In search of a strategic disturbance: some thoughts on the timing of spaying

David J. Waters
Department of Veterinary Clinical Sciences, Purdue University, and The Gerald P. Murphy Cancer Foundation, West Lafayette, IN

Abstract

The aim of this paper is to provoke a thoughtful re-evaluation of our assumptions regarding the health consequences of elective ovariohysterectomy in pet dogs. It proposes that we might re-shape our thinking about the physiological impact of the timing of spaying and commit ourselves to making spaying a strategic physiological disturbance. Several observations that may help to guide this re-shaping are offered. First, the scholarly manuscripts of the veterinary profession routinely describe study populations in terms of male versus female, as well as neuter status. This implies that sex differences in biology can lead to clinically significant differences between males and females, and that gonad removal might re-set the system in important ways. Taken together, this suggests that the concept of ovary removal as a physiological disturbance, although not talked about, is already deeply rooted in the minds of veterinarians. Second, we have an incomplete understanding of the association between the diagnosis of mammary cancer or pyometra and the life expectancy of female dogs. This lack of data regarding the impact that these two health hazards of ovary retention exert on overall longevity points to a high research priority. Further, a more rigorous evaluation of the impact that the timing of spaying has on health will require investigators to revise their vocabulary, replacing the categories "spayed" or "intact" with measures of actual lifetime ovary exposure. Finally, we might do well to mimic the mindset of scientists in the field of evolutionary developmental biology who know that timing is everything when it comes to discovering what strategic disturbances can nudge a biological process closer to an intended outcome. Optimistically, the author posits that on the horizon sits a new set of research questions that will drive a revised conception about what we should want to know about the timing of spaying and health.

Keywords: Aging, longevity, mammary cancer, neutering, ovarian conservation, ovariohysterectomy, sex differences, spay

The tacit truth: Ovary removal as a physiological disturbance

In my reading of the veterinary literature, very seldom do I come across a clinical case series in which the investigator does not inform the reader that "there were 48 females and 26 males". In most instances, I can also count on the author to advance the description to reveal that "28% of the females were intact, 72% were spayed". Evidently this means that authors (and presumably readers) acknowledge the possibility that being male or female might influence health outcomes – whether it be an increase in disease incidence or a poorer prognosis following treatment. Further, this sort of discourse implies that gonads might be the germ of such sex differences and that disposal of these endocrine organs might disturb the organism in a clinically significant way. It is ironic that virtually every author busies themselves in this inventory of gonadal whereabouts, yet no papers I can find refer to *spaying as a physiological disturbance*. This surprising omission, however, is not that difficult to explain if one accepts either of two possibilities: (1) Authors and readers do not really believe that gonads exert clinically relevant effects; or (2) Authors and readers do believe that gonads exert clinically relevant effects, and consider it so intuitively obvious that they do not feel compelled to question the proposition. I do not accept the first explanation. For if this is indeed the belief held by so many, then why are the scholarly manuscripts of our profession written to include such descriptions as standard fare? My hunch is that, among veterinarians, view number two is the prevailing belief. Apparently the relationship between gonads and health outcomes falls under the category of *tacit knowledge* – a feeling for how mammals work that requires no explicit explanation. It follows that if you remove gonads, you might re-set the system in important ways – in ways important enough to affect a diverse collection of outcomes ranging from the incidence or lethality of neoplastic diseases, to the way an individual responds to an immune challenge. This possibility is so deeply rooted that it is not talked about. Therefore it is

somewhat surprising that, despite these deep-seated beliefs, a physiological disturbance like spaying immature pet dogs is so widely advocated for its health-promoting attributes.[1]

Expanding our thinking about ovaries beyond reproduction: Sex and gonadal differences in health outcomes as signposts that can advance our understanding of biological systems

Sex-differences in biology and medicine go far beyond the obvious–beyond breast cancer and menstrual cycles. I believe that studying sex differences in health can open important doors, providing us with a more expansive view of how the body works. As a member of The Organization for Sex-Specific Differences, my research group has been exploring sex differences in healthspan as a possible tool to deepen our understanding of underlying factors that significantly impact who does or does not get disease.[2] We need a better handle on the triggers and physiological contexts that determine health, and dissecting out the underpinnings of sex differences in biology could go far to meet this need.

