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ORIGINAL CLINICAL ARTICLE

The vaginal microcirculation after prolapse surgery

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Abstract

Aims: Oxygen plays a crucial role in wound healing after prolapse surgery. Trauma to the vaginal vasculature might limit the delivery of oxygen to the surgical wound, which may negatively affect wound healing and regeneration of connective tissue. This possibly increases the future risk of recurrence. We aimed to determine the effects of vaginal prolapse surgery on the microcirculation of the vaginal wall.

Methods: We evaluated the vaginal microcirculation in healthy participants without known vascular disease undergoing anterior and/or posterior colporrhaphy. We used incident dark-field imaging for in vivo assessment before and after (1 day, 2 weeks, and 6 weeks) surgery. We studied perfusion (microvascular flow index [MFI]), angioarchitecture (morphology/layout of microvessels) and capillary density.

Results: Ten women were included. Interindividual differences were observed 1 day postoperatively with regard to perfusion and angioarchitecture. Microvascular flow at the surgical site was absent or significantly reduced in some participants, whereas normal microvascular flow was observed in others (MFI range 0–3). Perfusion and angioarchitecture had been restored in all participants after 6 weeks (MFI range 2–3), regardless of the extent of vascular trauma 1 day postoperatively.

Conclusions: The difference in the extent of vascular trauma between women undergoing seemingly identical surgical procedures suggests that some individuals are more susceptible to vascular trauma than others. Delivery of oxygen to the wound and subsequent wound healing may be compromised in these cases, which could be related to the development of anatomical recurrence. Future studies should investigate whether there is a relationship between the vaginal microvasculature and the recurrence of prolapse.

KEYWORDS

cystocele, microcirculation, microvasculature, native tissue repair, pelvic organ prolapse, rectocele, recurrence, vaginal surgery

1 | INTRODUCTION

Pelvic organ prolapse (POP) is the descent of the pelvic organs to or beyond the vaginal walls.[1] It is a common condition that can result in micturition symptoms, defecation symptoms, and sexual dysfunction.[2] The lifetime risk for women to undergo surgery for POP is estimated to be as high as 10%.[3] Reconstructive native

tissue repair (NTR) is the most commonly performed surgical procedure but unfortunately, high recurrence rates of up to 50% are reported after NTR.[4,5] Procedures with a synthetic implant have been shown to be more effective, but are currently under scrutiny because the risk of serious adverse events.[6-8] The high recurrence rates and lack of safe alternatives stress the need for improvement of NTR.

Vaginal wound healing may affect the outcome of NTR. Wound healing can be divided into four phases: hemostasis, inflammation, proliferation, and remodeling.[9] Especially in the proliferative phase, collagen is deposited to re-establish tissue integrity and strength.[9,10] For effective wound healing, with optimal production of collagen, oxygenation of the wound at a cellular level is essential.[11-13] The delivery of oxygen primarily depends on the capillaries of the microcirculation, and the delivery rate depends on the hemodynamic principles convection and diffusion.[14] Convection is quantified by flow, and diffusion is quantified by the spatial arrangement of capillaries. In other words, the higher the capillary density and the more continuous the flow, the better the delivery of oxygen.

Therefore, a microcirculation postoperatively in which flow is suboptimal or even absent may compromise oxygenation of the wound resulting from NTR, which in turn would compromise wound healing, thereby increasing the risk of recurrent POP. The importance of the microvasculature in postoperative wound repair and wound dehiscence has also been described in other (pre)clinical studies.[15-17]

It is currently unknown to what extent the vaginal microcirculation is damaged during surgery, and whether this damage is reversible. If we can accurately and quantitatively determine such vascular damage, it can be investigated whether there is a relationship between vascular trauma and the recurrence of POP. It would also allow comparison of vascular damage from different surgical techniques, and it could be investigated whether strategies aimed to improve angiogenesis (estrogen, vaginal laser therapy) can limit vascular damage, or enhance vascular restoration.

The vaginal microcirculation was studied previously with a handheld video microscope based on the incident dark field (IDF) imaging.[18-21] This technique allows for reproducible, noninvasive and in vivo assessment of the vaginal microcirculation. In the present explorative pilot study, we assessed the vaginal microcirculation with IDF imaging before and after prolapse surgery. We aimed to determine if the microcirculation can be studied postoperatively, whether surgery affects microvascular perfusion and angioarchitecture and whether the vasculature can be restored to a presurgical level.

