. There was still a net shift toward lower POP-Q stages although it did not attain statistical significance ( $p=0.314$ ) (data not shown)

Among the examined women who initially fulfilled the criteria for symptomatic prolapse almost half of them (47%;95% CI 38-57%) had the same stage after five years as they had at entry, both progression and regression had occurred. Regression was more common than progression (40%, 95% CI 31-49% versus 13%, 95% CI 7-19%).

In a sensitivity analysis we assumed that all women who had pelvic floor surgery in the follow-up period, to have POP-Q stage IV at follow up, if left unoperated. Even with this extreme assumption, regression was more common than progression.

Among the asymptomatic women with stage 0, 77% remained within this stage, 18% had progression to stage I and 5% to stage II. The only woman who went from stage 0 to stage II reported a vaginal delivery during follow up. Of the women initially in stage I 32% remained unchanged, 32% showed regression, while 32% had progression to stage II, and 3% to stage III. For 13 women with stage II at baseline, six remained unchanged, five regressed to stage 0 or I, while two showed progression to stage III.

**Table 6** Changes in distributions of POP-Q stages between the first examination in 2002 and second examination in 2008 among 116 women initially classified as having symptomatic prolapse and 72 women without symptoms indicative of symptomatic prolapse

POP-Q stage	Symptomatic prolapse in 2002		No symptomatic prolapse in 2002	
	2002	2008	2002	2008
0	2 (1.7)	24 (20.7)	22 (30.6)	32 (44.4)
I	25 (21.6)	23 (19.8)	37 (51.4)	18 (25.0)
II	72 (62.1)	54 (46.6)	13 (18.1)	19 (26.4)
III	13 (11.2)	15 (12.9)	0	3 (4.2)
IV	4 (3.5)	0	0	0

### Relation between changes in POP-Q stage and changes in symptom presentation

This analysis included the women who had answered the questionnaire and attended the gynecological examinations both at entry and at follow up ( $n=188$ ). No statistically significant associations were found between changes in POP-Q stages and changes in reported symptoms. Data were re analyzed stratified for age ( $<45$  and  $\geq 45$  years), restricted to women with symptomatic prolapse at entry and in a sensitivity analysis excluding women who had undergone POP and/or incontinence surgery after entry into the cohort but the results were similar.

### Conclusion

Mild to moderate pelvic organ prolapse is a dynamic condition, but only a small proportion of affected women get worse within five years.

## PROSPECTIVE EVALUATION OF VAGINAL PROLAPSE SURGERY (PAPER IV)

No serious peri- or postoperative complications occurred; the most common complication was urinary infection which occurred in 6.1% of cases.

### Anatomic and symptomatic outcome

Anatomical recurrences in operated compartment were 74/185(40.0%) and prolapse in a different compartment 16/185 (8.6%). More than half of the anatomical recurrences (57/90; 63.3%) were diagnosed within the one year follow up for all different procedures.

Recurrence including the anterior compartment was the most common regardless of procedure. The recurrence rate was highest for the single procedure in the anterior wall but the numbers of this procedure were small (n=7). The lowest recurrence rate was found for single procedure in the posterior wall (19%) although a considerable proportion was diagnosed with prolapse in another site at follow up. Among all the anatomical recurrences, less than half were symptomatic (44/90; 48.8%).

### Functional outcome

#### Urinary symptoms

Women with no UI preoperatively were diagnosed with de novo urge UI in 22.6%, de novo SUI 6.0% and de novo mixed 4.8 % at one year follow up.

After anterior repair without concomitant incontinence surgery women with SUI/mixed UI preoperatively had a resolution of SUI of 42.3% (11/26).

Women with urge UI/mixed UI preoperatively were relieved of urge UI in 33.7% (11/31) after anterior repair.

#### Bowel symptoms

Among all women who preoperatively reported difficulty emptying bowel (n=61) all but one underwent a posterior repair. Fifty-seven of them came to one year follow up visit and 75 % (95%CI: 64-87) were relieved of their symptom.

#### Dyspareunia

At the five year follow up 73/143 reported that they had been sexually active and 19 (26%) had symptoms of dyspareunia.

**Table 7** Functional symptoms preoperatively and at all follow up.

Time	Preop (n=185)	1 year (n=173)	3 year (n=152)	5 year (n=143)
Months; mean (SD) [range]		13.1(2.8) [5-29]	38.0(3.6) [27-51]	62.5 (5.8) [50-84]
<b>Mechanical symptoms</b>				
Vaginal bulging/discomfort	152 (82.2%)	24 (14%)	16 (10%)	28 (20%)
<b>Urinary symptoms</b>				
No incontinence	91 (49%)	83 (48%)	68 (45%)	70 (49%)
Urge incontinence	28 (15%)	51 (29%)	49 (32%)	30 (21%)
Stress incontinence	32 (17%)	20 (12%)	16 (10%)	13 (9%)
Mixed incontinence	34 (18%)	18 (10%)	18 (12%)	13 (9%)
<b>Bowel symptoms</b>				
No bowel symptoms	106 (57%)	118 (68%)	95 (62%)	74 (52%)
Diff emptying/Constipation	61 (33%)	25 (14%)	34 (22%)	41 (29%)
Gas incontinence	27 (15%)	27 (16%)	23 (15%)	36 (25%)
Faecal incontinence	21 (11%)	21 (12%)	9 (6%)	16 (11%)

### **Predictive factors for symptomatic recurrence**

Younger age and involvement of more than two sites preoperatively turned out to be significantly associated with having an anatomical recurrence compared to the women with no recurrence. No differences were found concerning parity, BMI or previous gynecological operations.

### **SF-36 at five year follow up**

At the five year follow up 85.3% (122/143) completed the SF-36 Health survey.

The SF-36 dimension scores were generally comparable to those of an age-matched reference group except for social functioning where the scores tended to be lower especially for women younger than 65 years old.

### **Conclusion**

This long-term follow up of standard prolapse surgery showed a high rate of anatomic recurrence but only half of the women were symptomatic. The compartment most prone to recurrence was the anterior wall. Most of the failures occurred within the first year after surgery. Our data showed an alleviation of mechanical symptoms and an improvement of difficulty emptying bowel after a posterior repair. This study also supports a certain improvement of stress and urge urinary incontinence after an anterior repair but also demonstrates the difficulty in predicting outcome of urinary incontinence in any individual woman



# GENERAL DISCUSSION

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## METHODOLOGICAL CONSIDERATIONS

### Study design

Clinical research falls into two general categories: experimental and observational, based on whether the investigator assigns exposure or not. Experimental trials can be subdivided into randomised and non-randomised. Randomised controlled trials are considered the gold standard in clinical research.

