Effects of vaginal prolapse surgery and ageing on vaginal vascularization
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Citation for published version (APA):
Weber, M. A. (2016). Effects of vaginal prolapse surgery and ageing on vaginal vascularization
CHAPTER 10

SUMMARY AND CONCLUSIONS
Summary and conclusions

Chapter 1 is the general introduction and describes the objectives of the thesis.

Part 1: Effects of vaginal prolapse and vaginal prolapse surgery on vaginal vascularization

In Chapter 2 we assess the effects of vaginal prolapse surgery using synthetic mesh on vaginal wall sensibility, vaginal vasocongestion and sexual function.

In a prospective single center study we included 16 women with previous native tissue repair for pelvic organ prolapse (POP), scheduled for vaginal mesh surgery. We assessed the Vaginal Pulse Amplitude, (VPA, representing vaginal vasocongestion) and vaginal wall sensibility before and six months after surgery, during non-erotic and erotic visual stimuli, using a validated vaginal combi-probe. Sexual function was assessed using validated questionnaires (Female Sexual Function Index (FSFI), Female Sexual Distress Scale-Revised (FDS5-R), and Subjective sexual arousal and affect questionnaire (SSAQ)). Vaginal vasocongestion under erotic conditions did not significantly alter after mesh implantation. This could indicate that previous native tissue repair had decreased preoperative vaginal vasocongestion levels to such extent that subsequent mesh surgery had no additional detrimental effect. Vaginal wall sensibility of the distal posterior wall was significantly increased after mesh surgery. This finding is not in line with three previous studies showing a decrease in vaginal wall sensibility after surgery. We hypothesized that implantation of mesh behind the anterior vaginal wall caused a different positioning of the probe on the posterior wall, resulting in a different sensation of the stimulus. This would suggest that vaginal wall sensibility measurements are difficult to interpret when used after vaginal mesh surgery. Sexual function as assessed with the questionnaires did not change significantly, however, the number of sexually active women included in our study was too small to draw conclusions on sexual function.

In conclusion, the results show that in women with a history of vaginal prolapse surgery, vaginal mesh surgery did not decrease vaginal vasocongestion or vaginal wall sensibility.
Vaginal vasocongestion prior to mesh surgery appeared to be lower than that of women never operated on. Apparently, native tissue repair decreased preoperative vaginal vasocongestion levels to such extent that subsequent mesh surgery had no additional detrimental effect.

In Chapter 3 we describe microcirculatory morphology and capillary density parameters using sidestream dark-field imaging (SDFI), and determine the feasibility and reliability of this method.

In nine healthy female volunteers non-invasive SDFI measurements were performed at two different time points in the luteal phase of their menstrual cycle. We chose this study group, free of comorbidity’s that could influence the microcirculation, for validation of the measurement technique. Measurements of microcirculatory morphology and vaginal capillary density were assessed independently by two observers. Agreement was expressed with mean differences between the measurements of both observers and the limits of agreement. Inter- and intra-observer agreement was quantified with the intra-class correlation coefficient (ICC). The SDFI device was easy in use, painless and well accepted by the participants. Morphologically, the vaginal microcirculation revealed an array of single hairpin-shaped capillary loops distributed homogeneously across an imaged tissue segment. This is comparable to what has been seen in other tissues (i.e., the tongue, gingival mucosa or nailfold capillary bed). Classifying the microcirculatory morphology with a microcirculatory architecture score ranging from an appearance of capillary loops to an appearance of the underlying vascular network without capillary loops (score 1 to 3) allowed a rapid recognition of sub-epithelial vascular patterns. The inter-observer assessments of the capillary density measurements and microcirculatory architecture score revealed very good agreement between the two observers.

In conclusion, this is the first report on both microcirculatory morphology and quantitative microcirculatory parameters of the vagina with the use of SDFI. Microvessels of the vagina show a recognizable pattern in this population of young, healthy women. SDFI gives a reproducible assessment of the vaginal microcirculation offering a wild field of applications.
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In Chapter 4 we evaluate whether vaginal microcirculation, as representative of vascularization, differs between women with and without POP.

