

A review of the equine oviduct: pathology, evaluation, and current treatments

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Abstract

The equine oviduct has a vital role in fertilization and early embryonic support in the mare. Its anatomy is unique compared to other domestic species, with a muscular sphincter at the uterotubal junction that allows selective transport of embryos but not unfertilized oocytes. Although oviductal pathology is believed to be an infrequent cause of subfertility, it remains a potential differential when other causes for pregnancy failure have been ruled out. This paper is a brief review of equine oviduct anatomy and functional characteristics, common pathologies, current diagnostic tools and treatments for clinically relevant pathology.

Keywords: Oviduct, PGE₂, paraovarian cyst, hysteroscopic hydrotubation

Introduction

Oviducts (uterine tubes) develop from the most anterior segment of fetal paramesonephric or Müllerian ducts.¹⁻² Concentric tissue layers of the oviduct from the external surface, to the oviductal lumen consist of: serosal surface, muscularis (longitudinal and circular muscular layers), submucosa, and mucosa. In a 500 kg mare, they are approximately 20 - 30 cm in length and travel a tortuous path in the mesosalpinx from the ovary to the tip of the uterine horn.¹⁻² The oviduct is divided anatomically into 3 sections: infundibulum, ampulla and isthmus. Infundibulum's funnel-shaped dilation at the proximal aspect of the oviduct covers the ovary's ovulation fossa and transports the oocyte through ciliary action to the ampullary region. Ampulla is the site of fertilization, comprising approximately half the length of the oviduct and is ~ 6 mm in diameter.¹⁻² Following fertilization, conceptus passes through the isthmus (2 - 3 mm in diameter) and enters the uterus at the uterotubal junction.¹⁻⁴ Luminal epithelium of the oviduct is lined with a simple columnar epithelium with varying degrees of ciliated and nonciliated cells.⁵ The branched folding of the mucosal folds is most elaborate and extensive in the ampullary region, where the isthmus has a more narrow lumen with short and non-branched mucosa folds. Regional differences in cilia density, mucosal folding, cytoplasmic granule characteristics and secretions have been reported. Unique anatomical and epithelial characteristics of each section of the oviductal lining suggest that each region of the oviduct likely has a distinctive microenvironment related to its functional role.⁵

The most unique aspect of the mare's oviduct is the muscular sphincter present at the uterotubal junction of the mare that selectively allows embryos, but not unfertilized oocytes, to pass into the uterus at ~ 5.6 - 6 days postovulation.⁶ Elegant work by Woods et al. demonstrated that prostaglandin E₂ (PGE₂) secreted by the embryo facilitated passage of embryo into the uterus.⁷⁻⁸ This muscular constriction at the uterotubal junction makes salpingitis rare in the mare compared to other species (e.g. cattle and swine). It is hypothesized that the decreased incidence of clinically recognized salpingitis in the mare is due to this sphincter preventing uterine infections from gaining access to the oviduct.

Function

Fertilization

The infundibulum sweeps the ovulated oocyte towards the ampullary region through concerted ciliary action and muscular contractions. Sperm are believed to gain access to the oviduct within seconds after intrauterine insemination, but must undergo capacitation before fertilization. Sperm entering the oviduct is believed to bind oviductal epithelium of the isthmus and subsequently be released in waves. Upon release, the oviductal environment facilitates capacitation. The specific environmental trigger within the oviduct responsible for sperm capacitation is not known, but the alkaline micro-environment of the oviduct may aid in sperm preparation, as well as specific secretions released from the oviductal

epithelium⁹⁻¹¹ Role of uncharacterized capacitation triggers present in the equine oviduct continues to be an important area of research, as elucidation will increase efficiency of equine *in vitro* fertilization.

