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Cap assisted hysteroscopy enables retrograde catheterization and hydrotubation of the equine oviduct

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Summary: Infertility in the brood mare with no clinically identifiable cause is of great concern for economic and emotional reasons. Diseases of the fallopian tube are a known cause of infertility in women; but due to the poor operational accessibility it is still an area with many unknowns in equine reproductive medicine. Previous studies indicate positive effects of catheterization and subsequent irrigation of the fallopian tube (hydrotubation) to remove cell debris and collagen masses that clog the lumen, preventing the oocyte from being fertilized or the embryos migration through the fallopian tube. As an alternative to flank laparoscopy, a hysteroscopic access using a catheter has been described, which led to increased pregnancy rates in supposedly sterile mares. With the technique described here, hysteroscopic access to the uterine papilla was possible in 22 standing, sedated mares in dioestrus. Use of an attachment cap for the endoscope and a specially developed, conical-tapered catheter with angiography guide wire made it possible to visualize the uterine papilla as well as secure access to the fallopian tube and subsequent hydrotubation. Of 22 papillae hysteroscopically controlled with a cap, 20 were successfully catheterized. The microbiological evaluation of endometrial swabs showed an increase in genital pathogens after the procedure. After completion of the hysteroscopy prostaglandin was always administered to induce oestrus. 7/9 (78%) patient mares with unexplained sterility became pregnant in the breeding season following the fallopian tube irrigation. Endometrial biopsies from the two mares remaining barren were classified in category III (foaling probability < 10%). The catheter system developed in this study in conjunction with the cap-assisted hysteroscopy enables safe targeting of the uterine papilla, as well as the subsequent catheterization and hydrotubation of the fallopian tube. To summarize, the minimally invasive technique described here can safely replace the surgical-operative flank access to the fallopian tube in mares with suspected obstruction of the fallopian tube lumen, and fertility was restored in 7 out of 9 mares.

Keywords: mare, infertility, Fallopian tube obstruction, hysteroscopy

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Introduction

In human medicine oviduct associated pathology is one of the main reasons for infertility (*Serafini* et al. 1989). Diagnostic and therapeutic approachability of the human oviduct is well established (*Kodaman* et al. 2004). Pathologic findings in the equine salpinx have been described as well. Infundibular cysts and adhesions, as well as collagenous masses and cysts within the ampulla were recognized in a variety of evaluated equine oviducts (*Tsutsumi* et al. 1979, *Medenbach* et al. 1999). However, tubal diagnostic accessibility in mares is limited so far by anatomic conditions of the utero tubal junction. The uterine papilla is supported by smooth muscles, building a sphincter (*Kranier* 1993). This anatomical peculiarity in horses limits possibilities for diagnostic and therapeutic approach significantly. Nevertheless, the equine fallopia tube is of great interest due to a notable number of clinically reproductive healthy mares not being able to conceive.

Currently diagnosis of oviductal pathologies in mares is in most of the cases based on clinical suspicion and by exclusion of other diseases of the reproductive organs. Visualization of tubal patency via contrast ultrasonography (*Wang* et al. 2017) is hardly feasible due to anatomical conditions. In previous studies fluorescent beads or starch grain were injected into the ovaries or the oviduct by transvaginal or laparoscopic approach and retrieved trough uterine lavage to evaluate oviducts consistency (*Arnold* and *Love* 2013, *Allen* et al. 1979), both invasive and expensive procedures.

In mares with a regular cycle, no visible hormonal imbalances, no pathologic findings in vulva, vagina, uterus, ovaries and inconspicuous findings in endometrial biopsy, oviduct associated blockage is considered as the most probable reason for infertility. For oviductal treatment mainly laparoscopic techniques are described for orthograde flushing of the oviduct (*Kollmann* et al. 2011) as well as topical application of prostaglandin E (PGE) (*Allen* et al 2006) using

its characteristics of stimulating oviduct dilatation and contraction (*Weber* et al. 1991, *Chiossi* et al. 2012). These techniques are performed under general anesthesia or in standing heavyly sedated mares. This means a serious procedure for the mare associated with the risk of peritoneal infection, high costs and high personnel expenditure. Techniques for successful hysteroscopic hydrotubation in standing sedated mares have been described, using a catheter with a length of 200 cm and an additional guide wire (*Inoue* 2013, *Inoue* and *Sekiguchi* 2018, *Schnobrich* 2016). Due to flushing trough the UTJ with physiological saline solution, oviductal blockage could be mechanically removed and pregnancy rates in allegedly infertile mares could be elevated (*Schnobrich* 2016). Comparison of pregnancy rates after laparoscopic PGE application and hysteroscopic hydrotubation of the fallopian tube showed no significant differences (*Walborn* et al. 2018) which indicates giving priority to the less invasive and equal effective method.

