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Effective options regarding spay or neuter of dogs

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Effective options regarding spay or neuter of dogs

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Editorial: Effective options regarding spay or neuter of dogs

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Editorial on the Research Topic
Effective options regarding spay or neuter of dogs

Introduction

Spaying of females and castration of males, collectively termed neutering, became a common practice for many dogs in the United States in recent decades, aimed at reducing relinquishment of dogs to animal shelters. Often performed at early ages, neutering of dogs prior to adoption from shelters often became a local or state legal requirement. However, scattered evidence began accumulating of some adverse effects of neutering with increases in certain cancers (1–5) and joint disorders (6). Emerging issues pertaining to spay-neuter provoked us to spearhead this Research Topic to provide an accessible resource to better understand current attitudes regarding neutering, surgical and alternative methods for neutering, and the behavioral and health effects of neutering dogs. These 16 research articles clarify some of the complexities associated with making decisions regarding spay and neuter of dogs; they have been of high interest to the general public.

Demographics and attitudes regarding neutered dogs

The research literature relevant to canine spay-neuter is widely dispersed and publications can be challenging to locate. Focusing on studies assessing attitudes to spaying of female dogs, Fausak searched three databases, CAB Direct, PubMed, and Scopus, to identify and characterize journals publishing most of the articles on this topic. For the 84 out of 642 articles identified as relevant on attitudes to female canine spaying, six journals each had published at least four articles. These journals either represented veterinary organizations or focused on reproduction. Most of these articles presented perspectives of veterinarians and a few had surveyed pet owners.

Changing patterns of dog ownership in Costa Rica were investigated by Flockhart et al. in 2020, with a goal of comparing results with earlier studies. They found a high rate of dog ownership: 76% of households, a sharp increase from prior studies reporting 53%, 50%, and 49% of homes with dogs, in 2000, 2003, and 2011, respectively. People living on farms

had the highest rate of ownership: 92%. Respondents reported that 67% of female dogs and 61% of males were neutered. This high neutering rate was a sharp increase from only 18% and 36% that previously had been reported in 2003 and 2011, respectively. Data provided evidence that "responsible pet owner" behavior had been increasing in Costa Rica.

Working in the Australian Capital Territory, Orr and Jones explored compliance with the legal requirement since 2001 for prepubertal desexing (neutering) for all cats and dogs. All cats are required to be desexed by 3 months of age, and all dogs by 6 months of age. Yet, very few of 52 responding veterinarians recommended that clients have their cat desexed at 3 months of age, as legally required. Almost half of veterinarians thought prepubertal desexing of cats was appropriate to prevent overpopulation. But over one-third of responding veterinarians did not realize that prepubertal desexing was mandatory, suggesting that the law may be poorly understood and supported by veterinarians.

Considering the possible impact of COVID-19 on elective neutering surgeries for dogs and cats, Guerios et al. explored whether the disease onset of COVID-19 was associated with a reduction in these surgeries. Records from 212 clinics reported 190,818 fewer neuter surgeries during years 2021-2022 than would have been expected if 2019 neutering levels had been maintained. Total surgeries for dogs decreased 19% and 14% in 2020 and 2021, respectively; surgeries for cats decreased 10% and 3%. If a similar rate of decline were experienced by all spay/neuter providers in the US, there would have been an overall deficit of more than 2.7 million spay/neuter surgeries during that 2-year period.

Exploring the possible effect of widespread neutering on the breeding of dogs, Dawson et al. presented a rationale arguing that a fundamental shift is required with collaboration of breeders and owners to promote inclusion of "proven" companion dogs in the gene pool–those likely to become good companions—rather than selecting dogs to breed that meet conformation or working/sporting standards. Details on breeding choices and puppy rearing should be documented, and based on knowledge, with breeders tested for suitability. Then, available companion dogs would more successfully meet the needs of modern urban dog owners. A new model is proposed, whereby responsible owners and breeders work together to produce dogs that are most suited for life as human companions.

Methods of altering reproductive capacity

Gonads are reproductive organs but also endocrine glands affecting normal metabolic, behavioral, and musculoskeletal health. Lifelong extremely heightened luteinizing hormone (LH) secreted after neutering, contributes to various disorders for both sexes (7). Thus, as a method to avoid the excessive LH secretion, Kutzler's review describes two gonad sparing surgeries that can be used to sterilize dogs. For females, ovary-sparing hysterectomy removes the uterus and much of the cervix, while leaving the ovaries intact. These females still experience regular estrous cycles but there is not vaginal discharge or risk for pyometra. For males, vasectomy is a quick surgery that involves bilateral removal and/or occlusion of a portion of the vas deferens. When performed on pediatric patients, these surgeries do not interfere with pubertal maturation. Once a dog is fully mature, the owner can still decide to remove the gonads.

Silva et al. investigated a simplified method of pain control with sedation and local anesthesia for use during castration of male dogs, avoiding general anesthesia as is done in humans and other species. Sedating dogs intramuscularly with xylazine and a sub-anesthetic dose of ketamine and administering lidocaine at the incision site and intratesticularly allowed dogs to be castrated humanely. This method avoided the expense of general anesthesia and the need for hospitalization.

Darounkolaei et al. compared ovariohysterectomy in large, deep-chested, mixed breed dogs performed in a conventional technique vs. an instrument shank-assisted ovariohysterectomy that was conducted by a single person. The new surgical method required use of four hemostats and two forceps and required less time to complete: averaging 34.7 min vs. 47.4 min. They concluded that the new method performed by just one person resulted in better time efficiency with less trauma and postoperative pain for the dog.

GnRH releasing implants desensitize the pituitary to the stimulatory effects of GnRH and block testicular function (testosterone and sperm production). Driancourt and Briggs provide an explanation and evaluation of the efficacy and safety research for two GnRH agonists: deslorelin and azagly-nafarelin. The deslorelin releasing implant is an adjunct or alternative for surgical sterilization of male dogs formulated for either at least six or 12 months. Azagly-nafarelin is a solid implant (Gonazon®) delivered 6-months to 1 year of suppressed fertility; however, it is not commercialized. The authors reviewed data on reversibility and long-term treatment and reported the treatment as having few adverse effects.

Behavioral and health effects of neutering

Much of the increased interest in spay-neuter stems from evidence of some adverse consequences. Bain addressed relationships among surgical procedures, animal behaviors, stressful animal experiences, and ethical dilemmas. Some surgical procedures can affect an animal's behavior, such as castration, and some pose an ethical dilemma, such as ear cropping and declawing. For these varied procedures, ameliorating pain, decreasing stressful experiences for the animal, and identifying and treating concurrent problem behaviors are hallmarks that can improve the welfare for the animal.

Hart et al.(a) evaluated mixed breed dogs in five body weight categories for their risks of one or more joint disorders associated with age of neutering, as compared with intact dogs. Only in the three weight categories of mixed-breed dogs weighing 20 kg or more, neutering before 1 year generally was significantly associated with risks of one or more joint disorders above that of dogs left intact, commonly to 3 times the level of intact dogs, with sex differences in the degrees of joint disorders associated with neutering.

In an evaluation of patient veterinary records for 35 breeds of dogs and effects of neutering age on joint disorders and cancers, Hart et al.(b) found major breed differences in

vulnerability to neutering. In most cases, the caregiver can choose the age of neutering without increasing the risks of these joint disorders or cancers. Subsequently, Hart and Hart reported that an additional five large breeds differed in their vulnerability to joint disorders and cancers with early neutering: German Shorthaired/Wirehaired Pointer; Mastiff, Newfoundland, Rhodesian Ridgeback, and Siberian Husky. Updated guidelines in this article covered 40 dog breeds. These results further emphasize the importance of personalized decisions regarding the neutering of dogs, considering the dog's breed, sex, and context.

Hart and Hart reviewed the ancient practice of castrating male animals and humans. Currently, the findings of breed-specific and sex-specific effects for age of neutering dogs have prompted considering a new paradigm with regard to this practice. This involves dealing with each individual dog in a personalized manner that includes consideration of the lifestyle situation when deciding upon the appropriate age of neutering to avoid increasing the risk of a joint disorder or cancer above that inherent for the breed.

For some inherited conditions, Oberbauer et al. reported that neutering is associated with an increased risk of expression. Neutering has also been associated with altered metabolism and a predisposition for weight gain in dogs, which may confound the detected risk association between neutering and disease expression. This article summarizes the effects of neutering on cancer, orthopedic, and immune disorders in the dog and also explores the potentially exacerbating factor of body weight.

When selecting and training service dogs, Zlotnick et al. found that those dogs neutered at <7 months had more than twice the risk for health-related dismissals as dogs neutered at any older age and this pattern held for orthopedic dismissals. Labradors were at higher risk for orthopedic-related dismissal than golden retrievers and all other breeds.

Early studies had shown improvements in male aggression after castration (8), but recent studies reveal greater fear aggression to strangers by neutered than intact males (9). Shorter exposure to gonadal hormones has been associated with greater fear and aggression for both males and females (10, 11), and longer exposure to gonadal hormones associated with fewer nuisance behaviors and health problems for both sexes (12). This growing body of research suggests that there is a relationship between dogs' age at neuter and the incidence of health and behavioral problems.

In summary

Issues regarding spaying and neutering dogs have become increasingly complex as more knowledge arises on interactions with diseases, behavior, welfare, and general health of dogs. The new paradigm involves assessing the lifestyle and entire situation of the particular dog as one decides whether and when to neuter a specific dog.

Author contributions

LH: Conceptualization, Writing – original draft, Writing – review & editing. BH: Conceptualization, Writing – review & editing. MK: Writing – review & editing. KA: Writing – review & editing.

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Conflict of interest

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PERSPECTIVE
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A Mapping Study of Veterinary Literature on Perceptions and Attitudes of Female Canine Spaying

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This is a mapping study conducted to evaluate the characteristics of where content that engages in perspectives or attitudes on female dog spaying is published. Three databases, CAB Direct, PubMed, and Scopus, were systematically searched. There were 84 out of 642 papers identified and screened for relevance on attitudes or perceptions on female canine spaying. These 84 articles were then examined for recurring authors, institutional representation, and publisher information. Additionally, information regarding the population being addressed, veterinarian or client, was noted with most literature addressing the veterinary perspective. Many important articles were published in a wide array of journals from many countries, which suggests the importance of not only browsing journals but also searching for relevant literature in databases like CAB Abstracts and MEDLINE.

Keywords: perspectives, literature, bitches, dogs, canine, female neuter, spay, ovariectomy

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INTRODUCTION

A great deal of literature and evidence has matured the veterinary approach and perspective toward spaying and neutering, as evidenced by *Frontiers in Veterinary Science* Research Topic: *Effective Options Regarding Spay or Neuter of Dogs* (1). Changing perspectives and risks associated with spaying female dogs can be found in databases as early as 1974 (2). This last decade has seen an explosion in literature regarding perspectives and attitudes in spaying female dogs, particularly an increase in either survey or ethnographic perspectives of specific populations regarding female canine spaying practices (3–13). Additionally, closer examination of a range of disease conditions has potentially been associated with early female spaying (14–29). Even guidelines and evidence-based systematic reviews as well as critically appraised topics have also been published over the past decade (30–36).

This mapping study has been used to identify the trend in literature questioning or examining the convention of spaying female dogs. The growth of evidence-based veterinary medicine has shown that many influential articles may exist outside the scope of typically browsed journal titles (37). This mapping study uses a similar systematic searching approach used in systematic reviews to make reproducible results. The literature retrieved was evaluated by identifying which journals, authors, institutions, countries, and timelines impacted attitudes and perspectives of female canine spaying over the history of veterinary medical literature.

METHODS

The goal of this mapping study was to create a transparent search strategy to identify characteristics of literature regarding female dog neutering in terms of client and veterinary perceptions, including associated risks. The primary approach to this mapping study is based on the concept set forth by Cooper (38). Modification includes conducting a systematized search for literature across three databases (CAB Direct, PubMed, and Scopus) on *female dog spaying*. Selection of which databases to search on female dog neutering was based on a review of database coverage of veterinary literature by Grindlay et al. (39). Specific database search strategies are available (see **Appendix A**), which included the use of terms for dogs (dog OR dogs OR canines OR canine OR canids OR beagles OR shepherds OR retrievers), spaying (spay* OR OHE OR ovariectomy OR ovariohysterectomy OR "female castration"), and perspectives (Perceptions OR attitudes OR practices OR perception OR ethical OR moral OR "best practices" OR "paradigm" OR evaluation).

Search results were collected and then uploaded into UC Davis Library-licensed *F1000 Workspace* (now *SciWheel*) Citation Management Software and deduplicated. Once deduplicated, a citation management.ris file was exported from *F1000 Workspace* (now *SciWheel*) and uploaded in systematic review software licensed by UC Davis Library, *Covidence* (Australia), under screening and set for only one reviewer (the author). Literature was then screened based on the inclusion/exclusion criteria established. Inclusion criteria included articles in English that included female dogs and spaying and incorporated analysis of cost or benefit, client perspectives, veterinarian perspectives, and addressing potential risks or benefits of spaying. Exclusion occurred with articles not in English, did not involve female dog spaying, focused on procedure (like analgesics or surgical approach), and were case studies.

Once all the articles were screened, they were exported from Covidence and brought into *F1000 Workspace* (now *SciWheel*) for extraction as a.CSV file and analyzed in *Microsoft Excel* (version 16.36).

RESULTS

There were 642 papers found between the three databases and deduplicated from 722 papers. Only 84 articles were identified to be relevant to perception of spaying and neutering including risk and assessment. Many articles were about procedural refinement including examination of surgical approach and analgesia. Another large group of articles were case reports that included patient signalment in the abstract. CAB Direct had 18% of articles about female dog spaying addressing attitudes and perspectives. PubMed had 13% of articles about female dog spaying addressing attitudes and perspectives. Scopus had 18% of articles about female dog spaying addressing attitudes and perspectives. See **Appendix A** for summary data of results.

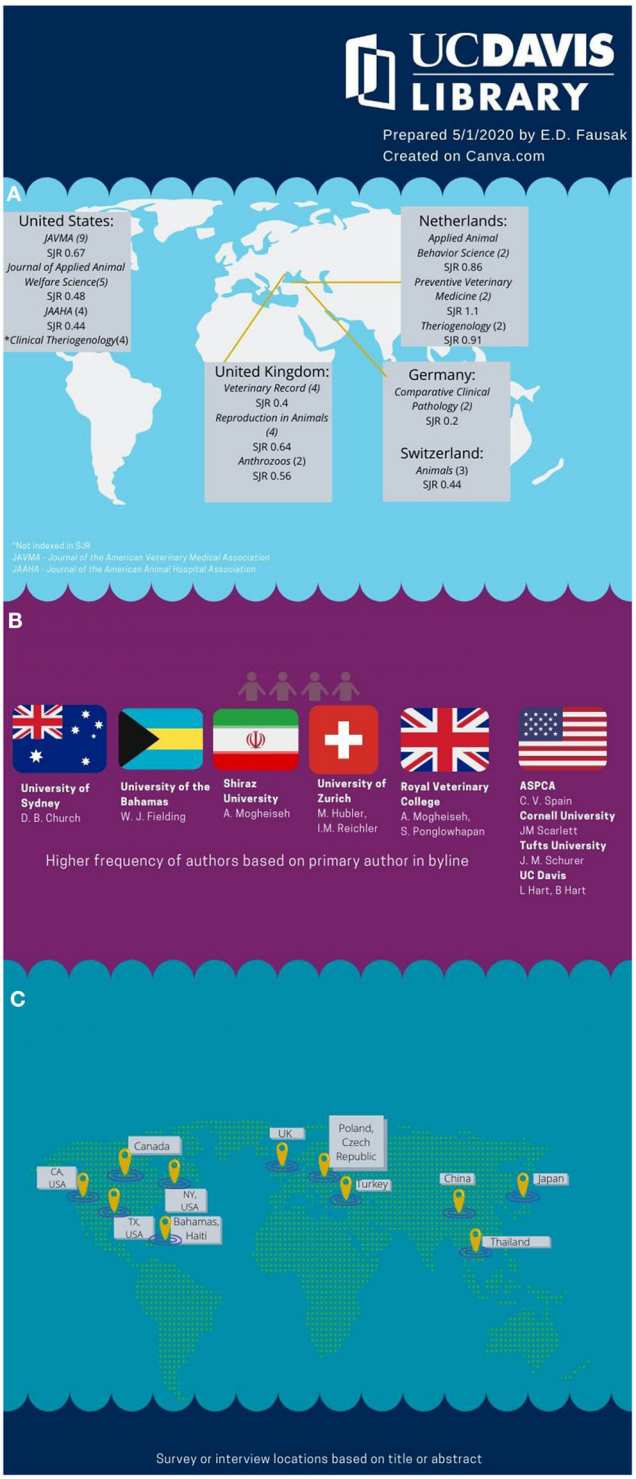

FIGURE 1 | Where perspectives on female dog neutering content is being published. **(A)** Journal (number of articles) and Scimago Journal Ranking (SJR). **(B)** WHO and WHAT Institutions are publishing on perspectives in female dog spaying. **(C)** Parts of the world surveyed or interviewed.

Journals

The first article retrieved in the databases that provides perspective on spaying and neutering programs was in *Vet Record* in 1974. Six journals had four or more articles pertaining to perceptions of spaying including the *Journal of the American*

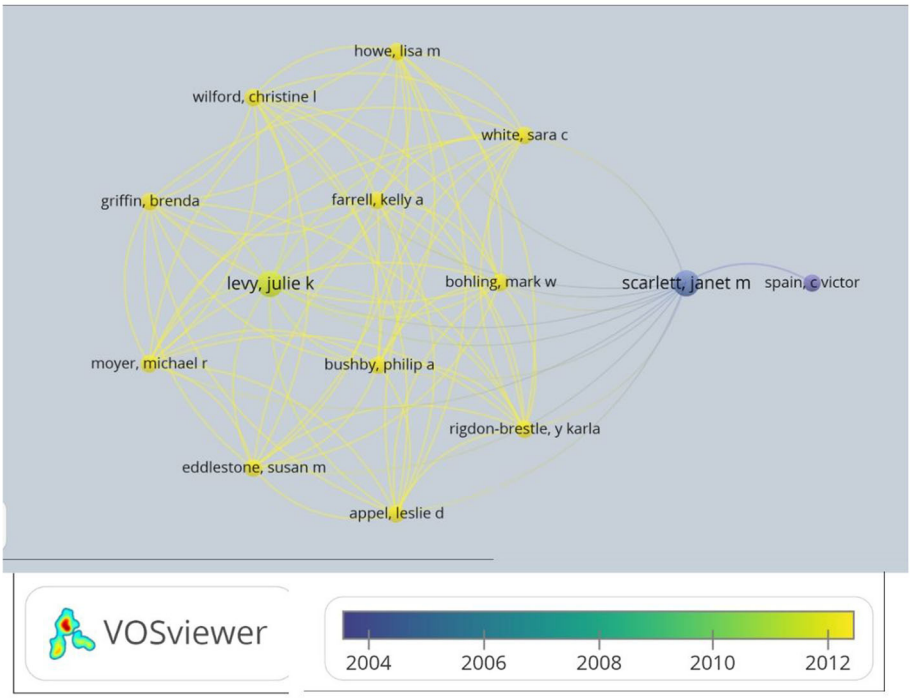

FIGURE 2 | Network analysis of authors. Analysis of authors with more than two publications and their relationship to each other. Built on VOS Viewer. Created by Nees Jan van Eck and Ludo Waltman at Leiden University—May 1, 2020.

Veterinary Medical Association (14, 18, 35, 36, 40–45), the *Journal of Applied Animal Welfare Science* (4, 5, 46–48), *Veterinary Record* (2, 49–51), *Reproduction in Domestic Animals* (29, 52–54), and *Clinical Theriogenology* (22, 26, 55, 56). All journals that had more than one article on the topic are listed with country of origin and Scimago Journal and Country Ranking in **Figure 1**.

Authorship and Institutional Contribution

Higher frequency of authors (more than one citation as primary name in by-line) that publish articles on perceptions and attitudes toward spaying include Church (University of Sydney, Australia) (17, 57), Fielding (University of Bahamas, Bahamas) (4, 5), Hart (University of California, Davis, USA) (22, 40, 58), Hart (University of California, Davis, USA) (22, 40, 58), Hubler (University of Zurich, Switzerland) (52, 59), Khalid (Royal Veterinary College, United Kingdom) (17, 57), Mogheiseh (Shiraz University, Iran) (60, 61), Ponglowhapan (Royal Veterinary College, United Kingdom) (17, 57), Reichler (University of Zurich, Switzerland) (29, 52, 59), Scarlett (Cornell University, USA) (36, 41, 62), Schurer (Tufts University, USA) (8, 9), and Spain (ASPCA, USA) (41, 62–65). See **Figure 1** for author affiliations. Additionally, **Figure 2** is a network map of authors by time created in software, VOS Viewer, created by Nees Jan van Eck and Ludo Waltman at Leiden University. Of 286 authors, 22 authors have at least two publications and 14 authors have clear network relationships starting with C. V. Spain of the ASPCA in 2004.

Surveyed Countries

The US was the most frequently surveyed country with Texas, California, and New York as the most frequently surveyed states (46, 48, 62, 66–68). Multiple surveys were conducted in the United Kingdom, Canada, and Japan (8, 9, 14, 58, 63, 69, 70) (see **Figure 1**).

Perspective and Dates of Publication

Most of the articles were written from the perspective of the veterinarian (85%). Many of the articles that address client perspectives utilized surveys or ethnographic data.

The most number of activities of publication on spaying perspectives have been over the last decade with 58 articles since 2010 (3–7, 9, 11–20, 22–29, 31, 35, 44, 48, 52, 54–56, 60, 61, 64, 67, 69, 71–85). The decade of 2000 produced 18 articles (36, 40–43, 46, 47, 49, 50, 57, 59, 62, 63, 66, 71, 86–89). The 1990s produced five articles with only one article published in the 1980s and two in the 1970s (2, 45, 51, 58, 68, 70, 90, 91).

CONCLUSIONS

There were 6,582 articles retrieved with search terms for female dog spaying in English. Of those articles, 642 were retrieved with perceptions or attitudes toward spaying, and 84 articles were screened to pertain to female dog spaying from a client or veterinarian perspective. Of the 642 articles, most were focused on the practice and refinement of spaying as a procedure and were excluded.

Of the top journals, it is probably not surprising that national veterinary organizational journals, like the *Journal of the American Veterinary Medical Association (AVMA)* and *Veterinary Record (BVA)*, are the most common journals to publish in when addressing changing perspectives or attitudes toward female dog spaying. Journals that look at reproduction like *Theriogenology*, *Clinical Theriogenology*, and *Reproduction in Domestic Animals* are also probably not a surprising source of this content. The broader and more holistic journals are of interest, like *Animals*, *Anthrozoos*, and *The Journal of Applied Animal Welfare Science*. Many journals that had relevant articles may not be regularly browsed by practitioners.

This mapping study's purpose is to identify literature that examines perspectives about spaying and identify where and when the literature is being published. It is beyond the scope of this paper to assess the quality or content of the literature discovered. This last decade has seen a large increase in literature about what age, in relationship to breed, that female dogs should be spayed. Most of this literature is published for the veterinary professional and very little from a consumer perspective.

What may be interesting to note is that a great deal of consumer health resources may or may not reflect the changes in perspective regarding spaying and neutering. For instance, a gold standard in client information resources, VIN's Veterinary Partner, makes no mention of recent literature on breed-specific concerns in spaying or neutering (92, 93). What is interesting is that most canine food companies like *Hill's Science Diet* or *Royal Canin* do recognize variations in spaying and neutering needs for different breeds (94, 95).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.559659/full#supplementary-material

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Owned dog population size and ownership patterns in Costa Rica

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Dogs (*Canis lupus familiaris*) are one of the most common pets around the world but ownership patterns and human-dog interactions have been changing, particularly in developing nations. We conducted household surveys in Costa Rica to characterize dog ownership, the owned dog population, where dogs were confined at night and in the morning, and behaviors regarding selected dog care issues. We also compared these results to similar questionnaires used in Costa Rica over the past 20 years. We found 76% of households in Costa Rica owned at least one dog and on average there were about 1.4 dogs owned per household. These dog ownership rates are higher than previous estimates. The probability of owning a dog was highest on farms and lowest in single family dwellings without a yard, higher among respondents that owned their homes and decreasing with increasing human population density The total number of owned dogs in Costa Rica was estimated to be 2,222,032 (95% confidence intervals: 1,981,497–2,503,751). The sterilization rate for homed dogs in 2020 was approximately 62% (females: 67%, males: 61%) which is higher than the 18% of owned dogs that were sterilized in a 2003 survey. Overall, only 1.2% (95% CI: 0.3–2.5%) of owned dogs slept on the street with a slightly higher proportion on the street at 8 am. The number of owned dogs roaming the streets at night nation-wide was estimated to be 27,208 (95% CI: 7,557–56,619) compared to 43,142 (95% CI: 20,118–73,618) on the street at 8 am. The number of unowned free-roaming dogs in Costa Rica has never been estimated but we can generate some idea of the size of the unowned dog population by determining the proportion of free-roaming dogs on the street wearing collars. There was a negative relationship between human population density and owned dogs being on the street meaning fewer dogs roam the streets in highly populated areas compared to less populated areas. Overall, we identify trends against which future progress can be measured and provide information that are critical in designing effective humane dog management programs in Costa Rica in the future.

KEYWORDS

animal welfare, dog ownership, management, free-roaming dogs, companion animal, pet

Introduction

Dogs (*Canis lupus familiaris*) are one of the most common pets around the world and play important roles in owners lives including companionship and protection (1). Free-roaming dogs, comprised of owned dogs that have unconstrained outdoor access some or all of the time and unowned dogs that move freely outside, can be vectors of disease (2), have impacts on the environment (3), and can cause injuries from interactions with people (4). In developing nations, especially those in tropical areas, dog ownership and outdoor access may be different than in fully developed nations (5). Further, the tolerance of free-roaming dogs may vary over space and time and depend on local context (6, 7). Permissive attitudes regarding free-roaming dogs in some countries, coupled with the perceived efficacy of sterilization as a dog management tool (8) could result in large number of free-roaming dogs. In turn, a large population of free-roaming dogs may lead to liability problems and risks to humans from interactions with dogs (9). Dog bites to humans are a risk wherever there are free-roaming dogs (10). Dog bite incidence may decrease following dog sterilization (11) presumably because agonistic interactions among dogs competing over a bitch in heat and from female dogs protecting puppies should be absent among sterilized dogs (12). Developing suitable management plans (e.g., vaccinating a certain proportion of free-roaming dogs per month) to reach societal objectives (e.g., reducing rabies prevalence in free-roaming dogs by 80%) requires, at a bare minimum, reasonable estimates of dog ownership, dog outdoor access, and population size but few estimates of these basic metrics are available (13).

Human-dog interactions have been changing around the world over the past fifty or more years. In North America in 1950, 30% of pet dogs were considered to be owned free-roaming dogs (14) yet today most pet dogs in North America are closely controlled (*via* leashes and visible and invisible fences) and owned free-roaming dogs probably constitute less than 1% of the total US dog population (unpublished data, ANR). Something similar to the changes that occurred in the USA in the last half of the 20th century appear to be happening now in Costa Rica. Freely roaming dogs were common in and around Heredia, Costa Rica in the 20th century but have declined significantly in the past 20 years [from observations by one of us (ANR) during visits to Costa Rica in 1999 and again in 2015]. We speculate that the presence of active shelter and education programs in the Heredia region (and in the San Jose valley) has led to changes in human-dog interactions in the San Jose valley but have no direct causal data supporting such a link.

This study describes survey work conducted in Costa Rica to generate a current baseline of dog ownership patterns, derive a population estimate across the country, and compare these results to previous surveys focused on dog ownership. The current surveys aimed to document continuing changes in dog ownership behaviors in Costa Rica based on a randomized, nationwide household survey. Two prior surveys of dog ownership in Costa Rica found that approximately half of all households owned a dog and that these homes owned on average about 1.6 dogs. These previous results provide a rare opportunity to compare the current study to previous conditions to monitor changes in the human-dog interaction over time.

Methods

Survey design and methods

We used a household survey, statistical modeling, and qualitative comparisons to understand patterns of dog ownership, outdoor access, and population size across Costa Rica. The survey was administered between August and September 2020 by TGM (https://tgmresearch.com/; Ho Chi Minh City, Vietnam) and posed questions to households about pets and animal-related issues *via* the internet or cell phones. Respondents were selected from registered online and mobile panels of participants from Costa Rica and restricted to adults only. The household survey focused on "owned" dogs regardless of their confinement status and recorded the number of owned dogs, where dogs sleep at night, and where dogs are at 8 am. We asked about where dogs were at 8 am to better understand the proportion of owned dogs that may be outside and unconfined at a time when dogs might be expected to be let outside after spending the night indoors or confined. We also asked if owned dogs were vaccinated against rabies, if they were sterilized, or had visited a veterinarian in the past year. For dogs that had visited a veterinarian in the past year we asked if the dog had visited for regular routine care or emergency care which provides some insight as to owner provisions of preventative care vs. emergency interventions. The survey recorded geolocation data so that dog ownership and human density of each household could be analyzed. The questionnaire used for the Household Survey is provided in Appendix 2.

Approximately half the human population of Costa Rica lives in the central valley around the capital, San Jose, but we were interested in determining country-level estimates that represented the national demographics. The country is divided into seven provinces that are further subdivided into 82 cantons and 488 districts. To obtain a representative sample while recognizing sample size and logistical constraints, we geographically stratified our sampling to match the proportion of the population in each province (Table 1) but oversampled in the Province of Heredia because we wanted to determine the extent to which residents in Heredia knew of and made use of a particular local shelter–the Asociacion Humanitaria.Para Proteccion Animal de Costa Rica (AHPPA), a partner in our ongoing research.

TABLE 1 Basic descriptive statistics for each province of Costa Rica and nationally of various attributes of dog ownership and interactions from a national household survey conducted in September 2020.

Province	Respondents	% Human population	# Dogs per household	% with dogs	Persons /HH	% Homes owned	Ave. # roaming dogs fed by neighbors	% Households with dog bite in last year
Alajuela	215 (16%)	20%	1.55	81.9%	3.71	65.6%	6.7	17.5%
Cartago	164 (12%)	11%	1.38	78.0%	4.05	68.3%	2.6	17.1%
Guanacaste	64 (5%)	8%	1.31	78.1%	4.33	40.6%	3.1	17.2%
Heredia	255 (19%)	10%	1.34	71.8%	3.75	51.4%	1.8	14.7%
Limon	66 (5%)	9%	1.77	87.9%	3.85	59.1%	2.2	12.3%
Puntarenas	96 (7%)	10%	1.51	81.3%	4.02	56.2%	5.8	14.9%
San Jose	489 (36%)	33%	1.38	73.4%	3.98	56.4%	1.9	16.2%
Total	1,349 (100%)	100%	1.42	76.5%	3.92	57.7%	3.1	16.0%

Before analysis, we used criteria to remove incomplete or biased responses. The criteria for removing responses were included the following:

a) if the geographic location was outside Costa Rica,
b) if the geographic location had identical latitude/longitude values with another location (when more than one person from the same household responded),
c) if the number of people in the household was >50 or zero,
d) if the dwelling type was not a farm, multi-unit building or single family home,
e) if the dwelling ownership was not either owned or rented;
f) or when the location was outside the spatial data sets (i.e., land use and population density) used to predict total dog population.

The final data set included 1,349 responses across the country from an initial sample of 1,626 responses.

Data analysis

Four analyses were conducted to understand dog ownership, the dog population, and dog confinement situation. A binomial generalized linear model (logistic regression) was used to explain the probability of dog ownership. A Poisson generalized linear model was used to explain the number of dogs owned per household. Multinomial generalized linear models were used to explain where dogs slept at night and where owned dogs were at 8 am. The explanatory variables that were considered in each model included:

a) age of the respondent (in both linear and quadratic forms),
b) dwelling type (farm, multi-unit building, single family home with yard, single family home without yard),
c) household size, and
d) dwelling ownership status (own or rent).

Additionally, geographic variables were extracted from the location of the respondents' residence including

a) elevation (considered in both linear and quadratic forms),
b) land use (5 categories:
   i) Broadleaf evergreen forest = 1,000 respondents,
   ii) Cultivated and managed terrestrial area = 288 respondents,
   iii) Built up areas = 30 respondents,
   iv) Broadleaf closed to open = 17 respondents,
   v) Shoreline = 11 respondents; (15),

c) province, canton, and population density at 1 km resolution (16).

The variable of elevation was used as a predictor for two reasons. First, given the large altitudinal relief differences found in Costa Rica (sea level to 3821 m) we were cognizant of the possibility of higher elevations having extreme conditions that might limit dog distributions at high elevations. In this case, we would have predicted lower dog abundance at higher elevations in a linear fashion. Second, given the observation that 70% of the population lives in the central valley, we wanted to account for the general observation that pet ownership per household is generally reduced in highly urbanized areas relative to rural areas (17). In this case, we would predict a curved relationship with the lowest dog abundance occurring at the elevation corresponding with the large, dense human population found in the central valley. Elevation could therefore be a useful metric for modeling spatial patterns across large geographies while simultaneously explaining variation in dog ownership patterns caused by environmental constraints and dense human populations that correspond with geographic anomalies.

All analyses were conducted using a stepwise model selection procedure to determine the most parsimonious explanatory model. The process began with a null model (intercept-only) and then moved on to models with singular effects of the variables listed above. Individual variables were added in a stepwise manner to check for improved model fit. Models that did not show a reduction in AIC (Akaike Information Criterion–see below) were ignored whereas models with improved fit were carried forward with the addition of further variables (18).

The models were ranked using AIC corrected for small sample size (AICc) where the model with the lowest AICc value is considered the best fit of the data. Models within 2 AICc units of the top model (<2 ΔAICc) are considered competing models and hold some support to explain the data (18). In cases where the competing models are simpler, or nested, versions of the top model, the added parameters of the top model are unlikely to provide much explanatory power and, in these cases, the simpler model is considered the most parsimonious (19). For each analysis, we present the mean and 95% confidence interval parameter estimates of the most parsimonious model.

To derive a country-level estimate of dog population size required extrapolating model estimates and associated uncertainty across the range of demographic and geographic variation in Costa Rica. Bootstrapping was therefore used to estimate dog population abundance across the diverse conditions found in Costa Rica and the proportion of dogs confined. Because our data was derived at the household-level and models contained geographic explanatory variables (e.g., elevation) extracted from the respondents location, the bootstrapping procedure required a location of an average random household during each simulation but we did not have a shapefile with household locations at any scale. To overcome this obstacle, we randomly placed 10,000 points within each of the 81 Cantons weighted by population density. Using this approach, the random locations were predominately in areas with the highest housing density and corresponding elevation. This approach accounted for variation in these variables on the landscape but appropriately weighted those factors based on clustering of households in urban areas. The point locations were used to extract both human population density, elevation, and land use values for the bootstrap simulations. As an example of the random point generation, Supplementary Figure S1 shows the population density and elevation for one Canton and the 10,000 random locations weighted by population density.

Each bootstrap simulation resampled the datasets by randomly selecting 2/3 of the original dataset with replacement. We then refit the best supported regression models from the model selection procedure described above and used the parameter estimates to derive predictions for each Canton. The predictions for each Canton were mean number of dogs per household. This figure was then multiplied by the number of households in the Canton to derive an estimate of the total number of owned dogs in the Canton. We also predicted the proportion of dogs in a Canton that were confined at both 8 am and at night (asleep in the house), on the street or in the yard. By multiplying the predicted population size in a Canton by these proportions we could estimate the number of dogs in each Canton confined in the house, on the street, or in the yard. By summing the population estimates of each Canton we produced an estimate of the number of owned dogs in Costa Rica. We then calculated the mean and 95% confidence intervals of the bootstrapped estimates to derive national population statistics. All modeling was conducted in Program R version 4.1.2 (20).

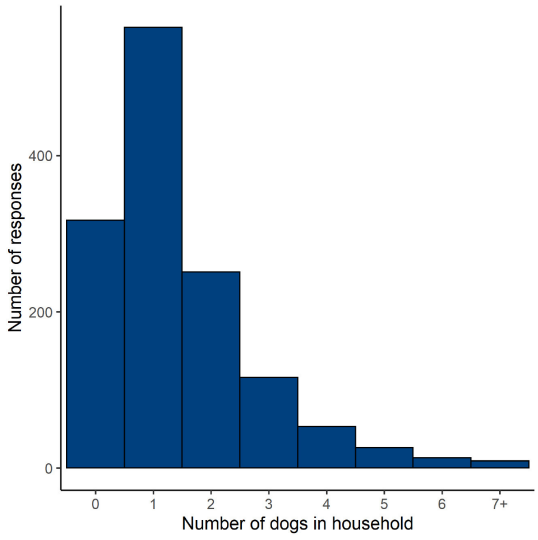

FIGURE 1
Histogram of the number of owned dogs per household from a survey of 1,349 respondents in Costa Rica.

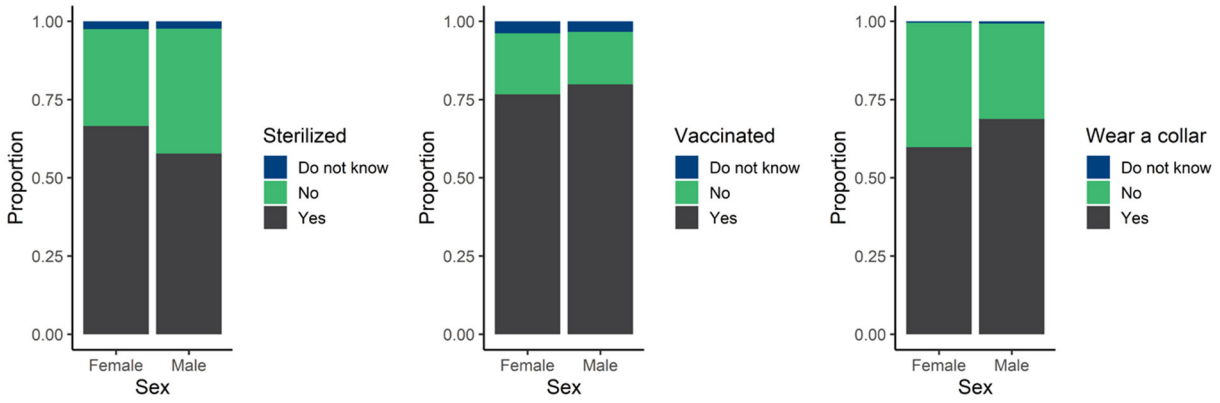

FIGURE 2
Proportion of male and female dogs that were sterilized, vaccinated, and wore a collar.

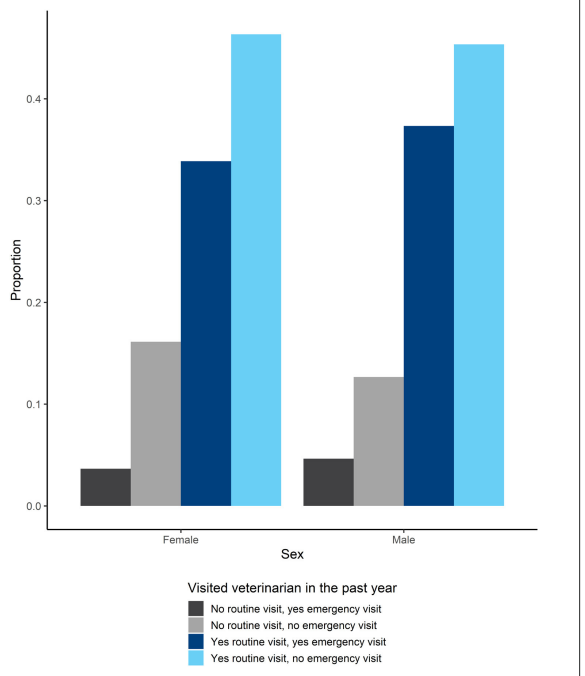

FIGURE 3
Proportion of male and female dogs whose owners knew if they had visited a veterinarian in the past year for routine care and emergency care.

Comparison to previous population estimates

Our qualitative assessment of changes in the human-dog relationship was done by comparing our population estimates to previously conducted surveys in Costa Rica. Two surveys were carried out by the World Society for Protection of Animals (WSPA–now World Animal Protection) in 2003 and 2011 but were focused on respondents living in the San Jose metro area. A national survey of the ownership of pet wildlife (but including pet dogs and cats) was also undertaken in 2000 asking if a household owned dogs but did not quantify the number of dogs per household (21). The study by Drews (21) surveyed 1,021 households based on random selection of 278 of the total 10,535 census segments across the country. Households were randomly selected for surveys until the sex and age quota for that segment was covered. Our survey (2020) incorporates questions that were asked in previous surveys and therefore, there is reasonably good "pre-treatment" data, which ultimately facilitates understanding changes in dog ownership patterns over the past two decades. We compared dog ownership patterns, number of dogs per household, national estimated dog population size, confinement location of dogs at night, and whether dogs were vaccinated against rabies, had been sterilized, or had visited a veterinarian during the past year. Given the similar methodology among the surveys (21), the comparison provides the opportunity to understand broad changes in dog ownership and help design a strong monitoring program as an integral component of the ongoing management program, rather than addressing monitoring as an afterthought.

Results

According to our survey results, 76% of households in Costa Rica own at least one dog (Figure 1) and on average there were 1.4 dogs owned per household (Table 1). The estimated mean number of roaming dogs fed by the neighbors of survey respondents ranged from 1.8 in Heredia Province to 6.7 in Alajuela Province and was 3.1 dogs across the country (Table 1). The proportion of households where one or more people were bitten by dogs in the past year was 16% and did not vary much

TABLE 2 A reduced candidate model list ranked using Akaike Information Criterion (AIC) to explain the probability of dog ownership of residents of Costa Rica.

Model	K	AICc	ΔAICc	Li	Wi	LL	∑Wt
Dwelling type + Ownership + Population density + Elevation^2	9	1,367.1	0	1	0.34	−674.48	0.34
Dwelling type + Ownership + Population density + Elevation^2 + Land use	15	1,367.6	0.5	0.78	0.27	−668.62	0.61
Dwelling type + Ownership + Population density + Elevation^2 + Household size	10	1,368.32	1.22	0.54	0.19	−674.08	0.8
Dwelling type + Ownership + Population density + Elevation^2 + Household size + Land use	16	1,368.84	1.74	0.42	0.14	−668.21	0.94
Dwelling type + Ownership	6	1,370.62	3.52	0.17	0.06	−679.28	1

The model producing the lowest AICc value is the best one. Variables considered include age [linear (Age) or quadratic (Age^2) form], land use, dwelling type, dwelling ownership status, population density, elevation (in linear or quadradic forms), household size, Province, and Canton. The Table includes the following columns: K–number of parameters, AICc–correction for small sample size, ΔAICc–difference between AICc for each model relative to the top model, Li–model likelihood, Wi–Akaike Information Criterion model weight, LL–model Log-likelihood, and ∑Wt–cumulative Akaike weight.

TABLE 3 Reduced candidate model list of models <10 ΔAICc ranked using Akaike Information Criterion (AIC) to explain the number of dogs owned per household of residents of Costa Rica.

Model	K	AICc	ΔAICc	Li	Wi	LL	∑Wt
Dwelling type * Ownership + Population density + Elevation^2+ Household size	16	4,120.93	0	1	0.81	−2,044.26	0.81
Dwelling type * Ownership + Population density + Elevation^2	15	4,125.32	4.38	0.11	0.09	−2,047.48	0.9
Dwelling type + Ownership + Population density + Elevation^2+ Household size	10	4,125.54	4.6	0.1	0.08	−2,052.69	0.98
Dwelling type + Ownership + Population density + Elevation^2	9	4,129.52	8.58	0.01	0.01	−2,055.69	0.99
Dwelling type + Ownership + Population density + Elevation^2 + Household size + Land use	16	4,130.59	9.65	0.01	0.01	−2,049.09	1

Variables in the models include age in either a linear (Age) or quadratic (Age^2) form, land use, dwelling type, dwelling ownership status, population density, elevation (in linear or quadradic forms), household size, Province, and Canton. For each variable are the Akaike Information Criterion corrected for small sample size (AICc), difference between AICc for each model relative to the top model (ΔAICc), model likelihood (Li), Akaike Information Criterion model weight (Wi), cumulative Akaike weight (∑Wt), number of parameters (K) and model Log-likelihood (LL).

by province (Table 1). The majority of respondents owned their home except in Guanacaste.

The majority of owned dogs were sterilized (61%), vaccinated (79%), and wore a collar (65%; Figure 2). Males were more likely to be vaccinated and wear a collar compared to females but less likely to be sterilized. More than three quarters of owned dogs had visited a veterinarian for routine care in the past year and about 35% of those dogs visited a veterinarian for emergency care. Of dogs that did not visit a veterinarian for routine care in the past year, only about 15% of those dogs visited a veterinarian for emergency care. There was a slight preponderance of males visiting a veterinarian for both routine and emergency care compared to females (Figure 3).

The best model to explain dog ownership included dwelling type, dwelling ownership, population density and a quadratic form of elevation (Table 2). The probability of owning a dog was highest on farms (92%) and lowest in single family dwellings without a yard (56%), higher among respondents that owned their homes (66%) compared to rented (50%), lowest at high human population density, and lowest at mid elevations around 800 m (Supplementary Table S1). The full list of candidate models is provided in Supplementary Table S2.

The number of owned dogs per household was best explained by dwelling type and ownership status, elevation, population density, and household size (Table 3). Age, Province, and Canton did not appear to strongly influence the number of owned dogs per household (Supplementary Table S3; although see Supplementary Tables S4, S5 for these estimates). Larger households had more owned dogs while more dogs per household occurred at low human population density (Figure 4). There was an interaction between dwelling type and ownership (Table 4) whereby the highest number of dogs per household occurred on rented farms while the lowest occurred in rented single family homes without yards (Figure 4). The total number of owned dogs in Costa Rica was estimated to be 2,222,032 (95% confidence intervals: 1,981,497–2,503,751).

The best predictors of where a dog was confined at night and at 8 am were elevation, dwelling type and human population density (Table 5). There was little effect of dog owners' age, province or canton of residence, land use, household size, dwelling ownership status, or land use on where dogs were confined (Supplementary Tables S6, S8). The majority of dogs were confined in the house or unconfined in the yard at night (in house: 66%; unconfined in yard: 28%) and in the morning (in house: 53%; unconfined in yard: 43%; Figure 5). Overall, only 1.2% (95% CI: 0.3–2.5%) of dogs slept on the street with a slightly higher proportion on the street at 8 am (Figure 5). There was a negative relationship between human population density and dogs being on the street or in the yard (both tethered and free) at night and at 8 am indicating that more dogs are confined to the house in more heavily populated areas (Supplementary Tables S7, S9). Therefore, there would likely be

TABLE 4 Parameter estimates and 95% confidence interval of the top model to explain the number of dogs per household owned by residence of Costa Rica.

Parameter	Estimate	95% confidence interval
Intercept	0.596	−0.033–1.226
Dwelling type:		
Multi-unit building	−0.122	−1.042–0.798
Single family with yard	−0.106	−0.729–0.517
Single family without yard	−0.906	−1.714–−0.097
Dwelling ownership:		
Own	0.433	−0.229–1.094
Rent	0.499	−0.280–1.278
Population density	−2.981e-5	−5.027e-5–−9.344e-6
Elevation	−5.315e-5	−3.521e-4–2.458e-4
Elevation^2	6.001e-8	−1.055e-7–2.255e-7
Household size	0.028	0.007–0.049
Multi-unit building: Own	−0.257	−1.257–0.743
Single family with yard: Own	−0.476	−1.161–0.209
Single family without yard: Own	−0.116	−1.005–0.773
Multi-unit building: Rent	−1.197	−2.267–−0.127
Single family with yard: Rent	−0.769	−1.573–0.035
Single family without yard: Rent	−0.647	−1.630–0.336

Intercept represents a farm.

fewer dogs roaming on the street in highly populated areas compared to less populated areas. The number of owned dogs roaming the streets at night nation-wide was estimated to be 27,208 (95% CI: 7,557–56,619) compared to 43,142 (95% CI: 20,118–73,618) on the street at 8 am (amounting to only 1–2% of owned dogs in the country.

Comparison to previous owned dog population estimates

There were three previous surveys of the owned dog population in Costa Rica; the results of the four surveys are provided in Table 6. In 2001, Carlos Drews reported that 53% of Costa Rican households had one or more dogs. In 2003 and 2011, the World Society for the Protection of Animals surveyed dog ownership in the San Jose metro area and reported on the dog ownership rates as well as on other human-dog relationships.

The current (2020) survey identified a much higher percentage of households owning dogs (76% vs. around half in the three previous surveys) and a higher number of dogs (1.86) per owning household. According to the latest survey, the number of dogs in Costa Rican households is double the estimate from about 10 years earlier (increased from around 1.06 million to 2.22 million).

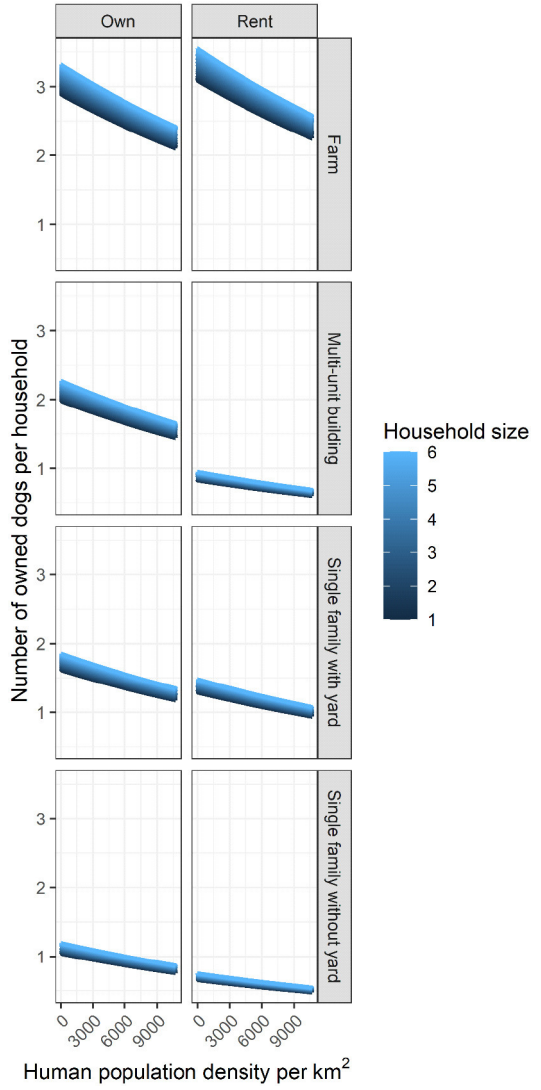

FIGURE 4
Mean predicted number of owned dogs by population density, household size, dwelling ownership type, and ownership status among residents of Costa Rica. All predictions are standardized to the mean elevation of 961 m for all respondents.

However, there are signs from other questions in the survey that the interaction with dogs of the average Costa Rican household has changed quite dramatically. In 2003, only 27% of dogs slept indoors at night and <20% were sterilized. In 2020, two-thirds of dogs were sleeping indoors at night and almost two-thirds were sterilized. These results indicate a substantial change in dog care among Costa Rican households in this century.

On average, the WSPA surveys reported that around 50% of Costa Rican households "own" dogs and that each owning household had an average of 1.67 dogs (for a total estimated dog population in 2011 in the metro area of 583,000).

TABLE 5 Reduced candidate model list of models <10 ΔAICc ranked using Akaike Information Criterion (AIC) to explain where owned dogs were confined at night and at 8 am according to dogs owners of Costa Rica.

Model	K	AICc	ΔAICc	Li	Wi	LL	∑Wt
At night							
Elevation^2 + Population density + Dwelling type	21	2,729.94	0	1	0.59	−1,343.7	0.59
Elevation^2 + Dwelling type	18	2,731.59	1.65	0.44	0.26	−1,347.6	0.85
Elevation^2 + Population density + Dwelling type + Province	39	2,733.34	3.4	0.18	0.11	−1326.74	0.96
Elevation^2 + Dwelling type + Province	36	2,735.21	5.26	0.07	0.04	−1,330.81	1
At 8 am							
Elevation^2 + Population density + Dwelling type	21	2,868.00	0	1	0.98	−1,412.72	0.98
Elevation^2 + Population density + Dwelling type + Province	39	2,876.35	8.35	0.02	0.02	−1,398.24	1

For each variable are the Akaike Information Criterion corrected for small sample size (AICc), difference between AICc for each model relative to the top model (ΔAICc), model likelihood (Li), Akaike Information Criterion model weight (Wi), cumulative Akaike weight (∑Wt), number of parameters (K) and model Log-likelihood (LL).

