Received: 12 September 2022 | Revised: 13 November 2022 | Accepted: 19 November 2022

DOI: 10.1111/andr.13349

ANDROLOGY WILEY

REVIEW ARTICLE

# Suspension of hostility: Positive interactions between spermatozoa and female reproductive tracts

Mariana F. Wolfner[1] | Susan S. Suarez[2] | Steve Dorus[3]

[1]Department of Molecular Biology and Genetics, Cornell University, Ithaca, New York, USA

[2]Department of Biomedical Sciences, Cornell University, Ithaca, New York, USA

[3]Center for Reproductive Evolution, Department of Biology, Syracuse University, Syracuse, New York, USA

**Correspondence**
Mariana F. Wolfner, Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY, USA.
Email: mfw5@cornell.edu

**Funding information**
NIH, Grant/Award Numbers: R37-HD038921, R01-HD059060; NICHD, Grant/Award Number: R21-HD088910

## Abstract

Interactions between spermatozoa and the female reproductive tract (FRT) are complex, in many cases poorly understood, and likely to contribute to the mechanistic basis of idiopathic infertility. As such, it is not surprising that the FRT was often viewed historically as a "hostile" environment for spermatozoa. The FRT has also been touted as a selective environment to ensure that only the highest quality spermatozoa progress to the oocyte for the opportunity to participate in fertilization. Recent advances, however, are giving rise to a far more nuanced view in which supportive spermatozoa × FRT interactions—in both directions—contribute to beneficial, even essential, effects on fertility. In this perspective article, we discuss several examples of positive spermatozoa × FRT interactions. We believe that these examples, arising in part from studies of taxonomically diverse nonmammalian systems, are useful to efforts to study mammalian spermatozoa × FRT interactions and their relevance to fertility and the advancement of assisted reproductive technologies.

**KEYWORDS**
cervix, female reproductive tract, fertility, spermatozoa, uterus

## 1 | INTRODUCTION

Successful sexual reproduction requires coordinated interactions between animals[1], gametes, and, in internal fertilizers, between the ejaculate and the female reproductive tract (FRT).[2–4] Studies of these phenomena have revealed how male and female players work together, including the requirement for binding between molecules on spermatozoa and egg surfaces for fertilization, (reviewed by Springate and Frasier[5]) or the requirement for genomes with complementary female and male imprinting to allow a mammalian zygote to develop properly.[6,7] Despite recognition of these many cooperative interactions, there has been the perception that interactions between spermatozoa and the FRT tend to be hostile in the sense that the FRT provides a selective environment for high quality spermatozoa. The concept of a hostile FRT has also resonated with evolutionary biologists, as a selective environment in which competition between ejaculates of different males provides a means for females to select the "best" spermatozoa (i.e., "sperm selection" or "cryptic female choice").[8,9] A hostile FRT, however, is hard to reconcile with the fact that spermatozoa are often stored and maintained within the FRT, extending the postmating period in which eggs can be fertilized.

Here, we review examples that led to the idea that the FRT is hostile to spermatozoa, and then present findings, mostly recent, that argue for a more-nuanced view in which there are positive effects of the FRT on spermatozoa and vice-versa. Our intent is not to present an exhaustive review of all relevant studies but rather to illustrate the more balanced view that is emerging with respect to interactions between spermatozoa and the FRT.