Observational studies can be descriptive or analytical. In analytic studies the occurrence of diseases is related to suspected causative factors (“risk factors”) and causal inferences are made in contrast to descriptive studies. Within analytical studies, cohort studies track people forward in time from exposure to outcome. In contrast, case-control studies work in reverse tracing back from outcome to exposure. Cross sectional studies are like a snapshot, which measures both exposure and outcome at one point.

Measures of association such as relative risk or odds ratio are the preferred way of expressing results of dichotomous outcomes and confidence intervals around these measures indicate the precision of these results<sup>121</sup>.

In choosing the most suitable type of study there are many factors to be considered.

For those questions where it is unethical to assign factors, investigators are limited to observational studies. Some exposures such as in our study, vaginal delivery with different interventions, overweight, constipation, heavy lifting would not have been possible to allocate for ethically or clinically.

An ideal study design to resolve a lot of our questions, both regarding symptoms, risk factors and the natural history of pelvic organ prolapse, would have been to assemble a cohort of nulliparous women, exposed to different risk factors and follow them over time. Eventually different groups would be formed with and without different symptoms and with and without pelvic organ prolapse. However for the study of a disease with a long latent period such as pelvic organ prolapse this type of research design take a long time to yield results, is very expensive and is susceptible to bias by differential loss to follow up<sup>122,123</sup>. Case control studies are, on the other hand, especially useful for outcomes that take a long time to develop but are dependent on the choice of appropriate controls.

Cross sectional studies cannot measure disease incidence but can assess disease prevalence and the relation between prevalence and possible exposures. It is also possible to use cross-sectional data for case control studies if the study includes prevalent cases and uses concurrent information about exposures. A case control study that is based on prevalent cases rather than new cases will not necessarily provide information about the causes of the disease. Cases in such a study are those who have the disease at a given point in time and will be more heavily weighted towards cases of long duration. Cross sectional information can also be used for longitudinal data with respect to causal hypotheses but recall bias can be a problem<sup>122</sup>.

We performed a large cross sectional study in Stockholm of the prevalence of symptomatic prolapse<sup>12</sup> from which papers I-III proceeded. Data from the cross sectional study gave us the opportunity to select a random sample of cases and controls, not only to validate the questionnaire<sup>119</sup> but also to study risk factors for POP (paper II)<sup>86</sup>. The standardized examination in the validation study was double blinded, both to the examiners and the women, which subsequently gave us the opportunity to analyze objectively observed anatomical findings with reported symptoms (paper I) and further prospectively follow the group of examined women with symptoms indicative of pelvic organ prolapse and a control group (paper III). Consequently this study design fulfilled several of our aims.

In paper IV, a descriptive study was used to follow a cohort of women who underwent surgical procedures for prolapse. A randomization to different surgical approaches would have been the ideal study and was discussed but faced several difficulties. Women presenting for prolapse surgery often have advanced pelvic organ prolapse with an involvement of more than one compartment, often in different combinations together with diverse symptoms of pelvic floor dysfunction. The restriction to a population with similar defects undergoing one standardized operation was not considered to be realizable.

### **Internal validity**

A study is internally valid if the study conclusions represent the truth for the individuals studied. Bias or systematic errors undermine the internal validity. Bias cannot be reduced by increasing sample size, only by proper study design and execution. Observational studies are more vulnerable to bias but are more representative of women in general than are participants in randomized controlled trials<sup>123</sup>. Some of the possible sources of bias in the studies of this thesis will be considered.

#### *Information bias (observation, classification or measurement bias)*

Although POP-Q provides an objective method of describing pelvic support a clinical examination of prolapse can be subjective. The measurements of POP-Q were performed by two different gynecologists in paper I and by a third gynecologist in paper III. We believed that by introducing a new examiner, who had not met the women before would avoid observation bias. In order to calibrate the POP-Q assessments the examiners jointly examined and discussed the measurements in the first 10 patients in both studies. The interexaminer agreement was good concerning all stages of prolapse but the interexaminer distinction between stage 0 and I was identified as the most difficult. Stage 0 represents an ideal level of support and to distinguish between stage 0 and I is recognized as probably without a clinical relevance<sup>20</sup>.

In paper I the questions used about bowel function were asked in the supplementary 72-item questionnaire which was administered after the gynecological examination. The reason for not including questions about bowel symptoms in the initial questionnaire was that they had not been shown to have any predictive value for identifying women with POP. Consequently, information communicated to the participants in paper I about their prolapse status, even if deliberately sparse, may have affected these answers. Such information would be expected to exaggerate associations, but since bowel symptoms, except for fecal incontinence in apical prolapse, were generally unrelated to pelvic floor defects, it appears that this did not significantly affect our results

Given a sensitivity of the initial questionnaire vis-à-vis anatomical prolapse of 66%, a specificity of 94% and a prevalence of POP of approximately 10%, the positive predictive value of the questionnaire was around 60%, while the negative predictive value was 97%. This means that



approximately 40% of the women classified as having symptomatic prolapse, in fact, did not likely have anatomic prolapse. Among women classified as being without symptomatic prolapse, on the other hand, no more than approximately 3% were, in fact, expected to have anatomic prolapse. The effect of this misclassification would be to underestimate associations with risk factors.

We also acknowledge the common problem in case control studies of family history bias and recall bias.

#### *Selection bias*

Among the women sampled for gynecological examination in paper I, only 57% of the symptomatic and 43% of the asymptomatic women attended.

In paper III 72% of those with symptomatic prolapse and 60% of control women attended the five-year follow up examination.

Although the distributions of age and gynecological histories among participating women looked very similar to those among all women invited, we cannot exclude the possibility that factors linked to the inclination to participate may have acted as effect-modifiers of the relationships between anatomical defects and subjective symptoms (paper I) and the observed deteriorations of POP-Q stage which were higher among women initially classified without symptomatic prolapse (paper III). In paper II we restricted our study to women with an intact uterus and no prior surgery for prolapse or incontinence. We postulated that symptoms and recall might differ among women who have undergone pelvic surgery. However, we believe that this selective mechanism should if anything have reduced the differences observed.

#### *Regression toward mean*

Regression toward the mean states that where a first measurement is higher or lower relative to the mean, the expected value of the second measurement will be closer to the mean than the observed value of the first measurement<sup>124</sup>. This was considered to be a contributory explanation for the counterintuitive general tendency to get better rather than worse over time among the women in paper III. Regression toward the mean is seen whenever there are repeated observations on a variable process, with selection for extreme values. Being symptomatic might be regarded as an extreme value in our original population-based survey investigation, and thus some regression towards less extreme values (being asymptomatic) is expected. On the other hand, our participants were not selected based on POP-Q stage; although biological variation or random fluctuations within the individual might explain some individual changes from higher POP-Q stages to lower (because division into levels creates “extremes”), these phenomena should also explain individual changes from lower stages to higher. Hence, the net effect in the entire study group should not be particularly sensitive to regression toward the mean, yet we observed a net flux toward lower stages. Accordingly, although regression toward the mean may explain some (or even much) of the observed improvement over time, it is unlikely to explain all.