In 17 women with POP-Q stage two or more and in 10 women without POP, SDFI measurements were performed. POP and non-POP sites were compared in seven women with a single compartment prolapse. Morphology of the microvessels was scored using the microcirculatory architecture and capillary tortuosity scores at four regions of the vaginal wall. Capillary density measurements were performed and microvascular flow was assessed with the use of the microvascular flow index (MFI). Architecture and tortuosity scores were similar for each anatomical region between women with and without POP and between the POP and non-POP site. The results in this study showed no significant differences in capillary density between the patients with and without POP except for the left vaginal wall; median capillary density in this location was higher in the control group. Although we do not have a pathophysiological explanation for this difference and we cannot exclude that this finding could be based on chance, it is interesting that in our previous study, despite good reproducibility, we observed more variations in measurements between observers for the left vaginal wall. We hypothesized that placement of the SDFI device in a straight angle on the left side of the vaginal wall could be more difficult for a right-handed investigator. No significant differences in capillary density were observed between the POP and non-POP site. Average MFI scores revealed a continuous flow for all four regions in patients with and without POP.

In conclusion, this is the first study quantifying vaginal wall microcirculation in patients with POP. Vaginal microcirculatory morphology, capillary density, and microvascular flow are similar in women with and without POP and in the compartment with and without POP.
Part 2: Effects of ageing and local oestrogens on pelvic floor disorders

Chapter 5 provides an evidence-based definition of vaginal atrophy (VA) and presents an overview of subjective and objective measurements of VA applicable in clinical practice and research.

A systematic literature search was performed to identify studies reporting on measurement properties of diagnostic instruments for VA. Additional searches aimed to document the definitions, diagnostic criteria, and outcome measures of VA. Specific symptoms for VA that were consistently described could be identified to suggest an evidence-based definition of VA. As subjective outcome measurements, seven scoring systems to assess the signs of VA during physical examination were identified. The most bothersome symptom (MBS) approach is most useful in clinical practice and research as it focuses on the most common symptoms of VA. As objective outcome measurements, numerous ways to assess vaginal cytology and vaginal pH were identified. We did not expect to find such a wide range in symptoms and diagnostic measurements. We believe that different settings (i.e., clinical practice and research) have different needs regarding the diagnostic instruments to assess presence and severity of VA. In clinical practice, subjective assessment is the first priority and this is warranted by evaluating symptoms according to the MBS approach and signs according to the vaginal physical examination scale (assessing the presence of vaginal wall petechiae, friability of the vaginal wall (defined as any bleeding occurring during examination), conization (markedly decreased elasticity), and absence of rugae). In the research setting, we recommend an objective assessment of VA by combining vaginal cytology (allowing measurement of the vaginal maturation index) and measurement of vaginal pH.

In conclusion, we propose to define VA as a common manifestation of oestrogen deficiency associated with specific symptoms of which the most common are: vaginal dryness, itching/irritation, and dyspareunia. In both clinical and research settings, subjective and objective measurements of VA should be combined.
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Chapter 6 evaluates if vaginal focal depth measurement using the Cytocam-INCIDENT Dark Field device could be a non-invasive method to quantify vaginal wall thickness.

Eight postmenopausal women with VA undergoing topical oestrogen therapy and nine controls above 40 years of age without symptoms or signs of VA were included. VA was diagnosed based on the presence of symptoms rated with the use of the MBS approach, the presence of specific signs at physical examination associated with VA and a vaginal pH equal or more than 5.5. We selected a study population with VA and compared measurements to a control group without VA because in this specific study population differences in vaginal wall thickness can be expected, especially after topical oestrogen therapy. Vaginal focal depth measurements (assessing the distance between the subepithelial microcirculation and the epithelial surface) were performed before and after treatment in the VA group and at two different time points in the control group. Pre-treatment focal depth more than doubled after a median of seven weeks of topical oestrogen treatment (80 μm [80-120 μm] to 220 μm [148-248 μm], P=0.02), whereas the measurements in the control group did not significantly change. Vaginal pH at baseline in the VA group differed significantly from the pH in the control group (5.5 vs 5.1 respectively, P<0.01). Vaginal pH did not change significantly after treatment in the VA group and between two time points in the control group.

In conclusion, with this study we achieved two important contributions to the field of urogynaecology; first, a new non-invasive measure of vaginal wall thickness was introduced using in vivo microscopy. Second, a significant increase in vaginal focal depth in patients with VA treated with topical oestrogens was reported. This innovative non-invasive measurement of vaginal wall thickness therefore has the potential to become the preferred objective criterion in the diagnosis of VA and evaluation of treatment effect.

In Chapter 7 we examine the available evidence for local oestrogen therapy in the treatment of pelvic floor disorders including VA, urinary incontinence (UI), overactive bladder (OAB), and POP.

