

Ovaries & Longevity

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A Healthier Respect for Ovaries

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A recent study by my research group appearing next month in *Aging Cell* reveals shortened longevity as a possible complication associated with ovary removal in dogs (1). This work represents the first investigation testing the strength of association between lifetime duration of ovary exposure and exceptional longevity in mammals. To accomplish this, we constructed lifetime medical histories for two cohorts of Rottweiler dogs living in 29 states and Canada: Exceptional Longevity Cohort = a group of exceptionally long-lived dogs that lived at least 13 years; and Usual Longevity Cohort = a comparison group of dogs that lived 8.0 to 10.8 years (average age at death for Rottweilers is 9.4 years). A female survival advantage in humans is well-documented; women are 4 times more likely than men to live to 100. We found that, like women, female Rottweilers were more likely than males to achieve exceptional longevity (Odds Ratio, 95% confidence interval = 2.0, 1.2 - 3.3; $p = .006$). However, *removal of ovaries during the first 4 years of life erased the female survival advantage*. In females, this strong positive association between ovaries and longevity persisted in multivariate analysis that considered other factors, such as height, adult body weight, and mother with exceptional longevity.

In summary, we found female Rottweilers who kept their ovaries for at least 6 years were 4.6 times more likely to reach exceptional longevity (i.e. live >30 % longer than average) than females with the shortest ovary exposure. Our results support the notion that how long females keep their ovaries determines how long they live.

In the pages that follow, I have attempted to frame these new findings in a way that will encourage veterinarians to venture beyond the peer-reviewed scientific text and data-filled tables of *Aging Cell* to consider the pragmatic, yet sometimes emotionally charged implications of this work. Call it a primer for the dynamic discussions that will undoubtedly take place, not only between practitioners and pet owners, but also within the veterinary profession. Call it a wake-up call for how little veterinarians have been schooled in the mechanistic nuts and bolts underlying the aging process. Call it an ovary story.

Do ovaries really promote longevity? Observed associations between exposures and outcomes may not necessarily be causal, so we explored alternative, non-causal explanations for the

association between ovaries and exceptional longevity in our study. But we found no evidence that factors which may influence a pet owner's decision on age at ovary removal — for example, earlier ovariectomy in dogs with substandard conformation or delayed ovariectomy to obtain more offspring in daughters of long-lived mothers — could adequately account for the strong association.

There is another aspect of our data pattern that gives us further confidence that ovaries really do matter when it comes to successful aging. A simple explanation for the observation that ovaries promote longevity would be that taking away ovaries increases the risk for a major lethal disease. In Rottweilers, cancer is the major killer. We found, however, that by conducting a subgroup analysis that excluded all dogs that died of cancer, the strong association between intact ovaries and exceptional longevity persisted. After excluding all cancer deaths, females that kept their ovaries the longest were 9 times more likely to reach exceptional longevity than females with shortest ovary exposure. *Thus, we observed a robust ovarian association with longevity that was independent of cause of death, suggesting that a network of processes regulating the intrinsic rate of aging is under ovarian control.* This work positions pet dogs, with their broad range of lifetime ovary exposure, to become biogerontology's new workhorse for identifying ovary-sensitive physiological processes that promote healthy longevity.

Interestingly, our findings in dogs surface just as data from women are calling into question whether those who undergo hysterectomy should have ovary removal or ovary sparing. In fact, our results mirror the findings from more than 29,000 women in the Nurses' Health Study who underwent hysterectomy for benign uterine disease (2). In that study, the upside of ovariectomy — protection against ovarian, uterine, and breast cancer — was outweighed by increased mortality from other causes. As a result, longevity was cut short in women who lost their ovaries before the age of 50 compared with those who kept their ovaries for at least 50 years. Taken together, the emerging message for dogs and women seems to be that when it comes to longevity, it pays to keep your ovaries.