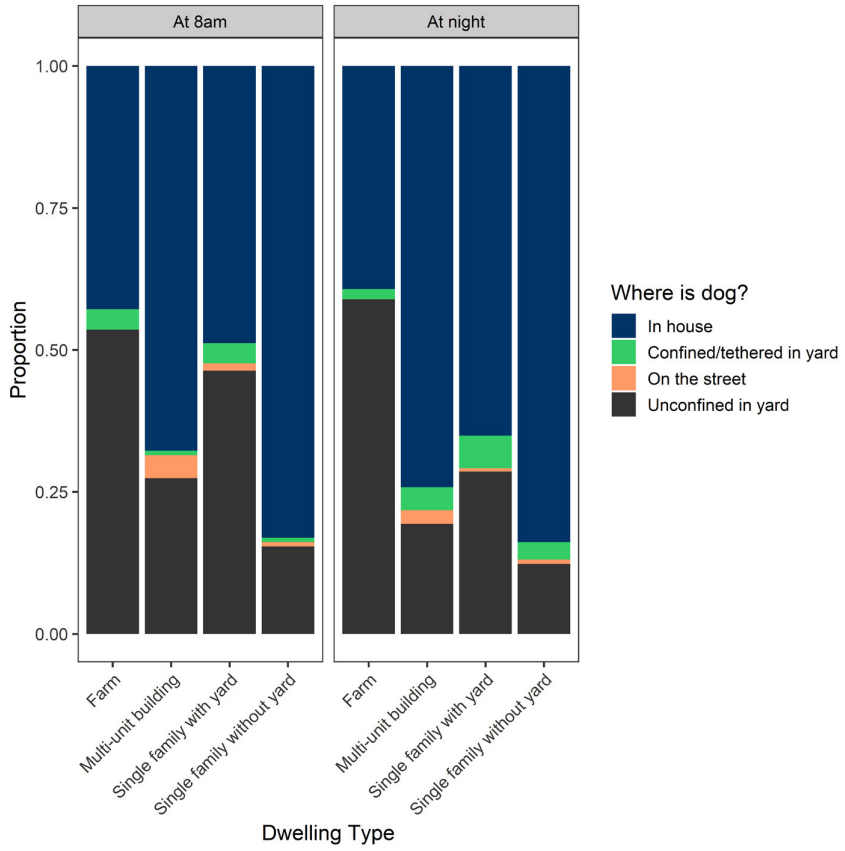

FIGURE 5
Descriptive statistics of where the proportion of owned dogs in Costa Rica occur at night and at 8 am by dwelling type as reported by dog owners.

The two WSPA surveys also documented substantial changes in human behavior over the 8 years from 2003 to 2011 (Table 6). These changes reflect an increase in "responsible" pet owner behavior with the average age of the dogs increasing and twice as many dogs sleeping indoors at night in 2011 compared to 2003. There was also an increase in the proportion of dogs being taken to a veterinarian every year and a halving of the number of dogs being allowed to roam outside without supervision. The survey this year (2020) indicates that the human-dog relationship continued to strengthen since 2011 (higher dog sterilization rates and higher proportion of owned dogs sleeping indoors).

Discussion

We produced models to explain dog ownership, the dog population, and locations where dogs are at different times of the day in Costa Rica based on a representative sample of residents. Our results suggest that the number of households that owned dog numbers may have increased (although these changes may be an artifact of the survey methods). Most dogs are confined to the house or yard overnight and early in the morning which amounts to few owned dogs roaming on the street during these times. Additionally, over the past two decades, the proportion of dogs that spend the night in the house has more than doubled. The vast majority of dogs in our survey had visited a veterinarian for routine care over the past year, were vaccinated, and had been sterilized. The patterns observed suggest a shift in care conditions provided to owned dogs over the past two decades in Costa Rica that offer benefits both to dog welfare and humans.

The 2020 survey found that almost three-quarters of households in Costa Rica currently own one or more dogs. As a result, more than 2 million dogs are predicted to be owned across the country. There was limited evidence that ownership patterns varied among provinces across the country but rather that ownership was better described by geography especially elevation, human population density, and dwelling type.

The factors that affect dog population numbers support an approach that would involve estimating dog population size across broad spatial scales. Dog ownership patterns also indicate where dog services might be best located to serve the companion animal industry. For example, we are aware of only a single animal shelter that, services a large portion of the San Jose central valley (approximately 1.5 million people). Our modeling could help to identify where shelters or veterinary clinics might best be located to serve community members. For instance, veterinary clinics may be located in areas with high dog ownership rates (e.g., areas dominated by single family homes with yards and high home ownership rates) whereas shelters may be located in areas prone to high relinquishment rates (e.g., areas with a high proportion of residents in rented homes). Furthermore, our estimates could be applied to understand how factors such as dog bites (which occurred in 16% of surveyed households in the past year) might be allocated among medical service facilities, especially if communities have more detailed spatial data of housing density, housing type, and ownership status that influences local dog abundance. Given the prevalence of dog ownership, considerations of the welfare of dogs and their owners should continue to garner future consideration by policy makers with respect to community planning, dog management, and veterinary service availability.

Very few owned dogs had free access to the streets at night or early in the morning and most owners reported that their dog was in the house during the night. Information such as this is important for community planning and monitoring the abundance and welfare of free-roaming dogs. First, our results indicate that management activities that occur during nighttime or early morning meant to target unowned free-roaming dogs are unlikely to encounter very many owned free-roaming dogs. For instance, in cases where dogs are trapped for sterilization activities (8), conducting these activities when the probability of capturing owned dogs is low is more likely to reduce issues with dog owners and maximize efforts toward the target population of unowned free-roaming dogs. Second, our results provide insights that are important for monitoring the free-roaming dog population from surveys that cannot differentiate the ownership status of dogs based on simple observations (22, 23). For example, surveys by observers to count free-roaming dogs in the early morning must make assumptions about the ownership of dogs based on features such as body coat or presence of collars (24, 25). Our data indicate that 33% of owned dogs do not wear collars and that only 1% of all free-roaming dogs roaming at night are actually owned. Therefore, only 0.33% of dogs observed during street surveys in Costa Rica at night should be wearing a collar. Given the lower probability of free access outside the home at night and morning with higher human population density, the proportion of owned dogs without collars will be even lower in the most populated urban areas. Third, the marked increase over 10 years from 27 to 66% of owned dogs being in the house overnight suggests that dog owner behavior has shifted toward reducing exposure and risk to owned dogs. Overall, this may indicate an improvement of welfare and living conditions of owned dogs in Costa Rica through a reduction in negative dog-dog or dog-wildlife interactions over the past two decades at the same time that dog ownership may have increased.

More than three quarters of owned dogs in Costa Rica visited a veterinarian for routine care over the past year. Compared to previous surveys in Costa Rica, these values are consistent over the past decade suggesting an upper boundary for dog owners obtaining regular veterinary care for their dog (In the USA, around two-thirds of owned dogs visit a veterinarian every year–AVMA 2017-2018). Given the proportion of dogs that had regular veterinary care, an almost equal proportion of dogs were sterilized and vaccinated. Interestingly, there were slight differences in sterilization rates between male and female dogs. Female dogs were more likely to be sterilized while male dogs were more likely to be vaccinated. Other studies in the USA also found female dogs have higher sterilization rates compared to males (26). These findings suggest some selectivity in acquiring veterinary services for owned dogs indicating that some dog owners will seek out veterinary care even if it is challenging (e.g., too expensive or considered too far to travel). At the same time, given that three quarters of dogs visited a veterinarian for routine care, there are likely some limiting factors that prevent other dog owners from accessing veterinary care. Identifying those limiting factors, and what actions could mitigate those factors, could contribute to a larger proportion of dog owners incorporating regular veterinary care into their

TABLE 6 Four dog surveys in Costa Rica in present century.

Statistic	Drews (National)	WSPA(San Jose Metro)	WSPA (San Jose Metro)	This study(National)
Year	2000	2003	2011	2020
% Homes with dogs	53%	50%	49%	76.5%
Dogs per owning household		1.65	1.67	1.86
Human population	3,962,372	4,164,053	4,633,086	5,094,118
Number households	1,100,000	1,190,000	1,300,000	1,509,789
Estimated dog population	970,000	981,800	1,063,800	2,222,030
Dogs per 1,000	245	236	230	436
Daytime–dog in house		19.5%	49.5%	
Nighttime–dog in house		26.5%	54.2%	65.9%
Vaccinated against rabies			75.5%	78.5%
At least one sterilized		18%	36%	61.5%
Visit the vet during year		61%	80%	76.5%

dog ownership efforts. As animal advocacy grows in Costa Rica, anecdotal evidence indicates the number of requests for animal sterilization and vaccination services outside the San Jose valley have been increasing.

The above features generate confidence that Costa Rica could serve as an excellent case-study for a large-scale, integrated, cooperative, and scientifically robust humane management program for dogs. The production of a current dog population size estimate with some estimates of the scope of the roaming dog "problem" should lead to an informed estimate of the resources and the timeline required to achieve the desired outcomes. The baseline assessment provided in this study functions as a yardstick against which to measure progress as the dog management program moves forward. Both the government of Costa Rica and a well-established local NGO have demonstrated a commitment to a humane dog management program in the last two decades. This indicates excellent prospects for program sustainability.

It is not clear why the current survey has produced a much higher estimate of the owned dog population although the survey method may affect estimates of dog ownership and dog numbers. In the USA, Patronek and Rowan (27) noted that surveys using Random Digit Dial (RDD) methods produced estimates of dog ownership and total pet dog numbers that were about 20% lower than surveys using Household Panel methods (where households who have agreed to complete mail surveys are recruited to be on a large panel). Recently, UK Pet Food (28) in the UK reported pet dog and cat estimates from an online survey in the United Kingdom in 2021 that were 40–50% higher than the pet dog and cat estimates that had been developed from face-to-face surveys conducted from 2012 to 2020. In the USA, the American Pet Products Association has been conducting surveys of the US pet population every 2 years since 1988, In 2012, they switched from conducting surveys *via* Household Panel methods to using online survey technology. From 1988 to 2010, the APPA reported that 38–40% of US households had a pet but subsequent surveys reported an increasing percentage of households owning dogs (reaching 48% in the most recent survey). It is suggested that estimates of total pet populations are influenced by the survey methods used. It appears that online surveys produce higher pet population estimates compared to household panel or face-2-face survey methods. It is not obvious why this might be so but we suggest that consumers of pet survey data be aware that different survey methods might produce different pet population estimates.

The large changes in human dog care behavior in the 21st Century indicated by the previous surveys (21) and our 2020 survey data are also supported by the growth in the membership of the veterinary college. According to reports from the Colegio de Veterinarios (the national oversight body for veterinary practice in Costa Rica). The number of new members joining the Colegio de Veterinarios annually increased from 10 in 1990 to 90 in 2010 (Karina Navarro, personal communication, 9 August 2017).

Our study, and the results drawn from a randomized questionnaire has some obvious limitations that warrant consideration. First, any survey is self-selecting as respondents cannot be forced to respond. We attempted to reduce the impact of this selection process by using a reputable survey company that maintains panels of respondents. These panels are assembled and assessed to ensure a represent sample can be obtained of the population of interest to reduce bias. We must also assume that all responses are true. Importantly, the questions asked were with regards to dog ownership and not with respect to dog management *per se*. Therefore, our findings should not be construed as indicating appropriate or effective management techniques or actions.

The changes in dog care and management are all in the direction of increasing control of, and care for, household dogs. The changes occurring in Costa Rica indicate that it is possible

to evolve relatively quickly from a culture where dogs are mostly permitted to roam and receive relatively little veterinary care to a culture of "homed" pets. Similar changes in human-dog interaction and the control of pet dogs occurred in the USA in the last 25 years of the 20th century when the number of unreturned (euthanized) unowned free-roaming dogs entering US shelters dropped from around 25% of the pet dog population to 5% (29).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

DF conducted the statistical analysis. All authors conceived the study, collected the data, and wrote and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

DF was employed by Flockhart Consulting. AR was employed by Wellbeing International. JB was employed by Great Basin Bird Observatory.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2022.946603/full#supplementary-material

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A Survey of Veterinarian Attitudes Toward Prepubertal Desexing of Dogs and Cats in the Australian Capital Territory

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Prepubertal desexing (neutering) has been a legal requirement for all cats and dogs in the Australian Capital Territory since 2001. All cats have to be desexed by 3 months of age, and all dogs are required to be desexed by 6 months of age. The role of veterinary attitudes and behaviors in the implementation of mandatory prepubertal desexing in the Australian Capital Territory is explored in this paper. An online survey was sent to all veterinarians registered in the Australian Capital Territory via the Veterinary Surgeons Board (VSB). The survey was designed as a cross-sectional study, hosted using the software REDcap® and analyzed using statistical program R®. A response rate of 14.9% (52/350) of registered veterinarians was achieved. Only 10% of respondents (5/52) recommended that clients have their cat desexed at 3 months of age, the legal maximum age for desexing in the jurisdiction. However, 40% of veterinarians (21/52) thought prepubertal desexing was an appropriate management strategy of cats to prevent overpopulation. Just over one-third of all veterinarians who responded (18/52; 35%) were not aware that prepubertal desexing was mandatory in the Australian Capital Territory. We conclude that prepubertal desexing might be poorly supported by veterinarians in the Australian Capital Territory, even though pets are legally required to undergo prepubertal desexing. As a result, veterinarians may unintentionally be limiting access to this procedure. This has wider policy consequences for Australian and overseas jurisdictions which are considering introducing mandatory prepubertal desexing.

Keywords: Australia, cats, desexing, dogs, mandatory, prepubertal, veterinarians

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INTRODUCTION

The practice of prepubertal desexing (PD) and early age desexing (EAD) of dogs and cats has been utilized in animal shelters since the 1980s as a tool to combat overpopulation (1). Although often used interchangeably, the two terms differ in intent. PD is primarily concerned with desexing animals before they reach sexual maturity or puberty, which is defined here as before 4 months of age in cats and 7 months in dogs (2). EAD on the other hand, is primarily concerned with desexing animals as early as is safely possible. In cats, this can be from 6 weeks of age or 800 g bodyweight for males and 1,000 g bodyweight for females. Dogs are also desexed from 6 weeks of age in EAD, but most practitioners wait until 1,000 g bodyweight is reached (3). The age and bodyweight used to determine time of desexing in EAD is based on clinician surgical and anesthetic experience (4).

The "traditional" age of desexing in cats and dogs is between 5 and 9 months of age (1, 5). A recent study into the attitudes and behaviors of Australian veterinarians toward PD reported that most veterinarians recommended desexing by 6 months of age (6). For most dogs desexed in this period, it will be prepubertal. However, many cats would have reached sexual maturity at this age, meaning a female cat could become pregnant prior to desexing. This eliminates one of the main benefits of desexing: avoiding unwanted pregnancies (7). Proponents of traditional desexing argue that it provides a safer anesthetic, reduced long-term medical or behavioral issues and is the age at which veterinarians are trained and are therefore most experienced and comfortable (1, 6). However, studies investigating the safety of EAD anesthetics have reported no significant difference in mortality or morbidity compared with traditional desexing (8) and studies into the risks of long term medical or behavioral issues are conflicting, with some showing a reduction in risk (7, 9, 10) and others showing an increased risk (7, 11, 12).

Medical concerns around PD include the risks presented by pediatric surgery and anesthesia, such as the increased risk of a patient experiencing hypoglycemia and hypothermia (13). Additionally, desexing is known to delay growth plate closure in a range of species (14). However, studies are conflicting when it comes to the relative risk of musculoskeletal disorders associated with PD of cats and dogs and traditional age desexing (9, 14, 15). The risk of obesity is likely increased for cats and dogs that are desexed, however no increase in risk has been found between PD and traditional desexed animals (16). Urinary problems such as urethral obstruction of cats and urinary incontinence in female dogs have also been linked to desexing, with PD suggested as a contributing factor to urinary incontinence in dogs (7, 17). There are also behavioral concerns around PD, with some studies finding noise phobias and sexual behaviors were increased in dogs desexed early (7). However, there have been positive behavioral findings for PD as well, with male cats found to display less aggression and urine spraying (18).

Early age desexing and PD are currently practiced in Australia by animal shelters such as the Royal Society for the Prevention of Cruelty to Animals (RSPCA) (19) and by private veterinarians who service shelters, rescue groups and breeders (1). Prepubertal desexing is not routinely practiced by private veterinary practitioners, however the Australian Veterinary Association's (AVA) policy on desexing does support practitioners who choose to use the procedure (4).

In most states and territories of Australia, the requirement for owners to get their companion animal desexed is not mandatory, but is encouraged through reduced council registration rates. There are, however, several jurisdictions which have introduced mandatory desexing in recent years (**Table 1**). This is significant for veterinarians, as only 18% of vets in a national survey conducted in 2013 reported being willing to desex dogs and cats at a younger age if government regulations required it (6).

Abbreviations: ACT, Australian Capital Territory; AVA, Australian Veterinary Association; EAD, Early-Age Desexing; PD, Prepubertal Desexing; RSPCA, Royal Society for the Prevention of Cruelty to Animals.

TABLE 1 | Details of mandatory desexing requirements in each state and territory of Australia.

State	Is there legislation mandating desexing?
Australian Capital Territory	Yes Section 74 of the *Domestic Animals Act 2000* makes it an offense to own an undesexed dog over 6 months old or an undesexed cat over 3 months old without a permit
New South Wales	No
Northern Territory	No
Queensland	No
South Australia	Yes Section 42E of the *Dog and Cat Management Act 1995* makes it an offense to own an undesexed dog or cat over 6 months old, with limited exemptions
Tasmania	Yes (cats only) Section 14 of the *Cat Management Act 2009* requires all cats over 6 months of age to be desexed, with limited exemptions
Victoria	No
Western Australia	Yes (cats only) Section 18 of the *Cat Act 2011* requires all cats over 6 months of age to be desexed, with limited exemptions

Section 74 of the Australian Capital Territory's (ACT) *Domestic Animals Act 2000* (the Act) has made PD a legal requirement since 2001, with dogs required to be desexed by 6 months of age. Cats were also originally required to be desexed by 6 months of age, however an amendment to the Act in 2007 saw the legislation change to require all cats to be desexed by 3 months of age. The requirement to desex cats by 3 months is unique in Australia. As mandatory desexing has now been in place in the ACT for over 18 years, we thought it appropriate timing to determine (a) if ACT residents were complying with this legislation, (b) if veterinarians in the ACT were offering this service, and (c) the attitudes and beliefs of veterinarians in the ACT toward prepubertal and mandatory desexing.

MATERIALS AND METHODS

A cross-sectional study design was used to survey veterinarians registered in the ACT about their attitudes and behaviors toward prepubertal and mandatory desexing of dogs and cats. The survey was hosted on REDCap, courtesy of The University of Sydney. A link to the survey was emailed to all registered veterinarians in the ACT by the ACT Veterinary Surgeons Board (VSB) and to all members of the AVA ACT Division in September 2017. The survey was open for 1 month.

The questionnaire consisted of 23 questions including six demographic questions, seven cat specific questions, and six dog specific questions (**Table 2**). Questions were inspired by previous studies (6, 20) with answers structured in a 5-point Likert style. The survey was trialed on three private practice veterinarians and reviewed by the AVA ACT Division committee prior to release. This study was

TABLE 2 | Survey of ACT registered clinical veterinarians on their attitudes and behaviors to prepubertal and mandatory desexing.

1. What is your position within the practice? *Associate veterinarian/Practice owner/partner*
2. How many veterinarians (full time equivalent) work at your practice?
3. What age bracket do you fall into? *18–24/25–34/35–44/45–54/55–64/65 or older*
4. How long have you been a practicing veterinarian? *Less than 3 years/3–5 years/5–10 years/10–20 years/More than 20 years*
5. What is the primary focus of your practice? *Small/mixed/equine/exotic/specialist other*
6. How would you describe the area where your practice is located? *Urban/suburban/rural*
7. At what age do you generally advise clients to have their CAT desexed? *Less than 3 months/less than 4 months/less than 5 months/less than 6 months/older than 6 months*
8. How often do you perform CAT desexing prior to 3 months of age? *Always/very often/sometimes/almost never/never/I don't perform desexing procedures*
9. How often do you perform CAT desexing prior to 6 months of age? *Always/very often/sometimes/almost never/never/I don't perform desexing procedures*
10. What are your main concerns regarding prepubertal desexing (less than 4 months) of CATS? Tick all that apply. *Increased anesthetic risks/increased difficulty of surgery/long term behavioral issues/long term medical issues/no concerns/other*
11. Do you currently recommend prepubertal desexing (less than 4 months) to new CAT owners, assuming there are no contraindications to surgery? *Always/very often/sometimes/almost never/never*
12. If you recommend prepubertal desexing (less than 4 months) to some CAT owners, but not all, generally under which circumstances DO you recommend it? Tick all that apply. *If the cat is from a rescue, pet shop or is to be re-homed early/if unwanted pregnancy or early oestrus is probably/if the desexing will prevent unwanted behavior (e.g., spraying)/if the cat will be exposed to FIV or other infectious diseases (e.g., outdoor access)/other/I always recommend prepubertal desexing of cats/I never recommend prepubertal desexing of cats*
13. Do you believe prepubertal desexing (less than 4 months) is an appropriate management strategy to prevent overpopulation of CATS? *Definitely/maybe/neutral/maybe not/definitely not*
14. At what age do you generally advise clients to have their DOG desexed? *Less than 3 months/less than 4 months/less than 5 months/less than 6 months/older than 6 months*
15. How often do you perform DOG desexing prior to 6 months of age? *Always/very often/sometimes/almost never/never/I don't perform desexing procedures*
16. What are your main concerns regarding prepubertal desexing (less than 6 months) of DOGS? Tick all that apply. *Increased anesthetic risk/increased difficulty of surgery/long term behavioral issues/long term medical issues/no concerns/other*
17. Do you currently recommend prepubertal desexing (less than 6 months) to new DOG owners, assuming there are no contraindications to surgery? *Always/very often/sometimes/almost never/never*
18. If you recommend prepubertal desexing (less than 6 months) to some DOG owners, but not all, generally under which circumstances DO you recommend it? Tick all that apply. *If the dog is from a rescue, pet shop or is to be re-homed early/if unwanted pregnancy or oestrus is probable/if the desexing will prevent unwanted behavior (e.g., roaming)/other/I always recommend prepubertal desexing of dogs/I never recommend prepubertal desexing of dogs*
19. Do you believe prepubertal desexing (less than 6 months) is an appropriate management strategy to prevent overpopulation of DOGS? *Definitely/maybe/neutral/maybe not/definitely not*
20. Prior to completing this survey today, were you aware that the ACT had mandatory desexing of cats from 3 months of age and dogs from 6 months of age? *Yes/No*
21. Do you believe prepubertal desexing should be mandatory? *Definitely/maybe/neutral/maybe not/definitely not*
22. Would you be interested in participating in a forum exploring the issues around prepubertal and mandatory desexing in the ACT? *Definitely/maybe/neutral/maybe not/definitely not*
23. Do you have any further comments?

approved by The University of Sydney Human Research Ethics Committee (no. 2017/657) and consent was obtained by implied informed consent via submission of the completed survey.

Data from RSPCA ACT was obtained via the software program ShelterBuddy® (RSPCA QLD 2012) by extracting data on all adult cats and dogs admitted to the RSPCA ACT Weston shelter from February 2017 to December 2017. Data from RSPCA NSW was obtained via their annual statistics report submitted to RSPCA Australia for the period of July 2016–June 2017. Z-scores were calculated for RSPCA ACT and RSPCA NSW data, with significant set at $p < 0.05$.

Data from Transport Canberra and City Services (TCCS) was obtained via requests for information between February 2018 and May 2018. TCCS is the ACT government department responsible for domestic animal management, including enforcement of PD legislation.

Survey responses were exported from REDCap to a spreadsheet (Microsoft Excel® 2010) and analyzed using R® (R Foundation for Statistical Computing, Vienna, Austria, 2016). Chi-squared testing was used to assess the relationship between veterinarian age and likelihood of engaging with PD. Ordinal logistic regression testing was used to consider the relationship between demographics and recommended age of desexing. McNemar's test for significance was used to measure the difference between veterinarian's concerns regarding PD for cats vs. dogs. Goodman-Kruskall gamma was calculated to measure the association between respondents reported performance of PD in cats and dogs, Gamma is a measure of concordance suitable to a doubly-ordered contingency table and has a range between −1 and 1. Similarly, the association between scores for other questions were assessed using Kendall's Tau, a rank correlation coefficient also suited to doubly-ordered contingency tables. Tau-b corrects for the presence of ties and also has a range between −1 and 1.

RESULTS

The survey was emailed to all registered veterinarians in the ACT, which as of July 2017 was 350 veterinarians. Excluding all veterinarians who listed their business address as either a government department, non-practicing, non-veterinary business or NGO, or a non-domestic animal veterinary business, a maximum of 211 of these veterinarians were assumed to be in clinical practice. A total of 59 email recipients activated the survey with 14.9% (52/350) of registered veterinarians completing the survey. Eight-seven percent of respondents identified as small animal practitioners (45/52) in suburban or urban locations (96%; 50/52), representing 25% (52/211) of clinical veterinarians in the ACT. Respondent demographics are summarized in **Table 3**.

Cats

Only 10% (5/52) of respondents recommended that clients desex their cats before 3 months of age. Most respondents advised clients to desex their cat before 5 months of age (38%; 20/52) or 6 months of age or older (40%; 21/52). When asked how often they desexed cats before 3 months of age, 37% stated almost never (19/52) and 13% never (7/52). No veterinarians indicated they always desexed cats before 3 months of age. Respondents were asked if they currently recommended PD to new cat owners, assuming there were no contraindications to surgery. Only 15% (8/52) always recommended PD for cats, with 46% indicating they almost never (33%; 17/52) or never (13%; 7/52) recommended the procedure. Where veterinarians recommended PD to some (but not all) cat owners, many cited population reasons for giving this advice, including if the cat was from a rescue, pet shop or was to be re-homed early (40%; 21/52) or if unwanted pregnancy or early estrus was probable (42%; 22/52). Anesthetic risk in PD was considered significantly more of a concern for veterinarians in cats compared to dogs ($p = 0.013$). Although many veterinarians did not recommend or practice PD, when asked if it was an appropriate management strategy to prevent overpopulation of cats, 77% answered positively with either maybe (37%; 19/52) or definitely (40%; 21/52).

Location of practice influenced a veterinarian's likelihood of recommending older ages of desexing. Veterinarians working in urban practices were less likely to recommend desexing at younger ages compared to veterinarians in suburban or rural practices (Odds Ratio [OR] = 8.99; confidence interval [CI] 2.38–40.66). Veterinarian age was a significant factor ($p = 0.025$) in how often veterinarians performed desexing on cats prior to 3 months of age, although no odds ratio for any particular group reached statistical significance and there was no significant age effect for recommending desexing at this age. Indeed, the relationship between age and frequency of recommending or performing desexing prior to 3 months was complex. Compared to the youngest group of veterinarians (those 25–34), those aged 35–44 and those over 55 tended to both recommend and perform desexing of cats prior to 3 months more often, but those 45–54, somewhat less often. Respondents who indicated they were practice owners or partners were more likely to perform desexing on cats under 6 months of age than associate veterinarians (OR = 7.10; CI = 1.50–37.82). No other significant demographic differences were found.

Dogs

No respondent indicated they advised clients to desex their dogs before 4 months of age. The majority (71%; 37/52) recommended clients desex their dogs at 6 months of age or older. As with cats, no respondents always desexed dogs before 6 months of age, however 27% (14/52) stated they very often desexed dogs before this age and another 40% (21/52) stated they sometimes did. Respondents were asked if they currently recommended PD to new dog owners, assuming there were no contraindications to surgery. Only 13% (7/52) indicated that they always recommended PD for dogs, with 42% responding they almost never (33%; 17/52) or never (10%; 5/52) recommended the procedure. Of the vets who did recommend PD of dogs to some owners, as with cats, many cited population reasons including if the dog was from a rescue, pet shop or was to be rehomed early (38%; 20/52) or if unwanted pregnancy

TABLE 3 | Demographics of survey respondents.

Parameter	Number of respondents	(%)
AGE		
25–34	17	33
35–44	14	27
45–54	12	23
55–64	7	13
65+	2	4
LENGTH OF TIME AS A PRACTICING VETERINARIAN		
<3 years	5	10
3–5 years	5	10
5–10 years	9	17
10–20 years	14	27
>20 years	19	37
POSITION WITHIN PRACTICE		
Associate	32	62
Practice owner/partner	20	38
PRIMARY FOCUS OF PRACTICE		
Small	45	87
Mixed	3	6
Specialist	3	6
Other	1	2
Equine	0	0
Exotic	0	0
PRACTICE LOCATION		
Rural	2	4
Suburban	30	58
Urban	20	38
FTE VETERINARIANS IN PRACTICE		
0–5	28	54
5–10	21	40
>10	3	6

or early estrus was probable (38%; 20/52). In addition, a further 33% (17/52) indicated they would recommend PD if the desexing would prevent unwanted behavior in dogs, such as roaming. Long-term medical issues in PD were significantly more of a concern for veterinarians for dogs compared to cats ($p < 0.001$).

Respondents were split on whether PD was an appropriate management strategy for dogs, with 33% (17/52) answering definitely and 33% (17/52) choosing to remain neutral on the question. Veterinarian age was a significant factor ($p = 0.027$) in how often veterinarians desexed cats prior to 3 months of age, although no odds ratio for any particular group reached statistical significance. All older age groups recommended desexing at 4–5 months of age more often than the youngest group of veterinarians (aged 25–34); this effect was least pronounced for those aged 45–54. No other significant demographic differences were found.

Mandatory Desexing

Veterinarians were asked what their main concerns were regarding PD (**Table 4**). They were also asked if they believed PD should be mandatory in the ACT. Almost half (46%; 24/52) responded definitely not, and 21% (11/52) maybe. Only 12% (6/52) said they definitely thought it should be mandatory. Finally, veterinarians were queried on their knowledge of the mandatory PD desexing laws present in the ACT. The majority of respondents (65%; 34/52) indicated they were aware of the laws, with the remainder (35%; 18/52) saying they were unaware.

There was a moderately strong, significant and positive association between performing PD in cats and performing PD in dogs [Goodman-Kruskall Gamma = 0.53 (0.33–0.74)]. There was a significant, weakly positive association between belief in desexing prior to 4 months of age as an appropriate cat overpopulation management strategy and the frequency of performing ($P = 0.002$; Kendall's Tau = 0.38) and recommending ($P = 0.003$; Kendall's Tau = 0.35) desexing prior to 3 months of age in cats. Likewise, there was a significant, weakly positive association between belief in desexing prior to 6 months as an appropriate dog overpopulation management strategy and the frequency of performing ($P = 0.021$; Kendall's Tau = 0.29) and recommending ($P = 0.030$; Kendall's Tau = 0.25) desexing prior to 6 months of age.

Data on incoming animals was obtained from RSPCA ACT's Weston shelter for a period of 12 months from January to December 2017. The Weston shelter is the only facility in the ACT which accepts stray cats, and one of only two facilities which accepts stray dogs, the other being the Domestic Animal Services pound facility. Adult animal (defined as over 9 months of age) reproductive status (desexed or entire) was assessed as part of the normal veterinary health check on intake. The data revealed on average, only 47.4% (278/587) adult dogs and 41.2% (316/767) adult cats were desexed upon intake to the shelter. RSPCA New South Wales (NSW) reported over the same period that 40.9% (3823/9337) of adult dogs and 38.7% (2468/6378) of cats that entered their facilities were desexed. Dogs entering the RSPCA ACT shelter were significantly more likely ($z = 3.061$; $p = 0.002$) to be desexed than those entering RSPCA NSW facilities. There was no significant difference ($z = 1.343$; $p = 0.180$) between RSPCA ACT and RSPCA NSW with cats entering facilities desexed.

TCCS data on infringements recorded against Section 74 of the Act revealed minimal breaches of the legislation. Unfortunately the data captured in the 16 years from 2001 to 2017 were paper based and unavailable for analysis. Electronic infringement management software was installed in September 2017, with 15 infringements issued under Section 74 (1) for keeping entire dogs without a permit from October 2017 to May 2018. During the same period, RSPCA ACT took in 166 entire dogs. No data were available for cats from TCCS.

TABLE 4 | Concerns around prepubertal desexing in dogs and cats in the ACT.

	Increased anesthetic risk	Increased difficulty of surgery	Long term behavioral issues	Long term medical issues	No concerns	Other
Cats	25 (48%)	6 (12%)	6 (12%)	15 (29%)	15 (29%)	6 (12%)
Dogs	15 (29%)	2 (4%)	8 (15%)	32 (62%)	12 (23%)	6 (12%)

DISCUSSION

Although surveys have previously been conducted into veterinary attitudes and behaviors toward PD in Australia (6, 20), this is the first research conducted specifically into veterinarians operating in a jurisdiction with mandatory PD. The ACT was chosen as a sample population to examine the dynamics between mandatory PD and veterinary attitudes and behaviors. Combined with data on rates of desexed animals and infringements given for breaching the legislation, this research explores the policy space where mandatory PD sits. The *Domestic Animals Act 2000* has required all dogs and cats to be desexed by 6 months since 2001, unless the owner has an exclusion permit. All cats have been required to be desexed by 3 months since the legislation was amended in 2007. Much commentary has taken place in the intervening years, with a review by the AVA in 2007 reporting rates of undesexed animals had not changed. This review concluded mandatory PD as a policy was ineffective, however it did not investigate the causes of this ineffectiveness further (21).

We sought to determine three outcomes from this research. First, we wanted to know if ACT residents were complying with mandatory PD desexing legislation. Second, whether veterinarians in the ACT were offering this service. And third, if the attitudes and beliefs held by veterinarians in the ACT potentially impacted on PD delivery.

The first aim was investigated by interrogating data from RSPCA ACT's Weston shelter. The data revealed that in 2017, on average, only 47.4% of adult dogs and 41.2% of adult cats were desexed upon intake to the shelter. This is despite the

introduction of mandatory desexing in the ACT 18 years ago. This period is longer than the average lifespan of both cats and dogs, which means that all dogs and cats should be desexed prior to entry to the Weston facility, if the population was compliant. It is useful to compare these figures with a jurisdiction that does not have mandatory desexing. RSPCA NSW reported in the 2017 calendar year, only 40.9% of adult dogs and 38.7% of adult cats entered their facilities desexed. Although the ACT had significantly more desexed dogs entering RSPCA facilities than NSW, it was still < half of all dogs presented. The rates of desexed cats entering RSPCA NSW facilities were comparable to the rates seen at RSPCA ACT. The demographics of animals entering RSPCA shelters are likely to differ from the general pet population somewhat, however these figures reveal a likely lack of compliance with desexing legislation by pet owners in the ACT.

Data from TCCS for the 7 months from October 2017 to May 2018 showed a low rate of infringements recorded against Section 74 of the *Domestic Animals Act 2000* when compared with the rates of non-desexed dogs entering the RSPCA ACT shelter. Indeed, the 15 infringements reported for those 7 months represent <10% (15/166) of entire dogs which entered RSPCA ACT's shelter during that period, suggesting that enforcement of the desexing legislation in the ACT is minimal.

Our research suggests that the ACT community is failing to comply with the mandatory PD legislation and the government is failing to adequately enforce it. Our next aim was to determine whether veterinarians in the ACT were offering PD and if their attitudes and beliefs impacted PD delivery to the community. The results indicate a veterinary population at odds with the mandatory PD legislation.

Ninety percent of surveyed veterinarians did not recommend cats be desexed before 3 months of age as stipulated in the Act. Half of all veterinarians almost never or never desexed cats before 3 months of age, and no veterinarian always desexed cats before 3 months of age. This may be due to owners not presenting their cats to veterinarians before 3 months of age, or veterinarians not recommending desexing at this age, or a combination of both. Certainly the survey results indicated most vets were not recommending PD in cats, whether this was at 3 months of age as required by the Act or by 4 months of age. This is at odds with veterinarians' views on PD as a management strategy to prevent cat overpopulation, with 40% believing it is definitely a good strategy. It seems as though surveyed vets were aware of the policy reasons for implementing PD but were not applying the policy to their own practices.

Most veterinarians did not recommend PD for dogs. Those veterinarians which did perform PD in dogs were found to also perform PD in cats. This indicates that those veterinarians who practiced PD did so consistently across species, even if they had concerns around PD. Less than one in five veterinarians always recommended PD to new dog owners. One in three stated they almost never recommended the procedure. These results are similar to those found with cats, however the response to PD in dogs was slightly more tempered, potentially because the PD age of 6 months in dogs sits within the traditional desexing range for many veterinarians. Concerns about PD differed between species, with veterinarians more concerned about anesthetic risk in cats compared to dogs. This may be due to a lack of specific training in PD as most veterinarians would have been taught to desex cats at the traditional age of 6 months (22). Unfamiliarity with a procedure promotes caution, however this appears to be unfounded. A large-scale review of mortality rates in EAD showed they were no higher than traditional age desexing (8).

Our research found our sample population of veterinarians in the ACT were not supportive of mandatory desexing. Just under half of all respondents indicated they thought desexing should "definitely not" be mandatory while only 12% thought it "definitely should" be mandatory. As veterinarians are major stakeholders in any law requiring a veterinary procedure, their engagement is essential. Previous research has identified that a legal requirement for PD in a jurisdiction would only cause 18% of veterinarians to desex earlier than they currently recommended (6). This has major implications for jurisdictions like the ACT where PD is mandated. It is difficult for the public to comply with the law if veterinarians choose not to offer the procedure.

Additionally, more than a third of respondents were unaware of the fact that PD desexing was mandatory in the ACT. It seems engagement with veterinarians on animal management legislation in the ACT is poor. Indeed, when veterinarians first register with the ACT VSB, they receive no information about mandatory desexing and microchipping laws in the ACT from the VSB or government.

There are several limitations to this study which may have had an impact on its conclusions. There is always the possibility of non-response bias in anonymous online surveys, with the results only identifying the thoughts of those who took an interest in the issue. Additionally, the response rate to this survey was low, although when taking into account the to the number of non-clinical veterinarians registered in the ACT, the response rate for clinical veterinarians is closer to 24.6% (52/211) than the overall reported rate of 14.9%.

Although the questions were modeled on previous research, some of the answer categories could have had more than one interpretation (e.g., <5 months could also be taken to be <4 months). As with all cross-sectional studies, any associations determined by the study are unlikely to demonstrate a true cause and effect relationship.

Policy developed without adequate stakeholder engagement will struggle to achieve its desired outcomes. In the case of mandatory PD in the ACT, it seems a combination of poor enforcement, stakeholder disengagement and a lack of community awareness has resulted in an ineffective law. Low levels of support from veterinarians for mandatory PD may also restrict the community's access to this procedure. This research suggests engagement and support

from veterinarians is critical for mandatory PD to be an effective policy.

ETHICS STATEMENT

This study was approved by The University of Sydney Human Research Ethics Committee (no. 2017/657).

AUTHOR CONTRIBUTIONS

BO and BJ: conceptualization, writing, review, and editing. BO: survey development, management, data curation, and project administration.

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COVID-19 associated reduction in elective spay-neuter surgeries for dogs and cats

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The rise in subsidized spay-neuter access helped drive the euthanasia of shelter pets in the US from an estimated 13. 5 million in 1973 to 1.5 million in 2019. When the arrival of the COVID-19 pandemic triggered lockdowns beginning in March 2020, many veterinary providers suspended nonessential services such as routine spay-neuter surgeries. The purpose of this study was to determine the impact of the COVID-19 pandemic on the volume of spay-neuter procedures performed by spay-neuter clinics. A retrospective study of patient data from 212 spay-neuter clinics using Clinic HQ practice management software was conducted from January 2019 through December 2021. The clinics collectively performed 1,217,240 surgeries in the pre-COVID baseline year of 2019. A sharp decline in surgeries began in March 2020 (−22%) and reached a nadir in April 2020 (−80%). Surgeries began to increase in May 2020 (−39%), before plateauing in July 2020 (−6%) and remaining slightly below the 2019 baseline in most months through the end of 2021. Compared to 2019, total surgeries decreased 13% to 1,059,388 in 2020 and decreased 3% to 1,184,274 in 2021. In 2020, when clinic disruptions were highest, the impact of the surgery cutbacks varied by geographic region, species, age, and source of animals. Compared with 2019, in 2020 surgeries decreased 17% in the Midwest region, 15% in the Northeast and West, and 11% in the South. Surgeries were reduced 19% in dogs and 10% in cats. When grouped by age, surgeries were reduced by 18% in geriatrics, 14% in adults, and 11% in juveniles. Reductions were similar for females (−14%) and males (−12%) and similar for unowned/organization-owned animals (−14%) and privately owned animals (−12%). In total, 190,818 fewer surgeries were performed by the 212 studied clinics in the 24 months from January 2020 through December 2021 than would be expected had 2019 levels been maintained. If a similar pattern was experienced by other spay/neuter providers in the US, it would suggest there is a deficit of more than 2.7 million spay/neuter surgeries that animal welfare organizations have yet to address.

KEYWORDS

SARS-CoV-2, dog, cat, pet overpopulation, shelter medicine, sterilization, castration, ovariohysterectomy

Introduction

Overpopulation of cats and dogs is a global concern. Efforts to manage their population and to reduce the number of animals taken in and euthanized by animal shelters have largely focused on surgical sterilization to reduce unintended reproduction (1). In the US, the first clinics focusing on high-volume spay-neuter emerged in the 1970s (2). By the 1990s, pediatric sterilization became widely accepted, shelters adopted "neuter-before-adoption" policies, and training programs were developed to teach efficient surgical techniques in veterinary schools (3–5). The rise in subsidized spay-neuter access helped drive the euthanasia of shelter pets from an estimated 13.5 million in 1973 (6) to 1.5 million in 2019 (7).

The Association of Shelter Veterinarians defined high-quality, high-volume spay-neuter (HQHVSN) as "efficient surgical initiatives that meet or exceed veterinary medical standards of care in providing accessible, targeted sterilization of large numbers of cats and dogs to reduce their overpopulation and subsequent euthanasia" (8). Mentorship programs and grants were developed to spawn hundreds of clinics specializing in HQHVSN across the US (9). As a high percentage of owned pets were sterilized, attention turned to unowned free-roaming community cats as the primary source of kitten births, inciting trap-neuter-return (TNR) programs to manage their population (10, 11).

In January 2020, the novel SARS-CoV-2 virus reached the US and quickly spread from state to state. The federal government declared a public health emergency in February followed by a national emergency the next month. This triggered states to institute lockdowns beginning in March 2020 that closed schools, businesses, and non-essential public services intended to reduce viral transmission and to preserve medical supplies and personal protective equipment (PPE) for use by healthcare providers. Like their human healthcare counterparts (12, 13), veterinary associations developed guidelines for triaging veterinary care during the pandemic lockdown. While there was no standardized list of essential procedures in veterinary medicine, they were generally grouped into procedures needed to relieve animal pain and suffering, to prevent imminent death or deterioration, and to protect public health (14–16).

While veterinary providers continued to focus on life-threatening emergencies, such as pyometra and dystocia, they largely suspended elective procedures such as preventive care, treatment of minor or chronic conditions, and routine spay-neuter surgeries. Routine spay-neuter surgeries traditionally performed daily at animal shelters and HQHVSN clinics were deemed non-essential. The increased use of telehealth as a substitute for seeing animal patients in person alleviated some veterinary needs during lockdown but could not address the growing gap in spay-neuter services (17–19).

The severe and prolonged pandemic-related decrease in spay-neuter services may have the potential to undermine progress made in controlling pet populations and euthanasia in shelters. The purpose of this study was to examine the impact of the COVID-19 pandemic on the number of spay-neuter procedures performed by HQHVSN clinics in the US.

Materials and methods

Data collection

Spay-neuter data for dogs and cats were collected by Clinic HQ (Clinic HQ Inc, Portland, OR), a cloud-based clinic management software program designed for practices focusing on spay-neuter and preventive healthcare services from January 1, 2019 to December 31, 2021. A total of 400 spay-neuter clinics in the United States used the software, which the company estimates included 13% of the approximately 3,000 spay-neuter practices in the US. Of these, 188 were excluded from the study because they did not use the software for the entire baseline year of 2019. Comprehensive patient datasets collected from the remaining 212 clinics from January 2019 to December 2021 were included in this study. This period spanned the 2019 pre-pandemic baseline year of normal operations, the spring 2020 pandemic lockdown during which non-essential services were curtailed, and the following months as restrictions lifted across the country. All clinics were identified by a unique identification number, and the information was collected and stored in an electronic format. No identifiable client, patient or clinic information was stored with the data available for the study.

The data were categorized for both dog and cat populations for the following variables: sex (male vs. female), age (pediatric $<$ 5 months, adult 5 months to 7 years, and geriatric $>$ 7 years), and ownership status. Ownership status included privately owned pets vs. unowned pets (community cats, pets from municipal and private shelters, and rescue organizations). Four geographic regions were used for analysis, based on the US census bureau regions (20): Northeast (Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont), Midwest (Indiana, Illinois, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, South Dakota, and North Dakota), South (Delaware, District of Colombia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, and Texas), and West (Arizona, Colorado, Idaho, New Mexico,

TABLE 1 Number of cats and dogs spayed or neutered, absolute change, and percentage change by month from January 2019 through December 2021.

Month	2019	2020	2021	Absolute (%) change 2019 vs. 2020	Absolute (%) change 2019 vs. 2021
January	101,565	106,226	97,114	+4,661 (+5)	−4,451 (−4)
February	93,216	97,340	91,511	+4,124 (+4)	−1,705 (−2)
March	101,779	79,089	111,257	−22,690 (−22)	+9,478 (+9)
April	101,151	19,818	101,432	−81,333 (−80)	+281 (0)
May	98,455	60,460	93,379	−37,995 (−39)	−5,076 (−5)
June	98,549	95,106	106,805	−3,443 (−3)	+8,256 (+8)
July	107,727	101,755	100,319	−5,972 (−6)	−7,408 (−7)
August	111,784	101,519	102,368	−10,265 (−9)	−9,416 (−8)
September	103,245	104,780	98,376	+1,535 (+1)	−4,869 (−5)
October	119,622	110,439	99,271	−9,183 (−8)	−20,351 (−17)
November	96,434	93,080	96,826	−3,354 (−3)	+392 (0)
December	83,713	89,776	85,616	+6,063 (+7)	+1,903 (+2)
Total	*1,217,240*	*1,059,388*	*1,184,274*	*−157,852 (−13)*	*−32,966 (−3)*

Montana, Utah, Nevada, Wyoming, Alaska, California, Hawaii, Oregon, and Washington).

Descriptive statistics

Data from 212 clinics from January 1, 2019 to December 31, 2021 were included in the analysis. The number of total surgeries performed each year and the absolute and percentage change from 2019 were determined for month, species, sex, age, ownership status, and geographical region.

Results

From a total of 400 spay-neuter clinics that currently used the software, 212 had complete spay-neuter surgery data for the entire 3-year study period. These clinics collectively performed 1,217,240 spay-neuter surgeries in the baseline year of 2019 (Table 1). Surgeries decreased 13% to 1,059,388 in 2020, then rebounded to 1,184,274 in 2021, still 3% below the baseline year. By December 2021, 8 clinics (4%) had temporarily closures, 4 clinics (2%) were permanently closed, and 2 clinics (1%) stopped performing spay-neuter surgeries and converted to wellness services only. In total, 190,818 fewer surgeries were performed by the 212 studied clinics in the 24 months from January 2020 through December 2021 than would be expected had 2019 levels been maintained.

Total surgeries per month were compared for the entire study period (Figure 1 and Table 1). The clinics started 2020 with 5% more surgeries in January and 4% in February than during the same period in 2019. A sharp decline in surgeries began in March 2020 (−22%) and reached a nadir in April 2020 (−80%) compared to the baseline year of 2019. Surgeries began to increase in May 2020 (−39%), before plateauing in June 2020 (−3%) and remaining slightly below baseline in most months throughout the rest of the study period (−17% to +9%).

Trends in the spay-neuter data for dogs and cats were reported as the total number of animals per year, absolute change from 2019, and percentage change from 2019 (Table 2) (Supplementary Tables I, II). In 2019, a majority of surgeries were performed in cats (66%) vs. dogs (34%), a pattern that remained consistent throughout the study period. Total surgeries decreased in both dogs (−19% in 2020; −14% in 2021) and cats (−10% in 2020; +3% in 2021). A majority of surgeries in 2019 were performed in females (53%) vs. males (47%), and this pattern persisted throughout the study period. Total surgeries decreased in both females (−14% in 2020; −4% in 2021) and males (−12% in 2020; −1% in 2021).

Adult-aged animals (5 months to 7 years) were the largest group in 2019 (69%), followed by pediatric animals (<5 months) (30%) and geriatric animals (more than 7 years) (1%). Total surgeries decreased in geriatrics (−18% in 2020; −16% 2021), adults (−14% in 2020; 0% in 2021), and pediatrics (−11% in 2020; −8% in 2021). A majority of surgeries were performed in owned animals (63%) vs. unowned animals (37%), a pattern that remained consistent throughout the study. Total surgeries decreased in both owned animals (−12% in 2020; −1% in 2021) and in unowned animals (−14% in 2020; −5% in 2021).

Clinics in the South region performed the highest proportion of total surgeries in 2019 (47%), followed by West (23%), Northeast (21%) and Midwest (9%). Total surgeries decreased in the Midwest (−17% in 2020; −8% in 2021), the

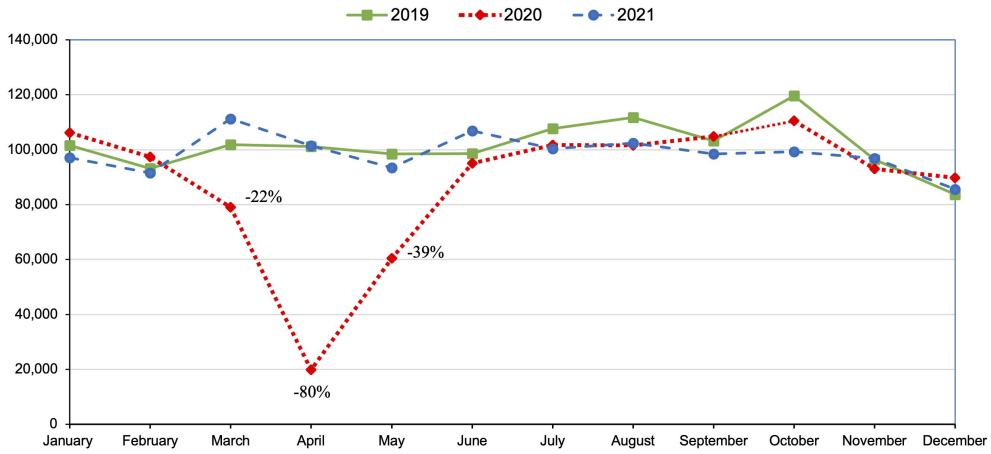

FIGURE 1
Number of cats and dogs spayed or neutered per month at 212 spay-neuter clinics in the US during baseline year 2019, and COVID-19 pandemic years 2020 and 2021.

TABLE 2 Number of cats and dogs spayed or neutered, by species, sex, age, ownership status, and US regions in 2020 and 2021 compared to the baseline year of 2019.

Variable	Category	2019	2020	2021	Absolute (%) change 2019 vs. 2020	Absolute (%) change 2019 vs. 2021
Species	Cat	806,886	728,555	832,688	−78,330 (−10)	+25,802 (+3)
	Dog	410,354	330,833	351,586	−79,520 (−19)	−58,768 (−14)
Sex	Male	568,727	498,899	560,915	−68,828 (−12)	−7,812 (−1)
	Female	648,513	560,489	623,359	−88,024 (−14)	−25,154 (−4)
Age[a]	Pediatric	362,244	321,419	333,654	−40,825 (−11)	−28,590 (−8)
	Adult	843,896	728,833	841,258	−115,063 (−14)	−2,638 (0)
	Geriatric	11,100	9,136	9,362	−1,964 (−18)	−1,738 (−16)
Ownership[b]	Owned	764,517	671,746	754,360	−92,771 (−12)	−10,157 (−1)
	Unowned	452,723	387,642	429,914	−65,081 (−14)	−22,809 (−5)
US Region	South	565,689	505,734	552,278	−59,955 (−11)	−13,411 (−2)
	Midwest	104,515	87,066	96,346	−17,449 (−17)	−8,169 (−8)
	West	288,665	245,821	295,824	−42,844 (−15)	+7,159 (+2)
	Northeast	258,371	220,767	239,826	−37,605 (−15)	−18,545 (−7)
Total		*1,217,240*	*1,059,388*	*1,184,274*	*−157,852* (−13)	*−32,966* (−3)

[a]Pediatric (<5 months), Adult (5 months−7 years), Geriatric (>7 years).
[b]Owned (privately owned pets), Unowned (community cats and pets from municipal and private shelters and rescue organizations).