2 | MATERIALS AND METHODS

An explorative pilot study was performed at the outpatient clinic of the Department of Obstetrics and Gynecology of a University Medical Center. The Institutional Review Board approved the study protocol under number METC 2014_137. The study was registered in a database for registration and publication of medical research involving human subjects under number NL49122.018.14.

2.1 | Participants

Women undergoing primary anterior or posterior colporraphy because of prolapse POP-Q stage 2 or more in either the anterior and/or posterior compartment were eligible for participation. Women received verbal and written explanation of the study guidelines and procedures. Written informed consent was obtained from all participants. Baseline characteristics were obtained from the electronic patient records. Women were excluded when they suffered from cardiovascular diseases (eg, uncontrolled hypertension, angina pectoris), inflammatory diseases (eg, rheumatoid arthritis, eczema) or diabetes mellitus, because these conditions can affect the microcirculation. Also, women were excluded when they were taking medications that could affect the microcirculation such as anticoagulants, anti-inflammatory- or immunosuppressive agents.

2.2 | Surgical procedures

All participants were operated under general anesthesia. Prolapse surgery was performed according to standardized surgical protocol. Hydrodissection with a saline solution with 1:200.000 adrenaline was performed in all participants, and running Vicryl 2.0 sutures were used for closure of the vaginal epithelium in all participants. All participants received a single administration of cefazoline/metronidazol and nadroparine per-operatively. A vaginal pack and indwelling catheter were given for the first 24 hours after surgery.

2.3 | Incident dark-field imaging

Imaging of the microcirculation was performed with the CytoCam (Braedius Medical, Huizen, The Netherlands), which is a handheld video microscope on the IDF imaging.[22] This technique was previously used for assessment of the vaginal microvasculature.[18-20] It was also used to study other surgical procedures and wound healing.[17] In short, IDF imaging enables visualization of the organ surface microcirculation by using epi-illumination.

Greenlight is absorbed by hemoglobin in the red blood cells flowing in the microcirculation. Hereby, magnified moving images can be recorded, representing the space that these flowing red blood cells occupy and thus demonstrate the functional microcirculation. This technique is built into an easy-to-use device that is composed of aluminum and titanium, has the shape and size of a pen (length 220 mm, diameter 23 mm, weight 120 g) and is commercially available. The CytoCam is connected to a device controller, which in turn is connected to a laptop (P50, Lenovo, Peking, China) that is used for image storage and analysis.

2.4 | Imaging procedures

The CytoCam was covered with a disposable cap and the tip of the camera was placed 3 cm above the hymen. The camera was adjusted for optimal focus and contrast, and measurements were recorded clockwise: starting from the midline of the anterior vaginal wall, left lateral, the midline of the posterior vaginal wall and right lateral. At each position, three 100-frame measurements were performed. Imaging 1 day postoperatively was performed at least 1 hour after removal of the vaginal tampon that was placed after surgery. On the operated vaginal wall (either the anterior or posterior wall) measurements were performed on the scar tissue, in the midline and up to 1 cm to the right and left of the scar, from 3 cm above the hymen to a maximum of 8 cm above the hymen. In total, twelve videos were recorded per patient per time point. The pressure of the device on the vaginal wall was avoided to prevent pressure artefacts (ie, disturbance of capillary flow). Participants were instructed to indicate if measurements were painful. Participants underwent measurements at different time points. Before the surgery (T0), 1 day postoperatively (T1), 2 weeks postoperatively (T2), and 6 weeks postoperatively (T3). Measurements were performed by two experienced investigators (AWK and CMD).

2.5 | Quality score assessment

Each video clip was assessed through a scoring system based on six parameters (illumination, focus, content, stability, pressure, duration); failure to meet a parameter disqualified a video clip from the analysis.

2.6 | Analysis of microcirculatory parameters

We analysed the parameters (a) microvascular flow index; (b) tissue angioarchitecture scores; and (c) capillary density. All parameters were validated in previous studies.[18-21,23] Scoring of the microcirculation was performed by one investigator who was blinded for the clinical data (LdW). Another investigator with extensive experience in scoring microcirculation (AWK) provided close supervision and was available as an independent arbiter when there was doubt during scoring. AWK also performed an additional analysis of 10% of the data, which demonstrated high agreement with the initial analysis by LdW. We qualitatively described the angioarchitecture that was observed at the surgical sites. All videos that could not be scored according to the normal tissue angioarchitecture scores, were discussed and described by at least two investigators.