The aim of this study was to conduct hysteroscopic oviduct catheterization in mares with a history of unexplained infertility and to establish a minimal invasive approach to the equine oviduct in standing sedated mares. This approach could be used for biotechnologies as well. Subsequently further development and improvement of the catheter were made to increase success rates and simplify the procedure.

Materials and methods

Animals

In preliminary tests standard hysteroscopically-guided retrograde ovi-ductal catheterization on both sides as described below was performed in seven mares in dorsal recumbency immediately after euthanasia, due to medical reasons. Black ink was used to visualize oviductal patency after successful catheterization. After catheterization and oviductal ink flushing, ovaries, fallopian tubes and tips of the uterine horns were removed to evaluate patency of the fallopian tubes and distribution pattern of the ink (Fig. 1).

Hysteroscopic oviductal catheterization was then carried out in 22 standing sedated warmblood mares of different sizes and breeds with an average age of 14.9 years (6–22 y). Nine of the mares were nulliparous, older than 6 years, 13 multiparous, barren for at least 2 years. Thirteen mares were held for educational purposes at the Clinic for Horses of the University for Veterinary Medicine Hannover. The other 9 mares were owned by clients, had a history of infertility and were sent to the Unit for Reproductive Medicine by their referring veterinarians. Average age of the client mares was 14.7 years (6–21 y); three of those were inseminated several times without establishing pregnancy, the other six mares had several foals but had been barren for the last two years at least. All mares had been handled by different veterinarians experienced in reproductive medicine before. Standard treatments for barren mares (e.g. uterine swap samples and biopsy, change of stallion for insemination) had been carried out in all cases without any conspicuous findings respectively leading to the conclusion of an extrauterine reason for infertility.

Experiments were performed in agreement with German animal welfare legislation and approved by the Lower Saxony State Office for Consumer Protection and Food Safety (33.8-42502-04-16/2284).

Clinical evaluations

Transrectal and ultrasonographic evaluations

Before hysteroscopy the mares' general health was checked and the genital organs were examined by transrectal palpation and ultrasonography (Logiq P5 US with probe 1739, 6–10 MHz; both GE Ultraschall, Solingen, Germany). General health, state of oestrus cycle and no pathologic findings of the uterus and ovaries were confirmed. Mares showing signs of endometritis (uterine fluid, vaginal discharge) were excluded. Only diestrus mares were included to ensure good visibility and accessibility of the uterine papilla and to make sure insufflated air could not escape through a dilated cervix following recommendations by *Bartmann* et al 1997.

Sampling

Mares' tail was wrapped with a clean bandage and held aside. The perineal region was cleaned with antimicrobial washing lotion with 4 % chlorhexidine gluconate (Hibiscrub®, Mölnlycke® Health Care AG, Schlieren, Germany) and water, and dried up with clean paper towels.

Before and after hysteroscopy, uterine swap samples were taken for microbiological evaluation as described before (*Spilker* et al. 2017). A sterile spreadable Polansky-speculum was inserted into the vagina, the external cervical os fixed with

