Treatment of vaginal vault prolapse

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Voor papa

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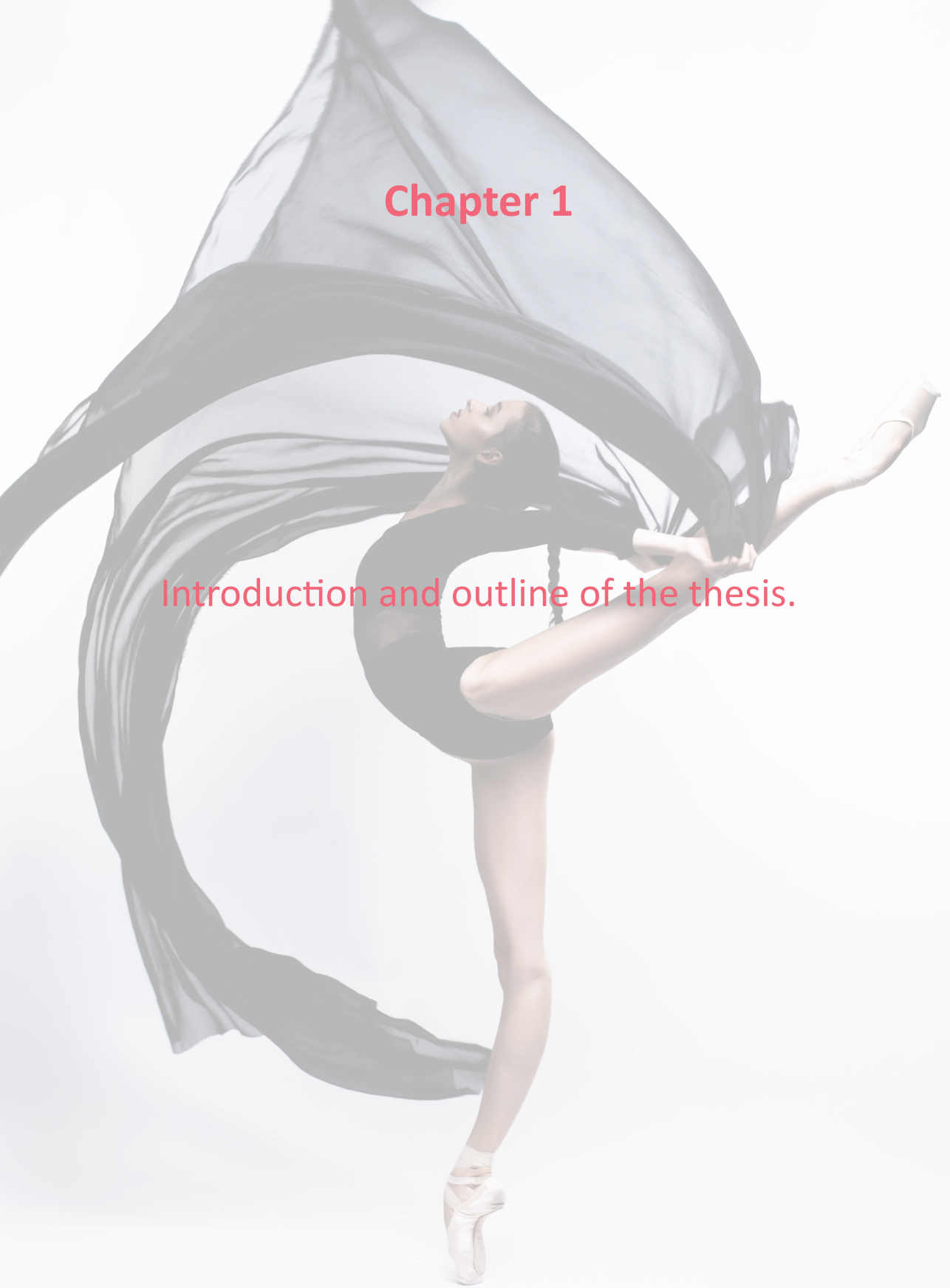

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GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Introduction

Pelvic organ prolapse

Pelvic organ prolapse (POP) is a common gynaecological condition, and its aetiology is multifactorial. Risk factors include increased age, vaginal childbirth, obesity, constipation, connective tissue disorders, obstetric factors (forceps, prolonged second stage of labour, macrosomia), race, heavy lifting and a family history of prolapse [1]. In a general Dutch female population aged 45-85 years, 75% of women had some degree of POP [2, 3]. POP can negatively affect women's quality of life by local physical effects (pressure, bulging, heaviness or discomfort) or its effect on urinary, bowel or sexual function. Around 10% of women undergo surgery at some time in their lives for the management of prolapse or urinary incontinence [3]. Consequently, about 13.000 surgeries are performed for this health problem in the Netherlands every year. [4]. Women tend to get older and older and due to this improved life expectancy, there will be an enormous extra demand for future prolapse treatment.

The vagina can be divided in three compartments: the anterior, posterior and apical compartment. A prolapse of the anterior vaginal wall leads to prolapse of the bladder and/or urethra, and is called a cystocele. A prolapse of the posterior vaginal wall is responsible for prolapse of the rectum or small bowel, referred as rectocele and enterocele. Prolapse of the apical compartment is known as uterine descent (if the uterus is in situ), or vaginal vault prolapse (VVP) after hysterectomy. POP can be present in one compartment, but usually more compartments are affected simultaneously [5].

This thesis studies treatments for pelvic organ prolapse and the following objectives are addressed:

- Should a symptomatic POP be treated conservatively or surgically? In case of surgical treatment; will a uterus preserving treatment, as the Manchester Fothergill procedure, give an advantage over a vaginal hysterectomy?
- How should women with a post hysterectomy vaginal vault prolapse be treated?

This chapter will clarify the background of the research questions and the gaps in research.

Conservative treatment of pelvic organ prolapse

POP can be treated conservatively or surgically. Conservative treatments include watchful waiting, pelvic floor muscle training and pessary treatment. Pelvic floor muscle training leads to a significantly greater improvement in patient satisfaction as compared to watchful waiting, although the clinical relevance of the difference is low [6]. Pessary treatment results in less POP symptoms compared to pelvic floor muscle training, and is cost effective. Therefore, pessary treatment should be advised over pelvic floor muscle training and watchful waiting [6, 7].

Although pessaries have been reported to be effective in reducing prolapse symptoms [8-13], 20-50% of women will discontinue their pessary use within 1 year [14, 15]. Side effects are reported to occur in half of the women and are the main reason for discontinuation [16]. Nowadays, pessaries are used by more than 85% of gynaecologists and 98% of urogynaecologists [17, 18]. Patient preference plays a very important role in the willingness to try a pessary. According to a Dutch study, 48% of treatment naïve women preferred surgery, 36% choose pessary treatment and 16% had no preference [19]. Two prospective trials comparing pessary with surgery for POP, report similar improvement in urinary, bowel, sexual function, and quality of life parameters [13, 20]. So, pessary treatment might be an equivalent therapy in the treatment of POP, as compared to POP surgery, probably with less risks and costs. However, randomized controlled trials of pessary treatment versus surgery for POP are lacking. In view of this dilemma, we decided to start a trial comparing pessary treatment to POP surgery [chapter 2].

Surgical treatment of pelvic organ prolapse

The aim of POP surgery is to reduce complaints, related to pelvic floor symptoms, by restoring anatomy of the vagina and surrounding visceral organs. Unfortunately, POP surgery could be accompanied by complications. Furthermore, there are significant cost implications for prolapse surgery, particularly while the index surgery has a quoted failure rate of up to 30% [13]. However, surgery for POP results in improvement of symptoms and quality of life in 80% of women and complications seldom lead to persistent morbidity [21].

An anterior colporrhaphy is considered as the standard surgical therapy for a cystocele, whereas a posterior colporrhaphy is the standard procedure for a rectocele [21]. For the surgical treatment of apical compartment a variety of techniques are described. Traditionally, vaginal hysterectomy was the standard treatment for uterine descent. However, discussion is ongoing whether or not vaginal hysterectomy is the rational first choice in the treatment of uterine descent, and interest in uterus preservation seems to be increasing [22, 23]. Uterus preserving techniques include sacrohysteropexy, sacrospinous fixation and Manchester Fothergill [24]. In a Dutch survey of all members of the Dutch Urogynaecological Society in 2011 and a nationwide registry from the Netherlands, the number and

type of surgical procedures (between 1997 and 2009) performed for pelvic organ prolapse were assessed. Vaginal hysterectomy, sacrospinous fixation, and the Manchester Fothergill procedure were the most frequently performed surgical interventions for uterine descent [5]. Unfortunately, no first-choice procedure could be determined for the surgical treatment for apical prolapse [24]. Currently, the choice of therapy mostly depends on the former training and personal experience of the surgeon. It is still unclear if the uterus preserving technique, Manchester Fothergill or a vaginal hysterectomy will be most effective for the treatment of POP. Therefore, we performed a retrospective study comparing vaginal hysterectomy with the Manchester Forthergill [chapter 3].

Treatment of vaginal vault prolapse

It has been estimated that one in nine women will undergo a hysterectomy during lifetime. Up to 10% of the women who had a hysterectomy because of prolapse symptoms, will subsequently need surgical repair for vaginal vault prolapse thereafter. [25]. The risk of prolapse following hysterectomy is 5.5 times higher in women whose initial indication for hysterectomy was genital prolapse as opposed to other indications [26]. A great variety of different surgical procedures to correct VVP have been reported [27-29]. Over 20 different treatment options for VVP have been described [chapter 6]. A standard approach or published guideline for the management of VVP is lacking. According to a survey we performed among all members of the Dutch Society for Urogynaecology in March 2017, there is no standard treatment of VVP in the Netherlands and the practice pattern variation is high [chapter 8]. Most responding urogynaecologists will perform pessary treatment as first-choice treatment, followed by sacrospinous fixation. The surgical management of first-choice for VVP is sacrospinous fixation, followed by laparoscopic and robotic sacrocolpopexy. The results of this survey correlate with a survey performed by the International Urogynaecological Association (IUGA) in 2002, which showed that 78% of the responders mentioned the sacrospinous fixation as the method of choice when treating vaginal vault prolapse [30]. Second choice treatment is the laparoscopic sacrocolpopexy, which has gained popularity since it was reported for the first time in 1994 [31]. Although the literature regarding laparoscopic sacrocolpopexy was limited and prospective comparative randomized trials were lacking, the laparoscopic sacrocolpopexy has been widely adopted by pelvic reconstructive surgeons. According to a Cochrane review [32], abdominal sacrocolpopexy was described as the first-choice treatment for VVP. However, laparoscopic sacrocolpopexy has potential advantages over laparotomy, as morbidity, hospital stay, post-operative pain and recovery are all supposed to be less and the aesthetic results are better. Nevertheless, the laparoscopic approach is more challenging and has a longer learning curve [33, 34]. Since the implementation of the laparoscopic sacrocolpopexy was growing, while evidence of this minimal invasive procedure was lacking, we started a randomized controlled trial to compare this

technique to the abdominal sacrocolpopexy [chapter 4]. Previous retrospective studies have shown less morbidity in favour of the laparoscopic method [36-38]. Prospective evaluation was lacking, specifically to compare differences in complication rates between both procedures. Therefore, we decided to perform a prospective trial comparing complications of both techniques [chapter 5].

Clearly a wide variety of treatments available for VVP are described in literature [chapter 6], resulting in a lack of consensus on the management of VVP [30, chapter 8]. However, the treatment of VVP has been investigated in several randomized clinical trials. Nevertheless, a systematic overview on the topic is still lacking. As an attempt to reach consensus about the treatment of VVP, we performed a systematic review and meta-analysis about the treatment of VVP [chapter 6]. The aim of this review is to compare the effectiveness of vaginal vault treatments in a systematic review and meta-analysis, combined with a network plot, using the most reliable evidence, coming from randomized controlled trials.

According to the results of our review there is still a gap in research on the treatment of VVP. Our randomized trial comparing laparoscopic to abdominal sacrocolpopexy shows an advantage for the laparoscopic procedure in hospital stay and equal effectiveness. Sacrospinous fixation is the most performed procedure according to a survey of the IUGA in 2002 and a survey in the Netherlands in March 2017. The laparoscopic sacrocolpopexy and the sacrospinous fixation treatment options have not been evaluated, head to head, in a randomized controlled trial. Therefore, we designed a new randomized multicentre trial comparing the laparoscopic sacrocolpopexy with the sacrospinous fixation, [chapter 7].

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Outline of the thesis

The main research questions:

Chapter 2 describes the subjective results of a prospective cohort study treated conservatively with a pessary or with pelvic organ prolapse surgery.

Chapter 3 presents a retrospective cohort study comparing the effectiveness of two surgical treatments for pelvic organ prolapse, concerning the Manchester Fothergill (uterus preserving) procedure and vaginal hysterectomy.

In **Chapter 4** a multi-centre randomized controlled trial is presented on the treatment of vaginal vault prolapse. Women with a symptomatic vaginal vault prolapse were randomized between an open abdominal sacrocolpopexy or laparoscopic sacrocolpopexy to evaluate functional and anatomical outcome (SALTO-trial).

Chapter 5 focuses on the complications of a prospective cohort treated with either open abdominal or laparoscopic sacrocolpopexy.

Chapter 6 describes the results of a systematic review and meta-analysis regarding the treatment of vaginal vault prolapse.

Chapter 7 provides a study protocol of a multi-centre randomized controlled trial to investigate the most common used treatment options for vaginal vault prolapse, comparing sacrospinous fixation with laparoscopic sacrocolpopexy.

Chapter 8 contains the general discussion, clinical implications and future perspectives.

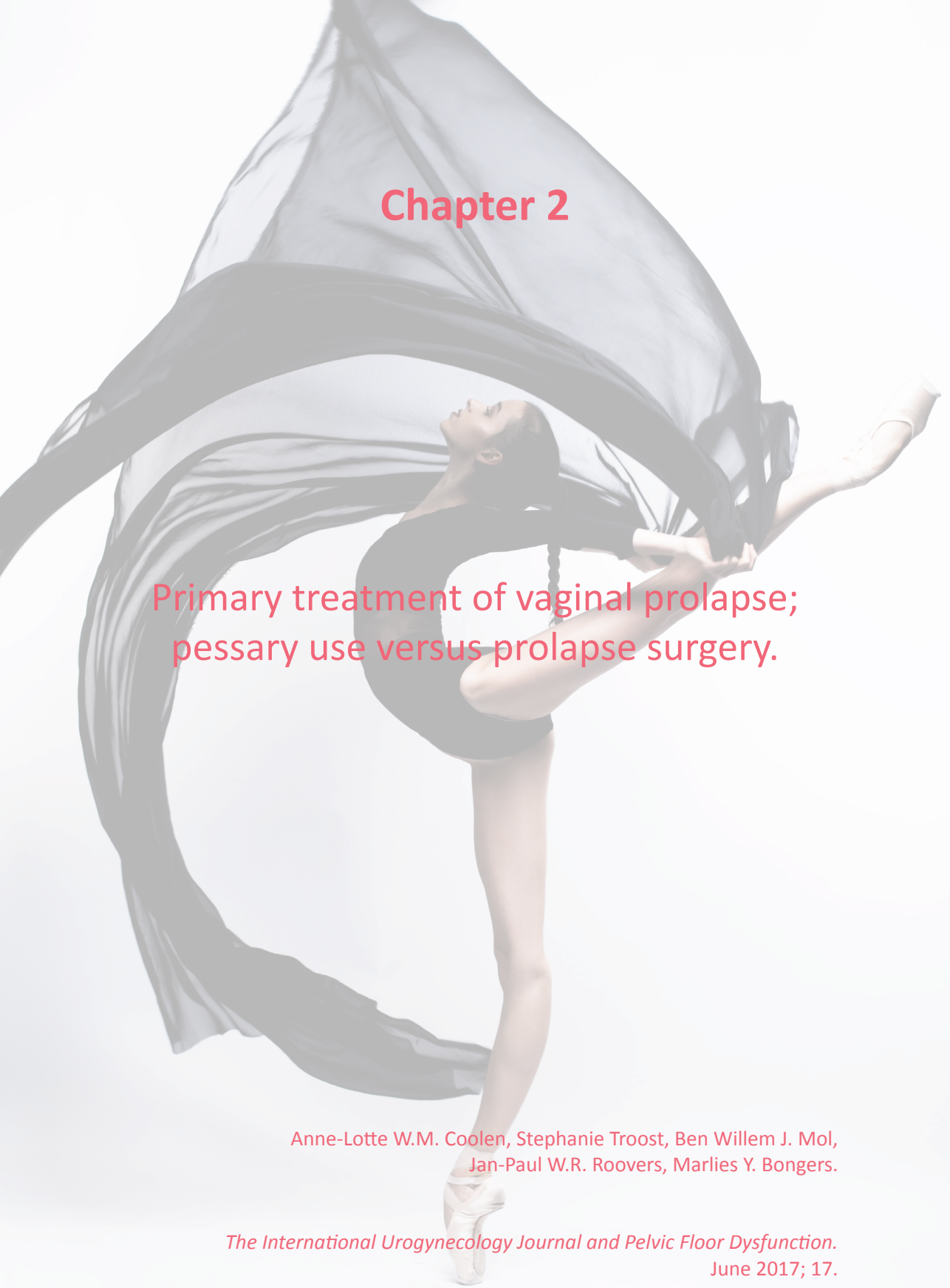
In **Chapter 9 and 10** a summary in English and Dutch is given.

Chapter 11 includes the valorisation addendum, which explains the significance of this thesis.

References

1. J.E. Jelovsek, C. Maher, M.D. Barber, Pelvic organ prolapse, Lancet (2007) 24:1027-38
2. MCP Slieker-ten Hove et al, The prevalence of pelvic organ prolapse symptoms and signs and their relation with bladder and bowel disorders in a general female population, International Urogynecology Journal and Pelvic Floor Dysfunction (2009) 20:1037-1045
3. AL Olsen, Epidemiology of surgically managed pelvic organ and urinary incontinence. Obstetrics and Gynecology (1997) 89 (4):501–6
4. J.P. Roovers, E.Everhardt, V.Dietz, F.Milani et al. Richtlijn prolapse van de nederlandse vereniging obstetrie en gynaecologie. Dutch Society of Obsetrics and Gynaecology. www.nvog.nl. (2017)
5. R.J. Detollenaere, J. den Boon, K.B. Kluivers, et al, Surgical management of pelvic organ prolapse and uterine descent in the Netherlands, International Urogynecology Journal (2013) 24:781-788.
6. Wiegersma, Panman, Effect of pelvic floor muscle training compared with watchful waiting in older women with symptomatic mild pelvic organ prolapse: randomised controlled trial in primary care. British Medical Journal (2014 Dec) 22;349: g7378.
7. C.M. Panmann, Effectiveness and cost-effectiveness of pessary treatment compared with pelvic floor muscle training in older women with pelvic organ prolapse: 2-year follow-up of a randomized controlled trial in primary care. Menopause (2016 Dec) 23(12):1307-1318.
8. GA Digesu, The relationship of vaginal prolapse severity to symptoms and quality of life. British Journal of Obstetrics and Gynecology (2005), 112:971–976
9. Fernando RJ, Thakar R, Sultan AH, Shah SM, Jones PW, Effect of vaginal pessaries on symptoms associated with pelvic organ prolapse. Obstet Gynecol (2006) 08(1):93–99
10. YM Komesu, Pelvic floor symptom changes in pessary users. American Journal of Obstetrics and Gynecology (2007) 197:620.e1–620.e6
11. A Kuhn, Sexual and organ function in patients with symptomatic prolapse: are pessaries helpful? Fertility and Sterility (2009) 5:1914–1918
12. Lamers BHC, Broekman BMW, Milani AL. Pessary treatment for pelvic organ prolapse and health-related quality of life: a review. International Urogynecology Journal and Pelvic Floor Dysfunction (2011) 22:637–64
13. Abdool Z, Thakar R, Sultan AH, Oliver RS, Prospective evaluation of outcome of vaginal pessaries versus surgery in women with symptomatic pelvic organ prolapse. International Urogynecology Journal and Pelvic Floor Dysfunction (2010) 22(3):273-8.
14. Broens-Oostveen MC, Mom RM, Lagro-Janssen AL, Genital prolapse; treatment and course in four general practices. Ned Tijdschr Geneeskd, (2004) 148(29):1444–1448, 17
15. Sarma S, Ying T, Moore KH, Long-term vaginal ring pessary use: discontinuation rates and adverse events. BJOG (2009) 116 (13):1715–1721
16. Broens-Oostveen WC, Mom RM, Largo-Janssen ALM. De genitale prolaps: behandeling en beloop in vier huisartspraktijken. Ned.Tijdschr.Geneeskunde. (2004) 148 (29); 1444-1448
17. Richter HE, Burgio KL, Brubaker L, Nygaard IE, Ye W, Weidner A et al, Continence pessary compared with behavioral therapy or combined therapy for stress incontinence: a randomized controlled trial. Obstet Gynecol (2010) 115(3):609–617, 2010 March
18. Atnip SD, Pessary use and management for pelvic organ prolapse. Obstet Gynecol Clin North Am (2009) 36(3):541–563
19. Thys SD, Roovers JP, Geomini PM, Bongers MY, Do Patients Prefer a Pessary or Surgery as Primary Treatment for Pelvic Organ Prolapse. Gynecol Obstet Invest. (2012) 74: 6-12
20. Lone F, Thakar R, Sultan AH, One-year prospective comparison of vaginal pessaries and surgery for pelvic organ prolapse using the validated ICIQ-VS and ICIQ-UI (SF) questionnaires. Int Urogynecol J (2015) 26:1305–131.
21. Vd Waarsenburg MK, vd Vaart CH. Pessary or surgery for symptomatic organ prolapse: study

protocol. Unpublished. Version 1.4, Oct 2014
22. Dietz V, Schraffordt Koops SE, van der Vaart CH, Vaginal surgery for uterine descent; which options do we have? A review of the literature. International Urogynecology Journal and Pelvic Floor Dysfunction (2009) 20:349–356
23. Zucchi A, Lazzeri M, Porena M, Mearini L, Constantini E, Uterus preservation in pelvic organ prolapse surgery. Nat Rev Urol (2010) 7:626–633
24. R.J. Detollenaere, J.den Boon, M.E. Vierhout, H.W.F. van Eijndhoven, uterussparende chirurgie versus vaginale hysterectomie als behandeling van descensus uteri, Ned.Tijdschr.Geneesk. (2011) 155:A3623
25. Dällenbach P, Kaelin-Gambirasio I, Jacob S, Dubuisson JB, Boulvain M, Incidence rate and risk factors for vaginal vault prolapse repair after hysterectomy. Int Urogynecol J Pelvic Floor Dysfunct (2008) 19(12):1623–1629.
26. J.O.L. Delancey, Anatomic aspects of vaginal eversion after hysterectomy, AJOG, (1992) 166 (6), part 1, 1717-1728.
27. Toozs-Hobson P, Boos K, Cardozo L et.al (1998). Management of vaginal vault prolapse. Br J Obstet Gynecol, 1998; 105(10): 1127-8
28. A. Uzoma, K.A. Farag, Vaginal vault prolapse, 2009, obestrics and gynecology international
29. C. Maher, Surgery for women with apical vaginal prolapse, Cochrane Database Syst Rev. (2016) 1;10
30. Davila GW, Ghoniem GM, Kapoor DS, Contreras-Ortiz O. Pelvic floor dysfunction management practice patterns: asurvey of members of the International Urogynecological Association. International Urogynecology Journal and Pelvic Floor Dysfunction (2002) 13(5):319-25.
31. Nezhat CH, Nezhat F, Nezhat C. Laparoscopic sacral colpopexy for vaginal vault prolapse. Obstet Gynecol. (1994) 84(5): 885–888.
32. Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women (review). Cochrane Database of Systematic reviews (2013) 4: 1-161.
33. Claerhout F, Deprest J. Analysis of the learning process for laparoscopic sacrocolpopexy: identification of challenging steps. International Urogynecology Journal and Pelvic Floor Dysfunction (2014) 25: 1153-1160.
34. Deprest J, Roovers JP. The challenge of implementing laparoscopic sacrocolpopexy. International Urogynecology Journal and Pelvic Floor Dysfunction (2014) 25:1153–1160.
35. T. E. Snyder and K. E. Krantz, “Abdominal-retroperitoneal sacral colpopexy for the correction of vaginal prolapse,” Obstet- rics and Gynecology (1991) 77 (6), 944–949.
36. M. F. R. Paraiso, M. D. Walters, R. R. Rackley, S. Melek, and C. Hugney, “Laparoscopic and abdominal sacral colpopexies: a comparative cohort study,” American Journal of Obstetrics and Gynecology (2005) 192(5); 1752–1758.
37. R. M. Freeman, K. Pantazis, A. omson et al., “A randomized controlled trial of abdominal versus laparoscopic sacrocolpopexy for the treatment of post-hysterectomy vaginal vault prolapse: LAS study,” International Urogynecology Journal and Pelvic Floor Dysfunction (2013) 24 (3); 377–384.
38. L. Klauschie, B. A. Suozzi, M. M. O’Brien, and A. W. McBride, “A comparison of laparoscopic and abdominal sacral colpopexy: objective outcome and perioperative differences,” International Urogynecology Journal and Pelvic Floor Dysfunction (2009) 20 (3); 273–279.



Chapter 2

Primary treatment of vaginal prolapse; pessary use versus prolapse surgery.

Anne-Lotte W.M. Coolen, Stephanie Troost, Ben Willem J. Mol,
Jan-Paul W.R. Roovers, Marlies Y. Bongers.

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Abstract

Objective To evaluate functional outcome after pessary treatment versus prolapse surgery as primary treatment for pelvic organ prolapse (POP).

Design Prospective cohort study.

Setting A Dutch teaching hospital.

Population Women with symptomatic POP ≥ stage 2 requiring treatment.

Methods Patients were treated according to their preference with a pessary or prolapse surgery.

Main outcome measures Primary endpoint was disease specific quality of life at 12 months follow-up, according to the prolapse domain of the Urogenital Distress Inventory (UDI) questionnaire. Secondary outcomes included adverse events and additional interventions. To show a difference of 10 points in the primary outcome, we needed to randomize 80 women (power 80%, α 0.05, taking 10% attrition into account).

Results We included 113 women (pessary group N=74; surgery group N=39). After 12 months, the median prolapse domain score was 0 (10-90th percentile: 0-33) in the pessary group vs 0 (10-90th percentile: 0-0) in the surgery group (p <.01). Differences in other domain scores were not statistically significant. In the pessary group, 28% (21/74) of the women had a surgical intervention versus 3% (1/39) re-operations in the surgery group (p=.01).

Conclusion In women with POP stage ≥ 2, having surgery, prolapse symptoms were less than in those who had a pessary, but 72% of women who were treated with a pessary did not opt for surgery.

Trial registration number: Dutch trial register NTR2856

Introduction

Pelvic organ prolapse (POP) is a common condition. In a general Dutch female population aged 45-85 years, 75% of women had some degree of POP [1, 2]. Around 10% of women undergo surgery at some time in their lives for the management of prolapse or urinary incontinence [2].

Pessaries have been used as conservative treatment since the beginning of recorded history. Nowadays, pessaries are used by more than 85% of gynaecologists and 98% of urogynaecologists [3, 4]. Patient preference plays a very important role in the willingness to try a pessary according to a Dutch study reporting that 48% of treatment naïve women preferred surgery, 36% pessary treatment and 16% had no preference [5]. However, relevant cost-savings can be realized as pessary therapy is inexpensive and costs are mainly related to doctor visits and treatment of side effects, which would even be less in case of self-management [6].

Although pessaries have been reported to be effective in reducing prolapse symptoms [7-12], 20-50% of women will discontinue their pessary use within 1 year [13, 14]. Side effects are reported to occur in half of the women and are the main reason for discontinuation [15].

The aim of POP surgery is to reduce bother, related to pelvic floor symptoms, by restoring anatomy of the vagina and surrounding visceral organs. Unfortunately, POP surgery could be accompanied by complications. Furthermore, there are significant cost implications for prolapse surgery, particularly when the index surgery has a quoted failure rate of up to 30% [16].

According to two prospective trials comparing pessary with POP surgery, women report similar improvement in urinary, bowel, sexual function, and quality of life parameters when treated with pessary or POP surgery [12, 17]. There are no comparing randomized controlled trials.

Although POP surgery has several advantages over pessary treatment since its definitive character, the risk for complications is higher and it might be less cost-effective. Since previous trials show promising results of pessary treatment, it might be an equivalent option in the treatment of POP, probably with less risks and costs.

In view of this dilemma, we decided to start a trial with a prospective cohort group treated with either pessary treatment or POP surgery, in order to individualize the counselling about treatment options and guide patients better to the decision process of the treatment of choice. The aim of this trial was to compare the disease specific quality of life after 12 months, between pessary treatment and surgery in women treated for POP. In this superiority trial, we assumed that POP surgery would lead to a higher disease specific quality of life compared to pessary treatment at 12 months after the start of treatment.

Methods

We aimed to perform a randomized controlled trial in a teaching hospital in The Netherlands comparing pessary treatment to prolapse surgery as primary treatment for pelvic organ prolapse. The study was approved by the ethical committee and is registered in the Dutch trial register (NTR2856). Women with a treatment preference who did not consent for randomization were asked to follow the same study protocol as part of a prospective cohort group. During the study, many women were found to have a strong preference for either one of the treatment options, and did not consent for randomization. Therefore, the RCT was prematurely ended, resulting in a prospective cohort group, including 6 randomized women and 107 women treated according to their preference. Women with a symptomatic pelvic organ prolapse POP-Q stage 2 or higher, who preferred to undergo treatment, were eligible for the trial. A symptomatic POP was defined as: POP-Q stage 2 or higher with bothersome urogenital symptoms. Women who had undergone previous surgical pelvic organ prolapse correction or urinary incontinence surgery, or who were treated with a pessary before, were excluded, even as patients with a contra-indication for surgical intervention. Furthermore, an isolated rectocele, without a prolapse of any other compartment was an exclusion since a solitaire rectocele might result in a lack of support for pessary treatment [12].
Eligible women with a symptomatic pelvic organ prolapse who met the inclusion criteria were counselled about POP and their condition by their own gynaecologist, one of a team of three urogynaecologists. Then the treatment options expectant management, pessary treatment and surgery were explained. After the consultation, women received written information about their condition and about the trial. They then got time to consider participation to the trial; being randomized or being part of the prospective cohort group. The interventions were either pessary treatment or POP surgery following patient's preference. If patients consented to be randomized, written informed consent was signed and randomization was performed.
Randomization was performed using opaque sealed envelopes. The treatment allocation ratio was 1:1 to either pessary treatment or surgery. No block randomization was performed. Participants and physicians were not blinded.

Pessary treatment

According to the judgement of the gynaecologist, both a shelf (Falk®) or ring pessary (with or without central support) could be used. No other pessaries were placed during the trial. Preferably a ring pessary was placed. According to the judgement of the physician a ring pessary with central support was placed in cases of apical descent, a shelf (Falk®) pessary was placed in cases of apical descent, extensive prolapse or lack of support of the ring pessary. The placement took place at the outpatient clinic, after fitting. A test pessary was used to evaluate the correct size of the pessary.

Patient tested this pessary, while walking around for 30 minutes. If the right size was found the pessary was inserted and the fitting was considered as successful. After placement, all participants received instructions about pessary treatment. If the initial fit was unsuccessful another size or the other pessary type could be used, according to the judgement of the gynaecologist. Discontinuation and expulsion was reported, even as the reason for discontinuation.
A follow-up visit was planned 6 weeks after placement and participants were instructed to return to the clinic if they had any complaints or if they lost the pessary. If participants were satisfied with the pessary, follow-up visits were planned every 3-4 months for pessary cleaning and vaginal inspection. During the follow-up period, the type or size of the pessary could be changed. All participating physicians were skilled in pessary fitting and performed at least 100 pessary fittings prior to start of the trial.

Surgical intervention

The surgical intervention consisted of the correction of all compartments that required surgery. The decision, which technique was used, and which compartments were treated, was left to the discretion of the gynaecologist, depending on the results of the physical examination and the complaints. Cystocele repair involved conventional anterior colporrhaphy. For uterine descent, different techniques were allowed. These techniques could be a vaginal hysterectomy with vault suspension or uterus preserving techniques like a sacrospinous fixation, Manchester-Fothergill procedure or a laparoscopic sacrohysteropexy. A coexisting rectocele was treated with a conventional posterior colporrhaphy. When stress incontinence was diagnosed prior to surgery, it was to the discretion of patient and surgeon to decide whether a concomitant incontinence procedure was performed or whether prolapse surgery only was performed first and later the indication for additional incontinence surgery was considered.
All procedures were performed under general anaesthesia or spinal anaesthesia. Prophylactic antibiotics were given per-operatively (metronidazole/cefalozine). As prophylaxis for thromboembolism per- and post-operatively subcutaneous low molecular weight heparine was administered. A urethral catheter was left in-situ and was removed at the second day post-operative in case of anterior colporrhaphy or at the first day in any other case. If the procedure was complicated with a bladder lesion, the catheter was removed after one week. In case of urinary retention after removal of the catheter at the first day, the catheter was re-inserted for another day.
Women were asked to complete a questionnaire pre-operative, and at 3-6 months after treatment and 12 months after treatment. All participants were asked to undergo a pelvic examination before treatment, at 6 weeks after treatment and when clinically indicated. Pelvic examination after one year was done, if they were still followed up by their physician. Randomized participants were invited

for examination after 12 months. During pelvic examinations, the prolapse stage was evaluated according to the Pelvic Organ Prolapse Quantification system (POP-Q) [18] in lithotomy position and during Valsalva. Other findings of the pelvic examination as vaginal erosion, vaginal discharge, atrophy, bleeding and urinary incontinence were also recorded.

The primary outcome of the study was functional outcome, evaluated by using the Urogenital Distress Inventory (UDI) [19] after 12 months. The UDI, is a Dutch validated questionnaire evaluating prolapse related symptoms. The UDI, is a disease specific validated questionnaire comprising 17 questions, to assess the presence and experienced discomfort of pelvic floor problems. The UDI consists of 5 domains: discomfort/pain, urinary incontinence, overactive bladder, genital prolapse, and obstructive micturition. The UDI scores were calculated for al 5 different domains [19]. These questionnaires also contain versions of the Defecatory Distress Inventory (DDI) [20] and the Incontinence Impact Questionnaire (IIQ) [19]. The questionnaires also contain questions about sexuality. If participants did not respond on the send questionnaire, they received a reminder. In case they ignored both questionnaires they were contacted by telephone to find out the reason for not returning the questionnaires.

In the pessary group, type and size of the pessary was recorded, as well as the amount of different types and sizes of pessaries. Side effects during pessary treatment like discharge, pain and blood loss were also registered. If pessary treatment was not successful, the failure reason was recorded. The collected data of the surgery group included type of surgery, procedure time, estimated blood loss, hospital stay and peri-operative complications.

Additional interventions could include physiotherapy and incontinence surgery for the pessary group and physiotherapy, incontinence surgery or recurrent prolapse surgery for the surgery group. Long-term complications and side effects were recorded in both groups. Remaining study parameters included age, body mass index, parity, pre- or postmenopausal status, presence of incontinence and use of oestrogens. Urinary stress incontinence was diagnosed in lithotomy position with a full bladder. Participants were asked to cough several times. If urinary leakage was seen, urinary incontinence was diagnosed. In case of a cystocele, redression of the cystocele was applied and the examination was repeated.

Sample size

Disease specific quality of life, using the Urogenital Distress Inventory (UDI) questionnaire, was the primary endpoint. A difference between both interventions of 10 points on the prolapse domain of the UDI 12 months after treatment, was considered to be clinically relevant [21]. Assuming a standard deviation of the score on this domain of 15 points, we needed 72 participants to show a statistically significant difference in the primary outcome (power of 80%, α error 0.05) [21]. Taking

into account 10% attrition, a number of 80 participants (40 in each arm) needed to be included. After the RCT was halted, we focused on the cohort group which was part of the trial, since randomization turned out to be very difficult. We included patients until both groups consisted of at least 40 participants.

Statistical analysis

The aim of the trial was to determine superiority of the primary endpoint (prolapse domain of the UDI) in the surgery group. For both non-randomized and randomized groups, data were analysed according to the intention to treat principle. The domain scores were calculated for UDI, DDI and IIQ at baseline and after 12 months for both groups. The scores of these domains vary between zero and 100. A high score on a particular domain indicates more bothersome symptoms or the worst quality of life. To examine differences between groups we used an unpaired T-test or Mann Whitney test for continuous variables depending on the distribution, while a Chi-square was used for dichotomous variables. The Wilcoxon signed-rank test is applied to the compare the domain scores before and after treatment for both groups separately. We used two-sided significance tests, and a p-value <0.05 was considered to indicate statistical significance. For dichotomous outcomes, we calculated relative risks and 95% confidence intervals. All analyses were done with IBM SPSS statistics 22 (IBM, Armonk, New York, United States).

Results

Between June 2009 and July 2014, we invited 113 women to participate in the study, of whom six women gave informed consent for randomization, and 107 women expressed a treatment preference and participated in the prospective cohort study (72 preferred pessary treatment and 35 preferred prolapse surgery). The remaining six gave informed consent for randomization (2 in the pessary group and 4 in the surgery group).

Based on the slow recruitment, we decided to halt the trial on 30 June 2014, leaving 6 women randomized and 107 women treated according to their preference. We performed an integrated analysis for randomized and non-randomized participants, resulting in 74 women initially treated with pessary and 39 initially treated surgically (figure 1).

Table 1 shows the baseline characteristics of the study population. The pessary group was significantly older than the operation group. Also, women in the pessary group had higher POP-Q stages of the anterior ($p<.001$) and posterior ($p=.02$) compartment than the surgery group. The surgery group did not include participants with POP-Q stage IV.

Table 1. Baseline Characteristics

	Pessary group N=74					Surgery N=39					*p-value*
Age (years) Mean (range)	63.2 (60.4-65.9)					57.6 (53.8-61.4)					*.02*
Body Mass Index (kg/m²) Median (IQR)	25.8 (25.0-26.6)					24.6 (23.5-25.7)					*.07*
Parity (n/m)											*.84*
0	0/74 (0%)					0/39 (0%)					
1	9/74 (12%)					4/39 (10%)					
2	35/74 (47%)					22/39 (56%)					
3	19/74 (27%)					8/39 (21%)					
≥4	11/74 (15%)					5/39 (13%)					
Menopausal status (n/m)											*.07*
Premenopausal	4/67 (6%)					6/35 (17%)					
Menopausal	0/67 (0%)					1/35 (3%)					
Postmenopausal	63/67 (94%)					28/35 (80%)					
Incontinence (n/m)											*.07*
No	33/70 (47%)					17/38 (45%)					
Stress	24/70 (34%)					20/38 (53%)					
Urge	11/70 (16%)					1/38 (3%)					
Mixed	2/70 (3%)					0/38 (0%)					
Oestrogen use (n/m)											*.45*
Yes	5/50 (10%)					2/37 (5%)					
No	45/50 (90%)					35/37 (95%)					
Pre-operative POP-Q Stage	**0**	**I**	**II**	**III**	**IV**	**0**	**I**	**II**	**III**	**IV**	
Compartment											
Anterior (%)	0	13	28	54	6	3	8	72	18	0	*<.01*
Apical (%)	1	43	36	17	3	0	62	26	13	0	*.34*
Posterior (%)	29	39	25	3	4	61	18	16	5	0	*.02*

Table 2 shows domain scores of the Urogenital Distress Inventory, Defecatory Distress Inventory, Incontinence Impact Questionnaire and sexual behaviour before treatment at baseline and after 12 months for both groups. At baseline the pessary group had an overactive bladder score of 11 (10-90th percentile: 0-44) vs 22 (10-90th percentile: 0-58) for the surgery group (p=.02). The baseline pain/discomfort domain was 16 (10-90th percentile: 0-63) in the pessary group vs 33 (10-90th percentile: 0-70) in the surgery group (P<.01). The pessary group had a baseline score of 0 (10-90th percentile: 0-22) vs 11 (10-90th percentile: 0-44) for the surgery group (p<.01) for the social impact of incontinence domain.

The prolapse domain of the Urogenital Distress Inventory at 12 months was the primary outcome (table 2). After 12 months, the median prolapse domain was 0 (10-90th percentile: 0-33) in the pessary group vs 0 (10-90th percentile: 0-0) in the surgery group (p<.01); meaning that in the pessary group, 10% of the participants had a score of 33 or more in the domain “genital prolapse”, compared to all participants of the surgery group with a score of 0 in this domain. Other domain scores were not significantly different. The UDI prolapse domain scores improved significantly for both groups at 12 months post-treatment (p <.01).

Table 2. Domain scores disease specific quality of life of both groups

	Baseline			12 months follow up		
			p-value			*p-value*
	Pessary N= 70	**Surgery** N=33		**Pessary** N=60	**Surgery** N=26	
Urogenital Distress Inventory						
Overactive bladder Median (10-90th percentile)	11.1 (0-44)	22.2 (0-58)	*.02*	0.0 (0-33)	5.6 (0-56)	*.56*
Incontinence Median (10-90th percentile)	16.1 (0-44)	24.2 (0-73)	*.16*	16.7 (0-35)	33.3 (0-50)	*.96*
Obstructive micturition Median (10-90th percentile)	0.0 (0-65)	16.7 (0-70)	*.02*	0.0 (0-35)	0.0 (0-33)	*.39*
Pain/Discomfort Median (10-90th percentile)	16.4 (0-63)	33.1 (0-70)	*<.01*	0.0 (0-33)	0.0 (0-33)	*.74*
Prolapse Median (10-90th percentile)	33.3 (0-98)	33.3 (0-86)	.64	0.0 (0-33)	0.0 (0-0)	*<.01*
Recurrent bladder infections (n/m)			*.16*			*.42*
Never	29 (41%)	12 (36%)		24 (40%)	12 (46%)	
Once	4 (6%)	7 (21%)		2 (3%)	3 (12%)	
Between 2-4 times	4 (6%)	3 (9%)		5 (8%)	1 (4%)	
More than 4 times	1 (1%)	0 (0%)		1 (2%)	0 (0%)	
Defecatory Distress Inventory						
Constipation Median (10-90th percentile)	0.0 (0-23)	0.0 (0-47)	*.09*	0.0 (0-17)	0.0 (0-55)	*.69*
Obstructive defecation Median (10-90th percentile)	0.0 (0-20)	8.3 (0-57)	*.28*	0.0 (0-18)	0.0 (0-33)	*.21*
Pain/Discomfort Median (10-90th percentile)	0.0 (0-33)	0.0 (0-17)	*.85*	0.0 (0-33)	0.0 (0-22)	*.25*
Incontinence Median (10-90th percentile)	0.0 (0-17)	0 (0-17)	*.58*	0.0 (0-33)	0.0 (0-0)	*.20*
Incontinence flatus Median (10-90th percentile)	0.0 (0-67)	33.3 (0-67)	*.09*	0.0 (0-33)	33.3 (0-67)	*.18*
Incontinence Impact Questionnaire						
Physical Median (10-90th percentile)	0.0 (0-48)	0.0 (0-50)	*.50*	0.0 (0-33)	0.0 (0-13)	*.07*
Mobility Median (10-90th percentile)	11.1 (0-44)	16.7 (0-56)	*.26*	0.0 (0-33)	0 (0-31)	*.71*
Social Median (10-90th percentile)	0.0 (0-22)	11.1 (0-44)	*<.01*	0.0 (0-11)	0.0 (0-9)	*.86*
Shame Median (10-90th percentile)	0.0 (0-32)	0.0 (0-33)	*.23*	0.0 (0-22)	0.0 (0-17)	*.99*
Emotional Median (10-90th percentile)	5.5 (0-43)	11.1 (0-67)	*.24*	0.0 (0-37)	0.0 (0-11)	*.31*
Sexuality	N=64	N=32		N=53	N=27	
Sexual intercourse (n/m)	42 (66%)	25 (78%)	*.21*	35 (68%)	21 (82%)	*.21*

UDI, DDI 0=not bothersome and 100=most bothersome IIQ, 0=best quality of life and 100=worst quality of life

Data concerning the initial treatment is presented in table 3. A ring pessary was used most in the pessary group (N=64, 87%), followed by shelf (Falk®) pessaries (N=10, 14%). No other types of pessaries have been used during the follow-up period. There were no patients in the pessary group in which we could not find a fitting pessary at the first visit. Anterior colporrhaphy anterior was the most performed intervention (74%) of the surgery group. Other performed techniques were laparoscopic hysteropexy (N=1, 3%), sacrospinous fixation (N=10, 26%), posterior colporrhaphy (N=10, 26%), Manchester Fothergill (N=2, 5%), transvaginal hysterectomy (N=3, 8%).
In the pessary group 49% (36/74) had a side effect. Most common side effects were vaginal discharge (20%) and vaginal pain (14%). No urinary tract infections or vaginal ulcers were reported. During the follow up period 36% (27/74) participants of the pessary group switch to another type or size pessary. Pessary expulsion occurred in 14% (10/74). The continuation rate at 12 months follow up was 60%. Reason for discontinuation were expulsion, urinary incontinence, vaginal pain, discharge, urinary incontinence and no reduction of the prolapse symptoms (table 3).
The mean operation time was 64 minutes (95% CI 54-75), and the median estimated blood loss was 100 ml (IQR 100-300). The median hospital stay was 2 days (IQR 2-3). There were two complications during surgery registered. In one woman, during an anterior colporrhaphy and posterior a diffuse bleeding occurred. This participant used vitamin K antagonists chronically which were bridged with subcutaneous low molecular weight heparine. The total estimated blood loss in this patient was 1000mL, but she recovered without needing transfusion. Another woman had a bleeding directly after a sacrospinous fixation combined with an anterior colporrhaphy. She received 4 packed cells due to a bleeding near the sacrospinal ligament, which could be treated conservatively with vaginal tamponade. She developed a hematoma and was re-admitted to the hospital for one day. The hematoma relieved spontaneously and was treated conservatively. Post-operative recovery was complicated by 4 participants with a urinary tract infection, 8 participants with urinary retention, and one participant with a bleeding. She was re-admitted and re-operated 12 days post-operative because of an arterial bleeding at the posterior vaginal wall.

Table 3. Initial treatment

	Pessary group N=74	Surgery group N=39
Type of pessary (n/m)		
Falk	14% (10/74)	
Ring	87% (64/74)	
Pessary expulsion (n/m)	14% (10/74)	
Side effects (n/m)	49% (36/74)	
Type of side effect (n/m)		
Vaginal discharge	20% (15/74)	
Vaginal pain	14% (10/74)	
Urinary incontinence	9% (7/74)	
Erosion	4% (3/74)	
Bleeding	1% (1/74)	
Continuation rates (n/m)		
4 weeks	81% (60/74)	
3 months	81% (60/74)	
6 months	64% (47/74)	
1 year	60% (44/74)	
Reason for discontinuation (n/m)		
Pessary expulsion	23% (7/30)	
Urinary incontinence	20% (6/30)	
Vaginal pain	20% (6/30)	
Vaginal discharge	17% (5/30)	
No symptom reduction	17% (5/30)	
Urinary retention	3% (1/30)	
Type of operation (n/m)		
ACR		39% (15/39)
LH		3% (1/39)
SFF + ACR		23% (9/39)
SSF + ACR + PCR		3% (1/39)
ACR + PCR		18% (7/39)
MF + ACR		3% (1/39)
MF + ACR + PCR		3% (1/39)
TVH + ACR + PCR		3% (1/39)
TVH + ACR		3% (1/39)
TVH		5% (2/39)
Operative time (minutes)		
Mean (95% CI)		64 (54-75)
Estimated blood loss (ml)		
Median (IQR)		100 (100-300)
Hospital stay (days)		
Median (IQR)		2 (2-3)
Complications during surgery (n/m)		5% (2/39)
Bleeding (n)		2
Complications during admission (n/m)		33% (13/39)
Urinary tract infection (n)		4
Bladder retention (n)		8
Bleeding (re-operation) (n)		1

ACR = anterior colporrhaphy, PCR = posteroior colporrhaphy, LH = laparoscopic hysteropexy, TVH = transvaginal hysterectomy, MF = Manchester-Fothergill, SFF = Sacrospinous fixation

In the pessary group, in 31% (23/74) a second intervention occurred versus 10% (4/39) of the surgery group (p=.01) as shown in table 4. The additional interventions of the pessary group contain POP surgery in 21 participants (28%), urinary incontinence surgery in 1 participant (1%) and physiotherapy in 1 participant (1%). In the surgery group 1 participant (3%) received a pessary, 2 other (5%) got a pessary combined with physiotherapy and 1 woman (3%) had recurrent POP surgery combined with physiotherapy.

Table 4. Additional interventions

	Pessary group N=74	**Surgery group** N=39	***p-value***
			.01
Additional intervention(n/m)	31% (23/74)	10 % (4/39)	
Physiotherapy (n)	1	0	
Pessary (n)	0	1	
Prolapse surgery (n)	21	0	
Incontinence surgery (n)	1	0	
Combined Additional interventions (n/m)			
Prolapse and incontinence surgery (n)	0	0	
Prolapse surgery and physiotherapy (n)	0	1	
Pessary and physiotherapy (n)	0	2	
Time till second intervention (months) Median (IQR)	3.0 (1.0-7.0)	10.0 (3.0-11.8)	*.17*

Discussion

Main findings

In our study, we found that treatment preference limits the willingness to undergo randomization. The comparison of both interventions showed that at 12 months follow up the pessary group reported more symptoms in the prolapse domain of the UDI, which was primary outcome. The pessary group had also more additional interventions whereas 28% of the women needed a surgical intervention versus 5% re-operations in the surgery group. Younger patients, with a higher POP-Q stage and more urinary symptoms that affect their social life, are more likely to choose POP surgery.