For example, in one study, sexually intact female dogs diagnosed with epilepsy lived for an average of six years after diagnosis; in contrast, males with epilepsy lived only two years after diagnosis.[3] Several possible explanations for these provocative observations come quickly to mind. Do females get a less severe form of epilepsy? Does being female increase the likelihood of response to treatment with anticonvulsant drugs? Do the factors that predispose males to epilepsy also predispose them to other life-shortening diseases or accelerated aging? Perhaps being female has no influence on the severity of disease, but for any given severity of disease, females are less likely to succumb because they are overall more robust than males. Taken together, there seems to be good rationale for exploring further the biology behind the apparent sex difference in the survival of canine epileptics.

Amidst all the attention paid to faithfully reporting sex and neuter status, why is there so little attention paid to the details of gonadal exposure? In a nationwide study examining the factors that influence longevity in Rottweilers, we discovered a female longevity advantage over males.[4] Moreover, in females there was a direct relationship between actual years of ovary exposure and likelihood of reaching exceptional longevity.[4] But as we looked more deeply we made another important discovery: *No previous peer-reviewed paper in the veterinary literature had evaluated the association between longevity and actual number of years of ovary exposure.* Instead, reports exposed readers to data on how long two groups of female dogs lived –"spayed" and "intact".[5,6] "Spayed" was the name given to bitches that lost their ovaries at some undetermined time during their lives. "Intact" was the name given to bitches that were still intact at the time of death. No wonder our results in female Rottweilers were considered so novel. No one had ever studied that relationship before.

Research priority: Clarifying the health hazards of ovary retention

To better understand the lifelong health consequences of ovariohysterectomy, we need studies situating the health hazards of keeping ovaries – in particular the risk of developing and dying from mammary cancer and pyometra – within the context of duration of lifetime ovary exposure and longevity. We need studies that will provide insights on *how the timing of spaying effects trade-offs that impact overall health*. Studies of bitches that make use of longevity as an outcome can do just that – integrating the risk and lethality of mammary cancer and pyometra with the risk and lethality of every other disease, as well as each individual's rate of physiologic decline.

To what extent does the diagnosis of mammary cancer or pyometra adversely influence life expectancy? This is a critical question which no previous report has ventured to answer. As a result of this knowledge gap, we cannot confidently say right now whether keeping ovaries for any particular duration of adult life cuts short the longevity of female dogs as a consequence of mammary cancer-related mortality. It is quite possible that, after one accounts for competing disease conditions and mortalities, a diagnosis of mammary cancer *does not* cut short the average dog's life expectancy. It seems that generating this kind of data could significantly change our perceptions and re-shape the kind of questions we are asking about the pros and cons of keeping or losing ovaries. Ultimately, this information would enable us to see more clearly what we might expect in terms of health outcomes if we delay ovariohysterectomy until a particular age during adulthood.

A need for new vocabulary: Evaluating the impact of timing of spaying will require replacing "spayed" or "intact" with measures of lifetime ovary exposure

If clinicians believe that gonads, as endocrine organs, might exert system-wide effects (for example, influencing the brain and other body parts of the aforementioned canine epileptics), then someone should be looking more closely at *dose-response* – paying attention to the timing of spaying. Few investigators have made much effort in defining their study populations in terms of actual years of ovary exposure. Instead they fall back on naming females as "spayed" or "intact" based upon gonadal status at the time of death, so-called dichotomous binning. All of us, as authors and readers of scientific reports, have grown accustomed to this lazy method of expressing lifetime ovary exposure. By ignoring actual years of ovary exposure, could we be developing misleading assumptions about the timing of spaying and its health consequences?

I have come to believe that this dichotomous binning approach creates more confusion than clarity. My research group has documented this potential for distorting inferences in a recent peer-reviewed publication.[7] Analytically, the categorizing of bitches as spayed or intact at the time of death is a blunt instrument that lacks rigor, falling far short of reliably representing biologically important differences in lifetime gonad exposure. What we need to probe more deeply is dose-response. For it is the timing of spaying that dictates the "window" during the life course when the body is under the influence of intact ovaries. This means not only the direct effects attributable to circulating factors produced by the ovary, such as estrogen, but also changes in pituitary function, such as the sustained increase in gonadotropin levels documented in spayed bitches.[8]

If we can agree that gonad removal disturbs normal physiology, it follows that *we might tap into spaying as a strategic disturbance – one that would optimize the organism for healthy longevity*. The challenge could be considerable, the payoff even greater. Finding the optimal window of ovary exposure for different breeds and different environmental contexts will be a challenging goal indeed. But the sooner we as clinicians fully embrace the notion that adult health outcomes are profoundly influenced by early life events,[9,10] the better we will be at helping pet owners make better decisions. With a deeper sense of life course perspective, the practice of "geriatric medicine" will grow beyond making recommendations about what are the best dietary supplements to give a dog after she has reached a ripe old age, to include making *superior early choices* that promote healthy longevity.[11] Our profession is in need of such chronological crusaders, schooled in the value of timing and life course perspective. It is logical that theriogenologists should play a leadership role in this evolutionary thinking.

