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FemStent – A Microstructured Polymer Stent for Enhanced Gamete Transport in Proximal Tubal Occlusion

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Abstract: Proximal Fallopian tube occlusion represents a significant cause of female infertility, limiting natural conception. To address this challenge, we proposed the *FemStent* previously – a polymer-based, bioresorbable, and self-expanding microstent. To accelerate the epithelialization of the inner stent surface and thus enable safe and uninterrupted passage of gametes, the concept of microstructuring was developed. Corresponding patent applications have been filed (EP 23200861, PCT/EP2024/077397). The current study analyzed the technical feasibility of microstructuring the inner stent surface. For this purpose, stainless steel mandrels were microstructured using femtosecond laser ablation and then used to manufacture tubular semifinished products made of poly-(L-lactide). Microstent prototypes were manufactured by using femtosecond laser cutting of polymer semifinished products with and without a microstructured inner surface. The microstent prototypes were subjected to comprehensive morphological analyses. An *in vitro* model system for particle tracking was developed to demonstrate the permeability of the fallopian tube stent for gametes. The results demonstrate the technical feasibility of a fallopian tube microstent with a clearly defined microstructured inner surface and provide evidence for improved gamete transport. Future *in vitro* studies in more elaborate models as well as future *in vivo* studies will provide further insights into optimizing the microstent's structure and function. This research lays the groundwork for an innovative gynecological intervention, potentially improving fertility outcomes in patients with proximal tubal occlusions in the future.

Keywords: Fallopian tube, microstent, femtosecond laser, microstructure, particle tracking velocimetry.

1 Introduction

Fallopian tube blockages are among the leading causes of female infertility, posing a significant challenge for many women. Currently available treatment approaches include *in vitro* fertilization, Fallopian tube surgery or transcervical catheterization [1]. Given the limitations of existing treatment options, our group previously introduced the concept of the *FemStent* – a polymer-based, bioresorbable, and self-expanding microstent [2].

For accelerated epithelialization of the inner stent surface and thus safe and uninterrupted passage of gametes, the concept of microstructured stent struts was developed (Fig. 1).

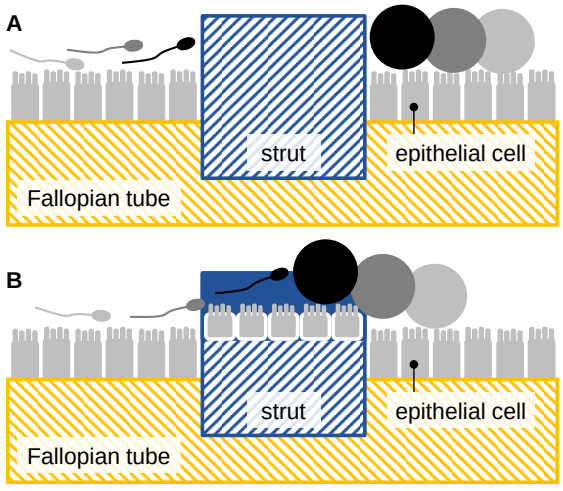

Figure 1: Schematic longitudinal section through a Fallopian tube. Detailed view of a microstent strut without (A) and with microstructure for local reduction of wall-thickness (B). Illustration of impaired (A) or optimized epithelialization and thus gamete movement in the strut region [3].

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Microstructuring represents an essential aspect of current patent applications [3]. Within the current study we analyzed the technical feasibility of a microstent with a microstructured inner surface.

2 Materials and methods

2.1 Manufacturing of microstents

Tubular semifinished products were manufactured by means of a dip-coating process. Stainless steel mandrels with a diameter of 2 mm and 55 mm in length were used. For a smooth inner surface, the mandrels were turned and polished to a diameter of 1.93 mm. For the manufacturing of microstents with a microstructured inner surface, the mandrels were processed by means of femtosecond laser ablation using a Monaco 1035-80-60 (Coherent Inc., USA) embedded into a 4-axis CNC system (Star Cut Tube Monaco, Coherent Munich GmbH & Co. KG, Germany). The surface of the mandrels is scanned with the laser beam (focus diameter 22 µm) line by line along the mandrel's longitudinal axis. In order to realize trenches having a width of 40 µm, nine lines were bunched such that their intensity envelop creates the desired trench (Fig. 2). The distance between the bunches was adjusted to obtain an inter-trench distance of 60 µm. A laser pulse energy of 10 µJ, a pulse repetition rate of 40 kHz, and a traverse speed of 5 mm s^{-1} were used. Process gas was argon at 5 bar.