Transportation

Following fertilization, the embryo must travel through the isthmus into the uterus. This movement is believed to be facilitated by ciliary action and oviductal contractions mediated by embryonic secretion of PGE and likely other factors. As mentioned, the early embryo passes into the uterus on days 5.5 - 6 and only through continuous application of PGE₂ to the oviduct, could earlier recovery of embryos from the uterus be achieved.⁷⁻⁸ This work was key to understanding the mechanism of the selective transport of the mare's oviduct and also potential for oviductal treatment. PGE₂ has 4 known receptors with biological activity: E1, E2, E3, and E4. Induction of EP1 and EP3 induce smooth muscle contraction, whereas EP2 and EP4 induce smooth muscle relaxation. Strong expression of the receptor EP2 and EP4 was demonstrated in the luminal epithelium of both the isthmic and ampullary regions of the horse oviduct, with less expression noted within the smooth muscle of these regions.¹² Exact role of how PGE₂ interacts with these receptors is not known. It is hypothesized to induce relaxation of the circular smooth muscle fibers and contraction of the longitudinal smooth muscle fibers in the wall of the oviduct. Delayed entry of the equine conceptus into the uterus allows the practitioner time to improve the uterine environment following ovulation without jeopardizing the health of the embryo. In cases of severe post-mating induced endometritis, mares can be given intrauterine lavages and treatments up to 3 days post ovulation, with usually minimal adverse effects.

Pregnancy support

Oviductal secretions during pregnancy have been evaluated and there is clear evidence that the presence of an embryo changes the oviductal environment to facilitate its support. Gene expression and protein expression patterns, as well as, secretory composition are altered by the presence of an embryo in the oviduct.¹³⁻¹⁴ The preimplantation embryo can utilize fatty acids produced by the oviduct through direct incorporation into lipid bilayers of the cell membrane and for energy production via β oxidation. Concentration and composition of fatty acids of the oviduct was higher than in plasma for arachidonic, eicosapentaenoic and dihomo- γ -linolenic acid, implying oviductal nutritional support for the early embryo.¹⁵ These studies continue to evaluate the role of the oviduct in early pregnancy support and provide information regarding the microenvironment required for the early embryo. This understanding may improve techniques for *in vitro* embryo production.

Pathology of the Oviduct

As a practitioner, oviduct pathology is rarely recognized as a clinical factor causing infertility or during routine reproductive examination of the mare. Despite this, postmortem evaluations of the oviducts of many mares revealed a high prevalence of macroscopic and microscopic lesions. In an early study by Salteil involving postmortem evaluation of oviducts from 325 mares, 87.7% (285/325) had at least 1 macroscopic lesion and 93.5% (116/124) had at least 1 microscopic lesion.¹⁶ Macroscopic lesions were predominantly adhesions, paraovarian cysts and thick fibrous bands. Microscopically, lesions included intraepithelial cysts, slight, focal lymphocytic infiltration in the infundibular-ampullary region and proteinoid material in the oviductal lumen. Proximal segments of the oviduct were more affected than distal segments. These findings are supported by others who demonstrated that salpingitis was common in the infundibular region (37%), compared to the ampullary (21%), or isthmic region (9%) had isthmitis.¹⁷⁻¹⁸ Increasing evidence for a higher incidence of salpingitis in the mare is emerging. In a recent study evaluating abattoir-derived tissues from Criollo mares, most (64%) had some degree of lymphocytic infiltration in the oviduct mucosa, with a lower incidence of neutrophilic (8%) and eosinophilic (4%) infiltration in oviducts. Additionally, this study demonstrated that oviductal inflammation can be present without endometrial inflammation.¹⁹ Both mild salpingitis and adhesions are difficult to detect with transrectal palpation and are likely under reported in clinical literature. Whereas the presence of oviductal pathology appears common in the literature, the presence of these lesions does not usually affect fertility. In Saltiel's abattoir study, 90.74% (40/54) of the pairs of oviducts collected from pregnant mares had at

least 1 macroscopic or microscopic lesion.¹⁶ This finding parallels clinical observations that oviducts are rarely identified as a cause of subfertility in the mare.