Northeast (−15% in 2020; −7% in 2021) and West (−15% in 2020; +2% in 2021), and the South (−11% in 2020; −2% in 2021).

Discussion

The COVID-19 pandemic led to a sudden and large reduction in the number of spay-neuter surgeries performed by spay-neuter clinics in March and April 2020. Surgeries began to rebound in May 2020, coinciding with the development of safety measures such as masking, physical distancing, testing, and curbside veterinary reception. In total, 190,818 fewer surgeries were performed by the 212 studied clinics in the 24 months from January 2020 through December 2021 than would be expected had 2019 levels been maintained. If a similar pattern was experienced by all 3,000 estimated spay-neuter clinics in the US, it would suggest a deficit of more than 2.7 million spay-neuter surgeries have accumulated by the end of 2021. The decrease in elective spay-neuter procedures observed in this study echoed a similar decline in elective surgical procedures in human medicine during the 7 weeks after the initial lockdown,

a return to near 2019 numbers in the following months, and a deficit in total number of surgeries performed by the end of the first year of the pandemic (21). Since pandemic conditions have not yet resolved as of August 2022, spay-neuter clinics have not yet returned to baseline productivity, and an ongoing workforce shortage of veterinarians and staff threatens the spay-neuter recovery, conditions are ripe for an increase in unwanted litters and a reversal of population control gains of the past decade (22). Veterinary and animal welfare organizations should prioritize recovery of spay-neuter capacity and focus on populations most at risk for unintended reproduction, poor welfare, or entering the animal shelter system.

Clinics performed nearly twice as many feline vs. canine surgeries in the baseline year, and reduced canine surgeries almost twice as much as feline surgeries during the pandemic. While it is unknown why this cohort of clinics experienced this pattern, it could be related to the urgency associated with cats being euthanized at twice the rate of dogs in shelters, the proliferation of TNR programs for community cats, and the ease of performing cat surgery while simultaneously maintaining physical distancing (17, 23). Cat reproduction is highly seasonal, peaking in spring and summer. The delayed return of full capacity spay-neuter clinics has now spanned three "kitten seasons," causing concern about population growth of free-roaming community cats (24).

Geriatric animals constituted the smallest age bracket in the baseline year and had the greatest reduction in surgery during the pandemic. Geriatric animals often require greater preparation for surgery, for example pre-surgical laboratory testing, and more intensive monitoring. This, combined with the fact that geriatric animals are at lower risk for unwanted reproduction, may explain the decrease in surgery for older animals (25, 26). The decrease in surgery was less marked for younger animals, with adults remaining the largest age group to have surgery throughout the study period. Adult animals are at immediate risk for reproduction, whereas juveniles would reach reproductive age after just a few months. Clinics performed a similar reduction in spays compared to neuters during the pandemic, even though female sterilization is most important for preventing unintended reproduction. The prolonged delay in return to normal spay-neuter operations is especially concerning for female cats as they can become pregnant as early of 5 months of age, which underpins the recommendation that cats be sterilized before 5 months of age (27).

Unowned pets (community cats and pets from shelters and rescue organizations) experienced a similar decrease in spay-neuter surgeries compared to privately owned pets. This may be related to the completion of pre-existing surgery appointments for owned pets as well as reduced numbers of animals held in shelters. Many animal shelters suspended "neuter-before-adoption" policies in order to quickly move shelter pets into permanent or foster homes as they sought to reduce shelter pet populations during the transition to essential services only (28, 29). Alternatives included releasing pets with contracts or vouchers to have them sterilized when spay-neuter capacity resumed or placement with "foster-to-adopt" agreements in which ownership was not transferred until documentation of sterilization was provided (30). In addition, the National Animal Care and Control Association (NACA) advised suspension of trapping and intaking healthy community cats or other animals not in immediate danger during the pandemic (29, 31).

The decrease in surgery coincided with the high number of COVID-19 cases early in the pandemic. In April 2020, there were nearly 400,000 reported cases of SARS-CoV-2 infection in the US. Of these, 54% were from states in the Northeast, leading to stricter business lockdowns in this region (32). The Midwest, West, and Northeast regions of the US had the largest proportional decline in spay-neuter surgeries. Pet population numbers in the Northeast in particular are generally in balance with demand for pets (6, 33), shelters are not overcrowded, and the per capita demand for HQHVSN services is lower than in other regions where pet overpopulation persists. In contrast, pet overpopulation, shelter crowding, and euthanasia for population control is highest in the South, where spay-neuter activity remains a high priority. Clinics in the South collectively performed the most surgeries before and during the pandemic and experienced the smallest proportional decline in surgeries during the pandemic. COVID-19 restrictions and mandates were lifted at different times for each state, which affected when shelters and clinics could begin returning to normal operations. Northeast states such as Connecticut, lifted most business restrictions in May 2021, while Southern states were less restricted throughout the pandemic (34). The future impact of the spay-neuter gap across regions is likely to be complex as it is influenced not just by the number of surgeries, but also by factors such as mild climates that support greater survival of offspring, the pre-existing number of free-roaming animals, particularly community cats, and regional access to low-cost veterinary care in underserved communities.

Guidelines specifically aimed at safe practices in spay-neuter clinics became available soon after the initial pandemic lockdown (24, 35). However, as the pandemic became prolonged, providers experienced staffing shortages associated with an ongoing veterinary workforce shortage compounded by the impact of the pandemic depleting staffing numbers due to SARS-CoV-2 infections, quarantines, and the need to stay home with children and other dependents (36). These staffing shortages threaten to undermine the recovery of HQHVSN programs and other animal welfare initiatives. When spay-neuter capacity is limited, providers can prioritize patients based on both safety and urgency (35, 37). When COVID activity is high and physical distancing is important, selecting animals and procedures that reduce personnel contact reduces the risk of workplace transmission (14). For example, use of intramuscular anesthetic induction protocols and selection

of smaller patients, such as puppies, cats, and small breed dogs, make it possible for a single staff member to prepare a patient for surgery. Surgery and recovery times are shorter in juveniles and small adults, enabling more surgeries to be completed when capacity is limited (38). In addition to treating reproductive emergencies, providers can prioritize animals most at risk for unintended reproduction, such as pregnant animals, mixed sex litters, females, and community cats, as well as animals at risk for behavior issues such as spraying by intact male cats.

Limitations of this study include the use of a single baseline year, whereas a longer time would have provided more information about temporal trends of spay-neuter surgeries prior to the pandemic. Focusing exclusively on clinics utilizing the Clinic HQ spay-neuter specialty software excluded evaluation of surgery trends in full-service practices and organizations utilizing other veterinary management software programs. However, this software is widely used in the HQHVSN industry. Given the size of the dataset and the broad geographical representation, the authors believe it is illustrative of spay-neuter trends across the US. Although significant differences as a function of species, age, ownership, and region were observed, the study design did not provide a means to determine the reason for the differences, whether they were intentional, or to what extent lockdowns, funding, and/or staffing played a role.

Conclusion

At the beginning of 2020, a cohort of 212 spay-neuter clinics that collectively performed more than 1 million surgeries per year were on track to increase surgeries by 5% over the previous year. The COVID-19 pandemic lockdown resulted in a drastic reduction of surgeries, from which the industry has not yet recovered. The high level of spay-neuter achieved over the past five decades is the single most important driver of reduced pet overpopulation and euthanasia in animal shelters. Veterinarians and animal welfare organizations should collaborate to prioritize recovery of spay-neuter capacity with a special focus on serving populations most at risk for unintended reproduction, poor welfare, or entering the animal shelter system.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

JL and GC conceptualized the research topic. GC, SG, and TP compiled the data sets. TD performed statistical analysis. SG, TP, and JL prepared the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Throwing the Baby Out With the Bath Water: Could Widespread Neutering of Companion Dogs Cause Problems at a Population Level?

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In many countries where companion dogs are popular, owners are strongly encouraged to neuter their dogs. Consequently, millions of dogs are neutered each year. In recent times considerable attention has been paid to the possible effects of such procedures on canine health and welfare. Less scrutinized are the potential ramifications of widespread neutering on the breeding of dogs and their continued success as human companions. This paper summarizes research investigating factors influencing the breeding and rearing of dogs most suited to companionship roles in contemporary, typically high-density, communities, and briefly reviews current breeder practices. It then argues that a fundamental shift to promote inclusion of "proven" companion dogs in the gene pool, as opposed to dogs meeting conformation or working/sporting standards, is required to successfully meet the needs of modern urban dog owners. A new model is proposed, whereby responsible owners and breeders work together to produce dogs most suited for life as human companions.

Keywords: responsible dog ownership, neutering practices, companion dog, dog breeding, anthrozoology

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INTRODUCTION

Dogs are popular companion animals and form relationships with owners that are often deeply important, with many owners perceiving their dogs as family members (1, 2). Out of this high regard was borne the idea of "responsible dog ownership," a set of behaviors that mark a person as a caring and accountable owner. Relevant behaviors include providing adequate food, water, training, exercise, and veterinary care (3). In many countries, "responsible dog ownership" also involves spaying and castration [e.g., neutering; (4)]. Some places have mandatory neutering laws (5), schemes discounting the procedures (6), and/or campaigns encouraging owners to neuter their dogs (7). These have culminated in neutering becoming a normative practice in countries such as the United States of America (USA), Australia, and New Zealand (8, 9).

As neutering procedures have become more common, the effects of neutering on canine health and behavior, and its use as a population management tool, have been examined (10, 11). Less attention has been paid to the possible effect of widespread neutering on the breeding of dogs and their success as human companions. This paper considers this issue.

HISTORY AND CURRENT CULTURAL UNDERSTANDING OF NEUTERING

At the beginning of the twentieth century, most dogs never saw a veterinarian (12, 13) and neutering was a relatively unknown procedure (14). This began to change in the early 1970s in the USA, when the size of the stray population attracted public attention and resulted in the opening of the first subsidized neutering clinic in 1971 (15).

Today, neutering is one of the most common surgeries performed on companion animals in many countries (16). In some cultures, having one's dog neutered is considered an essential part of being a "responsible owner," and rates range from ∼60–80% (9, 17). Prevalence varies tremendously, however, as a function of differing societal attitudes (18). In several European nations, such as Norway, neutering healthy dogs, perceived as unnecessary mutilation, is closely monitored or even prohibited (19). In such countries, neutering rates range from 43% to as low as 1% (20). Differences in neutering prevalence also exist within countries Diesel et al. (21), depending on factors such as socio-economic status (18, 22), owner gender (23), dog sex (21, 24), and owner perceptions regarding the practice and its implications (8, 23).

Downes et al. (25) identified several perceptions that act as barriers to neutering, including the financial costs, adequacy of alternative methods for preventing reproduction (i.e., high fences), and potential negative effects on the dog's health and welfare (25). Perceptions linked to pro-neutering attitudes included perceived positive health effects and a reduction in unwanted behaviors among neutered dogs. As companion dogs have moved from rural yards into urban bedrooms, expectations regarding behaviors once considered normal have changed.

THE IDEAL COMPANION DOG: WHAT DO WE WANT AND HOW CAN WE GET IT?

Ensuring that one's chosen dog is compatible with one's lifestyle is an important step in the acquisition process. For this reason, potential owners are often encouraged to investigate what kind of dog (e.g., breed, sex, age) would be most suitable (26). Research has shown that most people judge personality and behavior as the most important factors to consider when acquiring a dog (27). King et al. (28) found that favored traits for Australian owners included the degree to which a dog is affectionate, loyal, friendly, obedient, easily contained, and safe with children. Similar results were obtained when the same survey was administered in Italy (29).

While puppy temperament tests are notoriously unreliable in terms of predicting adult dog behaviors (30), evidence suggests that desirable canine characteristics, such as those identified by King et al. (28), are largely within the realm of human control. Canine personality refers to a constellation of psychological attributes that underpin consistent patterns of behavior and that are resistant to change (31). In most organisms, including dogs, personality is relatively fixed by adulthood, having developed due to interactions between the animal's genetically determined temperament and what they experienced during development (32). Both of these components reflect choices made by those who breed dogs.

Scott and Fuller (33) pioneered research on genetic contributions to canine personality through extensive experimentation with dogs of known heritage. Their work demonstrated the substantial influence genetics has on the development of traits such as emotional reactivity, trainability, problem solving, and aggressiveness. These findings have been explored more recently in large community-based cohorts and similar results have been obtained, particularly concerning traits such as shyness-boldness (34), affability (35), and aggressive tendencies (36). There has also been research to suggest that some traits may be passed onto offspring epigenetically as a result of parental experiences (37).

The second major influence on canine personality is each dog's environmental experience, particularly in the first few months of life (38). This is due to the period of heightened sensitivity to experiences that juvenile dogs undergo, which begins at 2–3 weeks of age and lasts until the puppy is ∼12–14 weeks old (33). As experiences in this time form the foundation for adult personality, it is strongly recommended that puppies be exposed, in a positive way, to the full range of experiences they are likely to encounter as adults (39, 40).

Ensuring that puppies are reared in a place plentiful in diverse experiences is an invaluable step to setting them up for the life they are likely to lead (41). Puppies who are reared inside a home, at least for a period of time, rather than in a kennel, have been found to perform better on tests that measure social attraction and cooperativity, and they display lower levels of aggression and apprehensive behavior (42, 43). The degree of human handling experienced has also been shown to be influential in the development of traits such as confidence, calmness, and stress resilience, with more experience leading to better outcomes (44–46).

CURRENT COMPANION DOG BREEDING PRACTICES

The demonstrated importance of genetics and early environment in determining behavioral predispositions makes it imperative to consider where companion dogs come from. Prior to the widespread introduction of neutering practices, dogs often bred indiscriminately, and people typically obtained their dogs for free from neighbors whose bitch had produced a litter (47). While this was problematic in terms of creating dog overpopulation, it meant that most of the dogs who produced offspring were well suited to the demands of the lives they were expected to lead. Those who weren't well-suited were disposed of. Today, strong demand for companion dogs, coupled with rapid urbanization, increased concern regarding the welfare of animals, particularly companion dogs, and high neutering rates, has resulted in a multimillion-dollar industry involving the selective breeding and selling of puppies (48). Widespread neutering means that humans intentionally control nearly all dog breeding in developed countries.

Only limited evidence exists regarding how dogs are bred, particularly about how breeding choices are made and how puppies are reared (49). One prominent group of breeders are those who breed purebred dogs as a hobby, often secondary to their participation in competitions with their dogs, such as conformation showing or agility. These breeders are usually members of interest groups such as kennel clubs and, in line with the regulations of these clubs, are expected to adhere closely to written breed standards, documents which stipulate the ideal characteristics of the breed, when selecting dogs for breeding (50). Breeders in this group breed ostensibly only to "improve the breed" as defined by this standard, rather than to meet the demands of the companion dog market (51, 52). This has led to exaggerated phenotypes associated with serious health problems (53). In addition, it may lead to production of dogs with behavioral characteristics more suited to their traditional roles as herders, retrievers or guard dogs, than they are to a life where they are expected to be friendly, obedient, affectionate, easily contained, and safe with children. While many hobby breeders do rear their puppies in their homes and sell most of them as companion animals, an additional concern is an emerging trend for "responsible" breeders in this group to neuter puppies prior to sale. This has implications in terms of the health and development of the puppies (54), but also means that breeders must select their breeding dogs at a very young age, prior to seeing how they develop as adults. It therefore serves to potentially remove many of the very best companion dogs from the gene pool.

Another broad group of breeders are commercial breeders, who breed for the primary purpose of making a profit. Unlike hobby breeders, commercial breeders often specifically produce dogs for the companion market (48). For their enterprise to be viable, these breeders usually operate on a larger scale than hobby breeders. One might question whether large-scale breeding facilities are able to provide adequate environmental stimulation and socialization practices for puppies (55). To some extent this depends on the dog-to-human ratio and the actual facilities available. Breeders who operate "puppy farms," are frequently condemned due to overcrowding, poor sanitation and other issues (55). However, even the best commercial establishments may be less able to provide the simulated "home environment" to which puppies destined for companionship life should be exposed. Bennett and Rohlf (56) and McMillan et al. (57) identified significantly more behavioral issues, such as fear, anxiety, and aggression, in dogs coming from pet shops, many of which source their puppies from commercial breeders.

The third, and likely the largest, companion dog breeder group is the general public (58, 59). Importantly, however, not all companion dog owners are equally likely to produce puppies. As described previously, in many developed countries, neutering companion dogs is considered an important aspect of responsible ownership. Hence, the very best companion dogs in the general community, those owned by responsible citizens who choose their dogs carefully and ensure they are reared correctly, are almost certainly those most likely to be neutered. Conversely, it is those companion dog owners who fail to perform the "responsible" behavior of neutering their dog who are perhaps most likely to breed. These "breeders" may also choose not to perform other "responsible" behaviors, such as selecting their dog carefully, testing it for genetic disorders, or evaluating the dog's suitability as a companion prior to allowing it to reproduce. In other words, they may not thoroughly consider the genetic and environmental factors known to be critical to optimal puppy development.

Irresponsibly bred puppies are at high risk of being relinquished. In fact, millions of puppies enter shelter and rescue systems each year (60). Very little information exists regarding the puppy rearing practices undertaken by shelters and rescues, though these are likely extremely variable and dependent on available resources. Such organizations have no control over which dogs are bred and often lack access to information about puppies' parentage. It is also likely that, in many cases, they may not be equipped with the knowledge, time, or resources to rear puppies in an environment that provides extensive or appropriate opportunities for socialization. Owners of dogs acquired from a shelter or rescue group have previously reported higher levels of undesirable traits, such as fearfulness and unfriendliness/aggression, though the likelihood is lower if the dog is acquired as a puppy (56, 61).

The main breeder groups identified above are by no means exhaustive, mutually exclusive or distinct. Many people who would describe themselves as hobby breeders do not breed purebred dogs but focus instead on specific breed crosses they believe are excellent human companions. Some commercial breeders do not focus solely on profit, but report paying careful attention to the welfare and suitability of their dogs (62, 63). Breeders in all groups routinely claim that they rear companion puppies in environments that set them up for success, and also that they ensure breeding dogs possess traits desired by companion dog owners. Whether these assertions are correct or not is difficult to assess, a situation that leaves both breeding dogs and the general public vulnerable to exploitation. For dog owners, the risks may be exacerbated by increased urbanization, which increases social demands on dogs but also means that many owners lack prior exposure to animals, a situation vastly different from just a few decades ago, when most community members were familiar with a broad range of domesticated animals. Current breeder practices, supported in part by the higher prices and increased demand for puppies associated with widespread neutering, may mean that many dogs end up in environments to which they are poorly suited, and that many dog owners end up with a dog which is poorly suited to their lifestyle and expertise.

BRINGING IT ALL TOGETHER: AN ALTERNATIVE APPROACH TO NEUTERING

To increase the chances of harmonious relationships forming between modern owners and their companion dogs, we believe three changes should be made to current breeding practices. First, it is imperative that breeding choices and puppy rearing processes, such as whelping and socialization procedures, are informed by empirically derived knowledge of best practice. We believe that all breeders should be educated to understand the critical roles they play in providing dogs suited for the

companion market, both through the adult dogs they choose to breed from and the early experiences they provide to puppies. To facilitate putting this education into practice, we believe that breeding choices and puppy rearing processes should be clearly documented and archived, with this information being provided to purchasers alongside other required documentation such as veterinary records and microchip information.

Second, we advocate that all dogs should be independently tested for suitability before being bred—much as breeders now advertise that their puppies' parents are successful show dogs, or that they are free from known genetic disorders, so they should be encouraged to advertise that independent testing has shown their breeding dogs to be well-suited behaviourally to life as human companions. We anticipate that responsible breeders would be willing to pay for this independent certification, much as they presently pay for genetic tests, eye screening and tests for hip dysplasia. Several behavioral tests exist to measure specific traits, such as the Socially Acceptable Behavior test (64), which measures aggression, or the Dog Mentality Assessment test (65), which examines levels of playfulness, curiosity, aggression, sociability, and chase-proneness. In the USA, the Canine Good Citizen program, administered by the American Kennel Club, takes <30 min to administer and is designed to identify dogs that meet ten objectives consistent with being a good companion dog. Any one of these tests could be used as a basis for developing an assessment suited to breeding dogs—dogs that are not themselves good companions are less likely to produce puppies able to excel at this role.

Third, a collaborative approach should be promoted between breeders and companion dog owners, whereby owners are invited to play a critical role in the breeding process. Whilst breeders may possess the skills necessary to breed dogs and rear puppies successfully, companion dog owners are often in the best position to enable dogs to "prove" themselves as suitable breeding dogs through observing their dog's responses to a range of relevant experiences.

These changes are achievable only if the current approach to neutering is altered. At present, widespread neutering of companion dogs undermines the production of suitable dogs by excluding thousands of ideal companions from the gene pool. These include dogs produced by "responsible" breeders, who are neutered before being sold as puppies or who come with a contract stipulating they be neutered by a certain age. They also include dogs owned by "responsible" owners, who ensure that their dogs participate in appropriate training and socialization activities and that they are fully integrated into the household, and who also "do the right thing" by ensuring that their dogs are neutered. While we agree that dogs with unknown histories should continue to be routinely neutered, as should dogs from parents known not to be suitable as companion dogs, we advocate for a more nuanced approach to neutering, in which puppies from dogs carefully chosen for their companionships traits and placed in homes with owners who agree to prevent breeding until their dog can be thoroughly evaluated, should have the opportunity to remain intact.

If, as adults, these dogs demonstrate suitability as breeding dogs, they could be temporarily returned to the breeder for breeding purposes. Alternatively, if the breeder does not have the resources and time to rear the puppies inside their home, select owners could whelp their bitch under close guidance of an experienced breeder. This model could provide puppies with an optimal early environment, closely approximating the one in which they will be expected to live as adults, and it would allow breeders access to a wider pool of dogs for breeding. It would also prevent the current situation, in which breeders must select which dogs to retain for breeding at a very young age, before adult traits are apparent. This could strengthen the gene pool and reduce inbreeding.

Such a collaborative approach to breeding, involving breeders working closely with some owners, is not entirely novel, with an internet search revealing similar approaches currently being used by some organizations breeding dogs to work as guide dogs or as assistance animals, as well as a small number of companion dog breeders. However, such practices are neither common nor well-documented, so it is unknown whether those individuals we located implement all of the above recommendations and/or how they do so. Furthermore, we could find no evidence of any formal evaluation of these programs, so it is not known to what extent they are successful.

To summarize, we propose a systemic restructure of the companion dog breeding industry that incorporates increased transparency regarding breeding choices and puppy rearing practices, temperamental evaluation of breeding dogs, and a collaborative relationship between breeders and owners that allows for more suitable dogs to remain within the gene pool. We acknowledge that this model is not without risk. Breeders and owners may disagree over many things, such as whether a particular dog is suitable for breeding and who owns any puppies produced. The potential for indiscriminate breeding also exists, and this could contribute to further overpopulation and increase pressure on shelters and rescue groups, although we think it is less risky at a population level than the current practice of removing the very best companion dogs from the breeding pool. Adverse situations could be prevented by careful recruitment of owners who are suitable, well-informed, and sufficiently supported, alongside clear contractual agreements that protect both the humans and dogs involved. Over the long term, a more considered approach to the breeding of companion dogs would help lessen the gap between owner expectations and the dogs available to them. However, this is only possible if attitudes toward neutering are addressed and "responsible ownership" is broadened to include a dynamic partnership between owners and breeders to produce dogs most suited for life as companions.

AUTHOR CONTRIBUTIONS

PB and JD conceived of the proposed idea. The manuscript was written and revised by JD with the support and contributions of TH, MR, and PB.

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MINI REVIEW
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Gonad-Sparing Surgical Sterilization in Dogs

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Elective sterilization of pet dogs is a common surgical procedure performed in veterinary practice. The main benefit of sterilization is population control and the reduction in euthanasia of unwanted dogs. The most common methods for sterilizing female and male dogs are ovariohysterectomy (spay; which removes both the ovaries and the uterus) and castration (neutering; which involves removing the testicles), respectively. However, any surgery that removes the gonads changes the animal in both positive and negative ways. There is mounting evidence supporting the long-term health complications associated with surgical sterilization with gonad removal. Gonads are not merely gamete-producing or ancillary sex/reproductive organs but rather they are necessary endocrine glands for normal metabolic, behavioral, musculoskeletal, and anti-neoplastic health. The purpose of this mini review is to describe two gonad sparing surgeries that this author has used to sterilize dogs. These surgeries can be performed on pediatric patients without interfering with pubertal maturation. Dog owners can make the decision when the dog is completely mature whether or not the gonads should be removed.

Keywords: mammary cancer, ovaries, ovary-sparing hysterectomy, testes, vasectomy

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Ovary-sparing hysterectomy (OSH) is a gonad-sparing sterilization technique first described in the literature over 40 years ago (1). This surgery removes the entire uterus and all (or most) of the cervix but leaves the ovaries intact and functional (**Figure 1**). The surgical approach is like a spay but the incision longer and more caudal to facilitate greater access to remove the cervix. Starting with the left uterine horn, follow it cranially to the ovary. It is not necessary to breakdown the ovarian suspensory ligaments but doing so may improve visibility of the cranial aspects of the uterine horns. Make a window in the broad ligament adjacent to the ovary and uterine horn and then place a clamp across the mesosalpinx containing the uterine tube. A ligation is placed in the crush created by the clamp and the area between the ligature and the clamp is sharply transected. It is extremely important that all of the uterine horn adjacent to the ovary is removed and this area is carefully inspected before the ovary is returned to its abdominal location. The procedure is repeated for the right uterine horn. The broad ligaments are broken down toward the uterine body similar to a traditional ovariohysterectomy. Clamps are placed across the cranial vagina & circumferential or transfixing ligatures are placed in the crush.

Some surgeons prefer to place clamps & ligate across the cervix but because of the cartilaginous nature of the canine cervix, it is the preference of this author to remove the entire cervix to ensure a more secure closure during ligation. The entire uterus must be removed, which is the reason for removing all (or at least part) of the cervix. It cannot be stressed enough that failure to completely remove the entire uterus will predispose for a pyometra. The closure of the abdominal and skin layers is similar to that of a routine ovariohysterectomy, which the exception that closure may take a little longer owing to a slightly longer incision.

Although the post-surgical recovery is also like a traditional ovariohysterectomy, bitches that have undergone an OSH will still experience routine estrous cycles and display an enlarged vulva (with no estrual bleeding because the uterus has been completely removed) and estrous behaviors (which includes a willingness to breed). Owners should be instructed to prevent

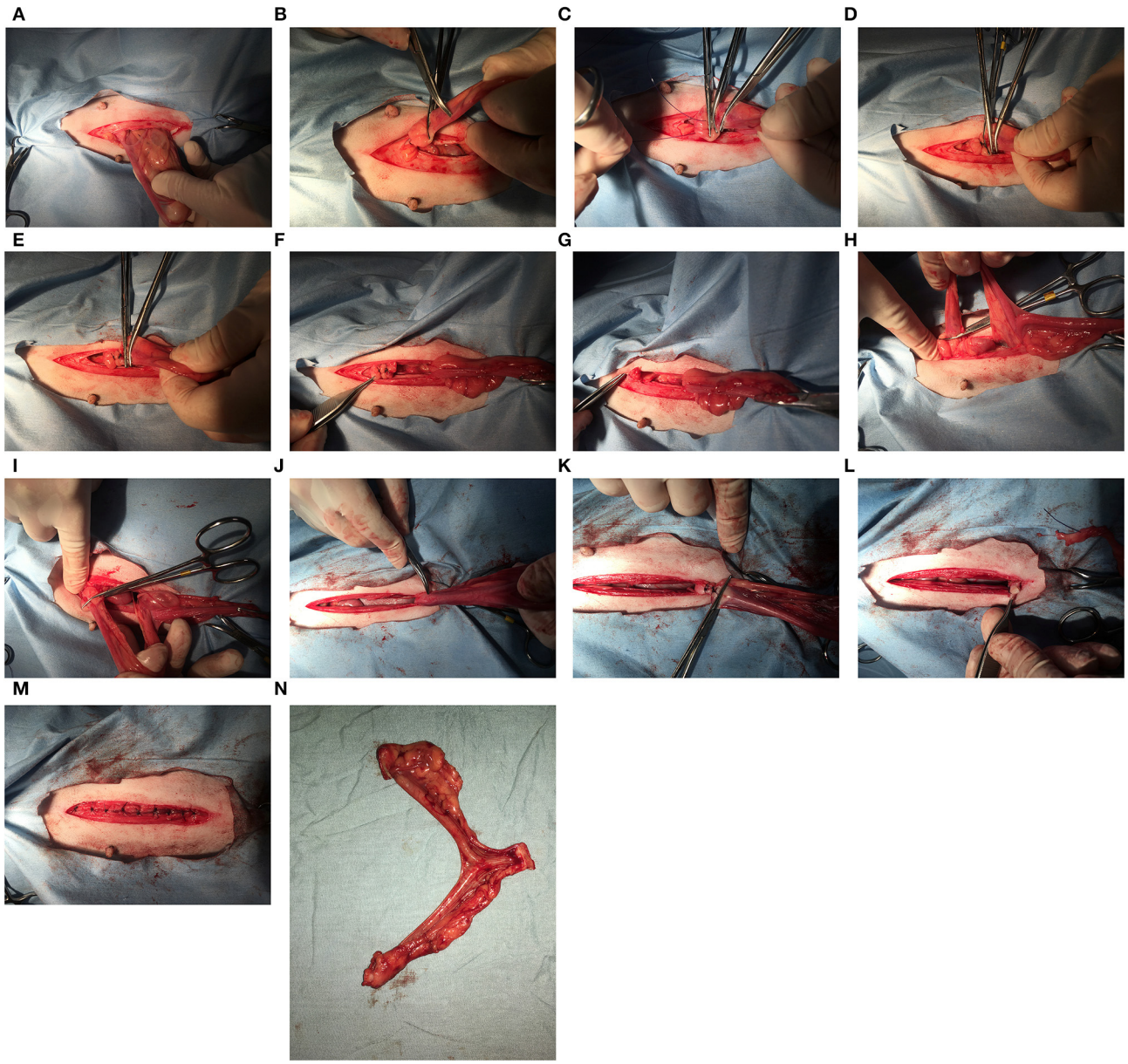

FIGURE 1 | When the ovary-sparing hysterectomy is properly performed, the entire uterus and all or part of the cervix must be removed. For the procedure documented here, the cranial part of the cervix was removed. For the following series of images, the left of the image is cranial. **(A)** The left uterine horn is identified and elevated out of the incision. It is not necessary to breakdown the ovarian suspensory ligament but doing so may improve visibility of the cranial aspects of the uterine horns. **(B)** A hemostat has been placed caudal to the left ovary and the cranial aspect of the uterine horn is at the tip of the second hemostat. **(C)** A hemostat is placed cranial to the tip of the uterine horn, and two additional hemostats are placed between this hemostat and the ovary. **(D)** A transfixing suture is placed in the crush of the most cranial hemostat. **(E)** A second transfixing suture is placed in the crush of the next most cranial hemostat. **(F)** The left proper ligament and uterine tube are sharply transected caudal to the two transfixing sutures. **(G)** The left ovary is observed for signs of hemorrhage before replacing into the abdomen. **(H)** The right uterine horn is identified and elevated out of the incision. **(I)** A hemostat has been placed cranial to the right uterine horn and the process from the left side is repeated. **(J)** After breaking down the broad ligaments, the uterine horns, and body are elevated and reflected caudally to expose the cervix. It may be necessary to length the incision to elevate the entire cervix out of the incision. **(K)** Two transfixing sutures are placed around the vagina caudal to the cervix (or around the caudal aspect of cervix, where it meets the vagina as shown here). **(L)** The cranial vagina/caudal cervix is sharply transected and the entire uterus is removed. **(M)** Closure of the body wall, subcutaneous tissues and skin are same as with a routine ovariohysterectomy. **(N)** Removal of the entire uterus and cervix.

females from mating until the vaginal closure is completely healed (∼60 days). After this time, there is minimal risk of vaginal injury. However, there are a few anecdotal reports of life-threatening injury (e.g., cranial vaginal rupture) following mating in bitches following OSH and following traditional ovariohysterectomy with an ovarian remnant. Dogs undergoing OSH are presumably at a greater risk for developing mammary cancer than those who were routinely spayed. However, it is important to note that in at least one study, none of the 120 ovarian intact females developed mammary cancer but two of the spayed females did (2). This suggests that the link between mammary cancer and ovarian exposure in dogs should be re-examined (3). In addition, it should be noted that OSH performed in women has been associated with a premature reduction in circulating anti-Mullerian hormone (AMH) concentrations and to an earlier onset menopause (4). It is not known what, if any, effect performing an OSH in dogs will have on ovarian reserve so this is an area that warrants investigation.

Vasectomy involves bilateral removal and/or occlusion of a portion of the vas deferens, rendering the animal infertile by preventing sperm from being ejaculated during copulation. The quick procedure is technically like the surgery performed in men, with the exception that it is accomplished under general anesthesia in dogs. Following induction of general anesthesia, the inguinal region is prepared for surgery. A single small (1–3 cm) midline incision is made cranial to the scrotum. Some surgeons prefer to make one incision over each vas. Caudal traction placed on the scrotum will put tension on the spermatic cord, facilitating identification. The cord is dissected from the surrounding fat and fascia and a small incision is made through the parietal vaginal tunic. The testicular vessels lie in lateral fold of the visceral vaginal tunic, while the vas deferens with the deferential artery & vein lie in the medial fold. The vas deferens is isolated and the deferential artery and vein are dissected from the surface of the duct. Ligatures are placed on either side of a small section of vas deferens and the duct is removed between the ligatures. Recanalization has been reported when the duct is simply severed. The parietal vaginal tunic is closed with fine absorbable suture and the skin is closed with an absorbable suture in a subcuticular pattern. The procedure is then repeated on the opposite side.

According to Schiff et al. (5), sperm are completely absent from the ejaculate within 24 h following vasectomy. Male secondary sex characteristics and behaviors, as well as androgen-dependent diseases, are not prevented, since androgens are still produced. Following the vasectomy, increased intraluminal pressure within the rete testis may result in irreversible damage within the seminiferous cell population and testicular degeneration. In addition, the epididymis becomes distends with sperm. Epididymal fluid may extravasate under pressure, inducing a sperm granuloma. Up to 33% of vasectomized men experience chronic scrotal discomfort in the scrotum (6). Recurrent scrotal dermatitis (presumable associated with the discomfort) has been reported in dogs following vasectomy (7).

Both of these gonad sparing techniques are accepted as alternative surgical sterilization methods by the American Veterinary Medical Association (https://www.avma.org/public/petcare/pages/spay-neuter.aspx). Veterinarians and pet owners need to discuss which sterilization procedure is best for the long-term health of their pet.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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ORIGINAL RESEARCH
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Castration of Dogs Using Local Anesthesia After Sedating With Xylazine and Subanesthetic Doses of Ketamine

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Orchiectomy is performed in some species using only sedation and local anesthesia to decrease the expense of performing the procedure using general anesthesia. The objective of this study was to determine if dogs can be castrated safely and painlessly by using only sedation and local anesthesia. After dogs were sedated with intramuscularly administered xylazine (1 mg/kg) and subanesthetic ketamine (1 mg/kg), testes and skin were anesthetized with 2% lidocaine (6 mg/kg, total dose) buffered with sodium bicarbonate. Systolic, diastolic, and mean blood pressures; heart and respiratory rates; and movement scores were determined before and during surgery when manipulations were most likely to cause pain. No dog reacted substantially to injection of the combination of sedatives, and no dog reacted noticeably to injection of lidocaine. During surgery, the average heart rate was reduced from baseline by 40–60 beats per minute, and the average respiratory rate was reduced by ∼10 breaths per minute. An overall reduction of arterial blood pressures was observed. All but one dog moved purposely in response to a toe pinch at the end of surgery. We found that sedating dogs intramuscularly with xylazine and a sub-anesthetic dose of ketamine and administering lidocaine at the incision site and intratesticularly allowed dogs to be castrated humanely and avoided the expense of general anesthesia and the need for hospitalization.

Keywords: dog, castration, local anesthetic, xylazine, subanesthetic ketamine

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INTRODUCTION

When anesthetic equipment is not available or large numbers of dogs must be castrated, chemical immobilization in conjunction with local anesthesia may be an economical and expeditious method of performing the procedure.

Orchiectomy in other species can be performed painlessly after injecting the testes or spermatic cords with local anesthetic. Men can be castrated using local anesthesia, often without sedation (1–4). Stallions also are often castrated while they are standing by using only sedation, local anesthesia, and a lip twitch for restraint (5).

In a study that evaluated the analgesic effect of intratesticular and incision line infiltration of local anesthetic (0.5% ropivacaine) (6), 7 of 11 sedated dogs were castrated with little or no movement. Because of substantial movement, four dogs in that study were given general anesthesia to complete the castration; however, the authors did not offer an opinion as to whether movement appeared to be in response to surgically induced pain or other environmental stimuli.

Silva Cuzmar et al. (7) investigated the use of sedation and local anesthesia for immobilizing dogs during castration. That study demonstrated that dogs can be castrated without causing signs of pain by administering xylazine for restraint, followed by administering lidocaine intratesticularly and subcutaneously at the site of incision. In that study, dogs did not display signs of pain as indicated by changes in vital signs and the lack of purposeful movement in the presence of surgical stimulation. We sought to bolster that study with another study in which blood pressure was monitored before and during surgery. Blood pressure has been shown to be a more sensitive indicator of nociception than heart rate (HR) during castration of stallions (8) or ovariohysterectomy of dogs (9). We also wanted to know if lidocaine administered at a standardized dose much less than the recommended maximum therapeutic dose for the dog [10 mg/kg (10)] would allow castration without evidence of pain. Because injection of lidocaine can be painful (11, 12), we also wanted to determine the effect of using buffered lidocaine for preventing signs of pain during injection of testes and the incision site. In our previous study (7), non-purposeful movement of dogs during surgery was common. We wondered if a sedative dose of ketamine in addition to xylazine HCL would decrease movement. For this study, we recorded time of administration of local anesthesia and start of surgery, information that would indicate the necessary time to wait before administering local anesthesia and expectation that the testes and skin are desensitized.

MATERIALS AND METHODS

Preparation of Dogs for Surgery

Twelve male dogs of various breeds underwent castration after owners signed a consent form allowing participation of their dogs in the study. This study was approved by the Universidad Austral de Chile Bioethics Committee for the Use of Animals in Biomedical Research (protocol No. 231/2015). Physical examinations were performed before the dogs were sedated. Dogs had been fasted overnight but were allowed access to water until they were sedated with xylazine HCl (1.0 mg/kg; Xilacina 2%, Centrovet, Santiago, Chile) and ketamine (1.0 mg/kg; Ketamina, Richmond Laboratories, Buenos Aires, Argentina) mixed in the same syringe and administered intramuscularly in the semitendinosus or semimembranosus muscle. Once recumbent, dogs were placed on a surgical table in left or right lateral recumbency and prepared for surgery with the upper pelvic limb flexed and elevated. After the surgical site was clipped of hair and scrubbed, lidocaine (6 mg/kg) was administered into the testes and site of cutaneous incision.

Physiological Values Assessed Before and During Surgery

Systolic (SAP), diastolic (DAP), and mean (MAP) blood pressures; heart and respiratory rates; and movement scores were determined at various time points ([1 through 12]) throughout the procedure. Heart and respiratory rates and SAP, DAP, and MAP were measured using a Data Scope Trio Patient Monitor (Datascope Corporation, Mahwah, NJ, USA) and a human pediatric blood pressure cuff (7.2–13 cm) (Tuff Cuff, Cas Medical Systems Inc., Branford, CT USA) applied to the base of the tail. For dogs without a tail, blood pressures were measured by attaching the cuff to a forelimb, slightly distal to the elbow. These values were determined with the dogs standing, before they were injected with sedatives [1], and thereafter, with the dogs in lateral recumbency, 3 min after administration of the sedatives [2], immediately prior to administering lidocaine [3], and during injection of lidocaine at each of three injection sites [4–6]. The same data were collected during the cutaneous incision [7], at the time of removal of each testis [8, 9], during closure of the wound [10, 11] and after pinching interdigital skin on a pelvic limb with a Halstead forceps after the last suture was placed [12]. Four assistants (two veterinarians and two veterinary students) collected these data. Each assistant was assigned to determine one of the following indicators of nociception: change in arterial blood pressures, respiratory rates, heart rates and movement. The assistants were assigned the same task for each castration. Data collected immediately before administering the sedatives were used as baseline [1]. Movement was subjectively graded on a scale of 0–3 where: 0 = no movement; 1 = slight to moderate, non-purposeful movement that did not interfere with surgical manipulations; 2 = purposeful movement that interfered substantially with surgery; and 3 = purposeful movement that made continuation of surgery impossible.

Administration of Local Anesthetic

Lidocaine HCl (Lidocalm® 2%, Drag Pharma, Santiago, Chile) diluted with 8.4% sodium bicarbonate (Laboratorio Sanderson S.A., San Joaquin, Chile) as a 9:1 ratio was divided into three equal doses and administered by the first author into each testis, and then, subcutaneously, on the midline, cranially to the scrotum. Testicular injections were made by inserting a 25-gauge, 16-mm needle at the median raphe and then directing the needle, from its subcutaneous location into the parenchyma of each testis without withdrawing the needle through the skin between injections. The time from the subcutaneous, prescrotal injection of lidocaine to the skin incision was recorded.

Surgical Procedure

Open castrations were performed using a prescrotal approach with the dog in lateral recumbency and its upper pelvic limb elevated in a flexed position. The pampiniform plexus and vas deferens were ligated together using a transfixion ligature of 2/0 or 3/0 polyglycolic acid (Safil, B. Braun Surgical S.A., Rubí, Spain). Subcutaneous tissue was closed with the same suture using a simple-continuous pattern. Skin was closed with non-absorbable 3/0 synthetic monofilament suture (Dafilon, polyamide, B. Braun Medical S.A., Bogotá, Colombia) using a simple-interrupted pattern. The first author performed all surgeries. All dogs were administered a single dose of ketoprofen (1 mg/kg IM) (KET-10, Drag Pharma Chile Invetec S.A., Lautaro 300, Quilicura, Santiago, Chile) and procaine penicillin G (20,000 IU/kg IM) after surgery. Time from placing the last skin suture until the dog was standing was recorded. Dogs that remained recumbent after the toe pinch were placed on a pad on the surgery room floor in lateral recumbency. The dogs were discharged between 4 and 6 h after they recovered from sedation. Owners

were contacted by telephone 4–5 days after surgery for their opinion of their dog's health.

Data Analyses

Statistical analyses were performed using a commercially available software package (JMP® 13.0.0, SAS Institute Inc., Cary, NC, USA). Data were assessed for normality by visual inspection of frequency distributions and by the Shapiro–Wilk test. Descriptive statistics, including mean, median, standard deviation, minimum, and maximum were calculated. Statistical tests were performed to test the null hypothesis that the means of each outcome variable assessing pain were equal at each time point during surgery. Normally distributed outcome variables (heart rate, respiratory rate, and arterial blood pressures) were analyzed using a mixed model analysis for repeated measures. Model fit was assessed by visual inspection of residual plots and comparison of the Akaike information criterion (AIC) for each model. *Post-hoc* multiple comparisons were performed using the Dunnett's test to compare each time point with baseline (time point 1). Movement scores were not normally distributed; thus, the Friedman's test, a non-parametric alternative for the repeated measures ANOVA, was used. The Steel method, a non-parametric alternative for the Dunnett's test, was used for multiple comparisons of movement scores with baseline. A value of $p < 0.05$ was considered significant.

RESULTS

Descriptive statistics for age and weight of dogs and lengths of different phases of the castration procedure are displayed in **Table 1**. No dog reacted substantially to injection of the combination of sedatives, and no dog reacted noticeably to injection of lidocaine. During surgery, the average heart rate was reduced from baseline by 40–60 beats per minute, and the average respiratory rate was reduced by ∼10 breaths per minute. The reduction in each of these rates from baseline values was statistically significant ($p_{time} < 0.0001$) (**Figure 1**). With the exception of time point 2 (3 min after administration of the sedatives), an overall reduction of arterial blood pressures were observed. The SAP, DAP, and MAP varied significantly over time ($p_{time} < 0.05$), but each outcome variable was significantly different from baseline only at one time point during surgery ($p_{diff} = 0.0011$, 0.0122, and 0.0103, respectively) (**Figure 2**). During surgery, movement scores were significantly lower than at baseline ($p < 0.0093$) at all time points, with the exception of time-point 12 (the time at which the toe pinch test was applied at the end of surgery), during which movement scores were similar to those at baseline ($p = 0.2262$) (see **Figure 3**). Four dogs stood in response to the toe pinch. Complications associated with the surgery other than slight swelling and redness of the incision site, were not reported by owners who were contacted by telephone at 4 or 5 days after their dog's castration. Hospital staff, who removed sutures 9–12 days after surgery, reported no owner complaints associated with the surgery.

TABLE 1 | Age and weight of castrated dogs, and time measurements of different phases of the castration procedure are summarized in this table.

Age (months)	Median	9
	SD	17
	Range	7–60
Weight (kg)	Mean	21.6
	SD	8.2
	Range	9.0–33.2
Minutes from injection of sedatives to injection of lidocaine	Mean	17.5
	SD	7.6
	Range	5.0–33.0
Duration of time during injection of lidocaine	Median	3.0
	SD	0.8
	Range	1.0–4.0
Minutes between injection of lidocaine to skin incision	Median	2.0
	SD	0.9
	Range	0.0–3.0
Surgery time (min) from incision to placement of the last suture	Mean	12.3
	SD	4.2
	Range	8.0–22.0
Minutes from placement of the last suture to standing position (likely influenced by the application of a toe pinch).	Median	2.0
	SD	5.3
	Range	0.0–14.0

The mean is displayed for normally distributed outcome variables, while the median was included as the measure of central tendency for non-normal data.

DISCUSSION

The physiological effects of noxious stimulation include increased heart and respiratory rates and blood pressure. Heart and respiratory rates and blood pressure did not increase during surgical manipulations in this study. These autonomic responses are modulated in the brain stem in response to noxious stimulation and are not necessarily evidence of pain, because nociception does not become interpreted as pain until noxious signals reach the cerebral cortex (13). Lack of an autonomic response to noxious stimulation is evidence that nociceptive inputs never reached the spinal tracts that carry nociceptive signals to the brain, where they could be interpreted as pain. Dogs moved not at all or only so minimally during surgery that the movement did not interfere with the surgical procedure. Most dogs (11 of 12) responded to a toe pinch applied at the end of surgery with purposeful movement, with some ($n = 4$) attaining a standing position, indicating cognitive perception of a noxious stimulus, not present during castration. Purposeful movement in response to the toe pinch test indicates that lack of response to surgical manipulations was due to the effects of lidocaine, rather than the analgesic effects of xylazine and the sub-anesthetic dose of ketamine. These findings support findings of the previous study that concluded dogs likely experience no pain during castration performed using only sedation and local anesthesia (7). In that study, dogs castrated using only sedation and local anesthesia showed no purposeful movement and no increase in heart or respiratory rate during the procedure.

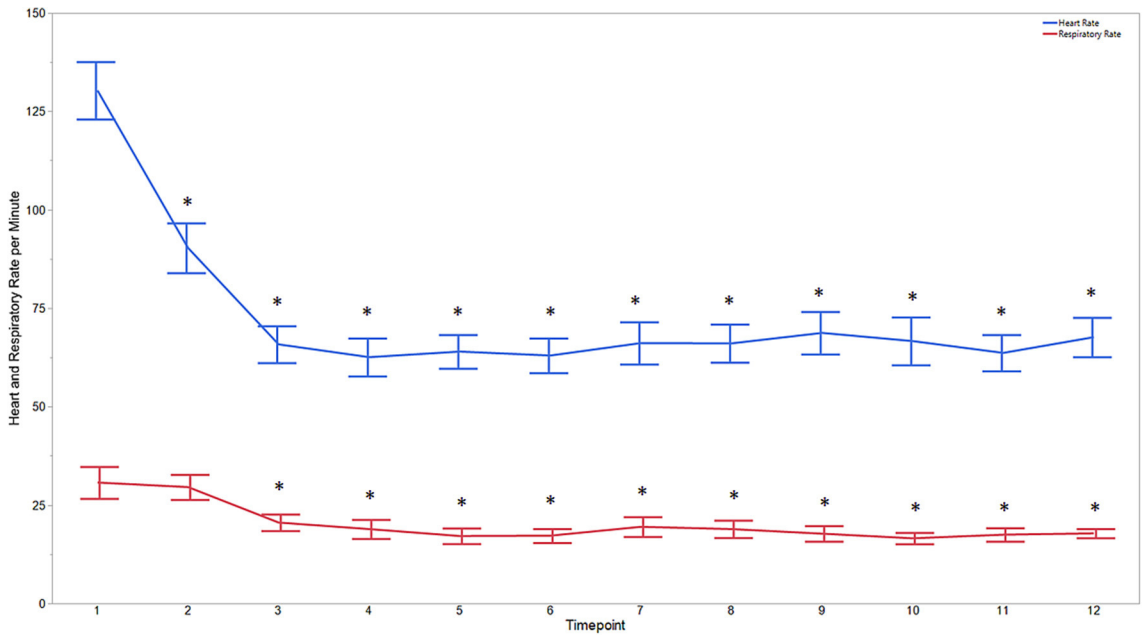

FIGURE 1 | Average heart and respiratory rates at 12 time points of dogs castrated while sedated with xylazine and a subanesthetic dose of ketamine. Time points are: 1 = baseline, before any drugs, 2 = 3 min post xylazine/ketamine, 3 = before testicle injection, 4 = during first testicle injection, 5 = during second testicle injection, 6 = during skin injection, 7 = during incision, 8 = during first testicle removal, 9 = during second testicle removal, 10 = during subcutaneous suture, 11 = during skin suture, 12 = after toe pinch. *Reflects significant difference to baseline (time point 1). Error bars were constructed using the SEM.

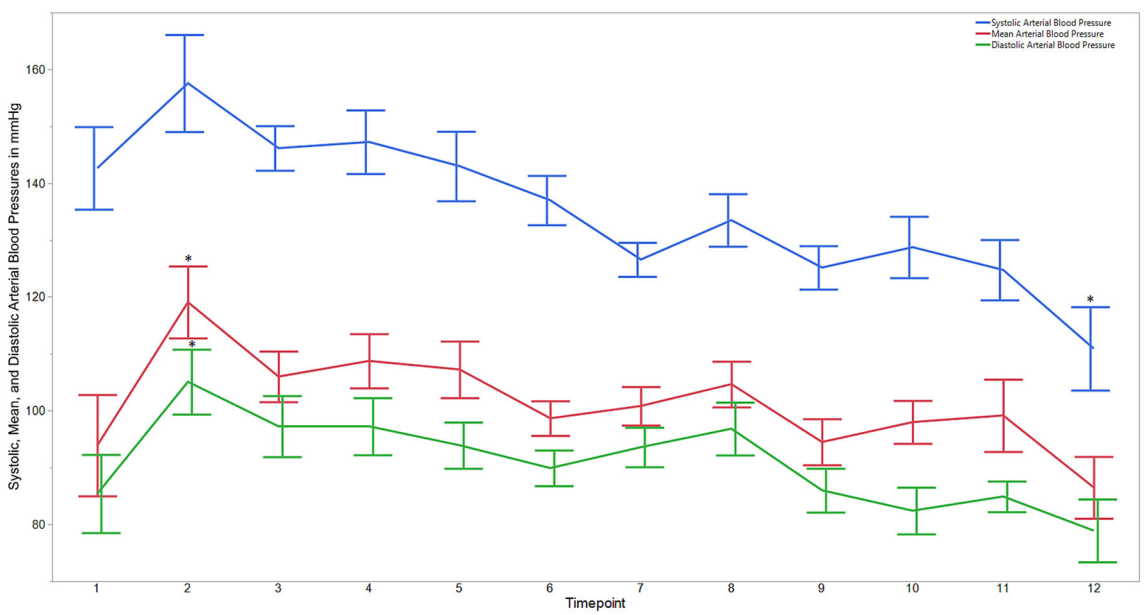

FIGURE 2 | Average systolic, mean, and diastolic arterial blood pressures for dogs castrated while sedated with xylazine and a subanesthetic dose of ketamine. Time points are: 1 = baseline, before any drugs, 2 = 3 min post xylazine/ketamine, 3 = before testicle injection, 4 = during first testicle injection, 5 = during second testicle injection, 6 = during skin injection, 7 = during incision, 8 = during first testicle removal, 9 = during second testicle removal, 10 = during subcutaneous suture, 11 = during skin suture, 12 = after toe pinch. *Reflects significant difference to baseline (time point 1). Error bars were constructed using the SEM.