S*trengths and limitations*

To our knowledge this is the first attempt for a randomized trial comparing pessary to surgery as primary treatment for women with POP. We could however randomize only 6 women, since a large majority of the eligible women had a strong preference for one of the treatment options. Therefore, we decided to halt the trail and report on the data of this prospective cohort study. Previous studies

reporting on women with pelvic organ prolapse also reported strong patient's preference for one of both interventions [11]. The likelihood of preferring pessary treatment over surgery increases as patients' age rises according to Lamers et.al. They conclude that surgery was preferred over pessary if POP stage increases and if POP symptoms are more bothersome and affect general well-being and patients who are sexually active also tended to prefer surgery over conservative treatment [11]. In our study population patient's preference plays an important role, to such a degree that randomization seemed to be very difficult.

Since most participating women were not randomized, selection bias is likely to play a role. It is possible that doctors counselled women differently depending on patient characteristics as age, comorbidity, sexual activity, POP stage, POP symptoms and how they affect their daily activities. Because the groups were not allocated by randomization, the baseline characteristics are significantly different. The heterogeneity between the treatment groups is a normal reflection of the daily practice. Previous prospective cohort studies reporting on women with pelvic organ prolapse also reported strong patient's preference for one of both interventions [11]. The pessary group in our study consists of older participants which is comparable to previous literature [11]. The POP-Q stages of the pessary group are higher unlike other literature, but complaints are more bothersome in the surgery group, which correspond with the present literature [11].

The unwillingness to be randomized is an outcome on itself, as it visualizes the strong differences between both interventions with respect to invasiveness, risk profile and impact. Since both treatment options are very divers, it leads to a strong preference for one of both treatment options. However, in the OPUS trial [22] the randomization group and the patient-preference group was compared and did not show any differences in baseline characteristics and results. This might suggest that a RCT is not the only study design that could provide useful additions to the present literature, and the results of our prospective trial add some valuable conclusions. Following the advice of several epidemiologist, we didn't perform separate analyses for our randomized and non-randomized group, since the randomized group was too small.

Interpretation

This prospective cohort study comparing pessary to surgery as primary treatment for pelvic organ prolapse generates some important lessons. As a randomized clinical trial comparing the two strategies turned out not to be feasible, our prospective study results can be used to counsel women. A strategy of pessary followed by surgery if needed, or a strategy with immediate surgery seem both effective options for these women.

Both groups report very low scores for almost all domains of the UDI, DDI and IIQ, which suggests both treatments to be effective. The pessary group reports more symptoms in the prolapse domain

of the UDI, which is statistically significant. However, the median score is still very low (0 (10-90th percentile: 0-33) for the pessary group vs 0 (10-90th percentile: 0-0)), which is probably clinically irrelevant. Previous studies have also shown pessaries to be effective in improving pelvic floor dysfunction [7-10]. In most papers is the improvement gained in both bulge and irritative bladder symptoms following pessary treatment [11] but two studies reported de novo stress urinary incontinence as well [23, 10]. Patients' satisfaction rates with medium-term pessary use are high (70–92%) [23, 24]. Two prospective cohort studies comparing pessary to surgery report similar improvement in urinary, bowel, sexual function, and quality of life parameters at 12 months follow-up [12-17].

The continuation rate of pessary treatment after 12 months was 60%, whereas 72% of the women in the pessary didn't had an indication for a surgical intervention. These results are very important since it illustrates that both treatments are very efficient to treat urinary, defecation and prolapse symptoms, since the domain scores of the UDI, DDI and IIQ after 12 months were very low, with a median score of 0.0 for most domains. Prospective trials report continuation rates between 50-80% after one year and 14-48% after five years [11], however evidence about re-interventions are lacking. Although no costs analysis was performed, these results suggests that the pessary group is more costs effective, since less surgery occurred and the domain scores of the UDI, DDI and IIQ at 12 months are low for both groups.

The patient population is not larger than 113 participants despite the long study period.

As the study was non-funded, we were not able to register all patients who declined to participate. Therefore, we could not provide reliable data about a denominator. We included patients until both groups consisted of at least 40 participants. Since it only concerns 6 randomized participants, we decided, following the advice of several epidemiologists, not to perform a separate analysis for the two groups, but to analyse both groups together and present our data as a prospective cohort instead of a RCT with a prospective cohort alongside.

Nevertheless, the results of our study provide evidence about continuation rates, additional interventions, quality of life and patients preference. These outcomes will help in order to individualize the counselling about treatment options and guide patients better to the decision process of the treatment of a symptomatic POP. Younger patients, with a lower POP-Q prolapse stage but more urinary symptoms, that affect their social life, are more likely to choose POP surgery. This agrees with the results of previous studies. A review on the topic shows that the probability of choosing pessary treatment over surgery increases as patients' age rises conform the results of our study. Surgery was preferred over pessary if POP symptoms are more bothersome and affect there general well-being [11].

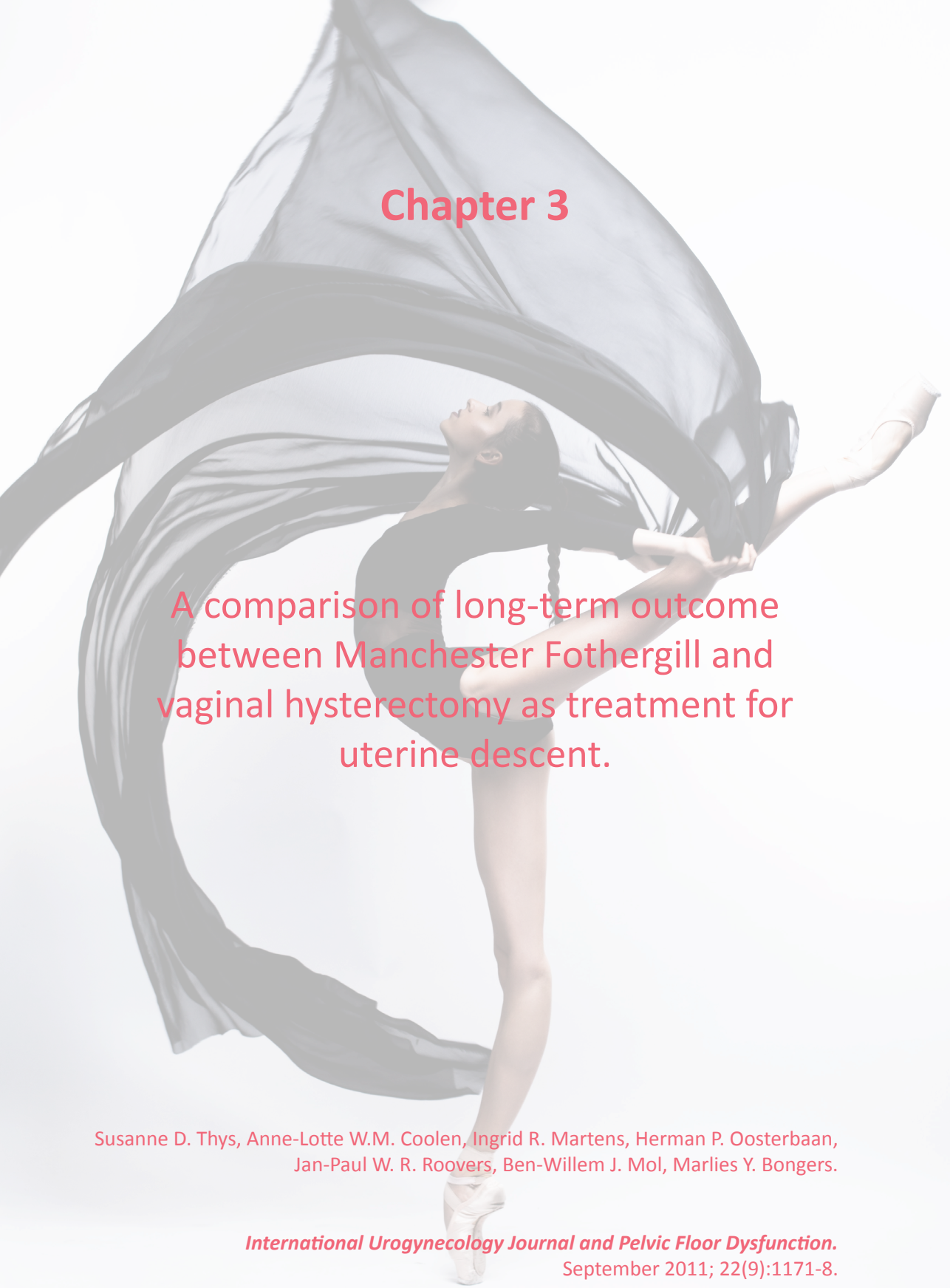
Conclusion

Women with POP stage 2 or more treated with a pessary are bothered more by prolapse symptoms and undergo more often surgery in the first year of follow-up as compared to patients who undergo surgery. However, pessary treatment prevents surgery in 72%, although prolapse symptoms are less in those who have been operated. These outcomes will help in order to individualize the counselling about treatment options and guide patients better to the decision process of the treatment of a symptomatic POP.

References

1. MCP Slieker-ten Hove 2009 et al, The prevalence of pelvic organ prolapse symptoms and signs and their relation with bladder and bowel disorders in a general female population, International Urogynecology Journal (2009) 20:1037-1045
2. AL Olsen, Epidemiology of surgically managed pelvic organ and urinary incontinence. Obstetrics and Gynecology 1997;89 (4):501–6
3. Richter HE, Burgio KL, Brubaker L, Nygaard IE, Ye W, Weidner A et al, Continence pessary compared with behavioral therapy or combined therapy for stress incontinence: a randomized controlled trial. Obstet Gynecol (2010) 115(3):609–617, 2010 March
4. Atnip SD, Pessary use and management for pelvic organ prolapse. Obstet Gynecol Clin North Am (2009) 36(3):541–563
5. Thys SD, Roovers JP, Geomini PM, Bongers MY, Do Patients Prefer a Pessary or Surgery as Primary Treatment for Pelvic Organ Prolapse. Gynecol Obstet Invest. (2012) 74: 6-12
6. Vd Waarsenburg MK, vd Vaart CH. Pessary or surgery for symptomatic organ prolapse: study protocol. Unpublished. Version 1.4, Oct 2014
7. GA Digesu, The relationship of vaginal prolapse severity to symptoms and quality of life. British Journal of Obstetrics and Gynecology (2005), 112:971–976
8. Fernando RJ, Thakar R, Sultan AH, Shah SM, Jones PW, Effect of vaginal pessaries on symptoms associated with pelvic organ prolapse. Obstet Gynecol (2006) 08(1):93–99
9. YM Komesu, Pelvic floor symptom changes in pessary users. American Journal of Obstetrics and Gynecology (2007) 197:620.e1–620.e6
10. A Kuhn, Sexual and organ function in patients with symptomatic prolapse: are pessaries helpful? Fertility and Sterility (2009) 5:1914–1918
11. Lamers BHC, Broekman BMW, Milani AL. Pessary treatment for pelvic organ prolapse and health-related quality of life: a review. International Urogynecology Journal and Pelvic Floor Dysfunction (2011) 22:637–64
12. Abdool Z, Thakar R, Sultan AH, Oliver RS, Prospective evaluation of outcome of vaginal pessaries versus surgery in women with symptomatic pelvic organ prolapse. International Urogynecology Journal and Pelvic Floor Dysfunction (2010) 22(3):273-8.
13. Broens-Oostveen MC, Mom RM, Lagro-Janssen AL, Genital prolapse; treatment and course in four general practices. Ned Tijdschr Geneeskd, (2004) 148(29):1444–1448, 17
14. Sarma S, Ying T, Moore KH, Long-term vaginal ring pessary use: discontinuation rates and adverse events. BJOG (2009) 116 (13):1715–1721
15. Broens-Oostveen WC, Mom RM, Largo-Janssen ALM. De genitale prolaps: behandeling en beloop in vier huisartspraktijken. Ned.Tijdschr.Geneeskunde. (2004) 148 (29); 1444-1448
16. Z Abdool, Prospective evaluation of outcome of vaginal pessaries versus surgery in women with symptomatic pelvic organ prolapse, International Urogynecology Journal (2011) 22:273–278
17. Lone F, Thakar R, Sultan AH, One-year prospective comparison of vaginal pessaries and surgery for pelvic organ prolapse using the validated ICIQ-VS and ICIQ-UI (SF) questionnaires. Int Urogynecol J (2015) 26:1305–1312
18. R.C. Bump, A. Mattiasson, K. Bø, L.P. Brubaker LP, DeLancey JO, Klarskov P, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol. 1996; 175(1):10–17.
19. Van der Vaart CH, de Leeuw JR, Roovers JP, Heintz AP. Measuring health-related quality of life in women with urogenital dysfunction: the urogenital distress inventory and incontinence impact questionnaire revisited. Neurourol Urodyn. 2003;22(2): 97-104.
20. Roovers JP, van der Blom JG, van der Vaart CH. Hysterectomy does not cause constipation. Dis Colon Rectum. 2008; 51 (7):1068-72.

21. Roovers JP, van der Vaart CH, van der Bom JG, Heintz AP. A randomised controlled trial comparing abdominal and vaginal prolapse surgery: effects on urogenital function. Br J Obstet Gynaecol. 2004; 111: 50-56.
22. J.T. Wei, I. Nygaard, H.E. Richter, C.W Nager, M.D.Barber (2012) A Midurethral Sling to Reduce Incontinence after Vaginal Prolapse Repair, N Eng J Med, 366:2358-67
23. Clemons JL, Aguilar VC, Tillinghast TA, Jackson ND, Myers DL (2004) Patient satisfaction and changes in prolapse and urinary symptoms in women who were fitted successfully with a pessary for pelvic organ prolapse. Am J Obstet Gynecol 190 (4):1025–1029
24. Bai SW, Yoon BS, Kwon JY, Shin JS, Kim SK, Park KH (2005) Survey of the characteristics and satisfaction degree of the patients using a pessary. Int Urogynecol J Pelvic Floor Dysfunct 16 (3):182–186
25. J.P. Roovers, E.Everhardt, V.Dietz, F.Milani et al. (2014) Concept richtlijn prolapse van de nederlandse vereniging obstetrie en gynaecologie. Dutch society of obsetrics and gynecologie. www.nvog.nl.
26. Jelovsek JE, Maher C, Barber MD (2007) Pelvic organ prolapse. Lancet 369(9566):1027–1038, 24
27. Adams E, Thomson A, Maher C, Hagen S. (2004) Mechanical devices for pelvic organ prolapse in women. Cochrane Database Syst Rev (2):CD004010
28. Cundiff GW, Weidner AC, Visco AG, Bump RC, Addison WA (2000) A survey of pessary use by members of the American Urogynecologic Society. Obstet Gynecol 95(6 Pt 1):931–935
29. Bai SW, Yoon BS, Kwon JY, Shin JS, Kim SK, Park KH (2005) Survey of the characteristics and satisfaction degree of the patients using a pessary. Int Urogynecol J Pelvic Floor Dysfunct 16 (3):182–186



Chapter 3

A comparison of long-term outcome between Manchester Fothergill and vaginal hysterectomy as treatment for uterine descent.

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Abstract

Introduction and hypothesis The objective of this study was to compare the Manchester Fothergill (MF) procedure with vaginal hysterectomy (VH) as surgical treatment of uterine descent.

Methods Consecutive patients who underwent MF were matched for prolapse grade, age and parity to consecutive patients treated with VH. Evaluated outcomes included functional outcome, morbidity, recurrence of pelvic organ prolapse (POP) and sexual function. Follow-up was performed using validated questionnaires.

Results We included 196 patients (98 patients per group). The response rate after a follow-up of 4–9 years was 80%. We found no differences in functional outcome and recurrence rates of POP between groups. Blood loss was significantly less and operating time was significantly shorter in the MF group. However, incomplete emptying of the bladder was more common in the MF group.

Conclusion The MF procedure is equally effective to the VH and should be considered as a surgical option that allows preservation of the uterus.

Introduction

Pelvic organ prolapse (POP) is a common medical problem, especially in elderly women. This condition may affect pelvic floor function, resulting in micturition, defecation and sexual symptoms [1]. The lifetime risk of having to undergo surgery for POP is reported to be 11% [2]. In most cases, the apical compartment is involved, and in approximately 70% of the surgical correction of POP, an apical compartment repair is part of the procedure [3].

Different surgical procedures for correction of this apical compartment have been described. Historically, the vaginal hysterectomy (VH) is the most common performed procedure for apical prolapse, combined with anterior and/or posterior colporrhaphy in case of concomitant anterior and/or posterior compartment prolapse, if necessary. The popularity of VH is not supported by the literature. Moreover, VH has two common disadvantages. First, vaginal vault prolapse has been described to be up to 43% [4]. Second, the incidence of enterocele after hysterectomy is reported to be up to 16% [5]. Furthermore, women may desire uterine preservation rather than hysterectomy [6].

In view of these arguments, gynaecologists may propose a uterus-preserving technique for apical compartment prolapse, such as abdominal sacrocolpopexy with preservation of the uterus, sacrospinous ligament fixation (SSF) or Manchester Fothergill (MF) procedure. The first two procedures are already evaluated in randomized controlled trials compared to the VH. A study of Roovers et al. showed less pain, better quality of life and better mobility during the first 6 weeks post-surgery when a VH is compared to the abdominal sacrocolpopexy [7]. Nevertheless, the functional outcome after 1 year did not differ. In a study of Dietz et al., the SSF is compared to the VH [8]. They showed a difference in risk for recurrent prolapse stage 2 or more of the apical compartment at 1 year follow- up of 17% in favour of the VH. No differences in quality of life and urogenital symptoms were found.

The MF is also described as a uterus-preserving procedure. This procedure includes the amputation of the cervix and has been evaluated far less compared to the other two techniques. This method was first performed in Manchester in 1888 by Archibald Donald. William Edward Fothergill extended the procedure in 1921 by suturing the cardinal ligaments on the remaining cervical stump [9]. In the modified MF procedure, the support of the uterosacral ligaments is also maintained [10]. This procedure has met limited popularity among gynaecologists, and in some articles, this procedure is described as an obsolete procedure [6]. However, three retrospective studies compared the MF and the VH. These retrospective studies show less morbidity in favour of the MF procedure [11, 12] but comparable functional and anatomical outcomes [13]. A design weakness of these studies is that the groups compared were not matched on, e.g. prolapse stage, age and parity. In the study by de Boer et al., a greater amount of women with a higher degree of POP of the apical compartment received a

VH, whereas the modified MF group comprised mainly women with lower stage prolapse [13]. In view of these recent developments, we studied the MF procedure and the VH regarding disease-specific quality of life (DSQOL), surgery-related morbidity and the long-term recurrence rates of POP.

Materials and methods

Study population

We performed a multicentre, retrospective matched cohort study. The study population consisted of patients who underwent either a MF or VH for primary apical compartment prolapse between January 2000 and December 2005. This study was performed in the Máxima Medical Centre (MMC) and the Jeroen Bosch Hospital (JBH), two Dutch teaching hospitals. Both types of operations were performed by experienced gynaecologists; all performed at least 50 MF and VH procedures.
The indication for the MF and VH were primary apical compartment prolapse if indicated, combined with anterior and/or posterior colporrhaphy. The treatment selection was based on the preference of the gynaecologist in consultation with the patient. Women who underwent combined prolapse and incontinence surgery were excluded [13]. First, we identified all women that were treated with a MF. The identified MF patients were then matched to VH patients for pre-operative grade of prolapse (Baden and Walker classification [14]), age and parity.

Surgical intervention

Manchester Fothergill procedure

In case of concomitant anterior colporrhaphy, this procedure was performed first. The cervix was held with a tenaculum forceps. The colporrhaphy was started with hydrodissection followed by a vaginal midline incision from the urethrovesical junction until the fold of the bladder at the cervix. The cervix was circumcised. The vaginal wall was separated from the bladder fascia, and the bladder was then dissected from the cervix over 2 to 3 cm. The peritoneal cavity was not opened. The bladder fascia was subsequently plicated under the bladder with a number of interrupted sutures Vicryl 2–0. In order to prevent an anterior enterocele, the most proximal plicating suture incorporated the cervix cranial to the level of subsequent cervical amputation. After removal of excessive vaginal epithelium, the vagina was closed with Vicryl 2–0 stitches. In case the procedure was not combined with an anterior colporrhaphy, the cervix was simply circumcised, and the bladder was dissected from the cervix over 2 to 3 cm. The next step was to identify the cardinal ligaments by palpating them at the lateral side of the cervix. The cardinal ligaments were marked on both sides. The cervix was now amputated over 1 to 2.5 cm depending on the amount of cervical elongation. The vaginal epithelium of the cervix was dissected from the cervix over 0.5 cm in order to get a better

application of the epithelium to the amputated cervix
after suturing. Haemostasis of the cervix and vaginal wall was achieved by cauterization. The cardinal ligaments which have been marked were now stitched on the anterior side of the cervix with two to three Vicryl 2–0 stitches. The anterior and posterior side of the cervix were re-epithelialized with Sturmdorf sutures.

Vaginal hysterectomy procedure

In case of additional anterior colporrhaphy, this procedure was performed before or after the vaginal hysterectomy at the discretion of the surgeon. The cervix was held with a tenaculum forceps and circumcised. The bladder was dissected and the anterior peritoneum was opened. Posteriorly, a similar procedure was performed, and the pouch of Douglas was opened. Now, the uterosacral ligaments were palpated and help with a forceps and cut and ligated with a Vicryl 2–0 suture which was left long. The uterus was removed in several steps with clamps and ligatures of Vicryl 1. After removal of the uterus, the adnexa were inspected. To ensure the position of the vaginal vault, it was fixated and sutured to the uterosacral ligaments which had been left long. The vaginal epithelium of the vault was closed with interrupted Vicryl 1 sutures.

Peri- and post-operative care

All patients received general or spinal anaesthesia during surgery, and antibiotics were given only as prophylactic during surgery. In both operations, a vaginal pack (for 12– 24 h) and a catheter were inserted after the procedure. In the MMC, patients received a trans-urethral catheter during 2 days post-operative or a supra-pubic catheter for 5 days post-operative. In the JBH, all patients received a trans- urethral catheter during 2 days post-operative.

Measurements

Our primary outcome was the prolapse domain score of the Urogenital Distress Inventory (UDI) [15]. Our secondary outcomes were morbidity (defined as pre-, intra- and post- operative characteristics and complications), recurrence of POP (defined as any type (anterior, posterior or apical compartment) and any stage of POP which required re- intervention), DSQOL and sexual function. We collected data from patient records at the time of operation, medical history, previous conservative treatment (pessary, physical therapy) and stage of prolapse from hospital record files. Data on recurrence rates were collected from patient record files and from the follow-up questionnaire. Some patients consulted another gynaecologist, general practitioner or physiotherapist because of prolapse complaints. These patients were stated as having a recurrence if

this consultation resulted in a re-intervention for POP. Re-interventions included physical therapy, a pessary or a repeated prolapse operation. Data on duration of surgery and admission, blood loss and complications related to surgery were registered from patient record files. The DSQOL was measured with validated questionnaires. In 2008, i.e. 3 to 8 years after the intervention, all patients were approached and asked to complete the Dutch validated version of the UDI, the Defecatory Distress Inventory (DDI) [16] and the Incontinence Impact Questionnaire (IIQ) [15]. The UDI and DDI consist of 19 and 12 items, and each item measures if micturition/prolapse or defecatory symptoms are present and to what extent the patient is bothered by this symptom. The latter was measured on a four-point Likert scale ranging from no complaints at all to severe complaints. The sub scores of the UDI were transformed into five domains, i.e. discomfort/pain, urinary incontinence, obstructive micturition, overactive bladder and genital prolapse. The sub scores of the DDI were transformed into five domains, i.e. obstipation, flatus, incontinence, obstructive defecation and discomfort/pain. These domains were scored on a scale from 0 (no complaints) to 100 (severe complaints). The IIQ covers five domains, i.e. physical functioning, mobility, emotional functioning, social functioning and embarrassment. The scores range between 0 (best quality of life) and 100 (worst quality of life). Finally, we asked the following four questions to assess sexual functioning: (1) “Are you sexually active?”, (2) “Do you experience sexual activity as satisfying or bothersome?”, (3) “Do you involuntary lose urine during intercourse?” and (4) “Do you experience pain during intercourse”. These four questions were measured on a four-point Likert scale ranging from no complaints at all to severe complaints.

Follow-up

Six weeks after surgery, patients underwent a standardized follow-up visit including assessment of pelvic floor symptoms and of the prolapse using the Baden and Walker classification. Follow-up data were collected from patient’s files and validated questionnaires (described below). When the patients did not respond to the mailed questionnaire, we contacted them by telephone and sent the questionnaire once again. For patients who completed and returned the questionnaire, the follow-up time was defined as time between the operation and the date the questionnaire was completed. The follow-up time of the patients who did not return questionnaires was defined as time between the operation and either the time of recurrence of POP diagnosed by their gynaecologist or the time of the last data collection from hospital files.

Power analysis

Based on previous studies, we considered a difference of 6 points in the prolapse domain score of the UDI to be clinically significant. Based on a standard deviation of 12 points, the calculated sample size per group was 82 patients (power 90%, $\alpha = 0.05$). Anticipating on 20% of patients not willing to respond to the questionnaire, we planned to include 98 patients in each group.

Statistical analysis

The MF group and the VH group were compared using the Students' t tests (for normal distributed data), the Mann-Whitney tests (for skewly distributed data) and chi-square analyses (for categorical variables). Time to recurrence of prolapse in the two groups were compared with a Kaplan-Meier curve and expressed using a hazard ratio with 95% confidence interval using Cox regression analyses. A log-rank test was applied to this curve to test significant differences in recurrence rates. A sub-analysis was performed concerning lower stage uterine descent (stages 1 and 2) and higher-grade uterine descent (stages 3 and 4).

The UDI-, DDI- and IIQ-specific domain scores were compared with the Mann–Whitney test. To analyse differences between the sexual activities, the Mann–Whitney test was also performed. All data were entered and analysed in a Statistical Package for the Social Sciences 17.0 database for Windows.

Results

In total, we included 196 patients, 98 in the MF group and 98 in the VH group. Table 1 shows the baseline characteristics of the studied population. The groups were comparable, but for the fact that there were more cases of single pessary treatment and combined treatment (physical therapy and pessary) in the VH group.

Table 1. Pre-operative characteristics

	MF (n=98)	VH (n=98)	p-value
Age (years)	62 ± 13	63 ± 11	.54 [a]
Body mass index (kg/m^2)	25 ± 3	25 ± 3	.91 [a]
Parity			.30 [b]
None	2 (2%)	0 (0%)	
1-4	75 (78%)	72 (76%)	
≥4	19 (20%)	23 (24%)	
Medical history			
Lung disease	6 (6%)	8 (8%)	.58 [b]
Abdominal surgery	36 (37%)	45 (46%)	.19 [b]
Menopausal status			.08 [b]
Pre-menopausal	13 (13%)	7 (7%)	
Menopausal	4 (4%)	11 (11%)	
Post-menopausal	80 (83%)	80 (82%)	
Duration of symptoms (months)	63 ± 95	34 ± 43	.10 [b]
Cystocele			.91 [b]
Stage 0	4 (4%)	2 (2%)	
Stage 1	5 (5%)	6 (6%)	
Stage 2	27 (28%)	30 (31%)	
Stage 3	54 (56%)	52 (53%)	
Stage 4	7 (7%)	8 (8%)	
Rectocele			.79 [b]
Stage 0	24 (26%)	17 (18%)	
Stage 1	38 (40%)	43 (46%)	
Stage 2	21 (22%)	22 (24%)	
Stage 3	8 (9%)	7 (8%)	
Stage 4	3 (3%)	4 (4%)	
Apical prolapse			.30 [b]
Stage 0	1 (1%)	1 (1%)	
Stage 1	38 (40%)	25 (26%)	
Stage 2	36 (38%)	48 (49%)	
Stage 3	14 (15%)	18 (18%)	
Stage 4	6 (6%)	6 (6%)	
Urinary incontinence	47 (48%)	46 (48%)	.55 [b]
Defecation problems	13 (13%)	24 (24%)	.29 [b]
Conservative treatment prior to surgery			.001 [b]
Pessary	44 (48%)	51 (52%)	
Physical therapy	6 (7%)	7 (7%)	
Combined	7 (8%)	21 (21%)	

Data are mean (standard deviation) or numbers (percent). *MF* Manchester Fothergill, *VH* vaginal hysterectomy.
[a] Student's *t* test. [b] Pearson's chi-square.

Table 2 shows the characteristics of the surgical procedure. In the MF group, blood loss was significantly less compared to the VH group: 250 ml (±210) versus 358 ml (± 235), respectively, p = 0.01. Furthermore, the operation time was significantly shorter in the MF group (67 min) as compared to the VH group (101 min), p = 0.01.

Table 2. Peri- and post-operative characteristics

	MF (n=98)	VH (n=98)	p-value
Peri-operative			
Type of anaesthesia			.27
Spinal	62 (64%)	51 (56%)	
General	35 (36%)	40 (44%)	
Surgery time (min)	67 ± 20	101 ± 22	.01[b]
Blood loss (min)	250 ± 210	358 ± 235	.01[c]
Complications	4 (4%)	4 (4%)	1.00
Bowel lesion	1 (1%)	0 (0%)	
Bladder lesion	0 (0%)	1 (1%)	
Haemorrhage	3 (3%)	3 (3%)	
Post-operative			
Hospital stay (days)	7 ± 2	7 ± 2	.95[b]
Complications post-operative	43 (44%)	37 (38%)	.38[b]
Type of complication			
Urinary retention (>150cc)	33 (34%)	11 (11%)	.01[b]
Urinary tract infection	17 (17%)	28 (29%)	.06[b]
Post-operative haemorrhage	1 (1%)	2 (2%)	.56[b]
Other complications	6 (6%)	6 (6%)	1.00[b]
6 weeks follow-up			
Urinary incontinence	16 (20%)	12 (13%)	.52[b]
Defecation problems	9 (9%)	8 (8%)	.70[b]
Sexual function			.82[b]
Dyspareunia	4 (18%)	5 (20%)	
None	9 (41%)	12 (48%)	
Uncomplicated	9 (41%)	8 (32%)	

Data are mean (standard deviation) or numbers (percent). *MF* Manchester Fothergill, *VH* vaginal hysterectomy. [a] Student's *t* test. [b] Pearson's chi-square. [c] Mann-Whitney test.

In the MMC, 29 patients in the MF group and one patient in the VH group received a supra-pubic catheter for 5 days post- operative. The other patients received a trans-urethral catheter during 2 days after surgery. Post-operatively, we found significantly more patients with a urinary retention in the MF group (34% versus 11%; relative risk (RR) 3.2 (95% confidence interval (CI) 12.1–34.8)), whereas there was a trend to less urinary tract infections in the MF group (17% versus 29%; RR 0.6 (95% CI 0.5–24.0); Table 2). We analysed the surgical morbidity such as urinary retention, urinary tract infections, hospital stay, post-operative haemorrhage and objectified recurrence rates and re-operation rates according to study site. We did not find (statistical significant) differences between both teaching hospitals (data not shown).

The questionnaire was returned by 78 patients who underwent a MF and 77 patients who underwent a VH, resulting in a response rate of 80% in both groups. Forty- one patients were lost to follow-up, nine patients because they had died, two patients because they suffered from dementia, whereas 29 patients could not be contacted. One patient lost to follow-up told us over the telephone that they did not want to complete the questionnaire. The median follow-up in this study was 6 (1.5–9.5) years.

Table 3 shows the recurrence rates. At a median follow- up time of 75 (17–112) months in the MF group and 68 (41–110) months in the VH group, we found no significant differences between POP symptoms for which patients needed professional consult, objectified recurrence rates and re-intervention rates. A sub-analysis between lower- degree and higher-degree prolapse according to objectified recurrence and re-operation rates shows also no differences between both interventions.

Table 3. Recurrence and re-interventions of POP after surgery

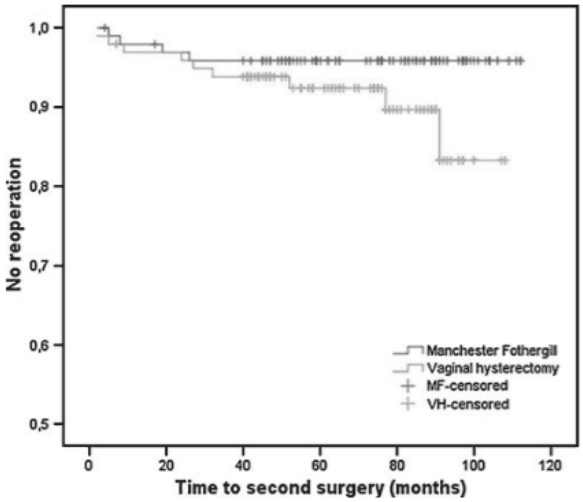
	MF (n=98)	VH (n=98)	p-value
Symptoms for which patient consulted professional	24 (25%)	20 (20%)	.49[b]
Objective recurrence	19 (19%)	18 (18%)	.86[b]
Following pre-operative stage of uterine descent			
Stage 1 and 2	16 (85%)	15 (83%)	
Stage 3 and 4	3 (15%)	3 (17%)	
Re-interventions[a]			
Conservative re-interventions	11 (11%)	14 (14%)	.52[b]
Physical therapy	8 (8%)	4 (4%)	
Pessary	1 (1%)	3 (3%)	
Combined	2 (2%)	7 (7%)	
Surgical re-intervention	4 (4%)	9 (9%)	.15[b]
Following pre-operative stage of uterine descent			
Stage 1 and 2	4 (100%)	7 (78%)	
Stage 3 and 4	0 (0%)	2 (22%)	
Kind of re-operation			.45[b]
Anterior colporrhaphy	1 (1%)	2 (2%)	
Posterior colporrhaphy	2 (2%)	5 (5%)	
Sacral colpopexy	0 (0%)	2 (2%)	
Amreich-Richter	1 (1%)	0 (0%)	
Time to re-operation (months)	72.03 ± 25.1	64.38 ± 23.1	.03[c]
Recurrence of POP, hazard rate (95% CI)	2.454 (0.75-8.00)		

Data are mean (standard deviation) or numbers (percent). *MF* Manchester Fothergill, *VH* vaginal hysterectomy.
[a] Some patients received both conservative and a surgical intervention. [b] Pearson's chi-square. [c] Log-rank test.

The average time to undergo a re-operation for recurrent prolapse was 9 months shorter in the MF group as compared to the VH group (log rank: p = 0.03); a Kaplan-Meier curve concerning time to re-operation after primary surgery of POP is shown in Fig. 1. Nevertheless, we did not find a significant difference in recurrence rates between the VH and MF procedure (hazard ratio for recurrence of POP between both groups is 2.5 in favour of the MF group (HRR 2.5, 95% CI 0.8–8.0)).

Table 4 shows the outcome of the quality of life questionnaires. No statistically significant differences in the UDI and DDI domain scores were found, although we found higher scores on the obstructive micturition domain in the VH group (p=0.06). We found no significant differences in IIQ scores, sexual activity, sexual satisfaction, pain and urinary incontinence during intercourse.

Figure 1. Kaplan Meier curve showing re-operation rates because of recurrent prolapse.



The *blue line* represents the Manchester Fothergill procedure. The *green line* represents the vaginal hysterectomy.

Table 4. Functional outcome of the follow-up questionnaire

	MF (n=98)		VH (n=98)		p-value
Urogenital Distress Inventory					
Discomfort/pain	79	18.0 (23.0)	75	15.6 (23.0)	.37
Urinary incontinence	78	17.1 (21.0)	76	14.9 (21.3)	.37
Obstructive micturition	78	3.0 (9.9)	76	8.0 (18.4)	.06
Overactive bladder	77	9.4 (15.7)	73	7.7 (17.8)	.21
Pelvic organ prolapse	78	11.0 (18.2)	77	11.6 (19.0)	.73
Defecatory Distress Inventory					
Constipation	78	8.7 (15.7)	77	5.1 (10.1)	.23
Flatus	78	25.0 (31.7)	76	20.4 (27.0)	.49
Incontinence	78	8.0 (17.2)	77	6.9 (15.5)	.89
Obstructive defecation	75	5.7 (11.4)	75	6.4 (11.6)	.58
Discomfort/pain	77	4.2 (11.5)	78	3.6 (11.5)	.38
Sexual function					
Sexually active (%)	42	53.8	42	54.5	
Satisfaction	42	67.0 (26.1)	42	67.9 (28.6)	.89
Not sexually active (%)	20	25.6	18	23.4	
Bother	17	17.5 (23.7)	18	14.7 (28.4)	.49
No response	16	20.5	17	22.1	
Dyspareunia	38	14.8 (25.2)	38	17.4 (30.6)	.63
Urinary incontinence during sexual intercourse	38	1.7 (7.5)	38	2.6 (9.0)	.88

Data are mean (standard deviation). Mann-Whitney test. *MF* Manchester Fothergill. *VH* vaginal hysterectomy.

Discussion

We performed a multicentre matched cohort study in 196 patients who underwent VH or MF as primary surgery for uterine prolapse. We found VH and MF to have similar recurrence rates and re-interventions. Blood loss and operation time were in favour of the MF procedure, whereas the risk on urinary retention was in favour of VH. A trend to more urinary tract infections was found in the VH group.

The study has a few limitations. First, our matching failed to correct for all differences in prognostic factors so the quality of a randomized controlled trial could not be realized. However, we did correct for those factors that are known to have prognostic value for our primary outcome. Second, the selection between the two surgical options was made by the gynaecologist. Indications to operate were all uterine descent, but technical or personal factors could have influenced the surgeons' selection. Third, because this study was retrospective, we were not informed about the moment that patients experienced a recurrent prolapse but only about the moment they underwent a re-intervention. This, however, is not a

significant problem as we are informed about the re-intervention rate of both procedures and rate this outcome as more relevant than asymptomatic recurrence of prolapse itself. Our study was strengthened by the large number of evaluated patients, the high response rate and the variety of clinically relevant outcome parameters that were reported on.

Although we did not observe a statistically significant difference in recurrence between both groups, the calculated hazard ratio was 2.5 in favour of the MF, which is clinically relevant. Also, the time to re-operation was significantly shorter in the VH group. It is difficult to come up with a good explanation for this finding. There are no previous studies comparing the time to re-intervention or re-operation between both procedures. An explanation could be that the cervical amputation, which makes part of the MF, decreases the experienced bother of recurrent prolapse. So even if a recurrence has developed, it may last longer to become symptomatic, whereas after vaginal hysterectomy, a less progressive prolapse could already cause bother. Another explanation could be that gynaecologists have a different attitude with respect to management of recurrent prolapse, based on their trust on the solidity of the procedure. This implicates that gynaecologists could be more ignorant to the development of a recurrent prolapse following MF than following vaginal hysterectomy which ultimately results in a difference in time to re-operation.

The observation that bladder retention was more common following a MF procedure had not been reported before and we have difficulties to give a solid explanation for this. An explanation might be that in the MF, more concomitant surgical procedures of the anterior compartment were performed. Another explanation may be that gynaecologists preferring MF procedure tend to be more liberable with combining the procedure with a Kelly plication which is known for its risk on urinary retentions

[17].

The difference in urinary tract infections can be explained by the kind of catheterisation. In the VH group, 99% of the patients received a trans-urethral catheter during the first 2 days after surgery compared to 70% of the patients in the MF group. Using the supra-pubic approach, there is a lower risk of urinary tract infections [18]. The significant difference in blood loss has been described before [11–13]. It can be explained by avoiding ligation of the uterine vessels. The observed outcomes on blood loss and operating time in favour of the MF were also described by de Boer et al. [13]. They also reported comparable outcomes of MF and VH with respect to recurrence rates as we did. We could not confirm the longer hospitalization following MF. Functional outcome was mostly comparable between both studies, but differences were found in the overactive bladder complaints and the obstructive defecation complaints. We suggest these symptoms could decrease after several years after surgery since we were not aware of any kind of treatment for these complaints. Nevertheless, we did not compare our domain scores pre- and post-operative in our study and are not familiar with the possible heterogeneity of these patients. As our study was the first that included questions about sexual functioning in the post-surgery follow-up, we cannot compare our results with prior studies. Nevertheless, we think that the overall sexual function is acceptable in both treatment groups.

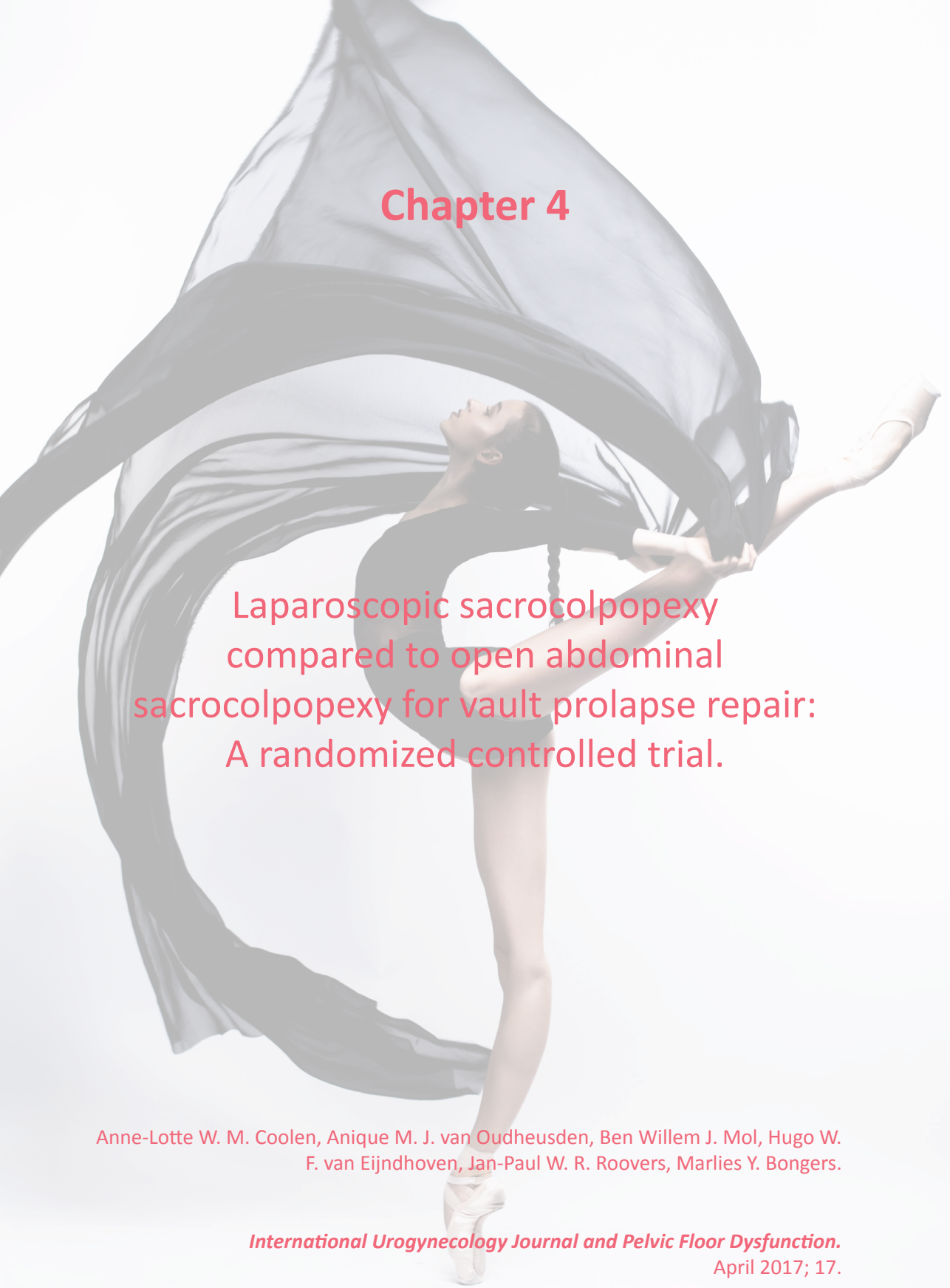
Whether or not to preserve the uterus is still a matter of debate. To preserve the uterus can be preferable to decrease peri- and post-operative morbidity and can also meet the patients' preference based on emotional, cultural and social motivation. Of course, in case of a uterus preservation technique, the gynaecologist has to make sure that the patient understands the possibility of incurring uterine and cervical pathology over time and the need for continued, routine surveillance measures to assess for such pathology [19, 20]. Compared to sacrospinous fixation, a more extensively evaluated and also more widely implemented uterus-preserving technique, MF is easier to learn, has a lower risk on post-operative pain and may carry a lower risk to adversely affect sexual well-being. A direct comparison between both techniques would be highly clinically relevant.

In conclusion, the MF and the VH have a comparable degree of functional outcome. As compared to VH, MF appears to carry a lower risk on recurrent POP. Based on our study, we conclude that the MF procedure is a viable option to surgically correct uterine descent and that it is certainly not an obsolete procedure. In comparison to sacrospinous fixation, MF may have lower morbidity and result in better anatomical outcome as the physiologic axis of the vagina is preserved. Our study design, however, does not allow a comparison between MF and sacrospinous ligament fixation as surgical correction of uterine descent and for that reason we suggest to perform a randomized controlled trial.

3

References

1. Hudson CN (1988) Female genital prolapse and pelvic floor deficiency. Am J Colorectal Dis 3:181-185
2. Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL (1997) Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 89:501–506
3. van Brummen HJ, van de Pol G, Aalders CI, Heintz AP, van der Vaart CH (2003) Sacrospinous hysteropexy compared to vaginal hysterectomy as primary surgical treatment for a descensus uteri: effects on urinary symptoms. Int Urogynecol J Pelvic Floor Dysfunct 14(5):350–355
4. Uzoma A, Farag KA (2009) Vaginal vault prolapse; review. Int J Obstet Gynecol. doi:10.1155/2009/275621
5. Ranney B (1981) Enterocele, vaginal prolapse, pelvic hernia: recognition and treatment. Am J Obstet Gynecol 140:53–57
6. Diwan A, Rardin CR, Kohli N (2004) Uterine preservation during surgery for uterovaginal prolapse: a review. Int Urogynecol J Pelvic Floor Dysfunct 15(4):286–292
7. Roovers JP, van der Bom JG, van der Vaart CH, Schagen van Leeuwen JH, Scholten PC, Heintz AP (2005) A randomized comparison of post-operative pain, quality of life, and physical performance during the first six weeks after abdominal or vaginal surgical correction of descensus uteri. Neurol Urodyn 24:334–340
8. Dietz V, van der Vaart CH, van der Graaf Y, Heintz P, Scraffordt Koops SE (2010) One-year follow-up after sacrospinous hyster- opexy and vaginal hysterectomy for uterine descent: a randomized study. Int Urogynecol J 21:209–216
9. Ayhan A, Esin S, Guven S, Salman C, Ozyuncu O (2006) The Manchester operation for uterine prolapse. Int J Obstet Gynecol 92:228–233
10. Donald A (1902) The operative treatment of prolapse of the uterus and vagina. J Obstet Gynaecol Br Emp 1:312
11. Thomas AG, Brodman ML, Dottino PR, Bodian C, Friedman F (1995) Manchester procedure vs. vaginal hysterectomy for uterine prolapse. A comparison. J Reprod Med 40:299–304
12. Kalagirou D, Antoniou G, Karakitsos P, Kalogirou O (1996) Comparison of surgical and postoperative complications of VH and Manchester procedure. Eur J Gynaecol Oncol 17:278–280
13. de Boer TA, Milani AL, Kluivers KB, Withagen MIJ, Vierhout ME (2009) The effectiveness of surgical correction of uterine prolapse: cervical amputation with uterosacral ligament placation (modified Manchester) versus vaginal hysterectomy with utero- sacral ligament placation. Int Urogynecol J 20:1313–1319
14. Baden WF, Walker TA (1972) Genesis of the vaginal profile: a correlated classification of vaginal relaxation. Clin Obstet Gyne- col 15(4):1048–1054
15. Van der Vaart CH, De Leeuw JP, Roovers JP, Heintz AP (2003) Measuring health related quality of life in women with urogenital dysfunction: the urogenital distress inventory and incontinence impact questionnaire revisited. Neurourol Urodyn 22:97–104
16. Van Brummen HJ, Bruinse HW, van de Pol G, Heintz AP, (2006) Defecatory symptoms during and after the first pregnancy: prevalences and associated factors. Int Urogynecol J 17:224–230
17. Hakvoort RA, Dijkgraaf MG, Burger MP, Emanuel MH, Roovers JP (2009) Predicting short-term urinary retention after vaginal prolapse surgery. Neurourol Urodyn 28(3):225–228
18. Niël-Weise BS, van den PJ Broek (2005) Urinary catheter policies for short-term bladder drainage in adults. Cochrane Database Syst Rev 20(3):CD004203
19. Costantini E, Mearini L, Bini V, Zucchi A, Mearini E, Porena M (2005) Uterus preservation in surgical correction of urogenital prolapse. Eur Urol 48(4):642–649
20. Skiadas CC, Goldstein DP, Laufer MR (2006) The Manchester- Fothergill procedure as a fertility sparing alternative for pelvic organ prolapse in young women. J Pediatr Adolesc Gynecol 19(2):89–93



Chapter 4

Laparoscopic sacrocolpopexy compared to open abdominal sacrocolpopexy for vault prolapse repair: A randomized controlled trial.

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Abstract

Introduction and hypothesis The objective was to evaluate the functional outcome after laparoscopic sacrocolpopexy versus open sacrocolpopexy in women with vault prolapse.