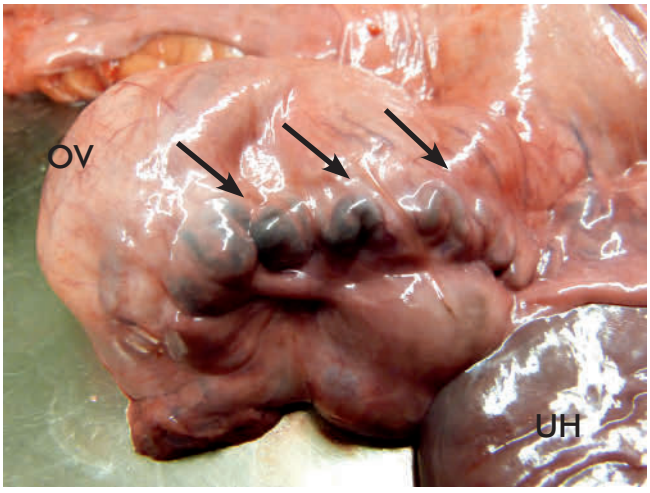

Fig. 1 Ovary (OV), oviduct (arrows) and Uterine horn (UH) removed during necropsy of mare, used in preliminary tests. Black ink was used for flushing the fallopian tube and prove oviducts patency. The meandering course of the fallopian tube from Ovary to Uterine horn tip can be retracted easily (Arrows). | *Ovar (OV), Oviduk (Pfeile) und Uterushorn (UH), entnommen nach Sektion. Schwarze Tinte wurde durch den Eileiter gespült um dessen Durchgängigkeit aufzuzeigen. Der meanderförmige Verlauf des Eileiters vom Ovar zur Uterushornspitze kann nachverfolgt werden (Pfeile).*

forceps by Götze modified by Albrechtsen and the double-guarded uterine swab (Minitübe® GmbH, Tiefenbach, Germany) introduced through the cervix under visual control with an electric torch. The swabs were kept in contact with the endometrium for 30 sec. Microbiological culturing and analysis was conducted by the Institute of Microbiology, University of Veterinary Medicine Hannover, Germany, as described by *Schöninger* et al. (2014).

Uterine biopsy

Uterine biopsies were collected with a sterile biopsy punch and fixed in 4% buffered formaldehyde. Sample processing, examination and evaluation was conducted by the Institute of Pathology, Faculty of Veterinary Medicine, University of Leipzig, Germany, as already described (*Schoon* et al. 1992, *Schoon* et al. 1997). Classification of endometria was implemented according to *Kenney* and *Doig* (1986).

Hysterocopy and oviductal catheterization

For hysteroscopy mares were restrained in stocks and sedated by intravenous injection with 0.01 mg/kg detomedine (Cepesedan, cp-pharma®, Burgdorf, Germany) and 0.02 mg/kg butorphanol (Butorgesic, cp-pharma®, Burgdorf, Germany). In addition, a non-steroidal anti-inflammatory drug was administered intravenously (flunixin-meglumine 1.1 mg/kg; Flunidol RPS, cp-pharma®, Burgdorf, Germany). Hysteroscopy was conducted as described before (*Bartmann* et al. 1997): the endoscope was inserted through the vagina by the examiner wearing a sterile glove. The endoscope was introduced through the cervix, the uterus then was insufflated with air until the bifurcation and both uterine horns were visible. The endoscope was advanced to both uterus horn tips to evaluate condition and appearance of the papilla uterine. Subsequently the catheter was inserted through the ostium uterinae papilla uterinae.

Post treatment, mares were reexamined the two following days to evaluate general and genital health. Special attention was paid to any signs of uterine inflammation (e.g. uterine fluid, intense endometrial swelling, vaginal discharge). In addition, intravenous treatment with non-steroidal anti-inflammatories (flunixin-meglumine 1.1 mg/kg; Flunidol RPS, cp-pharma®, Burgdorf, Germany) was continued for two days following catheterization. In presence of a responsive corpus luteum, mares were short cycled using intramuscular injection of PGF2α (Cloprostenol 0.5 µg/kg, Estrumate, MSD Animal Health®, Schwabenheim, Gemany).

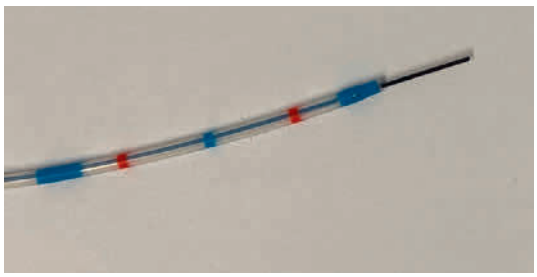

Fig. 2 ERCP-catheter with conical tip and inside metal ring (MTW® Endoskopie Manufaktur) with guide wire as insertion aid. *ERCP Katheter mit konischer Spitze und inneliegendem Metallring (MTW® Endoskopie Manufaktur) mit Angiographiedraht als Einführhilfe.*

Standard catheterization technique

For hysteroscopy, a videoendoscope (length 168 mm, diameter 12.8 mm; Olympus®, Hamburg, Germany) was used. Catheterization was performed with a catheter with an inner tube (length 2300 mm, diameter 1.8 mm; Pauldrach®, Garbsen, Germany).