2.6.1 | Microvascular flow

The microvascular flow was assessed to determine perfusion. Flow characteristics were assessed using the MFI. The MFI was developed and validated by Boerma and coworkers and tested for reproducibility.[23] This score is based on the determination of the predominant type of flow in four quadrants. This scoring system quantifies the microcirculatory perfusion as absent (0), intermittent (1), sluggish (2) or normal (3), providing an index for microcirculatory blood flow velocity. The MFI score per region was the score that occurred the most. When the MFI was 3 in all quadrants, this was considered a normally perfused microvasculature. Perfusion was reduced when the MFI was 1 or 2, and perfusion was absent when we observed an MFI of 0.

2.6.2 | Tissue angioarchitecture

Tissue angioarchitecture is the morphology or lay-out of the vascular network. This scoring method was devised and validated to provide rapid recognition of subepithelial vascular patterns and showed a high agreement between observers in a previous study with complete agreement in 93% of frames and ICC between observers of 0.78.[18] Three types of predefined sub-epithelial vascular patters may be recognized and classified with a score 1, 2, or 3.[18] In score 1 capillary loops are predominantly observed. This is considered to be the most favorable angioarchitecture score, which is most frequently seen in premenopausal women with a thicker vaginal epithelium.[20] The capillary loops are necessary to supply the avascular epithelium with oxygen and nutrients. In score 2, capillary loops and vascular networks are both seen. In score 3, the vascular network without capillary loops is seen. Score 3 angioarchitercure is associated with a thin epithelium of the vaginal wall. Figure 1 shows these three types of angioarchitecture. When the angioarchitecture did not meet one of these

predefined patterns, we qualitatively described the angioarchitecture.

2.6.3 | Capillary density

When the vascularization was classified as a microvascular architecture score of 1 or 2 (ie, capillary loops were identifiable), the video was judged suitable for the assessment of capillary density. The capillary density was determined by counting the number of capillary loops per visual field and expressed as the mean number of capillary loops per square millimeter (cpll/mm^2). The frame of each image was 1.55 mm × 1.16 mm, resulting in a total area of 1.8 mm^2. The capillary density score per region was calculated by averaging the frames and divided by 1.8 to obtain the unit cpll/mm^2. Assessment of capillary density was performed in the same way in previous studies regarding the vaginal microcirculation.[18-20]

2.7 | Sample size calculation

We did not perform a sample size calculation. We determined a convenient sample of 10 participants suitable for this explorative pilot study where within-subject effects were studied. We also considered this small sample size to be sufficient based on the findings of a previous study in nine healthy female volunteers, where it was concluded that the vaginal microcirculation can be consistently and reliably measured in a small sample.[18]

2.8 | Statistical analysis

We compared baseline measurements with postoperative measurements to determine surgical trauma and restoration of vascularization. Descriptive statistics were used to present the demographic variables. Non-normally distributed data were presented as medians with interquartile ranges. Normally distributed data were presented as means and standard deviations. Postoperative measurements (T1, T3) were compared to baseline measurements (T0) using a Wilcoxon signed-rank test for paired numerical data (capillary density) and McNemar test for paired categorical data (MFI and angioarchitecture). A $P \leq .05$ was considered to be statistically significant. All analyses were performed using the statistical software SPSS (IBM SPSS Statistics for Windows, Version 24.0).

3 | RESULTS

3.1 | Participants

Ten participants with a POP-Q stage ≥2 were included in this study. In these participants, there were 14 vaginal walls involved in the surgical procedures (9× anterior colporrhaphy, 5× posterior colporrhaphy). The mean age was 64 ± 7.5 years. All participants were Caucasian, parous and postmenopausal. Three participants used vaginal estrogens perioperatively, no participants were active smokers. No participants had known the vascular disease. It was feasible to perform IDF imaging with the CytoCam before and after surgery in all participants. In some participants, imaging 1 day postoperatively was complicated by excessive vaginal discharge or vaginal blood loss. Careful cleaning with a vaginal swab and repositioning of the CytoCam enabled correct imaging in all cases. The T2 measurement was only performed in four participants, mostly due to difficulties with the hospital visit in the postoperative recovery period. Therefore, we only report on the T0, T1, and T3 measurements, which were performed in all participants.