The most common pathology identified on reproductive examination in the oviductal region are cystic remnants referred to as fimbrial cysts (Hydatid of Morgagni), and paraovarian or uterotubal cysts. Fimbrial cysts are believed to be caused by formation of more than 1 ostium from the coelomic epithelium in fetal life.²⁰ Paraovarian cysts located closed to the uterus are believed to be remnants of the mesonephric ducts and tubules and are thin walled cysts lined by a columnar epithelium. They are usually abaxial to the uterus and oviduct (paraovarian cysts) or within the cranial edge of the fimbriae of the oviductal infundibulum (fimbrial cysts).^{3,20-22} These appear on transrectal ultrasonography as round to tubular, occasionally multi-loculated, thin-walled, anechoic to hypoechoic cysts, ranging from several millimeters to several centimeters in diameter. Most commonly they are identified between the tip of the uterine horn and the ovary itself and should be noted as they can often be mistaken for a dominant follicle when adjacent to the ovary or present on the infundibulum as it drapes over the ovulation fossa. Those large enough to displace the infundibulum from covering the ovulation fossa have been hypothesized by some authors to interfere with oocyte transport and removal has been recommended. While reports exist of these interfering with oocyte transport, they are usually considered an incidental finding when diagnosed.²³⁻²⁵ Monitoring size and character of the cysts is recommended, and only when failure to achieve pregnancy from that side is repeatedly noted, would intervention be recommended.

A large body of research has demonstrated the presence of gelatinous and proteinaceous accumulations in the oviductal lumen with variable adhesions to the oviductal epithelium.²⁶⁻²⁹ These masses are believed to occur due to the retention of ovulated material (oocytes, fibroblasts, gelatinous matrix) within the oviduct, and salpingitis. What effect these accumulations have on fertility is a topic of debate based on postmortem frequency and the seemingly minimal effect on mare fertility. What is interesting is that subfertile mares suspected to have oviduct dysfunction, can have their fertility improved by treatment with various methods to restore oviduct "patency." This begs the question whether these accumulations are pathologic and if so, when and at what point do they become an issue.

Hydrosalpinx is a rarely reported pathology of the equine oviduct. Hydrosalpinx is usually caused by stricture or congenital failure of normal formation of the oviduct. In 1 report, histological evaluation of the distended tube in a mare revealed a dilated lumen, a decreased in-folding of the wall into the lumen, and a lack of a defined muscle layer. It was hypothesized that the cause of hydrosalpinx in this case was a congenital absence of the infundibulum, resulting in a blind ampullar terminus.³⁰ Abscess formation, or severe salpingitis that is recognized on transrectal ultrasonography, palpation or laparoscopy is rare and usually requires treatment and/or removal of the affected oviduct or ovary. Oviductal neoplasia is rare, with adenoma and leiomyomas described.³¹ These cases usually include a history of infertility when ovulations occur from the affected side. Removal of the ovary is recommended unless oocyte recovery will be attempted to circumvent the oviductal pathology.

Diagnostic approach and treatment

Paraovarian cyst

Tentative diagnosis of a fimbrial or paraovarian cysts is usually made by serial transrectal palpation and ultrasonography. These are usually small (~ 1 - 8 cm), round to tubular, thin-walled, soft to firm, anechoic to hypoechoic fluid-filled structures, which are non painful on palpation. Evaluation with color flow Doppler should show no evidence of blood flow. Laparoscopic evaluation can be used to confirm diagnosis, but due to their low clinical significance, is usually not recommended. Any similar appearing structure found within the mesovarium or any region from the tip of the uterine horn extending cranial to the ovary within the supporting tissues are considered. Serial ultrasonography over several weeks usually detects little change in the structure with regards to size, though at times the segmentation or tortuosity of the structure may appear to change. Laparoscopic evaluation of the structures reveals a clear to orange filled, thin-walled structure, well circumscribed on the surface of the mesovarium or arising from the infundibular mucosa. Laparoscopic assessment is only recommended in cases where the

degree of interference of the cyst with the infundibulum's normal anatomy and function is suspected (failure to conceive with ovulations from that side). If severe adhesions and disruption of the normal anatomy is seen, and the mare has a confirmed history of pregnancy failure following ovulation from that side, surgery can be attempted to restore anatomy, reduce the cyst or remove the affected ovary. Removal of the ovary is recommended to increase efficiency of breeding as a dominant follicle can then only arise from the unaffected ovary and valuable time is not wasted. If oocyte aspiration is an option for the mare, the ovary is left and oocytes can be harvested, bypassing the affected oviduct.