Methods A multicentre randomized controlled trial was carried out at four teaching and two university hospitals in the Netherlands in women with symptomatic vault prolapse requiring surgical treatment. Participants were randomized for laparoscopic or open sacrocolpopexy. Primary outcome was disease-specific quality of life measured using the Urogenital Distress Inventory (UDI) questionnaire at 12 months' follow-up. Secondary outcomes included anatomical outcome and perioperative data. We needed 74 participants to show a difference of 10 points on the prolapse domain of the UDI 12 months after surgery (power of 80%, α error 0.05).

Results Between 2007 and 2012, a total of 74 women were randomized. Follow-up after 12 months showed no significant differences in domain scores of the UDI between the two groups. After 12 months, both groups reported a UDI score of 0.0 (IQR: 0–0) for the domain "genital prolapse", which was the primary outcome. There were no significant differences between the two groups (p = 0.93). The number of severe complications was 4 in the laparoscopic group versus 7 in the open abdominal group (RR 0.57; 95% CI 0.50–2.27). There was less blood loss and a shorter hospital stay after laparoscopy; 2 (IQR 2–3) versus 4 (IQR 3–5) days, which was statistically different. There was no significant difference in anatomical outcome at 12 months.

Conclusion Our trial provides evidence to support a laparoscopic approach when performing sacrocolpopexy, as there was less blood loss and hospital stay was shorter, whereas functional and anatomical outcome were not statistically different.

Trial registration number: Dutch trial register NTR3276

Introduction

Post-hysterectomy vaginal vault prolapse has a reported incidence of 0.36 to 3.6 per 1,000 woman years or a cumulative incidence of 0.5% [1, 2]. Abdominal sacrocolpopexy (ASC) is the most effective treatment for vaginal vault prolapse, with a success rate of 93–99%, and is now considered the first-choice treatment for vaginal vault prolapse [3–8]. Sacrocolpopexy is a procedure designed to treat apical compartment prolapse, including uterine or vaginal vault prolapse, in addition to multi-compartment prolapse [9, 10].

According to a Cochrane review on the subject, ASC led to a lower rate of recurrent vault prolapse and dyspareunia com- pared with vaginal sacrospinous ligament fixation [3]. Nevertheless, ASC is also associated with a longer operative time, recovery period and higher cost [11].

Laparoscopic sacrocolpopexy was first reported in 1994 [12]. Since then, it has gained in popularity, before any clinical advantage over the open abdominal procedure was proven. Although the literature regarding laparoscopic sacrocolpopexy was limited and prospective comparative randomised trials were lacking, the laparoscopic sacrocolpopexy has been widely adopted by pelvic reconstructive surgeons. Laparoscopic sacrocolpopexy has potential advantages over laparotomy, as morbidity, hospital stay, postoperative pain and recovery are all supposed to be less. Moreover, the anaesthetic result is better after minimally invasive sacrocolpopexy. However, the laparoscopic approach is more challenging and the literature reports a long learning curve associated with this technique [13, 14]. More importantly, it is unknown if the laparoscopic mesh fixation to the promontory results in an equal anatomical outcome, as it has been stated that as part of the laparoscopic approach, the fixation point is higher, which could result in a more vertical position of the vagina.

Previous studies comparing LSC with ASC showed less blood loss and a significantly shorter hospital stay in the laparoscopic group [15–17]. A randomised controlled trial comparing open laparoscopic with abdominal sacrocolpopexy in patients with a symptomatic vault prolapse, which was published during the follow-up period of our trial, reported significantly less blood loss, a higher haemoglobin level and a shorter hospital stay in favour of the laparoscopic group. There was no significant difference in anatomical outcome between the two groups [15]. The exclusion criteria of the published study were very strict, and only patients with at least a grade 2 vault prolapse, a BMI less than 35 and without urinary stress incontinence were included [15]. This does not match the patient population of the general practice. Our trial creates a realistic reflection of daily practice.

Considering the lack of evidence, we performed a randomised trial comparing LSC with ASC using disease specific quality of life as the primary outcome.

Materials and methods

We performed a multicentre randomized controlled trial com- paring ASC and LSC in four teaching and two university hospitals in the Netherlands. All hospitals take part in the Dutch consortium for women's health. The consortium is a collaborative network in clinical studies in the field of obstetrics and gynaecology. The study was approved by the ethical committee of the Máxima Medical Centre in Veldhoven (file number NL12130.015.06) and the Board of Directors of all participating hospitals, and was registered in the Dutch Trial Register (NTR3276).

Eligible women with vault prolapse who met the inclusion criteria were counselled about the trial. Vault prolapse was defined as a post-hysterectomy prolapse of the apical compartment. After written informed consent was given, randomisation was performed by an independent research secretariat located in Amsterdam after a phone call or e-mail by the coordinating investigator. The treatment allocation was done by opaque sealed envelopes in a 1:1 ratio to either laparoscopic sacrocolpopexy or open abdominal sacrocolpopexy. Women received a randomized case number to ensure that their data would be treated anonymously. No changes were made to the protocol after trial commencement, other than including more participating centres.

We included women with a history of hysterectomy presenting with symptomatic vaginal vault prolapse, with or without concomitant cystocele and rectocele, who chose to undergo surgery. Women who had undergone previous surgical correction of a vault prolapse were excluded, in addition to women with a contra-indication for a surgical intervention because of their general physical condition.

Surgical intervention

The intervention was either abdominal or laparoscopic sacrocolpopexy following randomisation. To exclude a learning curve for both surgical interventions and procedure bias, all participating gynaecologists had to have performed at least 50 procedures before the start of the study. The procedures were standardized as much as possible to confirm consistency. Participants received a bowel preparation the day before the operation. Prophylactic antibiotics were given peroperatively (metronidazole/cefazolin). As prophylaxis for thromboembolism per- and postoperatively subcutaneous low molecular weight heparin was administered.

Abdominal sacrocolpopexy

The abdominal sacrocolpopexy was performed by a laparotomy under general anaesthesia, preferably using a Pfannenstiel incision. The peritoneum from the promontory to the vault was incised to expose the rectovaginal and vesicovaginal fascia, extending to the sacral promontory. A

type 1 polypropylene mesh was used, which was cut into two pieces 3 cm wide and approximately 15 cm long. One piece of the mesh was attached between the vagina and the bladder anteriorly, and another as far down the posterior vaginal wall as possible using Ethibond, non-absorbable, synthetic and multifilament sutures from Ethicon. The mesh was fixated to the anterior part of the vaginal vault with four stitches, and six stitches
were used to fixate the mesh posterior. The two meshes were sutured to each other, after which only the posterior mesh was fixed to the longitudinal vertebral ligament by staples or non-absorbable sutures, depending on surgeon preference. Excess mesh was trimmed and removed. The mesh was re- peritonealised.

Laparoscopic sacrocolpopexy

Laparoscopic sacrocolpopexy was performed under general anaesthesia with four trocars, one for the scope and three side trocars. The essence of the procedure was the same as for the abdominal procedure. The vaginal vault was elevated with a vaginal probe. The peritoneum from the promontory to the vault was incised laparoscopically by scissors to expose the rectovaginal and vesicovaginal fascia. One piece of type 1 polypropylene mesh was attached anteriorly and another as low as possible on the posterior vaginal wall. The sutures, size of the mesh and its fixation were the same as in the abdominal procedure. The mesh was attached to the sacral promontory using staples and was peritonealised. All centres used polypropylene meshes and the same sutures.

Peroperative assessment

When stress incontinence was diagnosed preoperatively, it was up to the patient and her gynaecologist whether incontinence surgery was performed during the same procedure or in a second operation after evaluation of the sacrocolpopexy on the stress incontinence. A tension-free vaginal tape was used if incontinence surgery was indicated. No Burch colposuspensions were performed. Both procedures could be completed with any necessary concomitant vaginal operation after the vault suspension has been carried out. The decision to perform additional prolapse surgery was made by the surgeon after the sacrocolpopexy was completed.
A urethral catheter was left in situ and was removed at the first day postoperatively or as clinically indicated. If the procedure was complicated by a bladder lesion, the catheter was removed after 1 week. In the case of urinary retention after removal of the catheter on the first day, the catheter was re- inserted for another day.

Outcome measures

Women were sent a questionnaire preoperatively, at 3– 6 months postoperatively and 12 months postoperatively. Women were asked to undergo a pelvic examination preoperatively and at 6 weeks and 12 months postoperatively. The observer was an independent researcher/resident, who had not performed the surgery. The researcher was not blinded to the type of surgery.

The primary outcome of the study was functional outcome, which was evaluated using the Urogenital Distress Inventory (UDI) at 12 months' follow-up [18]. The UDI is a validated questionnaire evaluating prolapse-related symptoms. The questionnaires also contain versions of the Defecatory Distress Inventory (DDI) [19], the Incontinence Impact Questionnaire (IIQ) [18] and the Patient Global Impression of Improvement (PGI-I) [20] and questions about sexuality, which were secondary outcomes. Other secondary outcomes were procedure time, amount of estimated blood loss and hospital stay, perioperative complications, re-interventions and long-term complications. Re-intervention included incontinence or prolapse surgery. All collected data were registered in a case report form. Another secondary outcome was the composite outcome of success, defined as no prolapse beyond the hymen, no bothersome bulge symptoms, and no repeat surgery or pessary use for recurrent prolapse within 12 months [20, 21]. Remaining study parameters were body mass index, pre- or postmenopausal status, use of oestrogens, combined prolapse surgery or stress urinary incontinence procedures. The anatomical outcome using the Pelvic Organ Prolapse Quantification system (POP-Q) [22] was the secondary end- point. A pelvic examination was performed to evaluate the anatomical results of the prolapse repair.

Sample size

A difference between the two surgical techniques of 10 points between the two groups on the prolapse domain of the UDI 12 months after surgery was considered to be clinically relevant. Assuming a standard deviation of the score on this do- main of 15 points, we needed 74 participants to show a statistically significant difference in the primary outcome (power of 80%, α error 0.05) [23].

Statistical analysis

The trial was a prospective, randomised controlled trial conducted with the aim of determining the superiority of the primary endpoint (prolapse domain of the UDI) in the laparoscopic sacrocolpopexy group. Analysis was by intention to treat. The domain scores were calculated for the UDI, DDI and IIQ. To examine differences between groups we used an unpaired t test or Mann–Whitney test for continuous variables depending on the distribution, whereas a Chi-squared test was used for dichotomous variables. We used two-sided significance tests, and a p value <0.05 was considered to indicate statistical significance. For dichotomous outcomes, we calculated relative risks and 95% confidence intervals. We used the statistics package SPSS version 22 (IBM, Armonk, NY, USA).

Results

The results are reported by means of the IUGA/ICS recommendations for reporting outcomes of surgical procedures for pelvic organ prolapse [24] and the CONSORT statement (www.consort-statement.org). Between 2007 and 2012, we randomised 37 women to the laparoscopic sacrocolpopexy group and 37 to the open group (Fig. 1). One woman randomised to the laparoscopy group was very satisfied with a pessary, which she received to cover the time until the operation, and she cancelled surgery. In the abdominal group, one patient underwent a sacrospinous fixation of the vault prolapse because she was not happy with the randomisation result. Both women were included in the intention-to-treat analysis. In the laparoscopic group one procedure was combined with concomitant vaginal surgery, versus 3 in the open group. In both groups one procedure was combined with a tension-free vaginal tape (TVT-O). In the laparoscopic group, no concomitant vaginal prolapse surgery was performed, whereas in the open group, two procedures were combined with a posterior colporrhaphy.

At 12 months' follow-up, there were 14 questionnaires missing, of which 11 participants (15.5%) were unwilling to complete the questionnaires, 1 participant did not receive the intervention, 1 participant postponed the procedure until the end of the study period for private reasons and had not yet completed the 1-year follow-up, and 1 patient died 5 days after the intervention because of a complication of the intervention.

The number of missing questionnaires is presented in Fig. 1. All non-responders were contacted by telephone and most of them explained that they were doing well, which was a reason not to return the questionnaires. Patient characteristics of responders and non-responders were comparable.

Figure 1. Patient flow through each stage of the study

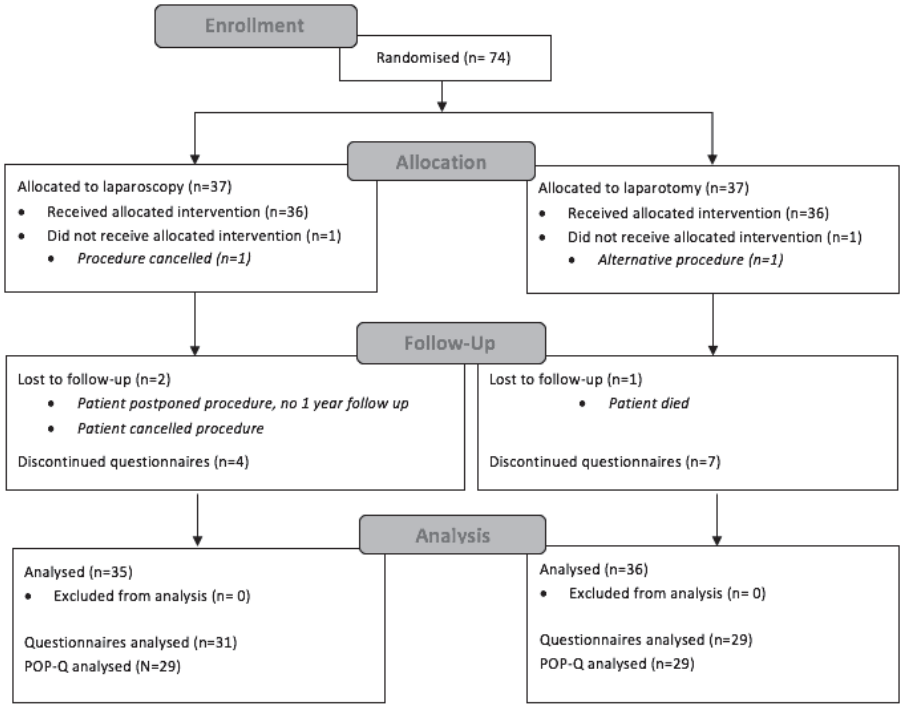


Table 1 shows the baseline characteristics of the study population. The median age of the study population was 65.2 (IQR 61–71) years in the laparoscopic group and 66.7 (IQR 64–73) in the abdominal group. Other baseline characteristics were also comparable, including the preoperative POP-Q stage

Table 2 shows UDI, DDI and IIQ scores before surgery and 12 months after surgery. Both groups reported after 12 months a UDI score of 0.0 (IQR: 0–0) for the domain “genital prolapse” ($p = .93$), which was the primary outcome. The domain “pain and discomfort” showed a score of 0.0 (IQR: 0–29) for the laparoscopic group versus 8.3 (IQR: 0–33) for the abdominal group ($p = 0.15$). The UDI domain scores improved significantly for both groups at 12 months post-surgery ($p \leq 0.001$). At 12 months’ follow-up, the PGI-I score of “very much better” was 25% (8 out of 31) for the laparoscopy group, and 26% (7 out of 27) for the open abdominal group. If we add the score of “much better” the percentages are 71% (22 out of 31) and 74% (20 out of 27), which was not statistically different ($p = 0.563$).

Table 1. Baseline characteristics

	Laparoscopic Sacrocolpopexy N=37					Open Abdominal Sacrocolpopexy N=37				
Age (years)										
Median (IQR)	65.2 (61-71)					66.7 (64-73)				
Body Mass Index (kg/m^2)										
Mean (range)	25.3 (18-32)					25.9 (21-33)				
Parity (n/m)										
0	2.9% (1/34)					0.0% (0/34)				
1	8.8% (3/34)					5.9% (2/34)				
2	41.2% (14/34)					41.2% (14/34)				
3	38.2% (13/34)					26.5% (9/34)				
≥4	8.8% (3/34)					26.5% (9/34)				
Menopausal status (n/m)										
Premenopausal	2.8% (1/36)					0% (0/37)				
Postmenopausal	97.2% (35/36)					100% (37/37)				
Incontinence (n/m)										
None	57.1% (20/35)					42.9% (15/35)				
Stress	5.7% (2/35)					8.8% (3/34)				
Urge	11.4% (4/35)					11.4% (4/35)				
Combined	25.7% (9/35)					37.1% (13/35)				
Estrogens use (n/m)										
None	10.3% (3/29)					17.2% (5/29)				
Local/Systemic	89.7% (26/29)					28.8% (24/29)				
History of gynaecological surgery (n/m)										
TVH only	36.1% (13/36)					20.6% (7/34)				
TVH & ACR	8.3% (3/36)					20.6% (7/34)				
TVH & PCR	2.8% (1/36)					5.9% (2/34)				
TVH & ACR/PCR	30.6% (11/36)					11.8% (4/34)				
TVH & later ACR & mesh	2.8% (1/36)					0% (0/34)				
TVH & ACR & later PCR	0% (0/36)					2.9% (1/34)				
TAH only	8.3% (3/36)					32.4% (11/34)				
TAH & PCR	2.8% (1/36)					5.9% (2/34)				
Laparoscopic hysterectomy	5.6% (2/36)					0% (0/34)				
Supracervical hysterectomy	2.8% (1/36)					0% (0/34)				
Pre-operative POP-Q Stage	**0**	**I**	**II**	**III**	**IV**	**0**	**I**	**II**	**III**	**IV**
Compartment										
Anterior (n)	3	3	13	9	2	6	5	13	5	3
Apical (n)	0	9	9	7	7	1	14	9	4	6
Posterior (n)	10	8	5	3	2	7	5	11	4	5
Pre-operative POP-Q										
	Aa -0.5 ± 1.4 (-3-2)	Ba 0.8 ± 2.3 (-3-4)	C 1.1 ± 3.1 (-6-6)			Aa -.5 ± 1.9 (-3-3)	Ba 0.3 ± 3.1 (-5-8)	C -0.1 ± 4.4 (-8-10)		
	GH 3.8 ± 0.8 (2-5)	PB 2.7 ± 0.5 (2-3)	TVL 7.9 ± 1.3 (6-11)			GH 3.7 ± 0.8 (3-5)	PB 3.1 ± 0.7 (2-4)	TVL 8.3 ± 1.5 (4-10)		
	Ap -1.5 ± 1.8 (-3-3)	Bp -0.6 ± 2.6 (-3-4)	D -			Ap -0.5 ± 1.8 (-3-3)	Bp 0.4 ± 3.0 (-4-8)	D -		

TVH = transvaginal hysterectomy, TAH = total abdominal hysterectomy,
ACR = anterior colporrhaphy, PCR = posterior colporrhaphy

Table 2. Domain scores disease specific quality of life

	Pre-operative		12 months post-operative		*p-value*
	Laparoscopic N=34	**Abdominal N=31**	**Laparoscopic N=31**	**Abdominal N=29**	
Urogenital Distress Inventory					
Overactive bladder					
Median (IQR)	33.3 (11-56)	44.4 (22-50)	0.0 (0-11)	5.6 (0-19)	*.30*
Incontinence					
Median (IQR)	16.7 (0-50)	16.7 (0-42)	16.7 (0-33)	16.7 (0-33)	*.52*
Obstructive micturition					
Median (IQR)	0.0 (0-33)	16.7 (0-58)	0.0 (0-13)	0.0 (0-0)	*.28*
Pain/Discomfort					
Median (IQR)	16.7 (0-50)	33.3 (17-33)	0.0 (0-29)	8.3 (0-33)	*.15*
Genital prolapse					
Median (IQR)	66.7 (58-92)	66.7 (33-67)	0.0 (0-0)	0.0 (0-0)	*.93*
Recurrent bladder infections (n/m)					
Never	22 (65%)	17 (57%)	26 (84%)	21 (75%)	.50
Once	8 (24%)	4 (13%)	4 (13%)	4 (14%)	
Between 2-4 times	1 (3%)	5 (17%)	0 (0%)	2 (7%)	
More than 4 times	3 (9%)	4 (13%)	1 (3%)	1 (4%)	
Incontinence de novo					
Urge incontinence			2	3	*.23*
Stress incontinence			5	4	*.69*
Defecatory Distress Inventory					
Constipation					
Median (IQR)	0.0 (0-17)	0.0 (0-33.3)	0.0 (0-17)	0.0 (0-17)	*.76*
Obstructive defecation Median (IQR)	4.2 (0-17)	8.3 (0-25)	0.0 (0-8)	0.0 (0-8)	*.56*
Pain/Discomfort Median (IQR)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	0.0 (0-17)	*.03*
Incontinence Median (IQR)	0.0 (0-17)	8.3 (0-33)	0.0 (0-0)	0.0 (0-17)	*.13*
Incontinence flatus Median (IQR)	33.3 (0-67)	33.3 (0-67)	0.0 (0-33)	0.0 (0-17)	*.48*
Incontinence Impact Questionnaire					
Physical					
Median (IQR)	25.0 (0-50)	0.0 (0-33)	0.0 (0-25)	0.0 (0-17)	*.66*
Mobility Median (IQR)	11.1 (0-33)	33.3 (11-44)	0.0 (0-28)	11.1 (0-25)	*.37*
Social Median (IQR)	11.1 (0-22)	11.1 (0-33)	0.0 (0-6)	0.0 (0-11)	*.47*
Shame Median (IQR)	0.0 (0-17)	16.7 (0-17)	0.0 (0-8)	0.0 (0-17)	*.92*
Emotional Median (IQR)	11.1 (0-33)	22.2 (0-33)	0.0 (00-22)	0.0 (0-25)	*.54*
Sexuality					
Sexually active	20 (63%)	14 (45%)	26 (93%)	26 (93%)	1.00
Dyspareunia					.23
Bother:					
Not at all	11	5	14	10	
Moderately	0	3	3	3	
Somewhat	4	4	1	0	
Quite a bit	2	1	0	0	
Not applicable	14	18	8	15	
Frequency coitus					.66
Never	17	18	11	15	
<1x/month	4	5	3	4	
1-2x/month	4	3	9	6	
1x/week	6	3	4	1	
>1x/week	1	2	1	2	

Clinical outcomes are presented in Table 3. In the laparoscopic sacrocolpopexy group blood loss was 86 mL (IQR 10– 100) vs 200 mL (IQR 100–300) in the abdominal group (p < 0.001). Hospital stay was 2 days (IQR 2–3) vs 4 days (IQR 3–5; p < 0.001). Duration of surgery (125 vs 115 min; p = 0.31), number of complications during surgery (5.6% vs 0%, p = 0.15), and number of complications during admission (5.6% vs 18.9%, p = 0.06) were not statistically significant different.

The laparoscopic group contains fewer complications, 4 in the laparoscopic group versus 7 in the open group, which is not significantly different (RR 0.57; 95% CI 0.50-2.27). In the open abdominal group the complications that occurred were more severe. One complication concerned a 79-year-old woman who presented with cardiac arrhythmia on the third day after surgery. She was diagnosed with sepsis and a bowel perforation was suspected. A relaparotomy was performed and the diagnose bowel perforation could be confirmed. She developed pneumonia and due to multi-organ failure, she died on the fifth day after surgery. The complication was considered a calamity and reported to the health care inspectorate.

Two other women in the open abdominal group had wound dehiscence that needed to be repaired surgically. One procedure carried out in the laparoscopic group had to be converted because of bleeding coming from the promontory. The total estimated blood loss of this procedure was 1.200mL.

Table 3. Clinical outcome

	Laparoscopic Sacrocolpopexy N=36	**Open Abdominal Sacrocolpopexy N=37**	***p-value***
Operative time (minutes)			
Median (IQR)	125 (108-135)	115 (94-129)	*.31*
Estimated blood loss (ml)			
Median (IQR)	86 (10-100)	200 (100-300)	*<.001*
Hospital stay (days)			
Median (IQR)	2 (2-3)	4 (3-5)	*<.001*
Complications during surgery (n/m)	5.6% (2/36)	0% (0/36)	*.15*
Bladder lesion (conversion)	1	0	
Bleeding (conversion)	1	0	
Complications during admission (n/m)	5.6% (2/36)	18.9% (7/37)	*.06*
Fatal bowel perforation	0	1	
Wound dehiscence	0	2	
Pulmonary embolism	0	1	
Ileus	0	3	
Wound infection	1	0	
Pyelonephritis (re-admission)	1	0	

Table 4 shows the surgical re-interventions for pelvic organ prolapse and occult/new urinary incontinence. In the laparoscopy group, there were 7 women in whom a re-intervention for prolapse or incontinence was performed, versus 4 in the open surgery group (RR 1.75; 95% CI 0.81–3.91). In both groups, 3 women had surgery for stress urinary incontinence. The laparoscopic group had 4 re-interventions for recurrent POP versus 1 in the open group (RR 4, 95% CI 0.84–5.73). All surgical re-interventions concerned the posterior compartment. No pessaries were placed as a re-intervention. At 12 months' follow-up, 2 participants in the laparoscopic group developed de novo urge incontinence, and 5 de novo stress incontinence, versus 3 and 4 respectively in the open abdominal group according to the questionnaires. There was no significant difference in these results between the groups.

Table 4. Surgical re-interventions for pelvic organ prolapse and occult/new urinary incontinence

	Laparoscopic Sacrocolpopexy N=36	**Open Abdominal Sacrocolpopexy N=37**	***p-value***
Re-intervention (n/m)	16.7% (7/36)	10,8% (4/37)	*.12*
Incontinence surgery	**3**	**3**	*1.00*
TVT-S	1	0	
TVT-O	1	3	
TOT	1	0	
			.17
Prolapse surgery	**4**	**1**	
Rectopexy	1	0	
Posterior colporrhaphy	2	0	
Enterocele repair	1	0	
Posterior vaginal mesh	0	1	

There were no significant differences between the groups in anatomical results 12 months postoperatively according to the POP-Q, as shown in Table 5. At the 12-months postoperative follow-up visit no mesh or suture exposure was seen during vaginal examination in the two groups. No other com- plications were seen at the 12 months' follow-up visit.

Table 5: 12 months post-operative POP-Q

	Laparoscopic Sacrocolpopexy N= 29					Open Abdominal Sacrocolpopexy N= 29					p-value		
Post-operative POP-Q Stage	**0**	**I**	**II**	**III**	**IV**	**0**	**I**	**II**	**III**	**IV**			
Compartment													
Anterior (n)	15	6	8	0	0	17	5	7	0	0	.87		
Apical (n)	23	6	0	0	0	27	2	0	0	0	.13		
Posterior (n)	14	7	7	1	0	13	6	10	0	0	.65		
Post-operative POP-Q													
	Aa -0.5 ± 1.4 (-3-2)		Ba 0.8 ± 2.3 (-3-4)	C 1.1 ± 3.1 (-6-6)		Aa -.5 ± 1.9 (-3-3)		Ba 0.3 ± 3.1 (-5-8)	C -0.1 ± 4.4 (-8-10)		*Aa* *.54*	*Ba* *.64*	*C* *.54*
	GH 3.8 ± 0.8 (2-5)		PB 2.7 ± 0.5 (2-3)	TVL 7.9 ± 1.3 (6-11)		GH 3.7 ± 0.8 (3-5)		PB 3.1 ± 0.7 (2-4)	TVL 8.3 ± 1.5 (4-10)		*GH* *.17*	*PB* *.62*	*TVL* *.76*
	Ap -1.5 ± 1.8 (-3-3)		Bp -0.6 ± 2.6 (-3-4)	D -		Ap -0.5 ± 1.8 (-3-3)		Bp 0.4 ± 3.0 (-4-8)	D -		*Ap* *.48*	*Bp* *.45*	*D* -

We asked our population at the 12 months' follow-up visit about their complaints and 4 of the participants mentioned (unexplained) pelvic pain; 1 in the laparoscopic group and 3 in the open abdominal group. In all four of these participants, pelvic pain was already present before the surgery, but it turned out to be worse 12 months after the procedure. If we look at the questionnaires, 8 participants in the laparoscopic group vs 13 in the abdominal group had pelvic pain after 12 months, which was not a significant difference (p = 0.056).

The composite outcome of success was 83.8% (31 out of 37) for the laparoscopy group and 89.2% (33 out of 37) in the open abdominal group. In both groups, there were no recurrences of stage 2 or higher of the apical compartment. Two patients in the laparoscopy group had bothersome bulge symptoms compared with 4 in abdominal group. Five participants of the laparoscopy group were re-operated for POP, versus 1 in the abdominal group.

According to the questionnaires, in both groups more participants became sexual active, there was less dyspareunia and the coitus frequency was increased at 12 months postoperatively (Table 2). There are no significant differences between the groups.

Discussion

Main findings

We performed a multicentre randomised trial that compared laparoscopic and open abdominal sacrocolpopexy in patients with a vaginal vault prolapse. There were no significant differences in quality of life related to micturition, prolapse and defecation in the two groups. Anatomical results were similar at 12 months after surgery. In the laparoscopic group, there was less blood loss during the procedure and the hospital stay was shorter.

Quality of life was the primary outcome in our trial. In both groups, the functional outcomes of the UDI domain scores were significantly improved, which supports previous findings of a high success rate for sacrocolpopexy [3–5]. Disease-specific quality of life was statistically equal after both laparoscopic

and open abdominal sacrocolpopexy. These results are in line with those of a randomised controlled trial by Freeman et al. comparing open abdominal with laparoscopic sacrocolpopexy, which was published recently [15]. In this study [15], there was also less blood loss and a shorter hospital stay after laparoscopy.

We chose disease-specific quality of life, using the UDI questionnaire, as the primary outcome of our study. As out- come definitions for evaluating prolapse surgery were improved after the start of the trial, after a publication by Barber et al. [25], we added the combined outcome measure (recurrent pelvic organ prolapse stage 2 or higher in the apical compartment, with bothersome bulge symptoms, and re-interventions), at 12 months' follow-up. This outcome measure was not specified in the study protocol.

There was no significant difference in anatomical outcome between the two groups in this trial [15]. These results correspond to the outcomes of our study. The results of similar functional and anatomical effects, and less blood loss and shorter hospital stay were also found in two other comparative cohort studies [16, 17].

We showed that sacrocolpopexy is an effective surgical treatment for women with a symptomatic vault prolapse. Although the focus of the sacrocolpopexy is mainly the apical and the anterior compartment, the posterior compartment improves as well. Besides anatomical improvement, patients have better scores in all domains of the disease-specific quality of life questionnaires.

There was a trend towards fewer complications in the laparoscopic group (11% vs 18.9%, RR 0.57; 95% CI 0.50–2.27). The complications in the open group were much more severe, including re-laparotomies and a fatal bowel perforation.

The study by Freeman et al. did not show any significant differences in complication rates either: 5.6% (2 out of 26) in the laparoscopic vs 7.4% (2 out of 27) in the open group. Complications in the laparoscopic group included opening of the vagina and one bladder injury. In the open group an area

of mesentery of the small bowel became detached and this required the resection of 10 cm of small bowel. In one other case, there was excessive bleeding from the sacrum, which required haemostatic bone wax [15].

One reason for our unexpected higher complication rate may be accurate documentation during a prospective trial. The trial consists of an unselected study population, in contrast with retrospective cohort studies. Furthermore, patients were referred from other centres for the sacrocolpopexy, which may influence the complexity of the patient population. Despite these possible explanations, it is still unusual that so many severe and rare complications occurred during this trial.

We did not see any mesh or suture exposure in our study population. Other trials reported rates of mesh-related complications of between 3 and 11% [5–8]. Our absence of mesh complications may be because our follow-up time was only 1 year, which is relatively short for the development of exposure.

The anatomical results of the initial surgery were similar, but participants who had undergone laparoscopic surgery had more re-interventions. The laparoscopic group had 4 re-interventions for recurrent POP versus 1 in the open group (RR 4, 95% CI 0.84–5.73), all concerning the posterior compartment. An ex- planation could be that two open procedures were combined with a posterior colporrhaphy in the same session versus no concomitant vaginal POP surgery in the laparoscopic group.

The inclusion period of our trial was 5 years, which is a long period for a multicentre trial with six participating centres. Many patients and gynaecologists preferred the laparoscopic procedure and the laparoscopic sacrocolpopexy was already being implemented in many participating centres, de- spite the fact that its clinical effectiveness was still unknown. Unfortunately, not all eligible patients were documented. Most participants were randomised in the last 3 years of the study by including more centres. Moreover, many procedures were performed by the same surgeon, as this gynaecologist visited some of the other sites to perform the laparoscopic sacrocolpopexy for the study population. The other procedures were performed by experienced surgeons who had been trained to perform the procedure the same way. This resulted in a homogeneous operation technique and frequent performance of the procedure.

Strengths and limitations

We performed a randomised controlled trial, which is considered the best type of study to assess the effectiveness of a procedure. Another strength of our trial is that procedures were all performed by experienced gynaecologists with a track record of more than 50 sacrocolpopexy procedures. A trial of Deprest et al. showed that it takes 60 procedures to effectively limit complications, owing to the challenging suture and dis- section skills that are needed for this technique [14]. The laparoscopic

sacrocolpopexy is a challenging, level 4 procedure. The laparoscopic technique has an advantage over an open abdominal procedure with regard to dissection, which is easier during laparoscopy because of the increased visual field. However, stitching is more difficult compared with the open technique because of a decreased degree of movement and two-dimensional vision. As a large number of patients are needed to acquire sufficient surgical skills, this procedure should only be performed by experienced surgeons.

A limitation of our study was the relatively high percentage of loss to follow-up (15.5%). The number of missing questionnaires was equal in the two groups. All non-responders were contacted by telephone and most of them explained that they were doing well, which was a reason not to return the questionnaires. However, patient characteristics of responders and non-responders were comparable; thus, we do not believe that the loss to follow-up has greatly affected our results.

Another limitation is that the patients and staff were not blinded to the intervention. Although patients were encouraged by the medical care staff to recover quickly and to not extend their admission for unnecessary reasons, there is still a chance of bias because of the type of incision that was used. This could affect the length of the hospital stay; however, 2 vs 4 days still constitutes a large difference of 2 days. Furthermore, the hospital stay was prolonged by the extended re-admission because of several complications in the abdominal group.

Interpretation

In conclusion, this randomised controlled trial comparing laparoscopic and open abdominal sacrocolpopexy showed no significant differences in functional and anatomical outcome, but there was less blood loss and a shorter hospital stay was shorter if the procedure was performed using the laparoscopic approach. Although this superiority study did not show a significant difference in the primary outcome (UDI prolapse domain), there is still evidence to support a laparoscopic approach as there was less blood loss, the hospital stay was shorter, and the anatomical and combined outcomes were not statistically different. Therefore, we recommend further implementation of the laparoscopic approach. However, given the learning curve, we advise low-volume centres to refer patients to a centre with laparoscopic expertise.

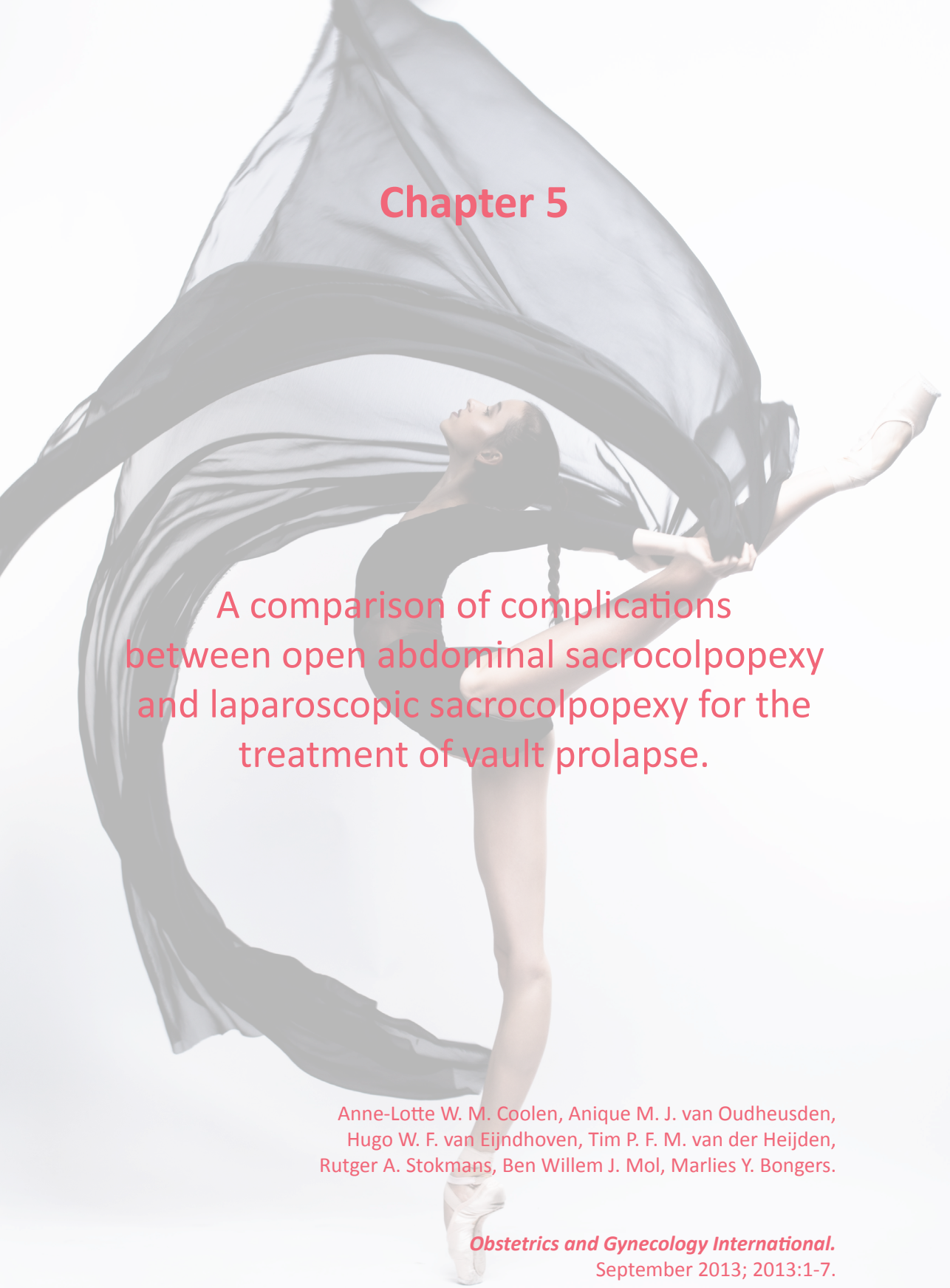
Conclusion

Our trial provides evidence to support a laparoscopic approach when performing sacrocolpopexy, as there was less blood loss and the hospital stay was shorter, whereas functional and anatomical outcomes were not statistically different.

References

1. Dällenbach P, Kaelin-Gambirasio I, Jacob S, Dubuisson JB, Boulvain M. Incidence rate and risk factors for vaginal vault prolapse repair after hysterectomy. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(12):1623–9.
2. Mant J, Painter R, Vessey M. Epidemiology of genital prolapse: observations from the Oxford family planning association study. BJOG. 1997;104(5):579–85.
3. Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women (review). Cochrane Database Syst Rev. 2013;4:1–161.
4. Snyder TE, Krantz KE. Abdominal-retroperitoneal sacral colpopexy for the correction of vaginal prolapse. Obstet Gynecol. 1991;77(6):944–9.
5. Timmons MC, Addison WA, Addison SB, Cavenar MG. Abdominal sacral colpopexy in 163 women with posthysterectomy vaginal vault prolapse and enterocele: evolution of operative tech- niques. J Reprod Med Obstet Gynecol. 1992;37(4):323–7.
6. Nygaard I, Brubaker L, Zyczynski HM, Cundiff G, Richter H, Gantz M, et al. Long-term outcomes following abdominal sacrocolpopexy for pelvic organ prolapse. JAMA. 2013;309(19): 2016–24.
7. Ganatra AM, Rozet F, Sanchez-Salas R, Barret E, Galiano M, Cathelineau X, et al. The current status of laparoscopic sacrocolpopexy: a review. Eur Urol. 2009;55(5)1089–1105.
8. Hilger WS, Poulson M, Norton PA. Long-term results of abdominal sacrocolpopexy. Am J Obstet Gynecol. 2003;189(6):1606–10.
9. Nygaard IE, McCreery R, Brubaker L, Connolly A, Cundiff G, Weber AM, et al. Abdominal sacrocolpopexy: a comprehensive review. Obstet Gynecol. 2004;104(4):805–23.
10. Parkes IL, Sveiky D. Sacrocolpopexy for the treatment of vaginal apical prolapse: evidence based surgery. J Minim Invasive Gynecol. 2014;21(4):546–57.
11. Khan A, Alperin M, Wu N, Clemens WQ, Dubina E, Pashos CL, et al. Comparative outcomes of open versus laparoscopic sacrocolpopexy among medicare beneficiaries. Int Urogynecol J. 2012; 24: 1883–91.
12. Nezhat CH, Nezhat F, Nezhat C. Laparoscopic sacral colpopexy for vaginal vault prolapse. Obstet Gynecol. 1994;84(5):885–8.
13. Claerhout F, Deprest J. Analysis of the learning process for laparoscopic sacrocolpopexy: identification of challenging steps. Int Urogynecol J. 2014; 25: 1153–60.
14. Deprest J, Roovers JP. The challenge of implementing laparoscopic sacrocolpopexy. Int Urogynecol J. 2014; 25: 1153–60.
15. Freeman RM, Pantazis K, Thomson A, Frappell J, Bombieri L, Moran P, et al. A randomised controlled trial of abdominal versus laparoscopic sacrocolpopexy for the treatment of post hysterectomy vaginal vault prolapse: LAS study. Int Urogynecol J. 2012;24(3):377–84.
16. Paraiso MF, Walters MD, Rackley RR, Melek S, Hugney C. Laparoscopic and abdominal sacral colpopexies: a comparative cohort study. Am J Obstet Gynecol. 2005;192(5):1752–8.
17. Klauschie JL, Suozzi BA, O'Brien MM, McBride AW. A comparison of laparoscopic and abdominal sacral colpopexy: objective outcome and perioperative differences. Int Urogynecol J Pelvic Floor Dysfunct. 2009;20(3):273–9.
18. Van der Vaart CH, de Leeuw JR, Roovers JP, Heintz AP. Measuring health-related quality of life in women with urogenital dysfunction: the urogenital distress inventory and incontinence impact questionnaire revisited. Neurourol Urodyn. 2003;22(2):97–104.
19. Roovers JP, van der Blom JG, van der Vaart CH. Hysterectomy does not cause constipation. Dis Colon Rectum. 2008;51(7): 1068–72.
1. Srikrishna S, Robinson D. Validation of the patient global impression of improvement (PGI-I) for urogenital prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2010; 21: 523–8.
2. Chmielewski L, Walters MD. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol. 2011; 205:

69.e1–8.
3. Bump RC, Mattiasson A, Bø K, Brubaker LP, DeLancey JO, Klarskov P, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol. 1996;175(1):10–7.
4. Roovers JP, van der Vaart CH, van der Bom JG, van Leeuwen JH, Scholten PC, Heintz AP. A randomised controlled trial comparing abdominal and vaginal prolapse surgery: effects on urogenital function. Br J Obstet Gynaecol. 2004; 111: 50–6.
5. Toozs-Hobson P, Freeman R. An international urogynaecological association (IUGA)/international continence society (ICS) joint report on the terminology for reporting outcomes of surgical procedures for pelvic organ prolapse. Int Urogynecol J Pelvic Floor. 2012; 23: 527–35.
6. Barber MD, Burbaker L, Nygaard I, Wheeler TL, Schaffer J, Chen Z, et al. Defining success after surgery for pelvic organ prolapse. Obstet Gynecol. 2009;114(3):600–9.



Chapter 5

A comparison of complications between open abdominal sacrocolpopexy and laparoscopic sacrocolpopexy for the treatment of vault prolapse.

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Abstract

Introduction Sacrocolpopexy is a generally applied treatment for vault prolapse which can be performed laparoscopically or by open laparotomy.

Methods Between October 2007 and December 2012, we performed a multicentre prospective cohort study in 2 university and 4 teaching hospitals in the Netherlands. We included patients with symptomatic post hysterectomy vaginal vault prolapse requiring surgical treatment, who either had abdominal or laparoscopic sacrocolpopexy. We studied surgery related morbidity, which was divided in pre-, peri-, and postoperative characteristics.

Results We studied 85 patients, of whom 42 had open abdominal and 43 laparoscopic sacrocolpopexy. In the laparoscopic sacrocolpopexy group, estimated blood loss was significantly less compared to the abdominal group: 192 mL (±126) versus 77 mL (±182), respectively (p≤ .001). Furthermore, hospital stay was significantly shorter in the laparoscopic group (2.4days) as compared to the abdominal group (4.2 days) (p≤ .001). The overall complication rate was not significantly different (p= .121). However, there was a significant difference in favour of the laparoscopic group in peri- and postoperative complications requiring complementary (conservative) treatment and/or extended admittance (RR 0.24 (95%-CI 0.07–0.80), p= .009).

Conclusion Laparoscopic sacrocolpopexy reduces blood loss and hospital stay as compared to abdominal sacrocolpopexy and generates less procedure related morbidity.

Introduction

The incidence of post hysterectomy vault prolapse requiring surgery has been estimated at 36 per 10,000 women years [1]. The risk increases cumulatively with years after hysterectomy and increases significantly in women whose initial hysterectomy was performed for genital prolapse [1–3]. In an aging population, the number of women that will seek medical help for a vaginal vault prolapse will increase due to an improved life expectancy and due to the aging population.

Surgery for pelvic organ prolapse, including vaginal vault prolapse, focuses on the restoration of the normal vaginal anatomy and normal bladder and bowel function. To date, a variety of different surgical procedures to correct vaginal vault prolapse have been reported [4]. These reconstructive techniques can principally be divided into vaginal or abdominal procedures. The abdominal approach can be performed open or laparoscopically. According to a Cochrane review on the subject, abdominal sacrocolpopexy is associated with a lower rate of recurrent vault prolapse compared to the vaginal sacrospinous fixation [5]. Success rates of abdominal sacrocolpopexy range between 93% and 99% [6, 7].

The first report of a laparoscopic approach for sacrocolpopexy was written in 1994 [8]. Laparoscopy has potential advantages in terms of reduced morbidity, shorter hospital stay, and convalescence. Surgically, it has been suggested that there is easier access and placement of the mesh down the posterior vaginal wall compared with the open procedure [9]. Previous studies showed less blood loss and a significantly shorter hospital stay in the laparoscopic group [5, 9, 10]. These studies show no significant difference in complication rate; however, in the abdominal group more severe complications occurred [9].

All previous studies have shown less morbidity in favour of the laparoscopic method, but prospective comparisons are lacking, specifically to evaluate differences in complication rates between both procedures. We performed a prospective cohort study to compare complication rates of the open abdominal sacrocolpopexy and the laparoscopic sacrocolpopexy.

Materials and Methods

We report on patients who underwent surgery for post hysterectomy symptomatic vault prolapse between 2007 and 2012. The study was performed in 4 teaching and 2 academic hospitals in the Netherlands. The study was approved by the ethical committees of all participating hospitals.

The patient population consisted of women with a history of hysterectomy followed by a symptomatic vault prolapse requiring surgical treatment. Patients having a contra- indication for sacrocolpopexy were excluded. Women who had undergone previous abdominal or vaginal vault prolapse surgery were also excluded.

The population of this study exists of prospectively enrolled patients who were eligible for both

surgical techniques (laparoscopy and open sacrocolpopexy) at time of inclusion. Part of the patients were placed in a group dependent on their own preference. Other patients participated in randomized clinical trial comparing laparoscopy and open surgery (ISRCT number: NTR3276) which is still enrolling, and were therefore allocated by blind randomization. This randomized trial is not the focus of the current report. All patients gave permission to use their medical data after signing written informed consent. Women received a case number to treat their data anonymously.

Surgical Intervention

Interventions were either abdominal or laparoscopic sacrocolpopexy. Patients received bowel preparation the day before the operation. Prophylactic antibiotics were given preoperatively, for example, metronidazole/cefazolin. As prophylaxis for thromboembolism pre- and postoperatively subcutaneous daltaparine was administered.

Looking at the design of this surgical intervention, the main goal of sacrocolpopexy is to reconstitute an adequate, safe, safe durable system of support and suspension vagina by replacing the impaired and/or detached native fascial tissue with a synthetic non-absorbable prosthesis.

Abdominal Sacrocolpopexy

The abdominal sacrocolpopexy was performed by a laparotomy under general anaesthesia. A Pfannenstiel incision was used preferably. One piece of type 1 polypropylene mesh was attached anteriorly and another as far down the posterior vaginal wall as possible. Both meshes were sutured to each other after which the posterior mesh was fixed to the sacrum. The mesh was peritonealised at several points.

Laparoscopic Sacrocolpopexy

The laparoscopic sacrocolpopexy was performed under general anaesthesia with four trocars, one for the scope and three side trocars. The procedure was the same as the abdominal procedure. The vaginal vault was elevated with a vaginal probe. the peritoneum was incised laparoscopically by scissors to expose the rectovaginal and vesicovaginal fascia, extending to the sacral promontory. One piece of type 1 polypropylene mesh was attached anteriorly and another as far down the posterior vaginal wall as possible. The mesh was attached to the sacral promontory using staples. The mesh was peritonealised at several points.