In this study, we found that surgery was possible soon after administration of local anesthetic with a median time of only 2 min between administration of lidocaine and commencement of surgery. In men, rapid onset of anesthesia of the testis after intratesticular injection of lidocaine was demonstrated, as painless testicular biopsy was possible when performed within

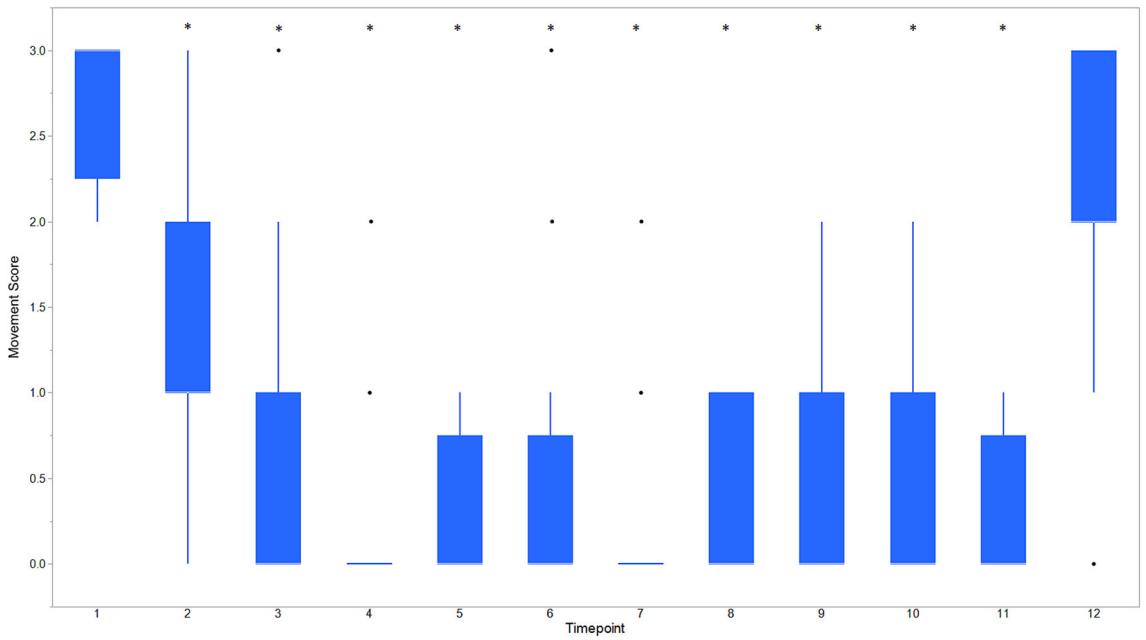

FIGURE 3 | Boxplot of movement scores for dogs castrated while sedated with xylazine and a subanesthetic dose of ketamine. Time points are: 1 = baseline, before any drugs, 2 = 3 min post xylazine/ketamine, 3 = before testicle injection, 4 = during first testicle injection, 5 = during second testicle injection, 6 = during skin injection, 7 = during incision, 8 = during first testicle removal, 9 = during second testicle removal, 10 = during subcutaneous suture, 11 = during skin suture, 12 = after toe pinch. *Reflects significant difference to baseline (time point 1) movement was subjectively graded on a scale of 0–3 where: 0 = no movement; 1 = slight to moderate, non-purposeful movement that did not interfere with surgical manipulations; 2 = purposeful movement that interfered substantially with surgery; and 3 = purposeful movement that made continuation of surgery impossible. *Reflects significant difference to baseline (time point 1). Individual black dots reflect outliers.

15 s after injection of lidocaine in scrotal skin and directly into the testicle (14).

Xylazine was chosen for sedation in the previous study of dog castrations performed with local anesthesia (7), because one of the aims of that study was to demonstrate an economical method of dog castration, and because other alpha2-adrenoreceptor agonists are not available in some countries. For the current study, a sub-anesthetic dose of ketamine was added to the sedation protocol to decrease the possibility of the dogs experiencing pain during intra-testicular injection of local anesthetic solution. Sodium bicarbonate was added to lidocaine for intratesticular injection of local anesthetic solution for the same reason, because lidocaine and other local anesthetic agents have a low pH, which may result a burning sensation during injection. Adding bicarbonate to the local anesthetic solution may decrease pain by raising the pH of the solution (11, 12). The sodium bicarbonate added to local anesthetic solution also increases the potency and the speed of onset of the local anesthetic solution (12, 15, 16). Pain experienced during intratesticular injection of local anesthetic solution might also be caused by rapid expansion of tissue; for this reason, injections were made with a small-bore needle to slow the rate of injection and to decrease pain associated with insertion of a needle.

Ketamine is often used at sub-anesthetic doses as a sedative in human patients. Ketamine administered at a sub-anesthetic dose appears to be particularly useful in emergency rooms for dealing with agitated patients and children, because its onset of action is about 5 min even when administered intramuscularly (17, 18), and because the incidence of side effects associated with its use is low (18–21). We administered ketamine at a fraction of the dose used in dogs (11 mg/kg) when combined with xylazine etc. (22), which would exert its effect by disconnecting the thalamocortical and limbic systems, effectively dissociating the central nervous system from outside stimuli to act as a potent analgesic permitting medical procedures to be performed without causing pain to the patient (21). Ketamine administered to human patients at a sub-anesthetic dose is also a potent analgesic (23, 24). Sub-anesthetic doses of ketamine do not significantly affect consciousness or arousal, and have no measurable cardiovascular or respiratory effects (25, 26).

The study has a number of limitations. Only young healthy dogs were studied, and the effects of the drug combination may be different in older or debilitated dogs. Although we monitored the basic aspects of cardiopulmonary function in this study, monitoring blood gases and cardiac output would have been ideal, so that the safety of the drug combinations used could have been better assessed. This was not possible, however, due to the circumstances of the study. Simultaneous administration of xylazine and ketamine to dogs, especial at high doses, can produce substantial hypoxemia (27); however, it is unlikely to be the case in the dogs of this study as they were not in a deep plane of surgical anesthesia. Emesis is sometimes a side-effect of administering xylazine to dogs (28); however, in the authors' experience emesis is unlikely to occur when xylazine is administered in association with ketamine. Nevertheless, the study did not evaluate dogs to determine if they maintained

a swallow reflex after sedation, which would have been an indication that the dogs could protect their airway in the event of emesis. Although no substantial reaction was observed during intratesticular administration of local anesthetic or during the surgical procedure in this study, there may be risk that some dogs may have an aggressive reaction toward personnel during these procedures.

We found that sedating dogs intramuscularly with xylazine and a sub-anesthetic dose of ketamine and administering lidocaine at the incision site and intratesticularly allowed dogs to be castrated humanely and avoided the expense of general anesthesia.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The animal study was reviewed and approved by Universidad Austral de Chile Bioethics Committee for the Use of Animals in Biomedical Research. Written informed consent was obtained from the owners for the participation of their animals in this study.

AUTHOR CONTRIBUTIONS

ES contributed to case recruitment and study execution. All authors contributed to study design and manuscript preparation. TP performed data analysis.

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Instrument shank-assisted ovariohysterectomy: a randomized clinical trial of surgical and pain alleviation efficiency of a single-person modified technique

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Objectives: To evaluate a modified ovariohysterectomy (OHE) technique performed by a single person and compare it with the conventional method based on time efficiency, trauma, and postoperative pain.

Methods: In a prospective, randomized, experimental study, 18 healthy, large, deep-chested, mixed-breed intact female dogs were randomly allocated to conventional ($n = 9$) and instrument shank-assisted ($n = 9$) groups. On the basis of video recordings, the various surgical step durations were analyzed: total surgery time (TST), pedicle intervention time (PIT), suspensory release time (SRT), shanking time (ShT), clamping time (ClpT), ligating time (LigT), and closure time (CT). The Glasgow composite pain scale short-form (GCMPS-SF), university of Melbourne pain scale (UMPS), and Visual Analogue Scales (VAS) were used to measure pain. C-reactive protein (CRP) fluctuation was also investigated. These evaluations were completed before and 6, 24, 48, and 72 h postoperatively.

Results: Instrument shank-assisted OHE was less time-consuming than conventional OHE ($p = 0.005$), improved PIT by 30.7% (6.44 min for both pedicles, $p = 0.014$), and correlated strongly with TST ($\rho = 0.862$, $p = 0.003$ and $\rho = 0.955$, $p = 0.000$, respectively). The two method's surgical step durations were also TST = 47.40 ± 9.9 vs. 34.70 ± 6.7 min, PIT = 20.96 ± 5.78 vs. 14.52 ± 3.73 min, SRT = 78.97 ± 69.10 vs. ShT = 20.39 ± 8.18 s ($p = 0.035$), ClpT = 50.66 ± 45.04 vs. 63.55 ± 37.15 s ($p = 0.662$), LigT = 12.82 ± 3.37 vs. 8.02 ± 3.11 min ($p = 0.005$), and CT = 16.40 ± 4.5 vs. 11.60 ± 2.5 min ($p = 0.013$), respectively. While both techniques inflicted pain on the animals, the novel approach resulted in a reduction of pain at T6 (GCMPS-SF, $p = 0.015$ and VAS, $p = 0.002$), T24 (UMPS, $p = 0.003$), and T48 (GCMPS-SF, $p = 0.015$ and UMPS, $p = 0.050$). Both methods exhibited a peak in CRP level after 24 h, which subsequently returned to baseline after 48 h. However, the shank-assisted method demonstrated a significantly lower reduction in CRP level at the 48-h compared to the other group ($p = 0.032$).

Conclusion: Instrument shank-assisted technique permitted ovarian removal without an assistant, less damage to animals and reducing its time when compared to a conventional technique, and resulting in an alternative that causes less surgical stress and fatigue. Further research with a larger population size is required to determine the serum CRP levels as an alternative pain biomarker.

KEYWORDS

instrument shank-assisted, ovariohysterectomy, pain score, deep-chest, dog, OHE

1. Introduction

Elective ovariohysterectomy (OHE) is one of the most common surgeries done on dogs and cats (1). However, there are still problems with this technique, despite how common it is. Prior to the start of the operation, inexperienced graduates are anxious about how to do OHE on their own, and after the procedure is finished, they are concerned with the reliability of ligatures. As they consider how to do this procedure at an acceptable speed, their anxiety will increase. When a surgeon acquires experience, new issues develop, such as how to properly perform a high-risk, quick surgery with several implications, such as hemorrhage (2, 3), surgical trauma, organ manipulation, inflammation (4, 5), surgical stress (6), wound healing, and acute pain. The frequency of ovarian remnant syndrome was increasing mostly among young surgeons because of a concern about vascular rupture while breaking the suspensory ligament and exposing the ovaries inadequately, particularly in patients with obesity or other comorbidities (7–9). According to Berzon's study, 1% of bitches experienced recurrent estrus following OHE by fourth-year veterinary students (2). However, the overall frequency of complications by final-year veterinary students was found to be as high as 29 (20.6%) out of 141 bitches, with 1 (5%) out of 20 experiencing post-surgical pseudopregnancy (7). As experience grows, less consideration is given to this problem. To achieve the aforementioned results, the surgeon may be skilled in rupturing the suspensory ligament to expose the ovaries and make their pedicle accessible for ligature placement (10). The success of the operation hinges on the surgeon's willingness to pull, compress, strumming, tear, or sever the suspensory ligament (11), which is accompanied by extensive tissue damage. Drastic tissue damage and the time-consuming nature of its execution have made it the leader in painful surgeries in veterinary medicine, particularly for inexperienced surgeons. The experts, anesthesiologists, surgeons, and experienced researchers have adopted OHE as the acute surgical pain model because of the intensity of the pain caused by an experienced surgeon's OHE (12–14). Acute postoperative pain has long been a problem for surgeons. Inadequate management of postoperative pain can result in a number of undesirable outcomes, including (1) physiological changes comprising tachycardia, hypertension (due to peripheral vasoconstriction, increased myocardial contractility, and systemic vascular resistance), cardiac arrhythmias, tachypnea, superficial respiratory pattern, pale mucous membranes, mydriasis, sialorrhea, and hyperglycemia (2), behavioral changes comprising vocalization (such as cries, whimpers, and growls), looking and licking the affected area, alteration of the facial expression (submissive attitude), self-mutilation, muscle stiffness or weakness, restlessness and anxiety, apathy and inactivity, aggression, fear, and depression, stereotypes, anorexia or hyporexia, reduction of grooming, prayer posture, sleep disorders, and (3) changes in biochemical parameters by the decrease of PaO_2, $PaCO_2$, HCO_3, and an increase of H^+, cortisol, lactate, and glucose (15–20), prolonging the recovery of patients (17, 21, 22). Despite these hazards, OHE is considered to be a very straightforward procedure, and numerous dog owners visit a veterinary clinic every day to have their pets spayed. Hence, the incidence of problems justifies the adoption of procedures, such as instrument shank-assisted OHE, as well as the many theories pertaining to surgical duration, pain, and trauma.

The length of surgery is a primary factor of the severity of postoperative issues, and it is inversely related to the surgeon's skills and expertise (13). Skill is considered in two fields: non-technical skills (e.g., knowledge, situational awareness, decision-making, conscientiousness, intraoperative communication, teamwork, and leadership) (23–25) and technical skills (psychomotor actions). The latter would be gained and empowered via an educational program known as Objective Structured Assessment of Technical Skills (OSATS), which has been thoroughly introduced and verified (26, 27). Besides these abilities, some surgical procedures, such as minimally invasive procedures, are time-consuming and instrument-dependent (28, 29), which may not be an option for some animals. Naturally, each operation consists of a succession of procedures with varying durations, since some are simpler than others, such as entering the abdominal cavity through the linea alba, while others, such as the anatomical access to the ovaries, provide challenges. Understanding the elements that determine the duration of surgical steps as well as the total duration makes it simpler and more objective to estimate its sufficiency and leads to a more trustworthy conclusion.

Animal pain is hard to judge because it depends on many things, such as the amount of pain, the type of injury, and the animal's own characteristics. As a result of the intricate nature of pain perception, several multidimensional questionnaires for qualitative pain assessment and validated behavioral scales have been developed to assess pain intensity in dogs (30, 31). Each of these methodologies assigns a different number of points to certain animal behavioral changes. The sum of the points indicates the observed pain level of the animal. Commonly used pain scales include the Glasgow composite measure pain scale (GCMPS-SF), the University of Melbourne pain scale (UMPS), and the Visual Analogue Scale (VAS), with corresponding ranges of 0–28, 0–24, and 0–10. Each of these solutions seems capable of filling some of the gaps left by the others, since they possess almost separate criteria with little overlap (32).

It is considered that the pain will always correspond to specific parameters that changed when the discomfort began or emerged. Clinical studies may describe a vast array of biomarker variations.

Some parameters represent a range of events, but others may be directly triggered by the existing pain. The inflammatory response to surgical trauma or stress (33) activates the hypothalamus, causing it to release corticotropin-releasing hormone and arginine vasopressin, both of which stimulate anterior pituitary adrenocorticotropic hormone production, which in turn stimulates cortisol secretion by the adrenal cortex (19). Cortisol levels vary based on the severity or grade of surgery. The surgical interventions were categorized based on the modified Johns Hopkins surgical criteria, which delineate three levels of invasiveness: grade I, indicating minimally invasive procedures; grade II, indicating moderately invasive procedures; and grade III, indicating highly invasive procedures (34). When comparing grade 2 and grade 3 operations to grade 1, these differences may be identified, but they cannot be separated. Cortisol is a commonly utilized measurement for assessing stress levels and has demonstrated efficacy in evaluating intraoperative noxious stimuli. However, its sensitivity may be inadequate for capturing the variations that arise from repeated intraoperative noxious stimuli in a single animal (35). Cortisol levels seem to fluctuate with age, gender, disease, and the degree of surgical or anesthetic invasiveness. As a result, based on the research conducted so far, it is difficult to determine which is the primary cause of the alterations (36). Glucose is another biochemical parameter that surgery affects, and its clinical monitoring appears straightforward. Growth hormone (somatotrophin) levels increase in response to surgery and trauma; their release from the anterior pituitary is promoted by hypothalamic growth hormone-releasing factor (37, 38), which has an anti-insulin effect by inhibiting glucose uptake and utilization by cells. However, glucose utilization by cells is limited during surgery due to high cortisol levels (39). As a consequence, blood glucose levels rise. Furthermore, cortisol and catecholamines promote glucose production. In addition, a hyperglycemic response may result from a drop in insulin concentration during induction of anesthesia and during surgery, resulting in insulin secretion failure. Ultimately, the surgical invasion causes an increase in blood glucose content (40). Regardless of the causes of elevated glucose levels, the amount of rise in simple operations is negligible (19). Immunological mediators such as cytokines or interleukins (ILs) such as IL-1, IL-6, and tumor necrosis factor-alpha (TNF-α) mediate the rapid activation of the immune system following surgery. The presence of IL-6 depends on the extent of the surgical tissue damage (20). Despite the fact that the plasma level of IL-6 molecules with a short half-life increases within 30–60 min and becomes substantial after 2–4 h with quick returns to baseline, the maximum level may be attained 24 h after major operations, which may be prolonged 48–72 h postoperatively (19, 41). IL-6 stimulates the release of proteins, especially C-reactive protein (CRP), from the liver to commence the "acute phase response," which comprises a variety of changes (19, 42). Based on a comparable study design (42), the postoperative CRP concentration increased more slowly and reached its peak after 48 h. After that, it went down at a slower rate, with a mean half-life of 62 h compared to 15 h for IL-6 (43). This might make it a valuable and accurate marker for regular diagnostics of systemic inflammation in dogs (44, 45) and a predictor of surgical trauma severity (46).

Therefore, one of the most difficult things for surgeons to do is choose a technique that will cause the least amount of damage, cause the least amount of pain after the surgery, and take the least amount of time. These are a trio of the key challenges for surgeons. The development or modification of minimally invasive techniques has only been able to improve the first two of these aspects, but with significant limitations (47). The aim of this study is to compare a modified OHE procedure that only needs one person to do it with the standard procedure in terms of time, trauma, and pain after the surgery. This will help researchers come up with a way to reduce the length of surgery, the amount of trauma, and immediate postoperative pain.

2. Materials and methods

2.1. Animals and study design

This research was authorized by the Iranian biomedical research ethics committee [IR.IAU.BABOL.REC.1399.004 (48), IR.IAU.BABOL.REC.1399.015 (49) and IR.IAU.BABOL.REC.1399.093 (50)] and conducted at the Babol branch of Azad University.

In a randomized controlled trial, 18 healthy, large, deep-chested intact female mixed-breed dogs were included. Animals were divided into two equal groups randomly by coin flipping, using a sterile suture sachet (51–53) (NZD) after inducing anesthesia and draping the surgical area. The sample size was evaluated using the software GPower 3.1.9.7. The presence of 9 dogs in each group resulted in a power of 0.9 (Power = $1 - \beta = 0.9$) for TST with effect size $d > 1.50$ at a significance level of = 0.05.

Shelter dogs with ASA I (the American Society of Anesthesiologists) physical status enrolled in the study (54). The physical exam checked the patient's heart rate (HR), breathing rate (RR), and rectal temperature (RT). It also checked for internal and external parasites, did a complete blood count, and looked at the Hb, PCV, CRP, and glucose levels in the blood. The study was conducted on bitches in diestrus, based on vaginal smear cytology. Animals with a body condition score between 4 and 6 out of 9 were chosen. Animals under 1 year old, in estrus, pregnant, or lactating, with a weak or no response to painful stimuli (a needlestick in the lower abdomen), with a history of physical or behavioral issues, or with abnormal vaginal secretions were excluded.

Each dog scheduled for surgery on a particular day spent 3 days before and 3 days after the surgery in a separate cage with free access to food and water. Ten days after surgery, the sutures were removed.

2.2. Anesthesia

The animal's resting vital parameters (HR, RR, and RT) were recorded before anesthesia. Anesthesia and analgesia were provided by acepromazine (10 mg mL^{-1}, Neurotranq; Alfasan, Woerden, Holland), midazolam (5 mg mL^{-1}, Midazolam; Caspian, Rasht, Iran), pethidine (100 mg 2 mL^{-1}, Petholan; Adeka, İstanbul, Turkey), medetomidine (1,000 mcg mL^{-1}, Dorbene Vet; Syva, León, Spain) and ketamine (50 mg mL^{-1}, Ketamine HCl Inj.; Rotexmedica GmbH, Trittau, Germany), and ketorolac (30 mg mL^{-1}, Ketorolac; Alborz Darou, Tehran, Iran). A 19G catheter was placed aseptically in the cephalic vein for a given lactated Ringer's solution (250 mL, lactated Ringer's solution; Shahid Ghazi, Tabriz, Iran) at a rate of 5 mL kg^{-1} h^{-1}.

The animals were premedicated by acepromazine at 0.02 mg kg^{-1}, midazolam at 0.5 mg kg^{-1}, meperidine at 2 mg kg^{-1}, medetomidine at 20

TABLE 1 The measures carried out during the conventional (n = 9) and Instrument Shank-assisted ovariohysterectomy (n = 9).

Steps	Time (min)	Medicines/Dose/Application	Rout/Location/Area
Anesthesia, Premedication[1st]	0 (Start)	Acepromazine (10 mg mL^{-1}), 0.02 mg kg^{-1}	IM
		Midazolam (5 mg mL^{-1}), 0.5 mg kg^{-1}	
		Meperidine (50 mg mL^{-1}), 2 mg kg^{-1}	
Vital parameters monitor			
– Electrocardiograph	1–2 min after laying down	Lead II	On the elbows and knees
– Blood pressure		Neo #4	On the carpus over radial artery
– Pulse oximeter		Veterinary SPO2 transducer	On the ear until induction, then on the tongue
IV catheterization	10	19G	Cephalic vein
Preventive antibiotic		Cefazolin (1 g vial^{-1}), 22 mg kg^{-1}	IV
Fluid therapy		Lactated Ringer's solution, 5 mL kg^{-1} h^{-1}	IV
Hair clip		No 40	Mid-chest to mid-thigh
Anesthesia, Premedication[2nd]	15	Medetomidine (1,000 mcg mL^{-1}), 20 mcg kg^{-1}	IM
		Ketorolac (30 mg mL^{-1}), 1 mg kg^{-1}	SC
Aseptic preparation	17	Povidone Iodine scrub (7.5%) and 70° ethyl alcohol, three times consecutively; then Povidone Iodine solution (10%) was applied	
Anesthesia, Induction	20–25	Ketamine (50 mg mL^{-1}), 4 mg kg^{-1}	IV, Anesthetic mixture
		Midazolam (5 mg mL^{-1}), 0.27 mg kg^{-1}	
Endotracheal intubation	Immediately after induction	A maximum size based on the rough estimation using the $\sqrt{}$ (Body weight×5)	Intraoral, mid-trachea
Anesthesia, Maintenance	As needed	Induction anesthetic mixture, 0.2–0.5 mg kg^{-1} based on the ketamine	IV, Anesthetic mixture
Intraoperative rescue analgesia	As needed	Ketamine, 0.5 mg kg^{-1}	during surgery based on HR and RR and surgical manipulation
End of surgery (the last skin suture)			
– Conventional – Instrument Shank-assisted	67–72 55–60		
Postoperative antibiotic	Every 8 h	Cefazolin (1 g vial^{-1}), 22 mg kg^{-1}	IM, for 3 days
Postoperative rescue analgesia	Every day	Ketoprofen, 2 mg kg^{-1}	IM, as needed, at cefazolin injection time evaluation as needed

IM, intramuscular; IV, intravenous; SC, subcutaneous; HR, heart rate; RR, respiratory rate.
1st: administration of the first part of pre-anesthetic drugs, which included Acepromazine, Midazolam, and Meperidine; 2nd: Administration of the second part of pre-anesthetic drugs which included Medetomidine and Ketorolac.

mcg kg^{-1}, and ketamine at 4 mg kg^{-1} IM. They received ketorolac at 1 mg kg^{-1} immediately before surgical asepsis. The maintenance of anesthesia was achieved by administering a consistent anesthetic mixture (ketamine at 4 mg kg^{-1} and midazolam at 0.27 mg kg^{-1}) at a variable rate of 0.2–0.5 mg kg^{-1}, depending on the ketamine levels present in the mixture. The administration of the anesthetic was monitored through the use of several parameters, including SpO2, ECG, non-invasive blood pressure measured through a blood pressure cuff (size #4) placed proximal to the carpus over the radial artery at five-minute intervals, and respiration. The surgical procedure and manipulation were also taken into account during the administration of anesthesia. The Pm-7000vet, manufactured by Wuhan Zoncare Bio-medical Electronics Co., Ltd., was used to monitor animals. The animals' cardiorespiratory parameters were monitored until they demonstrated full recovery.

A nociceptive response was defined as a 20% or more rise in heart rate over the base rate, accompanied with an increase in breathing frequency and blood pressure proportionate to a painful surgical procedure (20, 55, 56). Ketamine at 0.5 mg kg^{-1} was used for rescue analgesia during surgery. The timeline details of measures were provided in Table 1.

2.3. Surgery

2.3.1. The surgeon and surgical team

Two months after graduation, a female doctor of veterinary medicine (DVM) with minimum experience (according to the veterinary training course) in the conventional approach and no

expertise with the new methodology has been selected as the surgeon (NNM). The selected surgeon and surgical team underwent a one-week training course for each surgery 10 days prior to the start of the study. During the training course, one surgery was done on each technique by the advisor, and then the techniques were randomly performed on 12 dogs (6 dogs each technique) by the surgeon conducting the study. The random approach has been a coin toss (51–53); thus, the first-day method was determined by tossing a coin, and the next day the opposite technique must be followed. The study surgeries were performed by the same team under the supervision of the dissertation adviser (NZD).

2.3.2. Aseptic surgical preparation

In dorsal recumbency, the ventral abdomen was aseptically prepped after hair removal from mid-chest to the end of the pelvic symphysis and the inner thigh. During pre-surgical aseptic preparation, the skin was alternately scrubbed three times with 7.5% povidone-iodine and 70% ethyl alcohol. After the final povidone-iodine scrub is complete, a 10% povidone-iodine solution is applied to the surgical field (1).

2.3.3. Approach and incision length

A ventral midline celiotomy was performed immediately caudal to the umbilicus and extending one-third of the way to the pubic rim (11) for both methods, in order to achieve the same incision length (57, 58).

2.3.4. Surgical methods

2.3.4.1. Conventional (triple hemostatic) OHE

In the control group, the triple-clamp OHE (1) was done after entrance into the abdominal cavity and control of the uterine horn without a spay hook. During this method, the surgeon's dominant index finger is used to grab the left horn of the uterus. For organ manipulation, rat-toothed Crile forceps secured to the proper ligament were utilized. The suspensory ligament was strummed and released manually in the caudomedial direction. After creating a mesovarium window, two simple ligatures were placed on top of one another in the first clamp crush near the kidney. One transfixation ligature was then tightened in lieu of the middle clamp near the ovary [Polydioxanone (PDS II), 2–0]. The pedicle was transected and inspected for hemorrhage. The same techniques were then conducted on the contralateral pedicle. Separately, the cervix and uterine arteries were ligated (PDS II 2–0). Linea alba (PDS II 0), subcutaneous tissue (PDS II 2–0), and skin (monofilament Polyamide 0) were routinely closed. A stent bandage was then placed over the suture line.

2.3.4.2. Modified instrument shank-assisted OHE

After accessing the visceral organs, first the left uterine horn and ovary were seized. A hemostat forceps was placed on the proper ligament to manipulate the ovary and its pedicle (Figure 1A). Then a window was created in the broad ligament (Figure 1B), and one of the handles of a Mayo-Hegar needle holder was passed through this window (Figure 1C), then secured (Figure 1D). After securing the ratchets, the needle holder was positioned over the surgical incision on the abdomen (Figure 1D). While pulling the first hemostat (on the proper ligament), the second hemostat was put on the ovarian pedicle, as far away from the ovary as possible (between the ovary and the needle holder's locked handles) (Figure 1E). While doing this, with the second hemostat, the needle holder shanks were pushed along the suspensory ligament toward the viscera to attain the appropriate distance. After securing the second hemostat, it was placed crosswise on the needle holder's shanks so that it would not be dragged into the abdominal cavity and would stay visible to the surgeon outside the abdomen at all times (Figure 1F). The third and fourth hemostats were then inserted between the ovary and the second forceps (Figure 1F). These forceps have crushed the tissues in preparation for the installation of the ligature. After crushing the pedicle, the forceps were removed, and circumferential and transfixation ligatures were applied to the pedicle in the formed groove. The ovarian pedicle was sharply transected using a scalpel immediately after the transfixation ligature, while it was protected by a hemostat. Throughout the application of these steps, the second forceps remained firmly on the ovarian pedicle, preventing it from being dragged within. The needle holder was put down after being released (Figure 1G). After gently grasping the corner of the ovarian pedicle with tissue forceps, the second forceps was released. The ovarian pedicle was inspected for hemorrhage and then released. The procedures were repeated for the contralateral ovary. The remainder of the procedure up to the final skin gap suture was routinely performed (same as the triple hemostatic method).

2.3.5. Surgical time intervals

All surgeries were video captured, and the time intervals between each step were retrieved. The initiation of the incision and the final abdominal closure suture were considered the beginning and finish of the surgical procedure, respectively. These are the defined time intervals:

Total surgery time (TST): From the initial skin incision to the last skin suture of an abdominal incision.

Pedicle intervention time (PIT): From placing a hemostat on the proper ligament of the left ovary through cutting the right pedicle following the installation of its ligature; incorporating SRT, ShT, ClpT, and LigT for the left and right pedicles.

Suspensory release time (SRT): Digital strumming of the suspensory ligament.

Shanking time (ShT): From the end of windowing (the process of creating a window in the broad ligament) until the start of anchoring clamp placement. An *anchoring clamp* is a hemostatic clamp placed on the ovarian pedicle as far away from the ovary as possible to prevent dragging into the abdominal cavity.

Clamping time (ClpT): From the placement of the anchoring clamp to the completion of the last ligating clamp, near the ovary. The *ligating clamp* is a hemostatic forceps that is used to crush the ovarian pedicle and create a groove for the installation of the ligature. After the anchoring clamp, these forceps are secured to the pedicle on the ovary side.

Ligating time (LigT): From the beginning of the first simple ligature until the finish of the trans-fixing ligature of both pedicles.

Other surgical procedures time (OSPT): All surgical procedures, except PIT and CT.

Closure time (CT): Closure time starts from the linea alba to the last skin suture tying.

2.4. Pain assessments

There are many different kinds of subjective scoring systems, and some of them have been used in veterinary medicine (59). In

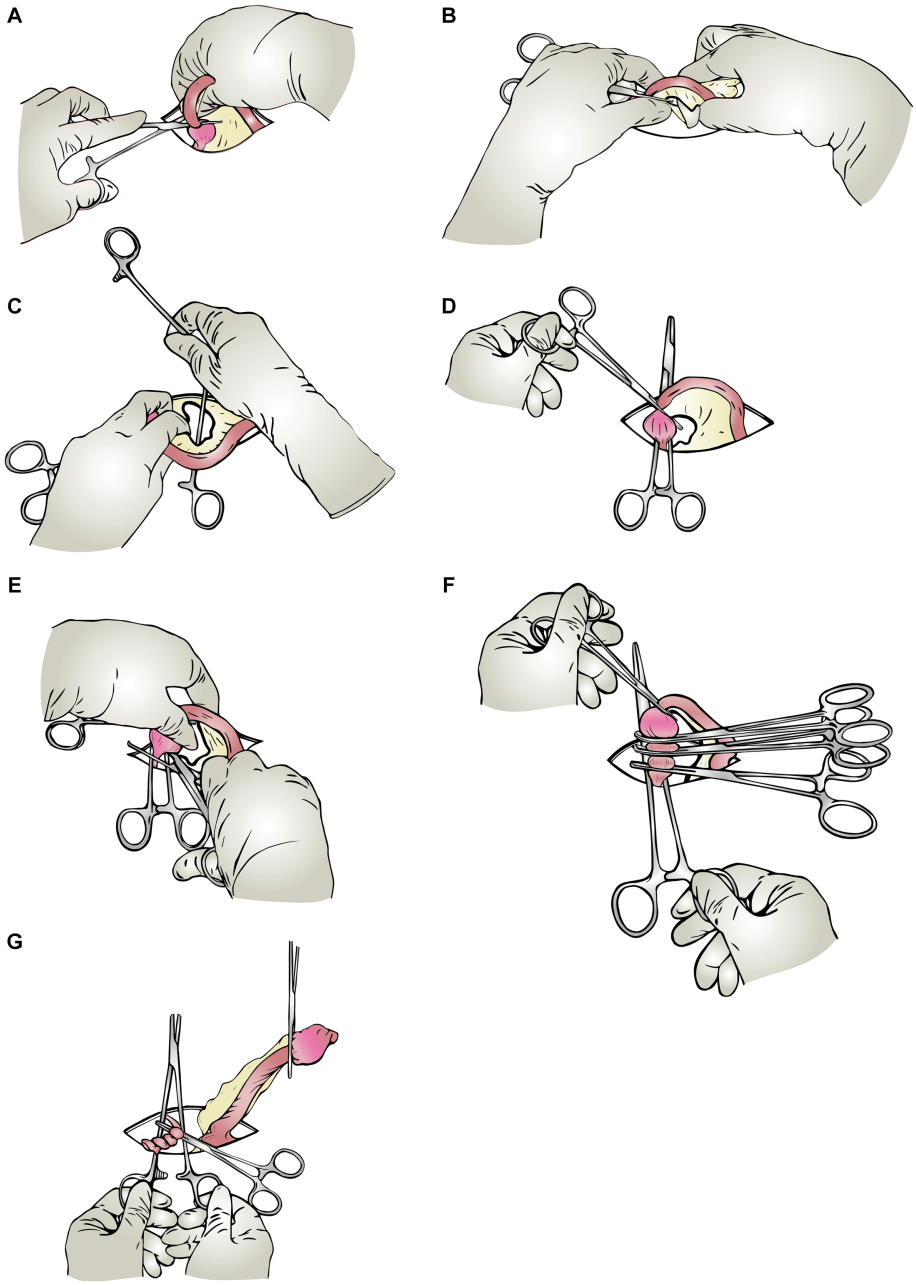

FIGURE 1
Schematic steps of the modified Instrument shank-assisted ovariohysterectomy. Most steps in this method are similar to the triple-clamp technique. Wherein the pedicle is retained outside the abdomen by a straight Ochsner hemostat placed on the shanks of a needle-holder crossly. **(A)** Proper ligament clamping: After identifying the uterine horn, the rat-toothed Crile forceps are placed on the proper ligament to manipulate the ovary and its pedicle. **(B)** Windowing: A window is created in the mesovarium with an index finger. **(C)** Shanking (needle holder's shank insertion): The needle holder's shank is passed through the created window in the previous step, and the ratchets are locked, so the ovarian pedicle locates between the shanks. **(D)** Shank-IN: The shanks are oriented crossly to the incision on the abdomen. **(E)** Applying the "Anchoring clamp" (The ovarian pedicle's 1st clamp): Holding the proper ligament forceps with one hand, push the anchoring clamp (first clamp), which is on the needle holder's shank, toward the viscera, and lock it on a suitable level of the ovarian pedicle. **(F)** Triple hemostatic: The "ligating clamps" were secured between the Anchoring clamp and the ovary out of the abdominal cavity to crush the tissue for ligature placement. **(G)** Ligation and shank-OUT: Apply two simple ligatures and one transfixing ligature close to the ovary in the crushed groove created in the previous step.

this study, postoperative pain was measured using the Glasgow composite pain scale short form (GCMPS-SF) (60), the University of Melbourne pain scale (UMPS) (61), and visual analogue scales (VAS) (62). A trained, male examiner (AB) who was single-blinded measured the post-surgical pain (30, 31). He became acquainted with the dogs the day before surgery. Moreover, the similar abdominal closure and the bandage have prevented the procedure from being identified. Multidimensional pain assessments were carried out 1 h before surgery (0) and 6-, 24-, 48-, and 72-h following skin suturing.

2.5. CRP

Five milliliters of blood were drawn from the lateral saphenous vein after the same pain evaluation times. The samples were kept at the temperature of the operation room for 20–25 min before being transported to the laboratory. The serum separated by centrifuging at 3,000 rpm for 15 min was stored in a microtube at −20°C until the research ended. CRP levels (mg L^{-1}) were determined using the CRP latex agglutination technique using the CRP-LIA kit, Bionik in the laboratory of the faculty (4, 33).

2.6. Postoperative medications

Antimicrobial therapy (63) was started intravenously (IV) during premedication and maintained intramuscularly (IM) every 8 h for 3 days following surgery at 22 mg kg^{-1} of cefazolin (Exir, Tehran, Iran) in both groups. Ketoprofen (Ketomax; Rooyandarou, Tehran, Iran) at 2 mg kg^{-1} IM was given to animals having a GCMPS-SF score of 6 or higher out of 24 (45); throughout the examination, the UMPS and VAS ratings were also examined as supplementary criteria for determining a ketoprofen prescription.

2.7. Statistical analysis

The SPSS program (IBM SPSS Statistics for Windows, version 26, IBM Corp., Armonk, NY, United States) was used to look at the data. Along with normality confirmation using the Shapiro–Wilk test (except LigT), the study recruited the suspicious non-normal parametric data (PID, SRT, ShT, ClpT, LigT, and OSPT) after normalization based on the concordance of skewness and kurtosis coupled with stem-and-leaf plots. The duration of surgical steps was analyzed using a *T*-test. The Pearson correlation coefficient was used to determine the relationship between PIT and TST.

The Friedman test analyzes the progression of pain changes. Using Related-Samples Friedman's Two-Way ANOVA by Ranks, we compared pain levels between evaluating time intervals throughout each surgical process. Using Kruskal-Wallis H tests on mean, a comparison of pain levels at assessing time intervals between two surgical techniques has been conducted. On the median, Independent-Samples Kruskal-Wallis H followed by Independent-Samples Fisher Exact Sig. (2-sided test, for samples less than 10) has been implemented on the information obtained from three behavioral pain assessment methods.

Variations in CRP were evaluated using repeated measures ANOVA, independent samples t-test, and general linear model-univariate tests.

The correlation between CRP and age, weight, HR, RR, and RT was shown using Pearson's correlation coefficient. The partial eta squared was used to figure out how CRP and the body condition score (BCS) are related. Spearman's rho correlation coefficient was used to determine the relation between surgical time intervals and pain (based on GCMPS-SF). The statistical significance level was set at $p < 0.05$.

2.7.1. Data availability statement

All relevant data is contained within the article: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

3. Results

3.1. Participants' signalment and vital sign

There were no significant differences in the distribution of dogs by weight ($p = 0.726$) or age ($p = 0.598$) between the two groups. The mean and SD of age, weight, vital parameters (HR, RR, and RT), and BCS are shown in Table 2.

3.2. Surgical time analysis

Instrument shank-assisted OHE displayed shorter TSTs than the conventional method (34.70 ± 6.7 and 47.40 ± 9.9 min respectively, $p = 0.005$). Table 3 provides a comparison of the methods' time intervals. According to the new method, SRT is identical to ShT. ShT required 74% less time than SRT ($p = 0.009$), and moreover, LigT improved by 37% ($p = 0.005$) with the novel approach. Additionally, the OSPT and CT got 26 and 29% shorter, respectively.

Figure 2 shows how time intervals have changed, and Table 3 gives a statistical analysis of the changes. In each compartment of this figure, the difference favors the Instrument shank-assisted method.

According to the comparable correlation pattern (64) between TST and PIT based on $\rho = 0.952$, $p = 0.0001$ and $\rho = 0.862$, $p = 0.003$ for conventional and instrument shank-assisted OHE, respectively, PIT plays a crucial role in TST during ovariohysterectomy. The correlation analysis of TST and ShT revealed that, from a temporal perspective, ShT alone did not significantly reduce TST ($\rho = 0.097$, $p = 0.804$).

During the conventional OHE, a single intraoperative hemorrhage in the ovarian pedicle was managed. The dog was excluded from the study. None of the dogs in either group had problems after surgery.

3.3. Pain

Using the Friedman test, pain score changes (Δ Pain in GCMPS-SF, UMPS, and VAS; Table 3) were statistically significant in both groups. The majority of the time, the data showed that the new method was associated with much less pain (Table 4 and Figures 3–5).

TABLE 2 Mean ± SD of age, weight, BCS, and preoperative vital parameters before anesthesia for the conventional ($n = 9$) and Instrument Shank-assisted ovariohysterectomy ($n = 9$).

Parameters	Conventional	Shank-assisted	*p*-value
Age	3.0 ± 1.9	2.6 ± 1.0	0.821
Weight	22.6 ± 4.3	21.8 ± 4.5	0.798
RT	38.7 ± 0.6	38.7 ± 0.3	0.877
HR	103.2 ± 25.0	106.0 ± 34.1	0.948
RR	29.3 ± 9.4	25.6 ± 5.0	0.622
BCS	4.7 ± 0.9	4.6 ± 0.9	0.422

BCS, body condition scoring; RT, rectal temperature; HR, heart rate; RR, respiratory rate. The significance level was set at 0.05.

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TABLE 3 Mean ± SD of different surgical steps time intervals recorded in the conventional ($n = 9$) and Instrument Shank-assisted ovariohysterectomy ($n = 9$) and correlation of surgical time intervals with total surgery time in deep-chested dogs.

Data	Units	Conventional	Shank-assisted	*p*-value
Time intervals				
TST	min	47.40 ± 9.9	34.70 ± 6.7	0.005
PIT	min	20.96 ± 5.78	14.52 ± 3.73	0.014
SRT	s	78.97 ± 69.10		}0.035
ShT	s		20.39 ± 8.18	
ClpT	s	50.66 ± 45.04	63.55 ± 37.15	0.662
LigT	min	12.82 ± 3.37	8.02 ± 3.11	0.005
OSPT	min	31.00 ± 7.0	23.00 ± 4.8	0.013
CT	min	16.40 ± 4.5	11.60 ± 2.5	0.013

Correlation*				
	ρ	*p*-value	ρ	*p*-value
TST vs. PIT	0.952****	0.000	0.862***	0.003
SRT	0.494	0.176		
ShT			0.097	0.804
ClpT	0.683**	0.043	0.754***	0.019
LigT	0.836***	0.010	0.618	0.076
TST vs. CT	0.768***	0.016	0.818***	0.007

TST, total surgery time; PIT, pedicle intervention time; SRT, suspensory release time; ShT, shanking time; ClpT, clamping time; LigT, ligating time; OSPT, other surgical procedures time; CT, closure time. *Pearson correlation stratification (very strong, strong, moderate, weak, and negligible): ****very strong, ***strong, **moderate. The significance level was set at 0.05.

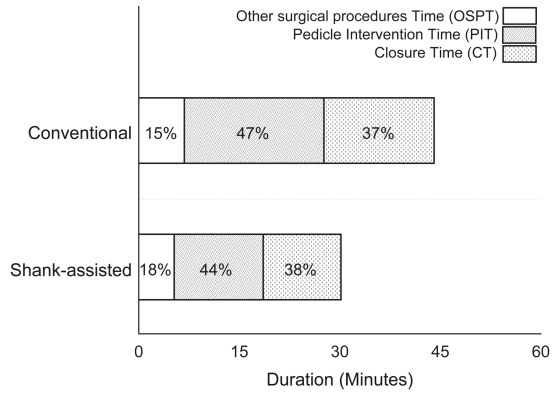

FIGURE 2
Comparison of the time spent performing different steps in the conventional method ($n = 9$) and new modified Instrument shank-assisted method of ovariohysterectomy ($n = 9$) in deep chested-dogs. OSPT, Other surgical procedures time, which consist of all surgical steps, except PIT and CT; PIT, Pedicle intervention time, which is from placing a hemostat on the proper ligament of the left ovary to cutting the right pedicle after placement of its ligatures; CT, Closure time, from the linea alba to the last skin suture tying.

3.3.1. Rescue analgesia

After the surgery, 36 pain assessments have been done in each group, ranging from T6 to T72. These pain assessments have been carried out at 6-, 24-, 48-, and 72-h following surgery on nine animals in each group. The animals were injected with rescue analgesics 13 times (T6: 6, T24: 3, T48: 3, and T72: 1 dog) in the conventional group and twice (T24: 1 and T72: 1, both for one dog) in the novel group. Using the conventional methods, 8 dogs were injected with rescue analgesic, whereas just 1 dog received it using the alternative method.

3.4. CRP

After 24 h, the highest serum CRP levels were observed in both groups. Figure 6 demonstrates that the conventional group's rate of rise accelerated more rapidly during the initial 6 h following surgery. The slope of the graph is determined to be $y = 24.328x - 18.072$ for traditional OHE and $y = 4.9556x - 1.5667$ for instrument shank-assisted OHE within the first 6 h. The traditional group observed a 4.9-fold increase in CRP acceleration on this basis. After 48 h, the Instrument shank-assisted OHE showed a significant decrease to baseline levels ($p = 0.032$; see Tables 5, 6). In contrast, although CRP levels decreased in the conventional group, they were not significantly different from their peak levels.

3.5. Correlations

The relationship between pain (as measured by GCMPS-SF, UMPS, and VAS), surgical time parameters, CRP, vital signs, age, weight, and BCS has been studied.

3.5.1. Surgical time intervals with pain

Spearman's rho correlation coefficient has studied the relationship between the overall surgical duration and the duration of the distinct phases. The analysis is described in full in Table 6, which is stated separately below.

Only pain in the conventional OHE exhibits a significant positive correlation with LigT at T72, according to GCMPS-SF.

Using the novel method, UMPS found significant negative relationships between pain and TST at T24 and T48. This study indicated that PIT has a vital function in lowering pain in T24.

The VAS has found a greater correlation between specific surgical stages and pain. GCMPS-SF, UMPS, and VAS were able to identify 1, 3, and 7 correlations, respectively, in this regard. In the new method, VAS identified an association between ClpT and less pain at T6 and T24, and between ClpT and OSPT at T48. This assessment method revealed that PIT, LigT, and most notably OSPT have a substantial effect on the incidence of pain on the third day following surgery in the conventional group (see Table 6).

3.5.2. CRP with pain

Using Spearman's rho correlation coefficient, CRP levels and pain were only shown to have significant moderate-to-strong negative relationships in five measurement points of total samples (two groups in total). These associations were detected at T24 (UMPS) and T72 (GCMPS-SF) in the conventional group and at T6 (VAS) and T48

TABLE 4 Median (Min–Max) of pain scores and Δ Pain$^{0-72}$ based on Glasgow composite pain scale short-form (GCMPS-SF), university of Melbourne pain scale (UMPS), and visual analogue scales (VAS) scales in the conventional ($n = 9$) and Instrument Shank-assisted ovariohysterectomy ($n = 9$) in deep-chested dogs.

			T0	T6	T24	T48	T72	p-value† (Δ Pain$^{0-72}$)
GCMPS-SF								
		Conventional	0 (0–0) (9)	**6 (2–14) (9)**	5 (3–10) (8)	**5 (2–8) (9)**	3 (1–12) (6)	0.002
		Shank-assisted	0 (0–0) (9)	**3 (2–5) (9)**	2 (0–6) (9)	**2 (0–4) (9)**	1 (0–7) (9)	0.000
p-value	Mean	K-W*	1.000	0.012	0.037	0.006	0.167	
	Median	K-W**		0.004	0.486	0.004	0.264	
		Fisher#		**0.015**	0.637	**0.015**	0.329	
UMPS								
		Conventional	0 (0–0) (9)	5 (2–8) (9)	**5 (3–10) (8)**	**5 (0–7) (9)**	3 (1–10) (6)	0.003
		Shank-assisted	0 (0–0) (9)	4 (1–6) (9)	**2 (1–4) (9)**	**1 (0–4) (9)**	2 (0–5) (9)	0.000
p-value	Mean	K-W*	1.000	0.099	0.002	0.018	1.000	
	Median	K-W**		0.058	0.002	0.016	0.264	
		Fisher		0.153	**0.003**	**0.050**	0.329	
VAS								
		Conventional	0 (0–0) (9)	**3 (1–5) (9)**	3 (1–6) (9)	2 (0–3) (9)	1 (0–6) (6)	0.002
		Shank-assisted	0 (0–0) (9)	**1 (1–2) (9)**	1 (0–4) (9)	1 (0–2) (9)	0 (0–5) (9)	0.001
p-value	Mean	K-W*	1.000	0.003	0.074	0.024	1.000	
	Median	K-W**		0.001	0.147	0.018	1.000	
		Fisher		**0.002**	0.335	0.057	1.000	

T0, before surgery; T6, 6 h after surgery; T24, 24 h after surgery; T48, 48 h after surgery; T72, 72 h after surgery; eGCMPS-SF, the short form of the Glasgow composite measure pain scale; UMPS, university of Melbourne pain scale; VAS, visual analogue scale. The bolded items show a statistically significant difference in a pain score between the two surgical procedures in each evaluating time intervals using the Kruskal-Wallis H analysis; Lowercase letters indicate statistical comparison of pain recorded at different assessment times in the same group using Related-Samples Friedman's Two-Way ANOVA by Ranks. †Friedman Test. *Independent-Samples Kruskal-Wallis H on mean. **Independent-Samples Kruskal-Wallis H on median. #Independent-Samples Fisher Exact Sig. (2-sided test) on Median (for samples less than 10). The significance level was set at 0.05.

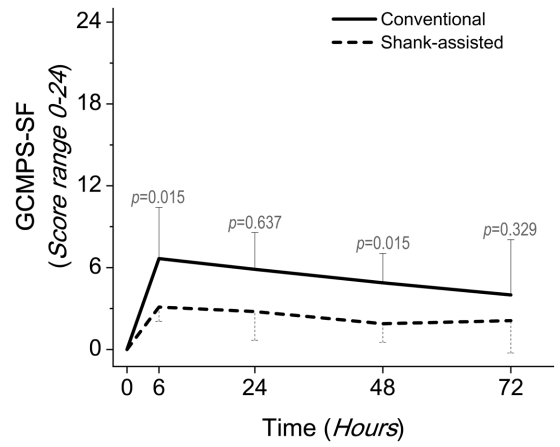

FIGURE 3
Comparing postoperative pain scores using the Glasgow composite pain scale short-form (GCMPS-SF) in the conventional method ($n = 9$) and new modified Instrument shank-assisted method ($n = 9$) of ovariohysterectomy in deep chested-dogs. The p-value was calculated using an Independent-Samples Kruskal-Wallis H on median followed by Independent-Samples Fisher Exact Sig. (2-sided test) on Median shows the statistical difference in sampling times between two groups.

(GCMPS-SF and VAS) in the instrument shank-assisted group, as shown in Table 7.

3.5.3. CRP with age, weight, vital signs, and BCS

Pearson's correlation coefficient indicated that there was no association between CRP changes and age, weight, HR, RR, and RT in both groups ($p > 0.05$). Partial eta squared (η P 2) was unable to identify a significant association between CRP and BCS using any of the two techniques.