Adhesions

Adhesions between the ovary and infundibulum are not easily identified by transrectal palpation or ultrasonography. Laparoscopic evaluation of the ovary and oviduct is often the best way to diagnose this pathology. Adhesions between the ovary and surrounding structures (GI tract, pelvic wall) are diagnosed through identifying abnormal anatomy on palpation. Indication for laparoscopic evaluation would be abnormal palpation and suspicion of adhesions with a history of infertility. Often mares with severe adhesions have a history of colic surgery, peritonitis, hemoabdomen or dystocia. These adhesions can form from the process of ovulation, salpingitis, peritonitis, trauma to the reproductive tract and unknown causes. They can vary from simple, string like adhesions, to thick fibrous bands that distort the relationship of the infundibulum to the ovulation fossa, which some speculate causes oocytes to be lost in the abdominal cavity.²² The decision to surgically remove or breakdown adhesions is based on how much these change the anatomy of the oviduct and reproductive history. Recently, mares presented for infertility and laparoscopic PGE₂ application to the oviducts had oviductal adhesions removed as part of their treatment with good success.³² The role of adhesion breakdown in restoring fertility needs further work and has not yet been critically assessed.

Salpingitis

Inflammation of the oviduct (salpingitis) is rarely diagnosed during a reproductive examination of the mare. Severe salpingitis may be recognized as a thickening and dilation of the oviduct on transrectal palpation and ultrasonography, or laparoscopically. Hysteroscopic examination is usually unrewarding due to the muscular sphincter and variable appearance of the mare's oviductal papilla. Even in mares' oviducts that have ultrasonographic appearance of dilation and luminal changes, the oviductal papilla often appears normal on hysteroscopy. Subclinical salpingitis is difficult to definitively diagnose without biopsy of the tissue, or postmortem evaluation. In most patients, this is a presumptive diagnosis based on transrectal palpation and ultrasonography of the oviduct. The oviduct is not easily identifiable with transrectal ultrasonography, so any thickening, intraluminal fluid, or discrepancy in size from the contralateral oviduct is suspicious. These findings in conjunction with unilateral infertility should increase suspicion of pathology in this region. Treatment may involve systemic antibiotics with good tissue penetration (enrofloxacin, oxytetracycline or chloramphenicol) following culture and sensitivity of fluid or tissue from the affected region. This may be obtained laparoscopically or empiric treatment may be elected to avoid peritonitis. Flushing of the oviduct surgically or through a hysteroscopic approach can be attempted, but in the case of infection, peritonitis must be considered potential sequelae. Severe salpingitis usually results in fibrosis and loss of oviduct function and the owner may choose unilateral ovariectomy.

Loss of oviductal function/patency

Often the loss of oviduct function is suspected when all other causes of fertility have been ruled out and the history suggests oviduct dysfunction. A history that is suspicious for oviductal pathology includes loss of ability to produce a pregnancy from unilateral or bilateral ovulations, despite ruling out all other causes of infertility (endometritis, adhesions, semen quality and sire, breeding management and timely ovulation relative to breeding, endocrine abnormality, genetic abnormality). Occasionally the patient has a history of dystocia, peritonitis, colic, or trauma in the reproductive tract or pelvic area. There have been several studies that have described methods of assessing oviductal patency, but due to the fine,

sensitive structure of the oviductal lumen, it is not clear if diagnostic methods for assessing patency could potentially cause a salpingitis and even create a problem.

Initial evaluations of patency described surgical exteriorization of the uterine horn and oviduct and flushing the oviduct (normograde and retrograde) with saline, air or new methylene blue to determine patency.^{22,25,32,34} These are invasive procedures and often the flushing was considered therapeutic. Complications associated with this procedure included oviductal rupture as it was believed that the flushing from oviduct to uterus (normograde) and as the luminal size narrowed, excessive pressure would cause a rupture, potentially permanently damaging the oviduct. If rupture occurred or surgical evaluation of the affected ovary revealed severe, unfixable pathology, the ovary was often removed.