### **External validity**

External validity refers to the generalizability of the findings. That is if the findings are applicable to other populations<sup>121</sup>.

Papers I-III were based on a random sample from the Stockholm female population via the continuously updated computerized population register comprising both women whose self-reports were consistent with pelvic organ prolapse and those whose answers did not indicate presence of pelvic organ prolapse.

We believe that the observed anatomic defects and the correlations with self-reported pelvic floor-related symptoms (paper I) among women who were not seeking care for urogynecological complaints were reasonably representative of their source population and generalizable to women with mild to moderate prolapse. The distributions of symptoms and anatomic defects among the 280 examined women, on the other hand, will not be generalizable to those in the entire 30-79 year-old female population in Stockholm. For study efficiency reasons we over-sampled among symptomatic women when selecting subjects for the gynecological examinations. The observation of short term natural history in women with mild to moderate symptomatic prolapse should not readily be generalized to women seeking care for pelvic organ prolapse which might represent a group of women with more rapid symptom and anatomical progression.

The case control study (paper II) was based on the same population sample but included all the prevalent cases and a random sample of controls among asymptomatic women. The estimated prevalence of symptomatic prolapse was consistent with the findings from other countries. We restricted the study to women without hysterectomy and no prior POP surgery which may challenge the generalizability, particularly with respect to populations with a high prevalence of hysterectomy. Moreover, it cannot be predicted whether or not the pelvic support defects in this population will advance to more severe prolapse and for this reason the results of the study cannot be readily generalized to apply to a prolapse of such severity that it necessitates surgical repair.

Surgically treated prolapse represents the severe end of the clinical spectrum of pelvic organ prolapse. The women included in paper IV were evaluated preoperatively and followed prospectively with high participation at long term follow up. We believe that our findings in paper IV are generalizable to women with advanced prolapse undergoing traditional vaginal reconstructive repair.

## **ASPECTS OF CLINICAL EVALUATION OF PELVIC ORGAN PROLAPSE**

### **Classification and definition**

The only prolapse classification that has attained international acceptance and recognition is the POP-Q classification but there are limitations and critics<sup>125</sup>. The definition of clinically significant prolapse is controversial. In the original article of POP-Q the absence of prolapse was defined as stage 0. Applying this definition to various populations 27-98% of women have pelvic organ prolapse<sup>126</sup>. Most clinicians would agree that women with POP-Q stages III and IV have the clinical condition of POP. The controversy lies above that what can be classified as “normal” or “abnormal”. A definition for POP as rather being  $\geq -1$  cm above the hymenal remnants (POP-Q stage II or greater) has been proposed<sup>3</sup>. The symptom most strongly correlated with the presence of advanced pelvic organ prolapse is vaginal bulging and the specific threshold for bulging protrusion symptoms appears to be near the hymen<sup>127</sup>. POP-Q stage II is defined as the most distal portion of the prolapse  $\geq -1$  cm but  $\leq +1$  cm to the plane of the hymen, hence symptomatic women with clinically apparent prolapse are lumped together with women who are asymptomatic. The POP-Q does not incorporate symptoms.

The distinction between POP-Q stage 0 and stage I has been suggested to be too specific and lack clinical relevance<sup>20</sup>. The stages in POP-Q were assigned based on expert opinion and not derived from scientific data<sup>127</sup>. A more simplified system of POP-Q with an absence of stage 0 has been suggested but no further testing of this system has been published<sup>20</sup>. Since the difference between stages 0 and I in POP-Q was of clinically questionable significance, and possibly also liable to observer bias, the analyses were repeated in both paper I and III after combining stage 0 and I categories. The results were remarkably similar.

Outcome after surgery faces the same problems of definition. Many women who may be categorized as “anatomic failures” are in fact satisfied with their postsurgical results <sup>112</sup>. The distinction between cure and failure after intervention was addressed in 2001 at a consensus conference on the terminology of female floor dysfunction <sup>3</sup>. Optimal anatomic outcome after intervention should still be considered as stage 0, but satisfactory outcome as stage I. A stage II should be regarded as a failed treatment. The authors concluded that there was insufficient evidence to include symptoms. In Paper IV we followed this recommendation for the classification of failure at the five year follow-up. When planning the study in 1997 the Beecham system was used at the clinic according to tradition. Since the POP-Q system was formally adopted as the standard for describing prolapse the classification was gradually changed during follow up. Anatomical recurrence according to Beecham in the first three years of follow up was a prolapse to the introitus without straining, which would correspond to at least POP-Q  $\geq$ stage II. The high participation in this study at the long term follow up and the fact that POP-Q provided a more objective system for describing pelvic support the assumptions was that our long term results were more adequately described according to POP-Q and will be more useful in the comparisons with other studies.

Another limitation to the POP-Q system is the assessment of paravaginal or lateral anterior vaginal support which is not addressed. Lateral defects are proposed to be more often related to urinary incontinence <sup>128</sup>. The studies performed in this thesis have not taken any considerations to diagnosing central or lateral defects.

## Symptoms

Women with prolapse may have a variety of pelvic floor symptoms and many symptoms associated with prolapse can also be experienced by women with adequate support. It is recognized that many of these symptoms may in fact be a result of co-morbidities of pelvic floor dysfunction. Symptoms have commonly been attributed to the observed prolapsed anatomic compartment but symptoms are often multiple and their concerns diverse. There have been a number of hospital-based studies, prospective <sup>23,25,26,126</sup> and retrospective<sup>36,129</sup>, comparing prolapse symptoms and findings on examination. The studies are based on investigated women complaining of prolapse but with no control group.

In Paper I, compartment-specific anatomic findings classified according to POP-Q was blindly correlated to self-reported pelvic floor-related symptoms among women who were not seeking care for urogynecological complaints. The symptom of “feeling of a vaginal bulge” was found to be specific to prolapse but not to any particular compartment. The association was stronger with anterior wall prolapse as was also the symptom “aggravation with heavy lifting”. Prolapse of the posterior wall was found to be somewhat less symptomatic in terms of mechanical symptoms but was found to have a strong association with stress urinary incontinence. This has not been shown in any other study. Rather, posterior wall prolapse stage II or greater has been shown to mask stress urinary incontinence<sup>130,131</sup>. Women in this study with posterior wall prolapse were younger and few had more advanced prolapse. Stress urinary incontinence is more common among younger women as are signs of an asymptomatic posterior wall prolapse <sup>6</sup> hence, in our study group, stress urinary incontinence and an asymptomatic weakness in the posterior compartment could be an early sign of pelvic floor dysfunction. Conclusions regarding the cause and effect of this relationship cannot be drawn from this study but pelvic organ prolapse has been shown to share risk factors with stress urinary incontinence. In concordance with other reports, bowel symptoms were not found to be associated with mild to moderate pelvic organ prolapse in any compartment. The data from this study

demonstrated that symptoms of prolapse were a poor guide to examination findings. This concurs with the data published recent years but this population based study is one of the first to also confirm this also in “non-patients” with mild to moderate prolapse.

