Effects of vaginal prolapse surgery and ageing on vaginal vascularization
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CHAPTER 1

GENERAL INTRODUCTION

Local estrogens for pelvic floor disorders: a systematic review


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Chapter 1

General introduction

Ageing and pelvic floor disorders

The female pelvic floor is a complex entity involved in multiple functions including support of the pelvic organs, micturition, defecation and sexual activity. Ageing affects pelvic floor anatomy and function; resulting in several disorders like pelvic organ prolapse (POP), lower urinary tract symptoms, vaginal atrophy (VA) and sexual dysfunction.

Vaginal atrophy

VA is a common condition in postmenopausal women with an estimate of 40% of postmenopausal women experiencing symptoms associated with VA like vaginal dryness, itching or irritation (1-3). There is no consensus on the most accepted definition of VA. Characteristics to assess the presence of VA are either subjective (symptoms reported by the patient or the clinical judgment of the practitioner) or objective (such as histological tests or assessment of the vaginal pH or maturation of the vaginal epithelium). Considering the often pale and thin aspect of the vaginal epithelium described in VA, VA could be a sign of impaired vascularization related to ageing. VA could be a marker of the vascularization of the underlying visceral organs and objective measurements of VA and the vascularization could enhance our understanding of a possible relationship between VA, vascularization and pelvic floor function. It is of interest to assess if VA and its possible associations with impaired vascularization and pelvic floor function are reversible. However, at this moment, there is a lack of consensus on the quantification of VA. Concerning the subjective measures to assess VA, there is a problem related to the definition and the variety in measurement tools. Concerning objective tests, the problems are related to the reproducibility of these tests, the applicability in daily practice, and their correlation with symptoms and severity of VA.

Urinary incontinence

Pelvic floor disorders include urinary incontinence; classified as stress urinary incontinence (SUI), urge urinary incontinence (UUI) and mixed urinary incontinence (MUI). Up to 70% of women relate the onset of urinary incontinence to their final menstruation (4). Although age is a well-known factor influencing the pelvic floor and
lower urinary tract anatomy and function, the exact underlying pathophysiological mechanisms are uncertain. The decline in available oestrogen after menopause has been described as a possible etiological factor. The tissues of the female urinary continence mechanism are sensitive to oestrogen; oestrogen may enhance urethral resistance by increasing the number of periurethral vessels that account for one-third of urethral pressure (5). Moreover, oestrogen can reduce the frequency and amplitude of detrusor contractions and so raise the sensory threshold of the bladder and provide relaxation of the detrusor muscle (6, 7).

*Pelvic organ prolapse*

Another common health problem related to ageing causing impaired pelvic floor function (i.e., micturition symptoms, defecation symptoms, and sexual dysfunction) is POP. POP is one of the most common reasons for gynecological surgery in women after the fertile period. Vaginal prolapse surgery aims to correct pelvic floor dysfunction by normalizing the anatomy of the vagina and its surrounding pelvic organs. However, little is known about the exact relation between anatomical repair and functional improvement. POP itself causes an altered anatomical position of the organ, resulting in symptoms like urgency, obstructive micturition or defecation, or incontinence for urine or feces. POP surgery intends to correct the anatomical position of the pelvic organs and by doing so improves pelvic floor function, however such anatomical correction is no guarantee for proper pelvic floor function. It could be that pelvic floor function remains disturbed due to mechanical forces and stretching of the tissue during surgery resulting in compression or overstretched of the innervation of the pelvic organs. Another explanation may be found in disturbed vascularization due to dissection and traction applied to the tissues, in particular the vaginal epithelium.

*The relevance of vaginal vascularization*

Vascularization of the vagina is supplied by the vaginal artery, the vaginal branch of the uterine artery, the internal pudendal artery and vaginal branches of the middle rectal artery (8). During sexual arousal, there is an increased vaginal blood flow causing vaginal engorgement and the formation of a plasma transudate which functions as a lubricant
that is of great importance during the sexual arousal phase (9). In addition to the increased blood flow, the venous drainage seems to be reduced, resulting in vasocongestion, increased genital sensitivity and genital and clitoral engorgement (10). There are numerous studies that assessed vaginal vasocongestion. Laan and van Lunsen (11) were the first to measure genital responses of healthy postmenopausal women. They showed that vasocongestion was significantly lower in non-oestrogenized postmenopausal women compared to premenopausal women before erotic stimulation. However, during subsequent erotic stimulation both groups showed similar increases in vasocongestion. This higher vasocongestion in premenopausal women in a non-aroused state, suggests that premenopausal women could be protected from experiencing pain or discomfort during sexual intercourse by a permanent nonsexual and oestrogen-dependent lubrication, whereas postmenopausal women might be more dependent on their arousal because of the lower blood flow in the non-aroused state (10).