Another method for patency determination has been attempting to recover small starch or colored microsphere beads applied over the infundibulum. These beads are inserted over the infundibulum through either a vaginal or laparoscopic approach. Love et al. used 15 μm microsphere colored beads (1 color for each side) applied laparoscopically over the infundibulum of the oviduct and then recovered uterine contents by uterine lavage 48 hours later. The oviducts were evaluated microscopically and compared to results of the beads recovered. The test was considered positive for oviductal intraluminal accumulations when no beads were recovered from that side in uterine lavage. Sensitivity and specificity of the test were 71.4 and 85.7% when compared to postmortem evaluation of the oviducts.³⁵ Although this approach is helpful in confirming suspicions, it is costly.

The downfall of these diagnostic tests for oviduct patency is the definition of “patency” or “normal function” is not clear. Dye and fluorescent microsphere beads do not mimic sperm entering the oviduct, the oviductal environment required for embryo growth, nor the coordinated passage from the ampulla to uterine lumen. In clinical practice, oviductal patency, or loss of function, is often a diagnosis of exclusion. This suspicion is reached when all the more common causes for subfertility/infertility have been ruled out (endometritis, ovulatory failure, semen quality, genetic abnormality). Several studies have demonstrated that treatment for oviductal “dysfunction,” usually attributed to lack of patency or “plugs,” have improved fertility in a specific subset of mares. Because the treatment has been successful when case selection is properly performed, many owners and clinicians elect to treat without a confirmed diagnosis prior to treatment.

Allen et al. demonstrated that laparoscopic application of PGE₂ gel to the oviducts of mares presented for chronic subfertility significantly increased fertility.³⁶ Other studies have echoed the benefit of this treatment in similar subsets of mares. It is believed that the PGE₂ causes contraction of the oviduct and opening of the oviductal muscular sphincter which allows accumulations to be expelled. Lavages of mares following treatment have recovered similar structures to the gelatinous oviductal plugs described. Hysteroscopic application of PGE₂ directly to the oviductal papillae using deep horn insemination technique did not seem to enhance embryo transport into the uterus, though some are using this approach instead of the laparoscopic approach with reported anecdotal success.³⁷ Dr. Inoue developed a hysteroscopic flushing technique that was first described in 2013, whereby a small catheter was placed in the oviductal papilla and sterile saline flushed retrograde.³⁸ This procedure resulted in similarly positive effects as laparoscopically administered PGE₂ in mares with suspected pathology. In a study comparing the 2 techniques, there was no significant difference in pregnancy rates following laparoscopic PGE₂ application (65%, 13/20) and hysteroscopic hydrotubation (71%, 35/49), in a similar subset of previously subfertile mares.³⁹ The hysteroscopic approach offers the advantage of not having to perform surgery and avoids the cost of the PGE₂ gel, but the disadvantage is inflammation caused by hysteroscopy and potential mechanical trauma to the oviduct from the procedure.

Recently, in 2018, Alvarenga’s group in Brazil demonstrated efficacy of an even simpler procedure.⁴⁰ In this, study PGE₁ instead of PGE₂ was used without surgery. Specifically, 1 tablet (200 μg of Misoprostol, CYTOTEC® Pfizer, Lake Forest, IL) was diluted in 3 ml of sterile water and is applied to the tip of the uterine horn lumen using a deep-horn insemination pipette, during diestrus. The mares were bred on the subsequent cycle. Within 2 cycles after the procedure, 68% (15/22) produced a pregnancy. This treatment provides a new and easy to use approach with minimal downsides for the practitioner in the field, does not risk peritonitis or trauma and is very cost effective.

Conclusion

The equine oviduct is imperative for successful fertilization, initial embryonic support, and selective transport of the early embryo into the mares' uterus. Due to the unique structure of the equine oviduct, salpingitis is rare, but other pathologies are potential differentials for subfertility.

Conflict of interest

Author claims no direct or indirect affiliation with any of the manufacturers listed in the text. Information regarding the equipment and various manufacturers is solely based on experience and is for the readers' reference only.

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