We performed a systematic search in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and the non-MEDLINE subset of PubMed from inception to May 2014.
Two reviewers independently selected randomized controlled trials evaluating the effect of topical oestrogens on symptoms and signs of VA and UI/OAB. All studies of topical oestrogen therapy in the treatment of POP were selected. Data extraction and the assessment of risk of bias were undertaken independently by two reviewers. We intended to perform a meta-analysis of the available data. However, due to a wide variation in outcome assessment of different pelvic floor symptoms, the variation in type and dosage of the investigated oestrogen treatment regimens and the variety in comparisons made, this was not feasible. This review therefore mainly summarizes and discusses the outcome and interpretation of individual studies. Overall, subjective and urodynamic outcomes, vaginal maturation and vaginal pH changed in favor of vaginal oestrogens compared to placebo. No obvious differences between different application methods were revealed. Low doses already seemed to have a beneficial effect. Studies evaluating the effect of topical oestrogen in women with POP are scarce and mainly assess symptoms and signs associated with VA instead of POP symptoms.

In conclusion, the decline in available oestrogen after menopause is a risk factor for development or worsening of pelvic floor symptoms. These symptoms are complex and multi-factorial. Topical oestrogen administration has proven to be effective for the treatment of VA and seems to decrease symptoms of OAB and UI. Literature suggests benefit for women with POP although more evidence is needed.

In Chapter 8 we present a study reporting both subjective and objective outcome data of postmenopausal women with stress urinary incontinence (SUI) treated with topical oestrogen.

A prospective multinational pilot study was performed in three participating centers (Groote Schuur Hospital, Cape Town, South-Africa; St George Hospital, Kogarah NSW, Australia; Academic Medical Center, Amsterdam, the Netherlands). A total of 68 postmenopausal women presenting with a complaint of SUI were enrolled and treated with topical oestriol cream during six weeks. The primary subjective outcome was the response to the Patient’s Global Impression of Improvement (PGI-I) Scale assessed at the follow-up visit after six weeks of treatment. The primary objective outcome was the vaginal pH, which was assessed before and after treatment. Secondary subjective
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outcomes were: The International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF), The Incontinence Impact Questionnaire (IIQ-7), The Urogenital Distress Inventory (UDI-6) and the Most Bothersome Symptom (MBS) approach. Secondary objective outcome was the erect cough pad test. Compliance was scored.

Half of the participants reported improvement on the PGI-I Scale after treatment. The response on the PGI-I Scale did not differ significantly between patients with or without vaginal dryness as their MBS, one of the most frequently reported symptoms associated with VA. Vaginal pH was significantly lower after treatment (median 5.3 [4.5-6.0] vs 5.0 [4.4-5.4, \( P=0.002 \)), demonstrating possible objective evidence of treatment benefit and supporting the high self-reported compliance. Improvement on the UDI stress domain was observed \( P=0.01 \). No statistically significant differences were found in the other subjective outcomes. Baseline and repeat cough pad tests demonstrated a wide variation with no significant difference. It turned out to be difficult to recruit postmenopausal women with pure SUI, often a concomitant urinary urgency or urge UI was present. In conclusion, our data show that local oestrogen therapy can reduce SUI symptoms in postmenopausal women. Topical oestrogen treatment is a safe and relatively cheap treatment that generates positive results regarding UI that is comparable to other conservative treatments.

Conclusions

Part 1

1. In women with a history of vaginal native tissue repair, subsequent vaginal mesh surgery does not decrease vaginal vasocongestion or vaginal wall sensibility any further.

2. Microvessels of the vagina show a recognizable pattern in young, healthy women. SDFI gives a reproducible assessment of the vaginal microcirculation offering a wide field of applications.

3. Vaginal microcirculatory morphology, capillary density, and microvascular flow are similar in women with and without POP and in the compartment with and without POP.
Summary and conclusions

Part 2

4. VA can be defined as a common manifestation of oestrogen deficiency associated with specific symptoms of which the most common are: vaginal dryness, itching, and irritation.

5. Vaginal focal depth measurement could form a new non-invasive measurement of vaginal wall thickness for example in the diagnosis and evaluation of treatment effect in women with VA.

6. Topical oestrogen administration has proven to be effective for the treatment of VA and seems to decrease symptoms of OAB and UI. Literature suggests benefit for women with POP although more evidence is needed.

7. Local oestrogen therapy can reduce SUI symptoms in postmenopausal women.