The surgical treatment of prolapse should not only aim at restoration of normal pelvic anatomy, it should also aim at the reestablishment or maintenance of normal urinary, rectal and sexual functions and when possible not causing the woman any adverse effects. The impact of surgery on associated pelvic floor symptoms has generally been poorly reported<sup>44</sup>

In paper IV mechanical, urinary and bowel symptoms were evaluated prospectively but there are few studies with which to compare our results with. Most studies are retrospective and have focused on anatomic outcome or have short term follow up. The anatomical outcome in our study did not correspond to subjective outcome. Despite an objectively observed recurrence of POP-Q  $\geq$  stage II only half of these women were symptomatic with respect to vaginal bulging. This observation has been reported by others<sup>112 125</sup>.

The prevalence of UI preoperatively in our patient population remained at an almost constant level postoperatively although for the individual women there were changes in type of UI.

Comparing our results with the meta-analysis in the Cochrane review of the surgical management of prolapse<sup>44</sup> our population showed lower rates of de novo SUI (10% vs 21%) which could possibly be explained by the large number of pessaries used preoperatively, unmasking occult SUI. The effect on urge UI and prolapse surgery is limited and inconclusive<sup>44</sup>. Both improvement in overactive bladder symptoms<sup>43,132</sup> and no changes have been reported<sup>133</sup> In concordance with the literature we found an improvement of difficulty emptying bowels after traditional posterior colporrhaphy<sup>55-57</sup> despite the fact that the relationship between stage of prolapse and bowel symptoms has been found to be weak<sup>45</sup>. A careful evaluation of patients’ bowel symptoms before planning surgical intervention for posterior prolapse is generally recommended considering other factors that can contribute to defecatory dysfunction<sup>134</sup> like functional motility disorders and dyssynergic defecation .

In paper III changes in pelvic support and symptom development were evaluated as well as the relationship between these respective parameters in a cohort of mostly non-seeking women with symptoms indicative of prolapse, with or without verifiable anatomical defects at time of entry.

At baseline the women reported symptoms of such quality and severity that presence of prolapse was deemed likely, and 98% of them, indeed, had anatomic prolapse of POP-Q stage I or higher (although a less impressive 75% had stage II or higher). Only a minority of these women with symptomatic prolapse reported symptom aggravation over time, and a larger proportion reported improvement. These findings that mild to moderate prolapse is a dynamic condition in which spontaneous regression can occur is largely consistent with the few studies published to date on this topic<sup>115,116</sup> even if their participants were older and postmenopausal. It is conceivable that some women adapt to their symptoms and fail to report them unless they progress<sup>135</sup>.

### **Risk factors**

Vaginal parity is a well-established risk factor for POP<sup>1,71</sup> but the specific obstetric risk factors remain controversial<sup>70</sup> This has been addressed and discussed in a previous published paper from this cross sectional study<sup>86</sup>. Multiple deliveries, episiotomy, histories of any rupture were found to be the main predisposing factors for symptomatic prolapse. Cesarean delivery was protective. No associations were found for other commonly quoted obstetric risk factors such as instrumental delivery<sup>11 92</sup> and weight of the largest infant<sup>13</sup>.

For the most frequently quoted non-obstetric risk factors for POP evidence is still lacking<sup>73</sup> and several of them were addressed in this thesis.

*Age*

Recent years studies have been inconsistent with respect to the age-prolapse association. Older women may be less aware of prolapse symptoms which affect the possibility of screening without clinical examination. In the source population for the present study the prevalence of symptomatic prolapse tended to level off at an age corresponding to menopause<sup>12</sup>. It appeared however from the clinical examinations in paper I that the involvement of an increasing number of compartments was associated with advancing age as the presence of more advanced prolapse (stage III and IV) even if the number of them were few.

Contradictorily in paper IV younger age and more compartments involved preoperatively were found to be significantly associated with having an anatomical recurrence after prolapse repair. We speculated in different explanations such as the caution of operating younger women with respect to maintaining sexual function, if younger women are physically more active which could possibly influence the risk of recurrence or if it reflected women with a higher risk due to genetic predisposition/connective tissue disorder or a result of greater birth-induced injury (muscle, nerve, fascia) relative to other women. Younger age as a risk factor for prolapse recurrence has previously been described<sup>136</sup>.

*Family history and conditions signaling weak connective tissue*

Independent associations with family history and conditions signaling weak connective tissue were found in our study. A family history of prolapse supports the hypothesis that certain women are genetically more predisposed to the condition consistent with previous findings<sup>76 78 14 79</sup>. In sister pairs, comparing nulliparous women and their parous sisters, a high concordance in prolapse stages has been observed which suggests a familial predisposition for pelvic support and a possible explanation why prolapse occurs in some nulliparous women<sup>137</sup>. White race is also considered as a risk factor, while African ethnicity is thought to be protective<sup>74,138</sup>. Race was not addressed in this thesis. We believe that almost all women in our studied populations were white. The hypothesis that hemorrhoids/hernia/ varicose veins can be clinical markers for connective tissue deficiency has been sparsely explored but in another Swedish population based study of factors associated with pelvic floor dysfunction this association could only be confirmed for urinary incontinence<sup>10</sup>. Although the association in our study of family history and POP may have been inflated due to information bias, the association between symptomatic prolapse and a history indicative of deficient connective tissue is less likely to be explained by such a bias. We postulated that most of the affected women in our study had never seen a doctor for their symptoms and had never been given a prolapse diagnosis.

*BMI*

BMI was independently associated with the presence of symptomatic prolapse. This was confirmed both in simple age- and parity-adjusted analyses and in the multivariable analyses. The POR point estimate tended to increase with increasing BMI although the confidence interval included 1 for underweight and obesity, the two categories with the lowest number of subjects. Even if increasing BMI is considered as one of the most consistent risk factors for POP data are conflicting<sup>139</sup>. Many of the assumptions are drawn from associations between stress urinary incontinence and POP. Numerous epidemiological studies have shown an association between obesity and urinary incontinence<sup>140</sup> however the evidence for the relationship between obesity and the prevalence of POP is more scarce.