## 2 | A BRIEF HISTORY OF THE PERCEPTION OF THE FRT AS HOSTILE TO SPERMATOZOA

In the field of mammalian reproduction, the perception that the FRT is hostile certainly seems understandable at face value, given that males inseminate millions (and in some species billions) of spermatozoa to fertilize relatively few oocytes.[10] In fact, this situation is certainly not limited to mammals: the bursa copulatrix of the brown garden snail (*Cantareus aspersus*) enzymatically digests 99.98% of the spermatozoa it receives.[11] While culling of substantial numbers of spermatozoa that enter the female can help decrease the chance of polyspermy, a phenomenon that is usually lethal to the oocyte, a number of additional reasons have been suggested for this apparent hostility. One relates to the female's need for immunological protection against infection by pathogens that are introduced into the FRT by the male during coitus. Although spermatozoan cells are not as genetically dissimilar to females' as are pathogens, they too stimulate both innate and adaptive immune responses in the FRT.[12,13] The FRT has also been thought to provide selective barriers to spermatozoa migration, perhaps "because only a small proportion of spermatozoa are competent."[14] Investigators of mammalian reproduction have long described the cervix as a barrier to spermatozoa migration in species that inseminate into the vagina (including humans and cows), emphasizing that the cervix steeply reduces spermatozoa passage to the uterus.[15–17] The mammalian uterus has also been considered hostile to spermatozoa, because coitus results in the massive migration into the uterus of neutrophils that subsequently trap and kill spermatozoa.[18] It has been proposed that, in order to reach the oviduct to participate in fertilization, spermatozoa must pass through the uterus before sufficient numbers of neutrophils enter the uterine cavity to destroy the spermatozoa within.[17] For example, bull (*Bos taurus*) spermatozoa trigger neutrophil invasion when they encounter thousands of glands that line the uterine cavity. Spermatozoa are quickly trapped in these glands and their interaction with glandular epithelium induces an inflammatory innate-immune response and neutrophil invasion.[19]

## 3 | HOWEVER, SPERMATOZOA × FRT INTERACTION IS NOT SOLELY HOSTILE OR SELECTIVE

Additional data have moved the view away from the idea that the FRT is solely hostile to spermatozoa. Studies have identified ways in which the FRT is supportive to spermatozoa, and even ways in which spermatozoa exert positive effects on the FRT (or female fertility, beyond simply fertilizing eggs). Below, we touch on some of the studies that have led to this revised, more balanced, view of spermatozoa × FRT interactions (as has also happened for other phenomena in reproductive biology; e.g., see references [1,5–7] for a small sampling).

*The FRT can help spermatozoa physically navigate toward the egg.*

A careful histological study of serial sections of spermatozoa in the cervices of naturally-mated cows[20] found that the walls of the cervical canal are lined with microgrooves that can be traced all the way through the cervix to the uterus, and that contain many spermatozoa. This led to the proposition that the microgrooves provide "privileged paths" for spermatozoa to swim through the cervix and avoid being carried away by the strong flow of mucus in the main canal that sweeps pathogens and cellular debris out to the vagina.[20] This was supported by subsequent advances in the understanding of spermatozoan hydrodynamics[21] in conjunction with technological developments in microfluidics[22] that enabled the creation of a device that models the microgrooves and fluid flows in the cervix. In this device, bull spermatozoa tended to swim upstream in microgrooves, a direction that would lead to the uterus in vivo. In contrast, the sexually transmitted bovine pathogen *Tritrichomonas foetus* failed to enter microgrooves and were swept downstream.[23,24] These findings indicate that that the cervix is not simply a barrier to spermatozoa but actually assists with spermatozoan migration toward the egg, while simultaneously protecting the uterus from pathogens. The situation is nuanced, however, because (as noted earlier) the cervix concomitantly imposes selection on migrating spermatozoa: human and bovine cervical mucus have been demonstrated to filter out spermatozoa with morphological and motility abnormalities.[25,26]

*The FRT can help sperm by modifying their molecular constitution.*

Mammalian spermatozoa are not fully mature and fertilization-competent when they leave the testis, or even after additional maturation within the epididymis. To be capable of fertilizing an oocyte, mammalian spermatozoa must undergo "capacitation"[27], a postejaculatory modification of spermatozoa (PEMS[2]) in which biochemical and physiological changes to spermatozoa lead them to acquire a form of motility that improves their migration through the oviduct and enables them to fertilize the egg.[28] Although capacitation can be induced in some species by incubating spermatozoa in a bicarbonate-buffered physiological solution containing energy metabolites and serum albumin,[27] in others it requires a more complex environment, suggesting the involvement of FRT secretions in this final and critical maturation step. Indeed, some candidate secretions have been identified. For example, in humans and other eutherian mammals, the oviduct-secreted glycoprotein oviductin (OVGP1) binds to spermatozoa, and purified recombinant human OVGP1 has been demonstrated to enhance human sperm capacitation.[29]