For dip-coating, a chloroform-based poly(L-lactide) (PLLA, Resomer L210, Evonik Health Care GmbH, Germany) solution (6 g PLLA in 200 ml chloroform) was used. The mandrels were repeatedly dipped into the polymer solution using a KSV NIMA Dip Coater (Biolin Scientific Holding AB, Sweden) at a withdraw speed of 400 mm min^{-1}. Following each dipping cycle, samples were dried for 2 min and rotated 180°. After 16 cycles, the target wall thickness of 100 µm was attained. After dip-coating, semifinished products were processed and microstents were cut by means of femtosecond laser ablation as described previously [4].

2.2 Morphological characterization of microstents

Surface morphology was analyzed using confocal laser scanning microscopy (LEXT OLS5100, Olympus Corp., Japan) and scanning electron microscopy (Quattro S, Thermo Fisher Scientific, USA) in low vacuum mode at 50 Pa and 5 to 15 kV. No further preparation of the samples was needed.

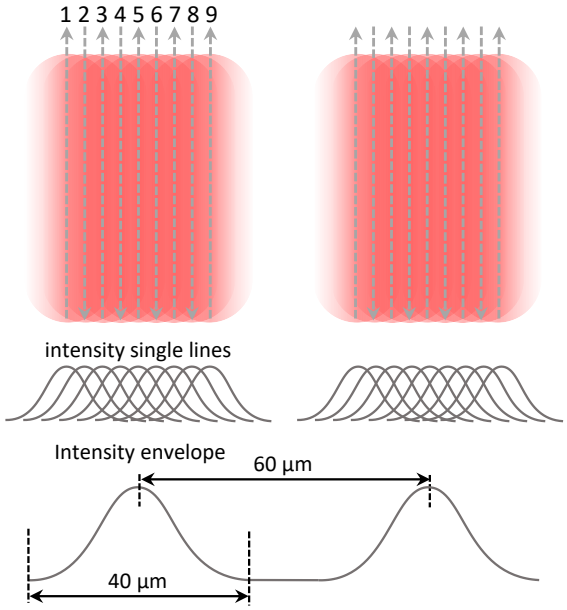

Figure 2: Strategy for milling the trenches. A bunch of 9 single lines form an intensity envelope having a width of 40 µm. The inter trench separation is 60 µm.

2.3 Development of a particle tracking test setup for *in vitro* gamete transport analyses

As a simplified *in vitro* model system for gamete transport through a Fallopian tube microstent, a particle tracking test bench was developed. The microstent was implanted into a silicone tube with an inner diameter of 2 mm and a wall-thickness of 1 mm and placed inside a test chamber. The chamber is linked to a fluid reservoir and an outlet with a collection basin behind it, in order to determine the volume flow. A high-speed camera (EoSens 12CXP+, Mikrotron, Germany) with a macro lens (35-08-14-000 MINI 2X/400FL Optem Fusion, Excelitas Technologies GmbH & Co. KG, Germany) and LED lighting (Constellation 120E15, Veritas, Integrated Design Tools, Inc., USA) were used. The test setup is depicted in Fig. 3.

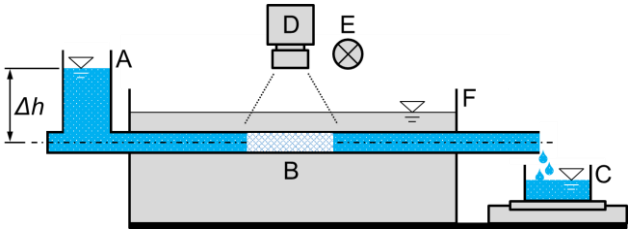

Figure 3: Schematic representation of the particle tracking test setup for *in vitro* gamete transport analyses: fluid reservoir (A), silicone tube with / without implanted microstent (B), collection basin on laboratory scale (C), high-speed camera setup (D), LED lighting (E) and fluid-filled test chamber (F). Fluid column *Δh* was kept constant during test.

As representative gametes, polystyrene particles with a diameter of 50 µm (PS-FluoRot-W22, microParticles, Germany) were added into the test fluid in the fluid reservoir. The fluid column Δh was adjusted to obtain a volumetric flow rate of 1.2 ml min^{-1}, corresponding to a mean fluid velocity of 6.5 mm s^{-1}, and kept constant during test.