Overweight and obesity may possibly also influence surgical effectiveness. Data on the outcomes of surgery for pelvic organ prolapse in obese women are insufficient to draw conclusions but a recent study showed upon similar anatomic and functional outcome after abdominal sacrocolpopexy in obese women ( $\geq 30$  kg/m<sup>2</sup>) compared to healthy-weight women even if the operation time was longer <sup>141</sup>. In a prospective trial examining risk factors for reoperation of POP and UI no association was found for BMI and surgical failures <sup>16</sup> In our prospective study of vaginal surgery for POP (Paper IV) we were not able to find an association between BMI and anatomical recurrence but other retrospective studies have found weight >65 kg to be associated with recurrence <sup>142</sup>.

#### *Chronic pulmonary disease*

Chronic cough is often implicated as a risk factor for POP also primarily based on the association with SUI <sup>99</sup> and the assumption that chronic conditions associated with increased intra-abdominal pressure, puts excessive strain on supporting structures and the pudendal nerve and its branches. No associations with chronic cough or asthma were found in this study. On the contrary, the odds of having symptomatic prolapse were found to fall with increased duration of the smoking habit. In the multivariable logistic regression model smoking duration, remained significantly and inversely related to symptomatic prolapse (POR 0.98 per year of smoking; 95%CI 0.96-0.99). It has been proposed that this inverse association may be mediated by decreased BMI <sup>143</sup> but the apparent protection remained after adjustment for BMI which suggests an independent effect of smoking.

#### *Heavy lifting*

Repetitive heavy lifting as a risk factor for POP was supported in our study. We tried to specify heavy lifting in terms of regularly lifted weight in kilograms over a time period exceeding six months but we did not ask for specific job descriptions. People spend a large percentage of their time working. Whether occupations that involve heavy lifting or extended periods of standing can cause damage to the pelvic floor has been addressed only in a few studies. The limitations of several of the studies are that the women classified themselves into self-described job categories which can introduce information bias <sup>104</sup>. More severe prolapse in lower income groups may reflect limited access to health care, with delayed presentation or recognition of POP. It may also reflect a knowledge barrier, where women of the lower socioeconomic status are less knowledgeable about treatment options.

## FUTURE CHALLENGES

### *Clinical definition and screening methods*

The disease status of pelvic organ prolapse requires a clinically relevant definition<sup>125</sup>. Changes in vaginal anatomy are exceedingly common especially in parous women but the level of normal versus abnormal support is not defined. Optimally the definition should also include bothersome symptoms. To date epidemiological studies would require all women to undergo a pelvic examination in order to assess the presence or absence of prolapse which is time consuming and expensive. The development of screening methods and evaluating these in high and low prevalence populations was an important concern in this cross-sectional study. The problem, similar to other studies, was that when applied to a general population the sensitivity dropped. A certain proportion of women with moderate and even advanced prolapse will be asymptomatic. Symptom-based questionnaires will thus underestimate the true prevalence of anatomic disease.

### *Identifying women at higher risk and prevention*

Caring for women with pelvic floor disorders has become an increasingly important component of women's health care<sup>144</sup>. Identifying risk factors amenable to prevention are of great concern but will only be possible if research clarifies the causative mechanisms.

Improvements in obstetric care have dramatically reduced maternal and fetal mortality during the 20<sup>th</sup> century and focus have shifted towards the reduction of morbidity<sup>145</sup>. Recognition of the associations between childbirth injuries to the pelvic floor and the long-term consequences has contributed to a growing interest in the effects of childbirth on the pelvic floor. Vaginal birth is the major determinant for pelvic floor dysfunction. Whether elective caesarean is totally protective of the pelvic floor is unclear<sup>146</sup>. Pregnancy itself has been suggested to have a role in the development of POP<sup>117,147</sup>. The risk for pelvic floor injury during child birth is a one of the factors driving caesarean delivery on maternal request in the US<sup>89,148</sup> and caesarean section have been associated with a lower risk of inpatient diagnosis of POP compared to vaginal delivery<sup>92,149</sup><sup>150</sup>. However only approximately 1/10 women would benefit from such an intervention<sup>151</sup>. Complications of caesarean section must also be considered<sup>152</sup>. Most women are delivered vaginally and yet the life time risk for a single operation for POP and UI is estimated to be only 11%<sup>15</sup> suggesting other factors to be involved. It is possible that future identification of women at higher risk for sustaining pelvic floor injury at time of vaginal delivery can play a role in the decision making process for selecting women to elective cesarean section<sup>79,153</sup>. Prospective studies should be a priority addressing pregnancy, labor, mode of delivery and the development of POP- when and how the injuries occur- in order to provide evidence to guide management during labor and delivery and minimize damage that may lead to pelvic floor dysfunction.

The inability to identify women with an apparently higher risk for the development of POP severely limits the current ability to counsel women on their personal risks relating not only to vaginal childbirth but also to a variety of life-style related factors. Little is known about the long term value of pelvic floor exercise, if women with early signs of pelvic floor dysfunction may benefit from education regarding overweight, prevention of constipation and avoidance of heavy lifting. Many parous women apparently show first and second degree prolapse but only a small proportion will progress to more severe symptomatic prolapse. Other women will instead present with stiffening of vaginal tissue with advancing age<sup>107</sup>. These clinical observations are not well understood.

*Treatment improvement*

Surgical procedures for prolapse are accompanied by a high risk of recurrence, approximately one third of surgically managed patients require reoperation<sup>15</sup>. Reoperation implies surgical failure but represents only patients who choose repeat surgery after failure and does not reflect patients that choose nonsurgical or no additional therapy<sup>154</sup>. The reoperations also include those patients who experience a new problem after surgery (development of prolapse in a different compartment).

Why operations fail in certain women is not clear- whether it is a result of the restorative technique or a failure to identify the defects involved or if it is merely a result of weak and damaged native tissue remains to be clarified. New techniques such as MRI might increase the ability to understand specific defects and operative failures. Multiple biologic and synthetic materials have been introduced to complement, reinforce or replace native tissue in reconstructive surgical procedures. In a recent review of graft use in POP repair the authors concluded that most studies were underpowered to detect differences for clinical outcomes, or did not describe power calculations and sample size estimates for primary and/or secondary outcomes, making it difficult to draw meaningful conclusions or show statistically significant differences<sup>155</sup>. It is also unclear whether there are certain subgroups of women who might be more likely to benefit from graft use or who may be at higher risk of developing adverse events.

Even if outcomes measures after reconstructive surgery have shifted towards an increased awareness of patients' goals and satisfaction in determining surgical success<sup>156</sup> the data on symptomatic outcome in these studies were very sparse<sup>155</sup>.