3.2 | The microcirculation 1 day postoperatively

In 2 of 10 participants, remarkable changes were observed between the microcirculation at T0 and T1. In these cases, a severely altered angioarchitecture with a dilated and expanded vascular network was observed at

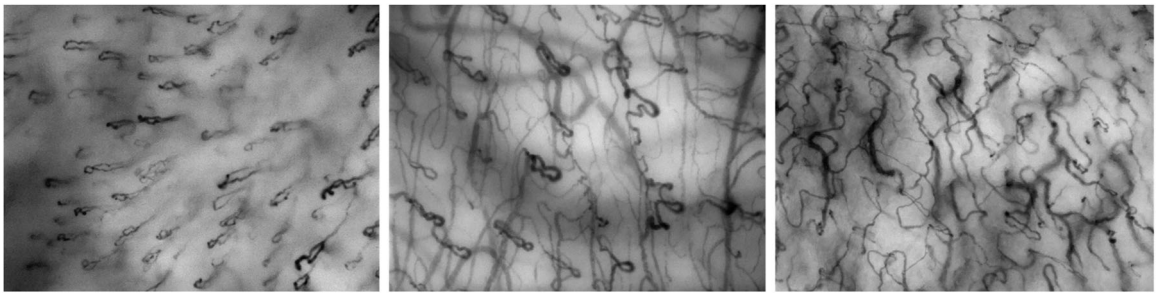

FIGURE 1 Screenshots of CytoCam videos with different types of angioarchitecture. Each image represents an area of 1.55 × 1.16 mm. Left: angioarchitecture score 1. Middle: angioarchitecture score 2. Right: angioarchitecture score 3

the surgical site 1 day postoperatively (Figure 2). In these individuals, we were not able to identify risk factors that could be associated with this damage. These participants did not use vaginal estrogen, did not smoke and the surgical procedures were identical to the procedures performed in other participants. It concerned one anterior vaginal wall and one posterior vaginal wall. We also observed areas with expanded capillary loops (Figure 2). At these locations, the capillary flow was absent and individual erythrocytes could not be identified within the microvessels. In other participants, smaller areas with extravasation of erythrocytes were observed, often next to a normally perfused microcirculation with a normal angioarchitecture (score 1, 2 or 3) (Figure 3, left). In these participants, the microcirculation appeared normally perfused (MFI 3) at the surgical site, all the way up to the incision (Figure 3, right).

3.3 | Analysis of microcirculatory parameters

3.3.1 | Microvascular flow index

The microvascular flow index (MFI) demonstrated differences between individuals and locations. In some participants, the MFI at the surgical site at T1 was 0, illustrating the absence of capillary flow and no perfusion of the microvasculature. In others, the MFI at the surgical site at T1 was 3, illustrating normal capillary flow and a normally perfused microcirculation. Overall, the MFI at the surgical site 1 day postoperatively was significantly lower than before surgery ($P = .03$). Microvascular flow at the nonsurgical sites was unaffected in all participants. After 6 weeks, the MFI scores of the surgical sites were comparable to the pre-surgical MFI scores of the surgical sites.

3.3.2 | Tissue angioarchitecture and capillary density

No differences were observed between T0, T1, and T3 regarding angioarchitecture scores ($P = .22$) and capillary density scores ($P = .48$). Surgery did not affect microvascular parameters of the nonsurgical sites in any of the participants.

4 | DISCUSSION

4.1 | Main findings

We demonstrated that vaginal angioarchitecture, microvascular perfusion, and recovery can be studied in vivo after prolapse surgery. We showed that prolapse surgery