The test fluid consists of a mixture of glycerine and water. This allows the refractive index of the fluid to be adapted to the refractive index of the silicone tube, enabling distortion-free tracking of the particles in the test fluid. The refractive index of the silicone tube was first determined using an Abbe refractometer (AR4, A.KRÜSS Optronic). Afterwards, a suitable mixture of glycerine and water was determined in order to achieve the same refractive index. The test fluid was also filled into the test chamber outside the silicone tube to minimize optical distortion. The particles in the test fluid were illuminated with the LED. The scattered light was detected by the cameras at 160 fps for 300 images.

Post-processing was carried out using DynamicStudio 7.6 (Dantec Dynamics, Denmark). An averaged image was first created and substracted from all images to eliminate unnecessary reflections. In addition, image arithmetic was used to increase the contrast between particles and background.

The particles were tracked manually within the image sequences of 300 images. At a frame rate of 160 fps, images were captured over a period of 1.875 s. The particles were tracked for at least ten frames. The mean distance of the particles from the vessel centreline and the flow velocity were calculated from the values.

3 Results

Manufactured microstents with a smooth or microstructured inner surface are depicted in Fig. 4. The images show that a microstructuring of the inner surface along the microstent's longitudinal direction could be successfully achieved.

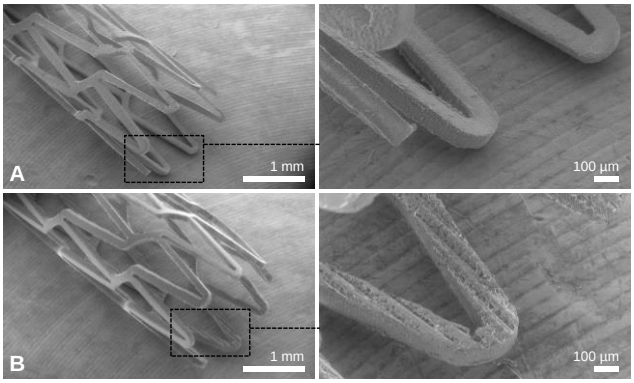

Figure 4: Scanning electron microscopy of a microstent with a smooth (A) or microstructured inner surface (B).

An exemplary measurement of the height profiles of the inner surface by using confocal laser scanning microscopy is shown in Fig. 5. With 46 µm wide trenches, a 64 µm trench spacing and a trench depth of 20 µm the dimensions of the molded microstructure correspond to the desired design.

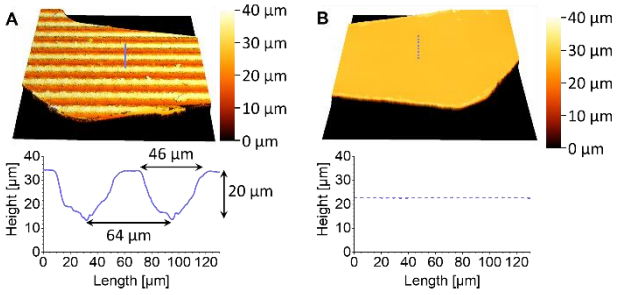

Figure 5: Morphology of the microstructured (A) and the smooth inner surface (B). Solid and dashed blue lines indicate the positions of the shown height profiles. The dimensions of the obtained surface structure matches the desired design shown in Fig. 2.

The results of *in vitro* particle tracking analyses are shown in Fig. 6 and Fig. 7. An exemplary snapshot of the analyzed field of view in the outflow region of a microstent with microstructured inner surface gives an impression of the number of particles (white dots) and enables a visualization of the expected flow velocity profile as a function of the radial position u(*r*).

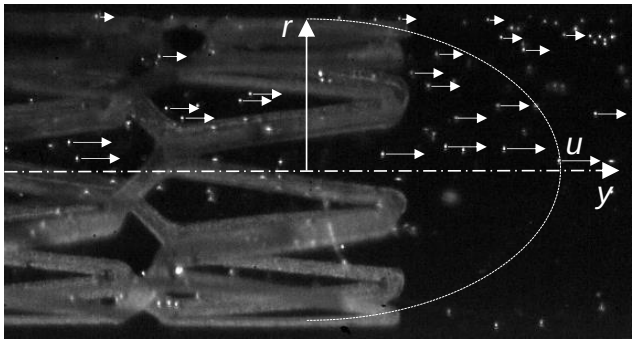

Figure 6: Exemplary snapshot of the analyzed field of view in the outflow region of a microstent with microstructured inner surface. Particles are visible as white dots. Visualization of the expected parabolic flow velocity profile *u(r)*.