It is important that patients can be adequately counseled prior surgery regarding not only anatomic outcome but also symptomatic outcome and the potential of developing new symptoms. Furthermore many common recommendations made after surgery to prevent recurrence such as restrictions of physical activity and heavy lifting are supported by limited data. Whether risk factors for reoperation are the same as those for the initial development of POP is not known.

In conclusion, there is a growing interest in causal factors for pelvic organ prolapse<sup>157</sup>. Our knowledge of POP is evolving but additional research is necessary to gain insight into the pathophysiology and to clarify risk factors in order to improve treatment and develop prevention strategies.



# CONCLUSIONS

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- Pelvic floor-related symptoms could not predict the anatomic location of the prolapse in women with mild to moderate prolapse. A feeling of a vaginal bulge was found to be specific for prolapse but not to any particular compartment, although the association was strongest with anterior wall prolapse. Stress incontinence showed a stronger association with posterior wall prolapse (Paper I)
- In addition to age and parity, genetic predisposition and non-obstetric strain on the pelvic floor (overweight, heavy lifts, and disturbed bowel habits) were found to be significantly associated with symptomatic prolaps. (Paper II)
- Longitudinal data of mild to moderate POP demonstrated the condition to be fluid, not only anatomically but also concerning bothering of symptoms (Paper III)
- Prolapse surgery showed a high rate of anatomic recurrence but only half of the women were symptomatic. Patients were primarily alleviated of mechanical symptoms. An improvement of difficulty emptying bowel after a posterior repair was noted and no aggravations of gas or fecal incontinence were observed. Our results demonstrate the difficulty in predicting outcome of urinary incontinence after prolapse surgery in any individual woman. (Paper IV)



# SVENSK SAMMANFATTNING

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Bäckenbottensvaghet hos kvinnor kan manifesteras sig som framfall av slidväggarna (främre och/eller bakre) och/eller som livmoderframfall. En viss svaghet i bäckenbotten kan ses hos nästan hälften av kvinnor som fött barn men förekomsten av ett symtomgivande framfall är betydligt lägre mellan 4-11% . Framfallsoperationer tillhör en av de vanligare gynekologiska operationerna och det utförs ca 6000 operationer i Sverige per år. Det finns förhållandevis få studier över förekomst, vilka symtom som korrelerar till framfallet, riskfaktorer och naturalförlopp. Utvärderingen av kirurgisk behandling är också sparsam.

De tre första studierna i denna avhandling baseras på en populationsbaserad tvärsnittsstudie som genomfördes i Stockholm 2002-2003. Ett validerat frågeformulär med fem frågor om framfallsrelaterade besvär tillsammans med frågor om ålder, barnafödelse, gynekologiska operationer och ansträngningsinkontinens skickades ut till 8000 kvinnor slumpvis utvalda ur befolkningsregistret. Av de 5489 (69%) kvinnor som svarade klassificerades 454 (8.3%) kvinnor som testpositiva för symtomgivande framfall.

Av de 454 kvinnorna kallades 206 kvinnor för gynekologisk undersökning och 206 av de 5489 testnegativa kvinnorna. Sammanlagt undersöktes 280 kvinnor (160 fall och 120 kontroller) enligt en internationellt standardiserad undersökningsteknik, POP-Q, av två gynekologer som var blindade för enkätsvaren. Uppgivna symtom från blåsa och tarm visade sig inte kunna förutsäga anatomiska fynd. Känslan av att något buktar ut ur slidan (globuskänsla) vara ett specifikt symtom för framfall oavsett lokalisation men framfall av främre slidväggen gav mer besvär. Ansträngningsinkontinens hade en starkare association med framfall av bakre slidväggen.

För att studera riskfaktorer för framfall sändes ett mer omfattande frågeformulär ut till de 454 kvinnorna samt 405 slumpvis utvalda kontroller. Samtliga undersökta kvinnor ingick.

Ålder, barnafödelse och ärftlighet för framfall var de starkaste riskfaktorerna men bindvävssvaghet (åderbräck, bräck, hemorrojder) och tillstånd med ökad belastning på bäckenbotten såsom övervikt, tunga lyft och förstoppning var också associerat med symtomgivande framfall.

För att studera naturalförloppet av framfall sändes ny enkät ut till de 160 undersökta testpositiva kvinnorna samt till de 120 kontrollerna efter 5 år. Alla frågor från ursprungsenkäten ingick samt kompletterande uppgifter inhämtades om operationer eller graviditeter efter 2002. Samtliga kvinnor kallades sedan för en ny blindad undersökning enligt POP-Q. De anatomiska fynden jämfördes med undersökningen 5 år tidigare samt den symtombild kvinnorna uppgivit vid respektive tillfälle. De flesta kvinnor som klassificerats med symtomgivande framfall uppgav minskade besvär av globuskänsla (64%; 95%CI 56-72%). Bland kontrollerna utvecklade 2% symtomet. Av de kvinnor som undersöktes igen efter 5 år (n=188) blev få förvärrade anatomiskt. Fler kontroller progredierade än de som var symtomatiska från början.

Under 1998-2000 opererades 248 kvinnor för framfall på Södersjukhuset varav 185 kvinnor ingick i en prospektiv uppföljning med avseende på operationsutfall, recidivfrekvens och symtomatiska besvär såsom globuskänsla, urininkontinens och tarmbesvär.

Kvinnorna följdes upp efter 2 mån, 1, 3 och 5 år med gynekologisk undersökning och symtombild. Den anatomiska recidivfrekvensen var hög, 48.6%, men mindre än hälften hade symtom. De flesta recidiven drabbade den främre slidväggen. Frekvensen av urininkontinens låg kvar på samma nivå 1 år efter operation. Av de kvinnor som inte hade urininkontinens innan operationen drabbades 22.6% av trängningsinkontinens och 6 % av ansträngningsinkontinens. De kvinnor som uppgav svårigheter att tömma tarmen blev förbättrade i hälften av fallen 1 år efter operationen. Kvinnorna blev framförallt botade från sin globuskänsla.



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KODNR.....

## Frågeformulär

1. Hur gammal är Du ?

2. Har Du fött barn ?

<i>Ja</i>	<i>Nej</i>
<input type="checkbox"/>	<input type="checkbox"/>

3. Hur många ?

4. Har Du genomgått någon gynekologisk bukoperation?

<i>Ja</i>	<i>Nej</i>
<input type="checkbox"/>	<input type="checkbox"/>

5. Har Du genomgått någon framfallsoperation?

<input type="checkbox"/>	<input type="checkbox"/>
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6. Har Du genomgått någon inkontinensoperation?

<input type="checkbox"/>	<input type="checkbox"/>
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7. Har Du besvär med att bli plötsligt kissnödig och har svårt att hinna fram till toaletten?