Although mammalian sperm capacitation has received the most attention, given its relevance to human fertility, mammals are far from the only animals in which spermatozoa are modified within the FRT to complete their maturation and gain fertilization competency. In fact, PEMs likely represent the rule rather than the exception among internally fertilizing organisms and include a diverse array of morphological, physiological, and biochemical processes.[2] PEMS can be structural alterations, such as removal of the "coats" in which some insects' (*Bombyx mori* silkmoths[30]; *Aedes aegypti* mosquitoes[31]) spermatozoa arrive in the female, transformation of millipede spermatozoa from little barrels to long ribbons in the FRT[32], or enzymatic release of spermatozoa from capsules (spermatophores) that contain them in moth (*Pieris*) FRT.[33] These changes presumably make spermatozoa

available for, and capable of, fertilization. In another example, the heads of spermatozoa from the marsupial *Sminthopsis crassicaudata* pivot in the oviducts making the spear-shaped spermatozoan assume a T-shape.[34] This structural modification is thought to enhance binding to and penetration of the zona pellucida that surrounds the oocyte.[35]

PEMS also include molecular changes to the spermatozoa within the FRT including the incorporation of female molecules. For example, the protein composition of *Drosophila* spermatozoa changes substantively after their entry, residence, and movement within the FRT, because of tight associations with female-derived proteins.[36] The association of female proteins with spermatozoa begins shortly after the latter enter the Drosophila FRT and increases with time, such that by four days after insemination almost 20% of spermatozoal protein composition (i.e., the sperm proteome) is female-derived. These female-derived proteins include metabolic enzymes and chaperones, which may provision spermatozoa and enhance their viability during long-term storage. Consistent with this idea, secretions of the reproductive glands of honeybee FRTs also appear to play an important supportive role for spermatozoa. Following their mating flights, when young queen bees mate with multiple drones, each ejaculate decreases the viability of spermatozoa from other males.[37] FRT secretions counter those effects,[37] allowing stored spermatozoa from different drones to be safely stored in the female's storage organs for long-term use. Notably, female-derived proteins in *Drosophila* spermatozoa were also found to overlap substantially with integral male-derived spermatozoa proteins. Although the functional significance of females supplementing the proteomic composition of sperm has yet to be determined, this observation generally supports the hypothesis that spermatozoa experience a molecular "hand-off" when transferred from males to female and that molecular continuity between the male and FRT may be critical to support spermatozoa during its protracted life history in the FRT.[36] One can also envision that female-mediated spermatozoa modification might permit female assessment of spermatozoa quality and/or distinguishing spermatozoa from the ejaculates of competing males,[2,36] but these hypotheses have not yet been tested.

*The FRT can store spermatozoa, keeping them viable and stable, and releasing them from storage at optimal times and rates for extended fertility.*

In many animals, spermatozoa are stored in the FRT, with gradual release into the FRT lumen (see Neubaum and Wolfner[38] for review). Although many species store spermatozoa for only hours or days, some species store spermatozoa for long periods of time. For example, many temperate bat species mate shortly before entering winter hibernation, and the females store spermatozoa until they emerge from hibernation in the spring, releasing the spermatozoa to fertilize their freshly ovulated oocytes.[39] Several species of temperate snakes also mate in the fall and their spermatozoa are held in the females until spring.[40] However, some other reptiles store spermatozoa for even longer periods. For example, a Western diamond-backed rattlesnake (*Crotalus atrox*) produced viable litters up to 6 years after isolation from males.[41] Other examples of species with long-term sperm storage include social insects,[42] birds,[43] amphibians,[44] and fishes.[45]

In many species of mammal, inseminated spermatozoa traverse the uterus and enter the uterotubal junction. From there, the spermatozoa begin to form a storage reservoir by binding to the wall of the FRT in the junction and/or lower isthmus of the oviduct. Here, the spermatozoa remain alive and eventually capacitate.[46] The FRT may then control the release of spermatozoa from the reservoir. This regulated release extends the window of opportunity for an ovulated egg to encounter a fertilization-ready spermatozoa and reduces the chances of polyspermic fertilization by reducing the rate at which spermatozoa reach oocytes.[47] Mammalian spermatozoa are retained in the oviduct storage reservoir by binding to the oviductal epithelium, and capacitation of the spermatozoa has been associated with spermatozoa detachment from this epithelium. For example, bull spermatozoa detached from isthmic epithelium after addition of heparin,[48] which has been demonstrated to induce capacitation in that species.[49] Also, mouse spermatozoa initiated capacitation-associated hyperactivated motility directly before detaching from epithelium in the spermatozoa storage reservoir, whereas nonhyperactivated mouse spermatozoa were not observed to detach.[50] However, we note that spermatozoa capacitation is a complex process. It is not known at what stage in the process that spermatozoa are released from storage—in some cases hyperactivated spermatozoa have been observed to detach and reattach to epithelium in oviducts.[51] This complexity provides multiple opportunities for the FRT to regulate spermatozoa detachment from epithelium and release from the isthmic reservoir.