The measured flow velocities of 30 trackable particles inside the field of view for a silicone tube without an implanted microstent as well as for a silicone tube with an implanted microstent with smooth inner surface or with microstructured inner surface are shown in Fig. 7. As a guide for the eye, a parabolic representation of the flow profile was implemented. Due to the narrowed flow cross-section at constant volumetric flow rate, overall higher flow velocities are measured for both microstent groups. As a simple average of the measured particle velocities a straightforward quantitative comparison between the groups was conducted. While this does not

directly represent the true mean velocity of the parabolic profile, a consistent basis for relative evaluation was calculated. For a blank silicone tube, a microstent with smooth inner surface and a microstent with microstructured inner surface, mean flow velocities of 4.4 ± 2.5 mm s^{-1}, 5.6 ± 2.7 mm s^{-1} and 5.9 ± 2.7 mm s^{-1} were calculated, ($n = 30$) respectively. The microstent with microstructured inner surface exhibited the highest mean velocities and a well-defined parabolic velocity profile, with relatively higher velocities near the wall compared to the other configurations.

4 Conclusion

Within the current work we demonstrate the technical feasibility of the *FemStent* – a fallopian tube microstent with a microstructured inner lumen. The initial experiments using the developed *in vitro* particle tracking test setup provide evidence for improved gamete transport through a Fallopian tube microstent with a microstructured inner surface.

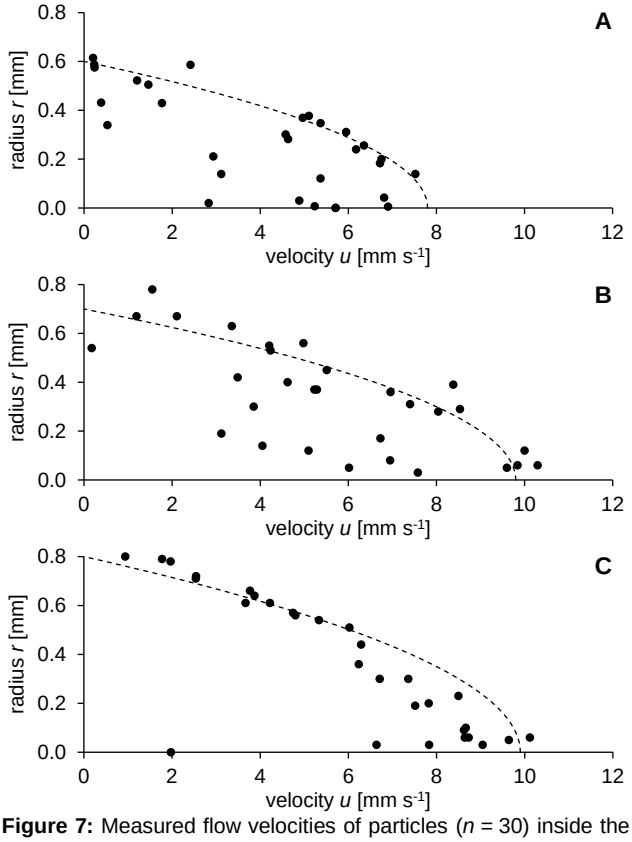

Figure 7: Measured flow velocities of particles ($n = 30$) inside the field of view for a silicone tube without an implanted microstent (A) as well as for a silicone tube with an implanted microstent with smooth inner surface (B) or with microstructured inner surface (C). As a guide for the eye, a parabolic representation of the flow profile was implemented.

The current study has several limitations that should be considered. The described *in vitro* model does not account for the anticipated improvement in epithelialization. The chosen 50 µm particles are sized between sperm cells and oocytes, necessitating more specific tests, particularly different particle sizes, in future particle image velocimetry (PIV) studies.

From the literature, complex *in vivo* models are known, for example for analysis of oocyte movement within the mouse oviduct [5]. The aim of the current study was a more simple *in vitro* model for assessment of gamete movement through different microstent structures under reproducible technical laboratory conditions. Future *in vitro* studies in more elaborate PIV models as well as future *in vivo* studies will provide further insights into optimizing the microstent's structure and function.

Author Statement

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