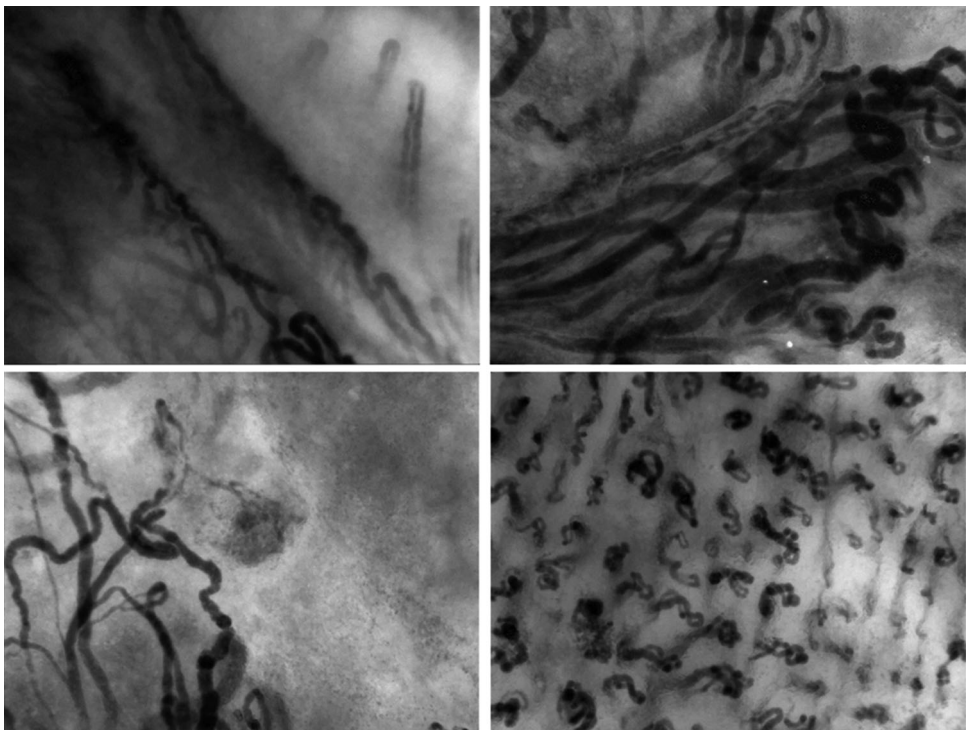

FIGURE 2 Screenshots of CytoCam videos, each image representing an area of 1.55 × 1.16 mm. A severely altered angioarchitecture with a dilated and expanded vascular network at the surgical site 1 day postoperatively. The capillary flow was absent and individual erythrocytes could not be discriminated. Bottom right: angioarchitecture type 1 with capillary loops can be distinguished, but the capillary loops are dilated and flow is absent

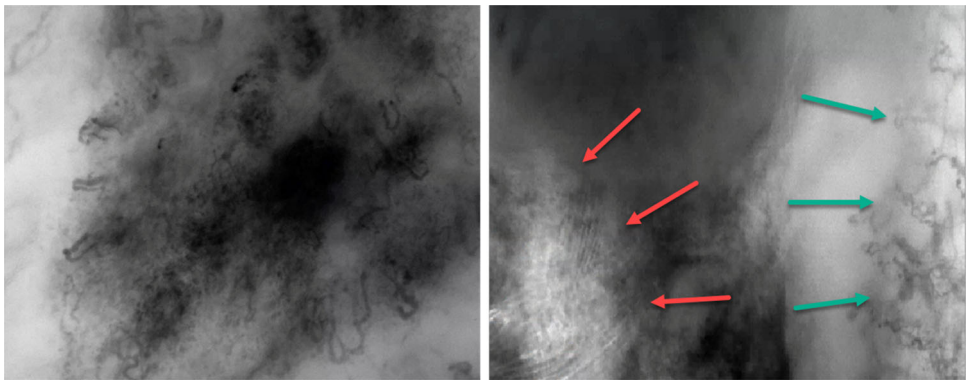

FIGURE 3 Screenshots of CytoCam videos. Each image represents an area of 1.55 × 1.16 mm. Left: areas with extravasation of erythrocytes are observed, imposing as a hematoma. The adjacent microcirculation was perfused normally. Right: video was taken at the surgical site one day postoperatively. Red arrows: suture (Vicryl 2.0) at the incision. Green arrows: normal flow (MFI 3) in the microcirculation and normal, type 2 angioarchitecture

can have a significant effect on the vaginal microcirculation and that effects vastly differed between subjects. Regardless of the extent of the vascular changes observed 1 day postoperatively, quantitative and qualitative parameters had been restored to a pre-surgical level in all participants 6 weeks after surgery, suggesting the microvasculature of the vaginal wall has the significant regenerative capacity.

4.2 | Interpretation of results

We have observed an altered angioarchitecture and an obvious reduction in vaginal wall microvascular flow in some participants 1 day postoperatively. The vascular damage may be the consequence of dissection and tissue handling during surgery, and the reduction in flow may be the consequence of intravascular coagulation and hemostasis to the incision. The interindividual differences in vascular damage are remarkable, since participants underwent seemingly identical surgical procedures. It could suggest that some individuals are more susceptible to vascular trauma than others. We were not able to identify specific risk factors in these participants that explain the vascular damage.