But before we all go out and buy T-shirts with some romantic imperative like "Save the Ovaries", perhaps we should step back and consider the following question: Why haven't previous dog studies called our attention to this potential downside of ovariectomy? Reviewing the literature, an answer quickly bubbles up. No previous studies in pet dogs have rigorously evaluated the association between ovaries and longevity. Two frequently cited reports (3,4) provide limited guidance because: (1) longevity data are presented as combined mean age at death for a relatively small number of individuals of more than 50 breeds of different body size and life expectancy; and (2) ovarian status is reported as "intact" or "spayed", rather than as number of years of lifetime ovary exposure. Comparing female dogs binned into the categories of "intact" versus "spayed" introduces a methodological bias that might lead one to conclude that ovaries adversely influence longevity, i.e. ovary removal promotes longevity. Because the reasons for ovariectomy (e.g., uterine infection, mammary cancer) increase with increasing age, it is expected that a large percentage of the oldest-dogs are binned as "spayed" despite having many years of ovary exposure. For example, a dog who at age 12 undergoes ovariohysterectomy for pyometra would be binned as "spayed", despite 12 years of ovary exposure. In our study, we employed a more stringent study design — restricting the study population to AKC registered, pure-bred dogs of one breed, carefully quantitating the lifetime duration of ovarian exposure — in order to lessen the likelihood of such bias. And we reasoned that studying veterinary teaching hospital-based populations of dogs with artifactually low life expectancies (for example, 3.5 years is median age at death for Rottweilers in the Veterinary Medical Data Base)(5) was an inappropriate vehicle to describe the influence that ovaries have on aging. So we cast a wider net and collected data from Rottweiler owners nationwide, focusing our attention on exceptional longevity, not average age at death, as our study endpoint.

Why study exceptional longevity? Why not average longevity? We thought studying the most exceptionally long-lived individuals would tell us something about what it takes to age successfully. It's the same rationale used by Thomas Perls and investigators of the New England Centenarian Study (6) and by other scientists who study long-lived humans in other parts of the world (7). The approach even garners support from the mathematical field. In a seminal book on the origins of creative genius, the mathematician Jacques Hadamard wrote: "In conformity with a rule which seems applicable to every science of observation, it is the exceptional phenomenon which is likely to explain the usual one." (8) Hadamard was trying to understand how the brain gets creative so he studied people with extreme creativity. When it comes to studying aging, we're solidly in the Hadamard camp. That is why in 2005 we

established the Exceptional Longevity Data Base, launching the first systematic study of the oldest-old pet dogs (9). But folks in the opposing camp might justifiably fire back: "Don't study extreme longevity. Extreme longevity is much more about luck than it is about genes, or environment, or ovaries."

So to address the possibility that the "strangeness" or outlier nature of dogs with exceptional longevity could be forging a misleading link between ovaries and longevity, we studied a separate cohort of Rottweiler dogs. This data set was comprised of 237 female Rottweilers living in North America that died at ages 1.2 to 12.9 years — none were exceptionally long-lived. Information on medical history, age at death, and cause of death was collected by questionnaire and telephone interviews with pet owners and local veterinary practitioners. In this population, we found females that kept their ovaries for at least 4.5 years had a statistically significant 37% reduction in mortality rate (1). This translated into a median survival of 10.4 years for females with more than 4.5 years of ovary exposure — 1.4 years longer than the median survival of only 9.0 years in females with shorter ovary exposure ($p < 0.0001$). *Taken together, if you take out ovaries before 4 years of age you cut longevity short an average of 1.4 years and decrease the likelihood of reaching exceptional longevity by 3-fold.*

Up to this point, my ovary story has centered around a summarizing of methodologies and results. The reader has been given opportunity to see the gist of our findings within the context of previous dog studies and late-breaking studies in women. Now, let us pivot our attention a bit away from the results to focus on the recipients of these results — DVMs and pet owners.