The vaginal microcirculation comprises all vessels with a diameter smaller than 100 micrometer including arterioles, capillaries and venules and is the site of nutrient exchange between the blood and tissue cells. It is the site from which hormones, gases (like oxygen and carbon dioxide), immune support, water and waste products are exchanged between blood and tissue cells (12). There have been numerous clinical investigations on microcirculatory alterations in various conditions including the process of wound healing (13), diabetes (14), hypertension and cardiovascular disease (15) and in septic patients (16, 17). The microcirculation is of particular importance in critically ill patients where the density of the microcirculation has proven to be significantly reduced, and this reduction seems to be most significant in non-survivors (18). There are four classes of microcirculatory alterations that have been associated with different states of cardiovascular compromise (19). Each of these types of microcirculatory alterations is associated with a reduced functional capillary density resulting in a loss of the ability of the microcirculation to transport oxygen to the tissue. Type 1 describes heterogeneity in the microcirculatory perfusion with capillaries with flowing red blood cells next to obstructed capillaries (19). This type of alteration can be typically seen in septic patients and the persistence of this type of microcirculatory alteration in combination with normalized systemic variables has been associated with organ dysfunction and mortality...
Type 2 microcirculatory alterations in which dilution of blood induced by excessive fluid therapy causes a loss of capillaries filled with red blood cells resulting in increased diffusion distances between the oxygen-carrying red blood cells and tissue cells. This type of alteration has been mainly described in cardiac surgery patients causing iatrogenic anemia, a risk factor in the development of organ dysfunction, especially renal failure (21, 22). Type 3 alterations, where vasoconstriction of arterial vessels results in microcirculatory ischemia or where raised venous pressures can cause microcirculatory tamponade and thereby causing compromised tissue oxygenation, have been described in several studies assessing vasopressor therapy in sepsis and shock (23, 24). Type 4 alterations are associated with tissue edema caused by capillary leak, which results in an increased diffusion distance between the red blood cells and the tissue (19). If these microcirculatory alterations are present then simply monitoring the systemic hemodynamic status can be inadequate in identifying the cause of cardiovascular compromise and monitoring the microcirculation is indicated to initiate adequate therapy to support patients at risk.

With the microcirculation as the main means of oxygen delivery to tissue cells, the function of organs seems to be directly dependent on the function of their respective microcirculation. Vaginal microcirculation could therefore play an important role in the proper metabolic support and health of pelvic floor organs and their function.

The assessment of vaginal microcirculation

The ability to inspect and measure vaginal microcirculation is a necessary first step to be able to study the role of the vaginal microcirculation in pelvic floor organs and their function. In the past, several indirect methods have been developed to evaluate vaginal blood flow, such as photoplethysmography, Doppler ultrasound and laser Doppler flowmetry (25-27). To study vaginal vascularization, our group has performed several experiments using photoplethysmography (28) which assesses the Vaginal Pulse Amplitude (VPA), a representative of vaginal vasocongestion. It measures the phasic changes in vaginal vasocongestion in the peripheral vessels with every heartbeat and is known as a reliable, specific, and sensitive measure, with increased amplitudes indicating increased vaginal vasocongestion (27). Disadvantage of this technique, as well as Doppler
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ultrasound and laser Doppler flowmetry, is that these techniques are unable to provide direct visualization of the microcirculatory anatomy and functionality.

The introduction of handheld bedside video microscope instruments such as orthogonal polarization spectral (OPS) imaging, sidestream dark-field (SDF) imaging and most recently Cytocam-incident dark field (IDF) imaging, have enabled direct visualization of the human microcirculation in solid organs and mucous membranes. OPS imaging can be regarded as the first generation handheld bedside imaging instruments. SDF imaging, a second generation microcirculation device, has been validated in the human nailfold microcirculation by comparison to OPS imaging and showed superior imaging capabilities with ease in quantifying vessel density (29, 30). The SDF technique is built into an easy to use hand held device and employs spectroscopic-based imaging principles via light-emitting diodes (LEDs) that emit green light by illuminating the tissue of interest where it is absorbed by hemoglobin in red blood cells, allowing detailed observations of subepithelial flowing erythrocytes in the microcirculatory beds (29). Recently a third generation hand held microscope has been clinically introduced that overcomes some limitations of the first and second generation devices (16). This device, called the Cytocam, uses an IDF imaging illumination system with high brightness LEDs able to provide a very short pulse time of two milliseconds. This combination results in a high penetration and sharp contours of moving red blood cells (31). It is lighter and easier in use than the first and second generation hand held devices and therefore minimizes pressure artifact problems (31). Cytocam-IDF has been compared to SDF imaging and detected more capillaries and provided better image quality than SDF imaging (31, 32). A new feature of the Cytocam is the quantitative focusing mechanism. This enables measurement of the focal depth, which is defined as the distance between the subepithelial microcirculation and the epithelial surface for optimal focus in microvascular imaging (33).