*It is not a one-way interaction: spermatozoa can have beneficial effects on females' fertility, beyond fertilizing eggs.*

It has been thought that the spermatozoa-induced neutrophil invasion of the uterus described above serves to (1) remove dead, abnormal, and excess spermatozoa, (2) kill the pathogens that enter the female tract during coitus, and (3) prevent the development of anti-spermatozoa antibodies via the adaptive immune system, an event that can lead to infertility.[12] Recently, evidence from mouse studies has pointed to an additional function: the uterine inflammatory response to spermatozoa prepares the endometrium for embryo implantation by promoting immune tolerance, thereby decreasing the likelihood that the embryo will be attacked by an immune response.[52] The results suggest that spermatozoa that do not participate in fertilization can nevertheless enhance fertility through the induction of inflammatory response by the innate immune system in the uterus, an observation worth potential clinical consideration.

Drosophila spermatozoa also play a role in enhancing fertility beyond their role in fertilization. These spermatozoa act as carriers of a seminal peptide ("sex peptide," SP[36,53,54]) that induces egg production, oviposition, spermatozoal release from storage, and a range of physiological and behavioral changes.[55,56] SP bound to spermatozoa in the sperm-storage organs is stably retained there for 10–14d, bound to the spermatozoa that have not yet been released to fertilize eggs. Over time, the active portion of SP is gradually cleaved from spermatozoa by a trypsin-like activity, freeing it to bind to its receptor[57] in the female and induce the physiological, behavioral, and reproductive effects noted above. Without spermatozoa, SP remains within

the female for only a few hours, being degraded in her circulatory system[58] without enough time to effect long-term changes. Thus, in this case as well, even a nonfertilizing spermatozoan can influence the FRT (and in this case beyond the FRT), increasing reproductive success.

## 4 | CONCLUDING PERSPECTIVES

While there is clear evidence for some "hostility" between spermatozoa and the FRT, we have described current evidence that shows that there are also important supportive effects of the FRT on spermatozoa (and vice versa) at various levels. This more nuanced view of spermatozoa × FRT interactions motivates new areas of investigation and application in reproductive biology. We believe that this view will also interest evolutionary biologists who study postcopulatory selective events,[8,9,59,60] such as sperm competition and cryptic female choice. In the future, ways in which spermatozoa-mediated immune effects could be leveraged to support implantation, as embryo implantation is considered to be the rate limiting step in the success of in vitro fertilization, including intracytoplasmic sperm injection (IVF/ICSI).[61] A better understanding of how innate immune responses to spermatozoa in the uterus help to prepare the endometrium for implantation could be applied to improving the preparation of patients' uteri for implantation of embryos created via IVF/ICSI.

Other mechanisms of positive FRT/spermatozoa interaction need to be elucidated, including (for example) the roles of female proteins that bind to spermatozoa in *Drosophila*. Such information could also guide the search for mammalian female proteins that bind to spermatozoa and support fertilization. Of relevance to reproductive medicine, assessment of human FRT proteins binding to spermatozoa could lead to therapeutic (or diagnostic) developments. Finally, knowing the mechanisms of spermatozoa selection by the FRT could improve the selection of spermatozoa for IVF/ICSI, where natural selection on, and modification to, the fertilizing spermatozoa are currently bypassed by laboratory preparation of semen samples and technician selection of the spermatozoa to inject into the oocyte during ICSI.[62] For example, better understanding of the mechanisms acting on spermatozoa within the mammalian FRT could inspire development of microfluidic devices that more faithfully reproduce the selective pressures encountered by spermatozoa in the FRT prior to using the sperm for IVF/ICSI.