We can start by tackling the question: Just how receptive will DVMs be to these new research findings? It's hard for old dogs to learn new tricks. But one thing is sure — blossoming change is rooted in real communication. The anthropologist Gregory Bateson wrote: "The pre-instructed state of the recipient of every message is a necessary condition for all communication. A book can tell you nothing unless you know 9/10ths of it already." (10). I call this "Bateson's Rule of the 9/10ths". If Bateson is right, then we will want to do something about the pre-instructed state of veterinarians. Because when it comes to the biology of aging, the state is virtually a blank slate. None of us received training in the biology of aging as part of our DVM curriculum — whether we graduated 30 years ago or last summer. Therefore, most DVMs are ill-prepared to receive messages examining the mechanistic underpinnings of the aging process. A Batesonian prescription for positive change would be to ratchet up the biology of aging IQ of practicing veterinarians. We agree. That is why we established the first gerontology training program for veterinarians in 2007 (11). We believe that by helping veterinarians "know" more about aging, they will be more able and more receptive to communicating the things that promote healthy longevity in their patients — things like preserving ovaries.

For certain, DVMs will be asked by pet owners to help them make their decision about age at spay in light of this new information. The question will be asked: Just how generalizable are these findings in Rottweilers to other segments of the pet dog population? It is impossible to say at this time. It will demand further study. Alas, 10 years from now, we might just find out that a longevity-promoting effect of ovaries in dogs is limited — limited to large breeds, urban but not rural dogs, or only those individuals with particular polymorphisms in insulin-like growth factor-1. These restrictions should not only be expected, they should be celebrated. It will mean that we have looked more deeply into how ovaries might influence healthy longevity. It will mean that our initial findings have been contextualized. And it is this contextualization of information that marks scientific progress — the kind of progress that guides sound clinical decision making. For it is context that determines meaning (12).

Our provocative findings in *Aging Cell* mean that it's time to re-think the notion that taking away ovaries has no significant downside to a dog's healthy longevity. Perhaps it would help us if we thought of lifetime ovary exposure as information — information that instructs the organism. Just how long and how healthy a female lives reflects what her cells, tissues, and organs thought they heard from the message received. Of course in biology, there is no single message but a symphony of messages, enabling each individual to successfully respond to environmental challenges. Our findings suggest that ovaries contribute that symphony. Taking

environmental challenges. Our findings suggest that ovaries orchestrate that symphony. Taking away ovaries in early or mid-life makes for muddled information, less than perfect music.

Information muddling can ensnarl decision-making. Our research takes an important first step toward disentangling the thinking about ovaries and longevity. We must never be paralyzed by the incompleteness of our knowledge. Our knowledge will always be incomplete — subject to revision, primed for further inquiry. This uncertainty, although invigorating for the investigator, is often painful for the practitioner who seeks simple, fact-driven algorithms to guide his action. Just as scientists will be called upon to forge ahead with their scientific inquiries, so too will practitioners be counted on to master the uncertainty. Together, we must navigate what the Danish philosopher-theologian Soren Kierkegaard called the gap “between the understanding and the willing.” That is, we must ask the right questions and make smart choices so that our action (the willing) is in synch with our knowledge (the understanding). Under just what circumstances will a particular individual benefit from specific lifestyle decisions? This is perhaps the most prescient, overarching question in the wellness and preventive medicine fields facing both human and veterinary health professionals today. How can we promote healthy longevity? Antioxidant supplementation or calorie restriction? Ovary removal or ovary sparing?

Undoubtedly, there will be protagonists and antagonists in this ovary story. The protagonists will be open-minded to following a new script. They will embrace the idea of ovary sparing for critical periods of time to maximize longevity. They might even recognize the need for some sort of “ovarian mimetic” in spayed dogs to optimize healthy aging. The antagonists in this story — the defenders of the old script — will dismiss as trivial the notion that ovaries regulate the rate of aging and influence healthy longevity. Lines will be drawn and opinions will fly. But *that’s what healthy debate is* — antagonists and protagonists keeping a high priority issue front and center, not allowing it to fade into the woodwork. It would seem that, in light of the new scientific findings, a contemporary dialogue should balance the potential benefits of elective ovary removal (13) with its possible detrimental effects on longevity.

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