Effects of vaginal prolapse surgery and ageing on vaginal vascularization
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GENERAL DISCUSSION
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General discussion

The first objective of this thesis was to assess the effects of vaginal prolapse surgery on vaginal vasocongestion and vaginal wall sensibility in patients with recurrent pelvic organ prolapse (POP). We showed that vaginal vasocongestion under erotic conditions did not significantly alter after vaginal surgery with 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 vaginal surgery with the use of synthetic mesh, which is not in line with 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.

Our second objective was to describe the vaginal microcirculation by assessing vaginal microcirculatory morphology and capillary density using sidestream dark-field imaging (SDFI). By performing measurements in a study group of healthy young female volunteers, free of comorbidity’s that could influence the microcirculation, we were able to validate the vaginal use of this measurement technique. The micro-vessels of the vagina show a recognizable pattern in this population of young and healthy women.

The third objective was to evaluate whether vaginal microcirculation, as representative of vascularization, differs between women with and without POP. We hypothesized that the vaginal microcirculation could be altered in POP due to stretching or compression of the pelvic organ tissues. However, vaginal microcirculatory morphology, capillary density and microvascular flow were similar in women with and without POP and in the compartment with and without POP. The fact that POP does not seem to alter the vaginal microcirculation resulted in no additional insight into the physiologic changes POP entails, but the consistency of the measurements in women with POP makes them very suitable for the evaluation of the effect of vaginal surgery on the microcirculation of the vagina.
Our fourth objective was to provide an evidence-based definition of vaginal atrophy (VA) and present an overview of subjective and objective measurements of VA applicable in clinical practice and research. As subjective outcome measurements, seven scoring systems to assess the signs of VA during physical examination were identified and also regarding objective outcome measurements numerous ways to assess vaginal cytology and vaginal pH were found. We did not expect to find such a wide range of symptoms, signs and diagnostic measurements. We defined VA as a common manifestation of oestrogen deficiency associated with specific symptoms of which the most common are: vaginal dryness, itching and irritation.

The fifth objective of this thesis was to evaluate if the assessment of vaginal focal depth could generate a non-invasive measurement to quantify vaginal wall thickness in women with VA treated with topical oestrogens. 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 found.

Our sixth objective was to examine the evidence for topical oestrogen therapy in the treatment of pelvic floor disorders. We intended to perform a meta-analysis of the available data, however, due to the 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. We therefore mainly summarized and discussed 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.

Our last objective was to subjectively and objectively assess stress urinary incontinence (SUI) symptoms in postmenopausal women before and after topical oestrogen therapy. It turned out to be difficult to recruit postmenopausal women with pure SUI, often a concomitant urinary urgency or urge urinary incontinence was present. However, our data do show that topical oestrogen treatment can reduce SUI symptoms in postmenopausal women.
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In this thesis we searched for methods to link the function of pelvic organs to physiological changes. The effects of POP and vaginal prolapse surgery on vaginal vascularization and the influence of ageing and topical oestrogens on pelvic floor disorders were examined. 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 introduced several physiologic tests.

Physiologic tests for pelvic floor function

Regarding the assessment of vaginal vascularization with the use of photoplethysmography we were able to assess changes in vaginal vasocongestion after surgery. Where photoplethysmography can be considered as a test to evaluate the maximum performance of the vaginal vascularization (by providing an erotic stimulus), measurements of the vaginal microcirculation give an indication of vascular function in the absence of a stimulus. The introduction of bedside optical spectroscopic-based imaging techniques such as SDFI and incident dark-field imaging (IDFI) has enabled easy to perform, and direct visualization of the human vascularization. With our first study on vaginal microcirculation we showed that SDFI provides an immediate and reproducible assessment of the vaginal microcirculation. This allowed us to examine the association between vaginal microcirculation and POP. As mentioned above, the consistency of the measurements in women with POP makes them very suitable for the evaluation of the effect of vaginal surgery on the microcirculation of the vagina. Measurements of the vaginal microcirculation could be applied in evaluations prior to surgical reconstruction, optimizing design of surgical incision approach or post-operatively to monitor repair and regeneration during the healing phase.