Standard technique was tested in seven euthanized mares, in five standing sedated experimental mares without local anaesthesia and in two experimental mares after dropping 2% lidocaine hydrochloride injection solution (Bela-pharm®, Vechta, Germany) on one papillas' surface previous to catheterization. Local anaesthasia of the papilla was supposed to avoid mucosal reaction and contraction of the muscles surrounding the uterine papilla.

Modified catheterization technique

Initially a catheter with an inner tube rounded metal tip (length 230 mm, diameter 1.8 mm; Besamungssonde, Pauldrach®, Garbsen, Germany) was used.

A cap for mucosal resection (MH-595, Olympus®, Hamburg, Germany) as described before by *Otzen* et al. (2016a, 2016b) and a guide wire for angiography (length 220 cm, 0.46 mm diameter; RF-GA 18263, Terumo, Leuven, Belgium) was added.

Before using the cap a general endoscopic overview of the uterine lumen and endometrium was gained. Subsequently the endoscope was removed, cleaned, the cap was added and the endoscope was reinserted.

To facilitate catheterization of the oviduct, the guide wire for angiography was inserted through the catheter tube to simplify introduction of the catheter and prevent multiple slippage of the catheter tip off the papilla uterina. By additional distal attachment of the cap for mucosal resection, proper positioning and fixation of the catheter close to the papilla uterina could be ensured.

The catheter has been improved multiple times by changing shape, material and width of the tip, differing to the version considered by *Inoue* (*Inoue* 2013, *Inoue* and *Sekiguchi* 2018) until the best combination was found to ensure oviduct catheterization and hydrotubation. The final version turned out to be an endoscopic retrograde cholangioprancreaticography (ERCP)-catheter with conical tip, with inside metal ring and Y-nozzel (length 215 cm, 1.6 mm diameter; MTW® Endoskopie Manufaktur W. Haag KG, Wesel, Germany) (Fig. 2).

Modified catheterization technique was tested in 5 mares, without the purpose of being bred afterwards, owned by the Clinic for Horses of the University for Veterinary Medicine Hannover and in 9 mares with a history of sudden infertility owned by clients.

Oviductal hydrotubation

Once the cathetertip was introduced through the ostium uterinae papillae uterinae, the guide wire was removed and a syringe filled with 10 ml sterile saline solution was adapted to the Y-nozzle. Saline solution was injected through the catheter. In most cases at the beginning of injection, high pressure had to be applied. Once the oviductal occlusion was removed, the saline solution was easily injectable. Backflush from the papilla occurred on average after 2–3 ml and was assessed as oviductal overflow. If injection was conductable with low to medium pressure 10 ml were used for flushing to improve the mechanical flushing effect. Color and consistency of backflowing liquid was recorded.

Results

In all seven euthanized mares uterine papilla was easy accessible, since there was no muscular tone or movement, and catheterization was feasible in all cases (14/14 oviducts); additional oviductal patency could be proved in all cases by injection of black ink through the papilla and subsequent evaluation during necropsy (Fig. 1).

One experimental mare had to be excluded from the experiment due to uterine fluid and signs of endometritis. Using the standard catheterization technique in 7 experimental mares 7/14 oviducts (50 %) could be entered and hydrotubated. Rounded metal tip of the catheter caused slippage of the papilla, and the inner hose lacked of stability during entering the oviduct. Manipulations led to excessive swelling in all 14 papillae. Combining the standard technique with application of lidocainehydrochloride in two experimental mares caused aggravation due to tissue reaction to the medical preparation. In consequence, oviductal catheterization wasn't possible. Duration until successful catheterization (if feasible) took more than 90 minutes.

Using the modified catheterization technique the cap allowed for fixation and alignment of all papillae uterinae. Of 22 mares (4 of experimental, 18 of client mares) papillae hysteroscopically controlled with a cap, 20 were successfully catheterized (Fig. 2–5). The technique allowed good and stable insertion of the catheter and flushing with 10 ml physiological saline solution. Movements of the catheter tip within the utero tubal junction were nearly eliminated. Total procedure duration (hydrotubation of both papillae) could be reduced to less than 60 min in all cases.