Both procedures were completed with any necessary vaginal operation after the vault suspension had been carried out. All centres used polypropylene meshes, the same sutures (vicryl) to attach the mesh to the vaginal vault and staples for attachment of the mesh to the sacrum. A urethral catheter

was le in situ and was removed after 24 hours postoperative or as clinically indicated. Study surgeons were skilled in performing one or both procedures. To exclude a learning curve, they needed to have performed at least twenty-five procedures prior to the start of participation of the study.
Data collection included duration of symptoms, body mass index, pre- or postmenopausal status, use of estrogens, combined prolapse surgery or stress urinary incontinence, procedure time, amount of estimated blood loss and hospital stay, and perioperative complications. Complications were defined as unintended and undesirable events or situations during or because of a medical intervention, which will have (temporary) negative effects on patients' wellbeing. Severe complications were defined as peri- and post- operative complications due to the surgical intervention requiring complementary (conservative) treatment and/or extended admittance. The Dutch complication registration of the NVOG (Dutch Society of Obstetrics and Gynaecology) [11] was used to separate minor from major complications.
Preoperative, at 6 weeks, and 1 year postoperative a pelvic examination was done according to the recommendations of the ICS (POP-Q classification) to evaluate the anatomical results of prolapse repair.

Statistical Analysis

Data were analysed based on intention to treat principle. To examine differences between groups we used an unpaired t-test for continuous variables and a chi-square or, if opportune, Fisher's exact test for dichotomous variables. A p-value of <0.05 was considered to be statistically significant. The statistical package used was SPSS 20.0.

Results

We included 85 patients in our study, of whom 42 had undergone open abdominal sacrocolpopexy and 43 had undergone laparoscopic sacrocolpopexy. Pre- and postoperative morbidity data could be analysed in all 85 patients. Table 1 shows the baseline characteristics of the studied population.

Table 1. Baseline characteristics (ITT-analysis)

	Laparoscopic Sacrocolpopexy N=45	Open Abdominal Sacrocolpopexy N=44	p-value
Age (years)			
Median (IQR)	66.2 (61.2-72.7)	67.6 (64.1-73.6)	.746
Body Mass Index (kg/m2)			
Median (IQR)	25.4 (22.5-27.4)	25.6 (23.9-28.3)	.805
Parity (n/m)			.311
0	2.4% (1/42)	0.0% (0/40)	
1	7.1% (3/42)	7.5% (3/40)	
2	42.9% (18/42)	45.0% (18/40)	
3	40.5% (17/42)	25.0% (10/40)	
≥4	7.1% (3/42)	22.5% (9/40)	
Menopausal status (n/m)			.543
Premenopausal	2.3% (1/44)	4.7% (2/43)	
Postmenopausal	97.7% (43/44)	95.3% (41/43)	
Incontinence (n/m)			.453
None	59.5% (25/42)	51.2% (21/41)	
Stress	4.8% (2/42)	7.3% (3/41)	
Urge	14.3% (6/42)	7.3% (3/41)	
Combined	21.4% (9/42)	34.1% (14/41)	
Estrogens use (n/m)			.122
None	94.3% (33/35)	82.4% (28/34)	
Local/Systemic	5.7% (2/35)	17.6% (6/34)	
History of gynecological surgery (n/m)			.143
TVH only	38.1% (16/42)	27.5% (11/40)	
TVH & ACR	9.5% (4/42)	5.0% (2/40)	
TVH & PCR	2.4% (1/42)	20.0% (8/40)	
TVH & ACR/PCR	28.6% (12/42)	12.5% (5/40)	
TVH & later ACR & mesh	2.4% (1/42)	0.0% (0/40)	
TAH & ACR & later PCR	0.0% (0/42)	2.5% (1/40)	
TAH only	9.5% (4/42)	27.5% (11/40)	
TAH & PCR	2.4% (1/42)	2.5% (1/40)	
Laparoscopic hysterectomy	4.8% (2/42)	0.0% (0/40)	
Supracervical hysterectomy	2.4% (1/42)	0.0% (0/40)	

TVH = transvaginal hysterectomy, TAH = total abdominal hysterectomy,
ACR = anterior colporrhaphy, PCR = posterior colporrhaphy

No significant differences were observed between both groups. Preoperative POP-Q was also not different in both groups (Table 2).

Table 2. Pre-operative POP Q

	Open abdominal sacrocolpopexy N=42	**Laparoscopic sacrocolpopexy N=43**	***P value***
Aa	-3 ± 1.8 (-3-3)	-0.5 ± 1.6 (-3-3)	.667
Ba	0.6 ± 2.8 (-5-8)	0.6 ± 2.3 (-3-4)	.766
C	-0.3 ± 4.2 (-8-10)	1.0 ± 2.3 (-6-6)	.092
GH	3.7 ± 0.8 (3-5)	3.7 ± 0.8 (2-5)	.361
PB	3.1 ± 0.5 (2-4)	2.5 ± 0.9 (0-3)	.102
TVL	7.9 ± 1.5 (4-10)	7.7 ± 1.3 (6-11)	.374
Ap	-.07 ± 1.7 (-3-3)	-1.2 ± 1.9 (-3-3)	.142
Bp	0.1 ± 2.7 (-4-8)	0.4 ± 2.5 (-3-4)	.444
D	-	-	

Table 3 shows perioperative data. In the laparoscopic sacrocolpopexy group estimated blood loss was significantly less compared to the abdominal group: 192 mL (±126) versus 77 mL (±182), respectively (p≤ .001). Furthermore, hospital stay was significantly shorter in the laparoscopic group (2.4 days) as compared to the abdominal group (4.2 days) (p≤ .001). Mean operation time in the abdominal group was 118 min, whereas the mean operation time in the laparoscopic procedure was 128 min (p= .254).

Table 3. Peri-operative data (PP-analysis)

	Laparoscopic Sacrocolpopexy N=43	**Open Abdominal Sacrocolpopexy N=42**	***p-value***
Operative time (minutes)			
Median (IQR)	120 (110-140)	120 (105-132)	*.884*
Estimated blood loss ml)			
Median (IQR)	50 (10-100)	200 (100-250)	*<.001*
Hospital stay (days)			
Median (IQR)	2 (2-3)	4 (3-5)	*<.001*

In the laparoscopic group 8 (18.6%) patients had one or more complications compared to 14 (33.3%) patients in the abdominal group which was not significantly different (RR 0.558 (95%-CI 0.26–1.19), p= .121). We divided complications in peri- and postoperative complications.

Perioperative complications are listed in Table 4. There were 5 (11.6%) complications in the laparoscopic group, versus 3 (7.1%) in the open abdominal group (p= .489). In the laparoscopic group in one case the procedure had to be converted to an open abdominal sacrocolpopexy due to a bleeding coming from the promontory. This bleeding resulted in a total estimated blood loss of 1200mL. This patient also developed an abdominal wall hematoma around the median laparotomy scar. In another patient, a bleeding of the right ovarian artery occurred while fixating the mesh to the promontory. The total estimated blood loss in this case was 200mL. In the laparoscopic group 2 bladder injuries occurred of which in one case the operation had to be converted to a vaginal procedure. In one patient in the laparoscopic group the mesh had to be fixated to the ventral abdominal wall because of poor visualization and excessive vascularization of the promontory.

In the open abdominal group one procedure had to be converted to intravaginal mesh procedure due to severe adhesions. In one patient in the open abdominal group some of the mesh sutures were put through the bladder, detected and cut by cystoscopy. One other patient had a bladder injury which was repaired directly.

Postoperative complications are also listed in Table 4. Most of the complications were found in the open abdominal group. There were 6 (14.0%) complications in the laparoscopic group, versus 13 (31.0%) in the open abdominal group (p= .086). In the laparoscopic group, there was one patient with atrial fibrillation and another patient had symptoms of angina pectoris; nevertheless, in both cases no cardiac ischemia could be diagnosed. There was one postoperative wound infection of the umbilical trocar incision and an abdominal wall hematoma; however, no complementary treatment was needed. In the abdominal group one patient died postoperatively because of multi-organ failure due to a sepsis after a bowel perforation. She had a relaparotomy but developed a pneumonia postoperatively and in combination with multi-organ failure and cardiac arrhythmia, this resulted in a fatal complication, 5 days postoperative. Two patients had a wound dehiscence which needed to be surgically repaired. One patient developed a pulmonary embolism which required therapeutic anticoagulant therapy. In three patients, which were 7.1% of the patients in the open abdominal group, an ileus was diagnosed. These three patients recovered after conservative treatment. In two patients, there was an abdominal hematoma; however, no complementary treatment was needed. One patient had temporary a mild delirium during admittance. Another patient had symptoms of dysuria in combination with fever caused by a urinary tract infection and was treated with antibiotics. Postoperatively, we found two patients in each group with urinary retention.

Three (7.0%) patients in the laparoscopic group and 12 (28.6%) patients in the abdominal group had peri- and postoperative complications due to the surgical intervention requiring complementary

(conservative) treatment and/or extended admittance which was significantly different (RR 0.24 (95%-CI 0.07–0.80), p= .009). When we separated the minor peri- and postoperative complications from the major complications according to the Dutch complication registration of the NVOG (Dutch Society of Obstetrics and Gynaecology) [11], there were no major complications in the laparoscopic group and 3 (7.1%) major complications in the abdominal group which is not statistically significant (p= .074). Two of these three major complications of the abdominal group are classified as category B because a re-operation was required to repair the wound dehiscence. The third complication was a category D complication since the complication was fatal [11].

Table 4. Patients with peri-operative & post-operative complications (PP-analysis)

	Laparoscopic Sacrocolpopexy N=43	Open Abdominal Sacrocolpopexy N=42	*p-value*
Peri-operative complications			*.479*
One or more complications	11.1% (5)	7.1% (3)	
Severe adhesions	-	2.4% (1)	
Bladder lesion	4.7% (2)	4.8% (2)	
Bleeding	4.7% (2)	-	
Alternative mesh fixation	2.3% (1)	-	
Post-operative complications			*.086*
One or more complications	14.0% (6)	28.6% (12)	
Fatal bowel perforation	-	2.4% (1)	
Wound dehiscence	-	4.8% (2)	
Pulmonary embolism	-	2.4% (1)	
Ileus	-	7.1% (3)	
Abdominal wall hematoma	2.3% (1)	4.8% (2)	
Cardiac complication	4.7% (2)	-	
Delirium	-	2.4% (1)	
Wound infection	2.3% (1)	-	
Urinary tract infection	-	2.4% (1)	
Urinary retention	4.7% (2)	4.8% (2)	
One or more treated complications*	7.0% (3)	28.6% (12)	*.009*
One or more major complications**	-	7.1% (3)	*.074*

* complications due to the surgical intervention requiring complementary (conservative) treatment and/or extended admittance

** According to the Dutch complication registration of the NVOG [21]

Six weeks postoperative there were 16 (18.8%) complications seen, which are shown in Table 5. There were 7 (16.7%) complications in the laparoscopic group, versus 9 (21.4%) in the open abdominal group (p= .527). In the laparoscopic group seven patients had complications of which five patients (11.6%) had constipation, one patient (2.3%) developed de novo stress urinary incontinence, and another patient (2.3%) had de novo urge incontinence. The complications of the open abdominal

sacrocolpopexy group consisted of three patients (7.1%) with de novo stress urinary incontinence, three patients (7.1%) had symptoms of constipation, another two patients (4.8%) had recurrent urinary tract infections and one patient (2.4%) had bothersome pain around the Pfannenstiel incision. Because all these complications could be a result of permanent loss of function, they are classified as category C complications according to the Dutch complication registration of the NVOG [11].

Table 5. Patients with complications 6 weeks post-operative (PP-analysis)

	Laparoscopic Sacrocolpopexy N=43	Open Abdominal Sacrocolpopexy N=42	p-value
Complications 6 weeks post-operative			.527
One or more complications	16.7% (7)	21.4% (9)	
Constipation	11.6% (5)	7.1% (3)	
De novo stress incontinence	2.3% (1)	7.1% (3)	
De novo urinary incontinence	2.3% (1)	-	
Recurrent urinary tract infections	-	4.8% (2)	
Bothersome pain around incision	-	2.4% (1)	

Discussion

We performed a prospective cohort study with 85 patients who underwent a sacrocolpopexy either abdominally or laparoscopically for vaginal vault prolapse. Morbidity was less in the laparoscopic group. Less blood loss during surgery and a shorter hospital stay were seen in the laparoscopic sacrocolpopexy group. The overall complication rate was not significant different in both groups; however, a trend was seen towards less complications in the laparoscopic group. Peri- and postoperative complications, due to the surgical intervention requiring complementary (conservative) treatment and/or extended admittance, was significantly different in favour of the laparoscopic group. No significant difference was seen in operation time.

Both the Cochrane collaboration and the National Institute for Clinical Excellence (NICE, UK) have recommended abdominal sacrocolpopexy with mesh as the optimal surgical treatment for vaginal vault prolapse [12, 13]. Both open and laparoscopic procedures appear equally effective in several case series [10, 14–17].

No large studies powered on complications rates of sacrocolpopexy have been done. On the other hand, many studies were done comparing open abdominal hysterectomy to laparoscopic hysterectomy performed for benign diseases. Two large trials of Garry et al. [18] and Maresh et al. [19] showed a significantly higher complication rate in the laparoscopic hysterectomy group. Nevertheless, hospital stay and postoperative pain were less in the laparoscopic group. We found

less (severe) complications in the laparoscopic sacrocolpopexy group. Our study showed similar results on morbidity in accordance to previous studies comparing open abdominal to laparoscopic sacrocolpopexy [5, 9, 10]. A randomized trial comparing laparoscopic to abdominal sacrocolpopexy performed by Freeman et al. [9] showed significantly less blood loss (56 versus 240 mL), less mean Hb drop (1.12 versus 2.33 mg/dL), shorter hospital stay (3.2 versus 4.1 days), and less morphine use (16 versus 32 mL) in the laparoscopic group. ere was no significant difference in complication rate, but in the abdominal group more severe complications occurred [9]. Our trial also showed more severe complications in the abdominal group. The overall complication rate of our study was not significantly different (p= .121). However, there was a significant difference in perioperative complications due to the surgical intervention requiring complementary (conservative) treatment and/or extended admittance in favour of the laparoscopic group (p= .009).

Nonrandomized cohort studies of Paraiso et al. [5] and Klauschie et al. [10] also showed less blood loss and a significantly shorter hospital stay in the laparoscopic group [5, 10]. There was no difference in complication rate between both studies [5, 10].

The complication rate of the laparoscopic group was 18.6% (8 patients) compared to a complication rate of 33.3% (14 patients) in the abdominal group. In the abdominal group 3 patients (7.1%) of the patients were diagnosed with an ileus postoperative. At six weeks postoperative 5 patients (11.6%) of the laparoscopic group developed defecation problems compared to 3 patients (7.1%) in the abdominal group. In the abdominal group 3 patients (7.1%) developed de novo stress incontinence. Bowel symptoms are also reported in other studies comparing laparoscopic to abdominal sacrocolpopexy [5, 9, 10]. Klauschie et al. [10] described one severe bowel obstruction in the abdominal group. In the study of Paraiso et al. [5] two patients developed an ileus in the abdominal group, small bowel obstructions occurred once in the laparoscopic group and twice in the abdominal group and one patient of the laparoscopic group, had severe constipation postoperatively. Freeman et al. [9] showed de novo urinary incontinence in both groups, mainly in the abdominal group (2 versus 4 patients) [9] which matches to our study results. In contrast with other studies comparing laparoscopic to abdominal sacrocolpopexy [5, 9, 10], no mesh exposure has been seen in our study population. Patients should be informed preoperatively about complications that occur in more than 5%. This means that constipation and urinary incontinence should be added to the counselling prior to a sacrocolpopexy. For the abdominal sacrocolpopexy counselling should also include the risk of ileus. Physicians should screen patients at risk for bowel symptoms and anticipate by prescribing prophylactic laxatives to prevent constipation.

The complication rate in our study is higher than prescribed in other studies comparing open abdominal to laparoscopic sacrocolpopexy. Differences in complications rates can be explained by our accurate complication registration. All minor and major complications were precisely documented resulting in honest prospective data. In contrast with other studies all complications are

mentioned and described, even when the complication was temporary and did not affect the operation, time of admission, or treatment. The study of Paraiso et al. [5] and Freeman et al. [9] prescribes only severe or permanent complications.

This study has a few limitations. Some patients were randomized as part of a larger trial that is not the focus of the current report. Not all included patients were randomized. We added a prospective cohort group of women with a history of hysterectomy followed by a symptomatic vault prolapse requiring surgical treatment. Only patients who were eligible for both surgical options were asked for our prospective cohort group. However, we did not expect study bias by including this prospective group to our randomized group because we focused on procedure-related morbidity. Patient's or physician's preference does not affect procedure morbidity. Furthermore, no significant differences in baseline characteristics were found.

Several studies showed that laparoscopic sacrocolpopexy is attended with less morbidity and less severe complications [5, 9, 10]. Our results also showed severe complications in the open abdominal group, including a fatal bowel perforation.

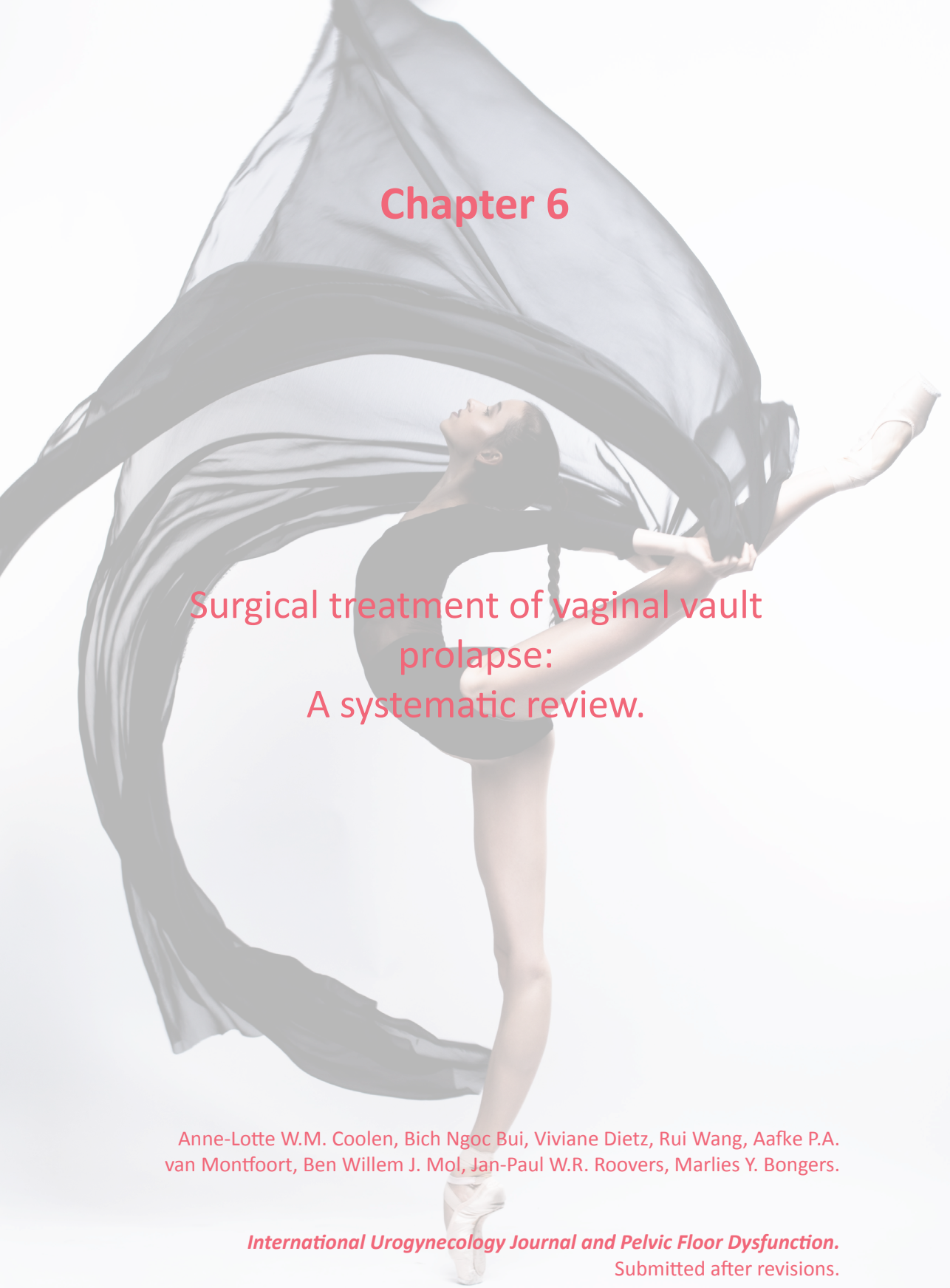
Conclusion

Laparoscopic sacrocolpopexy seems to be related to less procedure-related morbidity compared to open abdominal sacrocolpopexy concerning less estimated blood loss, hospital, and severe complications. Laparoscopic sacrocolpopexy is a safer treatment for vaginal vault prolapse compared to abdominal sacrocolpopexy whereas this technique does not prolong the operation.

References

1. J.Mant,R.Painter,andM.Vessey,"Epidemiology of genital prolapse: observations from the oxford family planning association study," British Journal of Obstetrics and Gynaecology, vol. 104, no. 5, pp. 579–585, 1997.
2. S. E. Swift, " The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic health care," American Journal of Obstetrics and Gynecology, vol. 183, no. 2, pp. 277–285, 2000.
3. M. Marchionni, G. L. Bracco, V. Checcucci et al., "True incidence of vaginal vault prolapse: thirteen years of experience," Journal of Reproductive Medicine for the Obstetrician and Gynecologist, vol. 44, no. 8, pp. 679–684, 1999.
4. P. Toozs-Hobson, K. Boos, and L. Cardozo, "Management of vaginal vault prolapse," British Journal of Obstetrics and Gynaecology, vol. 105, no. 10, pp. 1127–1128, 1998.
5. M. F. R. Paraiso, M. D. Walters, R. R. Rackley, S. Melek, and C. Hugney, "Laparoscopic and abdominal sacral colpopexies: a comparative cohort study," American Journal of Obstetrics and Gynecology, vol. 192, no. 5, pp. 1752–1758, 2005.
6. T. E. Snyder and K. E. Krantz, "Abdominal-retroperitoneal sacral colpopexy for the correction of vaginal prolapse," Obstetrics and Gynecology, vol. 77, no. 6, pp. 944–949, 1991.
7. M. C. Timmons, W. A. Addison, S. B. Addison, and M. G. Cavenar, "Abdominal sacral colpopexy in 163 women with post hysterectomy vaginal vault prolapse and enterocele: evolution of operative techniques," Journal of Reproductive Medicine for the Obstetrician and Gynecologist, vol. 37, no. 4, pp. 323–327, 1992.
8. C. H. Nezhat, F. Nezhat, and C. Nezhat, "Laparoscopic sacral colpopexy for vaginal vault prolapse," Obstetrics and Gynecology, vol. 84, no. 5, pp. 885–888, 1994.
9. [R. M. Freeman, K. Pantazis, A. Thomson et al., "A randomized controlled trial of abdominal versus laparoscopic sacrocolpopexy for the treatment of post-hysterectomy vaginal vault prolapse: LAS study," International Urogynecology Journal, vol. 24, no. 3, pp. 377–384, 2013.
10. J. L. Klauschie, B. A. Suozzi, M. M. O'Brien, and A. W. McBride, "A comparison of laparoscopic and abdominal sacral colpopexy: objective outcome and perioperative differences," International Urogynecology Journal and Pelvic Floor Dysfunction, vol. 20, no. 3, pp. 273–279, 2009.
11. "NVOG Complication registration form obstetrics and gynecology," 2006, http://www.nvog.nl/.
12. C.Maher, K.Baessler, C.M.Glazener, E.J.Adams, S.Hagen, "Surgical management of pelvic organ prolapse in women," Cochrane Database of Systematic Reviews, no. 4, 2010.
13. NICE, 2009, http://guidance.nice.org.uk/IPG283/Guidance/ pdf/English.
14. F. Claerhout, D. de Ridder, J. P. Roovers et al., "Medium-term anatomic and functional results of laparoscopic sacrocolpopexy beyond the learning curve," European Urology, vol. 55, no. 6, pp. 1459–1468, 2009.
15. A. M. Ganatra, F. Rozet, R. Sanchez-Salas et al., " The current status of laparoscopic sacrocolpopexy: a review," European Urology, vol. 55, no. 5, pp. 1089–1105, 2009.
16. N. Price, A. Slack, and S. R. Jackson, "Laparoscopic sacrocolpopexy: an observational study of functional and anatomical outcomes," International Urogynecology Journal and Pelvic Floor Dysfunction, vol. 22, no. 1, pp. 77–82, 2011.
17. J. W. Ross and M. Preston, "Laparoscopic sacrocolpopexy for severe vaginal vault prolapse: five-year outcome," Journal of Minimally Invasive Gynecology, vol. 12, no. 3, pp. 221–226, 2005.

18. R. Garry, J. Fountain, J. Brown et al., “Evaluate hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy,” Health Technology Assessment, vol. 8, no. 26, pp. 1–154, 2004.
19. M. J. A. Maresh, M. A. Metcalfe, K. McPherson et al., “The VALUE national hysterectomy study: description of the patients and their surgery,” BJOG: An International Journal of Obstetrics and Gynaecology, vol. 109, no. 3, pp. 302–312, 2002.



Chapter 6

Surgical treatment of vaginal vault prolapse: A systematic review.

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Abstract

Introduction The management of post-hysterectomy vaginal vault prolapse (VVP) has been investigated in several randomized clinical trials (RCTs), but a systematic review of the topic is still lacking.

Objectives The aim of this study is to compare the effectiveness of treatments for VVP.

Methods We performed a systematic review and meta-analysis of the literature about the treatment of VVP found in PubMed and Embase. Reference lists of identified relevant articles were checked for additional articles. A network plot was constructed to illustrate the geometry of the network of the included treatments.

Selection criteria Only RCTs reporting on the treatment of VVP were eligible, conditional on a minimum of 30 participants with VVP and a follow-up of at least 6 months.

Results Nine RCTs reporting on 846 women (size 95 to 168 women) met the inclusion criteria. All surgical techniques are associated with good subjective results, and without differences between the compared technique, with the exception of the comparison of VM vs LSC. LSC is associated with a higher satisfaction rate. The anatomical results of the sacrocolpopexy (laparoscopic, robotic and abdominal) are the best (62-91%), followed by the VM. However, the ranges of the anatomical outcome of VM were large (43-97%). The poorest results are described for the SSF (35-81%), which also correlates with the higher re-operation rate for POP (5-9%) (but also for incontinence and complications; 5-27%). The re-operation rate done for complications, recurrence prolapse and incontinence of VM was also high (13-22%). The most complications (Clavien-Dindo grade 2-5) are reported after ASC (2-19%), VM (6-29%) and RSC (51%). Mesh exposure was seen most often after VM (8-21%). Overall the sacrocolpopexy reports the best results at follow-up, with an outlier of one trial reporting the highest re-operation rate for POP (11%) [16]. Results of the RSC are to minimal to make any conclusion, but LSC seem to be preferable over ASC.

Conclusion A comparison of techniques was difficult because of heterogeneity; therefore, a network meta-analysis was not possible. However, the reported differences between the techniques were very minimal, the LSC seems to be the technique with the best results, in contrast to the SSF who seems to be associated with the poorest results. Nevertheless, all techniques have proved to be effective, and all trials reported good results for the anatomical and subjective outcome. Therefore, a standard treatment for VVP could not be given according to this review.

Introduction

More than 40% of women aged 40 and older have pelvic organ prolapse (POP) [1]. POP can negatively affect women's quality of life by local physical effects (pressure, bulging, heaviness or discomfort) or its effect on urinary, bowel or sexual function). Consequently, about 13.000 surgeries are performed for this health problem in the Netherlands every year [1].

The incidence of vault prolapse requiring surgery has been estimated at 36 per 10,000 women years [2]. The risk of prolapse following hysterectomy is 5.5 times higher in women whose initial indication for hysterectomy was genital prolapse as opposed to other indications [3]. The number of women with a symptomatic pelvic organ prolapse that will seek medical help is increasing [4]. Vaginal vault prolapse (VVP) is often associated with other compartment defects (cystocele, rectocele, or enterocele), which makes it a challenging condition to treat [5]. There is a growing recognition that adequate support for the vaginal apex is an essential component of a durable surgical repair for women with advanced prolapse [3 Because of the significant contribution of the apex to vaginal support, anterior and posterior vaginal repairs may fail unless the apex is adequately supported [6]. Current treatment options for VVP include pelvic floor muscle training, use of pessaries and surgery. [7] A variety of different surgical procedures to correct VVP have been reported [6, 8, 9]. According to our search over 20 different treatment options for VVP have been reported; abdominal sacrocolpopexy, laparoscopic sacrocolpopexy, robotic sacrocolpopexy, sacrospinal fixation, iliococygeus fixation, transvaginal mesh, posterior intravaginal slingplasty, Mayo culdoplasty, mc Call culdoplasty, high uterine sacral ligament fixation, laparoscopic uterine sacral ligament fixation, colpocleisis, abdominal presacral suspension, abdominocolporectopexy, pectinal ligament suspension, transobturator infracoccygeal hammock, Cooper ligament repair, abdominal round ligament colpopexy, infracoccygeal sacrocolpopexy, sacrocolpoperineopexy and abdominal sacrocolpopexy using xenograft, polypropylene, abdominal fascia or fascia lata. The best treatment of post-hysterectomy VVP remains controversial. The procedure that the surgeon eventually selects, is influenced by many factors, which include the nature, site and severity of the prolapse; whether there are additional symptoms affecting urinary, bowel or sexual function, the general health of the woman and the surgeon’s preference and capability [6].

The wide variety of the treatments available for VVP indicates the lack of consensus. Maher et.al. [6] reviewed the management of the apical prolapse in a Cochrane review, however the management of uterine descent and VVP are not separately investigated. Although this review is very complete and well written, it wouldn’t give consensus about the management for the VVP, since many studies were included about the treatment of the uterine prolapse. This is a source of bias, since the aetiology of a VVP differs from a uterine prolapse.

The management of post-hysterectomy VVP has been investigated in several randomized clinical trials, however a systematic overview of the topic is still lacking. The aim of this study is to compare the effectiveness of post-hysterectomy vaginal vault treatments in a systematic review and meta-analysis, combined with a network plot, using the most reliable evidence coming from randomized controlled trials.

Objectives

The aim of this study is to compare the effectiveness of post-hysterectomy vaginal vault treatments in a systematic review and meta-analysis of randomized controlled trials.

Methods

Types of studies

We included randomised controlled trials (RCTs) in which any treatment was compared with any other treatment for VVP. We excluded quasi-randomized studies (e.g. studies with evidence of inadequate sequence generation such as alternate days, patient numbers) and cross-over studies as they are associated with a high risk of bias. Trials reporting on the objective and/or subjective outcome of VVP treatments and conditional on a minimum of 30 participants and a follow-up of at least 6 months were eligible.

VVP was defined as a post hysterectomy prolapse of the apical compartment. Objective outcome was defined as the assessment of POP by a validated staging system, i.e. Pelvic Organ Prolapse Quantification System (POP-Q) [10] or the Baden-Walker System [11]. Subjective outcome was defined as the assessment of subjective symptoms resulting from POP by validated questionnaires. Trials reporting on the treatment of uterine prolapse solely were excluded.

Types of participants

Eligible trials included women seeking treatment for a symptomatic primary VVP. If trials reported on a combination of uterine prolapse and (non-)post-hysterectomy VVP they were excluded, if no sub analysis was performed of the group with a VVP.

Types of interventions

Eligible trials compared different types of treatment for VVP, including physiotherapy, pessary treatment, abdominal surgery (open, laparoscopic or robotic), vaginal surgery, native tissue repair and mesh surgery.

Types of outcomes

The outcome of the review is the objective (anatomical) and subjective ((disease specific) quality of life) outcome of VVP treatments. Objective outcome is defined as the assessment of POP by a validated staging system, i.e. Pelvic Organ Prolapse Quantification System (POP-Q) [10] or the Baden-Walker System [11]. Subjective outcome is defined as the assessment of subjective symptoms resulting from POP by validated questionnaires.

Other outcomes were age, follow-up time, blood loss during surgery, operating time, length of hospital stay, complications, any recurrent prolapse according to the POP-Q classification, repeat surgery for prolapse, mesh erosion and exposure, dyspareunia and de novo incontinence. We also collected data about any other reported anatomical outcome, success rates and its definitions, and items of the combined outcome measures of Barber et al (recurrent pelvic organ prolapse beyond the hymen in the apical compartment, with bothersome bulge symptoms, and re-interventions). However, data of the Barbers criteria were not available in many publications, therefore we couldn't report these data in this review. We looked for outcomes that could be pooled for meta-analysis, and if pooling was not possible, data was reported in a table to create a clear overview of all different outcome measurements of the trials.

Complications and mortality were recorded to assess the safety of the procedures. We classified the complications by the Clavien-Dindo complication classification, in order to compare the complications of the included trials. This classification consists of four severity grades of complications [10,12]. Complication were categorized into grade 1 to 5 (Grade 1: requires no treatment; grade 2: requires drug therapy; grade 3: requires a procedure or intervention; grade 4: IC/ICU organ or system dysfunction; grade 5: death), and complications of grade 3-5 were documented.

Search method

A systematic review of the literature on the treatment of post-hysterectomy VVP was performed according to the PRISMA checklist [13]. Studies were identified by searching PubMed (MEDLINE) and Embase, using the search term 'vaginal vault prolapse'. The last literature search was run on (25th of April 2017). An overview of our full electronic search strategy is presented in Appendix 1. Reference lists of identified relevant articles were checked for additional articles. No restrictions on language or publication year were applied, and foreign papers were translated. We did not impose any other limits on any of the searches.

Data collection

Titles and abstracts were assessed for eligibility by two independent reviewers (ALC and BNB). Disagreements were referred to a third reviewer (MYB or VD) to reach consensus. Data extraction was independently conducted by two authors (ALC and BNB) and recorded in a predefined data extraction sheet. The selection process can be referred to in the PRISMA flow chart (Figure 1).

Two reviewers (ALC and BNB) independently assessed the quality of the included trials utilizing the Cochrane Collaboration's tool for assessing risk of bias described in the Cochrane Collaboration Handbook [14]. Disagreements were discussed with a third reviewer (MYB) to reach consensus. Briefly, the tool we used addresses seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data, selective reporting and other sources of bias. Each domain is assigned a judgment, relating to the risk of bias for that trial, classified as 'low risk', 'high risk' or 'unclear risk' (appendix 1).

Data extraction and management

Data were extracted on type of intervention(s), number and age of trial participants, the trial's inclusion and exclusion criteria, the follow-up duration, type of treatment and type of outcome measure. Our outcome measure is the comparison of the objective and subjective outcomes of the trial interventions. Other extracted parameters are language of the article, blinding, baseline characteristics, details of the intervention, complications, adverse events, repeat surgery, recurrent prolapse and lost to follow-up.

Assessment of risk of bias in included studies

Risk of bias was assessed by using the Cochrane “Risk of bias” assessment tool [14] to assess selection (random sequence generation and allocation concealment); performance (blinding of participants and personnel); detection (blinding of outcome assessors); attrition (incomplete outcome data); reporting (selective reporting); and other bias. We presented the conclusions in the “Risk of bias” tables (figure 2-3).

Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

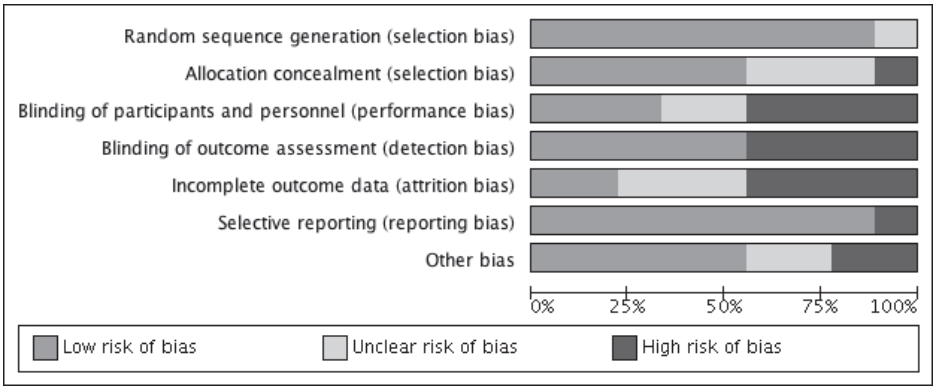
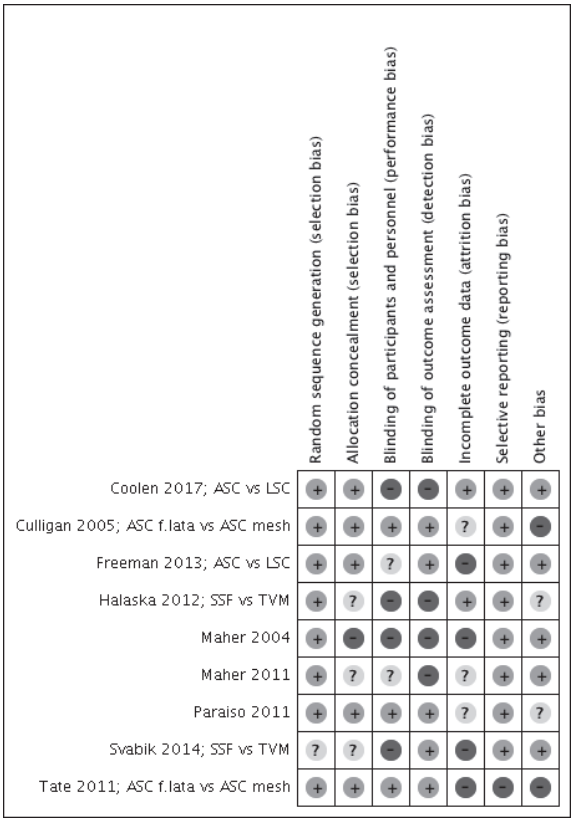


Figure 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Analysis

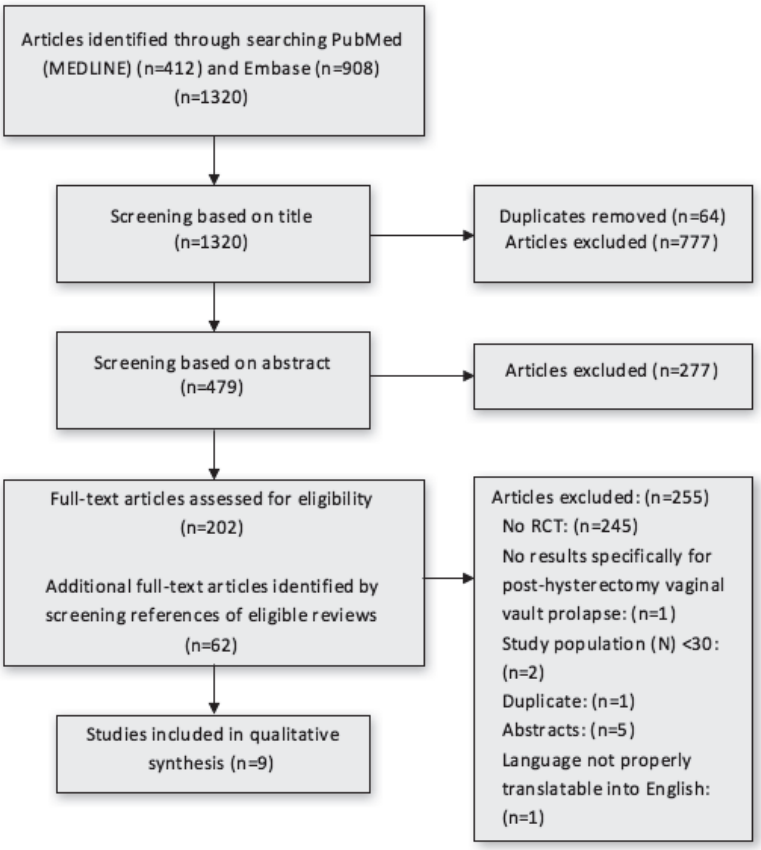
We plotted a network plot to illustrate the geometry of the network of the included treatments by using "mvmeta" package in Stata software (Version 12.0, Stata Corp, College Station, TX) [15].
For dichotomous data, we used the numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (ORs). For continuous data, if all studies reported exactly the same outcomes we calculated the mean difference (MDs) between treatment groups. We presented 95% confidence intervals for all outcomes. We analysed the data on an intention-to-treat basis (once randomized to an intervention the participants are analysed in that intervention and analysis includes all randomized participants) as far as possible. Review manager 5.3 was used for meta-analyses.
We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity by the measure of the I^2. An I^2 measurement greater than 50% was taken to indicate substantial heterogeneity [14], and a random-effects calculation was undertaken to express greater uncertainly by widening the confidence intervals.

Results

Study selection

The search of PubMed and Embase resulted in a total of 1320 hits. The selection process is illustrated in Figure 1, including explanation for exclusion of studies. Adjusting for duplicates, 1256 articles remained. After screening of titles and abstracts, 1054 articles were excluded. Eventually 202 full text articles were assessed for eligibility. References of eligible articles were screened on title and abstract, which resulted in 62 additional eligible full text articles. Out of 264 full text articles, 255 were excluded because they did not meet the inclusion criteria. A total of 9 RCTs met the inclusion criteria and were included in the systematic review.

Figure 1: PRISMA flow chart



Characteristics of included studies

All studies were randomized controlled trials level 1B according to the Oxford (UK) CEBM Levels of Evidence. All 9 RCTs are written in English. The follow-up ranged from 12 to 60 months.

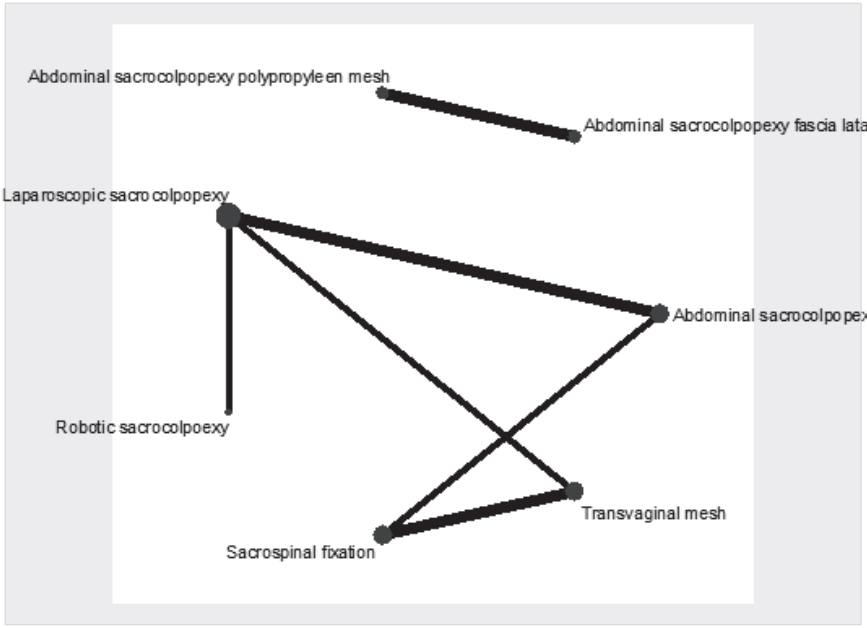
Participants

The included RCTs involved 846 participants operated for apical VVP. The main inclusion criteria entailed symptomatic vault prolapse indicated for surgical repair. The mean age of the participants in the RCTs ranged from 57 to 66 year. All participants had (post hysterectomy) VVP with or without concomitant cystocele and/or rectocele. The mean preoperative stage of pelvic organ prolapse ranged from stage 2 (7 RCTs, N = 668) to 3 (2 RCTs, N = 178). The mean parity ranged from 2 to 3. Furthermore, the mean body mass index ranged from 25.3 to 29 kg/m^2.

Interventions

A network plot was constructed (figure 4) to illustrate the geometry of the network of the included treatments. Two studies reported on ASC vs LSC [16, 17]. Two papers also reported on ASC and randomized between polypropylene and cadaveric fascia lata [18,19]. Another trial compared ASC to SSF [20]. Two RCT's randomized between SSF and VM (Total Prolift, Gynecare, Ethicon) [21, 22]. VM (Total Prolift, Gynecare, Ethicon) was compared to LSC in another trial [23], and LSC was compared to RSC [24] in one of the papers. The study of Tate [18] was a report of the 5 year follow up results of the same trial of Culligan [19] who reported 1 year follow up results.

Figure 4: network plot



Follow-up time

Six of the included studies had a follow-up time one year [16, 17, 19, 21, 22, 23] In two trials the follow-up time was two years [20, 23] and in one trial [18] a follow-up time of 5 years was administered.

Outcomes

All nine studies reported data in a form suitable for analysis on at least objective or subjective outcomes.

All trials reported objective outcome as anatomical outcome: one study used Baden Walker [20] and eight studies used the POP-Q classification [16, 17, 18, 19, 21, 22, 23 24]. Criteria for success were "no prolapse POP-Q ≥ stage 2" in three studies [19, 21, 23], or no prolapse Baden Walker > grade 1 [20]. Combined outcome measures for success were used by Coolen [16], Tate [18] and Svabik [22], although the items of the combinations were different. In two papers success was not defined [17, 24], but in both trials the POP-Q results were reported (Table 1).

Seven reported the subjective success by using validated questionnaires [16, 17, 21, 22, 23, 24] (Table 2). Many different questionnaires were used to assess the subjective outcome (table 2). Tate [18] and Culligan [19] did not report the subjective data they collected (according to their methods), however as part of a combined outcome measurement Tate did report some subjective data of their population.

Risk of bias

The assessment of risk of bias in the included studies is presented in figure 2-3.

Allocation

All trials were randomized trials and used adequate methods of allocation concealment [16-24]. For example, randomization by sealed envelopes or computer generated randomization. In four studies block randomization was used [17, 18, 19, 24]. Inclusion of these nine trials using well performed randomization, resulted in a low risk of selection bias. However, in one of these trials [19], four participants received the other intervention (polypropylene mesh instead of fascia lata) and were not analysed by the intention to treat principle, since they were analysed in the mesh group.

Performance and detection bias

In some trials blinding is very difficult since the type of incision is very different. However, patients were blinded in three trials [18,19, 24] and in one trial patients were blinded during their admission [17]. The operating staff could not be blinded, although the ward staff was blinded in two trials [17,18].

Blinding of outcome assessment at the follow-up consult was performed in five studies [17, 18,19, 22, 24]. In one study the observer was an independent researcher, who was not blinded [16]. Three studies did not report any blinding of the outcome observation [20, 21, 23].

Incomplete outcome data

In seven studies [16, 17, 18,19, 21, 22, 24] follow-up rates were described. The follow-up rates ranged between 69-97% with different follow-up periods. However, only two trials specified the reasons for lost to follow-up and looked at patient characteristics of responders and non-responders [16, 18], which was balanced between groups. It is unclear if missing data was imputed in any of the studies, which results in a risk of bias.

Reporting bias

Primary and secondary pre-specified outcomes were reported in nine papers [16-24]. However, data of several outcomes were not available to be used in a meta-analysis. Culligan [18] and Tate [19] did not report about the quality of life data they collected. Reasons for not reporting these data are not described.

Confounders

Baseline characteristics able to act as confounders were reported in nine studies [16-24]. However, Tate [18] described only the pre-operative POP-Q scores of the population. Significance between both groups is not relevant since all trials were randomized properly. Therefore, the risk of confounders is low.

Other risk of bias

In none of the studies another source of bias was found. However, funding was not described in all trials [18, 22]. Two trials were funded [17, 24], although these funding sources are not industry driven.

Results

Anatomical outcome

Objective success rates according to the POP-Q or Baden Walker classification, were extracted from 8 studies (n=793). All trials used their own definition of anatomical success. Success rates ranged from 62% to 93% for abdominal sacrocolpopexy (ASC) (n=284), 77% to 91% for laparoscopic sacrocolpopexy (LSC) (n=128), 35% to 81% for sacrospinous fixation (SSF) (n=165), 43% to 97% for transvaginal mesh (VM) (n=176) and was reported to be 88% for robotic sacrocolpopexy (RSC) (n=40) (Table 1).

Subjective outcome on urogenital symptoms and quality of life

Subjective outcomes, were extracted from 9 studies (n=846). Many different questionnaires were used to assess subjective outcome. No significant differences were seen for subjective success and quality of life. Only one trial (n=108) showed a higher satisfaction score in the LSC group compared to the VM group (Table 2).

Table 1: Objective anatomical outcome of randomised trials comparing treatments for vaginal vault prolapse.

Author	No. Patients	Follow-up (months)	Intervention	Assessment of subjective outcome	Criteria for success	Objective success rate	Re-operation (%)
Maher 2004	95 (6)	ASC 24 (6-60) and SSF 22 (6-58)	ASC vs SSF	Baden-Walker	No prolapse grade 2	85% vs 81%, p=0.78	
Culligan 2005	100 (11)	12	ASC: fascia lata vs polypropylene mesh	POP-Q	No prolapse ≥stage 2	68% vs 91%, p=0.007	
Tate 2011	100 (31)	60	ASC: fascia lata vs polypropylene mesh	POP-Q	Objective success: no prolapse ≥stage 2 Clinical success: no bulge or prolapse symptoms ánd point C $<^{1}/_{2}$TVL or any POP-Q point ≤0	62% vs 93%, p=0.02 90% vs 97%, p=0.61	
Freeman 2013	53	12	ASC vs LSC	POP-Q	Not defined	No difference	0 vs 1
Coolen 2017	74	12	ASC vs LSC	POP-Q	no prolapse beyond hymen, no bulge symptoms, and no repeat surgery	84% vs 89%	1 vs 5 (RR 4, 95% CI 0.84-5.73)
Maher 2011	108 (3)	24	LSC vs VM	POP-Q	Stage 0 or 1 prolapse at all vaginal sites	77% vs 43%, p<0.001	
Paraiso 2011	78 (17)	12	LSC vs RSC	POP-Q	Not defined	91% vs 88%, NS (stage 0-1) 9% vs 12% NS (stage 2)	
Halaska 2012	168 (17)	12	SSF vs VM	POP-Q	No prolapse ≥stage 2	61% vs 83%	
Svabik 2014	70 (0)	12	SSF vs VM	POP-Q	Point Ba, C or Bp <0 ánd Translabial ultrasound: bladder descent <10mm below the lower margin of the symphysis pubis on maximum Valsalva	35% vs 97%, p<0.001	

ASC = abdominal sacrocolpopexy, LSC = laparoscopic sacrocolpopexy, SSF = sacrospinous fixation, RSC = robotic sacrocolpopexy, VM = total vaginal mesh

Table 2: Subjective outcome of randomised trials comparing treatments for vaginal vault prolapse.