<i>Ja ofta</i>	<i>Ibland</i>	<i>Sällan</i>	<i>Nej alls</i>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8. Kan Du läcka urin vid kroppslig ansträngning som hasta, nysning, gång i nedförbacke eller hopp?

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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9. Har Du en känsla av att något buktar fram ur slickan?

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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10. Händer det Du har skavningsbesvär i underlivet?

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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11. Händer det att Du behöver lyfta upp främre slickväggen för att tömma blåsan/kunna kissa?

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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"Om Du svarat ja på någon av frågorna 7-11, besvara även nedanstående fråga".

12. Om Du anstränger Dig med tex tunga lyft, blir Dina besvär /sämre då?

<i>Ja ofta</i>	<i>Ibland</i>	<i>Sällan</i>	<i>Nej alls</i>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**OBS! Denna sida finns som separat dokument med "huvud"!**

## FRÅGEFORMULÄR nr 2

till kvinnor som genomgår vetenskaplig undersökning om framfall

Datum för ifyllning \_\_\_\_\_

1. Hur gammal är Du? \_\_\_\_\_ år
2. Hur lång är Du? \_\_\_\_\_ cm
3. Hur mycket väger Du? \_\_\_\_\_ kg
4. Hur mycket vägde Du vid 20 års ålder? \_\_\_\_\_ kg
5. Höftmått? (se bild hur du mäter detta) \_\_\_\_\_ cm
6. Midjemått? \_\_\_\_\_ cm
7. Har du någon gång minskat 5 kg eller mer i vikt under 6 månader?  
 Ja  
 Nej

8. Har du någon gång ökat 5 kg eller mer i vikt under 6 månader?  
 Ja  
 Nej

### Utbildning och yrkesarbete

9. Vilken utbildning stämmer bäst in på Dig? (Kryssa för det som gäller)

- Grundskola (folkskola, realskola)
- Gymnasium/yrkeskola
- Högskoleutbildning (t.ex. sjuksköterska, lärare)
- Annan (ange vad) \_\_\_\_\_

10. Har Du under den senaste 10-årsperioden haft ett stillasittande yrkesarbete? (sitter mer än 75 % av arbetstiden).

(Om du är pensionerad, var vänlig ange hur det var före pensioneringen. Om Du inte är yrkesverksam, ange om Du är stillasittande mer än 75% av tiden vanliga dagar)

- Ja
- Nej
- Vet ej

11. Har Du under Din yrkeskarriär haft ett arbete under längre period än 6 månader (inkl. hemarbete) som medfört tunga lyft dagligen?

- Nej, aldrig över 5 kg
- Ja, men aldrig över 10 kg
- Ja, men aldrig över 25 kg
- Ja, över 25 kg
- Vet ej

12. Ursäts Du för vibrationer / stötar under Ditt arbete?

- Ja
- Nej
- Vet ej

### Rökning

13. Röker Du idag?

- Ja
- Nej

14. Om nej, har Du tidigare rökt dagligen i 6 månader eller mer?

- Ja
- Nej
- Vet ej

Besvaras endast av den som röker / har rökt.

15. Hur många år har Du rökt? \_\_\_\_\_ år

16. Har många cigaretter brukar / brukade Du röka per dag?
- 1-10
  - 11-20
  - fler än 20

### Sjukdomar och operationer

17. Har Du eller har haft någon av följande sjukdomar? (kryssa för det som gäller)

Högt blodtryck	Ja <input type="radio"/>	Nej <input type="radio"/>
Astma	Ja <input type="radio"/>	Nej <input type="radio"/>
Kronisk hosta	Ja <input type="radio"/>	Nej <input type="radio"/>
Aderbräck på benen	Ja <input type="radio"/>	Nej <input type="radio"/>
Ljumsbräck	Ja <input type="radio"/>	Nej <input type="radio"/>
Hemorroider	Ja <input type="radio"/>	Nej <input type="radio"/>

18. Har Du opererat bort livmodern?

Ja  
 nej  
 vet ej

19. Är Du opererad för urininkontinens?

Ja  
 nej  
 vet ej

20. Har Du opererats i buken med ärr ovan naveln?

Ja  
 nej

21. Har Du opererats i buken med ärr nedom naveln?

Ja  
 nej

22. Är Du opererad för framfall?

Ja  
 nej  
 vet ej

23. Har Du en mamma eller syster som är opererad för framfall eller urininkontinens?

Ja  
 nej  
 vet ej

24. Har du en mamma eller syster som opererats för ljumsbräck eller åderbräck?

Ja  
 nej  
 vet ej

### Menstruation

25. Hur gammal var Du vid Din första menstruation? \_\_\_\_\_ år  vet ej

26. Har Du fortfarande menstruationer?

Ja  
 nej

27. Om nej, vid vilken ålder upphörde de \_\_\_\_\_ års ålder

28. Varför upphörde menstruationerna? (kryssa det som gäller)

Gravditet  
 Årstörning/anorexi  
 Borttagande av livmoder/äggstockar med operation  
 Klimakteriet  
 Vet ej  
 Annat

### Graviditet och förlösning

29. Har Du någon gång varit gravid? (Om nej, gå till fråga 46)

Ja  
 nej

30. Har Du fått missfall eller gjort abort?

Ja  
 nej

31. Har Du fött barn? (Om nej, gå till fråga 46)

- Ja  
 Nej

32. Om ja, hur många förlossningar? \_\_\_\_\_

33. Hur gammal var Du vid Din första förlossning? \_\_\_\_\_ år

34. Har någon förlossning varit tvilling eller trillingförlossning?

- Ja  
 Nej

35. Har något/några barn förlösts med kejsarsnitt? (Om nej, gå till fråga 37)

- Ja  
 Nej

Om ja, hur många? \_\_\_\_\_

36. Var kejsarsnittet /kejsarsnitten akut eller planerat?

- akut  
 planerat  
 både/och  
 vet ej

37. Ange antal barn, som vid förlossningen vägt

- |                    |       |
|--------------------|-------|
|                    | antal |
| • mindre än 2,5 kg | _____ |
| • 2,5 – 2,9 kg     | _____ |
| • 3,0 – 3,4 kg     | _____ |
| • 3,5 – 3,9 kg     | _____ |
| • 4,0 – 4,4 kg     | _____ |
| • 4,5 – 4,9 kg     | _____ |
| • mer än 5,0 kg    | _____ |

38. Är något/några av barnen förlöst/a med sugklocka?

- Ja  
 Nej  
 vet ej

39. Om ja, hur många? \_\_\_\_\_

40. Är något/några av barnen förlöst/a med tång?