### ACKNOWLEDGEMENT

The authors thank Kate Loveland and Wei Yang for the opportunity to write this review and for organizing the 2022 North American Testis Workshop to which it relates. The authors are very grateful to Scott Pitnick for helpful discussions, wording suggestions, and for pointing us to relevant PEMS cases. MFW thanks NIH grant R37-HD038921 and R01-HD059060 (to MFW and A. Clark) for support. SD thanks NSF grant DEB 1655840 and NICHD grant R21-HD088910 (both to SD, MFW, and S. Pitnick) for support.

### DATA AVAILABILITY STATEMENT

This is a review article; it contains no original data.

### ORCID

*Mariana F. Wolfner* https://orcid.org/0000-0003-2701-9505

### REFERENCES

1. Greenspan RJ, Ferveur JF. Courtship in Drosophila. *Annu Rev Genet*. 2000;34:205-232.
2. Pitnick S, Wolfner MF, Dorus S. Post-ejaculatory modifications to sperm (PEMS). *Biol Rev Camb Philos Soc*. 2020;95(2):365-392.
3. Bromfield JJ, Schjenken JE, Chin PY, Care AS, Jasper MJ, Robertson SA. Maternal tract factors contribute to paternal seminal fluid impact on metabolic phenotype in offspring. *Proc Nat Acad Sci USA*. 2014;111(6):2200-2205.
4. Schjenken JE, Robertson SA. The female response to seminal fluid. *Physiol Rev*. 2020;100(3):1077-1117.
5. Springate L, Frasier TR. Gamete compatibility genes in mammals: candidates, applications and a potential path forward. *R Soc Open Sci*. 2017;4(8):170577.
6. Surani MA, Barton SC. Development of gynogenetic eggs in the mouse: implications for parthenogenetic embryos. *Science*. 1983;222(4627):1034-1036.
7. McGrath J, Solter D. Nuclear transplantation in mouse embryos. *J Exp Zool*. 1983;228(2):355-362.
8. Eberhard WG. *Female Control : Sexual Selection by Cryptic Female Choice*. Princeton Univ. Press; 1996.
9. Birkhead TP, Moeller AP, Sutherland WJ. Why do females make it so difficult for males to fertilize their eggs? *J Theoret Biol*. 1993;161:60.
10. Sakkas D, Ramalingam M, Garrido N, Barratt CL. Sperm selection in natural conception: what can we learn from mother nature to improve assisted reproduction outcomes? *Hum Reprod Update*. 2015;21(6):711-726.
11. Rogers D, Chase R. Dart receipt promotes sperm storage in the garden snail Helix aspersa. *Behav Ecol Sociobiol*. 2001;50:122-127.
12. Akthar I, Marey MA, Kim Y, Shimada M, Suarez SS, Miyamoto A. Sperm interaction with the uterine innate immune system: toll-like receptor 2 (TLR2) is a main sensor in cattle. *Reprod Fertil Dev*. 2021;34(2):139-148.
13. Shibahara H, Wakimoto Y, Fukui A, Hasegawa A. Anti-sperm antibodies and reproductive failures. *Am J Reprod Immunol*. 2021;85(4):e13337.
14. Cohen J. Why so many sperms? An essay on the arithmetic of reproduction. *Sci Prog*. 1969;57:23-41.
15. Greenwald GS. Sperm transport in the reproductive tract of the female rabbit. *Science*. 1956;124(3222):586.
16. Hunter RHE. Significance of the epithelial crypts at the bovine uterotubal junction in the pre-ovulatory phase of sperm regulation. *Acta Vet Scand*. 1995;36:413-421.
17. Suarez SS, Pacey AA. Sperm transport in the female reproductive tract. *Hum Reprod Update*. 2006;12(1):23-37.
18. Alghamdi AS, Foster DN. Seminal DNase frees spermatozoa entangled in neutrophil extracellular traps. *Biol Reprod*. 2005;73(6):1174-1181.
19. Akthar I, Suarez SS, Morillo VA, et al. Sperm enter glands of preovulatory bovine endometrial explants and initiate inflammation. *Reproduction*. 2020;159(2):181-192.
20. Mullins KJ, Saacke RG. Study of the functional anatomy of bovine cervical mucosa with special reference to mucus secretion and sperm transport. *Anat Rec*. 1989;225(2):106-117.
21. Gaffney E, Gadelha H, Smith D, Blake J, Kirkman-Brown J. Mammalian sperm motility: observation and theory. *Ann Rev Fluid Mechanics*. 2011;43:501-528.