All about timing: Jack Horner's dangerous idea

The world-renowned paleontologist Jack Horner believes it's time to make a strategic disturbance.[12] His endgame is not the healthy longevity of pet dogs. Instead, his goal is to grow a dinosaur. Paleontologists know that birds are the only living descendants of the dinosaurs. So by carefully studying the developmental biology of the chicken, Horner plans to disturb the process at a key moment, biochemically nudging the avian developmental program toward hatching a beast with tail, teeth, and grasping forearms. He has a clear picture of what he wants to create – a living dinosaur – and he's betting that a strategic disturbance will make that goal a reality.

Some see Horner's directive as misinformed, even crazy. But I see a bigger picture in Horner's ponderings. He's not all that far out on a limb. His radical hypothesis fits squarely under the umbrella of one of science's hottest fields of inquiry known as evolutionary developmental biology or "evo-devo".[13,14] Investigators in this field are probing the process of evolution by studying the process of change in developing embryos. It turns out that not-so-subtle differences – the difference between hatching a beast with a front leg instead of a wing – are under the control of relatively few genes and whether those genes are switched on or switched off.

Horner is obsessed with timing and I think we should follow his lead. Horner knows that he will need to be very precise if he is to discover the critical sequence of developmental events that creates dinosaur-like, rather than chicken-like, traits. Without this attention to detail, he will surely fail.

Likewise, if our goal is to better understand the differences in health outcomes of female dogs with or without gonads, we will need to exercise similar precision. We will need to employ a vocabulary that best reflects the timing of critical life events, such as gonadectomy. *We will need to learn how to strategically disturb the system.* Instead of Horner's window of embryonic development, our challenge will be to explore more fully the post-natal windows during the life course when key exposures – such as ovary exposure – dictate the differences we are striving to achieve, differences that favor longevity and disease avoidance in our pets and in ourselves.

If, in the spirit of Jack Horner, I were permitted to put forward my own radical hypothesis it would be this. I would predict that, in large breed dogs prone to highly lethal forms of non-epithelial cancers (e.g. lymphoma, osteosarcoma, hemangiosarcoma) and whose body size means that cruciate ligament injury frequently leads to mobility issues that can precipitate earlier euthanasia, the age at spaying that optimizes longevity will be closer to six years than six months. Just the other day, I spoke with a small animal practitioner who had read about our work on ovaries and sex differences in longevity.[15] He commented: "I'm not so sure about what you're saying about ovaries promoting longevity. I've been practicing for 25 years and I can't honestly say that I appreciate a longevity difference between female and male dogs." I asked him: "Do you observe very many females who spend a sizeable percentage of their adult life with intact ovaries?" "No," he said, "we advise our clients to spay at six months." Enough said. My colleague's observations fit precisely within my emerging view of canine longevity – early ovary removal as the great homogenizer. I'm beginning to see ovaries as part of a system that promotes longevity.[16-18]

Time for a new set of questions

Perhaps the most prized products of research are the new questions that come. The astrophysicist Sir Arthur Eddington stated: "Progress is marked not so much by the problems we are able to solve as by the questions we are enabled to ask."[19] The biochemist N.W. Pirie took the notion one step further: "Clearly the process of formulating a question has a great psychological effect on the questioner; it focuses his attention on *what he thinks he wants to know*."[19] Reflecting on the last four decades, it is difficult to describe our profession as marching briskly toward a more complete understanding of the health consequences of retaining ovaries. Instead, I sense we have sunk into a somnambulistic state, passively accepting report after clinical report of dogs as "spayed" or "intact" as if this dichotomous substitute for actual years of lifetime ovary exposure was informative. I know – I wrote some of those reports. I took part in the sleepwalking for more than 20 years, waking up just a few years ago. Surely, this sleepy, indoctrinated behavior has shielded us from probing more deeply the question: What effect does the timing of spaying have on adult health outcomes?