- Ja  
 Nej

- vet ej

41. Om ja, hur många? \_\_\_\_\_

42. Har analysfinktern (ändtarmens slutningsmuskel) brutit i samband med någon av Dina förlossningar?

- Ja  
 Nej  
 vet ej

43. Fick Du en större bristning i slidan vid någon av förlossningarna?

- Ja  
 Nej  
 vet ej

44. Har Du blivit "klippt" i samband med någon av Dina förlossningar?

- Ja  
 Nej  
 vet ej

45. Hur lång tid hade Du värkar vid Din första förlossning?

- mindre än 1 timme  
 2-6 timmar  
 6-24 timmar  
 mer än 24 timmar  
 vet ej

### Läkemedel

46. Behandlas Du med läkemedel mot (kryssa för det som gäller)

- |                                   |                          |                           |                              |
|-----------------------------------|--------------------------|---------------------------|------------------------------|
| Högt blodtryck                    | Ja <input type="radio"/> | Nej <input type="radio"/> | vet ej <input type="radio"/> |
| Förstoppning                      | Ja <input type="radio"/> | Nej <input type="radio"/> | vet ej <input type="radio"/> |
| Psykisk sjukdom, t.ex. depression | Ja <input type="radio"/> | Nej <input type="radio"/> | vet ej <input type="radio"/> |
| Kromisk urinvägsinfektion         | Ja <input type="radio"/> | Nej <input type="radio"/> | vet ej <input type="radio"/> |
| Magsår                            | Ja <input type="radio"/> | Nej <input type="radio"/> | vet ej <input type="radio"/> |
| Blodfetsförhöjning                | Ja <input type="radio"/> | Nej <input type="radio"/> | vet ej <input type="radio"/> |
| Urinträngningar                   | Ja <input type="radio"/> | Nej <input type="radio"/> | vet ej <input type="radio"/> |

Besvaras av Dig som kommit upp i klimakteriet:

47. Får Du medicinsk behandling (hormoner) för klimakteriebesvär (övergångsåldern), t.ex. tabletter, plåster?

- Ja  
 Nej

48. Använder Du någon östrogenbehandling för slidans slemhinnor (vagitorier, kräm, östrogenring)?

- Ja  
 Nej

#### Kostvanor

49. Hur ofta äter Du kött?

- Dagligen, eller nästintill  
 Någon eller några gånger per vecka  
 Mer sällan än en gång per vecka

50. Äter Du grovt bröd, t.ex. fullkornsbröd eller knäckebröd regelbundet?

- Ja  
 Nej

51. Tar Du någon form av bulkmedel för avföringen (t.ex. Lunelax, Vi-Sibim, Laktulos, Duphalax) regelbundet?

- Ja  
 Nej

52. Hur ofta äter Du roigrönsaker (t.ex. morötter)?

- Dagligen, eller nästintill  
 Någon eller några gånger per vecka  
 Mer sällan än en gång per vecka

53. Hur ofta äter Du frukt?

- Dagligen, eller nästintill  
 Någon eller några gånger per vecka  
 Mer sällan än en gång per vecka

54. Tar Du regelbundet kosttillskott?

- Ja  
 Nej

55. Vilken typ av frukost passar bäst in när det gäller mängden mat som Du brukade äta för 10 år sedan?

- Jag åt ingen frukost  
 En kopp kaffe/te  
 Kaffe/te och smörgåsar  
 Kaffe/te, smörgåsar, fl, juice

56. Vilken typ av lunch passar bäst in när det gäller mängden mat som Du brukade äta för 10 år sedan?

- Jag åt ingen lunch  
 Bara något lätt, t.ex. yoghurt, frukt  
 Sallad, bröd, juice  
 Lagad mat (t.ex. kött/fisk och potatis)

57. Vilken typ av middag passar bäst in när det gäller mängden mat som Du brukade äta för 10 år sedan?

- Jag åt ingen middag  
 Något enkelt och snabbt, t.ex. en tallrik soppa  
 En "normal" portion lagad, varm mat  
 Full middag med bröd, sallad, dessert etc.

58. Hur många mellanmål brukade Du äta en vanlig dag för 10 år sedan?

- Jag åt inte mellanmål  
 En gång per dag  
 Två gånger per dag  
 Tre gånger per dag

#### Tarmvanor

59. Hur ofta har Du tarmtömning? (ryssa för det som gäller)

- varje dag  
 varje till varannan dag  
 varje till var tredje dag  
 1-2 ggr per vecka

- mer sällan än 1 ggr/vecka
- vet ej

60. *Besväras Du av alltför hård anföring?*

- Ofta, i stort sett vid varje tillfälle
- Ibland
- Sällan
- Aldrig

61. *Besväras Du av svårighet att tömma tarmen?*

- Ofta, i stort sett vid varje tillfälle
- Ibland
- Sällan
- Aldrig

62. *Besväras Du av smärtor vid anföring?*

- Ofta, i stort sett vid varje tillfälle
- Ibland
- Sällan
- Aldrig

63. *Har Du svårt att kontrollera gaser?*

- Ja
- Nej

64. *Läcker Du anföring?*

- Ja, ofta
- Ja, ibland
- Aldrig

Motion/fysisk aktivitet

65. *Arbetar Du med trädgårdsarbete på Din fritid?*

- Ja, ofta
- Ja, men sällan
- Nej

66. *Har tar/tog Du Dig till Ditt arbete under sommarhalvåret (Vid flera arbeten,*

*kryssa för det som är/var vanligast)*

- Promenad
- Med cykel
- Med tunnelbana, pendeltåg eller buss
- Med bil
- Arbetar/arbetade hemma
- Yrkesarbetar ej

67. *Promenerar Du regelbundet under sommarhalvåret (en eller flera gånger i veckan)?*

- Ja
- Nej

68. *Promenerar Du regelbundet under vinterhalvåret (en eller flera gånger i veckan)?*

- Ja
- Nej

69. *Försöker Du träna bäckenbotten (knipövningar) regelbundet?*

Om ja,

- Dagligen
- Inte dagligen men minst varje vecka
- Mer sällan än varje vecka
- Aldrig

70. *Motionerar Du regelbundet (mer än en halvtimme en eller flera gånger i veckan)?*

- Ja
- Nej

71. *Om ja, vilken typ av motion ägnar Du Dig åt? (kryssa för det/de alternativ som gäller)*

- Jogging
- Golf
- Simning
- Ridning
- Aerobics/Friskis och Svettis
- Cykling
- Lättare gymnastik
- Bollsport
- Tennis
- Styrketräning
- Promenad

Annat \_\_\_\_\_

72. *Hur många timmar per vecka motionerar Du?* \_\_\_\_\_ timmar

- Nej tack, jag vill inte vara med i studien.

**POSTA frågeformuläret i bifogade frankerade kuvert**

**Tack för Din medverkan!!**