The ability to inspect and measure vaginal microcirculation and vaginal focal depth provides an opportunity for clinical research aimed at improving our understanding of the physiological changes in pelvic floor disorders like VA, POP and its (surgical) treatment.
Oestrogen therapy: an intervention to attack the effects of ageing

Oestrogen seems to be of great importance in the function of the genital and lower urinary tract with oestrogen receptors being present in the urethra, bladder, vagina, and pelvic floor musculature (34). As mentioned above, the tissues of the female urinary continence mechanism are sensitive to oestrogen (5-7) and oestrogens and their receptors play a role in the supportive mechanism of the pelvis by controlling the synthesis and breakdown of collagen (35). Oestrogen therapy in pelvic floor disorders in postmenopausal women attempts to reverse the effects of ageing and thereby improve pelvic floor function. In the past, systemic hormone replacement therapies have been the focus of interest, more recently studies focus on topical oestrogens in the treatment of pelvic floor disorders as this reduces adverse effects. Oestrogen has been used to treat incontinence over a number of years, and there is evidence that topical oestrogen therapy may improve urinary incontinence (36). In contrast, systemic hormone replacement therapy seems to worsen urinary incontinence (37). The possible worsening of urinary incontinence with systemic oestrogen therapy as well as the concerns about adverse effects of systemic treatment, makes further evaluation of topical oestrogen therapy in the treatment of urinary incontinence of great value. The currently available evidence is based on relatively low numbers of patients and a wide range of types, dosages and duration of oestrogen treatment (36). The available evidence regarding vaginal oestrogen therapy in postmenopausal women with overactive bladder (OAB) symptoms (urinary urgency, frequency, nocturia, with or without urge urinary incontinence) is encouraging (38, 39). However, it is not clear if subjective improvement in OAB symptoms reflects a direct effect on lower urinary tract function or an indirect effect via reversing VA (40).

How oestrogen changes collagen metabolism related to POP is still unclear (41). One hypothesis is that oestrogen brings the collagen metabolism back to a premenopausal state (42). Consequently, oestrogen deficiency could weaken the supporting ligaments of the pelvic organs, as well as causing thinning of the vaginal epithelium (43). These factors could contribute to POP. Oestrogens alone or together with other forms of treatment (i.e., vaginal pessaries, pelvic floor muscle training or surgery), may help in the treatment...
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of POP by increasing synthesis of collagen and improving the strength of the vaginal epithelium.

An overall and up to date overview of the current evidence regarding topical oestrogen therapy in the treatment of pelvic floor disorders, including POP, is lacking.

Objectives of the thesis

In this thesis we search for methods to link the function of pelvic organs to physiological changes. We want to examine the effects of POP and vaginal prolapse surgery on vaginal vascularization and the influence of ageing and topical oestrogens on pelvic floor disorders. In our search to better understand the relationship between function and physiological changes in pelvic floor disorders like VA, POP and its (surgical) treatment, we will introduce several physiologic tests.

Part 1

1. To assess the effects of vaginal prolapse surgery on vaginal vasocongestion and vaginal wall sensibility in patients with recurrent pelvic organ prolapse
2. To describe the vaginal microcirculation by assessing vaginal microcirculatory morphology and capillary density using sidestream dark-field imaging
3. To evaluate whether vaginal microcirculation, as representative of vascularization, differs between women with and without pelvic organ prolapse

Part 2

4. To provide an evidence-based definition of vaginal atrophy and present an overview of subjective and objective measurements of vaginal atrophy applicable in clinical practice and research
5. To evaluate if the assessment of vaginal focal depth could generate a non-invasive measurement to quantify vaginal wall thickness in women with vaginal atrophy treated with topical oestrogens
6. To examine the evidence for topical oestrogen therapy in the treatment of pelvic floor disorders
7. To subjectively and objectively assess stress urinary incontinence symptoms before and after topical oestrogen therapy
In our search to better understand the relationship between function and vascularization and the influence of ageing and topical oestrogens on pelvic floor disorders. In this thesis we search for methods of POP by increasing synthesis of collagen and improving the strength of POP.

Objectives of the thesis

- To objectively and subjectively assess stress urinary incontinence symptoms before and after topical estrogen therapy
- To examine the evidence for topical estrogen therapy in the treatment of pelvic floor disorders, including POP
- To evaluate whether vaginal microcirculation, as a representative of vascularization, morphology and capillary density using sidestream dark field imaging as a marker of coronary artery disease in diabetes.
- To assess vaginal wall thickness in women with vaginal atrophy
- To describe the vaginal microcirculation by assessing vaginal microcirculatory revascularization.
- To examine the evidence for topical estrogen therapy in the treatment of pelvic floor disorders, including POP
- To measure vaginal wall sensibility in patients with recurrent pelvic organ prolapse
- To describe the vaginal microcirculation by assessing vaginal microcirculatory revascularization.
- To examine the evidence for topical estrogen therapy in the treatment of pelvic floor disorders, including POP.

References

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