4. Discussion

According to the present results, when implementing OHE with instrumental shank assisted technique, the surgery can be performed by one person with lesser surgical trauma. With the current solutions, digital strumming or sharp tearing of the suspensory ligament in deep-chested dogs has not only been a time-consuming process, but it has also failed to shorten the length of surgery and pain afterward (11). According to current research, a decrease of over 12 min in an alumnus surgeon's overall surgery length is a positive improvement (57). The reduction in surgical trauma has resulted in a slower increase in CRP levels and a shorter peak. These gains were made using the

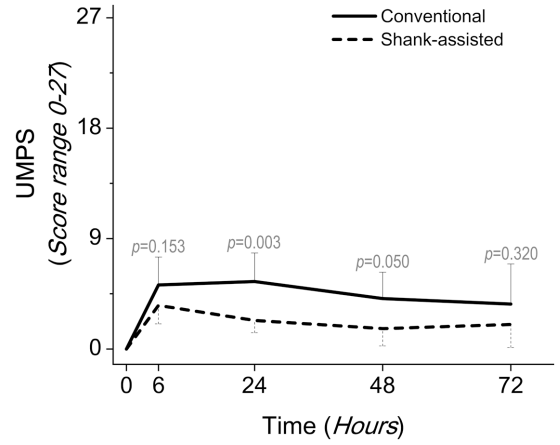

FIGURE 4
Comparing postoperative pain scores using the university of Melbourne pain scale (UMPS) in the conventional method ($n = 9$) and new modified Instrument shank-assisted method ($n = 9$) of ovariohysterectomy in deep chested-dogs. The p-value was calculated using an Independent-Samples Kruskal-Wallis H on median followed by Independent-Samples Fisher Exact Sig. (2-sided test) on Median shows the statistical difference in sampling times between two groups.

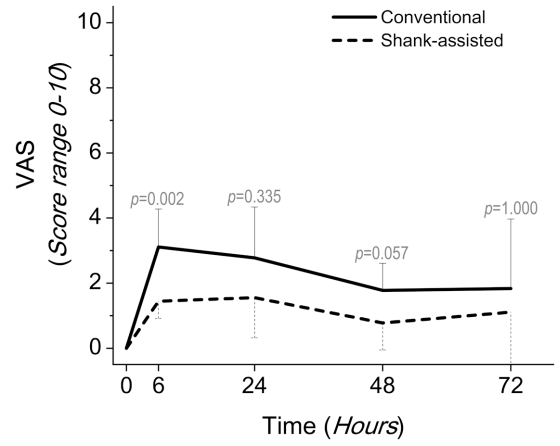

FIGURE 5
Comparing postoperative pain scores using the visual analogue scales (VAS) in the conventional method ($n = 9$) and new modified Instrument shank-assisted method ($n = 9$) of ovariohysterectomy in deep chested-dogs. The p-value was calculated using an Independent-Samples Kruskal-Wallis H on median followed by Independent-Samples Fisher Exact Sig. (2-sided test) on Median shows the statistical difference in sampling times between two groups.

same equipment and facilities at no additional expense due to a modest modification in the surgical approach.

4.1. Surgical perspectives

OHE, like many other surgical procedures, seems to get more challenging as the size and weight of the animal increase. As body mass increases, the chest sinks deeper, and it becomes more difficult

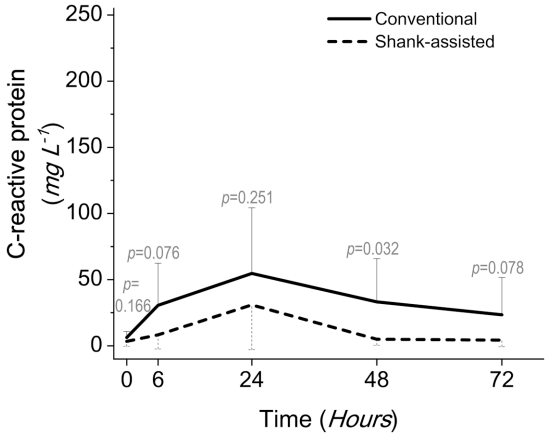

FIGURE 6
Comparing postoperative serum C-reactive protein levels following the conventional method ($n = 9$) and new modified Instrument shank-assisted method ($n = 9$) of ovariohysterectomy in deep chested-dogs. The p-value was calculated using an independent samples T-test shows the statistical difference in sampling times between two groups.

TABLE 5 Mean ± SD of the serum CRP concentration (mg L^{-1}) following the conventional ($n = 9$) and Instrument Shank-assisted ovariohysterectomy ($n = 9$) in deep-chested dogs.

Sampling time	Groups		p-value
	Conventional	Instrument shank-assisted	
T 0	6.3 ± 4.6^{b}	3.4 ± 3.8^{b}	0.166
T 6	30.6 ± 31.9^{ab}	8.3 ± 10.7^{b}	0.076
T 24	54.7 ± 49.6^{a}	30.9 ± 33.7^{a}	0.251
T 48	33.2 ± 32.7^{ab}	5.0 ± 4.4^{b}	**0.032**
T 72	23.4 ± 28.2^{ab}	4.4 ± 5.0^{b}	0.078

Small letters indicate statistical comparisons in a group between different sampling times. The p-value shows the comparison of two groups at each sampling time. T 0, before surgery; T 6, 6 h after surgery; T 24, 24 h after surgery; T 48, 48 h after surgery; T 72, 72 h after surgery. The significance level was set at 0.05. p, p-value, the bolded text shows a significant correlation.

to reach and release the suspensory ligament (11). In the present study, the same higher body weight range enhanced the ovarian exposure challenge, allowing the method to be generalized to various sizes of dogs and cats; however, it may be accompanied by fewer problems in smaller animals.

Insufficient exposure during OHE leads to incorrect technique execution and raises the risk of ovarian remnant syndrome (2). The instrument shank-assisted OHE keeps the ovary outside of the abdomen without an assistant while maintaining the suspensory ligament. In obese and deep-chested dogs, as well as for unskilled surgeons who require a longer incision, the surgical assistant is essential (1, 2). So, a small incision without tearing the ligament is another achievement of the modified method, which led to limited surgical complications including incisional swelling, seroma, infection, delayed healing, ventral body wall dehiscence, self-inflicted trauma, pain (65), and hemorrhaging (66).

During a suspensory ligament release (66), an inexperienced surgeon is more likely to break the blood vessel and induce

TABLE 6 The correlation of surgical time intervals with post-surgical pain, which was evaluated using GCMPS-SF, UMPS, and VAS behavioral pain scales, after the conventional ($n = 9$) and Instrument Shank-assisted ovariohysterectomy ($n = 9$) in deep-chested mixed-breed dogs.

Pain scales	Surgical time intervals	Methods															
		Conventional								Instrument shank-assisted							
		Pain 6		Pain 24		Pain 48		Pain 72		Pain 6		Pain 24		Pain 48		Pain 72	
		ρ	*p*	ρ	*p*	ρ	*p*	ρ	*p*	ρ	*p*	ρ	*p*	ρ	*p*	ρ	*p*
GCMPS-SF	TST	0.254	0.509	0.268	0.520	0.246	0.524	0.754	0.084	0.039	0.920	−0.343	0.366	−0.489	0.181	−0.309	0.418
	PIT	0.085	0.828	0.024	0.954	0.246	0.524	0.638	0.173	−0.208	0.591	−0.270	0.482	−0.282	0.462	−0.162	0.676
	SRT/ShT	0.356	0.347	0.098	0.818	0.042	0.914	0.116	0.827	0.321	0.400	0.405	0.279	0.068	0.861	0.359	0.343
	ClpT	−0.254	0.509	−0.073	0.863	0.314	0.411	0.493	0.321	−0.009	0.982	−0.555	0.121	−0.622	0.073	−0.373	0.322
	LigT	−0.034	0.931	0.073	0.863	0.610	0.081	0.899*	**0.015**	−0.303	0.428	−0.523	0.148	−0.316	0.407	−0.368	0.330
	CT	0.237	0.539	0.464	0.247	0.398	0.288	0.725	0.103	0.390	0.300	−0.093	0.812	−0.385	0.307	−0.111	0.776
	OSPT	0.254	0.509	0.293	0.482	0.271	0.480	0.754	0.084	−0.091	0.815	−0.449	0.225	−0.541	0.133	−0.352	0.353
UMPS	TST	0.118	0.762	0.393	0.336	0.220	0.569	0.348	0.499	−0.521	0.150	−0.705*	**0.034**	−0.670*	**0.048**	−0.336	0.376
	PIT	−0.068	0.863	0.417	0.304	0.458	0.215	0.522	0.288	−0.434	0.243	−0.685*	**0.042**	−0.385	0.307	−0.180	0.642
	SRT/ShT	0.135	0.729	0.528	0.179	0.441	0.235	0.319	0.538	−0.230	0.552	0.035	0.929	0.034	0.930	0.395	0.293
	ClpT	−0.051	0.897	0.246	0.558	0.186	0.631	0.319	0.538	−0.427	0.251	−0.557	0.119	−0.588	0.096	−0.220	0.570
	LigT	0.152	0.696	0.442	0.273	0.576	0.104	0.696	0.125	−0.085	0.828	−0.416	0.266	−0.299	0.434	−0.335	0.378
	CT	0.397	0.291	0.466	0.244	0.203	0.600	0.377	0.461	−0.655	0.055	−0.503	0.168	−0.590	0.094	−0.129	0.741
	OSPT	−0.034	0.931	0.405	0.319	0.407	0.277	0.638	0.173	−0.402	0.284	−0.613	0.079	−0.644	0.061	−0.323	0.396
VAS	TST	0.254	0.510	0.368	0.330	−0.059	0.879	0.638	0.173	−0.522	0.150	−0.422	0.258	−0.622	0.074	−0.193	0.618
	PIT	−0.009	0.982	0.368	0.330	0.218	0.573	0.880*	**0.021**	−0.433	0.244	−0.329	0.388	−0.472	0.199	−0.110	0.778
	SRT/ShT	0.289	0.451	0.564	0.113	0.564	0.113	0.698	0.123	−0.173	0.656	0.310	0.416	−0.027	0.946	0.578	0.103
	ClpT	0.149	0.703	0.197	0.612	0.149	0.703	0.395	0.439	−0.696*	**0.037**	−0.688*	**0.041**	−0.751*	**0.020**	−0.484	0.187
	LigT	0.035	0.929	0.291	0.448	0.287	0.454	0.820*	**0.046**	−0.346	0.361	−0.566	0.112	−0.330	0.386	−0.523	0.149
	CT	0.455	0.219	0.197	0.612	0.010	0.980	0.577	0.231	−0.520	0.152	−0.402	0.284	−0.508	0.163	0.000	1.000
	OSPT	0.009	0.982	0.616	0.078	0.149	0.703	0.941**	**0.005**	−0.435	0.242	−0.394	0.294	−0.720*	**0.029**	−0.304	0.426

ρ, Spearman's rho correlation coefficient; *p*, *p*-value, the bolded text shows a significant correlation; Pain 6, pain assessment 6 h after surgery; Pain 24, pain assessment 24 h after surgery; Pain 48, pain assessment 48 h after surgery; Pain 72, pain assessment 72 h after surgery; GCMPS-SF, the short form of the Glasgow composite measure pain scale; UMPS, university of Melbourne pain scale; VAS, visual analogue scale; TST, total surgery time; PIT, pedicle intervention time; SRT, suspensory release time; ShT, shanking time; ClpT, clamping time; LigT, ligating time; OSPT, other surgical procedures time; CT, closure time. *Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

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TABLE 7 The correlation of serum c-reactive protein levels with post-surgical pain, which was evaluated using GCMPS-SF, UMPS, and VAS behavioral pain scales, after the conventional (n = 9) and Instrument Shank-assisted ovariohysterectomy (n = 9) in deep-chested mixed-breed dogs.

Pain scales	CRP sampling times	Methods															
		Conventional								Instrument shank-assisted							
		Pain 6		Pain 24		Pain 48		Pain 72		Pain 6		Pain 24		Pain 48		Pain 72	
		ρ	*p*	ρ	*p*	ρ	*p*	ρ	*p*	ρ	*p*	ρ	*p*	ρ	*p*	ρ	*p*
GCMPS-SF	CRP 6	0.593	0.092	0.475	0.197	0.458	0.215	0.407	0.277	−0.182	0.639	−0.459	0.214	−0.130	0.739	−0.303	0.428
	CRP 24	−0.049	0.909	0.146	0.729	−0.195	0.643	−0.122	0.774	−0.498	0.173	−0.034	0.931	0.143	0.713	0.143	0.713
	CRP 48	−0.576	0.104	−0.280	0.466	−0.509	0.162	−0.492	0.179	−0.718*	**0.029**	−0.085	0.827	−0.051	0.896	0.043	0.913
	CRP 72	−0.551	0.257	−0.493	0.321	−0.638	0.173	−0.812*	**0.050**	−0.462	0.211	0.000	1.000	0.188	0.628	0.248	0.520
UMPS	CRP 6	0.245	0.526	0.304	0.427	0.321	0.400	0.152	0.696	−0.511	0.160	−0.034	0.931	−0.085	0.828	−0.111	0.777
	CRP 24	−0.626	0.097	−0.356	0.387	−0.638	0.089	−0.724*	**0.042**	−0.373	0.323	0.121	0.756	−0.243	0.529	−0.225	0.560
	CRP 48	−0.441	0.235	−0.153	0.695	−0.356	0.347	−0.356	0.347	−0.616	0.078	−0.068	0.861	−0.103	0.793	0.009	0.983
	CRP 72	−0.522	0.288	0.145	0.784	0.029	0.957	−0.058	0.913	−0.326	0.391	−0.034	0.930	0.198	0.610	0.240	0.533
VAS	CRP 6	0.140	0.720	0.009	0.982	0.114	0.771	−0.035	0.929	−0.779*	**0.013**	0.000	1.000	−0.087	0.825	−0.087	0.825
	CRP 24	−0.231	0.550	−0.043	0.913	−0.316	0.407	−0.162	0.676	−0.256	0.507	0.402	0.284	0.383	0.308	0.347	0.360
	CRP 48	−0.337	0.376	0.050	0.899	−0.069	0.859	−0.139	0.722	−0.713*	**0.031**	−0.160	0.680	−0.267	0.487	−0.205	0.597
	CRP 72	−0.577	0.231	−0.152	0.774	−0.213	0.686	−0.334	0.518	−0.220	0.569	0.303	0.428	0.440	0.235	0.468	0.204

ρ, Spearman's rho correlation coefficient; *p*, *p*-value, the bolded text shows a significant correlation; CRP, c-reactive protein; CRP 6, CRP sampling 6 h after surgery; CRP 24, CRP sampling 24 h after surgery; CRP 48, CRP sampling 48 h after surgery; CRP 72, CRP sampling 72 h after surgery; Pain 6, pain assessment 6 h after surgery; Pain 24, pain assessment 24 h after surgery; Pain 48, pain assessment 48 h after surgery; Pain 72, pain assessment 72 h after surgery; GCMPS-SF, the short form of the Glasgow composite measure pain scale; UMPS, university of Melbourne pain scale; VAS, visual analogue scale. *Correlation is significant at the 0.05 level (2-tailed).

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hemorrhage, which prompts the hurried application of surgical sponges. Stress has a negative impact on the non-technical skills of surgeons (67), leading Rodriguez et al. to conclude that intraoperative hemorrhage from an ovarian pedicle probably increased the retention of surgical sponges in veterinary patients (68). Therefore, removing ligament release from the surgical steps would likely reduce the frequency of hemorrhage and sponge retention; however, more research is required before a conclusion can be reached.

Hilgard's learning theory suggests that experience is a crucial component of the learning process (69). For unbiased comparisons, the study surgeries must be performed by a surgeon with no or equivalent prior experience in both methods. A minimum of surgeon experience in our study to the level of the veterinary training program according to conventional method seems to impose an inevitable minimal bias. However, the presence of an inexperienced surgeon could be a limitation of the present study. Given the possibility that a surgeon's lack of expertise might exacerbate surgical stress to the point where the impact of the technique is nullified, a week of training for each method prior to the research allowed the current study to reveal the smallest difference between the procedures. TST has been reported to take between 55 and 130 min for inexperienced surgeons (70, 71). Freeman et al. established an optimal duration of 45 min for inexperienced surgeons after six surgeries (70). In this study, an average of almost 40 min TST demonstrated that the surgeon's skill is enhanced by training before to the start of main operations, and demonstrating our surgeons' experience (71) made the findings more realistic (11, 13, 70). Alternatively, previous research on pilots has yielded five levels of skill acquisition, including novice, advanced beginner, competent, proficient, and expert (25); If each 10-min improvement for OHE corresponded to one level of improvement for the surgeon's expert, then our surgeon's 12.7 min reduction in surgical duration using the instrument shank-assisted technique would theoretically qualify her as "competent."

Surgical experience makes sick animals healthier (72). Sir Francis Galton thought that talent was completely innate (73), but experience is a learning growth (25). Yet, from a different perspective, the surgeon's experience may provide no more than a 25% health improvement (72). On the other hand, OHE is still known as a model of acute pain in research studies. So, when animal pain after a technique is still a problem even after experienced surgeons have used it, it is important to look at the technique itself instead of just how it is taught. Consequently, both correct training and the training of correct techniques are emphasized in the surgical training curriculum, and the new method may contribute to the promotion of the latter, as indicated by the high effect sizes reported in the present study.

The type of operation is a stressor for the surgeon (74). Mental (75) and muscle (76) fatigue can delay an operation. Aside from the fact that the stress was not directly evaluated in our study, time as a major component in calculating surgical stress (74, 77) has been meticulously recorded and analyzed. Controversial is the scenario in which the total surgery time is reduced beyond the time spent on the ovarian pedicle. The technical difference between the two methods was SRT and ShT only had a time difference of 58.58 s in favor of the modified method, but TST was improved by 12.7 min. Non-correlation of these variables with TST indicates they did not directly contribute to the difference in TST, while ovarian exposure caused roughly 63% quicker application of ligatures (4.8 min improvement). The remainder of the improved duration was divided into two parts: (1) 3.1 min from the major procedures in OSPT, which include the separation of the broad ligament on both sides, the second ovary access, uterine arteries ligature placement, and uterine body close and cut; and (2) 4.8 min from CT. The procedures conducted in OSPT and CT were comparable among techniques, although the Instrument shank-assisted OHE required significantly less time. When we were nearing the end of the surgery, or, in other words, when the surgeon had reached extreme fatigue, 4.8 min more time was required to close the abdominal wall using the conventional technique. Therefore, significant time reduction in the mentioned two parts could be related to less fatigue and stress, which was paved through the shorter LigT in the new method. Peeters and Kirpensteijn's unsuccessful attempt to reduce surgical time by utilizing ovariectomy (OVE) instead of OHE (58) is another example of the surgeon's mental and physical strain at this time, as they did not eliminate digital strumming. Due to the strong correlation between TST and LigT in the present study, it is evident that the modified instrument shank-assisted technique can reduce the impact of the time required to install the ligatures, which was the primary factor in the significantly longer surgical time when the previous technique was used. Additionally, the small standard deviation (78) in these two portions may indicate the surgeon's optimal state of stability and fewer technical obstacles during instrument shank-assisted OHE, which may require further investigation.

According to research findings, the surgeon's stress level may be enhanced due to a lack of familiarity with the members of the surgical team (67). While the present study did not measure the stress level of the surgeon, efforts were made to mitigate concerns regarding the presence of new team members. This was achieved through measures such as facilitating familiarity and collaboration among team members during the pre-study training course as well as maintaining a consistent surgical team.

Surgical supervisor changes complicate student-led surgical procedures (57). This study's experienced academic surgeon continuously supervised the surgical procedures, eliminating the possibility of this error, as observed in Harris's study due to a change in supervisor.

The time interval proportion found in this study could be used in general, even though an experienced surgeon could cut the total time needed for surgery. Hence, based on Shivley's yearly savings of 73.3 h (11), a 26.7% decrease in TST in instrument shank-assisted OHE could save 195.7 h (>2.5 times).

In concluding, as ovarian manipulation and pedicle ligatures were identified as the most essential procedures of OHE in a previous study (79), these findings have been meticulously confirmed in the present study. In the instrument shank-assisted OHE, a more accessible ovarian pedicle facilitated all subsequent steps of the surgery.

Due to the surgical discussion's focus on inexperienced surgeons, it is reasonable to assume that the significance of this technique will change as the surgeon's experience grows, whereas the pain-related advantages of this surgical technique will be discussed in a separate chapter, considering all surgeons to be subject to the implementation of this technique.

4.2. Pain perspective

The current study confirmed that, compared to instrument shank-assisted OHE, digital strumming of the ovarian pedicle during conventional OHE makes ligature placement more challenging, possibly due to unwanted visceral interferences or manipulations, prolongs the duration of surgery, and increases pain. Digital strumming is an unpleasant surgical procedure followed by considerable surgical trauma. Thereby, it is anticipated that modifying traditionally invasive procedures would improve patients' recoveries and well-being.

Subjective pain scales (44, 80) and, controversially, CRP have been used to measure pain since vital signs are not sensitive enough (81) and animals cannot communicate verbally (47). Several multidimensional structured behavior scales have been adapted for use in veterinary medicine (59), and the multidimensional GCMPS-SF for acute pain has been authorized for use in dogs (45, 60) with more sensitive and consistent results (82). The UMPS (which comprises six categories of physiological data) and VAS (with more flexibility) were used to compensate for the insufficiency of the GCMPS-SF and reduce the secrecy of the pain.

The results of pain assessments vary based on the experience and knowledge of the veterinarians, which are affected by age, gender, and time since graduation (31, 83). It was anticipated that using a trained, blinded assessor (30), a wound dressing, and three distinct pain scales would reduce the influence of qualitative variable bias in the current study. On the other hand, demographic data and dog acclimation before surgery suggest that individual pain tolerance, species, age, body condition, and environmental factors that can change or mask pain intensity are not confounding variables.

Since severe pain after surgery is often underestimated (84), it needs to be measured in a new surgical procedure (85). The perception of postoperative pain is dependent not only on surgical duration and technique (86), but also on analgesic type (87), dose, multimodality (88–90), the use of preventative analgesia (91), route of administration, and the pharmacokinetics of medications (92). Pain can result in delayed wound healing and surgical site infection (93), and bandages may not be adequate for preventing suture line contamination (94). So, surgeons prefer to modify surgical procedures to reduce postoperative pain (47). This was one of the most important goals of instrument shank-assisted OHE, which had an effect size d of >1.27, > 1.32, and > 1.77 and a power of 0.811, 0.836, and 0.968 at T6, T24, and T48, respectively, based on provided GCMPS-SF pain measurements.

Sampling time is essential for accurately determining pain on time. In this study, sampling times were adjusted according to four theoretical elements: (1) the clinical duration of action of the analgesic agent (meperidine, medetomidine, and ketorolac), which may provide enough pain relief; (2) the plasma half-life of the anesthetic selected for premedication, induction, and maintenance of anesthesia (acepromazine, midazolam, and ketamine), which may change the responses given for pain evaluation; (3) the minimum estimated duration for pain onset, peak, and subsidence; and (4) the pathophysiology of CRP turnover. By giving dogs nonsteroidal anti-inflammatory drugs (NSAIDs) before surgery to help with pain after surgery (95, 96), it was thought that ketorolac might be enough for the first few hours after surgery. However, the results have only shown that this is true for the new technique. It was anticipated that the pharmacologic effects of the long-half-life ($t_{½}$) drugs acepromazine (97), ketorolac (98, 99), and ketamine (nor-ketamine) (100) with residual effects of 7.1, 4.5 (or 10 based on relevant reference), and 6.2 h, respectively, would be felt from premedication until endotracheal extubation. Because sedatives, analgesics, and injectable dissociative anesthetics can change responses like facial expression, salivation, mydriasis, and cardiorespiratory parameters, which were evaluated in the GCMPS-SF, UMPS, and VAS, early pain assessment (<6 h) was not considered in this study.

The requirement of rescue analgesia may be regarded as a reliable indicator of the surgical technique's incompetence. According to a previous report in humans (101), after hip and knee arthroplasty, ketoprofen had the same analgesic effect as extradural morphine. Mathews et al. find that ketoprofen has a comparable impact to meloxicam and conclude that it could be a useful way for controlling postoperative pain (102). Similar to carprofen, meloxicam, and tolfenamic acid, ketoprofen produced excellent postoperative analgesia in cats, but with a lesser effect on tenderness (103). In the meantime, more recent studies indicate the administration of NSAIDs is superior to opioids due to faster recovery of normal functions and greater satisfaction with postoperative well-being (104). Nevertheless, these findings should be taken with care when applied to OHE in veterinary medicine. In the present study, animals that got rescue analgesia were not excluded, and 8 dogs in the conventional group who received rescue analgesia at 13 evaluation times were included for analysis. If getting rescue analgesics improved outcomes, the dogs in the first group were unable to demonstrate superior outcomes despite receiving frequent pain treatment. The number of animals administered rescue analgesics may be a reflection of the severity of surgical trauma and the invasiveness of the conventional technique. Receiving rescue analgesics in 1 dog out of 2 evaluation times can be attributed to greater well-being using the modified method and can be interpreted in two aspects: first, a standard protocol of analgesics is still recommended after surgery, and second, it may be useful in shelter or stray dogs that may not receive proper follow-up treatment, for example.

At 6 h postoperatively, eight out of nine dogs treated with the conventional method received rescue analgesia. This demonstrates at least two important points: (1) ketorolac provides inadequate postoperative analgesia for the conventional OHE performed by an inexperienced surgeon, although it has been used in humans to control moderate to severe post-operative pain, and it may be effective in dogs (105), as effective as flunixin, and more effective than butorphanol or a low dose of oxymorphone (106), by affecting opioid receptors centrally with comparable efficacy to morphine (99), and (2) the current modification has decreased postoperative pain to the point that ketorolac could control it, so that none of the dogs in the second group required T6 rescue analgesia.

Our "competent" surgeon has made the surgery quick and competitive in terms of time (see "Surgical perspective"). Since the new method causes less pain and this surgery is still done to create a model of acute pain for research, it is safe to assume that this surgical method is not limited to a certain group of surgeons, no matter how much experience they have, and that it is better to make it more general.

In addition to the psychological burden experienced by the surgeon, contemporary approaches have been developed to assess the degree of pain and surgical stress imposed on the patient. While

certain methods, including pupillometry, surgical pleth index (SPI), skin conductance, cardiovascular, and cardiorespiratory indices, require further advancements in sensor technology and interpretation algorithms to investigate animal responses to anesthesia and surgery, their applicability has not yet been confirmed. In the field of veterinary medicine, additional quantitative techniques have been introduced for animal assessment. These include the parasympathetic tone activity index (PTA index), which analyzes heart rate variability, and the bispectral index (BIS), which analyzes electroencephalography, with the potential for animal interpretation. Despite ongoing debates regarding the universal implementation of their use in all treatment procedures and drug protocols (107), the accessibility of these remedies may not always be assured. It is worth noting that the application of PTA as a means of assessing pain in conscious animals within the field of veterinary medicine is challenging. This is primarily due to the presence of unwanted movements by the animal, which directly impact heart rate variability. Consequently, alternative models capable of detecting these fluctuations should be employed (20, 32, 107, 108). The use of more recent medications, and therefore the recording of the quantity of anesthetics used (55) and the vital parameters throughout the operation, seems to be a large issue that would need review in separate research, other than that this technology was not available for the current study.

A number of different physiological parameters, such as plasma vasopressin, urine noradrenaline, and creatinine concentrations, have been suggested to assess the degree of irritation and pain caused by a surgical method. It appears that documenting additional facts and aiding in the final assessment of the effectiveness of the presented technique may be accomplished by comparing the changes in these parameters during anesthesia between the two methods. The conventional OHE involves applying extremely stretching stress to digitally strumming the suspensory ligament, while the new method involves keeping this ligament under tension all the way through the ligature placement process. Further research is warranted to compare the two methods from this perspective, as acute noxious stimuli during stretching of the pedicles can increase systolic blood pressure, heart rate, plasma vasopressin concentration, and urinary noradrenaline/creatinine ratio (55).

One of the initial observable events following surgery is the elevation in temperature and inflammation of the surgical site, attributed to enhanced blood circulation to the area where surgery was performed. Infrared thermography (IRT) is a proficient technique for assessing thermal variations in problematic areas, as it measures the surface temperature of the skin through thermographic maps. This technique may be used to recognize the localized changes in blood supply and localized increases in temperature that occur in response to stress. The assessment of the efficacy of local anesthesia through the analysis of alterations in surface blood circulation linked to sympathetic activity is among the additional functionalities of IRT (109). However, it has been observed that this technique has not demonstrated sufficient effectiveness in dogs (110). The present study suggests that while the implementation of IRT for evaluating pain and inflammation in the surgical approach area was effective, practical limitations arose due to the bandage covering the surgical site. Conversely, the thermographic assessment of regions where the suspensory ligament has been torn, situated on the roof of the abdominal cavity, may not be deemed reliable in theory. This is due to the fact that the heating of the dermis surface is directly linked to the local dermal microcirculation, which is under the control of the ANS. Nevertheless, the non-invasive nature of this method of evaluation may be an appealing subject for further research.

Pupil shape has been a key indicator for neurological assessment for over a century (111), and automated pupillometers have become increasingly important due to the difficulty of detecting the "reactive pupil" characteristic (112). In addition, assessing pupil reactivity using a pupillometer offers an objective, rather than subjective, evaluation of the neurological examination. Automated pupillometers can distinguish between canine conscious and anesthetic pupillary light reflex (PLR) and continuously assess an animal before, during, and after anesthesia (113). It seems that PLR devices could be useful in research like the current one, provided that the assessments are standardized.

Evaluation of a novel surgical procedure extends beyond surgical parameters and postoperative discomfort. Surgical invasiveness may be assessed separately. Based on past research, the invasiveness of the surgical procedure may be related to postoperative pain. Consequently, the question of surgical trauma severity is a separate topic that will be addressed further in "CRP perspective."

4.3. CRP perspective

In this study, the traditional OHE method was changed in a way that reduced the amount of trauma. With the new technique, the amount of surgery-related trauma had a smoother pattern and went back to normal almost 30% faster. These results predicted a shorter period of recovery time subsequent to instrument shank-assisted OHE.

The postoperative acute-phase response develops faster in dogs compared to humans. Tissue damage and pain after invasive surgery are associated with a rise in blood acute-phase proteins, primarily CRP, which may be a valuable diagnostic biological marker of early postoperative complications (114, 115). The CRP, a sensitive biomarker of infection (116), inflammation, and tissue damage (46), is more sensitive than serum cortisol (81) in detecting surgical trauma (13) and can assess various surgical procedures in dogs (33, 117), peaking 24 h postoperatively (42). The short half-life of canine CRP (19 h) makes it a useful marker for identifying the intensity of mild clinical stressors (33, 118, 119) whose effects dissipate more rapidly.

It has been stated earlier that the slope of changes is a reliable predictor variable for the expected peak (13). A five-fold smoother slope in the elevation of CRP concentration generated a milder peak after instrument shank-assisted ovariohysterectomy, so its return level to the base value showed a significant reduction at T48 compared to that of the animals in the opposite group. Thus, it is suggested that future research on the slope of the post-OHE CRP increase would also be planned to reduce study duration and be used for designing and scheduling postoperative analgesia protocols and lengths. As CRP is elevated approximately 6 h after a single stimulation (119), the present data revealed that there is no clinical necessity for sampling before 6 h after surgery. Moreover, because serum concentration peaks between 24 and 48 h in dogs (42, 115, 119), and CRP has a short half-life (33, 118, 119), the last measurement time of 72 h after surgery was appropriate for CRP return.

It has been imagined that OVE can satisfy surgeons' hopes by reducing the consequences of OHE. Moldal et al. did not find any differences in the levels of CRP, glucose, or iron in the blood between them. Therefore, the greatest trauma in OHE occurs during the surgeon's manipulation of the ovarian pedicle (86). Thereby, the instrument shank-assisted method's unique characteristic can be considered an advantage. By reducing manipulation of the ovarian pedicle through eliminating digital strumming, the surgical trauma has also been reduced to a level close to the lowest expected minimum. Experienced surgeons have the advantage of avoiding unnecessary organ manipulation (26, 27), which causes minimal surgical trauma and postoperative serum CRP concentration. Hence, the present modified technique, which entails less organ touch, presents surgical quality closer to that of an experienced surgeon.

It is not without merit to state that CRP concentrations seem to be a decent predictor of how invasive an operation is (120), despite some contradictory reports, such as that there is no correlation between the length of surgery and CRP, despite its rise (121), or that CRP concentrations may not be significant in the diagnosis of a disease (118). In the present study, the return to baseline after a moderate rise in CRP levels utilizing the instrument shank-assisted OHE, as contrasted to the conventional group's high CRP levels, suggests that the instrument shank-assisted OHE could be concluded as having a minor invasive nature.

The risk of infection is increased when abnormal CRP responses are seen 5 or 7 days following surgery (116). A progressive decrease in serum CRP content in both groups could indicate the absence of infection. It is not unlikely that a procedure requiring fundamentally less organ manipulation would result in improved recovery, but ultimate healing was not the focus of this study.

Finally, the pattern of CRP changes followed the pain charts without correlation, according to the data. So, at least when the surgery is minor, there may not be a statistical correlation between changes in the CRP and pain. This may be because of the wide range of its reported changes. In this instance, the CRP profile may be able to anticipate pain patterns, but it cannot be used to make statistical conclusions.

The CRP changes showed that OVE and other similar procedures cannot be the final solution to animal comfort, and modification of the surgical technique on the more severe parts of the surgery is necessary, whether it is the method proposed in the current study or other solutions that may be introduced later. Although the graphs of CRP and pain changes appear similar, establishing a definitive relationship or statistically significant correlation between them requires further research.

5. Conclusion

The current study supported the practicability of a single-person ovariohysterectomy in deep-chested adult mixed-breed dogs without tearing the suspensory ligament, along with a reduction in surgical length, CRP, and pain. On the basis of the results, there are still questions regarding the efficiency of using serum CRP concentration as an alternative pain assessment indicator.

6. Limitations and future research

Future studies evaluating physiological values, pain, the amounts of analgesics and anesthetics consumed during the operation, hemorrhage, heat loss, instrument handling errors, wound size, and more tissue handling can help determine the surgical technique more precisely. Intraoperative evaluations need an up-to-date drug anesthesia protocol, which was not available in this study because certain nonsteroidal anti-inflammatory drugs were not available in the area and veterinarians were not allowed to use opioids or isoflurane. Further research will be needed to compare the performance of surgeons with varying degrees of expertise and animals of varying ages, making it more difficult to generalize the findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The animal study was approved by Iranian biomedical research ethics committee IR.IAU.BABOL.REC.1399.004, IR.IAU.BABOL.REC.1399.015, and IR.IAU.BABOL.REC.1399.093. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

NZ: idea, project design, project implementation, statistical analysis, drawing illustrations manually, article writing, article translation, translation editing, and final proofing. SM: project design, project implementation, digitizing Illustrations, article writing, article translation, and translation editing. AB: project design, project implementation, article writing. NN: project design, project implementation, translation editing. SF: project implementation. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The correspondence supplied the idea of instrument shank-assisted OHE. This technique has been registered with the Patent Office-Real Estate Registration Organization of Iran under application number 140050140003000955, date of registration: 2021-04-25, patent number: 107195, date of patent: 2022-06-12, YEKTA identifier: 140150340003001229, verification code: 216204. Thereby, by releasing this article, the authors consider just the rights to intellectual property to be theirs.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2023.1210089/full#supplementary-material

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REVIEW
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Gonadotropin-Releasing Hormone (GnRH) Agonist Implants for Male Dog Fertility Suppression: A Review of Mode of Action, Efficacy, Safety, and Uses

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At present, only surgical sterilization is available for veterinarians and pet owners seeking suppression of fertility in male dogs, in most countries. An alternative contraceptive alternative approach is GnRH releasing implants that desensitize the pituitary to the stimulatory effects of GnRH and thereby block testicular function (testosterone and sperm production). Two GnRH agonists (deslorelin and azagly-nafarelin) have been researched in controlled release formulations for this purpose. A deslorelin-releasing biodegradable implant, marketed under the name Suprelorin®, has been available in Australia and New Zealand since 2007, the European Union (EU) since 2008, and received regulatory approval in China and Mexico in late 2019. Two versions of the implant are available, one labeled for a minimum of 6 months of fertility suppression in male dogs, and the other for a minimum of 12 months in male dogs. Another GnRH agonist (azagly-nafarelin) was also included in a solid implant (Gonazon®). Research results showed it delivered 6-months to 1 year of suppressed fertility; however, it is not commercialized. This review paper summarizes research on the mechanism of action for these technologies and compiles and interprets the research on efficacy and safety. New findings on usage of the deslorelin releasing implant in countries where veterinarians and pet owners have this option is shared. Research on off-label use of the product in male dogs is also reviewed. This review aims to aid in the evaluation of the deslorelin releasing implant as an adjunct or alternative for surgical sterilization of male dogs.

Keywords: male dog, sterilize, castrate, neuter, contracept, fertility control, chemical castration, non-surgical

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INTRODUCTION

Veterinarians, pet owners, animal welfare experts, and shelter practitioners seek to suppress fertility and/or reduce testosterone in male dogs for a variety of reasons, including avoiding siring unwanted litters, improving health and welfare, and reducing testosterone influenced behavior. The priority of these reasons for fertility control may differ according to the target population of dogs. Safety and efficacy are paramount for all cohorts. However, the relevance of factors such as duration of treatment, cost profile, accessibility, and administration process will all vary based on the target population, be it pets who are secure in a home, dogs in breeding programs, homeless animals in an animal shelter, or free-roaming or community dogs.

Despite this variety of reasons for treatment, for decades, the standard and often sole means of managing reproduction in male dogs has been surgical castration, also known as neutering. As a result, whereas there are presently multiple pharmaceutical options to treat many veterinary conditions, no pharmaceutical alternatives with regulatory approval are currently available besides the technology discussed in this review. A chemosterilant utilizing zinc gluconate neutralized by arginine and administered via intratesticular injection was approved in the United States in 2003. The product was unsuccessfully marketed from 2003 to 2005 and again from 2014 to 2016. That formula has been also approved in five other counties but is no longer on the market (1). Calcium Chloride dihydrate is a similar formula available via veterinary compounding only, also administered via injection into the testicles and providing permanent sterilization. Use is extremely limited (2). Since the 1980's, a variety of methods for non-surgical fertility control have been studied (3). Despite significant research in this field, in a wide range of approaches including active immunization against GnRH (4), selective destruction of the GnRH binding cells in the pituitary (5) and GnRH antagonist administration (6) no other alternatives have been successfully developed to date. The field received increased support with the Michelson Prize & Grants' 2008 pledge of $50 million in grants for a permanent non-surgical sterilant for male and female dogs and cats whose work continues as of the date of this publication (https://www.michelsonprizeandgrants.org/about/).

The two types of implants discussed in this review rely on different GnRH agonists and different technologies.

The deslorelin releasing implant (DRI/brand name Suprelorin®) was developed in Australia and is currently marketed by Virbac (Carros, France). There are two versions of this DRI. The 4.7 mg implant, which is labeled to suppress fertility in sexually mature male dogs for a minimum of 6 months, is approved for sale in Australia, the European Union (EU), New Zealand, China, and Mexico. It was launched in Australia and New Zealand in 2007, and in the EU in 2008. Approval in China and Mexico occurred in late 2019, with a launch in 2020 (personal communication, Christelle Demongeot Navarro, 26 February 2020 and 23 June 2020). The 9.4 mg implant, which is labeled to suppress fertility in sexually mature male dogs for a minimum of 12 months, is approved and sold in Australia and the EU (7)[1]. The DRI is placed beneath the skin between the dog's shoulder blades; it is not necessary to prepare the implantation site. The product can be repeatedly dosed to extend the period of fertility suppression. The implant is packed in a single use sterile syringe implant device. As packaged for sale, the product has a 3-year shelf life. The product should be stored in a refrigerator (2–8°C or 36–46°F) and not frozen (11).

[1]In addition to approval for suppression of fertility in sexually mature male dogs, the 9.4 mg dose of Suprelorin has been approved in the EU and Australia for suppression of fertility in male ferrets (8, 9). In the United States, 4.7 mg Suprelorin® F is a U.S. Food & Drug Administration (FDA) Indexed Product to manage adrenal gland disease in sterilized and sexually intact male and female ferrets (10). It is not FDA approved. Extra-label use of Suprelorin F is prohibited and grounds for removal from the market.

The azagly-nafarelin releasing implant (ARI—also called Gonazon®) developed by Intervet (Angers, France) was registered in Europe for a 1-year contraceptive effect in bitches, but was never launched. However, there were relevant studies exploring its potential in male dogs (12, 13) that provide useful data on mode of action, efficacy and safety. It is a silicone based solid implant (14 × 3 × 1 mm) containing 18.5 mg azagly nafarelin that is inserted subcutaneously preferably near the umbilicus.

This review paper begins with a discussion of the mechanism of action of both types of implants, followed by a summary of published data on their use for fertility control in male dogs.

Potential ancillary uses of the DRI in male dogs, as well as additional considerations related to health and behavior, are then discussed. The paper finally explores social considerations of the DRI implant, including veterinary survey data that offer preliminary insight on how and why this treatment is currently used in Europe as a lens into how the veterinary community views this non-surgical contraceptive.

THE MECHANISM OF ACTION OF GnRH AGONIST-RELEASING IMPLANTS

GnRH is a hypothalamic decapeptide, that acts at the top of the cascade that coordinates function of the hypothalamo-pituitary gonadal axis. It is released from specific GnRH-producing neurons in a pulsatile fashion. This pulsatile pattern of release stimulates production and release from the pituitary gland of the two key gonadotropins, follicle stimulating hormone (FSH), and luteinizing hormone (LH), which in turn control gonadal function (in males, testosterone production, and germ cell production, i.e., differentiation of spermatogonia to spermatozoa) (**Figure 1**).

To date, two GnRH agonists have been used in dogs to alter testicular function: deslorelin (14) and azagly-nafarelin (15). The structures of deslorelin and azagly-nafarelin (vs. the structure of native GnRH) are presented on **Table 1**. Both GnRH agonists display a peptidic sequence related to the sequence of native GnRH with modifications of three of its amino acids (at positions 1, 6, and 9) and deletion of its amino acid at position 10. The aim of these structural changes is to reduce sensitivity to proteolysis and increase biological activity (16). For example, deslorelin has been found to display a potency 10 or 100 times higher than native GnRH in a GnRH ligand binding test and an *in vitro* culture of rat pituitary cells, respectively (16). There is no similar potency information for azagly-nafarelin.

The purpose of the implant formulations used for dogs is to ensure release of their GnRH agonist content (deslorelin or azagly-nafarelin) for extended durations This was demonstrated in a pharmacokinetic study, published as an abstract (17) describing plasma deslorelin concentrations in dogs following treatment. Plasma deslorelin concentrations peaked ∼14 days after insertion of a 4.7 mg implant, reaching concentrations ranging from 200 to 2,000 pg/ ml. Concentrations then gradually decreased and reached undetectable levels at ∼80 days post-implantation (17). Comparable data on the 9.4 mg DRI is not

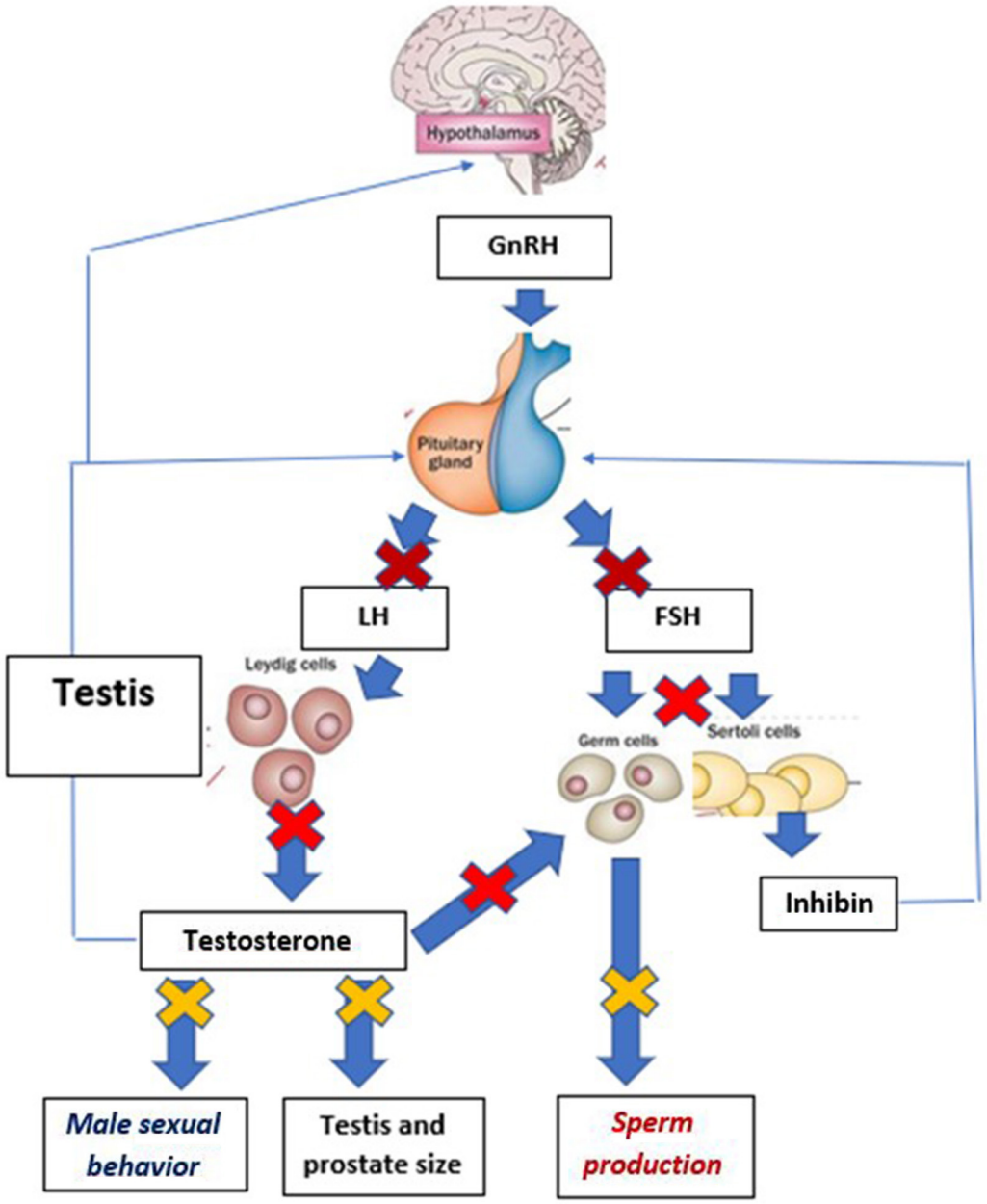

FIGURE 1 | Schematic presentation of the mechanisms involved in the prevention of reproductive function following the desensitization of the pituitary gland to GnRH. Thick arrows demonstrate stimulatory effects, while thin arrows document negative feed-back effects. For clarity of the graph, paracrine, and autocrine regulations within the testis have been omitted. Early effects of desensitization are pictured by ✖. Events occurring later in the cascade of inhibitory effects are shown by ✖ and final ones by ✖. Effects of GnRH desensitization on FSH concentrations in dogs are unknown, as there is no FSH assay validated for dog plasma and therefore no data.

published. The release profile of the ARI is not available from the scientific literature. However, an earlier version of the ARI generated release of steady azagly-nafarelin concentrations for up to 350 days (15). The continuous release of either GnRH agonist (deslorelin or azagly-nafarelin) triggers a cascade of biological events (**Figure 1**).

Continuous exposure of the pituitary cells to GnRH (after a brief stimulatory period, see section Safety and Side Effects GnRH Agonist Implants) triggers pituitary desensitization. Pituitary desensitization to GnRH is triggered by internalization of GnRH receptors (which are no longer present for binding on the cell surface) and inactivation of the intracellular signaling cascade.

Once desensitization of the pituitary cells to GnRH is initiated, LH concentrations fall to undetectable values, and therefore fail to support testosterone and sperm production. Such effects have clearly been demonstrated in male dogs (see below and **Figure 1**). In contrast, owing to the lack of validated FSH assay for dogs, the effects of either type of treatment on FSH secretion have not been established.

The downstream effects of the low gonadotropin concentrations associated with pituitary desensitization are presented in the next section.

DATA ON GnRH AGONISTS RELEASING IMPLANTS USE IN MALE DOGS

The suppression of LH and testosterone by the DRI and its effects on sperm numbers and morphology resulting in suppression of fertility were established in multiple studies either using early implant formulations (3, 6, or 12 mg deslorelin) (18–20) or final formulations (14, 21, 22), as well as clinical studies conducted as part of the regulatory approval process of 4.7 and 9.4 mg doses of Suprelorin.

The regulatory studies leading to approval of the 4.7 mg implant included dogs ranging from 10 to 40 kg (22–88 lbs) (14). Regulatory materials submitted to the European Medicines Agency advise that use in dogs outside this range should be subject to a risk/benefit assessment by the veterinarian. Other studies, did, however, test the DRI in dogs under 10 kg (14).

While the ARI implant was developed for contraception in bitches, two detailed studies were conducted in male dogs (12, 13). The combination of all studies with either implant allows comparisons between their respective clinical effects. In addition, some specific aspects (for example reversibility of suppression) could be better studied after the removal of the solid ARI than with the biodegradable DRI (that cannot be easily removed after 6 or 12 months *in situ*).

TABLE 1 | Comparative sequences of native GnRH, Deslorelin acetate, and Azagly-nafarelin.

Amino acids 1, 6, and 10 are the ones modified to generates GnRH agonists used in dogs.

Native GnRH: pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly.

Deslorelin acetate: H-Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-NHEt.CH_3CO_2H.

Azagly-nafarelin: H-Pyr-His-Trp-Ser-Tyr-D-2Nal-Leu-Arg-Pro-$NHNHCONH_2$.

Efficacy and Duration of Effect

Measures of efficacy discussed in this section include time to onset of any reduction in testosterone concentrations, time until the dog can be considered contracepted and duration of contraceptive effect. Variability in results are also discussed.

For both ARI and DRI, **Table 2** provides a summary of the cascade of events associated/causing prevention of testicular function. It provides evidence that there is a close coincidence between the time when testosterone concentrations reach undetectable values (0.1 ng/ml in most assays) and the time when semen displays features (total sperm numbers, motility, % of abnormal forms) incompatible with fertilization of a bitch (21).

TABLE 2 | Changes in relevant endpoints occurring after treatment with a deslorelin releasing implant (DRI) and azagly-nafarelin releasing implant (ARI) and comparison in measurements.

Implant	**Deslorelin releasing implant (DRI)**		**Azagly nafarelin releasing implant (ARI)**	
References	**Trigg et al. (14)[a]; *N* = 56 Romagnoli et al. (21)[b]; *N* = 6**		**Ludwig et al. (12); *N* = 8**	
End point and metric	**Time to first reduction (d)**	**Time to full reduction (d)**	**Time to first reduction (w)**	**Time to full reduction (w)**
LH concentrations	ND	ND	ND	Week 11[c]
Testosterone concentrations	Day 23–32[a]	Day 6–43[a] Day 64–75[a]	Week 1	Week 2–3
Testis size	ND	ND	Week 3	Week 17 (by 80%)
Prostatic size	ND	ND	Week 3	Week 5 (by 46%)
Erection allowing sperm collection	Day 22[b]	Day 30–35[b]	Week 3	Week 5 (semen from 1/8 dogs could be collected)
Sperm volume	Day 37–47[b]	Day 64–75[b]	Week 3 (by 70%)	No sperm collected in 7/8 dogs
Total sperm number in the ejaculate	Day 37–47[b]	Day 64–75[b]	Week 3 (by 55%)	No sperm collected in 7/8 dogs
Sperm motility	Day 23–32[b]	Day 64–75[b]	ND	No sperm collected in 7/8 dogs
% of Abnormal sperm	ND[a]	Increased to 70% by Day 35[a]	Unchanged (at 30%) on week 3	No sperm collected in 7/8 dogs

Note that the durations are expressed in days for the DRI studies vs. in weeks for the ARI studies. ND, not documented.

[a] *Data from Trigg et al. (14), N = 56.*

[b] *Romagnoli et al. (21), N = 6.*

[c] *Week 11 was the first time point when LH concentrations were assessed and only for the ARI.*

The cascade leading to shrinkage of the testicles and prostate followed by the inability to produce sperm during collection attempts and low sperm quality (low total sperm numbers, low motility, and increased proportion of abnormal forms) is presented on **Figure 1** and the timings of each of these events on **Table 2**. Irrespective of the implant used, testicles commonly shrink to <50% of the pre-treatment size (12, 20, 23). The proportion of motile sperm, total sperm numbers, and semen volume fall to very low values, incompatible with fertility (12, 21). Data on abnormal sperm following treatment are mixed with one study failing to find an effect on the percentage of abnormal sperm (21), while another one claiming overall a 10-fold increase in abnormalities of sperm tails (from 7 to 70%) at 35 days after treatment (14).