Author	No. Patients	Follow-up (months)	Intervention	Assessment of subjective outcome	Outcome(s)	Result(s)
Maher 2004	95 (6)	Mean ASC 24 (6-60) and SSF 22 (6-58), p=0.65	ASC vs SSF	UDI-6, IIQ, SF-36, Modified sexual function questionnaires, VAS for patient satisfaction	Subjective success rate Patient satisfaction	94% vs 91%, p=0.19 85% vs 81%, p=0.78
Culligan 2005	100 (11)	12	ASC: fascia lata vs polypropylene mesh	No outcome	No outcome	No outcome
Tate 2011	100 (31)	60	ASC: fascia lata vs polypropylene mesh	Clinical success: no bulge or prolapse symptoms ánd point C $<^{1}/_{2}$TVL or any POP-Q point ≤0	Combined subjective and objective outcome	90% vs 97%, p=0.61
Freeman 2013	53 (6)	12	ASC vs LSC	PGI-I, P-QOL, SF-36	Subjective outcome Quality of life	PGI-I score 1 and 2 combined 90% vs 80% No difference
Coolen 2017	74 (1)	12	ASC vs LSC	UDI, DDI, IIQ, PGI-I	Subjective outcome	No difference
Maher 2011	108 (3)	24	LSC vs VM	APFQ, P-QOL, VAS for patient satisfaction	Symptomatic prolapse Mean patient satisfaction Subjective outcome	2% vs 7%, p=0.18 OR 4.75 (95% CI 2.06-10.98) 87 ± 21 vs 79 ± 20, p=0.002 MD 8.09 (95% CI, 0.20 –15.98) No difference
Paraiso 2011	78 (17)	12	LSC vs RSC	PFDI-20, PFIQ-7, PISQ, EQ-5D	Subjective outcome Quality of life	No difference No difference
Halaska 2012	168 (17)	12	SSF vs VM	PISQ, UIQ, CRAIQ, POPIQ	Subjective outcome Quality of life	No difference No difference
Svabik 2014	70 (0)	12	SSF vs VM	ICIQ-SF, PISQ-12, POPDI, UDI, CRADI	Subjective outcome	No difference

ASC = abdominal sacrocolpopexy, LSC = laparoscopic sacrocolpopexy, SSF = sacrospinous fixation, RSC = robotic sacrocolpopexy, VM = total vaginal mesh
PGI-I = patient global impression of improvement, P-QOL = perceived quality of life scale, SF-36 = short form health survey, UDI = urogenital distress inventory, DDI = defecatory distress inventory, IIQ = incontinence impact questionnaire, PISQ = pelvic organ prolapse/urinary incontinence sexual questionnaire, EQ-5D = euroqol questionnaire, APFQ = Autralian pelvic floor questionnaire, P-QOL = prolapse quality of life questionnaire, VAS = visual analogue scale, POPIQ = pelvic organ prolapse impact questionnaire, ICIQ-SF = international consultation on incontinence questionnaire - Short Form, POPDI = pelvic organ prolapse distress inventory, CRADI = colo-rectal-Anal Distress Inventory, UIQ = urinary impact questionnaire, CRAIQ = colorectoanal impact questionnaire

Complications

The most reported complications were classified as grade 2 and grade 3 complications (Table 3 and 5). Grade 2 complications were reported in 6 out of 9 trials and comprised mainly of urinary tract infections; LSC n=6 [16, 23, 24], VM n=4 [21, 23], RSC n=5 [24], SSF n=5 [21], postoperative fever; ASC n=4 [19] or wound infection; ASC n=1 [20], RSC n=2 [24] and pulmonary embolism; ASC n=2 [16, 19]. The highest grade 3 complication rate was seen after VM (34.2%) [21]. Grade 3 complications were reported in all trials and comprised mainly of bladder lesions in 11 cases; ASC n=2 [19, 20], SSF n=2 [20, 21], VM n=3 [21], LSC n=5 [16, 17, 23, 24], RSC n=2 [24], bowel lesions in 3 cases; ASC n=1 [17], LSC n=1 [23], RSC n=1 [24], severe bleeding in 22 cases; ASC n=3 [17, 19, 20], SSF n=7 [20, 21], LSC n=1 [23], VM n=11 [21, 23] and mesh problems in 28 cases; ASC n=6 [18, 19, 20], LSC n=1 [23], VM n=19 [23], RSC n=2 [24].

Only one study [16] reported a grade 5 complication, which concerned a 79-year old patient with a fatal bowel perforation after ASC. Table 6 (appendix) presents an overview of all complications.

Intervention details

- *Operating time*

The mean operating time could be extracted from 7 studies (n=676) and ranged from 50 to 265 minutes (table 3). The shortest operating time was reported for the transvaginal mesh [23], whereas the longest operating time (with and without docking time) was reported for the robotic sacrocolpopexy [24].

- *Blood loss*

Mean amount of estimated blood loss during the intervention was extracted from 6 studies (n=598). The mean blood loss ranged from 34 to 306 mL (table 3). The least amount of blood loss was reported for the laparoscopic sacrocolpopexy [17], whereas the abdominal sacrocolpopexy was associated with the highest amount of estimated blood loss [20].

- *Duration of hospital stay*

The mean duration of hospital stay was reported in 5 studies (n=408) and ranged from 1.4 to 5.4 days (table 3). The shortest hospital stay was reported for the laparoscopic sacrocolpopexy [17] and the sacrospinous fixation [20]. The abdominal sacrocolpopexy was associated with the longest hospital stay [20].

Table 3: Clinical outcome

Author	Maher 2004	Culligan 2005	Tate 2011	Freeman 2013	Coolen 2017	Maher 2011	Paraiso 2011	Halaska 2012	Svabik 2014
Comparison	ASC vs SSF	ASC: fascia lata vs polypropylene mesh	ASC: fascia lata vs polypropylene mesh	ASC vs LSC	ASC vs LSC	LSC vs VM	LSC vs RSC	SSF vs VM	SSF vs VM
Operative time (minutes)									
Mean (range)	106 ± 37 (45-100) vs 76 ± 42 (26-300) (p<0.01)	233.4 ± 66.9 vs 227.3 ± 63.3 (p=0.40)	Not mentioned	131 ± 44 vs 144 ± 28 (p=0.24)	113 (68-180) vs 125 (85-240) (p=0.31)	97 (36-280) vs 50 (30-96) (p<0.001)	199 ± 46 (109-329) vs 265 ± 50 (191-381) (p<0.001)	80 (15-50) vs 65 (35-166) (p=0.001)	Not mentioned
Estimated blood loss (ml)									
Mean (range)	362 ± 239 (100-1100) vs 306 ± 201 (100-1000) (p=0.22)	264.7 ± 261.4 vs 247.2 ± 148.4 (p=0.68)	Not mentioned	240.4 ± 231.7 vs 56.15 ± 34.3 (p<0.01)	205 (10-650) vs 86 (0-1200) (p<0.01)	100 (20-300) vs 150 (21-500) (p=0.004)	Not mentioned	110 (10-528) vs 120 (10-814) (p=0.39)	Not mentioned
Hospital stay (days)									
Mean (range)	5.4 ± 2.2 (3-16) vs 4.8 ± 1.4 (3-10) (p=0.16)	Not mentioned	Not mentioned	4.1 ± 1.6 vs 3.2 ± 1.1 (p=0.02)	4.3 (2-12) vs 2.4 (1-4) (p<0.01)	2 (2-10) vs 3 (2-6) (p=0.01)	1.4 ± 0.5 (0.6-2.7) vs 1.8 ± 1.5 (0.8-10) (p=0.17)	Not mentioned	Not mentioned
Complications* % (n/m)									
Grade 1	0 vs 2.1% (1/48)	0 vs 0	0 vs 0	0 vs 0	0 vs 0	0 vs 0	0 vs 2.9% (1/35)	6.8% (5/73) vs 0	0 vs 2.8% (1/36)
Grade 2	2.1% (1/47) vs 0	4.3% (2/46) vs 5.6% (3/54)	0 vs 0	0 vs 0	2.7% (1/37) vs 5.6% (2/36)	3.8% (2/53) vs 10.9% (6/55)	9.1% (3/33) vs 28.6% (10/35)	6.9% (5/73) vs 8.9% (7/79)	0 vs 0
Grade 3	10.6% (5/47) vs 6.3% (3/48)	10.9% (5/46) vs 25.9% (14/54)	2.3% (1/44) vs 4.4% (2/45)	7.4% (2/27) vs 7.7% (2/26)	13.5% (5/37) vs 5.6% (2/36)	9.4% (5/53) vs 18.2% (10/55)	9.1% (3/33) vs 22.9% (8/35)	9.6% (7/73) vs 34.2% (25/73)	0 vs 5.6% (2/36)
Grade 4	0 vs 0	0 vs 0	0 vs 0	0 vs 0	0 vs 0	0 vs 0	0 vs 0	0 vs 0	0 vs 0
Grade 5	0 vs 0	0 vs 0	0 vs 0	0 vs 0	2.7% (1/37) vs 0	0 vs 0	0 vs 0	0 vs 0	0 vs 0

ASC = abdominal sacrocolpopexy, LSC = laparoscopic sacrocolpopexy, SSF = sacrospinous fixation, RSC = robotic sacrocolpopexy, VM = total vaginal mesh

*Grade 1: requires no treatment; grade 2: requires drug therapy; grade 3: requires a procedure or intervention; grade 4: IC/ICU organ or system dysfunction; grade 5: death

Recurrence of pelvic organ prolapse

In table 4 (and appendix table 7) follow-up results are presented of all included studies.

- *Point C*

All studies reported acceptable results for point C of the POP-Q classification at follow-up. The laparoscopic sacrocolpopexy is associated with the best anatomical result of the apical compartment [17], with point C of the POP-Q classification of -10 cm. The poorest anatomical of the apical compartment is after a sacrospinous fixation, with point C of -3.2 cm [22], followed bij Halaska [21] with point C at -4.94 cm after a SSF.

- *POP-Q stage < 2*

The variation of the success rates is wide. The lowest scores are reported for the SSF [20-22] and ASC with fascia lata [18, 19]; with a range of 35-69%. VM reports one of the lowest anatomical success rate of 43% [23], and the highest success rate of 97% [22]. It has to be taken into account that the POP-Q success rates are defined differently, which could be an explanation of the wide variation for the success rates of the surgical techniques.

- *Re-operations for POP*

The re-operation rate for POP seems to be the lowest after ASC, with a range of 0-3% and the VM, [21-23] with a range of 0-5% [20-22 All procedures report low re-operation rates for POP, except for the outlier of 11% for LSC [16]. However, in another trial [23] the re-operation rate after the laparoscopic sacrocolpopexy is the lowest (0%). The highest general re-operation rates (for POP, incontinence and complications) are reported for the VM (13-22%) [21-23] and SSF (5-27% [22, 23].

- *Mesh exposure*

The reported mesh exposure rate after a sacrocolpopexy is very low, without respect to the introduction technique of fixation material. Mesh exposure after a sacrocolpopexy ranges from 0-5% [16, 17, 18, 23, 24]. In contrast to the transvaginal mesh, which seems to be associated with an exposure rate of 8-21% after one year follow-up [21, 22, 23].

- *Dyspareunia*

Most trials did not report any significant difference between the investigated interventions, however in only two trials the numbers of participants were given. The dyspareunia rate varied between 3-20% [20, 22], and ASC and SSF were associated with the highest dyspareunia rate of 20% and 19%.

- *De novo incontinence*

Stress urinary incontinence was most seen after VM (38%) [22] and SSF (33%) [23]. However, most trials did not report data about incontinence.

Table 4: technique specific follow-up results after one year

Technique	ASC		LSC	RSC	VM	SSF
	Mesh	Fascia				
Studies	5	1	4	1	3	3
N=	186	29	154	40	176	165
POP-Q point C	Fre '13: **-6.63** (SD 1.35) Co '17: **-6.7** (SD 1.9) Ta '11: **-9.0** (SD 1.2) Vault to/beyond hymen Ma '04: **4%** (2)	Ta '11: **-8.1** (SD 2.7)	Fre '13: **-6.65** (SD 1.19) Co '17: **-6.5** (SD 1.6) Ma '11: **-7.48** (SD 2.62) Par '11: **-10** (range -11 to -5)	Par '11**: -9** (range -11 to -6)	Ma '11: **-6.11** (SD 2.72) Ha '12: **-5.99** Sva '14: **-6.2** (SD 1.29)	Ha '12: **-4.94** Sva '14: **-3.2** (SD 3.56) Vault to/beyond hymen: Ma '04: **19%** (8)
POP-Q stage<2	*Ma '04: **76% (**35/46) Co '17: **66%** (19/29) ‡Cu '05: **91%** (41/45) ‡Ta '11: **93%** (27/29)	‡Ta '11: **62%** (18/29) ‡Cu '05**: 61%** (30/44)	Co '17: **72%** (21/29) Ma '11: **77%** (41/53)	-	Ma '11: **43%** (23/55) Ha '12: **83%** ∫Sva '14: **97%**	*Ma '04: **69% (**29/42) Ha '12: **61%** ∫Sva '14: **35%**
Re-operations (for POP, incontinence, complications)	Ma '04: **13%** (6/47) Ta '11: **6%** (3/54) Fre '12: **11%** (3/27) Co '17: **19%** (7/36)	Ta '11: **4%** (2/46)	Ma '11: **6%** (3/53) Fre '12: **12%** (3/26) Co'17: **19%** (7/37)		Ma '04: **22%** (12/55) Ha '12: **13%** (11/85) Sva '14: **31%** (11/36)	Ha '12: **5%** (4/83) Sva '14: **18%** (6/34) Ma '04: **27%** (13/48)
Re-operations for POP	Ma '04: **2%** (1/47) Ta '11**: 2%** (1/54) Fre '13: **0%** (0/27) Co '17: **3%** (1/37)	Ta '11: **2%** (1/46)	Fre '13: **4%** (1/26) Co '17: **11%** (4/37) Ma '11: **0%** (0/53)	-	Ma '11: **5%** (3/55) Ha '12: **1%** (1/85) Sva '14: **0%** (0/36)	Ma '04: **6%** (3/48) Ha '12: **5%** (4/83) Sva '14: **9%** (3/34)
Mesh exposure	Fre '13: **0%** (0/27) Co '17: **0%** (0/37) Ta '11: **2%** (1/54)	Ta '11: **2%** (1/54)	Fre '13: **0%** (0/26) Co '17: **0%** (0/37) Ma '11: **2%** (1/53) Par '11: **0%** (0/38)	Par '11: **5%** (2/40)	Ma '11: **13%** (7/55) Ha '12: **21%** (16/79) Sva '14: **8%** (3/36)	
Dyspareunia	Ma '04: **20%** (9)	-	-	-	Sva '14: **6%** (2/34)	Ma '04: **19%** (9) Sva '14: **3%** (1/36)
De novo incontinence	Any incontinence: Fre '13: **15%** (4/27) UUI: Co '17: **8%** (3/37) SUI: Ma '04: **9%** (2/22) Co '17: **11%** (4/37)	-	Any incontinence: Fre '13: **8%** (2/26) UUI: Co '17: **5%** (2/37) SUI: Co '17: **14%** (5/37)	-	SUI: Sva '14: **38%** (13/34)	SUI: Ma '04: **33%** (8/24) Sva '14**: 8%** (3/36)

* Baden Walker grade 2, ‡= ≤ POP-Q stage 2, ∫= Ba, C of Bp above hymen

Table 5: technique specific complications

Technique	ASC		LSC	RSC	VM	SSF
	Mesh	Fascia				
Studies	5	1	4	1	3	3
N=	186	29	154	40	176	165
Complications						
Clavien-Dindo Grade 1	Ma '04: **0%** (0/47) Cu '05: **0%** Tate '11: **0%** Fre '13: **0%** Co '17: **0%**	Cu '05: **0%** Tate '11: **0%**	Fre '13**: 0%** Co '17: **0%** Ma '11: **0%** Par '11: **0%**	Par '11: **3%** (1/35)	Ma '11: **0%** Ha '12: **0%** Sva '14: **3%** (1/36)	Ma '04: **2%** (1/48) Ha '12: **3%** (2/73)
Clavien-Dindo Grade 2	Ma '04: **2%** (1/47) Cu '05: **6%** (3/54) Tate '11: **0%** Fre '13: **0%** Co '17: **3%** (1/37)	Cu '05: **4%** (2/46) Tate '11: **0%**	Fre '13: **0%** Co '17: 6**%** (2/36) Ma '11: **4%** (2/53) Par '11: **9%** (3/33)	Par '11: **29%** (10/35)	Ma '11: **11%** (6/55) Ha '12: **0%** Sva '14: **0%**	Ma '04: **0%** Ha '12: **7% (**5/73) Sva '14: **0%**
Clavien-Dindo Grade 3	Ma '04: **11%** (5/47) Cu '05: **22% (**12/54) Tate '11: **4%** (1/44) Fre '13: **7% (**2/27) Co '17: 14% (5/37)	Cu '05: **11%** (5/46) Tate '11: **2%** (2/45)	Fre '13: **8%** (2/26) Co '17: **6%** (2/36) Ma '11: **9%** (5/53) Par '11: **9%** (3/33)	Par '11: **23%** (8/35)	Ma '11: **18%** (10/55) Ha '12: **6% (**2/36) Sva '14: **6%** (2/36)	Ma '04: **6%** (3/48) Ha '12: **10%** (7/73) Sva '14: **0%**
Clavien-Dindo Grade 4	Ma '04: **0%** Cu '05: **0%** Tate '11: **0%** Fre '13: **0%** Co '17: **0%**	Cu '05: **0%** Tate '11: **0%**	Fre '13: **0%** Co '17: **0%** Ma '11: **0%** Par '11: **0%**	Par '11**: 0%**	Ma '11: **0%** Ha '12: **0%** Sva '14: **0%**	Ma '04: **0%** Ha '12: **0%** Sva '14: **0%**
Clavien-Dindo Grade 5	Ma '04: **0%** Cu '05: **0%** Tate '11: **0%** Fre '13: **0%** Co '17: **3%** (1/37)	Cu '05: **0%** Tate '11: **0%**	Fre '13: **0%** Co '17: **0%** Ma '11: **0%** Par '11: **0%**	Par '11: **0%**	Ma '11: **0%** Ha '12: **0%** Sva '14: **0%**	Ma '04: **0%** Ha '12: **0%** Sva '14: **0%**

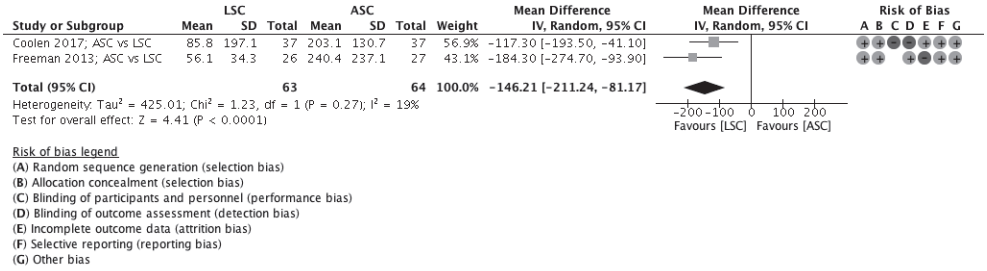
Meta-analysis

- *Abdominal sacrocolpopexy vs laparoscopic sacrocolpopexy*

1.1 Estimated blood loss, ASC vs LSC (figure 5)

The ASC was associated with less blood loss, as compared to LSC (MD -146 ml, 95% CI -211 to -81, 2 RCT's, n=127, I^2 19%, high quality evidence).

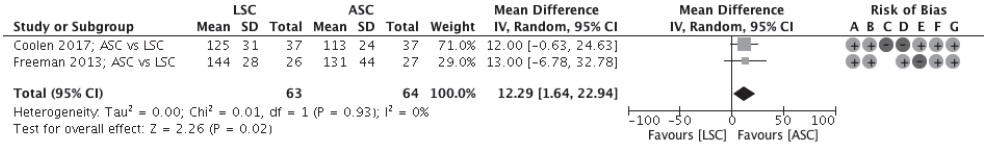
Figure 5. Forest plot of comparison: ASC vs LSC, outcome 1.1 estimated blood loss.



1.2 Operating time, ASC vs LSC (figure 6)

The operating time of the LSC is shorter than ASC, however this is not statistically different (MD 12.3 min, 95% CI -7 to 33, 2 RCT's, n=127, I^2 0%, high quality evidence)

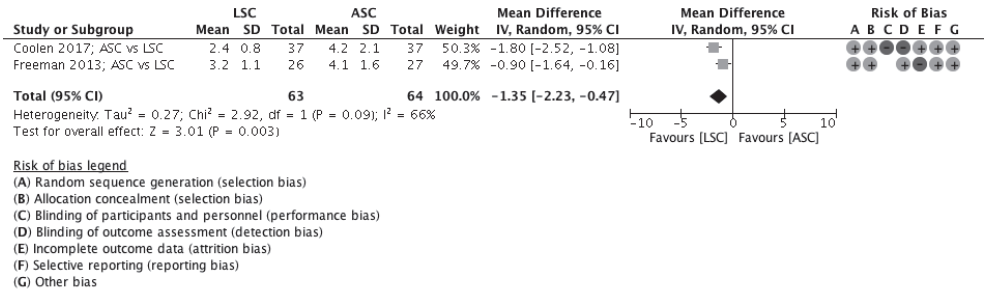
Figure 6. Forest plot of comparison: ASC vs LSC, outcome 1.2 operating time.



1.3 Length of hospital stay, ASC vs LSC (figure 7)

Length of hospital stay is shorter after a LSC compared to ASC (MD -1.4 days, 95% CI 1.7 to 23, 2 RCT's, n=127, I2 66%, high quality evidence).

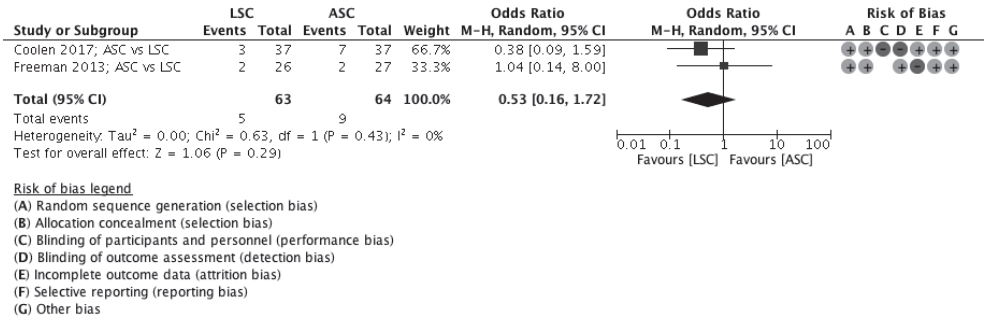
Figure 7. Forest plot of comparison: ASC vs LSC, outcome 1.3 length of hospital stay.



1.4 Complications, ASC vs LSC (figure 8)

There were more complications after an ASC than after a LSC, however this result is not a statistically different (MD 0.53 events, 95% CI 0.2 to 1.7, 2 RCT's, n=127, I^2 0%, high quality evidence). There were 5 reported complications in the LSC group versus 9 in the ASC group.

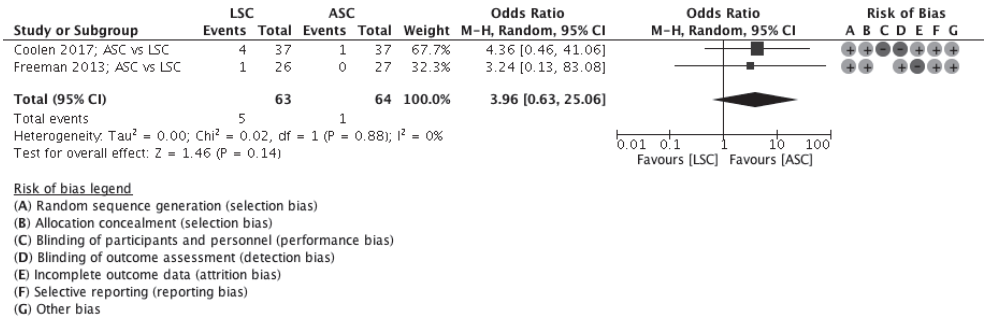
Figure 8. Forest plot of comparison: ASC vs LSC, outcome 1.4 complications.



1.5 Re-operations (for POP), ASC vs LSC (figure 9)

There was no statistically difference between re-operations for POP between ASC and LSC, however less re-operations were seen in the ASC group (MD 4.0 events, 95% CI 0.6 to 25, 2 RCT's, n=127, I^2 0%, high quality evidence). In the LSC group 5 re-operations were performed versus 1 in the ASC group.

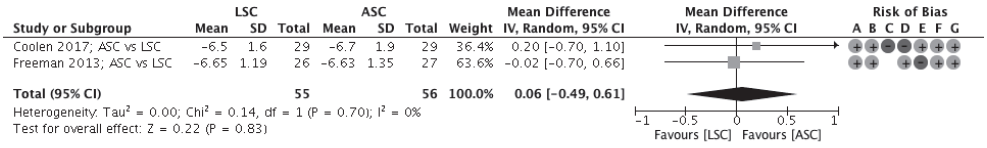
Figure 9. Forest plot of comparison: ASC vs LSC, outcome 1.5 re-operations (for POP).



1.6 POP-Q point C (at 1 year), ASC vs LSC (figure 10)

No differences were seen of POP-Q point C one year after an ASC of LSC (MD 0.06 cm, 95% CI -0.49 to 0.61, 2 RCT's, n=127, I^2 0%, high quality evidence).

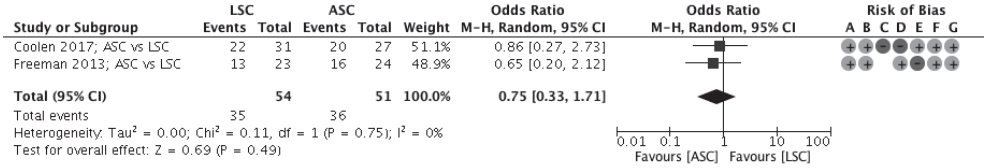
Figure 10. Forest plot of comparison: ASC vs LSC, outcome 1.6 point C (at 1 year).



1.7 PGI-I (at 1 year), ASC vs LSC (figure 11)

No differences were seen of the participants who scores "much better" and "very much better" on the PGI-I questionnaire, one year after an ASC of LSC (MD 0.75 participants, 95% CI 0.33 to 1.71, 2 RCT's, n=127, I^2 0%, high quality evidence).

Figure 11. Forest plot of comparison: ASC vs LSC, outcome 1.7 PGI-I (at 1 year).



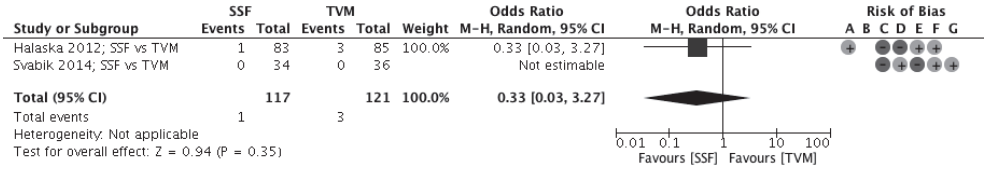
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

- *Sacrocolpopexy vs transvaginal mesh*

2.1 Complications, SSF vs VM (figure 12)

The complication rate of a SSF compared to VM was not statistically different, as the SSF group reported 1 complication and the VM group 3 (MD 0.33 events, 95% CI 0.03 to 3.27, 2 RCT's, n=238, I^2 n/a, medium quality evidence).

Figure 12. Forest plot of comparison: SSF vs VM, outcome 2.1 complications.

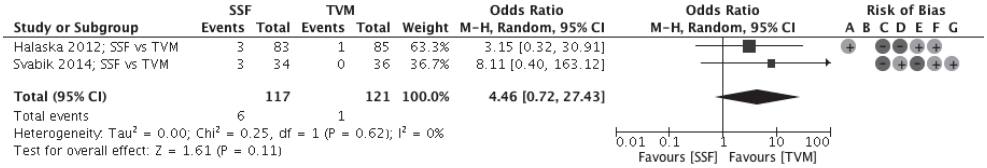


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

2.2. Re-operations (for POP), SSF vs VM (figure 13)

Less re-operations for POP were seen in the VM group, compared to SSF, however this was not statistically different (MD 4.5 events, 95% CI 0.72 to 27.43, 2 RCT's, n=238, I^2 0%, medium quality evidence). Six re-operations were described in the SSF group, versus one in the VM group.

Figure 13. Forest plot of comparison: SSF vs VM, outcome 2.2 re-operations (for POP).



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Discussion

Main findings

We performed a systematic review and meta-analysis, combined with a network plot, to compare the objective and subjective outcome of VVP treatments and to determine the most effective treatment. Ranges for objective success rates for the therapies of VVP were wide. Heterogeneity of outcome measures of the included trials was large. Therefore, a network meta-analysis was not possible.

All surgical techniques are associated with good subjective results, and without differences between the compared technique, with the exception of the comparison of VM vs LSC. LSC is associated with a higher satisfaction rate. The anatomical results of the sacrocolpopexy (laparoscopic, robotic and abdominal) are the best, followed by the VM. However, the ranges of the anatomical outcome of VM were large. The poorest results are described for the SSF, which also correlates with the higher re-operation rate for POP (but also for incontinence and complications). The re-operation rate of VM was also high. The re-operations after VM were done for complications, recurrent prolapse and incontinence. The most complications (grade 2-5) are reported after ASC, VM and RSC. Mesh exposure was seen most often after VM. Overall the sacrocolpopexy reports the best results at follow-up, with an outlier of one trial reporting the highest re-operation rate for POP [16]. Results of the RSC are too minimal to make any conclusions, but LSC seem to be preferable over ASC. Although differences are very minimal, the LSC seems to be the technique with the best results, in contrast to the SSF with the poorest results. However, all techniques have proved to be effective, therefore a standard treatment for VVP could nog be given according to this review.

Strengths and limitations

We performed a systematic review and meta-analyses of all randomized controlled trials available on the topic of the treatment of VVP. The wide variety of the treatments available for VVP indicates the lack of consensus for the treatment of VVP. This review resulted in an overview of the treatment of VVP using only RCT's as they provide the best level of evidence. Hopefully this review will be useful as a guideline in the daily practice and can be used as a guideline for new future trials. Although nine RCT's were included in this review, further trials are required to reach consensus on the treatment of VVP. Since the heterogeneity of these nine studies was large and a network-meta analysis could not be performed a treatment of preference for VVP could not be determined.

A network meta-analysis, also referred to as multiple treatment comparison meta-analysis or mixed treatment meta-analysis, offers a set of methods to visualize and interpret the wider picture of the evidence and to understand the relative merits of these multiple interventions, when multiple interventions have been used and compared for the same disease and outcomes. Unfortunately, we could not perform a network meta-analysis since the lack of a common reference intervention (standard treatment) and the many different comparisons of all VVP treatments. However, a network plot was constructed to illustrate the geometry of the network and we pooled several data to perform a meta-analysis (figure 4).

All kinds of treatment comparisons have been done, using different measurement tools and outcomes. Uniformity of standard treatment, measurement tools and outcomes makes comparisons of treatments for VVP possible, where after the best treatment could be determined. These measurement tool should be in line with the recommendations of ICS/IUGA [25]. Initiators of future trials should be aware of this heterogeneity and need to choose carefully which treatments they want to compare and which measurement tools and outcomes they need to use. Although a standard treatment for VVP could not be advised according to our review, it would be preferable to have a reference intervention. A reference intervention is necessary to perform a network analysis. However, in order to determine this reference intervention, more innovation, training and research needs to be done, to prove obvious superiority of a treatment. The international panel of experts of IUGA/ICS should also give recommendations for common reference interventions, in order to create uniformity and make comparisons of treatments possible. Meanwhile, according to the present literature, LSC is most likely to be this reference treatment, since it shows the best results. However, we should be aware that these results show only small clinical differences.

Not only a reference intervention, but also measurement tools and endpoints differ in all publications. Subjective outcome should include the presence or absence of vaginal bulge and patient satisfaction and quality of life can be measured by validated instruments that cover prolapse,

urinary, bowel and sexual function [25]. A recommendation which validated questionnaires should be used will be helpful. The POP-Q classification should be used for the anatomical outcome. Complications can be recorded in a systematic way by using the CTS classification system as advised by IUGA/ICS [25] or the Clavien-Dindo complication classification [12]. Success should be defined according to the combined outcome of Barber et.al (recurrent pelvic organ prolapse beyond the hymen in the apical compartment, with bothersome bulge symptoms, and re-interventions) [26]. Unfortunately, not all included trials used the POP-Q classification to evaluate the anatomical outcome and the subjective outcome was measured by many different questionnaires, some not even validated. Also, success was defined in many different ways. The same arguments count for the standardization of complications. All trials report complications at their own way, which could result in a risk of bias, since authors can choose to in- or exclude complications to their own choice. Complication registration should be recorded in a systematic way and described prior to the start of a trial. However, we structured the trial results and performed meta-analyses to compare the included treatments if possible.

We performed a systematic review using all available RCT's on the treatment of VVP. Many trials on the treatment of VVP of different quality have been published. Over 20 different treatment options for VVP have been reported. However, we choose only to use all RCT's since it represents the best level of evidence. As a consequence, not all possible treatments for VVP (including conservative treatments) are included in this review. In our opinion these non-randomized trials don't belong in this review since it's risk on bias. Therefore, promising treatments should be compared in well performed randomized trials after which they can be included in an update of this review. The aim of our review was to evaluate the best treatment of VVP treatments and to determine the most effective treatment, including conservative treatment. However, there were no trials on conservative treatment of VVP.

Interpretation of important outcome measurements

Anatomical objective outcome: All trials reporting on success had different definitions of success (table 1). The highest success rates were described for ASC (up to 93%), LSC (up to 91%) and VM (up to 97%). Since different success rate definitions were used, these data are difficult to interpreter. Therefore, we extracted data from all publications to look for identical outcome measures (table 4 and appendix table 7). Data for point C from the POP-Q was available for almost all trials. ASC and LSC reported the best scores, in contrast with the SSF which had the poorest POP-Q results for point C. Another anatomical outcome measurement was success define as POP-Q stage 2 or less. The best

result was associated with the ASC and in one of the trials the VM also scored very well. Again, the SSF was associated with the poorest results. It has to be taken into account that the definitions based on prolapse stage were also different, since some trials reported success as “no prolapse POP-Q stage >2”, and others “no prolapse POP-Q stage ≥2”. One trial reported on Baden Walker classification, and one other trial reported the position of the vault in relation to the hymen. Another difference is the POP-Q stage of any compartment, or some specific compartment. Nevertheless, again, the POP-Q stage data have to be interpreted with caution. Furthermore, anatomical overcorrection of the vault is possible during a sacrocolpopexy, opposite to any other surgical techniques. Adjacent to this, the anatomical result doesn’t completely reflect the patient satisfaction correctly, as described by Barber et al [26]. Therefore, other parameters such as subjective outcome are also very important.

Subjective outcome: Also for the subjective outcome, all trials used different definitions and measurement tools (table 2). This makes interpretation difficult. Only one trial showed a significant better result for patient satisfaction in the LSC group, compared to VM. As mentioned before, it would be preferable if ICS/IUGA could recommend validated questionnaires which can be used in future trials, in order to compare objective results. Unfortunately, we couldn’t extract any identical data about subjective outcome, to make the comparison easier. Also, we couldn’t extract enough data from the combined outcome recommended by Barber [26].

Re-operation: Although the absence of good comparable subjective and objective outcome measurements, re-operations for POP can be a reflection of the patient’s satisfaction and anatomical result. All trials report low re-operation rates for POP, with an outlier of 11% for LSC in one trial [16]. Based on these data we can conclude carefully that all techniques are effective, with the best results for ASC (0-3%) and VM (0-5%). However, the highest general re-operation rates (for POP, incontinence and complications), and a wide range in anatomical outcome are reported for the VM [21-23]. Others shows better results of VM, depending on which technique was used (AMS elevate system) [27, 28]. Different techniques were available to fixate the trans vaginal mesh for apical suspension. Prolift (Total Prolift, Gynecare, Ethicon) was used in all included trials in our review. This mesh needs to be fixated to the sacrospinal ligament for apical support. Surgical competence is probably an issue for the success of vaginal mesh surgery and could be an explanation of the wide range of effectiveness between several systems. Due to modifications and innovations, different techniques for VM are currently available. The single incision VM technique is a different procedure, with another fixation technique. It is unclear if the success of this vaginal procedure depends on surgical skills and learning curves, or on the used fixation technique. Surgical competence is probably an issue for the success of vaginal mesh surgery and could be an explanation of the wide range of effectiveness between several systems. The results of the SSF, where the vault also needs to be

suspended to the sacrospinous ligament differ from trial to trial [29, 30]. This supports our question, if success of vaginal surgery depends on surgical skills and learning curves and might result in surgical failures more easily.

Complications and mesh exposure: The highest complication rate was described for VM (31.6% Clavien-Dindo grade 3). These complications were often associated with mesh exposure, which correlate with the highest exposure rates for the VM technique (8-21%). Mesh exposure was reported in the literature before, ranging from 3.2-17% depending on the treated compartment [27, 31-33]. Although the exposure rate of 21% seems to be exceptionally high as compared to other studies, women treated with VM should be informed about the chance of exposure and the use of VM should be considered very well.

Serious adverse events and mesh related complications should also be taken into account for the LSC. The FDA recently issued a public health notification on the use of mesh in surgery for vaginal prolapse treatment. This however concerns the use of vaginal meshes for the treatment of vaginal prolapse, as opposed to abdominal mesh. According to our review the mesh exposure rate ranged from 0-5%, with a maximum follow-up time of 5 years. However, higher exposure rates of 10.5% are reported after ASC [34]. Nevertheless, the follow-up time of this trial was 7 years, which could be an explanation for the lower rate in the review. Although mesh complications need to be taken into account in the decision which treatment will be performed, the prevalence of these complications are less as compared to VM.

The ASC was the only technique which was associated with a Clavien-Dindo grade 5 complication. This is very rare, but unacceptable for elective surgery. Therefore, surgeons and patients should be aware of the complexity of this abdominal procedure.

Centralization of the surgical treatment of VVP should be considered. Prolapse is a common condition [35], however, VVP and its surgical repair is uncommon. The incidence of VVP requiring surgery has been estimated at 3.6 per 1000 women years [2]. In 2005, the admission rate for prolapse operations in France (1.14/1,000 women) and England (1.13/1,000 women) was very comparable [36]. Therefore, exposure of VVP surgery is limited for the individual urogynaecologist [37]. The practice variation is different between European countries, whereas 38.8% of the French POP operations concern level-1 suspensions, compared to 10.3% in the United Kingdom. In France, 6.9 % (n = 2531) of prolapse repairs were sacrocolpopexies and 14.9 % (n = 5467) sacrohysteropexies, whereas in England, 4.27 % (n = 1006 procedures) of prolapse operations were sacrocolpopexies (the number of hysteropexies were not available). Surgical trends change over time, whereas VM for VVP surgery was applied in 13% of the VVP procedures in the United Kindom [37]. If the absolute number

of a particular operation is low, exposure per physician is inherently low. Low individual turnover may create a problem of proficiency, unless there is a predefined strategy to centralize care. A trial of Deprest et al. showed that it takes 60 procedures to effectively limit complications [37]. The LSC is a challenging, level 4 procedure. As a large number of patients are needed to acquire sufficient surgical skills, this procedure should only be performed by experienced surgeons [16]. VM and SSF are associated with the highest re-operation rate (for POP, incontinence and complications) which might be explained by surgical failure, due to surgical skills. Therefore, centralization for these techniques should also be considered.

Future research

Since no best treatment for VVP could be determined, more research is needed. First of all, evidence about conservative treatment for VVP is lacking. A previous hysterectomy was reported as a risk factor for failure of pessary treatment [39], however satisfaction and continuation rates have not been studied. A study to evaluate efficacy of conservative (pessary) treatment should be considered. Effective conservative treatment can be the first-choice treatment in women suffering from VVP. Furthermore, since the Prolift (Total Prolift, Gynecare, Ethicon) is no longer available and innovations and modifications of the VM technique led to other VM techniques, a randomized trial comparing LSC to single incision VM should be performed. This could give more insight in the role of currently available VM techniques in the treatment of VVP, and if the type of used fixation system plays a role. Moreover, another gap in research is a RCT comparing SSF to LSC. Although LSC shows good results, SSF is the still the most performed surgical treatment for VVP [40]. These techniques have never been compared in a RCT, therefore we suggest to wait for the results of the trial registered under trial number: Netherlands Trial Register (NTR): NTR3977. At last, further research on promising therapies as LSC and VM need to continue. Innovations on mesh material, to reduce mesh related complications are needed, even as innovations on laparoscopic techniques.

Conclusion

A comparison of techniques was difficult because of heterogeneity; therefore, a network meta-analysis was not possible. However, the reported differences between the techniques were very minimal, the LSC seems to be the technique with the best results, in contrast to the SSF who seems to be associated with the poorest results. Nevertheless, all techniques have proved to be effective, and all trials reported good results for the anatomical and subjective outcome. Therefore, a standard treatment for VVP could not be given according to this review.

Appendices

Appendix 1. Full electronic search strategy PubMed (MEDLINE) and Embase.

Search strategy PubMed (MEDLINE)

1. vault prolapse*[tiab]
2. (Therapy/Narrow[filter]) AND (#1)
3. systematic[sb] AND (#1)
4. (#2 OR #3)

Search strategy Embase

1. exp vaginal vault prolapse
2. limit 1 to (evidence based medicine or consensus development or meta-analysis or outcomes research or "systematic review")
3. limit 2 to ("therapy (maximizes sensitivity)" or "therapy (maximizes specificity)" or "therapy (best balance of sensitivity and specificity)")
4. 2 or 3

Appendix 2: additional tables of outcomes

Table 6: complications

Complication*	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Maher 2004 ASC vs SSF	ASC: 0% (0/47) SSF: 2.1% (1/48) • 1 vaginal pain of unknown origin	ASC: 2% (1/47) • 1 wound infection SSF: 0% (0/48)	ASC: 10.6% (5/47) • 1 blood transfusion • 1 cystostomy • 2 incisional hernia procedures • 1 mesh rejection SSF: 6.3% (3/48) • 1 blood transfusion • 1 cystostomy • 1 rectovaginal hematoma	ASC: 0% (0/47) SSF: 0% (0/48)	ASC: 0% (0/47) SSF: 0% (0/48)
Culligan 2005 ASC: Fascia lata vs polypropylene mesh	Fascia: 0% (0/46) Mesh: 0% (0/54)	Fascia: 4.3% (2/46) • 2 postoperative fever Mesh: 5.6% (3/54) • 2 postoperative fever • 1 pulmonary embolism	Fascia: 10.9% (5/46) • 5 wound breakdown Mesh: 22.2% (12/54) • 2 ileus • 8 wound breakdown • 2 exposure of graft • 1 intraoperative bladder injury • 1 blood transfusion	Fascia: 0% (0/46) Mesh: 0% (0/54)	Fascia: 0% (0/46) Mesh: 0% (0/54)
Tate 2011 ASC: fascia lata vs polypropylene mesh	Fascia: 0% (0/44) Mesh: 0% (0/45)	Fascia: 0% (0/44) Mesh: 0% (0/45)	Fascia: 2.3% (1/44) • 1 graft exposure Mesh: 4.4% (2/45) • 2 graft exposure 1 removal of mesh required partial bowel resection resulting in a colostomy. 1 laparoscopic removal and developed necrotizing fasciitis postoperatively at the umbilical port site.	Fascia: 0% (0/44) Mesh: 0% (0/45)	Fascia: 0% (0/44) Mesh: 0% (0/45)
Freeman 2013 ASC vs LSC	ASC: 0% (0/27) LSC: 0% (0/26)	ASC: 0% (0/27) LSC: 0% (0/26)	ASC: 7.4% (2/27) • 1 detachment of an area of mesentery of the small bowel requiring resection of 10 cm of small bowel • 1 excessive bleeding of sacrum requiring haemostatic bone wax LSC: 7.7% (2/26) • 1 opening of the vagina • 1 bladder injury	ASC: 0% (0/27) LSC: 0% (0/26)	ASC: 0% (0/27) LSC: 0% (0/26)
Coolen 2017 ASC vs LSC	ASC: 0% (0/37) LSC: 0% (0/36)	ASC: 2.7% (1/37) • 1 pulmonary embolism	ASC: 13.5% (5/37) • 2 wound dehiscence • 3 ileus LSC: 5.6% (2/36)	ASC: 0% (0/37) LSC: 0% (0/36)	ASC: 2.7% (1/37) • 1 fatal bowel perforation

		LSC: 5.6% (2/36) • 1 wound infection • 1 pyelonefritis	• 1 bladder lesion • 1 bleeding		LSC: 0% (0/36)
Maher 2011 LSC vs VM	LSC: 0% (0/53) VM 0% (0/55)	LSC: 3.8% (2/53) • 2 urinary tract infection VM: 10.9% (6/55) • 3 urinary tract infection • 1 infected pelvic hematoma that settled with intravenous antibiotics • 2 mesh exposure (vaginal estrogen therapy)	LSC: 9.4% (5/53) • 1 cystostomy • 1 small bowel enterotomy • 1 blood transfusion • 1 mesh exposure (vaginal estrogen therapy + exposure correction) • 1 trocar hernia VM: 18.2% (10/55) • 1 blood transfusion • 5 mesh exposure (vaginal estrogen therapy + mesh exposure correction) • 4 mesh contractions	LSC: 0% (0/53) VM 0% (0/55)	LSC: 0% (0/53) VM 0% (0/55)
Paraiso 2011 LSC vs RSC	LSC: 0% (0/33) RSC: 2.9% (1/35) • 1 corneal abrasion	LSC: 9.1% (3/33) • 3 urinary tract infection RSC: 28.6% (10/35) • 5 urinary tract infection • 2 wound infection • 3 abdominal wall pain necessitating trigger point injection	LSC: 9.1% (3/33) • 2 cystostomy • 1 abscess RSC: 22.9% (8/35) • 2 cystostomies • 1 enterotomy • 2 small bowel obstruction • 2 mesh exposure (one was from tension-free vaginal tape) • 1 abscess	LSC: 0% (0/33) RSC: 0% (0/40)	LSC: 0% (0/33) RSC: 0% (0/40)
Halaska 2012 SSF vs VM	SSF: 2.7% (2/73) • 2 dyspareunia • 3 pelvic pain VM: 0% (0/79)	SSF: 6.9% (5/73) • 5 LUT infections VM: 8.9% (7/79) • 1 LUT infection • 6 mesh exposure (treatment: estrogen therapy)	SSF: 9.6% (7/73) • 1 bladder perforation • 6 severe bleeding VM: 31.6% (25/79) • 3 bladder perforation • 10 severe bleeding • 1 hematoma • 1 abscess • 10 mesh exposure treated by surgical resection	SSF: 0% (0/73) VM: 0% (0/79)	SSF: 0% (0/73) VM: 0% (0/79)
Svabik 2014 SSF vs VM	SSF: 0% (0/34) VM: 2.8% (1/36) • 1 mesh exposure, treated conservatively	SSF: 0% (0/34) VM: 0% (0/36)	SSF: 0% (0/34) VM: 5.6% (2/36) • 2 mesh exposure, resected during TVT-O procedure	SSF: 0% (0/34) VM: 0% (0/36)	SSF: 0% (0/34) VM: 0% (0/36)

ASC = abdominal sacrocolpopexy, LSC = laparoscopic sacrocolpopexy, SSF = sacrospinous fixation, RSC = robotic sacrocolpopexy, VM = total vaginal mesh

*Grade 1: requires no treatment; grade 2: requires drug therapy; grade 3: requires a procedure or intervention; grade 4: IC/ICU organ or system dysfunction; grade 5: death

Table 7: follow-up results after one year

Author	Maher 2004	Culligan 2005	Tate 2011	Freeman 2013	Coolen 2017	Maher 2011	Paraiso 2011	Halaska 2012	Svabik 2014
Comparison	ASC vs SSF	ASC: fascia vs polypropylene	ASC: fascia vs polypropylene	ASC vs LSC	ASC vs LSC	LSC vs VM	LSC vs RSC	SSF vs VM	SSF vs VM
POP-Q point C	Vault to/beyond hymen: ASC: 2 (4%) SFF: 8 (19%)	No difference	Fascia: -8.1 (SD 2.7) Mesh: -9.0 (SD 1.2)	LSC: -6.65 (SD 1.19) ASC: -6.63 (SD 1.35)	LSC: -6.5 (SD 1.6) ASC: -6.7 (SD 1.9)	LSC: -7.48 (SD 2.62) VM: -6.11 (SD 2.72)	LSC: -10 (range -11 to -5) RSC: -9 (range -11 to -6)	SSF: -4.94 VM: -5.99	SSF: -3.2 (SD 3.56) VM: -6.2 (SD 1.29)
POP-Q stage<2	*ASC: 35/46 (76%) SSF: 29/42 (69%)	‡Fascia: 30/44 (61%) Mesh: 41/45 (91%)	‡Fascia: 18/29 (62%) Mesh: 27/29 (93%)	not mentioned	LSC: 21/29 (72%) ASC: 19/29 (66%)	LSC: 41/53 (77%) VM: 23/55 (43%)	not mentioned	SSF: 61% VM: 83%	∫SSF: 35% VM: 97%
Re-operations for POP	ASC: 1/47 (2%) SSF: 3/48 (6%)	not mentioned	Fascia: 1/46 (2%) mesh: 1/54 (2%)	LSC :1/26 (4%) ASC: 0/27 (0%)	LSC: 4/37 (11%) ASC: 1/37 (3%)	LSC: 0/53 (0%) VM: 3/55 (5%)	not mentioned	SSF: 4/83 (5%) VM: 1/85 (1%)	SSF: 3/34 (9%) VM: 0/36 (0%)
Mesh exposure	not mentioned	not mentioned	Fascia: 1/54 (2%) Mesh: 1/54 (2%)	LSC: 0/26 (0%) ASC: 0/27 (0%)	LSC: 0/37 (0%) ASC: 0/37 (0%)	LSC 1/53 (2%) VM 7/55 (13%)	LSC: 0/38 (0%) RSC: 2/40 (5%)	VM: 16/79 (21%)	VM: 3/36 (8%)
Dyspareunia	ASC: 9 (20%) SSF: 9 (19%)	not mentioned	not mentioned	no difference	no difference according to questionnaire	no difference according to questionnaire	not mentioned	no difference	SSF: 1/36 (3%) VM: 2/34 (6%)
De novo incontinence	SUI: ASC: 2/22 (9%) SSF: 8/24 (33%)	not mentioned	not mentioned	Any incontinence: LSC: 2/26 (8%) ASC: 4/27 (15%)	UUI: LSC: 2/37 (5%) ASC: 3/37 (8%) SUI: LSC 5/37 (14%) ASC 4/37 (11%)	not mentioned	not mentioned	no difference	SUI: SSF: 3/36 (8%) VM: 13/34 (38%)

ASC = abdominal sacrocolpopexy, LSC = laparoscopic sacrocolpopexy, SSF = sacrospinous fixation, RSC = robotic sacrocolpopexy, VM = total vaginal mesh
UUI = urge urinary incontinence, SUI = stress urinary incontinence. * Baden Walker grade 2, ‡= ≤ POP-Q stage 2, ∫= Ba, C of Bp to above hymen

Appendix 3. Characteristics of included studies; systematic assessment

Maher 2004

Methods	Multi-centre (2 sites, Australia), RCT. 2-year follow-up
Participants	Inclusion criteria: women with symptomatic posthysterectomy vaginal vault prolapse that extended to or beyond the introitus. Exclusion criteria: women who had undergone a previous sacrocolpopexy or had a significantly foreshortened vagina.
Interventions	Abdominal sacrocolpopexy with Prolene mesh (N=47) versus vaginal sacrospinous colpopexy (N=48)
Outcomes	Primary and secondary outcomes were not specified. Outcomes: - subjective success (no symptomps of prolapse); - objective success (no vaginal prolapse ≥ grade 2 Baden Walker classification at any vaginal site during a Valsalva maneuver); - patient satisfaction on a visual analog scale (VAS) from 0 to 100 - SUI - overactive bladder - voiding dysfunction - constipation - obstructed defecation - fecal incontinence - sexual activity - dyspareunia - quality of life: SF-36, UDI, IIQ - re-interventions due to complications - complications - costs (US dollars)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Once agreeing to participate in the study, women were randomly allocated to the vaginal or the abdominal approach. Women with SUI were stratified to ensure equal representation in each group. Randomization lists were computer generated and held by the nonsurgical co-author.
Allocation concealment (selection bias)	High risk	Not described.
Blinding of participants and personnel (performance bias) *All outcomes*	High risk	Not described.
Blinding of outcome assessment (detection bias) *All outcomes*	High risk	Not described.
Incomplete outcome data (attrition bias)	High risk	7% of the women did not complete meaningful follow-up and approximately

All outcomes		10% did not complete full review. Reasons for loss to follow-up not described.
Selective reporting (reporting bias)	Low risk	No selective outcome reporting.
Other bias	Not applicable	None.