22. Suarez SS, Wu M. Microfluidic devices for the study of sperm migration. *Mol Hum Reprod*. 2017;23(4):227-234.
23. Tung CK, Ardon F, Fiore AG, Suarez SS, Wu M. Cooperative roles of biological flow and surface topography in guiding sperm migration revealed by a microfluidic model. *Lab Chip*. 2014;14(7):1348-1356.
24. Tung CK, Hu L, Fiore AG, et al. Microgrooves and fluid flows provide preferential passageways for sperm over pathogen Tritrichomonas foetus. *Proc Nat Acad Sci USA*. 2015;112(17):5431-5436.
25. Katz D, Morales P, Samuels S, O'verstreet J. Mechanisms of filtration of morphologically abnormal human sperm by cervical mucus. *Fertil Steril*. 1990;54:513-516.
26. Anilkumar R, D'evananthan TG, Pattabiraman S, Edwin M. Correlation between the spermatozoal characteristics and sperm penetration distance in polacrylamide gel and bovine cervical mucus. *Theriogenology*. 2001;55:685-691.
27. Gervasi MG, Visconti PE. Chang's meaning of capacitation: a molecular perspective. *Mol Reprod Dev*. 2016;83(10):860-874.
28. Yanagimachi R. Mysteries and unsolved problems of mammalian fertilization and related topics. *Biol Reprod*. 2022;106(4):644-675.
29. Zhao Y, Yang X, Jia Z, Reid RL, Leclerc P, Kan FW. Recombinant human oviductin regulates protein tyrosine phosphorylation and acrosome reaction. *Reproduction*. 2016;152(5):561-573.
30. Friedlander M, Gitay H. The fate of the normal-anucleated spermatozoa in inseminated females of the silkworm Bombyx mori. *J Morphol*. 1972;138:121-130.
31. Noble JM, Degner EC, Harrington LC, Kourkoutis LF. Cryo-electron microscopy reveals that sperm modification coincides with female fertility in the mosquito aedes aegypti. *Sci Rep*. 2019;9(1):18537.
32. Baccetti B, Dallai R, Bernini F, Mazzini M. The spermatozoon of arthropoda. XXIV. Sperm metamorphosis in the diplopod *Polyxenus*. *J Morphol*. 1974;143:187-245.
33. Meslin C, Cherwin TS, Plakke MS, et al. Structural complexity and molecular heterogeneity of a butterfly ejaculate reflect a complex history of selection. *Proc Nat Acad Sci USA*. 2017;114(27):E5406-E5413.
34. Bedford JM, Breed WG. Regulated storage and subsequent transformation of spermatozoa in the fallopian tubes of an Australian marsupial, Sminthopsis crassicaudata. *Biol Reprod*. 1994;50(4):845-854.
35. Bedford JM. Puzzles of mammalian fertilization–and beyond. *Int J Dev Biol*. 2008;52(5-6):415-426.
36. McCullough EL, Whittington E, Singh A, Pitnick S, Wolfner MF, Dorus S. The life history of Drosophila sperm involves molecular continuity between male and female reproductive tracts. *Proc Nat Acad Sci USA*. 2022;119(11):e2119899119.
37. den Boer SP, Baer B, Boomsma JJ. Seminal fluid mediates ejaculate competition in social insects. *Science*. 2010;327(5972):1506-1509.
38. Neubaum DM, Wolfner MF. Wise, winsome or wierd: mechanisms of sperm storage in female animals. *Curr Top in Dev Biol*. 1999;41:67-97.
39. Alonge MM, Greville LJS, Faure PA, Bentley GE. Immunoreactive distribution of gonadotropin-inhibitory hormone precursor, RFRP, in a temperate bat species (Eptesicus fuscus). *J Comp Neurol*. 2022;530(9):1459-1469.
40. Sever DM, Hamlett WC. Female sperm storage in reptiles. *J Exp Zool*. 2002;292(2):187-199.
41. Levine BA, Schuett GW, Booth W. Exceptional long-term sperm storage by a female vertebrate. *PLoS One*. 2021;16(6):e0252049.