In our study on vaginal focal depth in the diagnosis and treatment of VA we used in vivo microscopy to introduce a new non-invasive measure of vaginal wall thickness. Vaginal focal depth measurements have the potential to become the preferred objective criterion in the diagnosis of VA and our study shows it is of great value in the evaluation of treatment effect.

With these new physiologic tests outlined in this thesis it is not yet possible to completely understand abnormal pelvic floor function based on objective test results. The
fact that the etiology of pelvic floor disorders is complex and multi-factorial plays an important role, as well as the ongoing development of physiologic tests.

Ongoing developments in physiologic testing and implications for future research

Photoplethysmography has been the most commonly used method to evaluate vaginal blood flow so far. It is an example of an indirect measure of blood flow allowing measurement of phasic changes in vaginal vasocongestion in the peripheral vessels with every heartbeat. To generate a change in vasocongestion women are asked to watch erotic film material which forms a disadvantage as women are likely to refuse participation because they do not want to be exposed to erotic film material. Other methods exist to evaluate vaginal blood flow like duplex Doppler ultrasound, and laser Doppler flowmetry. However, these techniques do not provide direct visualization of vessels and capillaries. Dynamic MRI provides excellent visualization of anatomic detail, however, it is expensive, time consuming and machine availability can be a problem. The non-invasive and fast SDFI technique enables patient compliance without the need for lengthy appointments or the use of contrast materials. As mentioned in the introduction SDFI is a validated technique allowing detailed observations of sub-epithelial flowing erythrocytes in the microcirculatory beds. Disadvantages of SDFI measurements are the pressure-induced microcirculatory alterations (pressure artifacts) that are caused by probe application onto the tissue surfaces. These effects may lead to false interpretations of the actual perfusion (1). Another limitation is that the SDFI device requires hand-operated focusing, which could result in lengthy procedures for obtaining images of sufficient quality. The major short-coming of SDFI is, however, the inability to implement automatic image analysis which leads to time consuming off-line analysis which impairs the direct use of the images in clinical decision making and guidance of therapy (1). The latest generation handheld video-microscope called Cytocam-IDF has been validated by quantitative comparison of microcirculatory parameters to SDFI in sublingual tissue and has the advantage of providing better image quality, digital image recording and automatic analysis (2, 3). Moreover, Cytocam-IDF has a new quantitative focusing
mechanism which enables measurement of the focal depth as we used in our study assessing vaginal focal depth in women with and without VA and after treatment with topical oestrogen. Further evaluation of this measurement is of great value. The intra- and inter-observer variability of this measurement needs to be examined as well as its applicability in other gynaecological research areas. Future research will show the huge potential for other applications in the field of gynaecology of this non-invasive objective measurement of vaginal wall thickness.

The described physiologic tests in this thesis can be regarded as methods to give an indication of the oxygenation of the vaginal tissue. Beyond the scope of this thesis, but of relevance for a better understanding of function and dysfunction of the pelvic floor in the future, is the development of direct measurement of the oxygenation of vaginal tissue. Direct oxygenation measurements of the vaginal wall have, to the best of our knowledge, never been studied before. Possible methods to assess vaginal oxygen saturation can be with the use of oxygen pressure (pO2) electrodes, near-infrared spectroscopy (NIRS) or reflectance spectroscopy. Oxygen pressure electrodes measure pO2 on a tissue surface including at least 100 microvessels, including arterioles, capillaries and venules as well as interstitium and other cells, which all contribute to the pO2 value (4). For reflectance spectrophotometry tissue is illuminated with visible (white) light and the spectrum of the backscattered light is analyzed to calculate the oxygen saturation of the hemoglobin in the red blood cell. The device determines the hemoglobin oxygen saturation based on the differentiating absorption spectra of oxygenated and deoxygenated hemoglobin (4). Unfortunately, the tissue volume measured with this method is also not small often reporting a mean oxygen saturation which makes it difficult to draw conclusions on the presence or absence of hypoxic areas (4). NIRS is a technique that uses near-infrared light to measure oxy- and deoxyhemoglobin of the red blood cell (4). The applicability of these measurements vaginally could be the subject of future investigations.