Lack of libido (likely due to suppression of testosterone production), combined with an arrest of spermatogenesis at the spermatogonia/spermatocyte stage leading to azoospermia were shown as key factors involved in achieving contraception.

The approved label claim for the commercialized DRI is to prevent testicular function and block fertility in male dogs for a minimum of six (4.7 mg) or 12 months (9.4 mg). In 9/10 dogs of each of two dose groups, the 4.7 and 9.4 mg the DRI was shown in registration studies to consistently suppress testosterone (below the assay's limit of quantification, 0.1 ng/ml) for at least 180 and 400 days, respectively ($N = 10$/group) (14).

There are indications of a correlation between a dog's body weight and duration of fertility suppression, with a generally longer period of testosterone suppression observed in small dogs (weighing <10 kg) than in dogs over 10 kg (14). During clinical trials with the 4.7 mg implant, most of the smaller dogs (<10 kg) maintained suppressed levels of testosterone for more than 12 months following implantation (11, 14).

Variability in the duration of fertility suppression is generally large. In dogs ranging in weight from 10 to 25 kg ($n = 31$) and receiving the 4.7 mg deslorelin releasing implant, the duration of undetectable testosterone concentrations (under 0.1 ng/ml) ranged from 150 to 500 days (14). A similar variability was detected in dogs <10 kg ($n = 11$: 200–570 days). Furthermore, following the use of a 9.4 mg deslorelin implant in 10 dogs, undetectable testosterone concentrations ranged from 322 days post-implantation in the dog with the shortest duration, to more than 700 days in the two dogs showing longest response (14).

Duration of efficacy of the ARI was evaluated in two studies (12, 13). In the first one (12), two groups of dogs ($n = 4$/group) received the implant for 6 or 12 months. Undetectable testosterone concentrations (below 0.1 ng/ml) were maintained for the duration of the study for 4/4 dogs of the 6 months group and in 1/4 dogs of the 12 months group. Resumption of testosterone concentrations above 0.5 ng/ml was observed on days 223, 307, and 324 post-insertion in the 3 other dogs. In a second study, suppression of testosterone to undetectable concentrations for 6 months was observed in 46/53 dogs while 5/53 dogs displayed decreased but detectable testosterone concentrations. Failure (no testosterone suppression) was reported in 1/53 dogs (13). There were too few dogs to assess variation by weight category.

Variability in the time required to reach undetectable testosterone concentrations (hence demonstrating pituitary desensitization) is also well-documented (14, 20, 21). In one study in 56 dogs of three different weight groups (below 10 kg, 10–25 kg, and over 25 kg) receiving the 4.7 mg implant, testosterone concentrations reached undetectable values between 6 and 43 days following treatment (14). Romagnoli et al. (21) similarly used a 4.7 mg implant in a study of six dogs of varying weights (7.8–40.2 kg). Sterility (based on semen collection and sperm features in the ejaculate) was detected between 54 ± 21 days post-treatment. Neither of these studies reports a link between body weight of the treated dogs and this variability. Taking into account multiple studies on the subject, it can be stated that the onset of complete suppression of fertility with the 4.7 mg DRI implant may typically occur between 1 and 2 months after treatment. No data on this is available for ARI.

The mechanisms causing this variability are not understood. The links between the actual release profile of deslorelin or azagly-nafarelin by these implants and this variability remain to be explored.

Sexual behavior in males is driven by testosterone. Hence, in addition to having the potential to suppress testosterone and sperm production, blocking the effects of GnRH also reduces or abolishes the physiological response of penile erection and non-habituated behaviors related to sex hormones (3)[2]. Irrespective of the implant used, libido (as measured by thrusting action) was markedly reduced. In a study with the 4.7 mg DRI ($n = 55$), libido which was present pre-treatment in 70% of the 56 treated dogs, had decreased to 50% by Day 22 post-implantation and ceased between 30 and 35 days (14). In another study with the ARI, in which semen collections were attempted every other week, the last ejaculate could be collected during week 3 after treatment in 7/8 dogs and during week 5 in the last dog (12).

Reversibility and Retreatment

Veterinarians and clients may have different objectives for using GnRH agonists releasing implants. One goal is to achieve ongoing suppression of testicular function and fertility. A different goal may be to achieve temporary suppression of testicular function, to preview the effects of castration, or to delay the decision to breed a male dog. In all these scenarios, it is important to know when to re-implant, castrate or assume a dog can successfully sire a litter.

As the ARI is made of silicone, it can be surgically removed to end treatment and begin the sequence of events leading to resumption of testicular function. Such a sequence and the timing of the consecutive steps are presented in **Table 3**. Overall, it took around 24–26 weeks for testicles to grow back to their pre-treatment size and 29–30 weeks for "normal" sperm production to occur (12).

Studies of DRI demonstrate that testicular function, and semen quality return to normal values after the end of release of

[2]Note, researchers recorded thrusting action as a measure of libido; they did not specify if male dogs were in the presence of an estrous female to invoke the behavior.

TABLE 3 | Sequence of events occurring after the end of GnRH desensitization with a Gonazon implant ($N = 5$ dogs) (12).

	End point	Initiation of recovery (w)	Full recovery (w)
Step 1	Resumption of LH secretion[a]	Week 4 post-implant removal	Week 12 post-implant removal
Step 2	Recovery of testosterone concentrations[b]	Week 4 post-implant removal	Week 7 post-implant removal
Step 3	Recovery of testis size[b]	Week 6 post-implant removal	Week 24–26 post-implant removal
Step 4	Recovery of prostate size[b]	Week 8 post-implant removal	Week 16 post-implant removal
Step 5	Recovery of a normal sperm production[c]	ND	Week 29–30 post-implant removal

[a] *LH secretion post-treatment was only evaluated on two occasions: week 4 and week 12.*
[b] *Testosterone concentrations together with testicular and prostatic size were assessed weekly till week 12 then monthly (weeks 16, 20, and 24/26).*
[c] *Numerical data are only reported for the week 29–30 time window. ND, not determined.*

the GnRH agonist included in the implant (14), but the timing of resumption of fertility is variable (14, 18).

In contrast to the ARI, the DRI is fully degraded at the end of its release period. To maintain suppression of fertility, the DRI label recommends re-implanting at either 6-month (4.7 mg) or 12-month (9.4 mg) intervals. Data do not further address precise timing of resumption of reproductive function following use of the implant. An owner can monitor the signs of return to fertility in making a reimplantation decision. On the other hand, owners should understand that if they want to breed their dogs after using a DRI, return to fertility may be delayed.

Use of the DRI for long-term contraception therefore requires consecutive treatments. During registration studies, 10 dogs were implanted four consecutive times with a 4.7 mg DRI, and testosterone was monitored during and after treatment. Dogs were observed for any adverse events. The study demonstrated that re-implantation of previously treated dogs is safe and serves to continuously suppress fertility (14). The dossier submitted for regulatory approval in Europe reports safety and efficacy with four and five sequential treatments with the 4.7 mg implant (24). It is assumed the implant can be used for a longer duration but published studies documenting that are not found in the literature.

Safety and Side Effects GnRH Agonist Implants

Very few adverse effects were recorded during studies done with either type of implant with the exception of moderate swelling at the implant site commonly reported for 14 days for DRI (11), and a short term flare up phase described in this section.

Other side effects during the DRI release period were very uncommon (occurrence below 0.1% of the treated dogs) and limited to coat abnormalities or an owner reported reduction of general activity for some weeks after treatment (11, 22).

For the ARI, a study in 8 male beagles noted no local reactions at the site of implantation; no other adverse reactions were noted throughout the study period (6–12 months) (12). In a study with 53 male dogs being treated with the ARI as an alternative treatment to castration for benign prostatic hyperplasia (BPH) and for behavioral issues, minimal side effects were recorded (13).

During the first days post-implantation, there is a short-lived step during which exposure to the GnRH agonist has stimulatory effects on the pituitary gonadal axis ("flare-up phase"). During this "flare-up phase," an acute increase in serum testosterone occurs. This was documented in a study involving six dogs treated with the 4.7 mg DRI which identified increased testosterone concentrations between Days 1 and 5 post-treatment (25). In another study (21), a short-lived increase in semen motility was observed on days 9–17 post-implantation of a 4.7 mg DRI ($n = 6$). This flare-up period may cause transitory changes in behavior. In one study involving 24 dogs treated with a 4.7 mg DRI, owners reported an increase in sexual behavior in eight dogs 1 week after treatment, dropping to three dogs by week 3. Owners of five dogs reported increased aggression toward male dogs 1 week following treatment, dropping to two dogs by week 5 (22). Cautions are provided about using DRI in dogs with sociopathic disorders related to aggression (11), in part due to possible heightened behavior response during the flare-up phase.

This flare-up phase ends when desensitization of the pituitary cells to GnRH is initiated, at which point testosterone concentrations start dropping.

POTENTIAL ANCILLARY USES OF THE DESLORELIN RELEASING IMPLANT IN MALE DOGS

Research has revealed potential uses of GnRH agonist implants in male dogs beyond providing fertility suppression in sexually mature animals. Three off-label uses of the product are described below. Off-label research in female dogs and other species is beyond the scope of this paper[3].

Fertility Control in Prepubertal Male Dogs

In some countries, including Australia and the United States, veterinarian, and/or shelter recommendation of prepubertal sterilization of dogs is relatively common (26, 27). In the United States, it has been recommended that shelters perform neutering prior to adoption, as early as 6 weeks of age (28).

The appeal of surgical sterilization in young dogs in some countries begs the question of whether chemical fertility control in this age cohort is safe and effective. Efficacy in male puppies was documented by a small study in Beagle and mixed breed dogs treated at 4 months of age. Treatment of 4-month-old male

[3] A product profile and position statement on Suprelorin in female dogs and other species can be found at: https://acc-d.org/docs/default-source/Resource-Library-Docs/Suprelorin4P.

pups ($n = 4$) with a 4.7 mg DRI postponed puberty (defined using behavior and testicular size as end points) until 2.5 years of age (29). When a 9.4 mg DRI was used ($n = 4$), puberty failed to be detected before termination of the study, when dogs were between 2.5 and 3.2 years of age. No significant side effects on growth, size, or height were detected in this study (29). Given the limited sample size of this study, it is relevant to also note that in a study of nine prepubertal female dogs treated with DRI of both doses, neither body development (height, humeral length) nor body weight was affected by treatment, despite a significant delay in epiphyseal closure (30). These studies suggest that prepubertal treatment of dogs with GnRH agonist implants may be safely used to postpone puberty in dogs without interfering with their final size or height. No studies have been done with ARI on prepubertal dogs.

Treatment of Behavioral Problems in Intact Male Dogs

Some intact male dogs exhibit some behaviors that owners find objectionable. Surgical castration is commonly proposed by veterinarians to alleviate such behaviors in some dogs (31). Due to their ability to suppress testosterone, GnRH agonists releasing implants may also be useful for altering/minimizing behaviors related to testosterone. Improvements in sexually dimorphic male behaviors described as libido, hypersexuality, intermale conflict, and excessive territorial urine marking have all been described for DRI (32). The product label of the DRI in Australia specifies that the product can be used as an "aid in the control of unacceptable behavior."

In a study comparing the effects of surgical castration and treatment with a DRI on male dog behavior (22), 24 intact, sexually mature dogs of varied sizes and breeds received a 4.7 mg implant. They weighed 26.2 (±14.2) kg and were aged 41 (±22.6) months old. None of the dogs entered the study with a specific problem behavior as perceived by their owner. Owners assessed their behavior for seven weeks after treatment. Sexual behavior decreased in a majority of implanted dogs 3 weeks after treatment, and in all but two implanted dogs by 7 weeks (those two dogs' behavior had not changed). Owner reported aggression toward male dogs decreased in 79% of implanted animals by 5 weeks following treatment, and urine marking either remained stable or decreased in this timeframe.

In a study with the ARI (13), involving 26 dogs (age: 0.6–16 years, weight ranging between <10 kg and more than 30 kg) presenting hypersexuality, clinical signs decreased significantly in 24 dogs. Loss of libido was generally detected 8 weeks after implantation. In 19 dogs combining hypersexuality and aggressive behavior, a significant improvement of both conditions was detected in 10 of them as described by their owners (13)[4].

It appears that GnRH agonist releasing implants are an alternative for those seeking change in testosterone mediated behavior in male dogs, without undergoing castration, or as a trial to what might be achieved by permanent sterilization.

Treatment of Benign Prostatic Hyperplasia in Intact Male Dogs

Benign prostatic hyperplasia (BPH) is a common pathology of the intact male dog, with 47.5% of old (mean age 7–8.6 years) dogs ($n = 1{,}003$) displaying abnormalities in prostatic features when examined by ultrasonography (33). As prostatic growth is testosterone-dependent, GnRH agonists can be used to reduce the size of the prostate gland (23) and therefore alleviate clinical signs of BPH. DRI and ARI (13, 25) have been studied for this purpose.

Evaluation of the efficacy of DRI in dogs with clinical symptoms of BPH has been conducted in small studies. In one trial, where eight client-owned dogs diagnosed with BPH were treated with a 4.7 mg deslorelin implant and monitored for 24 weeks, the dogs' prostates shrunk steadily to 75% reduction at 16 weeks (34). A second study in six dogs with BPH using a 4.7 mg deslorelin implant reported a progressive shrinkage of prostate volume starting on day 11, becoming significant on day 37 and reaching minimal values (around 20% of its initial volume) on day 52 post-treatment (25). In another study using the ARI and involving 18 dogs, prostatic size had decreased by 45 and 59% at week 8 and 26 post-treatment, respectively. Clinical signs present at inclusion progressively vanished during the first 8 weeks post-treatment (13). Based on these 3 studies, it may be concluded that GnRH agonist releasing implants are an effective method to treat BPH. It is important to note that initially, due to the "flare-up" effect of deslorelin treatment, it is possible that clinical signs associated with BPH may increase for a short period of time.

ADDITIONAL CONSIDERATIONS FOR HEALTH AND WELFARE OF MALE DOGS

Beyond the direct effect of rendering a dog sterile, surgical neutering has been found to decrease the incidence of some health conditions, and increase that of others, as compared to dogs who remain intact. GnRH agonist releasing implants could, in theory, have the potential to impact the probability of certain undesirable conditions (such as obesity and cancer) while still offering contraceptive benefits. Although existing research is insufficient to draw conclusions about the effects of GnRH agonist releasing implants relative to surgical castration or no fertility control, the health conditions noted below are areas warranting further research.

Obesity

Gonadectomy is associated with higher incidence of obesity in dogs in several studies (35–37), and neutering is generally considered to be a risk factor for weight gain (38).

[4]In this study, researchers described the term hypersexuality as comprised of excessive mounting, whining, refusal of food uptake due to the presence of bitches in heat, and stray behavior; the term aggressiveness comprises aggressiveness against other dogs and man (including dominant behavior), either alone or in combination. Beyond the 10 dogs described in this passage, in another three dogs, signs of hypersexuality fully improved with an only partial improvement of the signs of aggressive behavior. In four cases, aggressive behavior did not improve while hypersexuality disappeared. Treatment had no effect on aggressiveness in two dogs, but signs of hypersexuality were partially improved.

There is very limited information documenting whether factors contributing to obesity following surgical sterilization also exist following fertility control using GnRH agonists releasing implants. Clinical studies with DRI were not designed to evaluate this outcome, as they were mostly involving small sample sizes (therefore generating a limited statistical power) of breeds with a wide range in body weights. In addition, the limited duration of such studies may have been too short to pick up long-term changes in body weight. Among the limited data that exist, one 5-month study found that 10 out of 14 adult male dogs demonstrated a voluntary increase in food intake following DRI treatment, although changes in weight were not measured (39). Two studies involving prepubertal dogs of each sex treated with DRI did not show notable differences in body weight over periods of 40 weeks ($n = 4$ controls and 9 treated dogs) (30) or 32 months following treatment ($n = 3$ controls and 8 treated dogs) (29) between treatment and control groups. However, sample sizes in these studies are believed to be too small to generate solid information.

The strongest evidence documenting body weight changes following fertility control with GnRH agonists was generated in a study in prepubertal bitches treated with an ARI (40). In this study, 20 Beagle bitches (10 pairs of sisters) were either treated with an ARI left *in situ* for 1 year or a placebo implant, and body weight was measured monthly. The experimental design (using pair of sisters allocated to specific treatments) optimized statistical power. This study demonstrated no increase in body weight in the sisters exposed to the ARI for the 12 months of treatment vs. the control pair. Additionally, in a follow up study of 53 client-owned male dogs receiving an ARI, 50/53 dogs did not demonstrate any increased appetite and weight gain according to their owners (13).

Although data on male dogs and DRI specifically are limited, if confirmed, less likelihood of weight gain might be an attractive feature of the implant rather than traditional neutering. In addition, obesity (if developed following fertility suppression using GnRH agonists) might be reversed by interrupting treatment. Further research in this area is needed both to explore the interaction between age of administration and the effect of treatment on body weight in male dogs, and to directly address a comparison between neutering vs. GnRH agonist implant treatment on body weight.

Cancer

In one published study comprising over 120,000 canine diagnostic records, prevalence of lymphoma, mast cell tumors, osteosarcoma, and adenoma/adenocarcinoma was increased in neutered male dogs relative to their intact counterparts (41). (It is important to note that this was not a prospective study and correlation does not prove causation).

With lymphoma specifically, the role of increased LH concentrations induced by neutering has been hypothesized to play a role in initiation of cancer because LH receptors have been detected in dog lymphocytes through use of immunohistochemistry and flow cytometry (42). Although additional research is needed to demonstrate that the LH receptors detected on lymphocytes are functional receptors that bind LH and activate the intracellular signalization cascade, treatment with GnRH agonist implants decreases serum LH, in contrast to the increased serum LH levels seen in surgically castrated dogs. Therefore, some have hypothesized that if the LH receptors found on lymphocytes are somehow related to the development of lymphoma, then GnRH agonist use, instead of surgical castration, may reduce the risk of lymphoma or its rate of progression. Research is needed to explore this hypothesis.

HUMAN ATTITUDES, BEHAVIOR, AND NON-SURGICAL FERTILITY CONTROL

When focusing on neuter status of companion animals in particular, human behavior is an essential variable. By extension, it warrants consideration when discussing ways GnRH agonist releasing implants can be of value for male dogs.

Drawing from studies conducted in various countries, there are a number of interconnected factors that have been shown to influence individual pet owners' choices regarding surgically neutering their dogs. These include the procedure's effects on an animal's reproductive capability, health, and welfare, and behavior, as well as personal beliefs about the procedure's associated pain or necessity (all of which can generate arguments for or against the procedure); the procedure's cost and accessibility; veterinary advice; and fundamental awareness and knowledge that castration is an option (27, 44–49).

It seems likely that if these factors influence decision-making regarding surgical castration, they could influence decision-making regarding non-surgical contraceptive alternatives, as well.

There are a limited number of studies on human behaviors regarding surgical castration compared to non-surgical fertility control for companion dogs in general (50–52), and fewer still on attitudes and behaviors regarding use of the commercialized DRI, Suprelorin specifically (53, 54). Surveys to date have been conducted among veterinarians. While not the ultimate decision-makers regarding use of a product or procedure, veterinarians are a key influencer of owners' and guardians' decisions around whether and how to control the dog's fertility. Despite their limited breadth, these studies provide insight into the reasons why the DRI is used in European countries and serve as a foundation for envisioning how the product might serve male dogs, as well as their owners and guardians.

In an online survey conducted in the United Kingdom and completed by 411 veterinary surgeons, 62% of respondents reported that they always recommend surgical neutering of male dogs not intended for breeding; a higher percentage (94%) do so for female dogs. Among the veterinarians surveyed 33% named Suprelorin as an alternative they offer to surgical neutering for male dogs (53).

A small online survey focused on Suprelorin was conducted with 14 European general practice veterinarians and reproductive specialists. Given the small sample size, results are anecdotal. Overall, respondents reported that ∼60% of their male canine patients are left intact, 25% are castrated, and 15% are treated with Suprelorin. All 14 respondents use Suprelorin in their

practices, with the majority having offered it in their practice for more than 5 years.

These veterinarians mainly treated male dogs with the 4.7 mg implant. In order of frequency, the reasons they recommend Suprelorin are:

- When surgery is a risk (age/risk of anesthesia)
- To provide reversible fertility suppression of breeding males
- When owners are reluctant to castrate
- As a "test-run" before surgical castration
- When male and female dogs are living in the same household for a temporary period
- To manage inappropriate behavior
- When owners want to avoid any risk of reproduction
- To treat BPH
- To treat perianal gland tumors.

Some practitioners reported using Suprelorin off-label in dogs and other species. In dogs, off-label uses included treatment of BPH in intact males and Alopecia X or sexual aggression in castrated male dogs, and both estrus suppression in female dogs and estrus induction in breeding bitches.

Respondents in this small survey reported that typically the veterinarian suggests use of Suprelorin more so than clients requesting it. They estimated that roughly 85% of veterinarians and about 50% of dog owners are aware of the product. These same professionals reported that about 80% of their clients are either extremely satisfied or somewhat satisfied with the product (equally divided).

IMPLICATIONS FOR USE OF THE DESLORELIN RELEASING IMPLANT

When viewing the possibilities of the commercially available DRI as an option for veterinarians and those caring for male dogs, here are a number of factors that are worth considering.

Dog Health and Behavior

Increasing research is taking place into the health effects of surgical castration. At present, findings are somewhat conflicting in terms of the "cost-benefit" analysis for castration, with variables including but not limited to dog breed, size, and age at the time of the procedure [see (43, 55–57)]. Assessments of behavior, and the effects of neutering on male dog behavior, are similarly complex.

This noted, data suggest that the DRI can have a positive effect on benign prostatic hyperplasia and on some behaviors in male dogs as reviewed in this paper. Equally significant, it offers the benefit of "trialing" the effects of castration on behavior or health considerations of interest to the particular dog owner.

Cost

The price of a DRI to the client includes the cost of the product itself, the labor cost for the veterinarian to conduct a physical exam on the animal and insert the implant and the mark up on both of these components.

In the small online survey of European veterinarians, there was significant variation in the cost to clients for treatment with the DRI; there was also significant variation in the cost of castration surgery. In general, the cost to the client of implanting a dog twice with the 4.7 mg implant would approach the cost of castration surgery (58).

The DRI is not an inexpensive alternative to surgical sterilization, particularly when repeat dosing is desired for ongoing fertility suppression. Its value may be better realized in other capacities, discussed below.

Owner Preferences and Access to Care

One of the primary values of the deslorelin releasing implant, in the authors' opinion, is fulfilling owner preferences for veterinary care. Veterinarians' survey responses to why they recommend a DRI suggest that there is some demand for alternatives to surgical castration.

There is value in giving pet owners a way to prevent their dog from reproducing without permanently altering his physical appearance, removing his testicles, or requiring surgery and associated anesthesia risk. In addition, the value of a "test run" prior to surgical castration, as some veterinarians noted, should similarly not be overlooked. Due to the fact that this DRI has the same effects on testosterone as surgical castration for its duration of efficacy, owners can preview whether their dog's behavior would change if he were castrated and make a better informed decision about how to proceed.

Finally, the technology could offer value to dog breeders to postpone breeding until a dog's initial quality as a stud can be assessed, or permit male dogs taking a break from breeding to interact with bitches without concern of unwanted litters and, potentially, undesired behaviors. However, the variability seen among individual animals, combined with general trends of duration of efficacy relative to the dog's size, need to be taken into account when planning for product use and breeding schedules.

CONCLUSION

GnRH agonists releasing implants offer a demonstrated safe, effective means of temporary chemical suppression of testosterone and of fertility without surgery. This suppression may be extended if several implants are used sequentially. Some effects of such treatments are similar to surgical castration, and others differ. This technology offers an alternative to meet owners' individual preferences and needs for veterinary care. Further research is warranted on potential health benefits of GnRH agonists releasing implants unrelated to fertility control.

AUTHOR CONTRIBUTIONS

JB conceived of the project. The manuscript was researched, written, and edited by MD and JB. All authors read and approved the final manuscript.

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Surgical and Behavioral Relationships With Welfare

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Veterinarians perform surgery for a number of reasons, from treating a problem to preventing future problems. There is an inextricable link between the physical and psychological aspects of an animal's health, and surgery is often a conduit to bridge that gap. Some surgical procedures can affect an animal's behavior, such as castration, and some pose an ethical dilemma, such as ear cropping and declawing. Ameliorating pain, decreasing stressful experiences for the animal, and identifying and treating concurrent problem behaviors are hallmarks of improving animal welfare. The purpose of this article is to outline some of these interrelationships and ethical dilemmas, providing evidence-based verification as applicable.

Keywords: animal, behavior, surgery, human-animal bond, medical, ethics, welfare

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INTRODUCTION

Problem behaviors are often cited as reasons for relinquishment and euthanasia of companion animals (1, 2). While not often thought to correlate with behavior, behavioral effects of surgery are commonly seen, but sometimes not fully understood. Surgery is a principal aspect of veterinary medicine, whether performed to treat a medical condition, to lower the incidence of disease, or for population control, and it is important to understand the impact that surgery has on the welfare and behavior of an animal. The effects on the behavior and, subsequently on the human-animal bond and welfare, should be taken into consideration when consulting with clients, either directly via the outcomes from the surgery, or via changes to the animal's behavior.

HISTORY

John Hunter (1728–1793) is credited as the founding surgeon in human medicine. Discoveries at this time helped advance this area of medical care, with a primary focus on treating battlefield trauma, progressing to the treatment of other medical problems unrelated to trauma. In the veterinary medicine, however, advancements were not quite so quick. Until the 1920s, veterinary surgery was mostly limited to neutering and wound repair. As an example, aseptic technique was not utilized in large animal surgery until after World War II.

To demonstrate the rising importance of surgery in veterinary medicine, the American College of Veterinary Surgeons (ACVS) was founded in 1965 (3). The ACVS is a specialty board recognized by the American Veterinary Medical Association (AVMA) Boards of Veterinary Specialties and sets the standards for advanced professionalism in veterinary surgery. Although there is a higher level of training for specialists, all veterinarians are legally allowed to perform surgery. It's uncertain what percentage of all surgeries are performed by specialists compared to those performed by veterinarians in general practice or in conjunction with shelter, rescue, or other organizations. Given the greater number of veterinarians in general practice, and that veterinarians performing up to 45–50 surgeries per day in shelters, it is likely that non-specialists perform more total surgeries (4).

Understanding the inter-relationship between medical and behavioral problems in animals has been a point of discussion for a number of years. Some of the earliest documentation of this relationship is in the area of feline inappropriate urination (5–7). One of the earliest review articles of medical differentials for problem behaviors was published in 2003 (8).

SURGERY PERFORMED FOR UNDERLYING PROBLEM BEHAVIORS

Some surgeries are performed as emergency procedures related to an underlying problem behavior. Examples include surgery to treat a cat presenting for being hit by a car (transitioned to an outside cat due to inappropriate elimination in the house), a dog requiring multiple extractions of broken teeth from escaping its crate (due to separation anxiety), or a dog requiring a gastrotomy to remove rocks (due to pica). Others are performed to prevent or "treat" problem behaviors.

Emotions often run high for clients when going to a veterinary clinic for an emergency, as frequently they must make a hurried decision about the healthcare of their pet. Effective communication doesn't need to take more time, but perhaps takes a more concerted effort to overcome potential limitations of not having a long-lasting relationship with a client (9). It takes time for veterinarians and their staff to become culturally competent to most effectively gather information, as well as be comfortable asking open-ended questions to more efficiently gather information. Informed consent plays a role in all aspects of veterinary surgery, whether emergency or elective (10). It is necessary, however, to be able to obtain consent in a more truncated fashion in an emergency, where shared decision making may not be at the forefront of the process. Training in successful communication has received more attention in veterinary schools as of late, and is listed as highly sought after by veterinary employers (11).

These skills provide veterinarians with tools to investigate how problem behaviors may play a role in the presenting complaint, a skill in which veterinarians currently lack experience (12, 13). While it is important to provide urgent care, once the animal is stabilized, veterinarians should investigate the underlying reasons for the presentation. Although an individual veterinarian, such as a veterinary surgeon or one who is working in emergency and critical medicine, may not directly address the underlying behavioral reason for surgery, they should acknowledge the existence and offer resources for referral or treatment. These resources can include referral back to the pet's primary veterinarian or to a veterinary behaviorist.

PERI-OPERATIVE PAIN MANAGEMENT

Surgery, by design, involves incisions and tissue manipulation. These interventions cause discomfort at best, and intractable pain at worst. Veterinarians are increasingly aware of the need to identify and treat pain, but are often presented with challenges, sometimes brought about by their underlying attitudes (14–16). There are even some misconceptions on how different dog breeds perceive pain (17). Aside from the concerns surrounding ameliorating pain, one must also consider the role that pain plays in problem behaviors (18).

Identifying pain in animals is a growing competency. Whereas previously it was thought that some pain post-op helps keep the animal quiet, thankfully these beliefs are changing. There are different checklists and criteria by which veterinarians can measure pain in animals (19). Even with these measurements, there is sometimes a lack of agreement between veterinarians when evaluating levels of pain (20, 21).

Control of pain, whether related to an underlying physiological condition or due to post-operative complications, can be attained via a number of methods, and include nonsteroidal medications, opioids, and local anesthetics, along with other means such as physical therapy. Pain management is the subject of an increasing number of research studies and subsequent books and book chapters (22–24).

PERI-OPERATIVE BEHAVIORAL MANAGEMENT

Behavioral management pre- and post-operative is also an integral part of decreasing stress surrounding these procedures. Many studies have demonstrated that animals exhibit stress-related behaviors and undergo physiological changes related to visiting a veterinary clinic (25–28). A study of dogs undergoing elective spay and neuter surgeries, with appropriate pain control, resulted in decreased interactive and exploratory behaviors, increased cortisol levels, short-term lymphopenia and eosinopenia, and long-term neutrophilia and monocytosis (29). It is uncertain whether these results were related to incomplete pain control or other stressors.

It is imperative that all staff in veterinary practices use appropriate means to alleviate anxiety, aside from pain control. These can include low-stress handling methods, playing music, and suitable housing. This is an increasing area of research, and many resources are available by which staff can learn and practice these techniques (30–37). Effective pharmacological interventions include trazodone, gabapentin, and transmucosal dexmedetomidine, as well as the use of pheromones (26, 38–42).

Kenneling animals in a veterinary clinic can be another source of stress. Kennels should be configured with the animal's physical and psychological comfort in mind whenever possible. One should remove collars and harnesses prior to placing in the kennel, as they can be choking hazards. If a cat is in a carrier, the open carrier can be placed inside the kennel until the cat exits the carrier, leaving the kennel in there as a hiding place for the cat.

All signs on the cage and notes in the medical record should be heeded, and the animal's behavior upon approach to the kennel should be assessed. Depending on the level of waste, etc., kennels should only be spot-cleaned during a patient's stay, and its "furniture" placed back in the same locations as the animal moved them. Of course, the kennel should be sanitized between patients or if the level of mess is at a critical level. The same towel and litterbox should be placed back into the cage if they are not

dirty, to maintain a familiar scent. Animals should be provided with a place in which to hide or hide behind, such as a box for a cat or a towel covering the kennel door for all species, aside from those that require 24 h per day observations.

Environment outside of the cage should also be managed. Animals are sensitive to noise levels and can hear sounds outside of our level of hearing. Keep noise levels to a minimum (<60 dB—quiet conversational level), and keep dogs away from cats. Also, be sensitive when opening and closing cage doors as the metal clanging is jarring. Music can be played to help block out other sounds, but should be played at a quiet level. Studies show a potential for classical music to have a calming effect on animals (33, 43–45). Cats prefer a much warmer environment than what we prefer, between 35 and 38°C. Offer cats large towels so that they can burrow underneath, if desired, to help them maintain their preferred ambient temperature.

Staff should educate clients on how best to perform specific medical procedures required at home, both to prevent problems from occurring, as well as to help owners perform procedures when necessary. As examples, if owners are taught how to clean out their dog's ears, or how to give medications safely and effectively, they will be more likely to give their pet appropriate medical care. Depending on the medical or surgical procedure performed, different handling techniques should be highlighted, such as wound care, bandage changing, physical therapy, and bladder expression. Overarching all of this is proper pain control and medical management; if something is painful, no amount of behavior modification or low-stress handling will help the animal tolerate procedures.

Crate training prior to surgery can dramatically improve a dog's ability to cope with post-surgical confinement. Most dog owners have heard of crate training, but may not know how to effectively implement it. It takes time, effort, and patience, but when used properly, it can be a positive experience for both the owner and their dog. A dog cannot be expected to tolerate being in a crate post-operatively if it had never been trained prior, and if placed into a crate without behavior modification ca exacerbate its anxiety (46). Resources are widely available, including in veterinary behavior textbooks (47–49).

While it is ideal owners follow the recommendation for 100% confinement post-operatively, this likely will not occur, and they should be given explicit advice on how to interact with their pet. Such instructions can include the proper use of a sling to help a dog walk, safe ways to carry a pet, and what collar and leash to use. They should be given assorted ideas on how to safely provide for low-activity mental exercises, including food puzzle and toys and training exercises, such as the Protocol for Relaxation[1] (50).

BEHAVIORAL TREATMENT OF UNDERLYING PROBLEM BEHAVIORS

It is critical to address the underlying problem behaviors associated with the condition for which an animal requires medical care. Many textbooks provide veterinarians with detailed information on diagnosing and treating a myriad of problems (47, 48, 51).

As is the case in all areas of veterinary medicine, it is important to have a correct diagnosis in order to properly treat behavior problems (52). In one study of urine marking cats, almost a third of veterinarians did not meet the criteria of correctly diagnosing urine marking. Of those that did not mention the classic symptom of vertical urine marking, only 10% said that they had success in treatment (53).

Treating problem behaviors can be summarized in a "Five Step Treatment Plan." These steps include management, relationship building, behavior modification (including desensitization and counterconditioning), tools, and pharmaceutical and other therapeutic treatments. While listed separately, they often overlap one another when one develops a treatment plan (54).

Management includes avoiding the trigger that causes the animal to either be placed into an undesirable emotional state, such as anxiety or fear, or display the unwanted behavior. Each time that the animal is in this situation it is then fearful or anxious. It also allows the animal to "practice" the behavior. An example of management is covering the front windows to prevent a dog from seeing passersby, thus, decreasing its barking behavior. Avoidance is also a safety recommendation, as a dog cannot be placed into a situation where it feels that it "needs" to bite someone.

Relationship building is a broad category covering educating the owner on an animal's emotional state (and the behavioral signs that signal such states), proper training techniques, and utilizing cues to teach an alternative behavior in a predictable and humane way. Some parts of this step can include: "Say Please" in which an animal is asked to perform a cue before a desired reward; and teaching cues that one can use to redirect in the future, such as "look" or "target." A significant portion of this step may be spent refocusing the owner from using harsh punishment-based training techniques that can instill fear and anxiety in animals which increases the likelihood of a problem behavior surfacing.

Behavior modification is primarily focused on systematic desensitization and counterconditioning (DS/CC) toward the trigger that causes the animal to feel distressed and display unwanted behaviors (55). This is a process in which a conditioned emotional response (CER) such as fear is extinguished by exposing the animal in a graduated manner to the fear-eliciting stimuli, and replaced with an alternative, competing response by pairing it with an eliciting stimulus that will trigger an opposing emotional or physiologic response. When creating a program for systematic DS/CC, a stimulus hierarchy is created which ranges from a level that elicits no discernable response to a level that elicits an extreme response. The animal is exposed to the first step in this hierarchy, where it shows a very mild response, such as noticing that the trigger is present, until the mild response is no longer being displayed. Once this occurs, the animal is exposed to the next step on the stimulus hierarchy. All the while the animal is presented with something that will change the emotional response to one that is favorable toward the trigger, such as a high-value treat.

[1]Available online at: https://championofmyheart.com/relaxation-protocol-mp3-files/

For example, a show cat may need to be bathed and dried prior to a show. If the cat is afraid of the sound of the blow dryer, the sound of the dryer can be paired with a favored food, which elicits pleasure. It is even more beneficial if the cat never gets this favorite food unless it is going through desensitization and counterconditioning. Counterconditioning occurs only if the new eliciting stimulus triggers a response powerful enough to supersede the original CER. If the cat is extremely afraid of the sound of the dryer, it is very likely that it will not eat in the presence of the blow dryer. By minimizing the intensity of the original conditioned stimulus, the new eliciting stimulus is likely to be salient enough to overcome it.

Tools are such products that are used to help implement management, relationship building, and behavior modification. Such tools include: muzzles, baby gates, and hiding places for cats (for management); clickers, treats, and toys (for relationship building); and leashes, harnesses, and treats (for behavior modification).

Pharmaceuticals and other therapeutic treatments are often needed to treat underlying anxiety that is hindering the effectiveness of behavior modification. Medications by themselves are not the answer, similar to how antibiotics are themselves not the answer for treatment of a cat bite abscess. Foundations of pharmaceutical interventions include quick-to-onset anti-anxiety medications, such as benzodiazepines, trazodone, gabapentin, and clonidine, and longer-to-onset medications, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Other therapeutics include pheromones, nutraceuticals, and special diets (56, 57).

There are specific behavioral treatments for the disorders for which surgical treatments have been suggested. Management, behavior modification, and perhaps the use of psychoactive compounds are the hallmarks of treatment for aggression, urine marking, barking, and scratching behaviors or, more specifically, the underlying reasons for these problems (58–60).

ELECTIVE SURGICAL PROCEDURES AND ANIMAL BEHAVIOR

Castration and Ovariectomy/Ovariohysterectomy

Americans have been enculturated over the past number of years that one must neuter companion animals to prevent unwanted litters. The current estimate is that a high percentage of dogs in the United States are neutered and, even though there are recent shifts toward later neutering, it is often performed prepubertally, prior to 6 months of age (61). A survey of veterinarians in New York state demonstrated that 70% of veterinarians routinely recommend neutering for all dogs and cats, while roughly 35% believed that client-owned animals should not be neutered until at least 6 months of age (62). There are different attitudes toward neutering in other countries. As an example, roughly 15% of veterinarians in the U.K. believe that pre-pubertal neutering is not desirable, compared to roughly 8% of veterinarians in Australia and New Zealand (63). Reasons veterinarians give for neutering, especially at a young age, include the prevention of mammary and prostate cancers in females and males, respectively, that it prevents or helps decrease the chance of problem behaviors in dogs, and that it decreases pet overpopulation. The AVMA has a policy supporting pediatric spay and neuter of dogs and cats to reduce the number of unwanted animals, stating "*veterinarians should use their best professional judgment based on the current scientific literature in deciding at what age spay/neuter should be performed on individual animals*"(64). This in contrast to the British Small Animal Veterinary Association, which while recommending it for population control, states "*Before neutering for reasons of undesirable behavior it is important to consult a veterinary surgeon or animal behaviorist to ascertain the role of sexual hormones in the development and maintenance of the behavior* (65).

There is conflicting research on the potential positive, as well as harmful, outcomes from neutering. Veterinarians frequently cite the prevention of mammary gland cancer as a reason to spay dogs. However, a recent meta-analysis of published studies found that the link between ovariectomy in females and mammary cancer is weak at best (66). The link between castration and prostate cancer in dogs is even weaker, with some research showing an increased risk of this cancer in castrated dogs (67, 68). Aside from these medical conditions, more research is emerging on the potential negative effects of these surgeries. Increases in other types of cancer (osteosarcoma, hemangiosarcoma, lymphosarcoma, and mast cell tumors), orthopedic disease, immune-related disorders, and urinary incontinence are reported (69–77).

Sexually dimorphic behaviors are defined as those predominantly seen in one sex or another, and many are associated with reproduction or mate attraction. These behaviors are more strongly affected by castration. Castration usually abolishes overt sexual behavior in males, except for the more experienced the male, the longer mating behaviors persist (78).

The effect of castration on cat behavior can be quite dramatic. Fighting, roaming, and spraying are markedly reduced or eliminated in 80–90% of cats, usually with a rapid decline (79). There is no evidence of a relationship between age at time of castration and persistence of these behaviors, and neutered cats can still display these behaviors. Of castrated male cats, 10% are reported to be problem urine markers, while 5% of spayed female cats are reported to be problem urine markers (80).

Castration's positive effects on dog behavior are not to the extent seen in cats. Most improvement is seen in urine marking, mounting, and roaming behaviors, all of which are predominantly sexually dimorphic behaviors. There are additional behavioral reasons for these behaviors. As with cats, urine marking can be a symptom of an underlying anxiety-related disorder. Unrelated to sexual behaviors, mounting behaviors can continue as way of social communication or in a display of hyper-arousal in castrated dogs. Roaming behavior, which is related to mate-seeking behavior, can also be due to escape behavior, a symptom of separation anxiety in dogs. As with cats, there is no evidence of relationship between age at time of castration and persistence of these behaviors (81).

There is conflicting evidence on the effect of neutering on aggression in dogs. One paper demonstrated there was a decrease

in aggression toward people and dogs after castration (81). However, another study found castrated dogs were no less likely to demonstrate aggression (82). Results from a paper evaluating the effects of gonadectomy in Viszlas were that the younger the age at gonadectomy for males and females, the earlier the mean age of diagnosis of a behavioral disorder (83). Results from another paper concluded that there was an increase in the odds of aggression toward unfamiliar people for all gonadectomized dogs compared with intact dogs. They determined this effect primarily seen in dogs gonadectomized at 7–12 months of age (82).

Ovariectomy usually abolishes sexual behavior in females. Alternatively, there is evidence that ovariectomy is correlated with an increase in aggression. One study demonstrated that, if a dog already displayed aggression as a juvenile, if spayed at <1 year of age, there was an increased chance of aggressive behaviors (84). The results of another study showed increased reactivity in spayed German Shepherd Dogs compared to those that were intact (85).

One must differentiate an ethical choice to neuter for pet population control, from a welfare choice for positively, or negatively, affecting an individual animal's welfare, which are both separate from the choice to neuter for the owner's benefit. While benefits of castration for cats are more conclusive, aside from population control, there is no definitive single recommendation for whether or not to neuter dogs, or at what age, and owners should make an educated decision after discussion with their veterinarian.

Tail Docking (Amputation)

This procedure, amputating the distal portion of the tail, is "traditional" for certain breeds, such as hunting breeds and terriers. Reasons cited to have the tail docked include the potential to prevent injuries and to be able to more easily pull a terrier out of the ground when hunting (86). In some circumstances, the breeder will dock the tails, while other times a veterinarian will do it, and it is usually performed within a few days of birth. In Australia, the procedure is regulated and "*…should only be carried out in respect of those breeds with a known history or propensity to injury and/or damage in their tails in the course of their normal activities for therapeutic and/or prophylactic purposes…*" (87). Some states have also regulated this procedure (88). National veterinary medical associations also have position statements about cosmetic surgeries, including the statement from the AVMA which "*…opposes ear cropping and tail docking of dogs when done solely for cosmetic purposes. The AVMA encourages the elimination of ear cropping and tail docking from breed standards*" (89, 90). And one large veterinary corporation has banned the procedure for cosmetic reasons (91).

A survey conducted in Australia found that 75% of veterinarians believed that tail docking causes significant to severe pain, with none believing that dogs do not experience pain during this procedure. In contrast, roughly 80% of breeders believed that puppies experienced either mild or no pain (92). While there should be no argument that this procedure is painful, as part of the tail is amputated, it is uncertain for how long the pain lasts. One paper suggests that the pain experienced is relatively short-lived in dogs undergoing tail docking, and that, at the time of publication, only 10% of veterinarians used analgesics (93). While there are limited studies in dogs, there is evidence of behavioral and physiological responses to pain in production animals undergoing tail docking procedures (94). There are also behavioral effects from this procedure. Dogs showed more cautionary behaviors toward a short-tailed dog. The hypothesis is that it may be more difficult for the dog with the docked tail to signal appropriately to other dogs (95).

There is some evidence that dogs with intact tails are more likely to sustain injury to the tail compared to dogs whose tails were docked (96, 97). However, another study demonstrated that only three out of 2,000 visits to an emergency clinic in Australia were due to tail injuries; all three of these were due to post-docking complications (98). Currently, there is no evidence that pain due to tail injuries of dogs with complete tails is worse or more difficult to manage than the potential for chronic pain from tail docking. Therefore, one should weigh the pain from an unlikely injury against certain pain from tail docking.

There are flawed arguments in favor of tail docking in dogs. The most flawed one is in favor of tradition. Arguments in favor of tradition reflect an inherent sense of superiority of humans, and a disregard for the status of dogs in our society, especially as we have transformed from an agrarian to more urban society. If tail docking is done to prevent unlikely injuries incurred while hunting, we should ask the question: what is the likelihood for a particular dog to actually hunt? Given these weak arguments, there is little evidence to support the continued practice of tail docking.

Ear Cropping (Cosmetic Otoplasty)

Ear cropping is a procedure in which the external pinna is reshaped to obtain an erect ear, usually performed when a dog is roughly 2–3 months of age. It is considered breed standard for some breeds, such as Doberman Pinschers and Great Danes. While breed clubs within the American Kennel Club (AKC) determine whether or not breed standard include cosmetic alterations via ear cropping or tail docking in order to show a dog in an AKC trial, owners of dogs with natural ears and tails report discrimination against them, as they are infrequently selected as winners (99, 100). Some states regulate ear cropping so that a licensed veterinarian must perform the procedure; Washington prohibits the procedure except when it is considered a customary husbandry practice (88). As with tail docking, some national veterinary medical associations have position statements against ear cropping in dogs, especially if done solely for cosmetic reasons (89, 90). As with tail docking, one large veterinary corporation has banned ear cropping for cosmetic reasons (91).

One erroneous argument made for ear cropping is to prevent illnesses and injuries in spaniels, terriers, other hunting dogs, and dogs with pendulous ears; however, there is no evidence to back up these claims (101). The etiology of otitis is related to many factors, including allergies, and breeds historically shown with cropped ears are no more likely to be diagnosed otitis (102–104). There should be no argument that this surgical procedure causes pain. As with tail docking, people will provide the argument in favor of "tradition" to support the continued practice of ear

cropping. Given these weak arguments, there is little evidence to support ear cropping.

Devocalization (Ventriculocordectomy)

Ventriculocordectomy is the partial or complete surgical removal of the vocal folds to reduce the volume of a dog's bark. Dogs still "bark," and if not prevented from vocalizing post-op, are able to regain the ability to produce some sound. This surgical intervention does not address underlying reasons for barking, such as anxiety, social facilitation, aggression, and stereotypies, as well as being a more breed-typical behavior (105–107). Treating only the symptoms of any problem can actually increase behavioral and physiological stress, as evidenced in research performed on the use of anti-bark collars (108). The results of this study demonstrated that, while both electronic and citronella spray bark collars decreased barking, dogs wearing either collar had an increase in plasma cortisol. Another study demonstrated behavioral and physiological (salivary cortisol and heart rate) responses to an electronic shock collar (109). As with other elective procedures, veterinary organizations have published position statements and white papers on this subject. The AVMA policy states that "*Canine devocalization should only be performed by qualified, licensed veterinarians as a final alternative to euthanasia after behavioral modification to correct excessive vocalization has failed and after discussion of potential complications from the procedure with the owner*" and has a literature review supportive of this (110, 111). Some states passed various laws limiting or banning this procedure, including Massachusetts, Rhode Island, and Ohio (88). As with tail docking and ear cropping, one large veterinary corporation has banned devocalization (91).

Owner factors come into consideration when veterinarians are presented with a dog for devocalization. Until a bill was passed in 2012, landlords in California were allowed to require that a dog be devocalized as a condition of leasing (112). There may be pressure from neighbors to have their dog stop barking, sometimes resulting in tickets and fines from municipalities. Owners are faced at minimum with continued judgement and coercion, and at the gravest, pressure to relinquish or euthanize their pet. While treatment options exist for the underlying reasons for barking, some owners may find it difficult to adhere to the treatment recommendations. As such, the decision to devocalize or not turns into not only a welfare issue, but also an ethical dilemma, with devocalization balanced against potential relinquishment or euthanasia.

Dental Procedures

Procedures range from vital pulpotomies, which is an endodontic procedure of capping only the canines or all of the teeth, to extracting only canine teeth, to extracting all of the teeth (113). Each of these procedures has the potential for a negative outcome, from failure of a crown resulting in a fractured tooth, to failure of a vital pulpotomy, resulting in an infected tooth root (114).

When these procedures are performed to "treat" aggression and prevent injury, it gives a false sense of security, as these dogs still can bite and cause crushing injuries. It does not eliminate the underlying motivation for aggression. If the animal is placed into a situation in which it feels that it must bite, its welfare is negatively impacted.

National veterinary organizations and specialty organizations have provided policy statements on such procedures. The AVMA is "*opposed to removal or reduction of healthy teeth in nonhuman primates and carnivores, except when required for medical treatment or approved scientific research*" (115). The American Veterinary Dental College supports the removal of crowns of teeth in selected cases where other corrective measures have failed, but also states that the removal of teeth will not prevent injury (116). As there is, at best, little safety benefit, weighed against the pain and other negative outcomes, to having these procedures done, they should not be performed.

Declawing (Onychectomy)

Onychectomy is the surgical removal of the P3 phalynx, done to prevent the ability of a cat to damage the environment or injure people or other pets. Anecdotally it is estimated that up to 24% of cats in the United States are declawed (117). In a study on scratching behavior in cats, 52% of cat owners reported their cat to inappropriately scratch in the house; 65% of these cats reported their cat to inappropriately scratch at least daily. Respondents excluded from this study included those who owned declawed cats; of those owners, 45% chose to have their cat declawed to prevent damage, and 27% to prevent injury to people or other pets (118).

Feline rescue organizations and shelters historically have promoted the idea that declawed cats have a higher likelihood of being aggressive or eliminating inappropriately. Research into the circumstances surrounding declawed cats in shelters did not bear the same results (119). There were significantly fewer declawed cats in the shelter studied than would be expected based on the population at large. Where only 9% of the sheltered cats were declawed, it is estimated that 24% of the feline population at large at the time of the study were declawed. Additionally, there were fewer cats in the shelter reported to bite compared to population at large. Declawed cats also were no more likely to be euthanized at the shelter compared to cats that were not declawed; however, declawed cats stayed at the shelter longer. Owners surveyed after the procedure stated that they were generally satisfied or very satisfied with the procedure, and evidence of negative outcomes on behavior is limited (119–123). These numbers could be influenced by bias on the owners' part, as they elected to have their cats declawed.

It should come as no surprise that evidence shows declawing causes pain in cats, in part due to a number of surgical sequelae including retained bone fragments, osteomyelitis, excessive tissue handling during surgery, and complications from bandaging (124). While pain is an expected outcome of any surgery and should be ameliorated appropriately, there is evidence that there is short- and long-term pain due to onychectomy (124–129). Behaviors indicative of pain, such as forepaw shaking and laying on their side, were seen in cats that were declawed compared to those having a sham procedure performed (125). Although veterinarians provide pain control post-operatively, it does not seem to have a substantial immediate positive effect on a cat's gait; however, in one study (130), their gait was considered normal

by 6 months (130–132). In another study, more cats were non- or limited-weight-bearing at discharge in control cats than in cats that received butorphanol post-operatively. By the second day, there were no differences between owner-assigned lameness scores (133).

Surgical methods and adherence to appropriate technique affect the outcome for declawing, as with all surgeries. A recent study demonstrated that 63% of cats had radiographic evidence of P3 remnants, and this was most highly correlated with back pain, periuria, and aggression (128). These results were seen far out from the surgery date. Other studies demonstrated that there were fewer negative welfare outcomes in cats in which a CO_2 surgical laser was used (127, 134). Another study demonstrated that cats that underwent an onychectomy compared to a tendonectomy showed evidence of more pain and short-term behavioral changes (135).

Veterinarians have an evolving view on declawing. Two separate studies of veterinarians in Canada and the United States came to similar conclusions. Results included ∼75% of veterinarians performed this procedure, most of them after counseling the owners about alternatives. Of these veterinarians, 60% of them performed the procedure less than monthly and between 10 and 15% performed it at least weekly (136, 137).

There are alternatives to declawing to prevent injury to people or other animals, or damage to the household. Physical alternatives include nail trims and nail covers (138). The benchmark of treatment includes behavior modification and environmental management, such as providing appropriate outlets for scratching and other species-typical behaviors and needs, preventing access to objects that one doesn't want scratched, and addressing the underlying reason for aggressive behavior (60, 118, 139–144).