Microbiological evaluation of swap samples previous to hysteroscopy showed genital pathogenic germs (mainly haemolytic streptococci and coagulase-negative staphylococci) in 8/18 mares (44 %), in four of these mares the sample was repeated the day after treatment – bacterial contamination remained the same. 10/18 (56 %) mares had inconspicuous uterine swap samples before treatment, six of those mares were reexamined the day after hysteroscopy, 3/6 mares (50 %) showed growth of pathogenic bacteriae. E. coli and/or ß-haemolytic streptococci were detected post treatment.

Biopsies were taken before catheterization procedure in experimental and client mares without a known status of endometrial functional condition. Out of 15 biopsies taken, in 13 chronic endometrial fibrosis was diagnosed, 2 biopsies (graded IIb and II) showed additional superficial inflammation

Fig. 3 Reusable endoscope attachment cap for mucosa resection (Olympus®) allows for proper fixation and alignment of the uterine papilla and prevents slippage of the catheter tip and therefore swelling and injuries of the utero-tubal-junction (UTJ). | *Die wiederverwendbare Endoskopaufsatzkappe zur Mukosaresektion (Olympus®) gewährleistet Fixation und Ausrichtung der Eileiterpapille und verhindert ein Abrutschen der Katheterspitze und somit Schwellungen und Verletzungen der papilla uterina.*

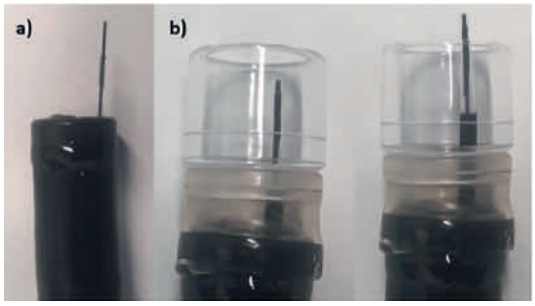

Fig. 4 Set up for UTJ catheterization: a) endoscope tip with catheter and guidewire inserted trough the working channel, b) Endoscope with cap and catheter with guidewire insterted trough working channel. | *Endoskop für Eileiterkathterisierung und Spülung: a) Endoskopspitze mit, in den Arbeitskanal eingeführtem Katheter und Führungsdraht, b) Endoskopspitze mit Aufsatzkappe und in den Arbeitskanal eingeführtem Katheter und Führungsdraht.*

Fig. 5 Catheter for oviduct hydrotubation inserted via ostium uterinae papilla uterinae (guide wire already removed), endoscope cap secures papillas' position and allows for safe and expeditious catheterisation. | *Katheter zur Eileiter Hydrotubation in die uteru-tubale Verbindung eingeführt (Führungsdraht bereits entfernt). Die Endoskopaufsatzkappe sichert die Position der Eileiter Papille und gewährleistet eine sichere und zügige Katheterisierung.*

of the endometrium, 3/15 (20%) were graded IIa (50–80% expected foaling rate), 5/15 (33%) were graded IIb (10–50% expected foaling rate) and 7/15 (47%) were graded III (<10% expected foaling rate).

All client mares (9/9) were inseminated following the treatment. In 7/9 (78%) mares pregnancy was established, 6/9 (67%) had gave birth to a healthy foal the following year.

The endometrial biopsy of two mares remaining barren were graded III (<10% expected foaling rate, according to *Kenney* and *Doig* 1986).

Discussion

The fallopian tube is known to play an essential role in sperm activation (*McPartlin* et al. 2009), fertilization, gamete maturation, transport and early embryonic development (*Leemans* et al. 2016). Fallopian tube obstruction, which is regularly diagnosed in infertile women, has also been described in mares (*Tsutsumi* et al. 1979, *Medenbach* et al. 1999, *Acland* and *Kenney* 1983). In the past, access to the oviduct in the mare for the treatment of blocked fallopian tubes was done laparoscopically from the flank (*Arnold* and *Love* 2013, *Allen* et al. 1979, *Kollmann* et al. 2011, *Allen* et al. 2006, *Weber* et al. 1991). In recent years, minimally invasive hysteroscopic procedures for fallopian tube catheterization and subsequent hydrotubation have been developed (*Inoue* 2013, *Inoue* and *Sekiguchi* 2018). The aim of this study was to establish cap assisted hysteroscopy to enable retrograde catheterization and hydrotubation of the equine oviduct. With the objective to develop an additional tool in equine reproductive medicine. Main focus was to ensure access to the uterine papilla by using a minimal invasive technique within a reasonable timeframe (<60 min.) to avoid irritation and contamination of the endometrium and the fallopian tube.