Implications for clinical practice
At the moment, the physiologic tests evaluated in this thesis are not (yet) suitable in a daily clinical setting. Photoplethysmography and vaginal wall sensibility measurements are a burden due to the setting in which measurements need to be performed. Regarding
the assessment of vaginal microcirculation, the SDFI device is easy in use and well tolerated by patients, however the required offline analysis of the microcirculatory parameters makes it an unsuitable method in a clinical setting due to the inability to achieve quick automatic microcirculation analysis for quantification needed for clinical decision-making (1, 2). The assessment of the vaginal microcirculation with the Cytocam-IDF device however, has great potential in the daily clinical setting as it is equipped with an application for direct microcirculation assessment recording the images digitally allowing automatic analysis. Specialized software is able to quantitatively assess the vessel diameters, vessel density and the flow velocity of red blood cells in the different vessels. Current studies are under way to validate this automatic software system.

As mentioned in the introduction of this thesis, VA is an interesting phenomenon, providing a possible marker for the vascularization of the pelvic floor organs in postmenopausal women. Up till now, consensus on the most accepted definition of VA was lacking. We provided an evidence-based definition of VA and an overview of the clinical value of subjective and objective measurements of VA. In clinical practice, we recommend the use of the most bothersome symptom (MBS) approach as a subjective, feasible and affordable measurement tool. In the clinical practice setting, the MBS approach should be combined with a physical examination. The ‘vaginal physical examination scale’ provides a reproducible and valid assessment of VA evaluating 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 clinical setting these subjective measurements should be combined with one objective measure that is easy to perform: the vaginal pH. Vaginal pH could be combined with the measurement of the vaginal maturation index (VMI, defined as the proportion of parabasal, intermediate, and superficial cells). Disadvantage of this measurement is however, that it is difficult (expensive and time consuming) to incorporate in clinical practice. Moreover, vaginal pH can vary due to patient characteristics like smoking, blood, semen, the presence of bacterial vaginosis or vaginal medications. With these issues in the objective assessment of VA, it is questionable how well we identify women with VA, but also how reliable we can assess the effects of interventions intended to treat VA. This is why vaginal focal depth measurement could be of great value in the diagnosis of VA
and in the evaluation of treatment effect. In our study of vaginal focal depth we showed the great potential of this measurement in the diagnosis of VA and in the evaluation of treatment effect. Moreover, vaginal focal depth could be of great value for other applications in the field of gynaecology, for example in other vulvar conditions (e.g., lichen sclerosis), POP or POP surgery.

In our study of vaginal focal depth measurements in women with VA treated with topical oestrogen therapy, we found a significant increase in vaginal wall thickness after oestrogen treatment, indicating that topical oestrogen reversed the thinning of the vaginal epithelial layer associated with the declining levels of endogenous circulating oestrogens in postmenopause. Topical oestrogen could therefore be a treatment method to attack the effects of ageing. We reviewed the available evidence of topical oestrogen therapy in the treatment of pelvic floor disorders related to ageing showing topical oestrogens to be effective in the treatment of VA. Moreover, there is evidence implicating a beneficial effect of vaginal oestrogen treatment on urinary incontinence and overactive bladder symptoms. Most of the available evidence regarding proven benefit concerns the symptom of urge urinary incontinence. Though topical oestrogen may improve stress urinary incontinence (SUI) in post-menopausal women, the evidence is limited and should be interpreted with caution due to the small sample sizes and the different types, dosages and durations of oestrogen treatment investigated. We performed a prospective multinational study where SUI symptoms were assessed subjectively and objectively after topical oestrogen treatment and found a beneficial effect of topical oestriol cream on symptoms of SUI.

Concluding message
Ageing affects pelvic floor anatomy and function, resulting in several disorders like pelvic organ prolapse, lower urinary tract symptoms and vaginal atrophy. The lack of knowledge regarding the effects of ageing on vaginal vascularization and the influence of vaginal vascularization, as the representative of oxygenation of the vaginal tissue, on pelvic floor function, underlines the relevance of this thesis. We introduced several physiologic tests to better understand the relationship between function of pelvic organs and vascularization of the vagina. We were able to develop a non-invasive method to assess
vaginal microcirculation and vaginal wall thickness, and we provided an overview of the available evidence regarding topical oestrogens reversing the effects of ageing in pelvic floor disorders. Although we are not yet at the point of clinical application of the introduced physiologic tests, the gained knowledge offers great potential for further research.
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References