Culligan 2005

Methods	Single-centre (USA), RCT. 1-year follow-up
Participants	Inclusion criteria: women with posthysterectomy vaginal vault prolapse scheduled for sacrocolpopexy through the Division of Urogynaecology and Reconstructive Pelvic Surgery at the University of Louisville Health Sciences Center. Exclusion criteria: not described.
Interventions	Abdominal sacrocolpopexy with cadaveric fascia lata (N=50) or polypropylene mesh (N=50)
Outcomes	Primary outcome: anatomic failure (prolapse ≥ POP-Q stage II) Secondary outcomes: - subjective outcome (quality of life, PISQ, ISI, constipation severity score, defecation diary, pain); not described in results - complications

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computerized blocked randomization scheme (using blocks of 8) was constructed to determine the type of material that would be used for the sacrocolpopexy.
Allocation concealment (selection bias)	Low risk	The researchers received only a stack of 104 opaque, numbered, sealed envelopes, each containing the assignment for the subject number on the outside of the envelope. Each patient's envelope was opened immediately before her surgery.
Blinding of participants and personnel (performance bias) *All outcomes*	Low risk	The following procedures were used to maintain the double-blinding within the study: the actual material used for a given colpopexy appeared in only 2 places: the dictated operative note and the master list of the randomization scheme. The master list for the randomization scheme generated was held by the statistician. All patients were made aware of the importance of their not knowing which material had been used for their surgery. During each surgery, members of the surgical team were reminded not to reveal the nature of the material used to the patient.
Blinding of outcome assessment (detection bias) *All outcomes*	Low risk	To avoid the possibility of patient steering, the researchers were unaware of the block size. The certified clinical research nurse who

		collected all of the data throughout the study period did not have access to the dictated operative notes or the master list of the randomization scheme.
Incomplete outcome data (attrition bias) *All outcomes*	Unclear	Although the randomization scheme called for an even 50/50 breakdown, there were 46 patients who received fascia and 54 who received polypropylene mesh. The reason for the discrepancy was that 4 patients randomized to receive fascia were actually given mesh because of a transient shortage of the Tutoplast material. A total of 89 patients (45 in the mesh group and 44 in the fascia group) returned for their 1-year follow-up visits. No reasons for loss to follow-up mentioned.
Selective reporting (reporting bias)	Low risk	No selective outcome reporting.
Other bias	High risk	Data presentation unclear, selective reporting of subjective outcome, complication minimally reported, re-interventions not reported.

Maher 2011

Methods	Single-centre (Australia), RCT. 2-year follow-up
Participants	Inclusion criteria: consecutive women referred to Wesley, Royal Brisbane's and Mater tertiary referral Urogynaecology unit with symptomatic stage 2 or greater (point C ≥ -1 POP-Q) vaginal vault prolapse. Exclusion criteria: - age < 18 years - inability to comprehend questionnaires, to give informed consent or to return for review - vault prolapse < stage 2 - unable to undergo general anesthesia - BMI >35 - 5 previous laparotomies - prior sacrocolpopexy or vaginal mesh prolapse procedure - vaginal length < 6 cm
Interventions	Laparoscopic sacrocolpopexy (N=53) versus total vaginal mesh with Total Prolift (Gynecare, Ethicon) (N=55)
Outcomes	Primary outcome: objective success rates at POP-Q sites Aa, Ba, C, Bp and Ap defined as less than -1 cm individually and as a total. Secondary outcomes: - patient satisfaction (VAS) - quality of life (Australian Pelvic Floor Questionnaire (APFQ), Kings College Pelvic Organ Prolapse quality of life (P-QoL) - complications - reoperations

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	After completion of study consent, research support staff were telephoned and allocation to the laparoscopic or vaginal surgery group from randomization list that were computer generated by the study statistician, stratified for urodynamic stress incontinence (SUI and occult SUI) with full allocation concealment, was completed.
Allocation concealment (selection bias)	Unclear	Method of allocation concealment not described.
Blinding of participants and personnel (performance bias) *All outcomes*	Unclear	Full allocation concealment. Other blinding not described.
Blinding of outcome assessment (detection bias) *All outcomes*	High risk	Not described.
Incomplete outcome data (attrition bias) *All outcomes*	Unclear	Described in the randomized trial flow diagram. No reasons for loss to follow-up described.
Selective reporting (reporting bias)	Low risk	No selective outcome reporting.
Other bias	Not applicable	None.

Paraiso 2011

Methods	Single-centre (USA), RCT. 1-year follow-up
Participants	Inclusion criteria: - posthysterectomy vaginal apex prolapse at Pelvic Organ Prolapse Quantitative stages 2–4 - age ≥ 21 years - desired laparoscopic surgical management Exclusion criteria: - contra-indication for general anesthesia - history of prior sacrocolpopexy - suspicious adnexal masses - history of pelvic inflammatory disease - morbid obesity (BMI ≥ 40) - history of prior or concomitant surgery for rectal prolapse
Interventions	Laparoscopic sacrocolpopexy (N=38) versus robot-assisted sacrocolpopexy (N=40)
Outcomes	Primary outcome: time from initial incision to skin closure (total operative time) Secondary outcomes: - total time the patient was in the operating room (operative room time) - time that the patient was under anesthesia from beginning of induction to extubation (anesthesia time) - time for specific parts of the case including robotic cart docking (docking time only

	applicable to robot) - complications - pain scale (visual analog scale, amount of narcotic and NSAIDs used during hospitalization - activity scale (Activity Assessment Scale, return to normal activities (visual analog scale)) - anatomic outcome (POP-Q) - quality of life (PFDI-20, PFIQ-7, PISQ, EQ-5D) - costs (US dollars)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Particpants were assigned randomly in a 1:1 ratio to one of two treatment groups. Treatment allocation was determined by a computer-generated randomization schedule with random block sizes (two to six) and stratified by surgeon.
Allocation concealment (selection bias)	Low risk	Treatment assignments were placed in consecutively numbered, opaque-sealed envelopes that were opened by the surgery scheduler immediately before scheduling the case because each procedure required different equipment that needed to be known before the day of surgery (on average this occurred 42 days before surgery).
Blinding of participants and personnel (performance bias) *All outcomes*	Low risk	Patients were blinded to their treatment assignment. Operating room and healthcare providers responsible for intraoperative and postsurgical care were informed not to discuss treatment assignment during the preoperative discussion or the postoperative period.
Blinding of outcome assessment (detection bias) *All outcomes*	Low risk	Research staff administering and collecting the study questionnaires and outcomes were blinded to the participant's treatment group for the entire duration of the study.
Incomplete outcome data (attrition bias) *All outcomes*	Unclear	Follow-up displayed in flow chart. Not a lot of loss to follow-up, but reasons for loss to follow-up are not described.
Selective reporting (reporting bias)	Low risk	No selective outcome reporting.
Other bias	Not applicable	None.

Tate 2011

Methods	Single-centre (USA), RCT. 5-year follow-up of Culligan 2005.
Participants	Inclusion criteria: women with post hysterectomy vaginal vault prolapse scheduled for abdominal sacrocolpopexy through the Division of Urogynaecology and

	Reconstructive Pelvic Surgery at the University of Louisville Health Sciences Center. Exclusion criteria: not described.
Interventions	Initial trial of Culligan 2005: abdominal sacrocolpopexy with cadaveric fascia lata (N=50) or polypropylene mesh (N=50). 5-year follow-up: cadaveric fascia lata (N=29) and polypropylene mesh (N=29).
Outcomes	Primary outcome: anatomic failure (prolapse ≥ POP-Q stage II) Secondary outcomes: - clinical relevant success, defined as a combination of a subjective component (no bulge or prolapse symptoms), an anatomic component (prolapse < POP-Q stage II) and the need for surgical re-treatment of pelvic organ prolapse - subjective outcome (interview by research nurse; quality of life, PISQ, ISI, constipation severity score, defecation diary, pain) - re-treatment (interview by research nurse) - complications

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	As previously reported, a computerized blocked randomization scheme (using blocks of 8) was constructed to determine the type of material that would be used for the sacrocolpopexy. The master list for the randomization scheme was held by the statistician.
Allocation concealment (selection bias)	Low risk	The researchers received opaque, numbered, sealed envelopes, each containing the assignment for the subject number on the outside of the envelope. To avoid the possibility of patient steering, the researchers were unaware of the block size. Each patient's envelope was opened immediately before surgery.
Blinding of participants and personnel (performance bias) *All outcomes*	Low risk	The design of the study was a "double-blinded randomized study". Only the surgical team was aware of the subject's assignment to a graft type. Throughout the initial 1-year as well as the 5-year follow-up period, all preoperative and postoperative outcome measures for both studies were obtained by a single, masked, clinical research nurse. The subjects were told by the surgeon which material they received after they completed the 1-year follow-up period. At the time of the 5-year follow-up visit, the subjects were asked not to reveal the type of graft material that had been used. Therefore, the clinical research nurse remained masked despite the fact that subjects were aware of their material type at the 5-year point. The principal investigator for the 5-year study did not perform any of the original surgeries and

		was masked to the type of graft material used.
Blinding of outcome assessment (detection bias) *All outcomes*	Low risk	Described above.
Incomplete outcome data (attrition bias) *All outcomes*	High risk	Fifty-eight of the 100 subjects (58%) returned for their 5-year visit—29/54 from the polypropylene mesh group and 29/46 from the fascia lata group. Eleven of the 100 subjects (11%) returned only questionnaires and therefore were not included in any of the analyses due to their lack of POP-Q examinations at 5 years. Thirty-one subjects did not respond, declined participation, and were lost to follow-up or had died of causes unrelated to the surgery. The follow-up rate did not significantly differ between treatment groups. The subjects who did not return for the 5-year follow-up were slightly older (60±12 years) than those who returned for follow-up (58±9 years), but the difference was not significant (p=0.44).
Selective reporting (reporting bias)	High risk	Primary and secondary outcome measurements are described in the methods and the same measurements are shown in the results.
Other bias	High risk	Data presentation unclear, selective reporting of subjective outcome.

Halaska 2012

Methods	Multi-centre (Czech Republic), RCT. 1-year follow-up
Participants	Inclusion criteria: all patients scheduled for surgery for vaginal prolapse with objectively verified symptoms by POP-Q ≥ stage II. Exclusion criteria: - pelvic malignancy - age < 18 years - history of radiotherapy of the pelvis - requiring hysterectomy
Interventions	Sacrospinous fixation (N=83) versus transvaginal mesh (Prolift; Gynecare/Ethicon) (N=85)
Outcomes	Primary outcome: prolapse recurrence (prolapse ≥ POP-Q stage II) Secondary outcomes: - quality of life (PISQ, UIQ, CRAIQ, POPIQ) - complications - reoperations (for prolapse recurrences)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random allocation to surgery was performed by one person (O.S.) using a computer-generated random sequence of zeros and ones.
Allocation concealment (selection bias)	Unclear	Not described.
Blinding of participants and personnel (performance bias) *All outcomes*	High risk	Not described.
Blinding of outcome assessment (detection bias) *All outcomes*	High risk	Not described.
Incomplete outcome data (attrition bias) *All outcomes*	Low risk	Loss to follow-up and data analysis are clearly described in the study's flow chart.
Selective reporting (reporting bias)	Low risk	No selective outcome reporting.
Other bias	Unclear	Data presentation unclear.

Freeman 2013

Methods	Multi-centre (UK), RCT. 1-year follow-up
Participants	Inclusion criteria: patients with symptomatic and bothersome vault prolapse ≥ POP-Q grade II with or without concomitant cystocele and rectocele. Exclusion criteria: - medically unfit for sacrocolpopexy - requirement for concomitant pelvic or stress urinary incontinence surgery (those patients who had “occult” stress urinary incontinence, i.e. on prolapse reduction only, were not excluded) - BMI>35 - previous abdominal or vaginal vault prolapse surgery
Interventions	Abdominal sacrocolpopexy (N=27) versus laparoscopic sacrocolpopexy (N=26)
Outcomes	Primary outcome: - anatomic outcome: POP-Q point C - subjective outcome: Patient Global Impression of Improvement (PGI-I) Secondary outcomes: - operating time - the distance at which the mesh was attached down the anterior and posterior walls - blood loss, haemoglobin - the need for concomitant posterior repair - pain assessment (VAS, opiate use) - length of stay - convalescence - return to usual activities - quality of life (P-QOL, SF-36)

	- complications - new onset/occult urinary incontinence (Birmingham bowel and lower urinary tract symptoms questionnaire) - further surgery by 1 year

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomized to a particular surgeon, but the randomization was blocked to ensure similar numbers of patients for each surgeon/procedure. Randomization to either of the two surgical procedures was by computer allocation, co-ordinated by the study statistician. The allocation to this design was generated using Genstat (8th edition). Randomization took place after the patient had been placed on the appropriate consultant's waiting list and informed consent had been given (for both procedures).
Allocation concealment (selection bias)	Low risk	Described above.
Blinding of participants and personnel (performance bias) *All outcomes*	Unclear	It was not possible to fully "blind" the patient to the type of operation because of the incisions. However, the ward staff who supervised analgesic requirements were blinded. The operation note was placed in a sealed envelope in the patient's notes and was only to be opened in an emergency. The abdomen was "bandaged", as for ASCP, following both procedures until the day of discharge. This was aimed at preserving blinding when the post-operative assessments were carried out and was only to be broken if there were complications requiring removal of the bandage.
Blinding of outcome assessment (detection bias) *All outcomes*	Low risk	At the 12-week visit the POP-Q examination was performed by the research fellow or surgeon before any other assessments to minimize bias and maintain blinding. To achieve this, the patient was positioned in the left lateral position by the research nurse and the examining doctor then carried out the POP-Q assessment blind to the identity of the patient.
Incomplete outcome data (attrition bias) *All outcomes*	High risk	There is a patient flow, but the exclusions and loss to follow-up are not described.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcome measurements are described in the methods and the same measurements are shown in the results.
Other bias	Not applicable	None.

Svabik 2014

Methods	Single-centre (Czech Republic), RCT. 1-year follow-up
Participants	Inclusion criteria: - posthysterectomy patients with at least two-compartment prolapse (with affected apical/vault compartment, ≥ POP-Q stage II - suffering from symptoms of prolapse - requesting pelvic floor reconstructive surgery - diagnosed with a complete unilateral or bilateral avulsion injury Exclusion criteria: - patients with prolapse and uterus in place - patients without levator ani avulsion - patients not requesting pelvic floor surgery
Interventions	Sacrospinous vaginal colpopexy (N=34) versus transvaginal mesh (Prolift Total; Gynecare/Ethicon) (N=36)
Outcomes	Primary outcome: anatomic failure based on clinical and ultrasound assessment, defined as: - Ba, C or Bp at the hymen or below ánd - on translabial ultrasound as bladder descent to 10 mm or more below the lower margin of the symphysis pubis on maximum Valsalva Secondary outcomes: - continence status assessment (clinical stress test and subjective evaluation (ICIQ-SF, PISQ-12, POPDI, UDI, CRADI)) - complications - reoperations (SUI, prolapse recurrence)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	The randomization process was carried out by computer, using patient hospitalization numbers, the night before surgery. Patients were informed about their allocation after the procedure.
Allocation concealment (selection bias)	Unclear	Described above.
Blinding of participants and personnel (performance bias) *All outcomes*	High risk	Patients were informed about their allocation after the procedure.
Blinding of outcome assessment (detection bias) *All outcomes*	Low risk	These postoperative clinical examinations were performed by a single examiner, who had not been involved with the surgical procedures and was unaware of a patient's procedure at the start of the assessment, although in some cases group allocation became obvious due to palpable mesh, mesh erosion or visibility of an SSF suture.
Incomplete outcome data (attrition bias) *All outcomes*	High risk	There is a patient flow, but no details about the follow-up.
Selective reporting	Low risk	Primary and secondary outcome

(reporting bias)		measurements are described in the methods and the same measurements are shown in the results.
Other bias	Not applicable	None.

Coolen 2017

Methods	Multi-centre (The Netherlands), RCT. 1-year follow-up
Participants	Inclusion criteria: women with a history of hysterectomy presenting with symptomatic vaginal vault prolapse, with or without concomitant cystocele and rectocele, who choose to undergo surgery. Exclusion criteria: - previous surgical correction of a vault prolapse - contra-indication for a surgical intervention because of general physical condition
Interventions	Abdominal sacrocolpopexy (N=37) versus laparoscopic sacrocolpopexy (N=37)
Outcomes	Primary outcome: functional outcome (UDI) Secondary outcomes: - other subjective outcomes (DDI, IIQ, PGI-I, questions about sexuality) - peri-operative outcomes (procedure time, blood loss, hospital stay, complications, re-interventions (incontinence, prolapse)) - anatomical outcome (POP-Q) - composite outcome of success, defined as no prolapse beyond the hymen, no bothersome bulge symptoms, no repeat surgery or pessary use for recurrent prolapse within 12 months

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	After written informed consent was given, randomization was performed by an independent research secretariat located in Amsterdam after a phone call or e-mail by the coordinating investigator. The treatment allocation was done by opaque sealed envelopes in a 1:1 ratio to either LSC or ASC. Women received a case number at randomization to treat their data anonymously.
Allocation concealment (selection bias)	Low risk	Described above.
Blinding of participants and personnel (performance bias) *All outcomes*	High risk	Participants and physicians were not blinded for the intervention, as blinding is impossible between the very different types of incision.
Blinding of outcome assessment (detection bias) *All outcomes*	High risk	Observers and physicians were not blinded for the intervention.The observer was an independent researcher, who had not performed the surgery.
Incomplete outcome data (attrition bias)	Low risk	At 12 months follow up there were 14 questionnaires missing, of which 11

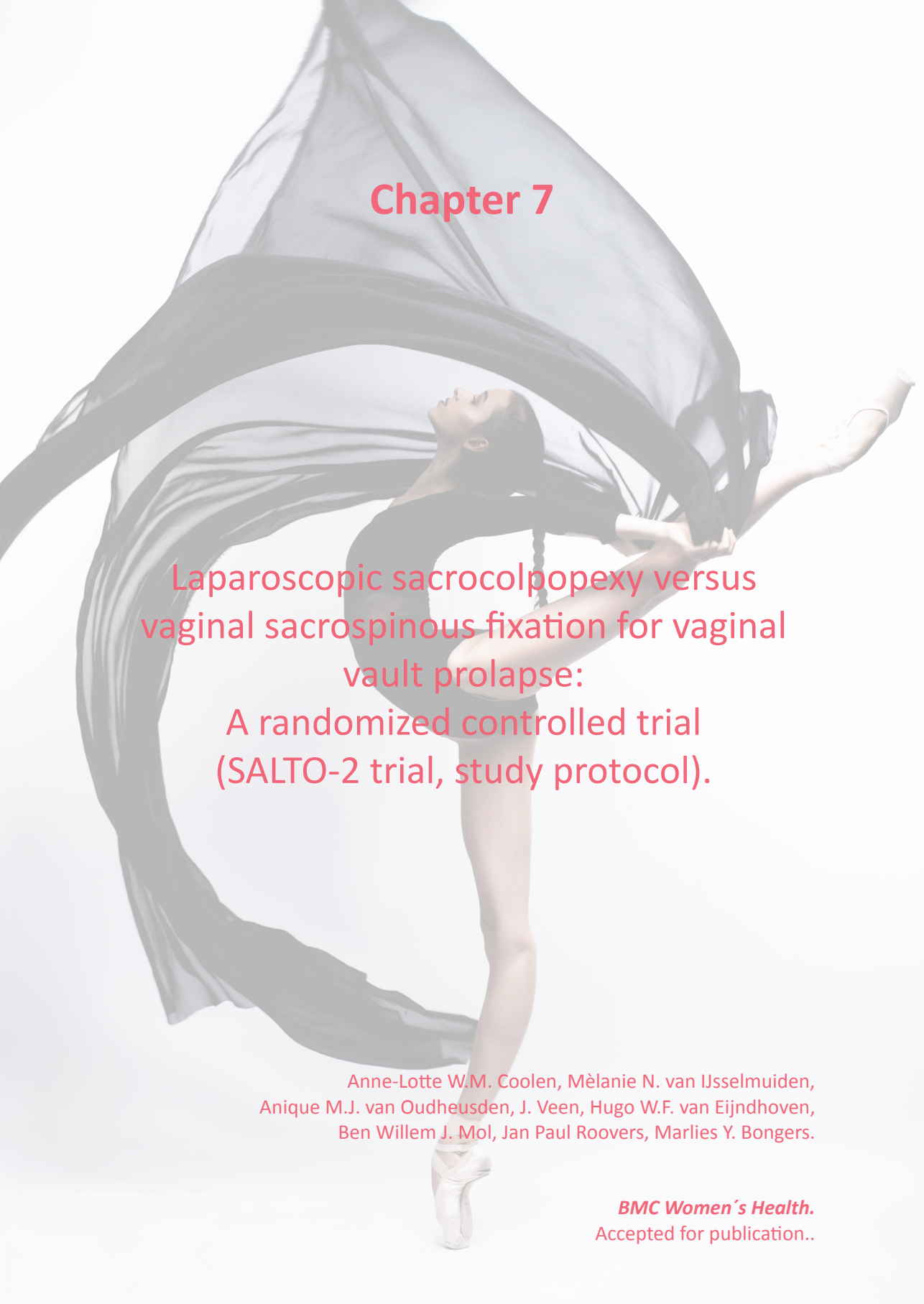
All outcomes		participants (15.5%) were unwilling to complete the questionnaires, two did not receive the intervention and one patient died five days after the intervention due to a complication of the intervention. The number of missing questionnaires is equal in both groups. All non-responders were contacted by telephone and most of them explained that they were doing excellent which was a reason not to return the questionnaires. Patient characteristics of responders and non-responders were comparable.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcome measurements are described in the methods and the same measurements are shown in the results.
Other bias	Not applicable	None.

References

1. J.P. Roovers, E.Everhardt, V.Dietz, F.Milani et al. Richtlijn prolapse van de nederlandse vereniging obstetrie en gynaecologie. Dutch Society of Obsetrics and Gynaecology. www.nvog.nl. (2017)
2. Dällenbach P, Kaelin-Gambirasio I, Jacob S, Dubuisson JB, Boulvain M, Incidence rate and risk factors for vaginal vault prolapse repair after hysterectomy. Int Urogynecol J Pelvic Floor Dysfunct (2008) 19(12):1623–1629.
3. J.O.L. Delancey, Anatomic aspects of vaginal eversion after hysterectomy, AJOG, (1992) 166 (6), part 1, 1717-1728.
4. R.J. Detollenaere, J.den Boon, M.E. Vierhout, H.W.F. van Eijndhoven, Uterussparende chirurgie versus vaginale hysterectomie als behandeling van descensus uteri, Ned.Tijdschr.Geneesk. (2011) 155:A3623
5. A.J. Woodruff, C.R. Christopher, J.C. Winters.Abdominal Sacral Colpopexy: Surgical Pearls and Outcomes. Female Urology. (2007) 8:399-404.
6. C. Maher, Surgery for women with apical vaginal prolapse, Cochrane Database Syst Rev. (2016) 1;10
7. Jia 2010. Systematic review of the efficacy and safety of using mesh in surgery for uterine or vaginal vault prolapse, Int Urogynecol J, (2010) 21 (11): 1413-31
8. Toozs-Hobson P, Boos K, Cardozo L et.al (1998). Management of vaginal vault prolapse. Br J Obstet Gynecol, (1998) 105(10): 1127-8
9. A.Uzoma, K.A. Farag, Vaginal vault prolapse (2009) obestrics and gynecology international
10. R.C. Bump, A. Mattiasson, K. Bø, L.P. Brubaker LP, DeLancey JO, Klarskov P, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol. (1996) 175(1):10–17.
11. Baden WF, Walker TA, Genesis of the vaginal profile: a correlated classification of vaginal relaxation. Clin Obstet Gynecol (1972) 15(4):1048–1054
12. D.Dindo, N. Demartines, P.Clavien. Classification of surgical complications. A new proposal with evaluation in a cohort of 6336 patients and results of survey. Ann Surg. (2004) 240: 205-13.
13. Liberati, D.G. Altman, et.al, The PRiSMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration, BMJ (2009) 339:b2700
14. Higgins, et.al, Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Collaboration. (2011) Version 5.1.0
15. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. (2013) 3;8(10):e76654.
16. Coolen ALWM, van Oudheusden AMJ, Mol BWJ, van Eijndhoven HWF, Roovers JWR, Bongers MY, Laparoscopic sacrocolpopexy compared with open abdominal sacrocolpopexy for vault prolapse repair: a randomised controlled trial. Int Urogynecol J. (2017) [Epub ahead of print]
17. R. M. Freeman, K. Pantazis, A. omson et al., "A randomized controlled trial of abdominal versus laparoscopic sacrocolpopexy for the treatment of post-hysterectomy vaginal vault prolapse: LAS study," International Urogynecology Journal and Pelvic Floor Dysfunction (2013) 24 (3); 377–384.
18. Tate SB, Blackwell L, Lorenz DJ, Steptoe MM, Culligan PJ. Randomized trial of fascia lata and polypropylene mesh for abdominal sacrocolpopexy: 5-year follow-up.Int Urogynecol J. (2011) 22(2):137-43
19. Culligan PJ, Blackwell L, Goldsmith LJ, Graham CA, Rogers A, Heit MH. A randomized controlled trial comparing fascia lata and synthetic mesh for sacral colpopexy. Obstet Gynecol. (2005) 106(1):29-37.

20. Maher CF, Qatawneh AM, Dwyer PL, Carey MP, Cornish A, Schluter PJ. Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse: a prospective randomized study. Am J Obstet Gynecol. (2004) 190(1):20-6.
21. Halaska M, Maxova K, Sottner O, Svabik K, Mlcoch M, Kolarik D, Mala I, Krofta L. A multicenter, randomized, prospective, controlled study comparing sacrospinous fixation and transvaginal mesh in the treatment of posthysterectomy vaginal vault prolapse. Am J Obstet Gynecol. (2012) 207(4):301.e1-7
22. Svabik K, Martan A, Masata J, El-Haddad R, Hubka P.Comparison of vaginal mesh repair with sacrospinous vaginal colpopexy in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion: a randomized controlled trial, Ultrasound Obstet Gynecol (2014) 43: 365–371
23. Christopher F. Maher, Benjamin Feiner, Eva M. DeCuyper, Cathy J. Nichlos, Kacey V. Hickey, Peter O'Rourke, Laparoscopic sacral colpopexy versus total vaginal mesh for vaginal vault prolapse: a randomized trial, AJOG (2011) 204: 360.e1-7.
24. Paraiso MF, Jelovsek JE, Frick A, Chen CC, Barber MD. Laparoscopic compared with robotic sacrocolpopexy for vaginal prolapse: a randomized controlled trial.Obstet Gynecol. (2011) 118(5):1005-1
25. Bernard T. Haylen, Christopher F. Maher, Matthew D. Barber, Sérgio Camarg0, et al, An International Urogynecological Association (IUGA) / International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapse (POP), Int Urogynecol J (2016) 27:165–194
26. Barber MD, Burbaker L, Nygaard I, Wheeler TL, Schaffer J, Chen Z, Spino C. Defining Success After Surgery for Pelvic Organ Prolapse, Obstet Gynecol. (2009) 114 (3): 600-9.
27. Kowalik CR, Lakeman MM, Oryszczyn JE, Roovers JO. Reviewing patients following mesh repair; the benefits, Gynecol Obstet Invest. (2016)
28. Stanford EJ, Moore RD, Roovers JP et.al. Elevate and uterine preservation: two-year results. Female Pelvic Med Renconstr Surg. (2015) 21 (4): 205-10.
29. Dietz V, Schraffordt Koops SE, van der Vaart CH, Vaginal surgery for uterine descent; which options do we have? A review of the literature. International Urogynecology Journal and Pelvic Floor Dysfunction (2009) 20:349–356
30. Roovers JP, van der Vaart CH, van der Bom JG, van Leeuwen JH, Scholten PC, Heintz AP. A randomised controlled trial comparing abdominal and vaginal prolapse surgery: effects on urogenital function. Br J Obstet Gynaecol (2004) 111: 50-56.
31. Altman D, Väyrynen T, Engh ME, Axelsen S, Falconer C Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med. (2011) 12;364(19):1826-36.
32. Glazener CM, Breeman S, Elders A, Hemming C, Cooper KG, Freeman RM, Smith AR, Reid F, Hagen S, Montgomery I, Kilonzo M, Boyers D, McDonald A, McPherson G, MacLennan G, Norrie J, Mesh, graft, or standard repair for women having primary transvaginal anterior or posterior compartment prolapse surgery: two parallel-group, multicentre, randomised, controlled trials (PROSPECT). Lancet. (2017) 28;389(10067):381-392
33. Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Brown J, Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database Syst Rev. (2016) 1;10
34. I. Nygaard, L. Burubaker, Long-term Outcomes Following Abdominal Sacrocolpopexy for Pelvic Organ Prolapse, JAMA (2013), 309 (9); 2016-2024
35. Abdool Z, Thakar R, Sultan AH, Oliver RS, Prospective evaluation of outcome of vaginal pessaries versus surgery in women with symptomatic pelvic organ prolapse. International Urogynecology Journal and Pelvic Floor Dysfunction (2010) 22(3):273-8.
36. Subramanian D, Szwarcensztein K, Mauskopf JA, Slack MC, Rate, type, and cost of pelvic organ prolapse surgery in Germany, France, and England. Eur J Obstet Gynecol Reprod Biol (2009) 144(2):177– 181.

37. Deprest J, Krofta L, Van der Aa F, Milani AL, Den Boon J, Claerhout F, Roovers JP. The challenge of implementing laparoscopic sacrocolpopexy. Int Urogynecol J. (2014) 25(9):1153-60
38. Deprest J, Roovers JP. The challenge of implementing laparoscopic sacrocolpopexy. International Urogynecology Journal. (2014) 25:1153–1160.
39. Fernando RJ, Thakar R, Sultan AH, Shah SM, Jones PW, Effect of vaginal pessaries on symptoms associated with pelvic organ prolapse. Obstet Gynecol (2006) 108(1):93–99
40. Davila GW, Ghoniem GM, Kapoor DS, Contreras-Ortiz O. Pelvic floor dysfunction management practice patterns: asurvey of members of the International Urogynecological Association. International Urogynecology Journal and Pelvic Floor Dysfunction (2002) 13(5):319-25.



Chapter 7

Laparoscopic sacrocolpopexy versus vaginal sacrospinous fixation for vaginal vault prolapse: A randomized controlled trial (SALTO-2 trial, study protocol).

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Abstract

Background Hysterectomy is one of the most performed surgical procedures during lifetime. Almost ten percent of women who have had a hysterectomy because of prolapse symptoms, will visit a gynaecologist for a surgical correction of a vaginal vault prolapse thereafter. Vaginal vault prolapse can be corrected by many different surgical procedures. A Cochrane review comparing abdominal sacrocolpopexy to vaginal sacrospinous fixation considered the open abdominal procedure as the treatment of first choice for prolapse of the vaginal vault, although operation time and hospital stay is longer. Literature also shows that hospital stay and blood loss are less after a laparoscopic sacrocolpopexy compared to the abdominal technique.

To date, it is unclear which of these techniques leads to the best operative result and the highest patient satisfaction. Prospective trials comparing vaginal sacrospinous fixation and laparoscopic sacrocolpopexy are lacking. The aim of this randomized trial is to compare the disease specific quality of life of the vaginal sacrospinous fixation and laparoscopic sacrocolpopexy as the treatment of vaginal vault prolapse.

Methods We will perform a multicentre prospective randomized controlled trial. Women with a post-hysterectomy symptomatic, POP-Q stage ≥ 2, vaginal vault prolapse will be included. Participants will be randomized to the vaginal sacrospinous fixation group or the laparoscopic sacrocolpopexy group.

Primary outcome is disease specific quality of life at 12 months follow-up. Secondary outcome will be the effect of the surgical treatment on prolapse related symptoms, sexual functioning, procedure related morbidity, hospital stay, post-operative recovery, anatomical results using the POP-Q classification after one and five years follow-up, type and number of re-interventions, costs and cost-effectiveness. Analysis will be performed according to the intention to treat principle and not as a per protocol analysis. With a power of 90% and a level of 0.05, the calculated sample size necessary is 96 patients. Taking into account 10% attrition, a number of 106 patients (53 in each arm) will be included.

Discussion The SALTO-2 trial is a randomized controlled multicentre trial to evaluate whether the laparoscopic sacrocolpopexy or vaginal sacrospinous fixation is the first-choice surgical treatment in patients with a stage ≥2 vault prolapse.

Trial registration number: Dutch trial register NTR3977

Background

Hysterectomy is one of the most performed surgical procedures during a women's lifetime. Almost 10% of women who have had a hysterectomy because of prolapse symptoms, will visit a gynaecologist for a surgical correction of a vaginal vault prolapse (VVP) thereafter. VVP can be corrected by many different surgical procedures. These symptoms are directly related to the prolapse and contain of pelvic pressure, bulging of the vaginal wall, dropping sensation in the vagina or backache. Other symptoms that are often present, are symptoms of the bladder, bowel and sexual problems[1]. These symptoms could affect the quality of life of these women severely. Therefore, an effective treatment is required.

The incidence of post-hysterectomy VVP requiring surgical treatment, has been estimated at 36 per 10,000 person-years[2]. The longer the time after hysterectomy, the higher the risk of vault prolapse. If the initial reason for hysterectomy was genital prolapse the risk increases significantly[1,2,3]. Women tend to get older and older and due to this improved life expectancy, there will be an enormous extra demand for future prolapse surgery.

Surgery for pelvic organ prolapse, including VVP, focuses on the correction of the normal anatomy of the vagina, resulting in normal function of the bladder and bowel. To date, a variety of surgical interventions to treat VVP surgically have been described[4]. These procedures can be performed vaginally or abdominally. The abdominal route can be performed as an open or laparoscopic sacrocolpopexy (LSC). The vaginal approach includes the vaginal sacrospinous fixation (VSF), which was first reported in 1958[5]. This is probably the most performed treatment modality of VVP at the moment. In a questionnaire of the International Urogynaecological Association (IUGA), which was performed in 2002, VSF was the most performed surgical correction for the VVP, as 78% of the responders reported the VSF as the first-choice treatment for VVP[6]. The LSC technique was developed in the footsteps of the abdominal sacrocolpopexy, and has, been implemented since then[7].

No randomized controlled trials comparing VSF and LSC have been performed. A Cochrane review shows that abdominal sacrocolpopexy is better compared to VSF. The recurrence rate of VVP was lower after an abdominal sacrocolpopexy (RR 0.23, 95% CI 0.07 to 0.77) and dyspareunia was less (RR) 0.39, 95% CI 0.18 to 0.86). However, the rates of recurrence surgery for prolapse show no statistical difference (RR 0.46, 95% CI 0.19 to 1.11). The VSF has a shorter operation time, lower costs and an earlier return to daily activities[8]. In none of the included studies disease specific quality of life was the primary outcome. Furthermore, in some of the studies no power analysis was done.

A cohort study comparing laparoscopic to abdominal sacrocolpopexy shows a significant reduction in hospitalization (1.8 ± 1.0 days vs 4.0 ± 1.8 days; $p < 0.0001$)[9]. A prospective cohort study comparing

laparoscopic to abdominal sacrocolpopexy that we performed prior to this study revealed a significant reduction in blood loss (77 ml (±182) versus 192 ml (±126) respectively, p= <.001) and hospital stay (2.4 days versus 4.2 days respectively, p= <.001) and less procedure related morbidity (RR 0.24 (95%-CI 0.07-0.80), p=0.009)[10].

The laparoscopic procedure seems to have advantages over the abdominal procedure

Since prospective trials comparing VSF and LSC sacrocolpopexy are lacking we plan to perform a RCT. The aim of this randomized trial is to compare the disease specific quality of life of the VSF and LSC as the treatment of VVP.

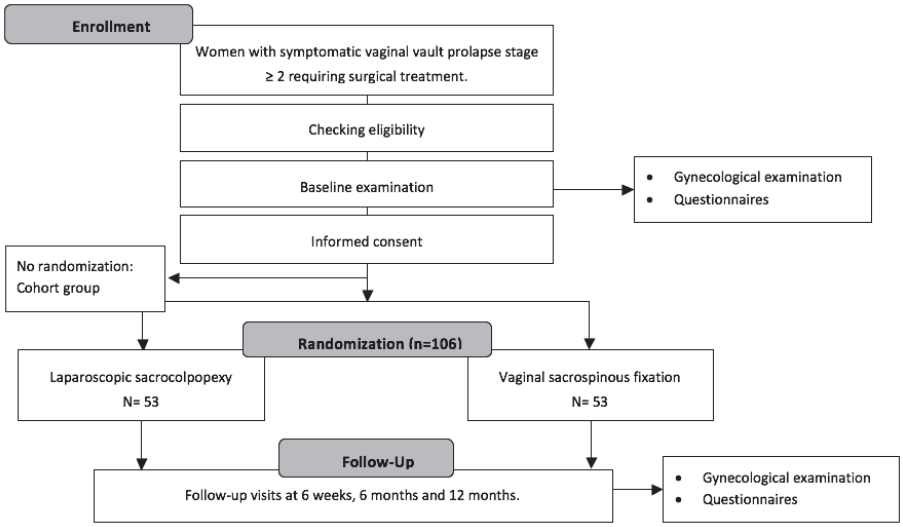
Methods / study design

Study design

The SALTO-2 trial is a randomized controlled multicentre trial and will be performed to compare VSF versus LSC for VVP. The follow-up time will be one and five years.

The trial will be a non-blinded trial, since it is impossible to blind the participating women and medical staff for the allocated technique, since one procedure will be performed vaginally and the other one laparoscopically, leaving small abdominal scars. However, a physician blinded for the intervention will perform follow-up examination. This will be another physician than the surgeon who performed the operation. The study design is presented in figure 1.

Figure 1: Study design



Objectives

The objective of this study is to determine whether LSC in women with vault prolapse, POP-Q stage 2 or higher, improves outcome in terms of disease specific quality of life, recurrence of prolapse, complications, hospital stay, post-operative recovery, sexual functioning, costs and costs-effectiveness, compared to VSF.

Hypothesis

Based on the literature, we expect that the LSC will be equally or more successful in correction of vault prolapse and its related disease specific quality of life as compared to VSF.

Participating hospitals

The trial will be performed in several teaching and academic hospitals in the Netherlands. The nine participating centres are Máxima Medical Centre, Isala Clinics, Spaarne Gasthuis, Catharina Hospital, Maastricht Academic Hospital, Gelre Hospital, Radboud Academic Hospital, Sint Lucas Andreas Hospital, VU Medical Centre and Martini Hospital. Before the start of the trial, a masterclass was organised to reach consensus on the details of operation technique of the LSC and VSF and evaluate the operation skills of the participating surgeons. All participating gynaecologists performed at least twenty-five procedures before the beginning of the trial to exclude a learning curve.
During this master class, which was attended by many experienced surgeons, several surgical steps of both procedures were discussed (for the sacrocolpopexy: type of mesh, type of sutures, number of sutures, dissection technique, re-peritonealisation, (no) obliteration of Douglas pouch. For the VSF: (no) hydro dissection type and number of sutures, concomitant prolapse surgery). Decisions which techniques should be used were made and recorded to reduce practice variation as much as possible and to carry out a uniform operation technique during the inclusion period.

Study population and recruitment

All patients with a symptomatic post-hysterectomy VVP stage 2 or higher (according to POP-Q classification) who need surgical treatment are eligible for the study.

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Symptomatic vault prolapse POP-Q ≥ stage 2 which needs surgical treatment
- Eligible for both surgical treatments
- Patients must be able to read Dutch

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Previous surgical treatment of vault prolapse
- Contra-indication for a surgical intervention
- Incapacitated patients, illiterate patients or patients with other language barriers

Patients with co-existing anterior/posterior defects or concomitant incontinence surgery can be included. Patients need to agree to return the questionnaires and visit the follow-up appointments.

Patients who don't want to participate in the trial because of a preference for one of both surgical options will be asked for a cohort group and requested to complete the questionnaires as well. This cohort group will be compared to the study population to analyse whether a patients preference will affect the quality of life.

Assessment for eligibility will be performed by a gynaecologist of the participating hospital. Women eligible for this trial will be counselled for the trial. Subsequently, written patient information is provided, which contains information on the objectives, design, methods, possible advantages and disadvantages of the study treatments, and information that non-co-operation with the study or withdrawal will not have consequences for their treatment. Before randomization, written informed consent will be obtained.

Interventions

Vaginal sacrospinous fixation

The patient is placed in lithotomy position. The sacrospinous ligament will be accessed through an incision following the length of the posterior vaginal wall, extending up to the vaginal vault. Blunt dissection is used to open the right pararectal space and locate the ischial spine. A 'window' is created through the rectal pillar, large enough for two fingers. Just lateral to the rectum and above the puborectal muscle, the right sacrospinous ligament-coccygeus muscle complex will be exposed. Three Breisky specula will be positioned, whereafter two Prolene 1-0 sutures will be placed under direct vision. These two permanent non-absorbable sutures will be put into the sacrospinous ligament at about 0.5 cm apart, with the lateral suture being placed about 2 cm from the ischial spine. The sutures will be attached to the vault on the suture line were the vault was closed after hysterectomy seeking the part with most connective tissue or ligament remains.

Laparoscopic sacrocolpopexy

Patients don't receive bowel preparation the day before the operation. Looking at the design of this surgical intervention, the main goal of sacrocolpopexy is to reconstitute an adequate, durable system of support and suspension of the vagina by replacing the impaired and/or detached native fascial tissue with a synthetic non-absorbable prosthesis. The LSC will be performed under general anaesthesia with four trocars, one for the scope and three side trocars. The vaginal vault will be lifted using a vaginal probe. The peritoneum will be dissected to expose the vesicovaginal and rectovaginal fascia, extending to the sacral promontory. Preparation of the rectovaginal and vesicovaginal fascia will be done as far down as possible. The preparated tissue and the size of the mesh will be measured and documented. One side of the polypropylene mesh will be attached anteriorly of the vaginal wall, and the other side as far down posteriorly as possible using absorbable sutures. As little as possible stitches will be used. Depending on the surgeon's preference, the mesh will be attached to the sacral promontory using staples or non-absorbable sutures. The mesh will be peritonealised at several points. The pouch of Douglas will not be obliterated.

The VSF can be performed under spinal or general anaesthesia, depending to the patient's and anaesthesiologist's preferences. The laparoscopic procedure will be performed under general anaesthesia. Both procedures will be completed with any additional vaginal surgery, if indicated, after the vault suspension has been carried out. For example anterior and posterior colporrhaphy may be performed during the same procedure. No vaginal mesh augmented procedures are allowed.

In both groups, prophylactic antibiotics and thrombosis prophylaxis will be given per-operatively. An indwelling urine catheter will be left in-situ and will be removed the first day post-operatively or as clinically indicated. Prolonged catheterisation will be recorded. If necessary, patients will receive analgesics according to the local hospital protocol. Patients are advised to withhold from heavy physical work for a minimal period of six weeks.
In case clinically indicated (complication or technical challenge to continue the procedure), the surgeon could convert to the other intervention. Participants will be analysed according to the intention to treat principle.

Data collection

Participants will be followed pre-operatively, until one and five years post procedure. At follow-up, several aspects will be evaluated:

- Clinical examination of the prolapse using POP-Q.
- UDI, the Dutch validated version of the Urogenital Distress Inventory, questionnaire comprising 17 questions, to assess the presence and experienced discomfort of pelvic floor problems. The UDI consists of 5 domains: discomfort/pain, urinary incontinence, overactive bladder, genital prolapse, and obstructive micturition. The total UDI score is defined as the average of the 5 domain scores, and can be used to assess cost effectiveness by measuring quality of life (van der Vaart 2003[11]).
- DDI, the Defecatory Distress Inventory is a standardized questionnaire measuring defecatory symptoms. The questions cover the following sections: obstructive defecation, constipation, fecal incontinence and pain related to defecation. Patients have more bothersome symptoms if they have a high score on a particular section. (Roovers 2008[12]).
- IIQ, the Incontinence Impact Questionnaire is a disease-specific quality of life questionnaire covering the five sections: physical functioning, mobility, emotional functioning, social functioning and embarrassment (van der Vaart 2003[11]).
- EQ-5D, EuroQol, is a general quality of life questionnaire, to evaluate health utilities and the corresponding quality adjusted life years (QALYs). This is the difference in quality of life caused by the treatment multiplied by the duration of treatment effect (Dolan 1997[13], Lamers 2005[14]).
- Medical cost questionnaire.
- PISQ, Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, to analyse sexual function in participants with urinary incontinence and/or pelvic organ prolapse (Occhino 2011[15]).