Experiments in euthanized mares showed reachability of the entire oviduct via hysteroscopic catheterization of the uterine papilla.

Treatments in standing sedated mares using standard technique showed: muscular tone of the uterine papilla and its respond to manipulation greatly complicated papilla cannulation. Mares' movements aggravated the procedure additionally. Position of the papilla within the cranial uterine horn varied widely between mares and turned out to be a further challenge. Adding a guide wire through the catheter allowed for better cannulation serving as insertion aid for the actual catheter.

Using the cap enabled fixation and proper positioning of the papilla. Allowing to insert the guide wire in a straight line into the oviduct simplified procedure and shortened duration significantly.

Before using the cap a general endoscopic overview of the uterine lumen and endometrium was gained. Subsequently the endoscope was removed, cleaned, the cap was added and the endoscope was reinserted. The authors consider this procedure to be necessary and appreciate the high diagnostic value of the hysteroscopic assessment of the entire endometrium as described by *Bartmann* et al. (1997). However, inserting the endoscope twice might increase the risk for contamination (*Schiemann* et al. 2001). On the other hand, *Köhne* et al. (2020) did not detect any significant differences in cellular immune response in mares between standard artificial insemination into the uterine body and hysteroscopic insemination. However, in subfertile mares, pregnancy rates are even reduced in mares bred by hysteroscopic insemination compared to standard AI (*Sieme* et al. 2004).

In this study, contribution of genital pathological bacteria can not be totally excluded as an additional cause for infertillity. Microbiological evaluation showed a shift in endometrial bacterial environment from physiological to pathological post treatment. Regarding pathogenesis of salpingitis in mares, germs like *Taylorella equigenitalis* (*Acland* and *Kenney* 1983), and *Chlamydia ssp.* (*Medenbach* et al. 1999) can be involved in oviductal blockage and can influence endometrial bacterial flora negatively. *Schiemann* et al. (2001) examined 8 healthy, diestrous mares five days after diagnostic hysteroscopy and found that 4 of 8 had pathogenic microbes. Furthermore, six mares showed inflammation and marked eosinophilia in histological specimens of endometrial biopsies. The authors recommended a follow-up treatment for mares that undergo hysteroscopy by intrauterine instillation of 100 ml of a mild 1% povidione iodine solution as recommended by *Bartmann* et al. 2008.

Previous studies reported an increase in pregnancy rates of mares with a history of unexplained infertility after hysteroscopic hydrotubation (*Inoue* and *Sekiguchi* 2018, *Schnobrich* 2016). Even though the aim of this study was to establish and improve the described technique, 7/9 client mares (78%) with unexplained infertility established pregnancy post treatment, proving efficiency of the treatment additional to the standard workup of allegedly infertile mares.

Pathogenesis and clinical appearance of blocked fallopian tubes might suggest the necessity of repetition of the treatment.

Conclusion

Oviductal catheterization is a valuable technique in equine reproductive medicine that provides new opportunities in treatment of infertile mares and in reproductive biotechnologies. It is tolerated well by standing sedated mares. Modifications of the catheter and the use of an endoscope cap simplified the procedure significantly and led to pregnancies in mares with a previous history of unexplained infertility. Treatment requires the surgeon to have sufficient experience to prevent potential damage to the fallopian tube from catheterization and hydrotubation. Post-treatment fertility should be further evaluated.

Author's contributions

Anna Tönißen, Daniela Tiedemann, Dominik Burger and Harald Sieme designed the study. Anna Tönißen, Lisbeth

Müller-Stephan, Daniela Tiedemann, Julia Gentz, Gunilla Martinsson, and Martin Köhne performed the experiments. Anna Tönißen and Harald Sieme wrote the manuscript. All authors read, amended and approved the submitted version of the manuscript.

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