42. Baer B, Armitage SA, Boomsma JJ. Sperm storage induces an immunity cost in ants. *Nature*. 2006;441(7095):872-875.
43. Sasanami T, Matsuzaki M, Mizushima S, Hiyama G. Sperm storage in the female reproductive tract in birds. *J Reprod Dev*. 2013;59(4):334-338.
44. Sever DM. Female sperm storage in amphibians. *J Exp Zool*. 2002;292(2):165-179.
45. Hankison S, Gangloff EJ, Fry B, et al. Effects of reliance on stored sperm on reproduction in the sailfin molly Poecilia latipinna. *J Fish Biol*. 2022.
46. Suarez SS. Mammalian sperm interactions with the female reproductive tract. *Cell Tissue Res*. 2016;363(1):185-194.
47. Hunter RHE. Polyspermic fertilization in pigs after tubal deposition of excessive numbers of spermatozoa. *JExpZool*. 1973;183:57-63.
48. Ardon F, Markello RD, Hu L, et al. Dynamics of bovine sperm interaction with epithelium differ between oviductal isthmus and ampulla. *Biol Reprod*. 2016;95(4):90.
49. Parrish JJ, Susko-Parrish J, Winer MA, First NL. Capacitation of bovine sperm by heparin. *Biol Reprod*. 1988;38(5):1171-1180.
50. Ho K, Wolff CA, Suarez SS. CatSper-null mutant spermatozoa are unable to ascend beyond the oviductal reservoir. *Reprod Fertil Dev*. 2009;21(2):345-350.
51. Demott RP, Suarez SS. Hyperactivated sperm progress in the mouse oviduct. *Biol Reprod*. 1992;46(5):779-785.
52. Schjenken JE, Sharkey DJ, Green ES, et al. Sperm modulate uterine immune parameters relevant to embryo implantation and reproductive success in mice. *Commun Biol*. 2021;4(1):572.
53. Peng J, Chen S, Busser S, Liu H, Honegger T, Kubli E. Gradual release of sperm bound sex-peptide controls female postmating behavior in Drosophila. *Curr Biol*. 2005;15(3):207-213.
54. Ravi Ram K, Wolfner MF. Sustained post-mating response in Drosophila melanogaster requires multiple seminal fluid proteins. *PLos Genet*. 2007;3(12):e238.
55. Kubli E. Sex-peptides: seminal peptides of the Drosophila male. *Cell Mol Life Sci*. 2003;60(8):1689-1704.
56. Hopkins BR, Perry JC. The evolution of sex peptide: sexual conflict, cooperation, and coevolution. *Biol Rev Camb Philos Soc*. 2022;97(4):1426-1448.
57. Yapici N, Kim YJ, Ribeiro C, Dickson BJ. A receptor that mediates the post-mating switch in Drosophila reproductive behaviour. *Nature*. 2008;451(7174):33-37.
58. Pilpel N, Nezer I, Applebaum SW, Heifetz Y. Mating-increases trypsin in female Drosophila hemolymph. *Insect Biochem Mol Biol*. 2008;38(3):320-330.
59. Parker GA. Sperm competition and its evolutionary consequences in the insects. *Biol Revs*. 1970;45:525-567.
60. Parker GA. Conceptual developments in sperm competition: a very brief synopsis. *Philos Trans R Soc Lond B Biol Sci*. 1813;375:20200061.
61. van Hoogenhuijze NE, van Eekelen R, Mol F, et al. Economic evaluation of endometrial scratching before the second IVF/ICSI treatment: a cost-effectiveness analysis of a randomized controlled trial (SCRaTCH trial). *Hum Reprod*. 2022;37(2):254-263.
62. Baldini D, Ferri D, Baldini GM, et al. Sperm selection for ICSI: do we have a winner. *Cells*. 2021;10(12):3566.

**How to cite this article:** Wolfner MF, Suarez SS, Dorus S. Suspension of hostility: Positive interactions between spermatozoa and female reproductive tracts. *Andrology*. 2023;11:943–947. https://doi.org/10.1111/andr.13349