- PGI-I, Patient Global Impression of Improvement, to evaluate the post-operative condition as compared to the condition before the surgical intervention. A single question is used to rate the condition, and the answer can be given on a scale from "1. Very much better" to "7. Very much worse" (Srikrishna 2010[16]).
- Pre-operative urodynamic examination is only necessary when clinically indicated.
- During the first 6 weeks post-operative (including the hospitalization), participants are asked to keep a diary, which includes the following sections: postoperative pain measured by Visual Analogue Score (VAS), used pain medication and the RI-10 recovery questionnaire. RI-10, the Recovery Index 10 is a questionnaire evaluating post-operative recovery. The questionnaire consists of 10 items using a 5 point-Likert scales. (Kluivers 2008[17]).
- To evaluate post-operative recovery and satisfaction three questions are added to the 12-month questionnaire:

1. Are you satisfied with the post-operative result?
   Answers: yes/no/don't know
2. Did the operation improve your symptoms?
   Answers: yes/no/don't know

Would you recommend the surgery to a friend?
Answers: yes/no/don't know

After inclusion, the following data will be recorded:

	POP-Q	UDI	DDI	IIQ	EQ-5D	Medical costs	PISQ	PGI-I	Diary	Satisfaction questionnaire
Baseline	x	x	x	x	x	x	x	-	-	-
6 weeks	x	-	-	-	-	x	-	-	x	-
6 months	-	x	x	x	x	x	x	-	-	-
1 year	x	x	x	x	x	x	x	x	-	x
5 years	x	x	x	x	x	x	x	x	-	x

Randomized participants will be scheduled for follow-up visits pre-operatively, at 6 weeks and one and five years post-operative. During these out-patient visits a physical examination including POP-Q will be performed and complications will be detected. The follow up visit at one and five years will be performed by a physician blinded for the intervention. This will not be the surgeon who performed the operation.

Post-operative recovery will be assessed by asking the patients to keep a diary during their hospital stay and in the first 6 weeks post-operative. The diary consists of the several sections: VAS pain score, pain medication and the RI-10 recovery questionnaire. A part of the questionnaire of the economic evaluation is also added to the diary.

Secondary outcome will be the effect of the surgical treatment on prolapse related symptoms, post-operative recovery, procedure related morbidity, sexual function, quality of life, anatomical results using the POP-Q classification until one year follow-up, type and number of re-interventions, costs and cost-effectiveness and long term complications. Other study parameters are:

- procedure time
- blood loss
- hospital stay
- post-operative pain medication
- post-operative pain score (visual analogue scale)
- peri-operative complications

Other study parameters are baseline values or parameters which might intervene with the main study parameter, like duration of symptoms, medical history, parity, body mass index, education/profession, smoking, atrophy, pre- or postmenopausal status, use of oestrogens or hormone replacement therapy, previous prolapse or stress incontinence surgery, previous pessary therapy, combined prolapse- or stress incontinence surgery and type of sutures and mesh during the intervention.

In case of loss to follow-up, participants will be contacted by telephone and asked for the reason for not returning the questionnaires or returning for follow-up visits. If necessary, the general practitioner will be contacted to gather additional information. Characteristics of responders and non-responders will be compared.

Economic evaluation

The costs of both surgical treatments will be compared. The direct costs of the VSF and LSC, like costs of operating time and use of materials, will be taken into account. Moreover, medication for post-operative pain reduction, length of hospital stay and admission for complications or re-interventions will be assessed. The economic evaluation will be conducted from a societal perspective including direct medical and direct non-medical costs. Home care, consisting of both professional care as well

as informal or family care will be evaluated. We will use a patient questionnaire to collect all the information of the additional home care. This questionnaire is added to the diary which will be kept by all patients. Productivity losses will not be included in the economic evaluation, since most of the participants will be over 55 years of age. To gather medical costs a case record form will be used. Cost components will be valued according to standard Dutch guidelines for economic evaluation (CVZ 2004). Actual costs will be estimated for the VSF and LSC and informal care will be valued by using shadow prices. These data will be used to perform a cost-effectiveness analysis.
To perform a cost-utility analysis, we will use the EuroQol questionnaire (EQ-5D). This is a disease non-specific quality of life questionnaire, to derive health utilities and the corresponding quality adjusted life years (QALYs). This is the change in quality of life induced by the treatment multiplied by the duration of treatment effect. QALYs can then be related to medical costs to arrive at a final common denominator of cost/QALY.

Primary and secondary outcomes

The primary outcome is the functional effect by evaluating disease specific quality of life at 12 months follow-up using the Dutch validated version of the Urogenital Distress Inventory (UDI). Secondary outcome will be the effect of the surgical treatment on other prolapse related symptoms as defecation and sexual problems and the anatomical results using the Pelvic Organ Prolapse Quantification (POP-Q) at one and five years follow-up. Other secondary outcomes are procedure related parameters as procedure time, estimated amount of blood loss, length of hospitalization, post-operative pain medication, post-operative pain score (visual analogue scale) and peri-operative complications, post-operative recovery, general quality of life, type and number of re-interventions, costs and cost-effectiveness and long term complications. Another secondary outcome will be the success rate according to Barbers' criteria. Success is defined as no prolapse of the vault beyond the hymen, no bothersome bulge symptoms (vaginal bulging and protrusion according to the validated questionnaire), and no repeat surgery or pessary use for recurrent vault prolapse[18].

Sample size calculation

We will consider the score of the UDI genital prolapse domain as primary endpoint. A difference between both surgical techniques of 10 points on the genital prolapse domain of the UDI one year after surgery, will be considered a clinically relevant difference between both groups[19]. The standard deviation of the score on this domain is 15 points[19]. With a power of 90% and a level of 0.05, the calculated sample size necessary is 96 (48 in each group).

The analysis will be performed by intention to treat. Odds ratios and 95% confidence intervals are calculated for all terms that are included in the regression model. Domain scores will be analysed using repeated measurement analysis.
Taking into account 10% attrition, a number of 106 patients (53 in each arm) will be included.

Randomization

The trial represents a multi-centre randomized controlled design. Eligible patients with vault prolapse who meet the inclusion criteria will be randomized when informed consent is signed. The treatment allocation ratio is 1:1 to either LSC or VSF. Stratified randomization will be used to achieve approximate balance of participating centres across study groups. The investigators or the participating surgeons are not aware of these series. Randomization will be performed by the coordinating researcher, after which the procedure can be planned. For randomization, opaque sealed envelopes will be used in order to conceal the allocation. To evaluate data anonymously, participants will receive a case number at randomization. Blinding for allocation of treatment is impossible because of the laparoscopic or vaginal approach which requires a different introduction and anaesthesia technique. However, the follow up visit at one and five years will be performed by a physician blinded for the intervention.

Statistical analysis

Data analysis

Data will be analysed based on intention to treat principle and stratified for centre. If the treatment effect is homogenous across centres we will also perform an un-stratified analysis. To examine differences between groups we use an unpaired T-test for continuous variables and a Chi-square or, if opportune, a Fisher's exact test for dichotomous variables.
For differences in UDI, DDI and IIQ domain scores, a repeated measurement analysis will be performed. Repeated measurements analysis provides information of the results over time. Two-sided significance tests will be used throughout. A P value of <0.05 will be considered to be statistically significant. Time to re-intervention will be compared with Cox regression and Kaplan Meier analysis. The statistical package used was SPSS 22.

Ethics and consent to participate

The study will be carried out in accordance with the principles of the Declaration of Helsinki. The SALTO-2 trial was approved in March 2014 (version 3.1.) by the Ethics Committee of the Máxima

Medical Centre Veldhoven (METC 1324) and the local Ethics Committees of the participating centres. Informed consent will be obtained before participants will be randomized. Participants are currently being recruited and enrolled. The date of first enrolment was 27.09.2013. If any important modifications will be made to the protocol, an amendment will be presented to the Medical Ethics Committee of the Máxima Medical Centre Veldhoven for consideration.

Discussion

LSC and VSF are generally performed procedures in pelvic care clinics all over the world. Although there is some literature about both surgical procedures, there is much heterogeneity in study populations and interventions. Furthermore, quality of life, which is the most relevant outcome to evaluate the effect of prolapse surgery, was no primary outcome of any of these studies[5, 6,10]. In our opinion the question which surgical intervention leads to the highest patient satisfaction for women with a stage 2 or higher VVP is still unanswered. Prospective trials comparing disease specific quality of life after VSF and LSC are lacking. Therefore, a sufficiently powered randomized controlled trial with long-term follow-up is required to provide evidence based decisions on the preferred treatment.

References

1. Swift S. The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic health care. Am J Obstet Gynecol 2000;183:277-285.
2. Mant J, Painter R, Vessey M. Epidemiology of genital prolapse: observations from the Oxford family planning association study. BJOG 1997;104:579-585.
3. Marchianni M, Bracco GL, Checcucci V, et al. True incidence of vaginal vault prolapse: thirteen years of experience. J Reprod Med 1999; 44:678-684
4. Toozs-Hobson P, Boos K, Cardozo L. Management of vaginal vault prolapse. Br J Obstet Gynecol. 1998; 105(10): 1127-8.
5. Sederl J. Zur operation des prolapses der blind endigenden sheiden. Geburtshilfe Frauenheilkunde. 1958; 18: 824-8.
6. Davila GW, Ghoniem GM, Kapoor DS, Contreras-Ortiz O. Pelvic floor dysfunction management practice patterns: asurvey of members of the International Urogynecological Association. Int Urogynecol J Pelvic Floor Dysfunction. 2002;/13(5):/319-25.
7. Nezhat CH, Nezhat F, Nezhat C. Laparoscopic sacrocolpopexy for vaginal vault prolapse. Obstet Gynecol. 1994; 84(5): 885-8.
8. Maher C, Feiner B, Baessler K, Glazener CMA. Surgical management of pelvic organ prolapse in women (Review). The Cochrane Collaboration. 2010, issue 8.
9. Paraiso MFR, Walters MD, Rackley RR, Melek S, Hugney C. Laparoscopic and abdominal sacral colpopexies: A comparative cohort study. Am. J Obstet Gynecol. 2005; 192; 1752-8.
10. Coolen ALWM, Bongers MY, Mol BWJM. A comparison of complications between open abdominal sacrocolpopexy and laparoscopic sacrocolpopexy for the treatment of vault prolapse. Obstet Gynecol Int. 2013;2013:528636. doi: 10.1155/2013/528636.
11. Van der Vaart CH, de Leeuw JR, Roovers JP, Heintz AP. Measuring health-related quality of life in women with urogenital dysfunction: the urogenital distress inventory and incontinence impact questionnaire revisited. Neurourol Urodyn. 2003;22(2):97-104.
12. J.P. Roovers, J.G. van der Blom, C.H. van der Vaart. (2008) Hysterectomy does not cause constipation. Dis Colon Rectum; 51 (7):1068-72. doi: 10.1007/s10350-007-9147-6
13. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-1108.
14. Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff. NTvG 2005;149:1574-8
15. Occhino et al. Validation of a visual analog scale form of the pelvic organ prolapse/urinary incontinence sexual function questionnaire 12. Female Pelvic Med. Reconstr. Surg. 2011 sept; 17 (5): 246-248.
16. Srikrishna S, Robinson D, Validation of the Patient Global Impression of Improvement (PGI-I) for urogenital prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2010;2:538-8
17. Kluivers et al. Clinimetric properties of 3 instruments measuring postoperative recovery in a gynecologic surgical population. Surgery. 2008 Jul;144(1):12-21
18. Barber MD, Burbaker L, Nygaard I, Wheeler TL, Schaffer J, Chen Z, Spino C. Defining Success After Surgery for Pelvic Organ Prolapse, Obstet Gynecol. 2009; vol 114 (3): 600-9
19. Roovers JP, Vaart vd CH, Bom vd JG, Leeuwen v JH, Scholten PC, Heintz AP. A randomised controlled trial comparing abdominal and vaginal prolapse surgery: effects on urogenital function. BJOG. 2004 Jan;111(1):50-6.

Chapter 8

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

This thesis studies treatments for pelvic organ prolapse and the following objectives are addressed:

- Should a symptomatic pelvic organ prolapse (POP) be treated conservatively or surgically? In case of surgical treatment; will a uterus preserving treatment, as the Manchester Fothergill procedure, give an advantage over a vaginal hysterectomy?
- How should women with a post hysterectomy vaginal vault prolapse be treated?

In this chapter, the main outcomes of the studies are summarized, the clinical implications will be discussed and suggestions for future research are made.

Should a symptomatic POP be treated conservatively or surgically?

In our study "Primary treatment of symptomatic pelvic organ prolapse" [chapter 2], we observed that treatment preference limits the willingness to undergo randomization between pessary treatment and POP surgery. Patient preference plays a very important role in the tendency to try a pessary. Previous prospective cohort studies reporting on women with pelvic organ prolapse, also reported strong patient's preference for one of both interventions [1]. Several patient characteristics correlate with the preference for either pessary treatment or POP surgery. In our study, we noticed that younger patients, with a higher POP-Q stage and more urinary symptoms that affect their social life, are more likely to opt for POP surgery. This was also reported by others, who described that the likelihood of preferring pessary treatment over surgery increases as patients' age rises and surgery was preferred if POP symptoms are more bothersome and affect general well-being [1]. Our study showed that women treated with a pessary, complain more of persistent prolapse symptoms and undergo more often surgery in the first year of follow-up as compared to patients who undergo surgery as primary treatment. However, 72% of women who were treated with a pessary, did not opt for surgery. Two prospective trials comparing pessary with POP surgery, report similar improvement in urinary, bowel, sexual function, and quality of life parameters when treated with pessary or POP surgery [2-4]. According to these findings we can't conclude which treatment is first choice to treat a primary symptomatic POP. However, our results will help in order to individualize the counselling about treatment options and guide patients better to the decision process of the treatment of a symptomatic POP. To discuss step by step the information gathered in our study with women suffering from POP, will help to choose the best treatment. Both treatment options are very diverse and extensive counselling will give patients the opportunity to choose the treatment of their own choice. Moreover, patients will have realistic expectations during and after POP treatment, if our study results are used to counsel.

The results of our study [Chapter 2] provide evidence to counsel about the effects and adverse events of both treatments. Therefore, a RCT comparing pessary to POP surgery is not necessary, but could still be relevant, as the question which treatment option leads to better results has not been answered. Furthermore, women who choose their own treatment might be more satisfied with their choice, as compared to treatment after randomization. Nevertheless, older participants were more likely to choose pessary treatment and only 28% opted for surgery. The choice of not being operated could be influenced by their age. Since there is an ongoing multicentre trial, PEOPLE study (NTR 4883), comparing pessary treatment to POP surgery [7], we are curious about these results.

In case of surgical treatment; will a uterus preserving treatment, as the Manchester Fothergill procedure, give an advantage over a vaginal hysterectomy?

First of all, patients and their physicians should decide if the treatment of choice should be conservatively or surgically. If chosen for a surgical treatment of a symptomatic POP, many techniques are described [8]. Traditionally, vaginal hysterectomy was the standard treatment for uterine descent. However, the discussion is ongoing whether or not vaginal hysterectomy is the rational first choice in the treatment of uterine descent, and interest in uterus preservation seems to be increasing [9, 10]. Uterus preserving techniques include sacrohysteropexy, sacrospinous fixation and Manchester Fothergill [8]. According to a Dutch survey among members of the Dutch Urogynaecological Society in 2011 and a Dutch nationwide registry [11], vaginal hysterectomy, sacrospinous fixation, and the Manchester Fothergill procedure were the most frequently performed surgical interventions for uterine descent [11]. Unfortunately, according to the evidence, the first-choice treatment for the surgical treatment of apical prolapse could not be determined [8]. Our retrospective cohort study compared two of the most frequently used techniques: the uterine preserving Manchester Fothergill and vaginal hysterectomy. Vaginal hysterectomy (VH) and Manchester Fothergil (MF) have similar recurrence rates and re-interventions in this retrospective trial. Although small differences were found (less blood loss and operation time in the MF group and less urinary retention in the VH group), both procedures seemed to be equal effective. These results correlate with previous studies comparing the same techniques [12-14].

Although the results of our study show minimal clinically relevant results, the MF and VH have never been compared in a RCT. Therefore, a RCT comparing MF to VH is still relevant, with long term follow-up, in order to determine which technique is preferable or to prove equivalency of both procedures. The MF procedure can also be compared to sacrospinous fixation (SSF), since an RCT of Dietz et.al. comparing VH to SSF [9] showed no difference in functional outcome and quality of life.

Also, other uterus preserving techniques should be evaluated, since advances in minimally invasive techniques have led to the development of laparoscopic uterus preserving procedures as the laparoscopic sacrohysteropexy. Therefore, the ongoing LAVA trial (NTR 4029), randomizing women with POP-Q stage ≥2 between laparoscopic sacrocolpopexy and SSF, is relevant.

How should women with a post hysterectomy vaginal vault prolapse be treated?

Up to 10% of the women who had a hysterectomy because of prolapse symptoms, will subsequently need surgical repair for vaginal vault prolapse thereafter [15]. Hysterectomy is a proven risk factor for POP, and also one of the top ten most common surgeries performed among Dutch women [16, 17]. The risk of prolapse following hysterectomy is 5.5 times higher in women whose initial indication for hysterectomy was genital prolapse as opposed to other indications [18].
All studies reporting on the incidence of POP after hysterectomy, use POP surgery as outcome and not POP itself [19]. Therefore, patients treated with conservative treatments (such as pelvic floor physiotherapy and pessary) or patients who do not seek help, are missing in these numbers, resulting in underestimated POP incidence numbers.
The number of laparoscopic hysterectomies is increasing: 14,447 hysterectomies were performed in 2010 in the Netherlands of which 11.7% laparoscopic, compared to 1.6% in 2005 [17]. Long-term consequences as POP after laparoscopic hysterectomy have not yet been studied. Therefore, it is necessary to perform a cross-sectional cohort study of women after different approaches of hysterectomy. To investigate the impact of this problem, a long-term follow-up trial on hysterectomized women should be performed. The recently started POP-UP study will review the incidence of pelvic organ prolapse after laparoscopic hysterectomy compared to vaginal hysterectomy. The risk of vaginal vault prolapse (VVP) can then be included more specifically in counselling of a hysterectomy.

In case of post-hysterectomy VVP, great variety of different surgical procedures to correct VVP has been reported [20-22]. However, evidence about conservative treatment for VVP is lacking. A previous hysterectomy was reported as a risk factor for failure of pessary treatment [23], however satisfaction and continuation rates have not been studied. A study to evaluate efficacy of conservative (pessary) treatment should be considered. Effective conservative treatment can be the first-choice treatment in women suffering from VVP.

A standard approach or published guideline for the management of VVP is lacking. In order to assess the variations in treating VVP among gynaecologists, we performed a survey under members of the Dutch Society for Urogynaecologie in March 2017. The knowledge of these practice variation will help to design protocols and future research questions for the treatment of VVP, since it gains insight in the daily practice of Dutch urogynaecologists. All members of the Dutch Society for Urogynaecology were invited by email to participate in a web based survey from March to April 2017. The aim of this study was to describe practice pattern variation (PPV) among Dutch gynaecologists regarding treatment of VVP. Practice pattern variation (PPV) is the difference in care that cannot be explained by the underlying medical condition.

The results are presented in table 1. The response rate consisted of 104 gynaecologists with a special interest for urogynaecology. The level of experience was divided, and most urogyaecologists work in a non-academic teaching hospital.

Of the respondents, 81 (77.9%) performed pessary treatment as the first-choice treatment for VVP, followed by sacrospinous fixation in 14 respondents (13.5%), laparoscopic and robotic sacrocolpopexy in 4 (3.8%) respondents. Almost all respondents, 102 (98.2%), are willing to perform pessary treatment in women with a symptomatic VVP.
Procedures used by respondents to treat VVP were: sacrospinous fixation (n=95, 91.3%), laparoscopic sacrocolpopexy (n=38, 36.5%), abdominal sacrocolpopexy (n=22, 21.2%), robotic sacrocolpopexy (n=21, 20.2%), vaginal mesh (n=21, 20.2%), posterior intravaginal sling (n=4, 3.8%), colpocleisis (n=67, 64.4%), other (not specified) (n=6, 5.8%).
The first-choice surgical treatment of VVP was sacrospinous fixation among 95 (91.3%) respondents, followed by laparoscopic sacrocolpopexy (n=15, 14.4%) and robotic sacrocolpopexy (n=14, 13.5%). More than half of the respondents (n=55, 52.9%) refer their patients to another centre, in case necessary. Main reasons for referral were for laparoscopic sacrocolpopexy (67.3%), vaginal mesh (50.9%) and robotic sacrocolpopexy (38.2%).

Table 1. Treatment of vaginal vault prolapse

	N (%) N=104
Characteristics of respondents	
Years since completing residency	
<5	**16 (15.4%)**
5-10	**24 (23.1%)**
11-15	**20 (19.2%)**
16-20	**19 (18.3%)**
>20	**25 (24%)**
Practice type	
Academic hospital	**9 (8.7%)**
Non-academic teaching hospital	**65 (62.5%)**
Nonteaching hospital	**30 (28.8%)**
Treatment of vaginal vault prolapse	
First choice treatment for vaginal vault prolapse	
Pessary treatment	**81 (77.9%)**
Sacrospinous fixation	**14 (13.5%)**
Laparoscopic sacrocolpopexy	**4 (3.8%)**
Robotic sacrocolpopexy	**4 (3.8%)**
Posterior intravaginal sling	**1 (1.0%)**
Abdominal sacrocolpopexy	**0 (0%)**
Vaginal mesh	**0 (0%)**
Pessary treatment as treatment for vaginal vault prolapse	
Yes	**102 (98.1%)**
No	**2 (1.9%)**
Colpocleisis as surgical treatment for vaginal vault prolapse	
Yes	**73 (70.2%)**
No	**31 (29.8%)**
First choice surgical treatment for vaginal vault prolapse	
Sacrospinous fixation	**69 (66.3%)**
Laparoscopic sacrocolpopexy	**15 (14.4%)**
Robotic sacrocolpopexy	**14 (13.5%)**
Abdominal sacrocolpopexy	**3 (2.9%)**
Posterior intravaginal sling	**2 (1.9%)**
Vaginal mesh	**1 (1.0%)**
Colpocleisis	**0 (0%)**
Referral to another centre for vault prolapse surgery	
Yes	55 (52.9%)
For:	
Laparoscopic sacrocolpopexy	37 (67.3%)
Vaginal mesh	28 (50.9%)
Robotic sacrocolpopexy	21 (38.2%)
Posterior intravaginal sling	6 (10.9%)
Abdominal sacrocolpopexy	5 (9.1%)
Sacrospinous fixation	1 (1.8%)
Colpocleisis	1 (1.8%)
Other	3 (5.5%)
- Laparoscopic/robotic sacrocolpopexy	2
- Combination with rectopexy	1
No	49 (47.1%)

This survey concludes that there is no standardized method of treatment of VVP in the Netherlands and the PPV is high. Pessary treatment is preferred as first-choice treatment by most urogynaecologists, followed by sacrospinous fixation. The first-choice surgical management of VVP is sacrospinous fixation, followed by laparoscopic and robotic sacrocolpopexy. These results of our survey are in line with a previous survey of the Urogynaecological Association (IUGA) in 2002 [24].

In this thesis, several treatments of VVP have been evaluated in a RCT [chapter 4, 25] and review [chapter 6]. The reported differences in outcome between the techniques available for VVP are very minimal according to our findings. However, abdominal sacrocolpopexy is considered as the first-choice treatment for VVP, according to a Cochrane review of the surgical management of POP [26]. Although our trial [chapter 4, 25, NTR 3276] provides evidence to support a laparoscopic approach over the abdominal approach when performing a sacrocolpopexy, as there is less blood loss and shorter hospital stay, whereas functional and anatomical outcome were equal for both treatment options. These results are in line with another randomized trial on the same topic [27].
According to our review [chapter 6], the reported differences in outcome between the techniques available for VVP are very minimal. All techniques have proved to be effective, and all trials reported good results for the anatomical and subjective outcome. Therefore, the first-choice treatment of VVP could not be given according to this review. Laparoscopic sacrocolpopexy (LSC) seems to be the technique with the best results, and the SSF the technique with the poorest results [chapter 6]. The results of vaginal mesh (VM) in our review are also poor, in terms of complications and re-operation rate (for complications, incontinence and POP), and a wide range in anatomical outcome [chapter 6].

Different techniques were available to fixate the vaginal mesh for apical suspension. Prolift (Total Prolift, Gynecare, Ethicon) was used in all included trials in our review. This mesh needs to be fixated to the sacrospinous ligament for apical support. It is unclear if the success of this vaginal procedure depends on surgical skills and learning curves. Surgical competence is probably an issue for the success of vaginal mesh surgery and could be an explanation of the wide range of effectiveness between several systems. Due to modifications and innovations, different techniques for VM are currently available. The single incision VM technique is a different procedure, with another fixation technique. All trials, included in our review, comparing VM to other techniques have been performed with the Prolift (Total Prolift, Gynecare, Ethicon). A randomized trial comparing LSC to a single incision VM technique could give more insight in the role of currently available VM techniques in the treatment of VVP, and if the type of used fixation system plays a role.

The results of the SSF, where the vault also needs to be suspended to the sacrospinous ligament differ from trial to trial [9, 28, chapter 6]. This supports our question, if success of vaginal surgery depends on surgical skills and learning curves and might result in surgical failures more easily.

Although LSC shows good results, SSF is still the most performed surgical treatment for VVP, according to our survey of March 2017. These two techniques have never been compared in a RCT, therefore we started the SALTO 2 multicentre trial [chapter 7, NTR 3977] comparing SSF versus LSC in case of VVP. According to a Cochrane review, dyspareunia was less after sacrocolpopexy as compared to SSF [26]. Therefore, the results on sexual function, which will be evaluated in this trial, are of great importance. Furthermore, patient preference is important for physicians to understand, which treatment characteristics are important to patients. A patient preference study should be a valuable addition to the present literature and should be added to the SALTO-2 trial (NTR 3977).

The main reason why a standard treatment of VVP could not be determined is the large heterogeneity of outcome measures of the trials included in our review [chapter 6], which made a network meta-analysis impossible. A network meta-analysis, offers a set of methods to visualize and interpret the wider picture of evidence and to understand the relative merits of these multiple interventions when multiple interventions have been used and compared for the same disease and outcomes. Unfortunately, we could not perform a network meta-analysis since the lack of a common reference intervention (standard treatment) and many different comparisons of all VVP treatments. All kind of treatment comparison have been done, using different measurement tools and outcomes. Nevertheless, a network plot was constructed to illustrate the geometry of the network of the included treatments. Initiators of future trials should be aware of this heterogeneity and need to choose carefully which treatment they want to compare and which measurement tool and outcome they will use.

Not only a reference intervention, but also measurement tools and outcome differ in all publications. Uniformity of standard treatment, measurement tools and outcome makes comparison of treatments for VVP possible, where after the best treatment could be determined. The measurement tools should be in line with the recommendations of ICS/IUGA [29]. Subjective outcome should include the presence or absence of vaginal bulge, and patient satisfaction. Quality of life can be measured by validated instruments that cover prolapse, urinary, bowel and sexual function [29]. A recommendation which validated questionnaires should be used, will be helpful. The POP-Q classification should be used for the anatomical outcome. Complications can be recorded in a systematic way by using the CTS classification system as advised by IUGA/ICS [29] or the Clavien-

Dindo complication classification [30]. Success should be defined according to the combined outcome of Barber et.al [31].
Although a standard treatment for VVP could not be advised according to our review, it would be preferable to have a reference intervention. A reference intervention is necessary to perform a network analysis. However, in order to determine this reference intervention, more innovation, training and research needs to be done, to prove obvious superiority of a treatment. The international panel of experts of IUGA/ICS should also give recommendations for common reference interventions, in order to create uniformity and make comparisons of treatments possible. Meanwhile, according to the present literature, LSC is most likely to be this reference treatment, since it shows the best results. However, we should be aware that these results show only small clinical differences.

Surgical treatment of vaginal vault prolapse with mesh

Although the LSC shows promising results, serious adverse events and mesh related complications should be taken into account. The FDA recently published a public health notification on the use of mesh in surgery for vaginal prolapse treatment. This however concerns the use of vaginal meshes for the treatment of vaginal prolapse, as opposed to abdominal mesh, used during sacrocolpopexy. Nevertheless, patients' awareness of the mesh related complications, due to media coverage, is reflected in reserved use of vaginal and abdominal mesh. Even though our trial [chapter 4, 25, NTR 3276] showed no mesh exposure or erosion, which was in line with the results of the trial of Freeman [27]. According to our review [chapter 6] the mesh exposure rate ranged from 0-5%, with a maximum follow-up time of 5 years. However, higher exposure rates of 10.5% are reported after abdominal sacrocolpopexy (ASC) [32]. The follow-up time of this trial was 7 years, which could be an explanation for the higher rate of exposure compared to the SALTO trial [33]. Although mesh complications need to be taken into account, the prevalence of these complications is less in LSC as compared to VM (8-21% according to our review). The 5 and 10 years follow-up results of our trial [chapter 4, 25, NTR 3276] are of great importance, especially to evaluate mesh erosion and exposure. Since no consensus on the best treatment has been reached yet, further research on promising therapies as LSC and VM need to continue. Innovations on mesh material, to reduce mesh related complications are needed. Innovations on the laparoscopic techniques should also continue, for example in evaluating different fixation points as in the pectopexy procedure [34] or different promontory fixation techniques (thackers, staplers, sutures) [35].
The question is, if centralization of these challenging, but promising techniques is preferable, in order to reduce (mesh) complications and optimize success rates.

Future research

Primary treatment of symptomatic POP

Randomized controlled trial comparing pessary to POP surgery [PEOPLE study, NTR 4883]

Surgical management of POP of the apical compartment

- Randomized controlled trial comparing Manchester Fothergill to sacrospinous fixation/vaginal hysterectomy
- Randomized controlled trial comparing laparoscopic sacrohysteropexy to sacrospinous fixation [LAVA trial, NTR 4029]
- Cross-sectional cohort study of women to review the prevalence of symptomatic and asymptomatic vaginal vault prolapse after laparoscopic hysterectomy compared to vaginal hysterectomy [POP-UP trial]

Treatment of VVP

- Prospective cohort study of conservative treatment for VVP
- Randomized controlled trial comparing laparoscopic sacrocolpopexy to sacrospinous fixation [SALTO-2, NTR 3977]
- Randomized controlled trial comparing VM (single incision) to laparoscopic sacrocolpopexy
- Patient preference of VVP treatment; discrete choice experiment

Surgical treatment of VVP with mesh

- Long term follow-up of randomized controlled trial comparing abdominal to laparoscopic sacrocolpopexy [SALTO trial, NTR 3276]
- Prospective cohort study on innovations in mesh materials

General conclusion

According to this thesis several conclusions could be made:

- In case of primary treatment of POP, pessary treatment could be considered over POP surgery, resulting in 72% of women who did not opt for surgery, although prolapse symptoms are less in those who have been operated. Patient preference plays an important role in treatment choice.
- In case of uterine descent, the Manchester Fothergill procedure is equally effective to the vaginal hysterectomy and should be considered as a surgical option that allows preservation of the uterus.

- Laparoscopic sacrocolpopexy is preferable over the abdominal procedure as a surgical treatment of vaginal vault prolapse, as there was less blood loss and hospital stay was shorter and less procedure related morbidity, whereas functional and anatomical outcome were not statistically different.
- According to a survey among all members of the Dutch Society for Urogynaecology in March 2017, there is no standard treatment of VVP and the practice pattern variation is high. A standard approach or published guideline for the management of VVP is lacking.
- A comparison of techniques for the treatment of VVP was difficult because of heterogeneity of the trials; therefore, a network meta-analysis was not possible. However, the reported differences between the techniques were very minimal, the LSC seems to be the technique with the best results, in contrast to the SSF who seem to be associated with the poorest results. Nevertheless, all techniques have proved to be effective, and all trials reported good results for the anatomical and subjective outcome. Therefore, a standard treatment for VVP could not be given according to this review, and the management of VVP includes several treatment options.

References

1. Lamers BHC, Broekman BMW, Milani AL. Pessary treatment for pelvic organ prolapse and health-related quality of life: a review. International Urogynecology Journal and Pelvic Floor Dysfunction (2011) 22:637–64
2. Lone F, Thakar R, Sultan AH, One-year prospective comparison of vaginal pessaries and surgery for pelvic organ prolapse using the validated ICIQ-VS and ICIQ-UI (SF) questionnaires. Int Urogynecol J (2015) 26:1305–131.
3. Abdool Z, Thakar R, Sultan AH, Oliver RS, Prospective evaluation of outcome of vaginal pessaries versus surgery in women with symptomatic pelvic organ prolapse. International Urogynecology Journal and Pelvic Floor Dysfunction (2010) 22(3):273-8.
4. Broens-Oostveen MC, Mom RM, Lagro-Janssen AL, Genital prolapse; treatment and course in four general practices. Ned Tijdschr Geneeskd, (2004) 148(29):1444–1448, 17
5. Sarma S, Ying T, Moore KH, Long-term vaginal ring pessary use: discontinuation rates and adverse events. BJOG (2009) 116 (13):1715–1721
6. Broens-Oostveen WC, Mom RM, Largo-Janssen ALM. De genitale prolaps: behandeling en beloop in vier huisartspraktijken. Ned.Tijdschr.Geneeskunde. (2004) 148 (29); 1444-1448
7. Vd Waarsenburg MK, vd Vaart CH. Pessary or surgery for symptomatic organ prolapse: study protocol. Unpublished. Version 1.4, Oct 2014
8. R.J. Detollenaere, J.den Boon, M.E. Vierhout, H.W.F. van Eijndhoven, u uterussparende chirurgie versus vaginale hysterectomie als behandeling van descensus uteri, Ned.Tijdschr.Geneesk. (2011) 155:A3623
9. Dietz V, Schraffordt Koops SE, van der Vaart CH, Vaginal surgery for uterine descent; which options do we have? A review of the literature. International Urogynecology Journal and Pelvic Floor Dysfunction (2009) 20:349–356
10. Zucchi A, Lazzeri M, Porena M, Mearini L, Constantini E, Uterus preservation in pelvic organ prolapse surgery. Nat Rev Urol (2010) 7:626–633
11. R.J. Detollenaere, J. den Boon, K.B. Kluivers, et al, Surgical management of pelvic organ prolapse and uterine descent in the Netherlands, International Urogynecology Journal (2013) 24:781-788.
12. Thomas AG, Brodman ML, Dottino PR, Bodian C, Friedman F, Bogursky E, Manchester procedure vs. vaginal hysterectomy for uterine prolapse. A comparison. J Reprod Med (1995) 40:299–304
13. Kalagirou D, Antoniou G, Karakitsos P, Kalogirou O, Comparison of surgical and postoperative complications of VH and Manchester procedure. Eur J Gynaecol Oncol (1996) 17:278–280
14. de Boer TA, Milani AL, Kluivers KB, Withagen MIJ, Vierhout ME, The effectiveness of surgical correction of uterine prolapse: cervical amputation with uterosacral ligament placation (modified Manchester) versus vaginal hysterectomy with utero-sacral ligament placation. Int Urogynecol J (2009) 20:1313–1319
15. Dällenbach P, Kaelin-Gambirasio I, Jacob S, Dubuisson JB, Boulvain M, Incidence rate and risk factors for vaginal vault prolapse repair after hysterectomy. Int Urogynecol J Pelvic Floor Dysfunct (2008) 19(12):1623–1629.
16. Lykke R, Blaakaer J, Ottesen B, Gimbel H. Pelvic organ prolapse (POP) surgery among Danish women hysterectomized for benign conditions: age at hysterectomy, age at subsequent POP operation, and risk of POP after hysterectomy. Int Urogynecol J (2015) 26(4):527-532.
17. Centraal bureau voor statistiek (statline.cbs.nl), Nederland
18. J.O.L. Delancey, Anatomic aspects of vaginal eversion after hysterectomy, AJOG, (1992) 166 (6), part 1, 1717-1728.

19. Altman D, Falconer C, Cnattingius S, Granath F. Pelvic organ prolapse surgery following hysterectomy on benign indications. Am J Obstet Gynecol (2008) 198(5):572.e1-572.e6.
20. Toozs-Hobson P, Boos K, Cardozo L et.al (1998). Management of vaginal vault prolapse. Br J Obstet Gynecol, (1998) 105(10): 1127-8
21. A.Uzoma, K.A. Farag, Vaginal vault prolapse (2009) obestrics and gynecology international
22. C. Maher, Surgery for women with apical vaginal prolapse, Cochrane Database Syst Rev. (2016) 1;10
23. Fernando RJ, Thakar R, Sultan AH, Shah SM, Jones PW, Effect of vaginal pessaries on symptoms associated with pelvic organ prolapse. Obstet Gynecol (2006) 108(1):93–99
24. Davila GW, Ghoniem GM, Kapoor DS, Contreras-Ortiz O. Pelvic floor dysfunction management practice patterns: asurvey of members of the International Urogynecological Association. International Urogynecology Journal and Pelvic Floor Dysfunction (2002) 13(5):319-25.
25. Coolen ALWM, van Oudheusden AMJ, Mol BWJ, van Eijndhoven HWF, Roovers JWR, Bongers MY, Laparoscopic sacrocolpopexy compared with open abdominal sacrocolpopexy for vault prolapse repair: a randomised controlled trial. Int Urogynecol J. (2017) [Epub ahead of print]
26. Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women (review). Cochrane Database of Systematic reviews (2013) 4: 1-161.
27. R. M. Freeman, K. Pantazis, A. omson et al., "A randomized controlled trial of abdominal versus laparoscopic sacrocolpopexy for the treatment of post-hysterectomy vaginal vault prolapse: LAS study," International Urogynecology Journal and Pelvic Floor Dysfunction (2013) 24 (3); 377–384.
28. Roovers JP, van der Vaart CH, van der Bom JG, van Leeuwen JH, Scholten PC, Heintz AP. A randomised controlled trial comparing abdominal and vaginal prolapse surgery: effects on urogenital function. Br J Obstet Gynaecol (2004) 111: 50-56.
29. Bernard T. Haylen, Christopher F. Maher, Matthew D. Barber, Sérgio Camarg0, et al, An International Urogynecological Association (IUGA) / International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapse (POP), Int Urogynecol J (2016) 27:165–194
30. D.Dindo, N. Demartines, P.Clavien. Classification of surgical complications. A new proposal with evaluation in a cohort of 6336 patients and results of survey. Ann Surg. (2004) 240: 205-13.
31. Barber MD, Burbaker L, Nygaard I, Wheeler TL, Schaffer J, Chen Z, Spino C. Defining Success After Surgery for Pelvic Organ Prolapse, Obstet Gynecol. (2009) 114 (3): 600-9.
32. I. Nygaard, L. Burubaker, Long-term Outcomes Following Abdominal Sacrocolpopexy for Pelvic Organ Prolapse, JAMA (2013), 309 (9); 2016-2024
33. Coolen ALWM, van Oudheusden AMJ, Mol BWJ, van Eijndhoven HWF, Roovers JWR, Bongers MY, Laparoscopic sacrocolpopexy compared with open abdominal sacrocolpopexy for vault prolapse repair: a randomised controlled trial. Int Urogynecol J. (2017) [Epub ahead of print]
34. Sarlos D, Brandner S, Kots L, et al. Laparoscopic sacrocolpopexy for uterine and post-hysterectomy prolapse: Anatomical results, quality of life and perioperative outcome—A prospective study with 101 cases. Int Urogynecol J Pelvic Floor Dysfunct (2008) 19:1415–1422
35. S. Troost, J. Veen, A. Coolen, M. Bongers, laparoscopic sacrocolpopexy: sacrcal mesh pull out strength of various promonotory fixation techniques, abstract IUGA (2016)

Chapter 9

Summary

SUMMARY

This thesis focused on the treatment of pelvic organ prolapse, and vaginal vault prolapse specifically. Prolapse of the apical compartment after hysterectomy is known as vaginal vault prolapse (VVP). Pelvic organ prolapse (POP) can be treated conservatively and surgically. A wide variety of treatments available for POP and VVP are described in literature [chapter 6, 1] without a conclusive advice for a standard treatment for POP and VVP [1, 2]. This chapter summarizes the findings of the research we conducted in order to reach consensus on the best treatment of vaginal vault prolapse.

Chapter 1 outlines the aim of the thesis, and is formulated into three questions.
Since a wide variety of treatments are described for VVP, we performed a survey among all members of the Dutch Society for Urogynaecology in March 2017. The purpose of this survey is to assess the variations among gynaecologists in treating VVP. Of the respondents, 81 (77.9%) performed pessary treatment as the first-choice treatment for VVP, followed by sacrospinous fixation in 14 respondents (13.5%), laparoscopic and robotic sacrocolpopexy in 4 (3.8%) respondents. The result of this survey demonstrates that there is no standardized method of treatment of VVP in the Netherlands and the practice pattern variation is high. A previous review and survey on the practice pattern variation for the treatment of first choice for apical prolapse showed that no preference treatment could be determined for uterine descent [1, 3].
Therefore, we formulated the aims of this thesis in the following questions:

- Should a symptomatic POP be treated conservatively or surgically? In case of surgical treatment; will a uterus preserving treatment, as the Manchester Fothergill procedure, give an advantage over a vaginal hysterectomy?
- How should women with a post hysterectomy vaginal vault prolapse be treated?

Should a symptomatic POP be treated conservatively or surgically?

Chapter 2 studies the subjective results of a prospective cohort study treated conservatively with a pessary or with pelvic organ prolapse surgery.
The aim of the study was to evaluate functional outcome after pessary treatment versus prolapse surgery as primary treatment for POP. Women with symptomatic POP ≥ stage 2 requiring treatment were included. Patients were treated according to their preference with a pessary or prolapse surgery. Primary endpoint was disease specific quality of life at 12 months follow-up, according to the prolapse domain of the Urogenital Distress Inventory (UDI) questionnaire. Secondary outcomes included adverse events and additional interventions.

We included 113 women (pessary group N=74; surgery group N=39). After 12 months, the median prolapse domain score was 0 (10-90th percentile: 0-33) in the pessary group vs 0 (10-90th percentile: 0-0) in the surgery group (p <.01). Differences in other domain scores were not statistically significant. In the pessary group, 28% (21/74) of the women had a surgical intervention versus 3% (1/39) re-operations in the surgery group (p=.01).
In conclusion, in women with POP stage ≥ 2, having surgery as primary treatment, prolapse symptoms were less compared to women who had a pessary as primary treatment, but 72% of women who were treated with a pessary did not opt for surgery.

In case of surgical treatment; will a uterus preserving treatment, as the Manchester Fothergill procedure, give an advantage over a vaginal hysterectomy?

Chapter 3 presents a retrospective cohort study comparing the effectiveness of two surgical treatments for pelvic organ prolapse, concerning the Manchester Fothergill (uterus preserving) procedure and vaginal hysterectomy.
The objective of this study was to compare the functional outcome of the Manchester Fothergill (MF) procedure versus vaginal hysterectomy (VH) as surgical treatment of uterine descent. Consecutive women who underwent MF were matched for prolapse grade, age and parity to consecutive women treated with VH. Primary outcome was disease specific quality of life, according to the prolapse domain of the Urogenital Distress Inventory (UDI) questionnaire.
We included 196 participants (98 participants per group). The response rate after a follow-up of 4–9 years was 80%. We found no differences in functional outcome according to the quality of life questionnaires and recurrence rates and re-interventions between groups. Blood loss was significantly less and operating time was significantly shorter in the MF group. Incomplete emptying of the bladder was more common in the MF group. However, obstructive micturition, according to the UDI, was more common in the VH group.
In conclusion, the MF procedure is equally effective to the VH and should be considered as a surgical option that allows preservation of the uterus.

How should women with a post hysterectomy vaginal vault prolapse be treated?

In Chapter 4 a multi-centre randomized controlled trial is presented on the treatment of vaginal vault prolapse. Women with a symptomatic vaginal vault prolapse were randomized between an open abdominal sacrocolpopexy and laparoscopic sacrocolpopexy to evaluate functional and anatomical outcome (SALTO-trial).

The objective was to evaluate the functional outcome after laparoscopic sacrocolpopexy versus open sacrocolpopexy in women with symptomatic vault prolapse POP-Q ≥ stage 2 requiring surgical treatment. Primary outcome was disease-specific quality of life measured using the Urogenital Distress Inventory (UDI) questionnaire at 12 months. Secondary outcomes included anatomical outcome and perioperative data.

A total of 74 women were randomized. Follow-up after 12 months showed no significant differences in domain scores of the UDI between the two groups. After 12 months, both groups reported a UDI score of 0.0 (IQR: 0–0) for the domain "genital prolapse", which was the primary outcome. There were no significant differences between the two groups (p = 0.93). The number of severe complications was 4 in the laparoscopic group versus 7 in the open abdominal group (RR 0.57; 95% CI 0.50–2.27). There was less blood loss and a shorter hospital stay after laparoscopy; 2 (IQR 2–3) versus 4 (IQR 3–5) days, which was statistically different. There was no significant difference in anatomical outcome at 12 months.

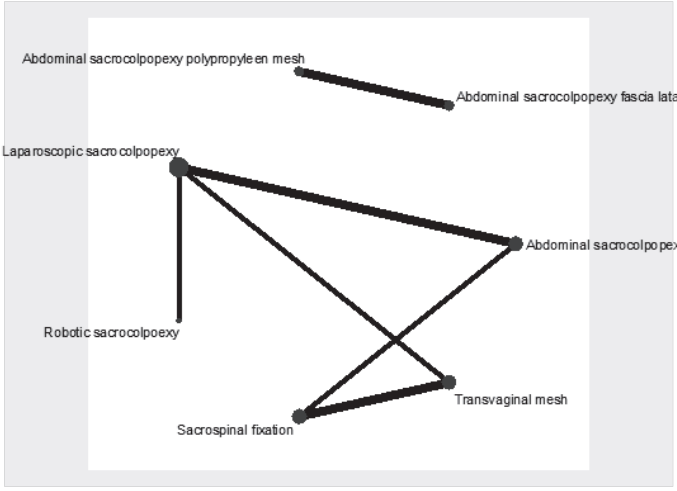
To conclude, our trial provides evidence to support a laparoscopic approach when performing sacrocolpopexy, as there was less blood loss and hospital stay was shorter, whereas functional and anatomical outcome were not statistically different.

Chapter 5 focuses on the complications of a prospective cohort treated with either open abdominal or laparoscopic sacrocolpopexy. The aim of the study was to evaluate surgery related morbidity after laparoscopic vs abdominal sacrocolpopexy. We included patients who either had abdominal or laparoscopic sacrocolpopexy to treat their symptomatic vaginal vault prolapse. Focus of the study was procedure related complication. We studied surgery related morbidity, which was divided in pre-, peri-, and postoperative characteristics. Complications were defined as unintended and undesirable events or situations during or because of a medical intervention, which will have (temporary) negative effects on patient well-being. Severe complications were defined as peri- and post-operative complications due to the surgical intervention requiring complementary (conservative) treatment and/or extended admittance. The Dutch complication registration of the NVOG (Dutch Society of Obstetrics and Gynaecology) was used to divide minor and major complications.

We included 85 women, of whom 42 had open abdominal - and 43 laparoscopic sacrocolpopexy. In the laparoscopic sacrocolpopexy group, estimated blood loss was significantly less compared to the abdominal group: 192 mL (±126) versus 77 mL (±182), respectively (p ≤ .001). Furthermore, hospital stay was significantly shorter in the laparoscopic group (2.4 days) as compared to the abdominal group (4.2 days) (p ≤ .001). The overall complication rate was not significantly different (p = .121). However, there was a significantly difference in favour of the laparoscopic group in peri- and postoperative complications requiring complementary (conservative) treatment and/or extended admittance (RR 0.24 (95%-CI 0.07–0.80), p = .009). We concluded that laparoscopic sacrocolpopexy reduces blood loss and hospital stay as compared to abdominal sacrocolpopexy and generates less procedure related morbidity.

Chapter 6 describes the results of a systematic review and meta-analysis regarding the treatment of vaginal vault prolapse. The aim of this study is to compare treatments for VVP. We performed a systematic review and meta-analysis of the literature about the treatment of VVP found in PubMed and Embase. Reference lists of identified relevant articles were checked for additional articles. A network plot was constructed to illustrate the geometry of the network of the included treatments. Only RCTs reporting on the treatment of VVP were eligible, conditional on a minimum of 30 participants with VVP and a follow-up of at least 6 months.
Nine RCTs reporting on 846 women (size 95 to 168 women) met the inclusion criteria. A comparison of techniques was difficult because of heterogeneity; therefore, a network meta-analysis was not possible. Nevertheless, a network plot was constructed to illustrate the geometry of the network of the included treatments (figure 1).

Figure 1: network plot



All surgical techniques are associated with good subjective results, and without differences between the compared technique, with the exception of the comparison of VM vs LSC. LSC is associated with a higher satisfaction rate. The anatomical results of the sacrocolpopexy (laparoscopic, robotic and abdominal) are the best, followed by the VM. However, the ranges of the anatomical outcome of VM were large. The poorest results are described for the SSF, which also correlates with the higher re-operation rate for POP (but also for incontinence and complications). The re-operation rate of VM was also high. The re-operations after VM were done for complications, recurrence prolapse and incontinence. The most complications (grade 2-5) are reported after ASC, VM and RSC. Mesh exposure was seen most often after VM, which also reflects in the highest dyspareunia rate. Overall the sacrocolpopexy reports the best results at follow-up, with an outlier of one trial reporting the highest re-operation rate for POP [4]. Results of the RSC are to minimal to make any conclusion, but LSC seem to be preferable over ASC.
In conclusion, a comparison of techniques was difficult because of heterogeneity; therefore, a network meta-analysis was not possible. However, the reported differences between the techniques were very minimal, the LSC seems to be the technique with the best results, in contrast to the SSF who seem to be associated with the poorest results. Nevertheless, all techniques have proved to be effective, and all trials reported good results for the anatomical and subjective outcome. Therefore, a standard treatment for VVP could not be given according to this review.