As with procedures mentioned previously, some national veterinary organizations and other animal-related organizations have published policy statements on declawing (145, 146). The Canadian Veterinary Medical Association "*opposes elective and non-therapeutic Partial Digital Amputation (PDA), commonly known as declawing or onychectomy, of domestic cats*" (146). The AVMA published a detailed literature review that summarizes the pros and cons of this procedure, as well as outline alternatives (147). The Cat Fanciers' Association and The Canadian Cat Association do not allow declawed cats to be shown in sanctioned shows (148, 149). And most recently, three large veterinary corporations have banned elective declawing surgeries (150). Some municipalities, and even some countries, have banned this procedure (88, 151–153). Until a bill was passed in 2012, landlords in California were allowed to insist that a cat be declawed as a requirement for leasing (112).

Despite declawing performed not infrequently, and despite the research on this procedure producing equivocal results if performed correctly with appropriate pain control, there is no direct benefit to a cat to be declawed, other than potentially remaining in the household and not being relinquished or euthanized for problem scratching behavior.

SUMMARY

Veterinary medicine is more than the sum of its parts. It is not medical OR behavioral, it is treating an animal as a whole; these boundaries blur as we understand more their interrelationship. With this knowledge, it remains imperative for veterinarians to understand the potential behavioral consequences of surgery, and understand the underlying motivations for problem behaviors in pets. It is also incumbent amongst veterinary professionals to be champions for the welfare of the animal, and be able to communicate those points to owners and the public.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Assisting Decision-Making on Age of Neutering for Mixed Breed Dogs of Five Weight Categories: Associated Joint Disorders and Cancers

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The early neutering of male and female dogs and its relationship to an increased risk of joint disorders and some cancers has recently become a concern, raising questions about the standard practice in the U.S. and much of Europe of neutering by 6 months of age. A noteworthy recent finding from this center is that there are major breed differences with small-dog breeds generally showing little vulnerability to neutering compared with breeds of larger body size. These findings on purebreds raise questions for dog owners and veterinarians about mixed-breed dogs. The purpose of this study was to examine a sample of mixed breed dogs of five weight categories using the same veterinary hospital database and diagnostic criteria for joint disorders and cancers as used in the newly published paper on 35 breeds and previous papers on the Golden Retriever, Labrador Retriever, and German Shepherd Dog. The weight categories were <10 kg (739 cases), 10–19 kg (546 cases), 20–29 kg (992 cases), 30–39 kg (604 cases), and over 40 kg (258 cases). Males and females were analyzed separately, as were various ages at neutering. The joint disorders examined were hip dysplasia, cranial cruciate ligament tear or rupture, and elbow dysplasia. The cancers were lymphoma, mast cell tumor, hemangiosarcoma, and osteosarcoma. There was no significant increased occurrence of one or more cancers, compared with intact dogs, in any weight category. However, in the three categories of dogs weighing 20 kg or more, neutering before 1 year generally was significantly associated with risks of one or more joint disorders above that of dogs left intact, commonly to 3 times the level of intact dogs, with sex differences in the degrees of joint disorders associated with neutering. For the dogs in the two weight categories <20 kg, no increased risks were found for joint disorders. This information can be useful to dog caregivers in deciding on the age at which to neuter specific dogs, and for veterinarians offering guidance to pet owners.

Keywords: spay, neuter, hip dysplasia, cranial cruciate ligament, elbow dysplasia

INTRODUCTION

Neutering male and spaying female dogs (both referred to as neutering) at or before 6 months of age has become routine in the US and much of Europe (1). In the US several states require neutering of all dogs before being released for adoption even if this is well before 6 months of age.

In the meanwhile, investigations have revealed that joint disorders and some cancers may increase in association with early neutering. For example, one study found that hip dysplasia and cranial cruciate ligament tears or ruptures were more likely in neutered than intact males and females (2). Another study found that neutering was associated with a 3-fold increase in excessive tibial plateau angle (3), which is a risk factor for cranial cruciate ligament disorders. Among studies on specific breeds are those on the Golden Retriever, Labrador Retriever, and German Shepherd Dog, revealing an increase in the incidence of one or more of the joint disorders with neutering in the first year to 2–4 times the 3–5% incidence in intact dogs (4–6).

Certain cancers are also known to be more likely in neutered than intact dogs. The occurrence of lymphoma was found to be higher in spayed than intact females (7), as was the occurrence of mast cell tumors (8) and hemangiosarcoma (9). In Golden Retriever females spaying at any age tested, up through 8 years of age, increased the risk of one or more of the cancers by 2–4% (5). A study of over 40,000 dogs utilizing the Veterinary Medical Database found that neutered males and females were more likely to die of cancer than intact dogs (10).

Neutering appears to even have an effect on brain function. A study from 2001 on older male dogs revealed that neutering males was associated accelerated signs of age-related cognitive dysfunction (11). A recent finding along these lines was that the absence of estrogen due to spaying was associated with accelerated brain aging in females (12).

Another paper gives data on increased risks of joint disorders and some cancers associated with neutering in some 35 breeds of dogs, and reveals wide breed-specific variability with some breeds having little vulnerability to neutering and other breeds rather pronounced vulnerability (13). Given that the majority of dogs adopted are of mixed breeds, the goal of this study was to derive data-based information for mixed breed dogs for guidance on the best age to neuter to avoid increasing the risks of joint disorders and cancers typically associated with neutering for those wishing to neuter adopted puppies. The intention was to use the same veterinary hospital database and diagnostic criteria for the diseases as was used with the published studies on the retrievers and German Shepherd Dogs and the paper on 35 breeds of dogs.

METHODS

Ethics Statement

No animal care and use approval was required because, in conformity with the campus policy, faculty of the University of California-Davis, School of Veterinary Medicine, are allowed use of the record system for research purposes. Strict confidentiality of the owners and their dogs was maintained.

Subjects

To handle the wide range of body sizes, and to address the issue that body size may influence vulnerability to neutering, five weight categories were established. These were: Small < 10 kg (<22 lbs.), Medium 10–19 kg (22–42 lbs.), Standard 20–29 kg (43–64 lbs.), Large 30–39 kg (65–86 lbs.), and Giant 40+ kg (87+ lbs.).

Study Parameters

The computerized record system of the Veterinary Medical Teaching Hospital (VMTH) at the University of California, Davis, with over 50,000 new cases currently per year, dating back 20 years, was used for the database. The occurrence of joint disorders, namely hip dysplasia (HD), cranial cruciate ligament tears or rupture (CCL), and elbow dysplasia (ED) were examined the same as in previous studies on the retrievers and German Shepherd Dog (4–6). Typically there were signs of lameness, difficulty in moving, and/or joint pain, and diagnosis was confirmed by orthopedic examination, radiographic evidence, and/or surgery. The diagnosis was made at the VMTH, or by the referral hospital and confirmed at the VMTH.

Records were also examined for the occurrence of cancers—those that had been reported to be increased with neutering, namely lymphoma (LSA), hemangiosarcoma (HSA), mast cell tumor (MCT), and osteosarcoma (OSA). For females, mammary cancer (MC), pyometra (PYO), and urinary incontinence (UI) also were tracked. The diagnosis of cancers was based on the presence of a tissue mass, lumps on the skin, or enlarged lymph nodes, and confirmed by appropriate blood cell analyses, chemical panels, histopathology, cytology, and/or imaging. PYO was confirmed by ultrasonic evidence and/or after removal of the uterus. UI was confirmed by frequent urination, urinalyses, and exclusion of urinary tract infection and/or other disease. If a diagnosis was listed in the record as "suspected," the case was excluded from the analysis for that specific disease. Prostate cancer in males, sometimes considered as comparable to mammary cancer, was not tracked because of the low incidence−−0.35% (14). If the cancer did occur more frequently, it would have been interesting to follow because the cancer tends to increase in incidence with neutering (14).

Joint disorders, cancers including MC, PYO, and UI were examined with regard to dogs neutered at < 6 mo., 6–11 mo., 1 year (12–23 mo.), or 2–8 years, or left intact. Appointments were tracked through 11 years of age. Because the median age of diagnosis of MC is about 10 years (15) tracking dogs through 11 years of age would be insufficient to catch many cases even if the case record had information extending to that age.

The case records of neutered dogs that developed a disease of interest were examined to confirm that the dog was neutered prior to the diagnosis or signs of the disease. If the dog developed signs of the disease prior to neutering, the dog was considered intact for that disease. However, it was still listed as neutered for any disease that occurred after neutering. If a disease of interest occurred before 12 months of age, the dog was removed for that disease analysis, but included in analyses of other diseases. The number of cases for various diseases therefore varied in the final analyses for different diseases.

TABLE 1 | Suggested guidelines for age of neutering for five mixed breed weight groups.

Suggested Guidelines for Age of Neutering: 5 Mixed Breed Groups								
	Males				Females			
	Leave intact	Choice	Beyond 11 months	Beyond 23 months	Leave intact	Choice	Beyond 11 months	Beyond 23 months
Small		✓				✓		
Medium		✓				✓		
Standard			✓				✓	
Large			✓				✓	
Giant				✓			✓*	

*Consider neutering beyond 11 months due to weight.

Summary of spaying and neutering guidelines based on findings regarding joint disorders and cancers. The term "choice" means there was no increased risk for any age of neutering.

In most instances, neutering age was not included in the records, and the cases were not included in the analyses. Of course, with the intact dogs, this was not an issue and this meant there were proportionately more intact cases in each weight category than would be expected in the general population. However, the specific proportions of intact or neutered dogs with a disease were not affected by the overrepresentation of intact dogs.

With regard to the data on joint disorders, there is the possible effect of body weight, as manifested in body condition score (BCS), because neutering is recognized as predisposing dogs to increased BCS and the occurrence of joint disorders (16). In previous papers (4–6) we found that among neutered dogs, the occurrence of joint disorders was not related to BCS; in the current paper BCSs are not reported.

Statistical Analyses

In the neutered and intact groups, survival analysis was used to test for differences with respect to the hazard of a joint disorder or cancer while adjusting for the differences in time at risk for a disease. *Post hoc* comparisons among the subgroups were based on least squares means of the hazard within each subgroup. The groups were compared initially using a Kaplan Meier life table analysis. Where the Kaplan Meier test showed significance at the $p < 0.05$ level, both the log-rank and Wilcoxon tests were used for further analyses. Joint disorders are expected to be seen at a similar risk throughout a dog's lifespan, so the log-rank test was used initially. If the log-rank test did not show significance but the Wilcoxon test did, the Wilcoxon test result was reported with significance level and marked by an asterisk. The reverse rule of thumb was used with cancers. For all statistical tests, two-tailed levels of significance were set at $p < 0.05$ and reported as either $p < 0.05$ or $p < 0.01$. Each weight group and sex was analyzed separately, and the *P*-values are reported in the tables for weight categories in **Appendix 1**.

RESULTS

A short paragraph below for each weight group summarizes the main findings on joint disorders and cancers for both males and females, and MC, PYO, and UI for females. Also included is a summary, for those wishing to neuter, with a suggested guideline for neutering ages for males and females to avoid increasing the risks of a disease under consideration.

In **Appendix 1**, each weight group is represented on a separate page and the numbers of intact and neutered males and females are given. In the **Appendix**, the percentages of dogs with each of the diseases are given for intact males and intact females as well as those neutered at various age ranges. Statistical analyses compared the occurrences of joint disorders and cancers between intact dogs and dogs of each neuter age. If the comparison was significant at either the $p < 0.05$ or $p < 0.01$ level, the data were bolded and the *p*-value was given. The detailed datasets are available online (Figshare, doi: 10.6084/m9.figshare.7231010).

Table 1 is a very brief summary of spaying and neutering guidelines based on findings regarding joint disorders and cancers for each weight group. In **Appendix 2** the mean age of last entry in the record for dogs in each weight group is given. Across all weight groups within the study range the mean age of last entry for intact males was 6.0 (range 5.13–6.73), for neutered males was 5.0 years (range 4.19–6.08), for intact females 4.9 (range 4.32–6.65), and for neutered females 5.1 years (range 4.19–6.08).

General Findings

In the five weight categories of mixed breed dogs, those weighing 20 kg and above had significant increases in joint disorders with early neutering. For those left intact, the occurrence of a joint disorder ranged in the Standard dogs from 1 and 4% for males and females, respectively, to 9 and 17% in the Giant male and female dogs, respectively. For Standard dogs neutered in the first year, the occurrence of joint disorders ranged from 5% and up to 12% in male and female dogs, respectively. It rose to 28% in Giant male dogs neutered at <6 months but did not increase in the Giant female dogs. In the two weight groups below 20 kg there was no significant increase in incidence of joint disorders above that of the intact dogs.

Of the cancers followed, the occurrence in intact dogs reached as high as 15% (higher in the heavier weight categories of dogs). There were no evident increases with neutering of males or females in any age and weight group, however the occurrences of cancers merit vigilance by the caregivers. The occurrences of MC, PYO, and UI in females are listed for each weight

group. The following are brief summaries for each of the five weight categories.

Small < 10 kg (< 22 lbs.)

The study population was 152 intact males, 201 neutered males, 148 intact females, and 238 spayed females for a total of 739 cases. Just one intact male had a joint disorder, and no joint disorders were reported in neutered males. For intact females, 2% had a joint disorder, with no evident increase with spaying. For intact males, just 1% had a cancer and neutering was not associated with any evident increase. For intact females, 4% had a cancer and with spaying there was no increase in cancers above that of intact females. In intact females, 6% were diagnosed with MC as were 5% of those spayed at 2–8 years. PYO was diagnosed in 3% of intact females. In early-spayed females no UI was reported. Lacking a noticeable occurrence of increased joint disorders or cancers with neutering, those wishing to neuter a male or a female should decide on the appropriate age.

Medium 10–19 kg (22–42 lbs.)

The study population was 94 intact males, 114 neutered males, 90 intact females, and 248 spayed females for a total of 546 cases. Just one intact and one neutered male had a joint disorder. In intact females, 5% had a joint disorder with no increase with spaying. For cancers in intact males, 7% had a cancer with no increase with neutering. For intact females, 2% had cancer with no increase with spaying. In intact females, 7% were diagnosed with MC, as were 4% of those spayed at 2–8 years. The occurrence of PYO was diagnosed in 5% of intact females. UI was diagnosed in 4–6% of females spayed at < 6 mo. through 1 year. Lacking a noticeable occurrence of increased joint disorders or cancers with neutering, those wishing to neuter a male or female should decide on the appropriate age.

Standard 20–29 kg (43–64 lbs.)

The study population was 154 intact males, 257 neutered males, 129 intact females, and 452 spayed females for a total of 992 cases. This is the size category of Golden Retrievers, Labrador Retrievers, and German Shepherd Dogs. Of intact males, 3% had a joint disorder. At neutering periods < 6mo. and 6–11 mo., the occurrences rose to a significant 5% ($p < 0.05$ and $p < 0.01$ respectively). In intact females, 4% had a joint disorder, but at spay intervals of < 6 mo. and 6–11 mo., the occurrences rose significantly to 10 and 12 percent ($p < 0.05$ and $p < 0.01$, respectively). There was no increase in joint disorder occurrence with neutering beyond 12 months of age in either sex. The occurrence of cancers followed for intact males and females was 3%, and this was not noticeably increased with neutering at any age. In intact females, 4% were diagnosed with MC and 5% were diagnosed with PYO. Among females spayed at 2–8 years, 2% had MC. UI was diagnosed in 3% of females spayed at <12 months. For those wishing to neuter, the suggested guideline for both males and females, given the risks of joint disorders in those neutered early, is to delay neutering to 12 months of age or beyond.

Large Mixed Breed 30–39 kg (65–86 lbs.)

The study population was 176 intact males, 196 neutered males, 57 intact females, and 175 spayed females for a total of 604 cases. Of intact males, 8% had a joint disorder. This occurrence was significantly increased with neutering at < 6 mo. to 17% ($p < 0.01$) and to 11% with neutering at 6–11 mo. ($p < 0.01$, combined with < 6 mo.). With intact females, the occurrence of joint disorders was 0 percent, but with spaying at < 6 mo. this level was significantly increased to 10% ($p < 0.05$) and at 6–11 mo. to 23% ($p < 0.01$) The occurrence of cancers followed for intact males was 15%—higher than the neuter groups but not a significant difference. Similarly, in intact females, this measure was 13%, and higher than any spay group, but not significantly differing. In intact females, 2% were diagnosed with MC, and 4% of females spayed at 2–8 years had MC. PYO was diagnosed in 7% of intact females. UI was diagnosed in 9% of females spayed at < 6 mo., a non-significant increase over the 0% of intact females. For those wishing to neuter, the suggested guideline for both males and females, given the risks of joint disorders in those neutered early, is to delay neutering to 12 months of age or beyond. This also avoids the vulnerability to UI in early-spayed females.

Giant Mixed Breed 40+ kg (87+ lbs.)

The study population was 88 intact males, 107 neutered males, 17 intact females, and 46 spayed females for a total of 258 cases. Of intact males, 9% had a joint disorder. Neutering at < 6 mo. was associated with a significant, 3-fold, increase to 28% ($p< 0.01$), and the significant increase continued through neutering at 6–11 mo. ($p < 0.05$) and 1 year ($p < 0.05$), at the 11% level still higher than the intacts. In intact females, 17% had a joint disorder, an occurrence that did not significantly increase with spaying. The occurrence of cancers for intact males was 10% and for intact females, 6%. There were no significant increases in this measure for either sex with neutering at any age. In intact females, none was diagnosed with MC, although PYO was diagnosed in 16%. Of females spayed at < 6 mo., UI occurred in 9%. The suggested guideline for males, for those wishing to neuter, given the marked occurrence of joint disorders at neuter periods through 1 year, is to delay neutering until the male is 2 years of age. Those wishing to spay a female should decide on the appropriate age; keeping in mind the large body size and age of musculoskeletal maturation; it is suggested to wait until 1 year.

DISCUSSION

One major finding from the present study is that despite the dogs being of mixed breeds, there was uniformity in the relationship of body weight and association of neutering with increased risks of joint disorders. The cutoff of 20 kg, where dogs above this point are significantly at risk for joint disorders, but those below this cutoff are not of significant increased risk, offers those adopting puppies, and wishing to neuter, some useful guidelines for ages of neutering with regard to avoiding the increased risk of painful and disabling joint disorders.

There was no clear picture with the cancers followed, undoubtedly reflecting the diversity of breeds involved in mixed breed dogs and the breed-specific differences with regard to vulnerability to different cancers.

This study focuses primarily on dogs going up through their middle-age years, and presents extensive data on diseases having early onsets, prior to dogs' elderly ages. A limitation is that the study has little data going into the second decade of canine life when diseases such as mammary cancer become more frequent.

For those adopting a mixed breed puppy from a shelter or other source, the data in this study suggest that the risks of a joint disorder following early neutering can be predicted on the basis of the dog's body weight. Those that are expected to reach at least 20 kg as adults have a significantly increased risk of one or more joint disorders that is up to 20% above the level of intact dogs. The guidelines for age of neutering are offered in the Results Section above. If the mixed breed puppy is partially of an identifiable breed, such as Labrador Retriever, one could check the breed for cancers as well as joint disorders for guidance regarding the age for neutering. Pet owners and veterinarians can consider this information when making decisions or recommendations regarding the age for neutering a dog that will be in a specific adult weight category.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: Figshare, doi: 10.6084/m9.figshare.7231010.

ETHICS STATEMENT

Ethical review and approval was not required for the animal study because no approval was required to use hospital records. Written informed consent for participation was not obtained from the owners because it was not needed for hospital records.

AUTHOR CONTRIBUTIONS

BH, LH, and AT: conceived and designed study. AT, BH, and LH: collected and complied and analyzed data. NW: statistical analyses. BH, LH, AT, and NW: drafted and edited manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.00472/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Assisting Decision-Making on Age of Neutering for 35 Breeds of Dogs: Associated Joint Disorders, Cancers, and Urinary Incontinence

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Neutering (including spaying) of male and female dogs in the first year after birth has become routine in the U.S. and much of Europe, but recent research reveals that for some dog breeds, neutering may be associated with increased risks of debilitating joint disorders and some cancers, complicating pet owners' decisions on neutering. The joint disorders include hip dysplasia, cranial cruciate ligament tear or rupture, and elbow dysplasia. The cancers include lymphoma, mast cell tumor, hemangiosarcoma, and osteosarcoma. In previous studies on the Golden Retriever, Labrador Retriever and German Shepherd Dog, neutering before a year of age was associated with increased risks of one or more joint disorders, 2–4 times that of intact dogs. The increase was particularly seen with dogs neutered by 6 months of age. In female Golden Retrievers, there was an increase in one or more of the cancers followed to about 2–4 times that of intact females with neutering at any age. The goal of the present study was to expand and use the same data collection and analyses to cover an additional 29 breeds, plus three varieties of Poodles. There were major breed differences in vulnerability to neutering, both with regard to joint disorders and cancers. In most cases, the caregiver can choose the age of neutering without increasing the risks of these joint disorders or cancers. Small-dog breeds seemed to have no increased risks of joint disorders associated with neutering, and in only two small breeds (Boston Terrier and Shih Tzu) was there a significant increase in cancers. To assist pet owners and veterinarians in deciding on the age of neutering a specific dog, guidelines that avoid increasing the risks of a dog acquiring these joint disorders or cancers are laid out for neutering ages on a breed-by-breed and sex basis.

Keywords: elbow dysplasia, hip dysplasia, cranial cruciate tear, lymphoma, mast cell tumor, hemangiosarcoma, osteosarcoma

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INTRODUCTION

In the U.S. and much of Europe, the practice of neutering male and spaying female dogs (herein both referred to as neutering) has become routine (1) and is increasingly being performed at, or before, 6 months of age. At the same time, several investigations have revealed that joint disorders and some cancers may increase in association with neutering of males and/or females. For example,

in studies that did not focus on specific breeds or ages of neutering, one found that hip dysplasia and cranial cruciate ligament tears or ruptures were significantly more likely in neutered than intact males and females (2). Another study found that neutering was associated with a 3-fold increase in excessive tibial plateau angle (3), which is a risk factor for development of cranial cruciate ligament tears or rupture. Neutering is reported to be a risk factor for canine intervertebral disc herniation in Dachshunds (4). Certain cancers are also known to be more likely in neutered than intact dogs. The occurrence of lymphoma was found to be higher in spayed than intact females (5), as was the occurrence of mast cell tumors (6) and hemangiosarcoma (7). A study of over 40,000 dogs utilizing the Veterinary Medical Database found that neutered males and females were more likely to die of cancer than intact dogs (8). A recent finding was that the absence of estrogen from spaying females was associated with accelerated brain aging (9). Another recent report from the Golden Retriever Lifetime Project is that neutering at <6 months increases the risk of cranial cruciate ligament injury (10). Most of the studies cited above offer no useful clinical information or guidelines with regard to the various diseases that may occur in association with neutering in a specific breed.

In an attempt to address the absence of breed-specific information on joint disorders and cancers associated with neutering, we undertook a project focusing on various specific breeds using data collection and analyses with our extensive veterinary hospital database where the same diagnostic criteria could be applied to all breeds. We started with popular breeds well-represented in the database, initially with the Golden Retriever (11, 12), Labrador Retriever (12) and German Shepherd Dog (13). The joint disorders examined included cranial cruciate ligament tears or rupture (CCL), hip dysplasia (HD) and elbow dysplasia (ED). The cancers examined, which previous studies found could be affected by neutering, were lymphoma/lymphosarcoma (LSA), hemangiosarcoma (HSA), mast cell tumors (MCT), and osteosarcoma (OSA).

In the Labrador Retrievers, Golden Retrievers, and German Shepherd Dogs, there was an increase in the incidence of one or more of the joint disorders with neutering in the first year in males and females to 2–4 times >3–5% incidence in intact dogs. In female Golden Retrievers, neutering at any age was associated with an occurrence of one or more of the cancers followed to 2–4 times higher than the 5 percent incidence in intact females. But in male Golden Retrievers, and in male and female Labrador Retrievers and German Shepherd Dogs, there was no evident increase in cancers above that of the dogs left intact. Preliminary analyses from some small-dog breeds revealed no apparent increased risks of joint disorders with neutering. Thus, the research that had been undertaken revealed a wide range of breed-specific differences in disease vulnerability to neutering.

The purpose of this study was to analyze, in a variety of additional breeds, the increased risks, if any, of the above specified joint disorders and cancers associated with neutering male and female dogs at various ages, so as to increase the information available to pet owners and veterinarians for consideration when making decisions regarding neutering specific dogs. We added 29 new breeds to the study, separating three varieties of Poodles, for a total of 32 breed groups (referred to as breeds); this made a total of 35 breeds with the Goldens, Labs and German Shepherds included. The goal was to use the same veterinary hospital database and diagnostic criteria for the diseases as was used with the published studies on the retrievers and German Shepherds so as to allow for direct comparisons among various breeds. The primary purpose was to offer readers some evidence-based information on breed-specific differences with vulnerability to neutering, including suggested guidelines for neutering ages to avoid increasing long-term health risks of neutering, if any. A secondary, unforeseen, purpose was to document breed-specific differences in the increases in some cancers associated with removal of gonadal hormones, as an area for possible research on genetic aspects of cancer occurrence.

METHODS

Ethics Statement

Hospital records of the Veterinary Medical Teaching Hospital (VMTH) provided the retrospective dataset used. In conformity with the campus policy, faculty of the University of California-Davis, School of Veterinary Medicine, are allowed use of the record system for research purposes. No animal care and use committee approval was required, and strict confidentiality of the owners and their dogs was maintained.

Subjects Breed Categories

In addition to the Golden Retriever, Labrador Retriever, and German Shepherd Dog, the other breeds chosen for this project included those most frequently occurring in the database and those chosen to obtain a sampling of giant breeds or small-dog breeds. The final list of 35 (including three varieties of Poodle) represented in the present study are, alphabetically, the: Australian Cattle Dog, Australian Shepherd, Beagle, Bernese Mountain Dog, Border Collie, Boston Terrier, Boxer, Bulldog, Cavalier King Charles Spaniel, Chihuahua, Cocker Spaniel, Collie, Corgi (Pembroke and Cardigan combined), Dachshund, Doberman Pinscher, English Springer Spaniel, German Shepherd Dog, Golden Retriever, Great Dane, Irish Wolfhound, Jack Russell Terrier, Labrador Retriever, Maltese, Miniature Schnauzer, Pomeranian, Poodle-Miniature, Poodle-Standard, Poodle-Toy, Pug, Rottweiler, Saint Bernard, Shetland Sheepdog, Shih Tzu, West Highland White Terrier, and Yorkshire Terrier.

Study Parameters

The present study examined the occurrence in both sexes of the joint disorders: HD, CCL and ED. Also examined in both sexes were the cancers LSA, HSA, MCT, and OSA, because these had been shown in some multi-breed studies to be increased in risks with neutering. In addition, mammary cancer (MC), pyometra (PYO), and urinary incontinence (UI) were examined in female dogs. Of interest was the possible association of early neutering and the occurrence of intervertebral disc disorders (IDD) in the Corgi and Dachshund, two breeds known to be at risk for these diseases. All of the above diseases were examined with regard to dogs neutered in one of the age periods of: < 6 mo., 6–11 mo., 1

year (12 to < 24 mo.) or 2–8 years, or left intact. The diseases were tracked until the dogs were last seen at the hospital, or through 11 years of age, if seen past their 12th birthday.

Mammary cancer is a late occurring cancer with the median age of diagnosis being 10.1 years in one study (14). Tracking cancers through 11 years of age would be presumably sufficient to catch most cases of MC if the case record had information extending to that age. However, most case records did not extend to that age. As an additional point of comparison, percentages of MC occurrence were looked at in just females tracked through 8 years of age or beyond, including diagnosed MC cases beyond the 12th birthday cut-off, which was the cut-off used for all other data.

Data Collection and Presentation

The computerized hospital record system of the VMTH provided the dataset. The hospital, with currently over 50,000 cases admitted per year, is a secondary and tertiary facility as well as being a primary care facility. The statistical evaluations, with standardized diagnostic criteria applied to various diseases and taking into account sex and different ages of neutering, required a large database with a computerized record system. The study focused on proportional differences in disease occurrences between the neuter age groups and intact dogs of the same breed and sex.

The study period represented 15 years of data for most breeds. The inclusion criteria were date of birth, age at neutering (if neutered), and age of diagnosis or onset of clinical signs for diseases of interest. As mentioned, age at neutering was designated as < 6 mo., 6–11 mo., 1 year (12 to < 24 mo.), and 2–8 years (2 to < 9 years). The term "early neutering" is sometimes used below to refer to neutering in the first year, combining cases for both the < 6 mo. and 6–11 mo. neuter periods. For MC, PYO, and UI, only females were examined. While UI does occur in males, it is predominantly an issue in females.

For all neutered dogs that developed a disease of interest, records were examined to confirm that the dog was neutered prior to the diagnosis or signs of the disease. If the dog developed signs of the disease prior to neutering, the dog was considered intact for analysis of that disease. However, for any disease that occurred after neutering, the dog was considered neutered for analysis of that disease. For any disease of interest that occurred before 12 months of age, the dog was removed from that disease analysis, but included in analyses of other diseases. Therefore, the number of cases for various diseases varied in the analyses for different disease occurrences.

The age at neutering was sometimes not included in the hospital records, so telephone calls to the referring veterinarians were made to obtain the neutering dates or ages. Nonetheless, there were many neutered dogs where age at neutering was not available from the VMTH records or the referring veterinarian, so these dogs were excluded from the study. Of course, this was not an issue with the sample of intact dogs, so there were proportionately more intact cases in the final dataset for each breed than would be expected in the general population. However, the proportion of dogs with a disease, whether intact or neutered, was not affected by the overrepresentation of intact dogs in the database.

The criteria for disease diagnoses were the same as in previous studies on the retrievers and German Shepherd Dog (11–13). A dog was considered as having a disease of interest if the diagnosis was made at the VMTH, or by a referring veterinarian and later confirmed at the VMTH. For joint disorders (HD, ED, and/or CCL), dogs typically presented with signs of lameness, difficulty in moving, and/or joint pain. The diagnosis was confirmed by orthopedic examination, radiographic evidence, and/or surgery. In Dachshunds and Corgis, where intervertebral disc disorders (IDD) is a concern, the diagnosis included herniation, rupture, extrusion, protrusion, fracture, compression, stenosis, or spinal cord injury. For cancers (LSA, HSA, MCT, OSA, MC), the diagnosis was based on the presence of a tissue mass, lumps on the skin or enlarged lymph nodes, and confirmed by chemical panels, appropriate blood cell analyses, imaging, histopathology, and/or cytology. PYO was confirmed by ultrasonic evidence and/or post-surgically after removal of the uterus. UI was confirmed by clinical signs of abnormally frequent urination, urinalyses and exclusion of urinary tract infection and/or other disease. If a diagnosis was listed in the record as "suspected" based on some clinical signs but not confirmed, the case was excluded from the analysis for that specific disease, but the dog was included in other disease analyses.

Although body condition scores have been reported to be a factor in the occurrence of joint disorders (3, 15), our previous studies on the retrievers and German Shepherd Dog found no significant relationship when body condition scores were compared between dogs with and without a joint disorder. Therefore, in the current paper the body condition score is not reported for each breed.

Statistical Analyses

Survival analysis was used to test for differences with respect to the hazard of a disease in the neutered and intact groups, while adjusting for the differences in time at risk for a disease. The groups were initially compared using a Kaplan Meier life table analysis. *Post-hoc* comparisons among the subgroups were based on least squares means of the hazard within each subgroup. For comparisons where the Kaplan Meier test showed significance at the $p < 0.05$ level, both the log-rank and Wilcoxon tests were used for further analyses. Because joint disorders are expected to be seen at a similar risk throughout a dog's lifespan, regardless of age, the log-rank test was used initially for the joint disorders. If the log-rank test did not show significance but the Wilcoxon test did for joint disorders, the Wilcoxon test result was reported with significance level and an asterisk. The reverse rule of thumb was used with cancers where the first test examined was the Wilcoxon test, since the risk of cancer is expected to be higher in older dogs. If the Wilcoxon test did not show significance but the log-rank test did for cancers, the log-rank test result was reported with significance level and an asterisk. For all statistical tests, the two-tailed statistical level of significance was set at $p < 0.05$ and reported as either $p < .05$ or $p < 0.01$. Each breed was analyzed separately, and there were no statistical comparisons between

breeds. However, the overall findings with each breed allow for some general comparisons.

Data Presentation

For each breed represented on a separate page in **Appendix 1**, the numbers of intact and neutered males and females are given. In the tables, the percentage of dogs with each of the diseases and the percentage having at least one of the joint disorders and at least one of the cancers (except MC) was calculated for intact males and intact females as well as those neutered at various age ranges. Statistical analyses compared the occurrences of joint disorders and cancers between each neuter period and intact dogs. If the comparison was significant at either the $p < 0.05$ or $p < 0.01$ level, the data were bolded and the p-value was given. The detailed datasets are available online (Figshare, doi: 10.6084/m9.figshare.7231010). Three breeds for which findings have been previously published (Golden Retriever, Labrador Retriever, German Shepherd Dog) are included to present an overall picture in the same **Appendix 1**. The data for these three breeds were expanded through 11 years of age, to provide continuity among breeds and diseases.

For each breed, a short paragraph summarizes the main findings on joint disorders (HD, CCL, ED), cancers (LSA, HSA, MCT, OSA) for both males and females, and MC, PYO and UI for females. For Dachshunds and Corgis, the occurrence of IDD is listed for both sexes. Survival analyses were not done on IDD occurrence because the condition represented so many different disease diagnoses. Also included in the breed summary information is a suggested guideline for neutering age for males and females to avoid increasing the risks of a disease under consideration. When there was no noticeable occurrence of an increase in joint disorders or cancers with neutering, the guideline statement was made that those wishing to neuter should decide on the appropriate age (or briefly stated as choice in **Table 1**). When neutering at < 6 months was associated with an increased disease risk but no increased risk was evident with neutering beyond 6 months, the default recommended guideline was neutering beyond, 6 months.

RESULTS

The breed-by-breed findings are presented in four different formats. One format, seen in this section below, is a short paragraph for each breed. The occurrence of the joint disorders and the cancers followed is reported for the intact and neutered dogs, and the increase in the two disease types over that of the intact dogs, if significant, is reported. Other findings are also mentioned if appropriate, such as IDD occurrence in Dachshunds and Corgis. A second format, represented in **Table 1**, is a very brief summary of spaying and neutering guidelines based on findings regarding joint disorders and cancers for each breed, allowing the reader to quickly scroll through the various breeds. In the third format, the data-based findings, with statistical notations for each breed, are reported in **Appendix 1**. In the fourth format, the raw data allowing the reader to perform their own calculations, if desirable, is available in Figshare.

The mean age of last entry was calculated for intact and neutered males and females for each breed and presented in **Appendix 2**. Across all breeds the mean age of last entry in the record for neutered males was 5.5 years (range 3.71–6.54), for neutered females 5.7 years (range 4.21–6.97), for intact males 4.9 (range 4.15–7.11), and intact females 4.7 (range 3.41–6.32). Upon perusal of the data, it is evident that the mean age of data entry for intact dogs was younger than that of neutered dogs, especially for females, where there is disparity of almost 1 year. To address the issue of whether the lower age of last entry for intact dogs could have resulted in a lower rate of disease occurrence in intact dogs in either joint disorders or cancers, we examined data of dogs where the last entry was at 8 years or beyond. We looked at three breeds with the largest databases (Golden Retrievers, Labrador Retrievers, and German Shepherd Dogs) and where there were significant differences in disease diagnoses between early neutered and intact dogs. Using these parameters, the occurrences of joint disorders in Golden Retrievers for those neutered at ≤ 6mo. vs. intact, in males, there was a 6-fold difference (18% vs. 3%) and in females 3-fold (25 vs. 8%). For male Labrador Retrievers, the figures were 22 vs. 8% and in females 33 vs. 10%. For male German Shepherd Dogs, the figures were 33 vs. 2% and for females, 29 vs. 9%. For cancers in female Goldens, the figures were 26 vs. 14%. The incidence figures, although not sufficient for meaningful statistical analyses, are consistent with the larger database where all ages are included. Thus, while the age of the last visit is a limitation for analyses on late-occurring cancers and joint disorders, the examples chosen for dogs seen at the age of 8 years or beyond are consistent with the overall results presented here; these results appear to represent what would be seen in the general situation.

GENERAL FINDINGS

Looking at the occurrences of these joint disorders and cancers, it is clear that most breeds are unaffected for these diseases by age of neutering. Vulnerability to joint disorders associated with neutering is generally related to body size. Small-dog breeds – Boston Terrier, Cavalier King Charles Spaniel, Chihuahua, Corgi, Dachshund, Maltese, Pomeranian, Poodle-Toy, Pug, Shih Tzu, Yorkshire Terrier – do not appear to have an increased risk in joint disorders with neutering compared to the breeds of larger size. However, in the breeds of larger body size there were differences among the breeds with the two giant breeds – Great Danes and Irish Wolfhounds – showing no indication of increase in one or more joint disorders with neutering at any age.

Although the occurrence of MC was tracked, the female mean age at the last hospital visit for all breeds ended short of the reported, late-onset mean age of MC occurrence in intact female dogs. Thus, the low occurrence of MC in intact females (typically under 6 percent) cannot be expected to represent the actual incidence over a female's lifetime. When the percentage of MC was calculated for only those dogs seen through 8 years of age or older (including cases diagnosed past the 12th birthday), the results did not appear appreciably different than the percentages seen using the study age range. However, the number of dogs

TABLE 1 | Suggested Guidelines by Breed for Age of Neutering.

	Suggested guidelines for age of neutering: 35 breeds									
	Males					Females				
	Leave intact	Choice	Beyond 6 months	Beyond 11 months	Beyond 23 months	Leave intact	Choice	Beyond 6 months	Beyond 11 months	Beyond 23 months
Australian Cattle Dog		✓						✓		
Australian Shepherd		✓					✓			
Beagle				✓			✓			
Bernese Mt. Dog					✓		✓			
Border Collie				✓					✓	
Boston Terrier				✓			✓			
Boxer					✓					✓
Bulldog		✓					✓			
Cavalier King Charles Spaniel		✓					✓			
Chihuahua		✓					✓			
Cocker Spaniel			✓							✓
Collie		✓							✓	
Corgi			✓				✓			
Dachshund		✓					✓			
Doberman Pinscher	✓									✓
English Springer Spaniel		✓							✓	
German Shepherd					✓					✓
Golden Retriever				✓		✓				
Great Dane		✓					✓			
Irish Wolfhound					✓		✓			
Jack Russell Terrier		✓					✓			
Labrador Retriever			✓						✓	
Maltese		✓					✓			
Miniature Schnauzer		✓					✓			
Pomeranian		✓					✓			
Poodle (Toy)		✓					✓			
Poodle (Miniature)				✓			✓			
Poodle (Standard)					✓		✓			
Pug		✓					✓			
Rottweiler				✓				✓		
Saint Bernard		✓						✓		
Shetland Sheepdog		✓								✓
Shih Tzu		✓								✓
West Highland White Terrier		✓					✓			
Yorkshire Terrier		✓					✓			

Summary of spaying and neutering guidelines based on findings regarding increased risk of joint disorders and cancers. The term "choice" means there was no increased risk for any age.

seen through age 8 or beyond was fairly small, so the analysis results might change with an increased sample size of these older dogs.

The following are brief summaries for each of the breeds along with suggested guidelines for age of neutering. See **Appendix 1** for the complete data set, including statistical analyses for each breed.

Australian Cattle Dog

The study population was 61 intact males, 58 neutered males, 48 intact females, and 70 spayed females for a total of 237 cases. In this sample, 5 percent of intact males and 2 percent of intact females were diagnosed with one or more joint disorders. Neutering males was not associated with any increased risk in joint disorders, but there was an association with spaying females

at < 6 mo. where the risk of a joint disorder increased to 15 percent ($p < 0.05$). The occurrence of cancers was low for males and females left intact (0 and 3 percent, respectively). There were no evident occurrences of the cancers in dogs neutered at various ages. The occurrence of MC in intact females was 6 percent and in those spayed at 2–8 years, 6 percent. For females left intact, 4 percent were reported with PYO. UI was not reported in any of the spayed or intact females. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males, those wishing to neuter should decide on the appropriate age. In females, the increased risk of a joint disorder with spaying occurred only at the < 6 mo. range, so the suggested guideline is spaying at, or beyond, 6 months.

Australian Shepherd

The study population was 93 intact males, 135 neutered males, 76 intact females, and 136 spayed females for a total of 440 cases. In this sample, 3 percent of intact males and 4 percent of intact females were diagnosed with one or more joint disorders. Neutering males and females was not associated with any evident increased risk in joint disorders. The occurrence of cancers was 9 percent for intact males and, in contrast, only about 1 percent for intact females. Neutering males did not appear to be associated with an overall increased risk of cancers above the rather high level of intact males. However, spaying females at 6–11 mo. and at 2–8 years was associated with a 7–8 percent risk in cancers which may have reached significance with a larger sample size. The occurrence of MC in intact females was zero, but was 8 percent in females spayed at 2–8 years. For females left intact, 5 percent were reported with PYO. UI was reported in just 1 percent of early-spayed females. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males, those wishing to neuter should decide on the appropriate age. The guideline for females is the same while also maintaining vigilance for the cancers which may be associated with spaying beyond 6 months, or else leaving the female intact and being vigilant for MC.

Beagle

The study population was 42 intact males, 82 neutered males, 45 intact females and 87 spayed females for a total of 256 cases. Just 2 percent of intact males were diagnosed with one or more joint disorders, but with neutering at 6–11 mo. joint disorders increased 7-fold to 15 percent, which may have reached significance with a larger sample size. None of the females left intact or spayed had a joint disorder. None of the intact males or females was diagnosed with any of the cancers followed. There was no evident increased occurrence of cancers in neutered males and females. There was no occurrence of MC in intact or late-spayed females. There was 1 case of PYO in intact females (2 percent). UI was reported in only 2 percent of early-spayed females.

For males, in light of a possible increase in joint disorders for those neutered at 6–11 mo., the suggested guideline is to delay neutering males until beyond a year of age. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered females, those wishing to neuter should decide on the appropriate age.

Bernese Mountain Dog

The study population was 59 intact males, 74 neutered males, 37 intact females, and 65 spayed females for a total of 235 cases. The percentage of intact males with at least one joint disorder was 4 percent and for intact females, 11 percent. Neutering males any time prior to 2 years of age was associated with a significant increase in at least one joint disorder to 23–24%, about a 6-fold increase over intact males ($p < 0.01$). Spaying females before 6 mo. increased the likelihood of a joint disorder to over 3-fold that of intact females, but this did not reach significance. The occurrence of one or more of the cancers followed was 9 percent for both intact males and intact females. There was no evident increase in cancer risk in males related to neutering, but with females, spaying at <6 mo. was associated with a 2-fold increase above that of intact females. There was no occurrence of MC in females, whether left intact or neutered at any age, and a 5 percent occurrence of PYO in intact females. There was no occurrence of UI in intact or spayed females. Reflecting the increased risk of joint disorders for males, the suggested guideline for neutering males is delaying neutering until well-beyond 2 years. Lacking a significant occurrence of increased joint disorders or cancers in neutered females, those wishing to neuter should decide on the appropriate age.

Border Collie

The study population was 105 intact males, 85 neutered males, 88 intact females, and 121 spayed females for a total of 399 cases. In this sample 2–3% of intact males and females were diagnosed with one or more joint disorders, and neutering males and females was not associated with any evident increased risk in joint disorders. The occurrence of one or more of the cancers followed in intact males was 2 percent and none for females left intact. For males, there was a significant increased risk in one or more of the cancers to 13 percent with neutering at 6–11 mo. ($p < 0.05$), and for females there was a significant increase in the cancers to 11 percent with spaying at 6–11 mo. ($p < 0.01$). The occurrence of MC in intact females was just 1 percent, and for PYO, 4 percent. UI was reported in just one spayed female. The suggested guideline for neutering, given the significant risk of cancers, is holding off neutering of both sexes until beyond a year of age.

Boston Terrier

The study population was 75 intact males, 67 neutered males, 54 intact females, and 96 spayed females for a total of 291 cases. None of the intact or neutered males or females was diagnosed with one or more joint disorders. For cancers, the story is a bit different in that 5 percent of intact males were diagnosed with one or more cancers and 10 percent of males neutered at <6 mo., and 12 percent of males neutered at 6–11mo. had cancers ($p < 0.01$, the two neuter periods combined). For females, 2 percent of intact females had one or more of the cancers and with spaying, there was no evident increase of cancers. The occurrence of MC in intact females was 2 percent and for PYO, 7 percent. UI was 2

percent in early-spayed females. In light of the significant increase in cancers in males with neutering through 11 months of age, the suggested guideline for males is delaying neutering to beyond a year of age. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered females, those wishing to neuter should decide on the appropriate age.

Boxer

The study population was 220 intact males, 203 neutered males, 128 intact females, and 210 spayed females, for a sample size of 761 cases. Males and females left intact had just a 2 percent occurrence of joint disorders, with neutered males and females showing no apparent increase in this measure. The occurrence of one or more of the cancers followed in intact males was 17 percent, and for intact females, 11 percent. Neutering males before 2 years significantly raised the risk of a cancer over that of intact males to 32 percent ($p < 0.01$). The same pattern of increase in cancers was seen in spaying females with up to 20 percent of females having one or more of the cancers with spaying done before 2 years, an increase that was not significant, but with an expanded database may have been. There was no occurrence of MC in intact females. PYO was diagnosed in 2 percent of intact females. Just 1 percent of spayed females were diagnosed with UI. Given the risk of increased cancers, the suggested guideline for both sexes is to delay neutering until beyond 2 years of age.

Bulldog

The study population was 198 intact males, 156 neutered males, 90 intact females, and 114 spayed females for a sample of 558 cases. The occurrence of joint disorders in intact males was 7 percent and 5 percent in intact females. Neutering at <6 mo. raised the incidence to 15 percent for males and to 18 percent for females, which did not reach significance for either. The cancers followed occurred at the 6 to 7 percent level in intact males and females. There were no significant increases above this with neutering males or females. The occurrence of MC in females left intact was 1 percent and 2 percent with spaying at 2–8 years. There was a 2 percent occurrence of PYO in intact females and no UI in early spayed females. Lacking a significant occurrence of increased joint disorders or cancers in neutered males or females, those wishing to neuter should decide on the appropriate age, but some people may wish to be cautious in view of the possible apparent risk in joint disorders.

Cavalier King Charles Spaniel

The study population was 51 intact males, 72 neutered males, 87 intact females, and 76 spayed females, for a sample size of 286 cases. For males and females left intact, the occurrences of one or more joint disorders were just 4 and 1 percent, respectively, and for both sexes neutering was not associated with any increase in this measure. The occurrences of cancers in intact males were 2 percent and zero for intact females. For both sexes neutering was not associated with any increase in this measure. The occurrence of MC in females left intact was zero. The occurrence of PYO was 2 percent in intact females. There was no occurrence of UI in spayed females. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males or females, those wishing to neuter should decide on the appropriate age.

Chihuahua

The study population was 261 intact males, 189 neutered males, 298 intact females, and 289 spayed females for a total sample of 1,037 cases. For both males and females, neither those left intact, nor those neutered at any age had a noteworthy occurrence of a joint disorder. The cancers followed in both intact and neutered males and females were <5 percent with no evident increase with neutering at any age. The occurrence of MC in females left intact was 1 percent, and in females neutered at 2–8 mo., 4 percent. In intact females, PYO was diagnosed in 2 percent. There was no UI diagnosed in any of the spayed females. Lacking a noticeable occurrence of increased joint disorders or cancers with neutering in either sex, those wishing to neuter should decide on the appropriate age.

Cocker Spaniel

The study population was 71 intact males, 112 neutered males, 61 intact females, and 127 spayed females, for a sample size of 369 cases. The occurrence of at least one joint disorder was seen in 1 to 3 percent of the intact males and females. Neutering males at <6 mo. was associated with a significant increase of this measure to 11 percent ($p < 0.01$). Spaying females was not associated with an increase in joint disorders. The occurrence of one or more of the cancers followed was 6 percent in intact males with no increase with neutering. Although there was no occurrence of cancers in intact females, this measure rose significantly to 17 percent in females spayed between 1 and 2 years of age ($p < 0.01$), entirely due to MCT. For females left intact, 11 percent were diagnosed with MC and 5 percent with PYO. None of the spayed females developed UI. The suggested guideline for males is neutering beyond 6 months of age. Given the increased cancer risk for females spayed at a year of age, the suggested guideline is delaying spaying until beyond 2 years of age.

Collie

The study population was 29 intact males, 26 neutered males, 24 intact females, and 37 spayed females, for a sample size of 116 cases. The occurrence of at least one joint disorder was seen in 7 percent of the intact males and in none of the intact females. None of the neutered males or females had a noteworthy occurrence of a joint disorder. The occurrence of one or more of the cancers followed was 11 percent for intact males and none for the intact females. There was no evident increase of cancers in males with neutering, and in females, there was an increase of cancer to 40 percent in those spayed at <6 mo., which may have reached significance with a larger sample size. For females left intact, 4 percent were diagnosed with MC, and 16 percent were diagnosed with PYO. Of females spayed at 6–11 mo., 13 percent had UI. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males, those wishing to neuter a male should decide on the appropriate age. For females, given the apparent risks of cancers with spaying at < 6 mo. and UI with spaying at 6–11 mo., the guideline is to delay spaying until the female is a year old.

Corgi (Welsh), Pembroke and Cardigan

The study population was 42 intact males, 78 neutered males, 50 intact females, and 70 spayed females, for a total sample size of 240 cases. Although these are two breeds, they vary only a little in size, so these two breeds are combined for statistical analyses and display of data. The occurrence of at least one joint disorder in intact males was 5 percent and for intact females 6 percent. There was no significant increase in this measure in males or females with neutering. This is one of the breeds where intervertebral disc disorders are a concern, and in 3 percent of intact males and 8 percent of intact females, IDD was reported. In males neutered before 6 months, the occurrence of IDD reached 18 percent, and in females there was no increase with neutering. The occurrence of one or more of the cancers followed was 5 percent in intact males and 6 percent in intact females. In neutered males and females, there was no evident increase in cancers. For females left intact, the occurrence of MC was 8 percent, and there was zero occurrence of PYO. There was no diagnosis of UI in spayed females. The suggested guideline for age of neutering for males, given the increase in IDD with neutering at < 6 mo., is beyond 6 months. Lacking a noticeable occurrence of increased joint disorders, IDD, or cancers with neutering females, those wishing to neuter a female should decide on the appropriate age.

Dachshund

The study population was 177 intact males, 170 neutered males, 99 intact females, and 212 spayed females, for a total sample size of 658 cases. Joint disorders were basically absent in males and females, left intact or neutered. This is a breed plagued by intervertebral disc disorders, and in this sample 53 percent of intact males and 38 percent of intact females were diagnosed with a form of IDD. There was no evident increase in this measure with neutering of males or females. The occurrence of the cancers followed was <1% in both intact males and females, with no indication of an increased risk with neutering. For females left intact, the occurrence of MC was 1 percent and for PYO, 4 percent. None of the spayed females developed UI. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males or females, those wishing to neuter should decide on the appropriate age.

Doberman Pinscher

The study population was 109 intact males, 91 neutered males, 53 intact females, and 108 spayed females, for a sample size of 358 cases. The percentage of intact males with at least one joint disorder was 2 percent and 0 percent for intact females. There was no evident increase in this measure with neutering males. For females, spaying within 11 months resulted in an increase in joint disorders of 11 percent, which did not reach significance**.** The occurrence of one or more of the cancers followed for both intact males and intact females was 2 percent. In neutered males at the 1 year and 2–8 year periods, there was a non-significant increase in occurrence of cancers to 6 percent and 13 percent, respectively. For females, there was no noteworthy increase in cancers with spaying at any time. The occurrence of MC in females left intact was 2 percent and 4 percent for those spayed at 2–8 years. There was a 7 percent occurrence of PYO in intact females. UI was a significant risk in females spayed at any age up to 2 years, ranging from 25 percent in the females spayed at < 6 mo. ($p < 0.01$) to 19 percent for those spayed between 1 and 2 years ($p < 0.05$). The suggested guideline, based on fragmentary results, for males is to leave the male intact or neuter before 1 year of age to avoid the possible increased risk of cancers seen in those neutered beyond a year of age. For females, the suggested guideline, also based on limited data, given the risk of UI in early spayed females, and the possible increased risk of a joint disorder, is to consider delaying spaying until beyond 2 years of age.