For many of us, our argument supporting the health benefits of ovariohysterectomy prior to adulthood has its foundation in the trusted mantra: "If we don't spay early, we won't prevent mammary cancer". You may find yourself imprisoned by this notion that was instilled in you during your training; indeed the idea that early spaying protects against mammary cancer figured prominently in my own training.[20] But just how confident are we that the diagnosis of mammary cancer in female dogs is a harbinger of premature death? I keep hearing the echo of Pirie's words. *If we are willing to begin to ask new questions, we will discover there is much more that we should want to know about the timing of spaying and health*. If we can openly acknowledge ovariohysterectomy as a physiological disturbance, we can begin to more rigorously explore its consequences, which may be linked to health outcomes yet unseen. By shifting the debate away from "Should we spay, should we not?" toward a new question "What age at spaying best promotes healthy longevity", we prepare the necessary ground for making spaying a strategic disturbance.

References

1. Root Kustritz MV: Determining the optimal age for gonadectomy of dogs and cats J Am Vet Med Assoc 2007;231:1665-1675.

2. Waters DJ, Chiang EC, Cooley DM, et al: Making sense of sex and supplements: differences in the anticarcinogenic effects of selenium in men and women. Mutation Res 2004;551:91-107.
3. Berendt M, Gredal H, Ersboll AK, et al: Premature death, risk factors, and life patterns in dogs with epilepsy. J Vet Intern Med 2007;21:754-759.
4. Waters DJ, Kengeri SS, Clever B et al: Exploring mechanisms of sex differences in longevity: lifetime ovary exposure and exceptional longevity in dogs. Aging Cell 2009;8:752-755.
5. Bronson RT: Variation in age at death of dogs of different sexes and breeds. Am J Vet Res 1982;43:2057-2059.
6. Michell AR: Longevity of British breeds of dog and its relationships with sex, size, cardiovascular variables and disease. Vet Rec 1999;145:625-629.
7. Waters DJ, Kengeri SS, Maras AH et al: Probing the perils of dichotomous binning: how categorizing female dogs as spayed or intact can misinform our assumptions about the lifelong health consequences of ovariohysterectomy. Theriogenology 2011;76:1496-1500.
8. Reichler IM, Hung E, Jochle W et al: FSH and LH plasma levels in bitches with differences in risk for urinary incontinence. Theriogenology 2005;63:2164-2180.
9. Brown DW, Anda RF, Tiemeirer H et al: Adverse childhood experiences and the risk of premature mortality. Am J Prev Med 2009;37:389-396.
10. Brown DW, Anda RF, Felliti VJ et al: Adverse childhood experiences are associated with the risk of lung cancer: a prospective cohort. BMC Public Health 2010;10:20.
11. Waters DJ: Cellular and organismal aspects of senescence and longevity. In: Wilmoth JM, Ferraro KF, eds. Gerontology perspectives and issues. New York: Springer Publishing Company; 2007. p. 63-87.
12. Horner J, Gorman J: How to build a dinosaur. New York: Dutton; 2009.
13. Wagner GP: What is the promise of developmental evolution? Part I: Why is developmental biology necessary to explain evolutionary innovations? J Exp Zool 2000;288:95-98.
14. Wagner GP: What is the promise of developmental evolution? Part II: A causal explanation of evolutionary innovations may be impossible. J Exp Zool 2001;291:305-309.
15. Nolen RS: Rottweiler study links ovaries with exceptional longevity. J Am Vet Med Assoc 2010;236:496.
16. Parker WH, Broder MS, Chang E et al: Ovarian conservation at the time of hysterectomy and long-term health outcomes in the Nurses' Health Study. Obstet Gynecol 2009;113:1027-1037.
17. Mason JB, Cargill SL, Anderson GB, et al: Transplantation of young ovaries to old mice increased life span in transplant recipients. J Gerontol A Biol Sci Med Sci 2009; 64:1207-1211.
18. Waters DJ: Aging research 2011: exploring the pet dog paradigm. ILAR J 2011;52:97-105.
19. Pirie NW: Selecting facts and avoiding assumptions. In: Berthoff AE, ed. Reclaiming the imagination. Upper Montclair (NJ): Boynton/Cook Publishers Inc.; 1984. p. 203-211.
20. Schneider R, Dorn CR, Taylor DON: Factors influencing canine mammary cancer development and postsurgical survival. J Natl Cancer Inst 1969;43:1249-1261.