Chapter 7 provides a study protocol of a multi-centre randomized controlled trial to investigate the most common used treatment options for vaginal vault prolapse, comparing sacrospinous fixation to laparoscopic sacrocolpopexy. The aim of this trial is to compare the short- and long-term outcome and mainly the disease specific quality of life of the laparoscopic sacrocolpopexy and vaginal sacrospinous fixation as the treatment of vaginal vault prolapse. Women with a post-hysterectomy symptomatic vaginal vault prolapse POP-Q stage ≥2 vault prolapse will be included. A total of 106 (53 in each group) participants will be randomized to the laparoscopic sacrocolpopexy group or the vaginal sacrospinous fixation group.
Primary outcome is disease specific quality of life at 12 months follow-up. Secondary outcome will be the effect of the surgical treatment on prolapse related symptoms, sexual functioning, procedure related morbidity, hospital stay, post-operative recovery, anatomical results using the POP-Q classification after one and five years follow-up, type and number of re-interventions, costs and cost-effectiveness.

Chapter 8 contains the general discussion, clinical implications and future perspectives.

General conclusion

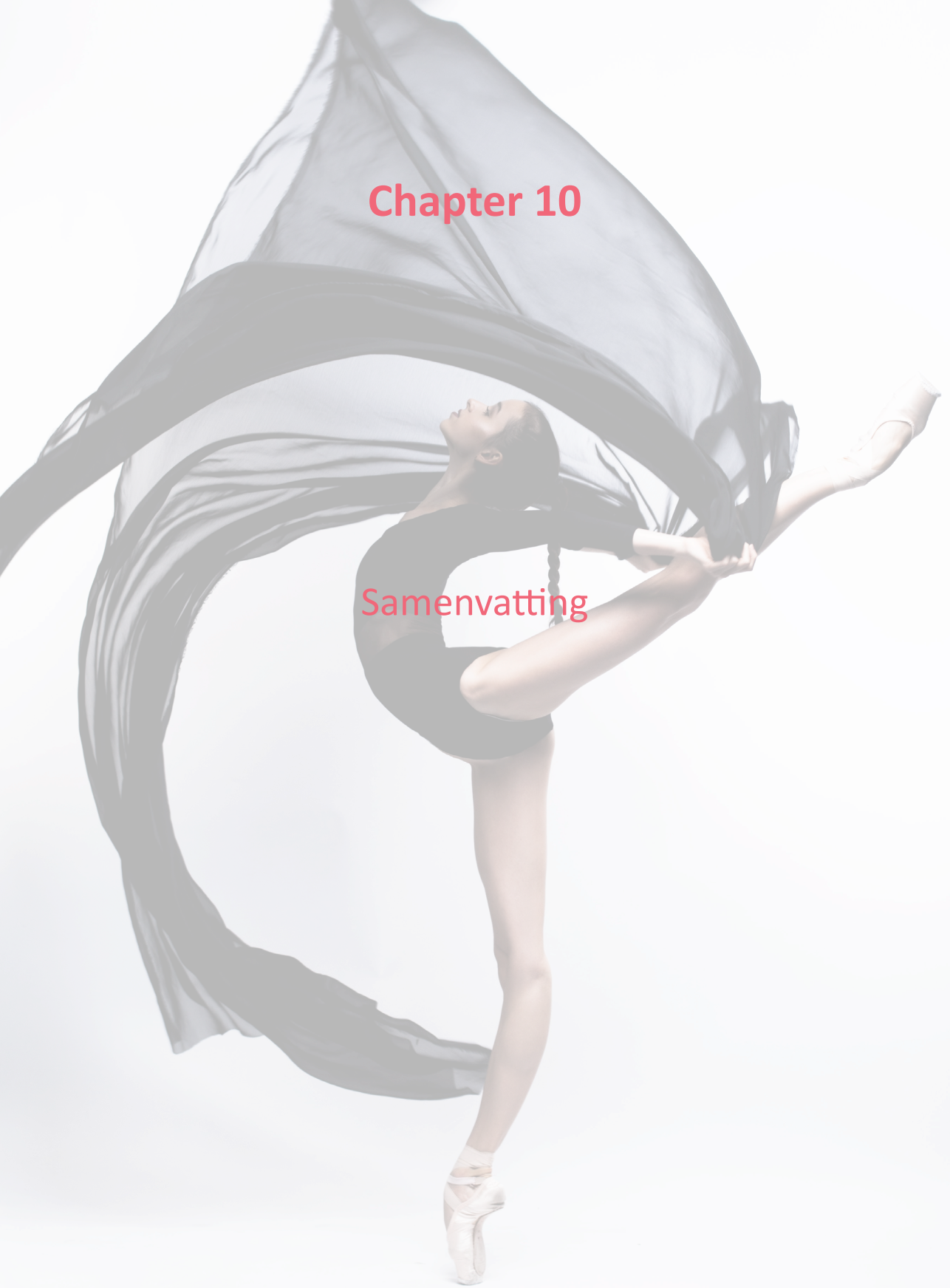
According to this thesis several conclusions could be made:

- In case of primary treatment of POP, a pessary could be considered since 72% doesn't opt for surgery after treatment, although prolapse symptoms are less in those who have been operated.
- If surgery is chosen as the primary treatment of POP, the Manchester Fothergill procedure should be considered as a surgical option that allows preservation of the uterus.
- Laparoscopic sacrocolpopexy is preferable over the abdominal procedure as a surgical treatment of VVP. According to a survey among all members of the Dutch Society for Urogynaecology in March 2017, there is no standard treatment of VVP and the practice pattern variation is high. Many surgical techniques have proved to be effective, however a standard treatment of VVP could not be given.

References

1. R.J. Detollenaere, J.den Boon, M.E. Vierhout, H.W.F. van Eijndhoven, Uterussparende chirurgie versus vaginale hysterectomie als behandeling van descensus uteri, Ned.Tijdschr.Geneesk. (2011) 155: A3623
2. Davila GW, Ghoniem GM, Kapoor DS, Contreras-Ortiz O. Pelvic floor dysfunction management practice patterns: asurvey of members of the International Urogynecological Association. International Urogynecology Journal and Pelvic Floor Dysfunction (2002) 13(5):319-25.
3. R.J. Detollenaere, J. den Boon, K.B. Kluivers, et al, Surgical management of pelvic organ prolapse and uterine descent in the Netherlands, International Urogynecology Journal (2013) 24:781-788.
4. Coolen ALWM, van Oudheusden AMJ, Mol BWJ, van Eijndhoven HWF, Roovers JWR, Bongers MY, Laparoscopic sacrocolpopexy compared with open abdominal sacrocolpopexy for vault prolapse repair: a randomised controlled trial. Int Urogynecol J. (2017) [Epub ahead of print]

Chapter 10



Samenvatting

SAMENVATTING

Dit proefschrift richt zich op de behandeling van genitale prolaps, en voornamelijk op de behandeling van vaginatopprolaps. Een genitale prolaps is een verzakking van de vrouwelijke geslachtsorganen. Een vaginatopprolaps is een verzakking van het middelste compartiment na een uterusextirpatie. Een genitale prolaps kan zowel conservatief als chirurgisch behandeld worden. Er zijn vele behandelingen voor een genitale prolaps en een vaginatopprolaps beschreven in de literatuur [hoofdstuk 6, 1], zonder dat er een advies gegeven kan worden welke de standaardbehandeling van genitale prolaps en vaginatopprolaps zou moeten zijn [1,2]. Dit hoofdstuk geeft de bevindingen van het wetenschappelijk onderzoek weer, dat verricht is om consensus te bereiken over de beste behandeling van de vaginatopprolaps.

Hoofdstuk 1 geeft het doel van dit proefschrift weer. Gezien het feit dat er vele behandelmogelijkheden voor de vaginatopprolaps zijn beschreven, hebben we in maart 2017 een enquête verricht onder alle leden van de Werkgroep Bekkenbodem van de Nederlandse Vereniging voor Gynaecologie en Obstetrie (NVOG). Het doel van dit onderzoek is het nagaan van de variatie in behandeling van vaginatopprolaps onder gynaecologen. Onder de respondenten passen 81 gynaecologen (77.9%) pessarium therapie toe als behandeling van eerste keus voor vaginatopprolaps. Dit werd gevolgd door de sacrospinale fixatie (SSF) door 14 (3.8%) respondenten en een laparoscopische of robot sacrocolpopexie door 4 (3.8%) gynaecologen. De resultaten van deze enquête demonstreren dat er geen standaardtherapie is voor de behandeling van vaginatopprolaps in Nederland en dat de praktijkvariatie groot is. Een enquête die eerder gedaan werd om te kijken naar de praktijkvariatie in de behandeling van descensus uteri liet tevens zien dat er geen standaardbehandeling kon worden vastgesteld voor dit apicale compartiment [1,3].
Om die reden is het doel van dit proefschrift geformuleerd aan de hand van drie vragen:

- Zou een symptomatische genitale prolaps conservatief of chirurgisch behandeld moeten worden? Indien een chirurgische behandeling aan de orde is; geeft een uterussparende techniek als de Manchester Fothergill dan meer voordelen dan een vaginale uterusextirpatie?
- Hoe zouden vrouwen met een vaginatopprolaps behandeld moeten worden?

Zou een symptomatische genitale prolaps conservatief of chirurgisch behandeld moeten worden?

Hoofdstuk 2 beschrijft de subjectieve resultaten van een prospectief cohort van vrouwen die werden behandeld met een pessarium of prolapschirurgie.

Het doel van de studie was het evalueren van de functionele uitkomst na pessariumtherapie versus prolapschirurgie, als primaire behandeling van genitale prolaps. Vrouwen met een symptomatische genitale prolaps, POP-Q ≥ stadium 2 die een behandeling nodig hadden, werden geïncludeerd. Patiënte werden behandeld, aan de hand van hun eigen voorkeur, met een pessarium of prolapschirurgie. De primaire uitkomstmaat was ziekte gerelateerde kwaliteit van leven, aan de hand van het prolapsdomein van de "the Urogenital Distress Inventory"(UDI) vragenlijst, na 12 maanden follow-up. De secundaire uitkomstmaten betroffen onder andere complicaties en aanvullende behandelingen.

We hebben 113 vrouwen geïncludeerd (pessarium groep N=74; prolapschirurgie groep N=39). Na 12 maanden was de mediaan van het prolapsdomein 0 (10-90^{e} percentiel: 0-33) in de pessarium groep versus 0 (10-90^{e} percentiel: 0-0) in de prolapschirurgie groep ($p < .01$). Dit komt overeen met weinig tot geen klachten in beide groepen. De verschillen in de andere domeinen (overactieve blaas, incontinentie, obstructieve mictie, pijn/discomfort en recidiverende blaasontstekingen) waren niet statistisch significant. In de pessarium groep kreeg 28% (21/74) van de vrouwen alsnog een chirurgische interventie versus 3% (1/39) re-operaties in de chirurgie groep ($p=.01$).

Concluderend, vrouwen met een genitale prolaps POP-Q ≥ stadium 2 die prolapschirurgie als primaire behandeling ondergingen, hadden minder prolapsklachten dan vrouwen die primair een pessarium kregen. Hoewel 72% van de vrouwen die behandeld werden met een pessarium niet opteerde voor prolapschirurgie na 12 maanden follow-up.

Indien een chirurgische behandeling aan de orde is; geeft een uterussparende techniek als de Manchester Fothergill dan meer voordelen dan een vaginale uterusextirpatie?

Hoofdstuk 3 presenteert een retrospectieve cohortstudie die de effectiviteit van twee chirurgische behandelingen voor genitale prolaps vergelijkt, betreffende de Manchester Fothergill (uterus sparende) procedure en de vaginale uterusextirpatie.

Het doel van de studie was het vergelijken van de functionele uitkomst na twee verschillende chirurgische behandelingen van descensus uteri: een Manchester Fothergill procedure versus vaginale hysterectomie. Opeenvolgend werden vrouwen die een Manchester Fothergill ondergingen

gematched aan patiënten die middels een vaginale hysterectomie behandeld waren, op prolapsgraad, leeftijd en pariteit. De primaire uitkomst was ziekte gerelateerde kwaliteit van leven, aan de hand van het prolapsdomein van de "the Urogenital Distress Inventory"(UDI) vragenlijst.
We includeerde 196 vrouwen (98 vrouwen per groep). De respons na een follow-up duur van 4-9 jaar was 80%. We vonden geen verschillen tussen beide groepen in functionele uitkomst (aan de hand van de kwaliteit van leven vragenlijsten), recidieven en re-interventies. In de Manchester Fothergill groep was het bloedverlies significant minder en de operatieduur korter. Hoewel een retentieblaas meer voor kwam in de Manchester Fothergill groep, kwam obstructieve mictie, volgens de UDI, vaker voor na een vaginale hysterectomie.
Concluderend, de uterus sparende Manchester Fothergill procedure is even effectief als een vaginale uterusextirpatie en zou overwogen moeten worden als chirurgische behandeling.

Hoe zouden vrouwen met een vaginatopprolaps behandeld moeten worden?

In **hoofdstuk 4** wordt een multicentrisch gerandomiseerde studie gepresenteerd over de behandeling van de vaginatopprolaps. Vrouwen met een symptomatische vaginatopprolaps werden gerandomiseerd tussen een laparotomische sacrocolpopexie en een laparoscopische sacrocolpopexie om de functionele en anatomische uitkomst te evalueren (SALTO-studie). Bij deze techniek wordt middels een matje (mesh) de vaginatop gefixeerd aan het promotorium. Deze mesh wordt via het abdomen per laparoscopie of laparotomie aan de vaginatop en het promotorium bevestigd.
Het doel van de studie was om de functionele uitkomst na een laparoscopische sacrocolpopexie te vergelijken met een laparotomische sacrocolpopexie bij vrouwen met een symptomatische vaginatopprolaps POP-Q ≥ stadium 2, welke chirurgische behandeling behoefte. De primaire uitkomstmaat was ziekte gerelateerde kwaliteit van leven, aan de hand van het prolapsdomein van de "the Urogenital Distress Inventory" (UDI) vragenlijst, na 12 maanden follow-up. De secondaire uitkomsten betroffen de anatomische uitkomst en perioperatieve data.
In totaal werden er 74 vrouwen gerandomiseerd. Na 12 maanden was er geen significant verschil in domein scores van de UDI tussen beide groepen. In beide groepen werd een UDI domein score van 0.0 (IQR 0-0) gerapporteerd voor het domein "genitale prolaps", wat de primaire uitkomstmaat was. Dit was geen significant verschil (p= .93). Het aantal complicaties was 4 in de laparoscopie groep versus 7 in de laparotomie groep (RR 0.57; 95% CI 0.50–2.27). Er was minder bloedverlies en een kortere opnameduur na een laparoscopische ingreep; 2 (IQR 2–3) versus 4 (IQR 3–5) dagen, dit was statistisch significant. Er was geen significant verschil in anatomische uitkomst na 12 maanden.
Concluderend biedt onze studie bewijs voor het aanbevelen van een laparoscopische sacrocolpopexie boven een laparotomische benadering, gezien het feit dat er minder bloedverlies en

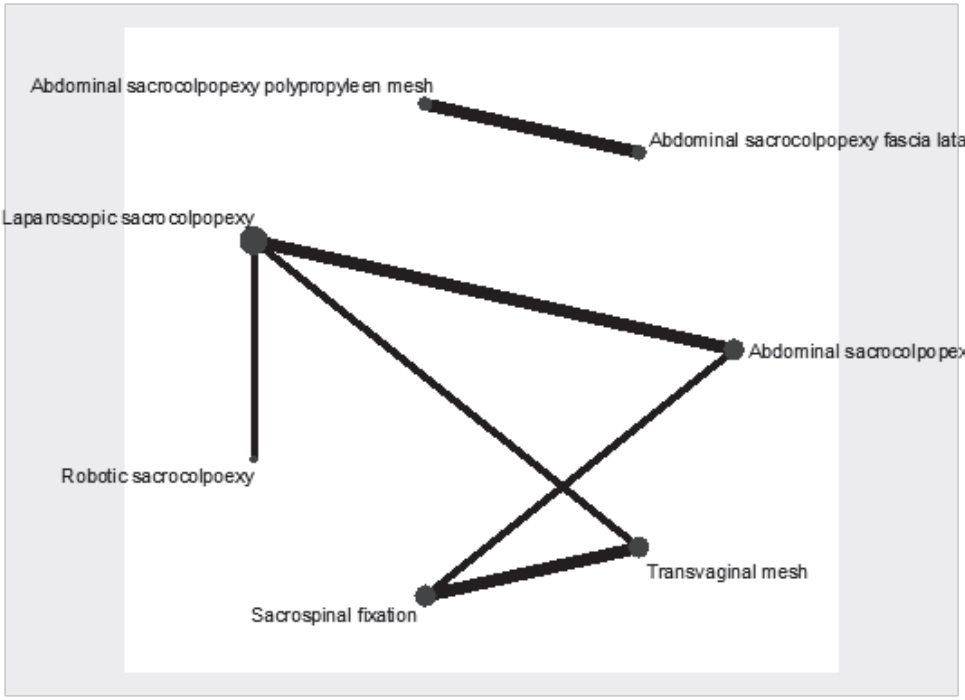
een kortere opname duur was, en zowel de functionele als de anatomische uitkomst niet verschillend was.

Hoofdstuk 5 concentreert zich op de complicaties die zijn opgetreden bij een prospectief cohort van vrouwen die werden behandeld middels een laparotomische sacrocolpopexie of een laparoscopische sacrocolpopexie. Het doel van de studie was om de morbiditeit ten gevolge van de chirurgische interventie te evalueren na een laparoscopische versus laparotomische sacrocolpopexie. We includeerde patiënten die een laparoscopische of laparotomische sacrocolpopexie ondergingen als behandeling van een symptomatische vaginatopprolaps. De studie richtte zich voornamelijk op de complicaties ten gevolge van de ingreep. We bestudeerden chirurgie gerelateerde morbiditeit, wat verdeeld was in pre- peri- en postoperatieve karakteristieken. Complicaties werden gedefinieerd als onbedoelde en onwenselijke events, of situaties tijdens of door een medische interventie, die een (tijdelijk) negatief effect hebben op de gezondheid van de patiënt. Ernstige complicaties werden gedefinieerd als peri- en postoperatieve complicaties door de chirurgische interventie, waardoor aanvullende (conservatieve) behandeling en/of verlengde opname noodzakelijk was. De Nederlandse complicatieregistratie van de Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) werd gebruikt om te differentiëren tussen “minor” en “major” complicaties.
We hebben 85 vrouwen geïncludeerd, waarvan 42 een laparotomische en 43 een laparoscopische sacrocolpopexie ondergingen. In de laparoscopische sacrocolpopexie groep was het bloedverlies significant minder in vergelijking tot de laparotomische groep: 192 mL (±126) versus 77 mL (±182), respectievelijk ($p \leq .001$). Daarnaast was de opnameduur significant korter in de laparoscopie-groep (2.4 dagen) in vergelijking met de laparotomie-groep (4.2 dagen) ($p. \leq .001$). Het totale aantal complicaties was niet significant verschillend ($p= .121$). Wanneer alleen werd gekeken naar peri- en postoperatieve complicaties waarvoor een aanvullende (conservatieve) behandeling en/of verlengde opname nodig was, werd een significant verschil in het voordeel van de laparoscopie-groep gevonden (RR 0.24 (95%-CI 0.07–0.80), $p = .009$). We concludeerden dat de laparoscopische sacrocolpopexie de hoeveelheid bloedverlies en de opnameduur reduceert, in vergelijking tot de laparotomische sacrocolpopexie, en dus met minder morbiditeit gepaard gaat.

Hoofdstuk 6 beschrijft de resultaten van een systematische review en meta-analyse omtrent de behandeling van de vaginatopprolaps. Het doel van de studie was het vergelijken van behandelingen voor vaginatopprolaps. We verrichtten een systematische review en meta-analyse van alle literatuur die gevonden werd in PubMed en Embase, omtrent de behandeling van de vaginatopprolaps. Ook referenties van relevante artikelen werden gescreend. Een netwerk plot was gegenereerd om de geometrie van het netwerk van geïncludeerde behandelingen te illustreren. Alleen gerandomiseerde

studies over de behandeling van de vaginatopprolaps kwamen in aanmerking, met een minimum van 30 participanten met vaginatopprolaps en een follow-up duur van minstens 6 maanden.
Negen studies voldeden aan de inclusiecriteria, die samen over 846 (95-168) vrouwen rapporteerden. Een vergelijking van de technieken was moeilijk door de heterogeniteit; om die reden was ook een netwerk meta-analyse niet mogelijk. Desondanks werd een netwerk plot gegenereerd om de geometrie van het netwerk van geïncludeerde studies te illustreren (figuur 1). Deze netwerk plot geeft de verschillende vergelijkingen weer van alle geïncludeerde studies.

Figuur 1: network plot



Alle chirurgische technieken gaven goede subjectieve resultaten, en er waren geen verschillen tussen de vergeleken technieken, met uitzondering van de vergelijking vaginale mesh versus laparoscopische sacrocolpopexie. De laparoscopische sacrocolpopexie is geassocieerd met een hogere tevredenheid. De sacrocolpopexie (lapascopisch, robot en laparotomisch) laat de beste anatomische resultaten zien. Dit werd gevolgd door de vaginale mesh behandeling, alhoewel de spreiding van de resultaten na een vaginale mesh groot zijn. De slechtste anatomische resultaten worden beschreven voor een sacrospinale fixatie. Deze sacrospinale fixatie is tevens geassocieerd met meer re-operaties voor genitale prolaps, incontinentie en complicaties. Het aantal re-operaties

na een vaginale mesh is ook hoog. Deze re-operaties na vaginale mesh chirurgie werden gedaan voor complicaties, recidief prolaps en incontinentie. De meeste complicaties (Clavien Dindo grade 2-5) werden gerapporteerd na een laparotomische sacrocolpopexie, vaginale mesh en robot sacrocolpopexie. Mesh exposure werd het meest gezien na vaginale mesh chirurgie, die ook geassocieerd is met het vaker voorkomen van dyspareunie.
In het algemeen laat de sacrocolpopexie de beste resultaten zien, met uitzondering van één studie die juist de meeste re-operaties voor genitale prolaps rapporteert [4]. Er zijn dusdanig weinig resultaten bekend omtrent de robot sacrocolpopexie, dat daar geen conclusies over getrokken kunnen worden. De resultaten van de laparoscopische sacrocolpexie lijken gunstiger dan die van de laparotomische sacrocolpexie.
Concluderend, was een vergelijking van de technieken moeilijk door de heterogeniteit; waardoor een netwerk meta-analyse niet mogelijk was. Hoewel de gerapporteerde verschillen tussen de verschillende technieken minimaal waren, lijkt de laparoscopische sacrocolpexie de beste resultaten te laten zien. Desondanks lijken alle technieken effectief, en rapporteren alle studies goede anatomische en subjectieve resultaten. Daarom kan een standaard behandeling voor de behandeling van de vaginatopprolaps niet vastgesteld worden aan de hand van deze studie.

Hoofdstuk 7 bevat een studieprotocol van een multicentrisch gerandomiseerde studie om het effect van de meest gebruikte chirurgische behandelingen voor de vaginatopprolaps te onderzoeken, waarbij de sacrospinale fixatie wordt vergeleken met de laparoscopische sacrocolpopexie (SALTO 2). Het doel van de studie is het vergelijken van de korte- en lange termijn uitkomsten van de laparoscopische sacrocolpopexie en vaginale sacrospinale fixatie als de behandeling van de vaginatopprolaps. Vrouwen met een vaginatopprolaps POP-Q ≥ stadium 2 worden geïncludeerd. In totaal worden 106 (53 in elke groep) vrouwen gerandomiseerd behandeld middels een laparoscopische sacrocolpopexie of een sacrospinale fixatie.
De primaire uitkomstmaat is de ziekte gerelateerde kwaliteit van leven na 12 maanden. Secondaire uitkomsten zijn het effect van chirurgie op de prolapsklachten, de seksuele functie, de morbiditeit ten gevolge van de ingreep, opnameduur, postoperatief herstel, anatomisch resultaat (volgens de POP-Q-classificatie één en vijf jaar na de ingreep), type en aantal re-interventies, kosten en kosteneffectiviteit.

In hoofdstuk 8 zijn de algemene discussie, klinische implicaties van dit onderzoek en toekomstperspectieven beschreven.

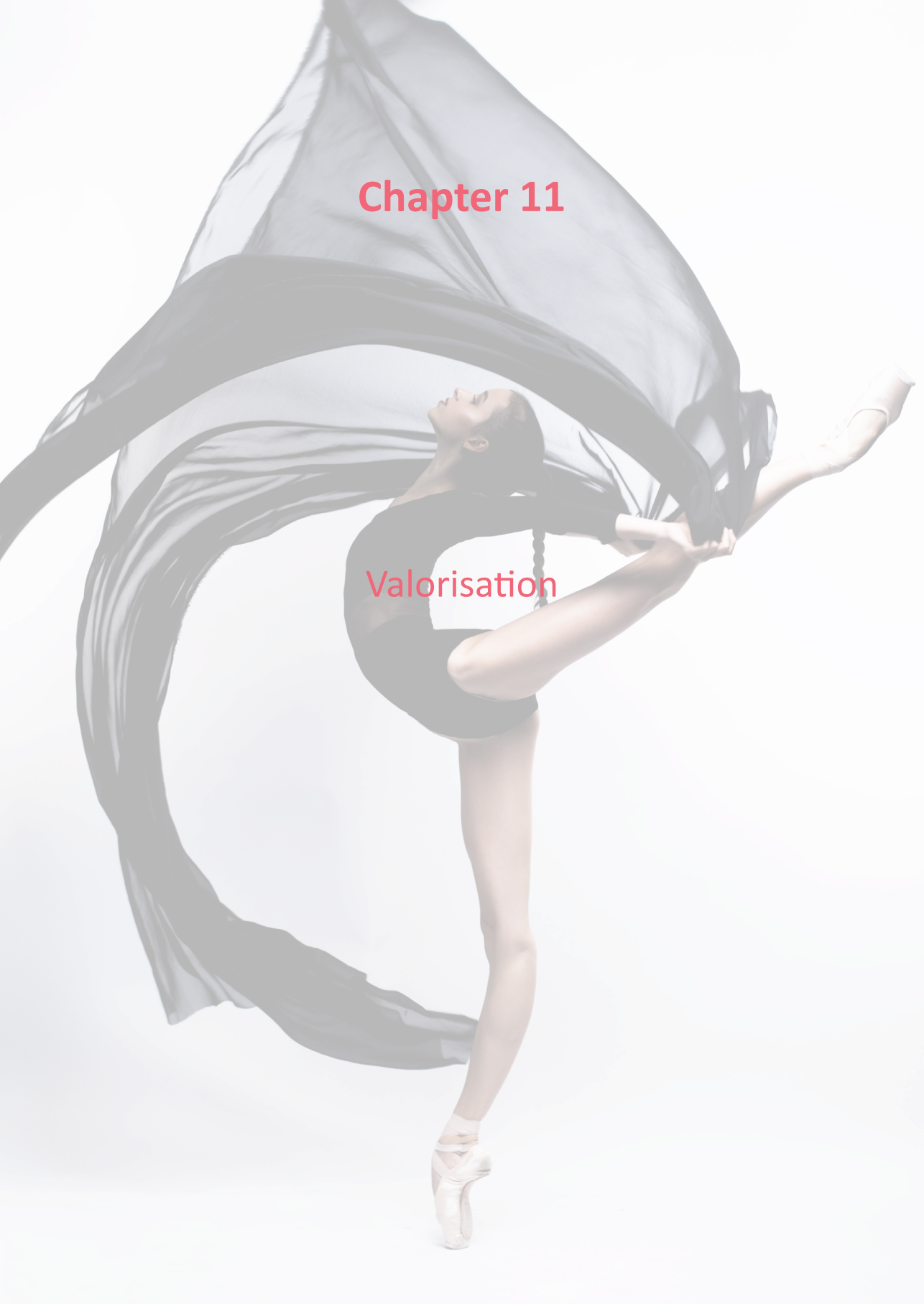
Algemene conclusie

Aan de hand van dit proefschrift kunnen de volgende conclusies getrokken worden:

- In geval van de primaire behandeling van genitale prolaps kan een pessarium overwogen worden, aangezien 72% niet voor een chirurgische behandeling opteert na het starten van pessariumtherapie. Echter, prolapsklachten zijn minder aanwezig bij vrouwen die een chirurgische behandeling ondergingen.
- Indien voor porlapschirurgie gekozen is als de primaire behandeling van genitale prolaps, zou de Manchester Fothergill (uterus sparende) procedure overwogen moeten worden.
- Laparoscopische sacrocolpopexie is te prefereren boven laparotomische sacrocolpopexie als behandeling van vaginatopprolaps. Er is tot op heden geen standaardbehandeling van vaginatopprolaps en derhalve is de praktijkvariatie groot. Vele chirurgische technieken blijken effectief, alhoewel een standaardbehandeling voor de vaginatopprolaps niet kan worden vastgesteld aan de hand van dit proefschrift.

References

1. R.J. Detollenaere, J.den Boon, M.E. Vierhout, H.W.F. van Eijndhoven, Uterussparende chirurgie versus vaginale hysterectomie als behandeling van descensus uteri, Ned.Tijdschr.Geneesk. (2011) 155: A3623
2. Davila GW, Ghoniem GM, Kapoor DS, Contreras-Ortiz O. Pelvic floor dysfunction management practice patterns: asurvey of members of the International Urogynecological Association. International Urogynecology Journal and Pelvic Floor Dysfunction (2002) 13(5):319-25.
3. R.J. Detollenaere, J. den Boon, K.B. Kluivers, et al, Surgical management of pelvic organ prolapse and uterine descent in the Netherlands, International Urogynecology Journal (2013) 24:781-788.
4. Coolen ALWM, van Oudheusden AMJ, Mol BWJ, van Eijndhoven HWF, Roovers JWR, Bongers MY, Laparoscopic sacrocolpopexy compared with open abdominal sacrocolpopexy for vault prolapse repair: a randomised controlled trial. Int Urogynecol J. (2017) [Epub ahead of print]



Chapter 11

Valorisation

VALORISATION ADDENDUM

Why is this thesis relevant?

The treatment of pelvic organ prolapse (POP) has been studied for many years and many different conservative and surgical treatments have been developed. The most optimal treatment will restore the anatomy, resulting in improvement of disease specific quality of life. Preferably, this treatment has a low risk of complications and recurrence of POP. The studies presented in this thesis focus on the effectiveness of different treatments for POP.

Relevance

Pelvic organ prolapse (POP) is a common gynaecological condition, and its aetiology is multifactorial. Risk factors include increased age, vaginal childbirth, obesity, constipation, connective tissue disorders, obstetric factors (forceps, prolonged second stage of labour, macrosomia), race, heavy lifting and a family history of prolapse. In a general Dutch female population aged 45-85 years, 75% of women had some degree of POP. POP can negatively affect women's quality of life by local physical effects (pressure, bulging, heaviness or discomfort) or its effect on urinary, bowel or sexual function. Around 10% of women undergo surgery at some time in their lives for the management of prolapse or urinary incontinence. Consequently, about 13.000 surgeries are performed for this health problem in the Netherlands every year. About 30-50% of women who underwent POP surgery are confronted with recurrent POP. Women tend to get older and older and due to this improved life expectancy, there will be an enormous extra demand for future prolapse treatment.

Pessaries have been used as conservative treatment since the beginning of recorded history. Although pessaries have been reported to be effective in reducing prolapse symptoms, 20-50% of women will discontinue their pessary use within 1 year. Side effects are reported to occur in half of the women and are the main reason for discontinuation. Unfortunately, POP surgery could be accompanied by complications. Furthermore, there are significant cost implications for POP surgery, particularly when the index surgery has a quoted failure rate of up to 30%. In view of this dilemma, we decided to start a trial with a prospective cohort group treated with either pessary treatment or POP surgery, in order to individualize the counselling about treatment options and guide patients better to the decision process of the treatment of choice. We found that women treated with a pessary are bothered more by prolapse symptoms and undergo more often surgery in the first year of follow-up as compared to patients who undergo surgery. However, pessary treatment prevents

surgery in 72%, although prolapse symptoms are less in those who have been operated. These outcomes will help in order to individualize the counselling about treatment options and guide patients better to the decision process of the treatment of a symptomatic POP.

If chosen for a surgical treatment of a symptomatic POP, many techniques are described. Traditionally, vaginal hysterectomy was the standard treatment for uterine descent. However, the discussion is ongoing whether or not vaginal hysterectomy is the rational first choice in the treatment of uterine descent, and interest in uterus preservation seems to be increasing. Unfortunately, according to the evidence, the first-choice treatment for the surgical treatment of apical prolapse could not be determined. Our retrospective cohort study compared two of the most frequently used techniques: the uterine preserving Manchester Fothergill and vaginal hysterectomy. Vaginal hysterectomy (VH) and Manchester Fothergill (MF) have similar recurrence rates and re-interventions in this retrospective trial. Although small differences were found (less blood loss and operation time in the MF group and less urinary retention in the VH group), both procedures seemed to be equal effective.

Up to 10% of the women who had a hysterectomy because of prolapse symptoms, will subsequently need surgical repair for vaginal vault prolapse thereafter. Hysterectomy is a proven risk factor for POP, and also one of the top ten most common surgeries performed among Dutch women. The risk of prolapse following hysterectomy is 5.5 times higher in women whose initial indication for hysterectomy was genital prolapse as opposed to other indications. In case of post-hysterectomy vaginal vault prolapse (VVP), great variety of different surgical procedures to correct VVP has been reported. A standard approach or published guideline for the management of VVP is lacking. In this thesis, several treatments of VVP have been evaluated in a RCT and review. Although, abdominal sacrocolpopexy is considered as the first-choice treatment for VVP according to a Cochrane review on the topic, our trial provides evidence to support a laparoscopic approach over the abdominal approach. These results are in line with our review, although the reported differences in outcome between the techniques available for VVP are very minimal. All techniques have proved to be effective, and all trials reported good results for the anatomical and subjective outcome. Therefore, the first-choice treatment of VVP could not be given according to this review.

Although laparoscopic sacrocolpopexy (LSC) shows good results, sacrospinous fixation (SSF) is still the most performed surgical treatment for VVP, according to our survey of March 2017. These two techniques have never been compared in a RCT, therefore we started the SALTO 2 multicenter trial comparing SSF versus LSC in case of VVP.

Target groups

The results of this thesis are interesting for physicians, general practitioners, patients and the medical industry. Together we need to determine what the best treatment for POP is and continue innovations on existing and new techniques and materials.
The survey we conducted in March 2017 concludes that there is no standardized method of treatment of VVP in the Netherlands and the practice pattern variation is high. These results of our survey are in line with a previous survey of the Urogynaecological Association (IUGA) in 2002. The procedure that the surgeon selects, is influenced by many factors, which include the nature, site and severity of the prolapse, the general health of the patient and of course the surgeon's preference and capability. Unfortunately, this decision is not always based on evidence. The results presented in this thesis on the effectiveness of the different treatment options for POP, will contribute to further improvement of patient counselling and development of guidelines and would therefore hopefully lead to an increase in patient satisfaction and reduction of complications and recurrences.

Activities and innovation

All our results have been submitted to scientific research journals. We also had the opportunity to discuss our findings nationally and internationally to gain more attention for our work. Since no consensus on the best treatment has been reached yet, further research on promising therapies need to continue. Therefore, we conducted a multicentre randomized controlled trial comparing laparoscopic sacrocolpopexy to sacrospinous fixation; the SALTO-2 trial [chapter 7].

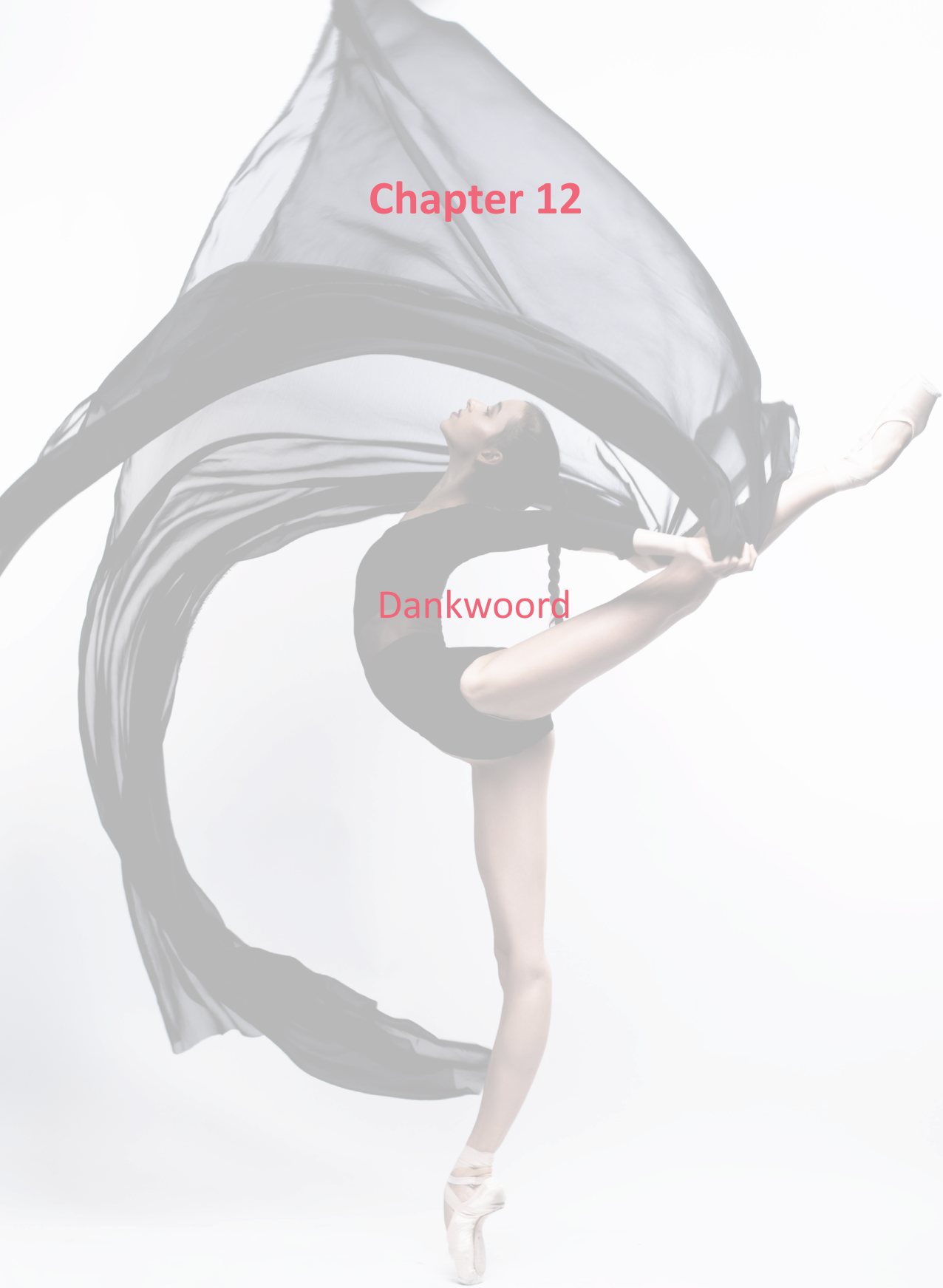
Schedule and implementation

In order to evaluate treatments for POP, and to determine the best treatment, with the lowest complication and recurrence rates, further research is necessary. The relevant ongoing trials and the relevant future research on the topic are described in the general discussion of this thesis [chapter 8]. Several existing treatment options should be evaluated in prospective RCT's to determine the best treatment for the apical (vault) prolapse. Innovations, training and research on techniques and materials also needs to continue in order to optimize success rates and minimalize complications.

However, the heterogeneity of outcome measures and standard treatments in the present literature is high. Therefore, a network meta-analysis was not possible, and the best treatment for VVP could not be determined. Initiators of future trials should be aware of this heterogeneity and need to choose carefully which treatments they want to compare and which measurement tools and outcomes they need to use. The measurement tools should be in line with the recommendations of ICS/IUGA.

Chapter 12

Dankwoord



DANKWOORD

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Lieve Pepijn, Mr P, Pepi, Snoetie, door jou heeft dit proefschrift een enorme eindsprint gekregen. Je hebt me namelijk vanaf onze eerste kennismaking laten inzien hoe fantastisch je bent. Doordat er een "vrouwelijke jij" op komst was, wilde ik zorgen dat mijn vrije tijd alleen nog maar aan jullie besteed hoefde te worden, en niet meer aan het proefschrift. Je bent een lief, vrolijk, ondernemend en sociaal mannetje. Je bent ook een gekkie en je zorgt elke dag voor een lach op mijn gezicht. Ik geniet altijd van je aanwezigheid en ik ben ontzettend trots op je. Je bent ook mijn geheugensteuntje voor het record dat ik gevestigd heb met dit proefschrift. Chapter 7, slechts 3 dagen voor je geboorte gesubmit, is volgens mij namelijk het langst ingediende artikel ooit. Gelukkig werd het na 26 maanden geaccepteerd voor publicatie.

Lieve Philou, Little Lou, Snoezie, Snuisje, we hebben het elkaar niet makkelijk gemaakt tijdens de zwangerschap. Ik heb werkelijk alles wat ik had aan energie en doorzettingsvermogen gebruikt om te zorgen dat ik optimaal van je kon genieten zodra je geboren zou worden. Dat is gelukkig dubbel en dwars gelukt, ik geniet elke dag zo ontzettend veel van jou en Pepijn sinds je in ons leven bent. Ik geef je groot gelijk dat je de eerste kans die je zag pakte om geboren te worden. Je bent een heel mooi en lief meisje, ik ben ontzettend trots op je. Ondanks dat de tijd die we tot nu toe samen doorbrachten nog niet zo lang is, laat je me elke dag genieten en voel ik me elke dag gelukkig. Ik ben heel blij dat we nog heel veel tijd samen gaan doorbrengen.

Lieve Rutger, lieve Prutje, lieve lepel, lieve papa van mijn kindjes. Wat ben ik blij dat deze "indringer" uit ons leven verdwenen is. Veel van onze vrije tijd, bracht ik met "haar" door. Gelukkig weet je zelf wat het betekent en gaf je me die ruimte om aan het proefschrift te werken. Ook heb je me geholpen als het me te veel dreigde te worden. Gelukkig zorgen we samen ook voor voldoende ontspanning en gezelligheid en houden we ons leven avontuurlijk. We kunnen allebei veel hooi op onze vork hebben, en dingen kunnen pas niet als bewezen is dat het echt niet kan. We zijn samen

een goed team en ik denk dat dit belangrijk is als je beide naast je drukke werk en gezin moet promoveren.
Lieverd, je bent de liefde van mijn leven. Je maakt me gelukkig door te zijn wie je bent. Ik ben trots op het leven dat we samen hebben met elkaar, onze kinderen, ons huis en ons sociale leven. Ik kan niet vaak genoeg zeggen hoeveel ik van je hou en hoe blij ik met je ben. Dankje dat je er altijd voor me bent, dankje dat je me met je nuchtere mannen redenatie af tot de orde roept als dat nodig is, dankje voor de vele knopen die je voor me doorhakt, dankje dat je verliefd op me bent, dankje dat ons huis altijd opgeruimd is, dankje dat je zo'n fantastische vader voor onze kindjes bent en dankje voor chapter 5.

Lieve mama, allerliefste mama van de wereld. Dat ben je altijd gebleven, hoewel er wel een nek-aan-nek-race is ontstaan sinds 11 mei 2015. Dit boek is eigenlijk ook van jou, aangezien ik niet zou weten hoe ik het anders zou hebben kunnen afronden als je me niet zo geholpen had. Mijn mama-dag vond plaats bij jou, zodat ik er weer wat hoofdstukjes kon uit persen. Later waren het niet alleen de mama-dagen, maar ook de weekenden en alle andere vrije dagen en uurtjes. Op de eerste proefschrift-vrije oma-dag zouden we wat leuks gaan doen, maar doordat je elke 3 minuten mijn jurk zag opspannen zijn we toch maar thuisgebleven. Nog geen 24 uur later werd je uit bed gebeld om uit te helpen bij de volgende bevalling van die week.
Door de fijne en stabiele jeugd die jij en papa aan mij gegeven hebben, heb ik kunnen worden wie ik nu ben. Jullie hebben me onvoorwaardelijk gesteund en veel liefde gegeven. Jullie hebben me op de juiste manier gestimuleerd en de kansen geboden om te komen waar ik nu ben. Ik ben trots op mijn ouders en ons hechte gezin. Daarom ben ik ook blij dat we niet ver van elkaar vandaan wonen. Je steunt me in werkelijk alles. Je kwam bijvoorbeeld voor me op als ik uit de klas gezet was (want bij biologie moeten we eerst piemels tekenen, waarom zou dat dan bij wiskunde opeens niet mogen) en je rijdt direct naar me toe als ik verdrietig ben (omdat bijvoorbeeld mijn borstvoeding mislukt is). Je staat altijd voor je kinderen en kleinkinderen klaar; niets is je teveel gevraagd. Je bent mijn hele leven al van alle grote tot de allerkleinste dingen die in mijn leven spelen als eerste op de hoogte. Sinds papa er niet meer is, is er veel gebeurd; zowel positief als negatief. We zijn er nog hechter door geworden als gezin, en we hebben elkaar veel nodig gehad. Wat zou het fijn geweest zijn als papa bij al deze life-events aanwezig zou zijn geweest als steun, of om het geluk met ons te delen en bijvoorbeeld 20 september naast je kon zitten. Ik ben blij dat de mama- en oma-dagen inmiddels een stuk minder wetenschappelijk onderbouwd zijn en dat we wat meer van de gewone dingen in ons leven kunnen genieten.

Lieve papa, ik draag dit proefschrift aan je op. Het schrijven van dit proefschrift, naast mijn fulltimebaan en naast alle life events (positief en negatief) die maar bleven komen, is een van de moeilijkste dingen in mijn leven geweest. Ondanks dat je me leerde om “alles eruit te halen wat erin zit”, leerde je me ook om te genieten van het leven. Om die reden heb ik dit proefschrift niet mijn leven laten beheersen (op enkele laatste maandjes na). Het ambitieus zijn en jezelf af en toe verliezen in je werk heb ik van jou. We hebben ook op een hele harde manier geleerd dat er naast werk nog veel meer belangrijke dingen zijn in het leven. Denkend aan jou, ben ik dan ook altijd op zoek naar de juiste balans tussen werk, familie en gezelligheid. Je vond het ook belangrijk dat we gelukkig zijn, en gelukkig kan ik daar volmondig “ja” op beantwoorden. Ik schreef dit boekje ook, om in de toekomst er de vruchten van te kunnen plukken in de zoektocht naar de baan waar ik van droom, in de hoop dat ik dit geluk nog heel lang vast kan houden. Daarnaast heb je ook nog heel concreet iets aan mijn proefschrift bij gedragen; dankzij jouw “platinum for life” KLM pasje heb ik mijn vlucht naar Canada niet gemist, waar ik de data van een van mijn studies ging presenteren.
Het schrijven van dit boek is een van de moeilijkste dingen geweest in mijn leven, maar het alle moeilijkste in mijn leven is om jou te moeten missen. Het is moeilijk dat er zo veel gebeurd is sinds je er niet meer bent en dat je niet (lijfelijk) bij de verdediging kan zijn. Ik had je ook zo graag als opa van mijn kindjes willen zien. Pepijn weet inmiddels gelukkig al wie je bent, hoewel af en toe het onderscheid tussen “opa Rien” en “aubergine” nog wat lastig voor hem is. Ik reken toch op je aanwezigheid 20 september. Zorg dat je er bent en laat de champagne maar vast koud leggen daarboven.

CURRICULUM VITAE

Anne-Lotte Coolen werd op 30 juli 1985 geboren in Helmond. Zij behaalde haar VWO diploma in 2003 aan het Jan van Brabant College te Helmond. Hetzelfde jaar startte ze met de opleiding Geneeskunde aan de Universiteit van Maastricht. In 2009 haalde ze haar artsenexamen. Hierna werkte ze als semi-arts en ANIOS gynaecologie/obstetrie in het Máxima Medisch Centrum. Tijdens dit assistentschap startte ze, onder leiding van prof.dr. M.Y. Bongers en prof.dr. B.W.J. Mol met het onderzoek zoals beschreven in dit proefschrift. In januari 2012 startte ze in dit ziekenhuis met de opleiding tot gynaecoloog in het Máxima Medisch Centrum. De laatste jaren van de opleiding besteedt zij aan differentiaties in de minimaal invasieve gynaecologie, urogynaecologie en gynaecologische oncologie.
Anne-Lotte Coolen is getrouwd met Rutger Stokmans. Ze zijn de trotse ouders van hun zoon Pepijn (2 jaar) en dochter Philou (4 maanden).

Anne-Lotte Coolen was born on the 30th of July in Helmond, The Netherlands. After finishing secondary school at the Jan van Brabant College in Helmond in 2003, she started her medical study at Maastricht University. In 2012 she graduated from medical school. After this, she worked as a resident at the department of Obstetrics and Gynecology in the Máxima Medical Centre. During this period she started the PhD research, which resulted in this thesis, under supervision of prof.dr. M.Y. Bongers and prof.dr. B.W.J. Mol. She started her specialist training in January 2012 in the Máxima Medical Centre. She spends the last years of her residency to differentiations in minimal invasive gynaecology, urogynaecology and gynaecological oncology.
Anne-Lotte Coolen is married to Rutger Stokmans. They are the proud parents of their son Pepijn (2 years) and daughter Philou (4 months).

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