Because estrogen has vasoactive effects, it possibly also improves the resilience of the vaginal microcirculation, which makes vascular damage during surgery less likely to occur. All participants that were using vaginal estrogen (n = 3), had normal angioarchitecture and flow at T1. The sample size of the current study is however too small to draw conclusions from this, and it should be investigated in a larger patient sample whether vascular damage is less likely to occur in women using estrogen. Based on the aforementioned numbers, a study comparing an estrogen-exposed group to a nonestrogen group should have a sample of at least 40 participants to have an 80% chance of detecting a relevant decrease in alteration of angioarchitecture 1 day postoperatively.

The fact that no significant differences were observed when comparing microcirculatory parameters before and 6 weeks after surgery, suggests that the vaginal microcirculation has significant capacity to recover. Given the apparent regenerative capacity of the microcirculation, it can be argued that microvascular damage will be of limited effect on surgical outcome, since the microcirculation was restored in all participants at 6 weeks. However, it can also be argued that a damaged microcirculation in the first days after the operation is in fact detrimental, since the synthesis of collagen has been shown to start 48 hours after surgery, and continues until day 7.[9,10] Therefore, when the microcirculation is dysfunctional in the first week after surgery, the delivery of oxygen to the surgical wound could be limited. Consequently, the synthesis of collagen would be inhibited, leading to a weaker vaginal wall.[11,13] While this may not cause problems in an early stage, a weaker vaginal wall could be more prone to anatomical recurrence years later.

4.3 | Clinical implications and future perspectives

This study demonstrated that IDF imaging can be used to study vaginal microcirculation after prolapse surgery. Therefore, it can be studied if there is a correlation between vascular damage and long term surgical outcome. Also, (novel) strategies that aim to improve the outcome of prolapse surgery by enhancing vascularization and oxygenation, can be evaluated. Future studies evaluating the effect of such therapies could include assessment of the microcirculation, as objective, non-invasive outcome measurement of vaginal surgery. Other

future applications include microcirculatory assessment of (newly developed) vaginal implants, in which case angiogenesis can be studied as a key representative of scaffold integration.[24] Also, a recent study demonstrated that IDF imaging can be used to study leukocyte recruitment and adhesion to the endothelium, as hallmarks of systemic inflammation.[25] This is potentially interesting when the inflammatory response to vaginal implants is studied.

4.4 | Strengths and limitations

The current study allowed us to noninvasively study the vaginal microcirculation perioperatively and in vivo. Limitations of this study include the small sample size, which allowed us to merely perform an explorative analysis. Larger sample size would be necessary to define the magnitude and clinical relevance of the observed changes in the microcirculation, and to identify which factors are predictors of these changes. Second, it was difficult for participants to come to the hospital 2 weeks after surgery, because of prescribed restrictions in activities, such as traveling and driving a car. Consequently, we did not study this data point. Third, the focal depth of the CytoCam is limited to 300 μm, indicating that imaging of the deeper, fibromuscular layers of the vaginal wall, is not optimal. Healing of these deeper layers is especially important in prolapse repair and prevention of recurrent POP. Unfortunately, to date, there are no alternative techniques that allow imaging of the microvasculature in this detail of deeper layers. Nevertheless, we consider the status of the more superficial vasculature to be a representative of the vascularization of the deeper layers of the vaginal wall. Fourth, images with a severely altered angioarchitecture could not be assigned an angioarchitecture score and were therefore excluded from quantitative angioarchitecture analysis. Therefore, the overall angioarchitecture scores at T1 underestimate the true effect of surgery on angioarchitecture.

5 | CONCLUSIONS

Incident dark-field imaging can be used to study vaginal microcirculation after prolapse surgery. Microvascular flow and angioarchitecture show interindividual differences after prolapse surgery, suggesting that some women are more susceptible to surgically-induced vascular trauma than others. Future studies should investigate whether there is a relationship between vascular damage and long term surgical outcome, and explore the potential of therapies such as vaginal estrogen therapy to decrease vascular damage during surgery.

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CONFLICTS OF INTEREST

Prof. Ince is listed as the inventor of SDF imaging on related patents owned by the Academic Medical Center (AMC). He receives no royalties or benefits from this license. Braedius Medical, which is a company owned by a relative of Prof. Ince, has developed and designed a handheld microscope called Cytocam-IDF imaging. Prof. Ince has no financial relationship with Braedius Medical of any sort (ie, has never owned shares or received consultancy or speaker fees from Braedius Medical). Prof. Ince runs an internet site (https://microcirculationacademy.org) that offers services (eg, training, courses, and analysis) related to clinical microcirculation

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