English Springer Spaniel

The study population was 52 intact males, 57 neutered males, 37 intact females, and 66 spayed females for a total sample of 212 cases. In males and females left intact, the occurrence of one or more joint disorders was 5 and 8 percent, respectively. Among males and females neutered at various ages, there were no noteworthy increases in joint disorders. The cancers followed occurred in the intact males and females at a 6 percent level, and neutering at any age was not associated with any evident increase in this measure in either sex. In intact females, MC was diagnosed in 6 percent, and for those spayed at 2–8 years, 15 percent. PYO was not reported in any of the intact females. Spaying females at 6–11 mo. was associated with a 13 percent occurrence of UI, which may have reached significance with a larger sample size. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males, those wishing to neuter should decide on the appropriate age. For females, given the increased risk of UI in those spayed before 1 year, the suggested guideline is to delay spaying until a year of age.

German Shepherd Dog

The study population was 514 intact males, 272 neutered males, 173 intact females, and 298 spayed females for a total of 1,257 cases. In males and females left intact, the occurrence of one or more joint disorders was 6 and 5 percent, respectively. Neutering males at <6 mo., 6–11 mo. and 1–2 years was associated with increased risks of this measure to 19, 18 and 9 percent, respectively ($p < 0.01$). Spaying females at <6 mo. and 6–11 mo. was associated with a 20 and 15 percent level of increased risk ($p < 0.01$), and spaying at 1–2 years with a 5 percent risk level ($p < 0.05$). The occurrence of one or more of the cancers followed for intact males and females was 3 percent and 2 percent, respectively. Neutering at the various ages was not associated with any appreciable increased risk in cancers followed. The occurrence of MC in intact females was 5 percent and for those spayed at 2–8 years, 6 percent. Of intact females, 3 percent were reported with PYO. UI ranged up to 9 percent for females spayed from <6 mo. through 1 year of age ($p < 0.05$–0.01). The suggested guideline for males, given the risks of joint disorders, is delaying neutering until over 2 years of age. For females, with the same joint issues as males plus the risks of UI, the suggested guideline is delaying spaying until over 2 years of age.

Golden Retriever

The study population was 318 intact males, 365 neutered males, 190 intact females, and 374 spayed females for a total of 1,247

cases. In intact males and females, the level of occurrence of one or more joint disorders was 5 percent and 4 percent, respectively. Neutering males at <6 mo. and at 6–11 mo. was associated with risks of 25 percent and 11 percent, respectively ($p < 0.01$). In females, spaying at <6 mo. and at 6–11 mo. was associated with risks of 18 percent and 11 percent ($p < 0.01$, when combined). The occurrence of one or more of the cancers followed in intact males was a high 15 percent and for intact females 5 percent. Neutering males at <6 mo. and at 6–11 mo. was associated with increased risks of cancers to 19 and 16 percent, respectively ($p < 0.01$). Spaying females at <6 mo. and at 6–11 mo., was associated with increases in cancers to 11 and 17 percent, respectively ($p < 0.05$, when combined) and spaying at 1 year and at 2–8 years was associated with increased risks of 14 percent ($p < 0.01$, when combined). The occurrence of MC in intact females was 1 percent and for those spayed at 2–8 years, 4 percent. For females left intact, 4 percent were reported with PYO. No cases of UI were reported in females spayed at any age. The suggested guideline for males, based on the increased risks of joint disorders and cancers, is delaying neutering until beyond a year of age. The suggested guideline for females, based on the increased occurrence of cancers at all spaying ages, is leaving the female intact or spaying at one year and remaining vigilant for the cancers.

Great Dane

The study population was 90 intact males, 103 neutered males, 69 intact females, and 91 spayed females for a total sample of 353 cases. This is a giant breed where one might expect a high risk of joint disorders. However, both intact males and females have low levels of joint disorders, just 1 and 2 percent, respectively. For both males and females, there was no evident increase in this measure with neutering. The occurrence of one or more of the cancers followed in intact males was 6 percent and for intact females, 3 percent. There was no evident increase in this measure of cancers with neutering in either sex. In intact females, MC was diagnosed in just 2 percent and PYO in 6 percent. In early-spayed females, no UI was reported. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males or females, those wishing to neuter should decide on the appropriate age. However, given the large body size, and physiology of late musculoskeletal development, neutering well-beyond year 1 should be considered.

Irish Wolfhound

The study population was 30 intact males, 19 neutered males, 21 intact females, and 16 spayed females for a total of 86 cases. Even with the small number of cases, this breed was chosen for analyses because of the large body size: challenging the Great Dane for height, and where one might expect an increased risk of joint disorders. In this sample, 7 percent of intact males and none of the intact females had a joint disorder. No joint disorders were seen in neutered males or females. With the intact males and females, the incidences of one or more cancers were 8 percent and 21 percent, respectively. With neutering males at 1 year, there was an increase in cancer occurrence to 25 percent ($p < 0.05$). There was no evident increase in cancers in neutered females above the relatively high level in intact females. There was no occurrence of MC in intact females or those spayed late. For females left intact, 5 percent were reported with PYO. UI was not reported in any of the spayed or intact females. The suggested guidelines for males given the increased occurrence of cancers around at ages 1–2 years, is neutering beyond 2 years. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered females, those wishing to neuter should decide on the appropriate age. However, given the large body size, and physiology of late musculoskeletal development, some may want to consider neutering females well-beyond year 1.

Jack Russell Terrier

The study population was 92 intact males, 87 neutered males, 84 intact females, and 113 spayed females for a total sample of 376 cases. As in other small dogs, joint disorders were rare; none of the intact males, and just 2 percent of intact females had one or more joint disorders. Neutering was not associated with any increase in this measure in either sex. In intact males, 3 percent, and in intact females none, had one or more of the cancers followed. There was no evident increase in cancer occurrence in either sex with neutering at any age. In females left intact, MC was seen in 1 percent, as was PYO. In those spayed at 2–8 years, MC was diagnosed in 3 percent. UI was not diagnosed in any females. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males or females, those wishing to neuter should decide on the appropriate age.

Labrador Retriever

The study population was 714 intact males, 381 neutered males, 400 intact females, and 438 spayed females for a total of 1,933 cases. One or more joint disorders were reported in 6 percent of both intact males and intact females. This measure was significantly increased to 13 percent for males neutered before 6 mo. ($p < 0.01$). In females spayed at <6 mo. and 6–11 mo., the risk of a joint disorder was 11–12 percent for each period ($p < 0.01$, spay periods combined). The occurrence of cancers followed was 8 percent and 6 percent, respectively, for intact males and females. Neutering at the various ages was not associated with any evident increased risk in the cancers. The occurrence of MC in intact females was 1 percent and for those spayed at 2–8 years, 2 percent. For females left intact, 2 percent were reported with PYO. UI was reported at a low rate (2–3%) in females spayed at various ages though 1 year. Given the significant occurrence of joint disorders in males neutered at < 6 mo., the suggested guideline for males is neutering beyond 6 months. For females, given the increased risks of joint disorders with spaying through 11 months of age, the suggested guideline is delaying spaying until beyond a year of age.

Maltese

The study population was 49 intact males, 72 neutered males, 65 intact females, and 86 spayed females for a total sample of 272 cases. As mentioned in **Appendix 1**, the Maltese and Chihuahua vie for the smallest breeds and the Great Dane and Irish Wolfhound for the largest, but all four breeds share a low predisposition to joint disorders. For the Maltese in both sexes, there was no occurrence of joint disorders in either those

left intact or neutered. Virtually the same picture emerges with cancers, with only one of 64 intact females being diagnosed with a cancer. There was no occurrence of MC in the intact females and only one case among the 19 females spayed at 2–8 years. PYO was seen in none of the intact females. UI did not occur in any of the females.

Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males or females, those wishing to neuter should decide on the appropriate age.

Miniature Schnauzer

The study population for this small-dog breed was 47 intact males, 63 neutered males, 25 intact females and 96 spayed females for a total sample of 231 cases. There was virtually no occurrence of any joint disorders in males or females either left intact or neutered. The incidence of cancers in intact males was 4 percent and in females, zero percent. There was no indication of cancer increase related to neutering in either sex. There was no occurrence of MC in any of the females left intact or spayed, and a 4 percent occurrence of PYO in intact females. None of the females was diagnosed with UI. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males or females, those wishing to neuter should decide on the appropriate age.

Pomeranian

The study population was 84 intact males, 69 neutered males, 65 intact females, and 104 spayed females for a total sample of 322 cases. As with other dogs of small body size, both males and females had no occurrences of joint disorders in either those left intact or neutered. With regard to cancers, for both males and females left intact, the occurrence of cancers was zero, and there was no indication of increased cancer risk related to neutering in either sex. There was just one case of MC in females left intact, and 7 percent with PYO. None of the females was diagnosed with UI. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males or females, those wishing to neuter should decide on the appropriate age.

Poodle, Toy

The study population was 49 intact males, 53 neutered males, 58 intact females, and 78 spayed females for a total sample of 238 cases. While the AKC registers all the Poodle varieties as the same breed, the three main varieties are dealt with separately here because of differences in size. In intact males, 4 percent had one or more joint disorders and in intact females there was no occurrence of a joint disorder. In neutered males and females, there was no evident increased risk of a joint disorder. There was a 2 percent occurrence of cancers in intact males and none in intact females. In neutered males and females, there was no noteworthy occurrence of cancers. In intact females, there was only a single case of MC and no case of PYO in intact females and no occurrence of UI in spayed females. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males or females, those wishing to neuter should decide on the appropriate age.

Poodle, Miniature

The study population was 41 intact males, 60 neutered males, 30 intact females, and 69 spayed females for a total sample of 199 cases. The AKC registers the Toy, Miniature, and Standard Poodle varieties, all as the same breed. However, because of differences in size, the varieties of Poodles are dealt with separately here. There was no occurrence of a joint disorder in intact males or females. However, in males neutered at 6-11 mo., there was a significant 9 percent occurrence of joint disorders ($p < 0.01$), reflecting CCL. In spayed females, there was no occurrence of a joint disorder. In intact males and females, there was a 5 and zero percent occurrence of cancers, respectively. There was no indication of increased cancer occurrence related to neutering in either sex. The only occurrence of MC in females was one female that had been spayed at 2–8 years. Of intact females, 6 percent developed PYO. Just one female spayed at <6 mo. developed UI. The suggested guideline for males, based on the significant occurrence of a joint disorder with neutering at 6-11 mo., is delaying neutering until a year of age. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered females, those wishing to neuter should decide on the appropriate age.

Poodle, Standard

The study population was 47 intact males, 88 neutered males, 53 intact females, and 87 spayed females for a total sample of 275 cases. The AKC registers the Toy and Miniature, along with the Standard Poodle, as all being Poodles. However, because of differences in size, the varieties of Poodles are dealt with separately here. There was a 2 percent occurrence of joint disorders in both intact males and females. In males neutered at <6 mo., there was a non-significant increase to 8 percent, and in spayed females, there was no occurrence of joint disorders. The occurrences of cancers in intact males and females were 4 and 2 percent, respectively. In males neutered at 1 year of age, the occurrence of one or more cancers rose to a significant 27 percent ($p < 0.01$), all due to the increased risk of LSA. In females, there was no significant increase in cancers with spaying. There was a 4 percent occurrence of MC, and a 2 percent occurrence of PYO in the females left intact. Just one female spayed beyond 2 years later developed UI. The suggested guideline for males, based on the occurrence of one or more cancers with neutering at 1 year, is to delay neutering until 2 years of age. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered females, those wishing to neuter should decide on the appropriate age.

Pug

The study population was 96 intact males, 106 neutered males, 63 intact females, and 118 spayed females for a total sample of 383 cases. In intact males and females, the occurrences of joint disorders were zero and 2 percent, respectively. In neutered males and females, there was no evident increased occurrence of joint disorders. The level of occurrence of one or more cancers in intact males was 6 percent and in intact females, 8 percent. Neutering males and females did not lead to any evident increase in risk of a cancer. There were no cases of MC in females left intact or

spayed at any time, and there was a 5 percent occurrence of PYO in the intact females. None of the females was diagnosed with UI. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males or females, those wishing to neuter should decide on the appropriate age.

Rottweiler

The study population was 315 intact males, 152 neutered males, 143 intact females, and 239 spayed females for a total sample of 854 cases. Joint disorders are a major concern in this breed with 8 percent of intact males and 16 percent of intact females having one or more joint disorders. In males, neutering at <6 mo. and at 6-11 mo. resulted in 10 percent and 22 percent occurrences (combined $p < 0.05$). In females, spaying at <6 mo. resulted in a significant 43 percent occurrence ($p < 0.05$), the main joint disorder being CCL. The cancers followed occurred in the intact males and females at 16 and 11 percent, respectively. These relatively high occurrences of cancers in intact males and females were not increased by neutering at any age. Of females left intact or spayed at 2–8 years, 8 and 5 percent were diagnosed with MC, respectively. In intact females, 12 percent were diagnosed with PYO. With regard to UI, 1 percent of intact females had UI, and in females spayed at <6 mo. and 6-11 mo., 4 and 6 percent, respectively had UI. The suggested guideline for males, given the risk of joint disorders for those neutered at 6-11 mo. or earlier, is neutering beyond a year of age. For females, given the increased risk of joint disorders with neutering at < 6 mo., the suggested guideline is spaying beyond 6 months.

Saint Bernard

The study population was 26 intact males, 27 neutered males, 18 intact females, and 23 spayed females for a total sample of 94 cases. This breed was chosen because of the large size. In intact males and females, the occurrences of one or more joint disorders were 8 percent and 6 percent, respectively. While there was no evident increase in joint disorders with neutering males, in females spayed at <6 mo., joint disorders increased to a significant 100 percent ($p < 0.01$). The cancers followed occurred in intact males and females at 4 and 11 percent, respectively. With neutering males and females, there were no noteworthy increases in cancers. There was no occurrence of MC in either the intact or spayed females. In intact females, PYO was diagnosed in 15 percent There was no occurrence of UI in spayed females. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males those wishing to neuter should decide on the appropriate age. The suggested guideline for females given in the increased risk of joint disorders with neutering at < 6 mo., is neutering beyond 6 months. However, given the large body size, some may wish to consider neutering well-beyond 1 year of age.

Shetland Sheepdog

The study population was 31 intact males, 30 neutered males, 20 intact females, and 52 spayed females for a total sample of 133 cases. There were no joint disorders in intact males and just one in the intact females. In neutered males, the only joint disorder was in one of the males neutered at <6 mo. and in females there was no joint disorder associated with spaying. The occurrence of cancers in intact males was 6 percent and in intact females, zero. There were no evident increases in cancers in neutered males or females. There was no occurrence of MC in intact or spayed females and a 14 percent occurrence of PYO in intact females. Spaying at 6-11 mo. resulted in a 6 percent occurrence of UI, but at 1 year a 33 percent occurrence. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males, those wishing to neuter should decide on the appropriate age. However, to avoid the high level of UI occurrence in females, one could consider spaying females at, or beyond, 2 years.

Shih Tzu

The study population was 104 intact males, 112 neutered males, 77 intact females, and 139 spayed females for a total sample of 432 cases. In this small-dog breed there were no occurrences of joint disorders in either intact or neutered males and females, revealing virtually no vulnerability in this regard. There was no occurrence of the cancers followed in intact males and females. In neutered males there was no occurrence of cancers. However, in females, the occurrence of cancers for those spayed at 6-11 mo. was 7 percent and at 1 year this measure reached a significant 18 percent ($p < 0.01$). MC occurred in 3 percent of intact females. PYO occurred in 5 percent of intact females. UI was not reported in any females. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males, those wishing to neuter should decide on the appropriate age. The picture is very different for spaying females where the increased risk of cancers started with spaying at 6-11 mo., reaching 18 percent with spaying at year 1. The suggested guideline for females is to delay spaying until the female is 2 years of age. Another possibility is to spay a female a month or two before 6 months to avoid the increased risk of cancers.

West Highland White Terrier

The study population was 35 intact males, 33 neutered males, 28 intact females, and 46 spayed females for a total sample of 142 cases. Just one intact male had a joint disorder, and other than this, no joint disorders were reported in intact females or in neutered males or females. None of the intact males or females had any of the cancers followed. There were no noteworthy occurrences of the cancers in neutered males or females. There were no occurrences of MC in either intact or neutered females, and a 7 percent occurrence of PYO in intact females. The occurrence of UI was 14 percent for females spayed at <6 mo. and 6 percent at 6-11 mo. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males or females, those wishing to neuter should decide on the appropriate age. However, for females, one could consider delaying spaying until a year of age to avoid the risk of UI.

Yorkshire Terrier

The study population was 134 intact males, 178 neutered males, 144 intact females, and 229 spayed females for a total sample of 685 cases. There were no joint disorders reported in intact males, and in intact females, just 1 percent. In neutered males and females there were no noteworthy occurrences of joint

disorders. In intact males and intact females, just 1 percent were reported with at least one of the cancers followed. In both neutered males and females, none of the cancer occurrences was noteworthy. In intact females, the occurrence of MC was 1 percent as was the occurrence with spaying at 2–8 years. PYO was reported in 7 percent of intact females. No UI was reported in any of the intact or spayed females. Lacking a noticeable occurrence of increased joint disorders or cancers in neutered males or females, those wishing to neuter should decide on the appropriate age.

DISCUSSION

Since the reporting from this center of increased risks of joint disorders and some cancers in Golden Retrievers, Labrador Retrievers, and German Shepherd Dogs (11–13), the appropriate age of neutering has become a common point of discussion (16–18). With the evidence-based information on the risks, if any, of joint disorders, cancers, PYO and UI associated with neutering at different ages for males and females of various as dog breeds, dog owners, and their veterinarians, can use this information to select an age for neutering for the long-term health of their companion dogs on a case-by-case basis.

The overall major finding from the present study is that there are breed differences – and sometimes sex differences – with regard to the increased risks of joint disorders and cancers associated with neutering at various ages. For example, with the Boston Terrier, neutering females at the standard 6 month age did not increase the risks of joint disorders or cancers over that of dogs left intact, but with males, neutering before a year of age was associated with a significant increase in cancers. The opposite effect with genders was seen in the Cocker Spaniel where neutering at 6 months was not associated with an increase in joint disorders or cancers in males, but in females there was a significant increase in risk of cancers to 17 percent with neutering before 2 years.

Another important finding that holds across several breeds is that with the small-dog breeds – Cavalier King Charles Spaniel, Chihuahua, Corgi, Dachshund, Maltese, Pomeranian, Poodle-Toy, Pug, Shih Tzu, Yorkshire Terrier –the occurrences of joint disorders were close to zero in both the intact and neutered males and females. In these small-dog breeds, the occurrence of cancers was low in both those kept intact and neutered. Two exceptions were the Boston Terrier and Shih Tzu where there was there a significant increase in cancers with neutering.

As noted in the results section, the mean date of last entry per patient in the hospital record ranged from about 4.5 to 5.5 years, which means the data especially represent rather early-occurring joint disorders and cancers. The perspective taken here is that it is the early occurring joint disorders and cancers that are the most impactful on the human caregivers, both emotionally and financially, as well as their dogs. To just delay neutering by a year or so to lower the risk of a joint disorder or cancer in those breeds where the issue is relevant, is a noteworthy goal, making it worthwhile to discuss appropriate ages to neuter with caregivers who have a new puppy.

A suggested guideline for the use of the data presented here for those who may wish to focus on a breed or two, is to first scroll through **Table 1** to peruse the breeds for a brief look at the neutering guidelines for the breeds of interest. The next step could be to refer to summary paragraphs in the Results section, which present the major findings with a suggested guideline for neutering age. Then for a third step, one could turn to **Appendix 1** for detailed joint disorder and cancer tabular data as well as data on MC, PYO, and UI. Our intention is to offer readers data-based information to make case-by-case decisions about age of neutering. As is clearly evident in the breed-specific data presented, one cannot make a generalization for all dogs about age of neutering guidelines.

As mentioned, this study involved 35 breeds, counting the three varieties of Poodles as three breeds. Thus, most breeds registered by AKC or other comparable agencies were not covered. The breeds chosen were the most popular, and with the largest dataset in our records, or were included to sample the largest range of breed sizes as was feasible. Hence, some of the largest breeds (e.g., Great Dane, Irish Wolfhound) and smallest breeds (Miniature Schnauzer, West Highland White Terrier) were included despite lower numbers of patient records. While with some of the most popular breeds there were over 1,000 cases in the database, most breeds ended up with 200 to 500 cases which was sufficient for statistical analyses where the impact of neutering was substantial.

A suggestion for those interested in a breed not covered in this study is to find a breed or two closest genetically to the breed of their interest in order to get an estimate of the various disease risks, if any, associated with neutering. However, one needs to bear in mind that even genetically related breeds may vary a great deal. An example is seen when comparing Golden and Labrador Retrievers, using the data from this study, where in the Labrador, there was no increase in cancer risk above that of intact dogs with neutering, but in the female Golden, the risk of a cancer with neutering increased to 2–4 times that of the 5 percent level of intact females. The popular Poodle breed provides another example, where there are three major varieties in size, the Standard, Miniature, and Toy. In the Standard, neutering males at 1 year was associated with a highly significant increase in the risk of a cancer (mainly LSA) to over six times that of intact males, whereas in the Miniature, there was no increase in cancers with neutering but a significant increase in joint disorders (mainly CCL) with neutering at 6-11 mo.

A likely mechanism by which early neutering may lead to a joint disorder is related to disturbance of the closure of the long-bone growth plates by gonadal hormone secretion as the animal approaches maturity (19, 20). We have proposed that neutering much before the closure of growth plates allows the long bones to grow a little longer than normal, and may sufficiently disturb joint alignments in some neutered dogs to lead to a clinically-apparent joint disorder.

Given the frequency with which early neutering is performed in dogs, it seems surprising that osteoporosis has not been examined given that in humans, chronic loss of gonadal hormones is associated with osteoporosis (21). It could be that the wolf ancestor of the dog had one breeding season and that

the bone structure of mature dogs was not as affected by seasonal fluctuations of gonadal hormones as with a permanent gonadal hormonal loss in humans.

One of the frequently mentioned advantages of early neutering of female dogs is protection against MC (22). There may be important genetic, breed-line differences in the occurrence of MC that are not portrayed in our database. However, relevant to the discussion of MC is the recent meta-analysis of published studies on neutering females and MC, finding that the evidence linking neutering to a reduced risk of MC is weak (23). In the data gathered in this study, through 11 years of age, the occurrence of MC in females left intact was rarely above 6 percent and frequently 2 percent or less. For those neutered at < 6 months, there was, as expected, no occurrence of MC. Obviously with most cases of intact females not followed through 11 years, and with the 12-year cut-off for those that were followed, many occurrences of MC were missed. However, it seems reasonable, that if MC was a common occurrence in intact females that this disease would have been more frequent in the intact females followed. Further, a very late onset of MC would seem less disturbing to pet owners than the much earlier onsets of joint diseases and other cancers.

For males, there is some concern that neutering beyond puberty will increase the likelihood of a problem behavior such as aggression. However, studies show that while neutering males can reduce aggression to people or other dogs in about 25 percent of males, neutering prior to puberty is no more effective in preventing this problem than is neutering in adulthood in resolving the problem (24, 25).

This paper deals primarily with the risks of diseases that are seen within a given breed and sex. Comparisons between breeds are difficult to interpret, in part because of differences in developmental and physiological factors between breeds including those between smaller and larger breeds. In the text we have reported the occurrences of various diseases in percentages but in statistical analyses the actual data are used. When disease incidence is particularly low in one or more neutering subgroups, the ability to detect significant differences will be low, but there still could be differences which may or may not have been evident in the statistical analyses.

There are at least two major limitations to this study. First, relatively few breeds are covered compared to those included in the various breed registries of kennel clubs and canine organizations. This limitation was necessary so as to apply the same diagnostic criteria for diseases covered across all breeds, using the same database, and the necessity of having sufficient cases for analyses. Second, no information is available as to the reasons the owners or others chose to neuter, or not to neuter their dogs. In California, the vast majority of dogs are neutered, and since 2005 it is legally required for dogs to be neutered prior to adoption from an animal shelter or humane society (26); many breeders impose the same requirement.

In conclusion, the data presented should provide to veterinarians and interested puppy caregivers data-based information for the best age for neutering to avoid increasing the risk of joint disorders and some cancers beyond that of leaving the dog intact. Readers can note that an elevated risk for a joint disorder or cancer occurs in relatively few of these breeds. In other words, with most breeds or sexes, neutering can apparently be done without referral to a particular age, at least with regard to the joint disorders or cancers covered in this study. Of course, individual factors must be taken into account. For puppies of mixed breed, another paper that is currently in press provides data-based information dealing with age of neutering and the risk of one or more joint disorders as a function of the dog adult weight category (27). This information can also help inform decisions on age of recommended neuter in purebred dogs where the breed is not covered in our data.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: (Figshare, doi: 10.6084/m9.figshare.7231010).

AUTHOR CONTRIBUTIONS

BH, LH, and AT: conceived and designed study, collected and complied, and analyzed data. NW: statistical analyses. BH, LH, AT, and NW: drafted and edited manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.00388/full#supplementary-material

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Assisting decision-making on age of neutering for German Short/Wirehaired Pointer, Mastiff, Newfoundland, Rhodesian Ridgeback, Siberian Husky: associated joint disorders, cancers, and urinary incontinence

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Spaying female and castrating male dogs, hereinafter referred to as neutering, is a US convention for the first year in the dog's life. Research on 35 breeds of dogs revealed that early neutering increases risks of joint disorders, such as hip dysplasia (HD), elbow dysplasia (ED), or cranial cruciate ligament (CCL) tear, or cancers, such as lymphosarcoma (LSA), mast cell tumor (MCT), hemangiosarcoma (has), or osteosarcoma (OSA), for some breeds. Joint disorder risks are heightened for some larger breeds and for mixed-breed dogs weighing more than 20 kg. Some breeds had elevated risks for cancers. Several other research teams have reported health complications associated with neutering. The study goal includes using the same methodology for data collection and analyses as in the study on 35 breeds for five additional dog breeds weighing at least 20 kg. The breeds were: German Short/Wirehaired Pointer, Mastiff, Newfoundland, Rhodesian Ridgeback, and Siberian Husky. Major differences among breeds appeared in vulnerability to joint disorders and cancers with early neutering: male and female Pointer breeds had elevated joint disorders and increased cancers; male Mastiff breeds had increased CCL and LSA and females had non-significant elevated CCL risks; female Newfoundland breeds had heightened risks for joint disorders and males had non-significant elevated risks; female Ridgeback breeds had heightened MCT with very early neutering; and Siberian Huskies showed no significant effects on joint disorders or cancers, but female breeds showed a non-significant but elevated CCL. Updated guidelines cover 40 dog breeds. These results further emphasize the importance of personalized decisions regarding the neutering of dogs, considering the dog's breed, sex, and context.

KEYWORDS

hip dysplasia, elbow dysplasia, cranial cruciate ligament tear, lymphosarcoma, mast cell tumor, hemangiosarcoma, osteosarcoma, 40 dog breeds

Introduction

In the 1980s−90s, the prevalence of neutering dogs increased in the United States, with concerns about overpopulation and hopes to reduce behavioral problems. Neutering refers to castration of male breeds, generally involving surgical removal of the testicles, or spaying of female breeds (ovariohysterectomy), including removal of both the uterus and ovaries. Alternatives that also prevent reproduction but are performed far less frequently include vasectomy of male breeds and tubal ligation of female breeds or removing the uterus and/or ovaries. For female breeds, laparoscopic methods are used in ovary-sparing hysterectomy and ovariectomy (1). Chemical/hormonal sterilants have also been administered to male and female dogs.

Surgical methods for neutering puppies became popular and assured the prevention of reproduction in dogs adopted from shelters. Neutering of male dogs was accelerated by studies showing a decrease in aggression toward family members in a minority of neutered dogs (2–4). However, in the 2000s, concerns grew about the behavioral and health impacts of neutering for some dogs, creating a complicated picture of the likely effects of neutering a specific dog at certain ages. Research has emphasized that several cancers (5–8) and joint disorders (9, 10) were more common in neutered than intact dogs, but there is a lack of information to inform veterinary practice.

For more breed, sex, and age-of-neutering information, patient records of Golden Retrievers were examined for risks of joint disorder, such as hip dysplasia (HD), elbow dysplasia (ED), or cranial cruciate ligament (CCL) tear, or cancer, such as lymphosarcoma (LSA), mast cell tumor (MCT), hemangiosarcoma (HSA), or osteosarcoma (OSA) (11). Age of neutering had major specific effects on risks for male and female dogs for the abovementioned three joint disorders and four cancers. Subsequently, 35 breeds (12) and 3 weight classes (13) of mixed breeds were examined for the roles of age of neutering on these health risks. Regarding joint disorders, some heavier dog breeds (over 20 kg) were at higher risk than lighter weight dogs. This pattern was also found with mixed-breed dogs, where those over 20 kg were more likely to have a significantly higher risk of joint disorders when neutered than intact. Other genetic diseases were found to have increased expression with neutering, especially when performed early and for female breeds (14). A further problem with neutering is that it results in lifelong extremely high secretion of the luteinizing hormone, having effects on receptors throughout the body, perhaps altering aggressive and fearful behaviors and various other disorders (15).

Dog owners' decisions on whether and when to neuter their dogs often are influenced by concerns about behavioral effects of neutering. Several recent studies have reported increased fear aggression in both male and female breeds having less exposure to gonadal hormones. Client surveys using the CBarq data have found that less lifetime exposure to gonadal hormones is associated with increased fearfulness and aggression in female (16) and male (17) dogs. A study with another database reported that dogs with longer exposure to gonadal hormones had fewer health issues and problem or nuisance behaviors (18).

With data published in 2020 on 35 breeds and mixed breeds of dogs highlighting the vulnerability of some large dogs to increased risks of joint disorders with early neutering (12, 13), and data of several more years available, hospital data were examined to identify any additional breeds of large dogs with sufficient data for similar analyses as previously used. This study reports results of five additional large breeds of male and female dogs that had a sufficient case load for analyses, all weighing more than 20 kg: German Wire/Shorthaired Pointer, Mastiff, Newfoundland, Rhodesian Ridgeback, and Siberian Husky. Some evidence already highlights the vulnerability of the five breeds to these conditions. Orthopedic Foundation for Animals (OFA) presents summary reports for abnormal hips and elbows: German Shorthaired Pointer−3.8% and 1.2%; Mastiff−20.5% and 15.7%; Newfoundland−25.9% and 23.6%; Rhodesian Ridgeback−4.4% and 6.5%; Siberian Husky−0.3% and 0.1% (19), respectively. These are data combined for intact male and female dogs, assessing the dogs for breeding. A comprehensive study of HD and CCL in male and female dogs by Witsberger et al. reported rates of the two disorders as follows: German Shorthaired Pointer−3% and 3%; Newfoundland−17% and 9%, the highest scores of all breeds examined; Siberian Husky−2% and 2% (10), respectively. In general, this study also reported heightened risks of both HD and CCL for neutered male dogs. A study of dogs <2 years of age with CCL, compared with age-matched controls, found that Mastiff and Newfoundland were two of the nine breeds at an increased risk for CCL (20). Neutering caused increased risks for both male and female dogs. An Egyptian study reported that 23% of Siberian Huskies had HD (21): figures were very different from those of the OFA and Witsberger's group. For various types of Mastiffs, cancer was the most common cause of mortality for 47% of dogs: OSA, 50% of cancer cases; LSA, 14%; HSA, 7% (22). In the US, in 2002, an available but unpublished paper on Rhodesian Ridgebacks from a breeder citing data by C. Roethal reported rates for MCT of 3.5% and HD of 2.2%; in Australia, in 2006, the rates for both conditions were very low: 0.2% (23). The unpublished paper mentioned that the breeding of Ridgebacks in the U.S. has reduced the HD incidence from 11.8% for dogs born before 1980 to 3.4% for dogs born in 2003/2004. Scores on a dog breed such as those from the OFA are derived from intact dogs that are being considered for breeding, representing a different pool than dogs in the general population of that breed.

This project sought to clarify the effects of age at neutering for these five breeds with joint diseases and cancers for dogs at the University of California Veterinary Medical Teaching Hospital. The methods were consistent with those in the earlier studies assessing diagnoses of three joint disorders and four cancers, as well as urinary incontinence (UI), pyometra (PYO), and mammary cancer (MC), with the status of intact or specific age of neutering. The specific objective was to identify the recommended ages for neutering of male and female dogs of these five breeds that did not increase the risks of a joint disorder or cancer. This information would inform veterinarians and their clients on how to optimize the age of neutering.

Method

Patient records of the Veterinary Medical Teaching Hospital were reviewed for the five additional breeds weighing more than 20 kg with over 200 cases. The neuter status of each included animal was identified and specified as intact or neutered. The use of alternative procedures for neutering was not often observed or recorded. It is presumed that virtually all patients had conventional surgical neutering and that very few animals had less common alternative procedures, particularly any in which the dog retains the gonadal hormones.

Ethics statement

The retrospective dataset was obtained from the Veterinary Medical Teaching Hospital (VMTH)'s hospital records. The campus policy allows the faculty of the University of California, Davis, to use the records for research. No animal care and use committee approval was required. Strict confidentiality for owners and their dogs was maintained.

Study parameters, data collection, and presentation

Parameters, as in previous studies (11–13), examined occurrences of joint disorders: HD, CCL and ED and cancers: LSA, HSA, MCT, and OSA in both sexes. Mammary cancer (MC), pyometra (PYO), and urinary incontinence (UI) were examined in female dogs, and UI was examined in male breeds. The abovementioned diseases were examined for dogs left intact or neutered in the age periods: <6 months, 6–11 months, 1 year (12 to <24 months), or 2–8 years. The diseases were tracked through the dogs' last patient visit until 11 years of age.

The statistical evaluations, considering sex and different ages of neutering, required a large database. The study focused on proportional differences in disease occurrences between the neuter age groups and intact dogs of the same breed and sex.

The study period represented 21 years of data, from 1 January 2000 through 31 December 2020. The inclusion criteria were the date of birth, age at neutering (if neutered), and age of diagnosis or onset of clinical signs for diseases of interest. The term "early neutering" is sometimes used below to refer to neutering in the 1st year, combining cases for both the <6 months and 6–11 months neuter periods. Female dogs were examined for MC, PYO, and UI and male dogs for UI. For all neutered dogs that developed a disease of interest, records were examined to confirm that the dog was neutered before the diagnosis or onset of signs of the disease. If the dog developed signs of the disease before neutering, the dog was considered intact for the analysis of that disease. However, for any disease that occurred after neutering, the dog was considered neutered for the analysis of that disease. For any disease of interest that occurred before 12 months of age, the dog was excluded from that disease analysis but included in analyses of other diseases. Thus, the number of cases for various diseases varied in the analyses for different disease occurrences.

When the age of neutering was not mentioned in the hospital records, telephone calls were made to the referring veterinarians to obtain the neutering dates or ages. When the age of neutering could not be obtained, the dog was excluded from the study, which was not an issue with intact dogs, so proportionately more intact cases appear in the final dataset for each breed than would be expected in the general population.

The criteria for disease diagnoses were the same as in previous studies on Golden Retrievers, 35 breeds, and mixed-breed dogs (11–13). A dog was considered as having a disease of interest if the diagnosis was made at the VMTH or by a referring veterinarian and later confirmed at the VMTH. For joint disorders (HD, ED, and/or CCL), dogs typically presented with signs of lameness, difficulty in moving, and/or joint pain. The diagnosis was confirmed by orthopedic examination, radiographic evidence, and/or surgery. UI was confirmed by clinical signs of abnormally frequent urination, urinalyses and exclusion of urinary tract infection, and/or other diseases. If a diagnosis was listed in the record as "suspected" based on some clinical signs but not confirmed, the case was excluded from the analysis for that specific disease, but the dog was included in other disease analyses.

Statistical analyses

As in previous studies (11–13), survival analysis was used to test for differences with respect to the hazard of a disease in the neutered and intact groups while adjusting for the differences in time at risk for a disease. The groups were initially compared using a Kaplan–Meier life table analysis. *Post-hoc* comparisons among the subgroups were based on least squares means of the hazard within each subgroup. For comparisons where the Kaplan–Meier test showed significance at the p-value < 0.05 level, both the log-rank and Wilcoxon tests were used for further analyses. Because joint disorders are expected to be seen at a similar risk throughout a dog's lifespan, regardless of age, the log-rank test was used for joint disorders. Conversely, cancers were examined with the Wilcoxon test since the risk of cancer is expected to be higher in older dogs. In contrast to previous studies (11–13) using this methodology, no asterisk was used in the joint disorder results to indicate significance seen only in the Wilcoxon test because all significant joint disorder results for the Wilcoxon test were also significant for the log-rank test. Similarly, no asterisk was used in the cancer results to indicate significance seen only in the log-rank test because all significant cancer results for the log-rank test were also significant for the Wilcoxon test. For all statistical tests, the two-tailed statistical level of significance was set at a p-value of < 0.05 and reported as either a p-value of < 0.05 or a p-value of < 0.01. Each breed was analyzed separately, and there were no statistical comparisons between breeds. However, the overall findings with each breed allow for some general comparisons.

Data presentation

For each of the five breeds in Appendix 1, the numbers of intact and neutered male and female dogs are given. Tables show

percentages of dogs with each disease. Statistical analyses compared the occurrences of joint disorders and cancers between each neutering period and intact dogs. If the comparison was significant at either the p-value of < 0.05 or p-value of < 0.01 level, the data were bolded and the p-value was given. The detailed datasets are available online (Figshare, 10.6084/m9.figshare.24280054).

Results

The breed-by-breed findings are presented in four formats. First, a short paragraph describing the occurrences of joint disorders and cancers for intact and neutered dogs for each breed is given below, with significant increases in disease types over intact dogs reported. Second, Table 1 presents guidelines reflecting research findings for all 40 breeds that have been studied, including the five breeds reported here. Third, the data-based findings, with statistical analyses for each breed, are reported in Appendix 1. Fourth, the raw data are available in Figshare.

General findings

Data for these five large breeds of dogs provide cautionary information regarding neutering. The breeds were all rated in the top 50 by the American Kennel Club (AKC) in 2022 (23). Four breeds showed significantly elevated diagnoses with early neutering, and the fifth breed had some non-significant elevated scores. Brief summaries on results for each breed and suggested guidelines for neutering age are given below.

German Short/Wirehaired Pointer

This dog enjoys increasing popularity, currently ranked #10 by AKC (24). These Pointers are used in hunting and excel in being highly trainable (25). The study population consisted of 150 intact male, 89 neutered male, 90 intact female, and 114 neutered female dogs, for a total sample of 443 cases. In intact male and female dogs, the occurrence of a joint disorder was 3% and 2%, respectively. CCL was slightly elevated for male dogs neutered before 1 year, and the occurrence of joint disorders was highly elevated for female breeds neutered before 6 months, with 38% having at least one joint disorder. Intact male and female breeds had a 6% and 1% likelihood of cancer, respectively. Male breeds neutered before 6 months had significantly elevated rates of MCT and HSA, both 8%, over intact male breeds with MCT (2%) and HSA (1%). Female breeds neutered before a year had a significantly increased risk for LSA, 11%. There were no cases of MC or pyometra among neutered female breeds, but intact female breeds had a 4% rate for each of these. Intact female breeds had no UI, but those neutered before 1 year had an insignificant increase to 6%; male dogs had almost no cases of UI. Given the increased rates of both joint disorders and cancers for both male and female dogs with early neutering, the suggested guideline is neutering no earlier than 12 months of age.

Mastiff

This giant breed ranking #37 (24) weighs around 150 pounds. For a couple thousand years, Mastiffs guarded and protected households. They are above average in aggression toward other dogs and family and only average in trainability, so they are challenging to manage (25) but very favored by many people (22). The study population consisted of 148 intact male, 61 neutered male, 70 intact female, and 82 neutered female dogs, for a total sample of 361 cases. Intact male and female dogs had a 6% and 9% risk of at least one joint disorder, respectively. Neutering male dogs before 2 years resulted in a significantly elevated risk for a joint disorder, mainly due to CCL; neutering before 1 year was a 21% risk, and neutering at 1 year of age was a 15% risk. Although not significant, female dogs neutered before 1 year had a 20% risk of a joint disorder. Intact male and female dogs had 7% and 2% risks of having at least one cancer, respectively. Male dogs neutered before 1 year had a significantly elevated risk of cancer, 28%, whereas female dogs lacked any elevated risk. Intact female dogs had a 12% rate of PYO. The guideline is to neuter male dogs no earlier than 24 months of age due to joint disorders. With female dogs, it is suggested to neuter no earlier than 12 months of age due to a non-significant elevated incidence of cranial cruciate ligament tear and also due to the large body size.

Newfoundland

Weighing over 100 pounds, this breed is currently ranked #42 (24) and, due to its love for water, has a history of assisting in maritime environments. The Newfoundland is non-aggressive and low in activity, but is average on demand for affection and is average on trainability, making for a very large dog somewhat easy to manage (25). The study population consisted of 74 intact male, 40 neutered male, 59 intact female, and 39 neutered female dogs, for a total sample of 212 cases. Intact male and female dogs had 10% and 7% rates of having at least one joint disorder, respectively. Males' rates after neutering were not significantly elevated, but females' rates for having a joint disorder were significantly elevated: 39% were affected when neutered in the 1st year. There were no cancers in intact female dogs, and only a 3% rate for intact male dogs, with no significant elevations with neutering. Neutering female dogs before 1 year was associated with an 18% prevalence of UI, though not a significant increase over intact female dogs. Cases of MC and PYO were rarely recorded. The spaying guideline for female dogs is to neuter no earlier than 12 months of age. Despite no significant data against early neutering, it may be a cautious choice to neuter male dogs no earlier than 12 months of age due to the large body size of the breed.

Rhodesian Ridgeback

Imported from South Africa, this breed is currently ranking #41 (24). Blended from the native Ridgeback and European breeds, the Ridgeback is well above average in aggression and somewhat above average in trainability, with low activity and affection (25). The

TABLE 1 Suggested neutering age guidelines for 40 breeds by breed and sex.

Suggested neutering age guidelines for 40 breeds						
	Males			Females		
	No earlier than 6 months	No earlier than 12 months	No earlier than 24 months	No earlier than 6 months	No earlier than 12 months	No earlier than 24 months
Australian Cattle Dog	X			X		
Australian Shepherd	X			X*		
Beagle		X		X		
Bernese Mountain Dog			X	X		
Border Collie		X			X	
Boston Terrier		X		X		
Boxer			X			X
Bulldog	X			X		
Cavalier King Charles Spaniel	X			X		
Chihuahua	X			X		
Cocker Spaniel	X					X
Collie	X				X	
Corgi	X			X		
Dachshund	X				X	
Doberman Pinscher	Leave Intact					X**
English Springer Spaniel	X				X	
German Shepherd			X			X
German Short/Wirehaired Pointer		X			X	
Golden Retriever		X		Leave Intact		
Great Dane	X			X		
Irish Wolfhound			X	X		
Jack Russell Terrier	X			X		
Labrador Retriever	X				X	
Maltese	X			X		
Mastiff			X		X	
Miniature Schnauzer	X			X		
Newfoundland		X			X	
Pomeranian	X			X		
Poodle (Toy)	X			X		
Poodle (Miniature)		X		X		
Poodle (Standard)			X	X		
Pug	X			X*		
Rhodesian Ridgeback	X			X		
Rottweiler		X		X		
Saint Bernard	X			X		
Shetland Sheepdog	X					X**
Shih Tzu	X					X
Siberian Husky	X				X	
West Highland White Terrier	X			X		
Yorkshire Terrier	X			X		

Summary of spaying and neutering guidelines based on findings regarding joint disorders and cancers. *Australian Shepherd and Pug female dogs had no statistically significantly elevated joint disorders or cancers with early neutering. Nonetheless, they are examples of breeds with more joint disorders and/or cancer cases among the early neutered animals, and these may have become significant in a larger dataset (12). **This recommendation for Doberman Pinscher and Shetland Sheepdog females is based on their elevated risks of UI, not joint disorders or cancers (12).

study population consisted of 54 intact male, 69 neutered male, 30 intact female, and 56 neutered female dogs, for a total sample of 209 cases. Intact male and female dogs had 14% and 13% risk for at least one cancer, respectively. Neutering female dogs before 6 months provided the only significant increase in cancers, with a 25% rate of MCT compared with the 3% rate in intact female dogs. MC, PYO, and UI were rarely recorded in these female dogs. The guideline is to neuter no earlier than 6 months for male dogs and at least that for female dogs, given their cases of MCT with early neutering.

Siberian Husky

This breed ranking #21 (24) is the most popular breed and fastest of the sled dogs. Historically, from the Siberian Chukchi people and then also the Alaskan Inuit culture, Huskies are quite high on aggressive traits and excessive barking and are only average for trainability (25). The study population consisted of 64 intact male, 77 neutered male, 48 intact female, and 77 neutered female dogs, from a total sample of 266 cases. Intact male and female dogs both had a 2% risk for joint disorders. Although neutering resulted in no significant risks for joint disorders over that of intact dogs, female dogs neutered before 1 year had a 12% chance of CCL, which would perhaps be significant with a larger dataset. Intact male and female dogs had 10% and 6% risks of at least one cancer, respectively, with no elevation associated with neutering. MC and PYO in intact female dogs were both 2%, but their prevalence in female dogs neutered 2–8 years were 9% and 4%, respectively. However, neither of these results was significant. The guideline is to neuter male dogs no earlier than 6 months of age. Given a trend for elevated CCL in early neutered female dogs, it is a cautious choice to neuter female dogs no earlier than 12 months of age.

Discussion

This study extends the available information on five additional large breeds of dogs, showing their vulnerability to increased joint disorders and/or cancers with early neutering. As with results from previously studied breeds, the increased risks were specific for each breed. Regarding the mechanism of some increases in joint disorders with early neutering, larger dogs are known to have closure of the growth plates at higher ages than smaller dogs. Unfortunately, systematic data by breed on growth plate closure or puberty are not available. However, it was reported that the giant breeds, such as Great Danes, Mastiffs, or Saint Bernards, sometimes have closure at ages beyond the published ranges for dogs, reflecting their delays of closure of some long bones by the periods of up to 3–6 months beyond typical published data (26). The earlier closure in smaller dogs is generally accepted, and in one study, smaller dogs and cats were found to show earlier ranges of ages of closure (27). Another study of large and small breeds of dogs reported that large breeds had closure of their growth plates at a later chronological age (28).

This group of dogs showed a much lower incidence of hip and elbow disorders/abnormalities for intact Mastiff and Newfoundland dogs than OFA records of dogs being screened as breeders (percentage of HD followed by the percentage of ED): Mastiff: male, 2% and 2%–female, 6% and 4% vs. 21% and 16% of combined males and females from OFA; Newfoundland: male, 3% and 3%–female, 2% and 3% vs. 26% and 24% of combined male and female dogs from OFA. The higher OFA incidences of HD and ED in these two very large breeds may reflect more strict measures of abnormality than is symptomatic enough to lead to a diagnosis and also could be influenced by breed differences in geographic areas or by an elevated proportion of dog owners contacting the OFA due to the dog's known issues or expected issues with these disorders. Using data from 1954 to 2003, Witsberger et al. examined HD and CCL and reported high rates for male and female Newfoundland dogs: 17% and 9% (10). The same two disorders in the current dataset resulted in HD and CCL rates for dogs neutered in the 1st year: male: 9% and 22%; female: 13% and 38%. The rates for intact dogs were as follows: male: 3% and 10%; female: 2% and 7%, suggesting that early neutering causes much of the very high rate for Newfoundlands. Male dogs neutered at 2–8 years had no joint disorders, but 18% of the female Newfoundland dogs had CCL.

The results with German Short/Wirehaired Pointers having increased risks for both joint disorders and cancers due to the age of neutering are somewhat unusual. Owners can be advised to delay neutering until 1 year and reduce these risks. With female Rhodesian Ridgebacks, the increased risk for MCT with very early neutering is easily avoided by waiting until the dog is 6 months old. The vulnerability of female Siberian Huskies to CCL with neutering before 1 year, while not significant, suggests that a cautious choice would be to wait until the dog is 1 year of age.

These decisions ultimately depend on the owners' preferences. The data can be complicated. As an example, the female Doberman has no increased risk for joint disorders or cancers if neutered beyond 12 months of age, as shown in Table 1. However, neutering between 1 and 2 years of age was associated with very elevated risks for UI—19% of female dogs.

Recovery from neutering is more problematic for older dogs than when still a puppy: perhaps creating a transient welfare challenge compared with neutering at younger ages. Neutering when the dog is older is also more expensive for the client. As mentioned earlier, increased fearfulness may be associated with neutering for some dogs (16, 17), a heightened risk for an ongoing issue with behavior and for the welfare of the dog. The situation has become increasingly complex when compared with the past practice of neutering most dogs early in life. Currently, dog owners are likely to be considering several factors when making their decisions on whether and when to neuter their dogs. Veterinarians can play an important educational role in providing information that relates to the clients' particular situations and objectives with their dogs.

These results offer information on the earliest ages to consider neutering without increasing risks for the mentioned joint disorders or cancers. Whether or not to neuter is a separate question for consideration by the handler consulting with the veterinarian. Some dog owners will prefer not to neuter the dog, and if reproduction is planned for the dog, neutering will at least be delayed. Humane societies placing dogs have complex considerations given the high risk for some dogs placed to be allowed to mate and some laws requiring neutering of dogs prior to placement. Alternative methods are increasing, and increasing numbers of clinicians are offering them. Perhaps some humane

societies will begin offering options for preventing reproduction that does not involve gonadal hormone withdrawal, at least for large dogs.

Limitations

Although a variety of alternative methods exist and are being developed to prevent the reproduction of male and female dogs, our data did not include information on these other methods. The results reported here are due to gonadal hormone withdrawal and/or increase in gonadotropic hormones; thus, it is likely that other methods of removing gonadal hormones would have similar results.

Conclusions

Decisions on whether and when to neuter a specific dog are complicated and reflect a consideration of the dog's breed, health status, and living situation, as well as available information pertaining to risks for these joint disorders and cancers. These varied results highlight the complex effects of neutering and the age at which it is conducted. They point to the importance of personalized decision-making regarding the neutering of dogs, with consideration of relevant information available on the dog's breed and sex, as well as aspects of the dog's lifestyle.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: Figshare, 10.6084/m9.figshare.24280054 – When accepted. Current private link — https://figshare.com/s/eaefceb41c81372cafbf.

Author contributions

LH: Project administration, Writing – original draft, Supervision, Conceptualization. AT: Project administration, Writing – review & editing, Validation, Supervision, Formal analysis, Data curation. BH: Investigation, Conceptualization, Writing – review & editing. NW: Writing – review & editing, Software, Methodology, Formal analysis. ML: Writing – review & editing, Investigation. MB: Writing – review & editing, Investigation. JL: Writing – review & editing, Investigation. MH: Writing – review & editing, Investigation. SC: Writing – review & editing, Investigation. JC: Writing – review & editing.

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An Ancient Practice but a New Paradigm: Personal Choice for the Age to Spay or Neuter a Dog

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Extensive practice and knowledge of the methods and effects of castration of male livestock and even humans has been widespread since ancient times, but only a few decades ago did neutering (including spaying) become a routine part of canine husbandry. In the US, the 6-month neuter became standard practice. Only recently, however, have some of the consequences of this major physiological alteration become evident. As the data-based study on 35 breeds reveals, there are major breed differences associated with effects of neutering, especially with early neutering, including increased risks of joint disorders and some cancers. The study of mixed-breed dogs reveals that the risk of joint disorders is increased in the large dogs. Implications of breed-specific and sex-specific effects for age of neutering have prompted the consideration of a new paradigm with regard to this practice. This involves focusing on each individual dog when deciding upon the appropriate age of neutering to avoid increasing the risk of a joint disorder or cancer above that inherent for the breed. For many breeds, particularly the smaller dogs, no effects were found for the age of neutering on joint disorders and the cancers followed. In these cases, the caregiver has a wide range of choice for neutering without increasing the dog's risk for these diseases. In the future, additional research may reveal more about other increased risks for age-related cognitive dysfunction or elevated levels of luteinizing hormone caused by gonad removal, and lead to revised guidelines.

Keywords: castration, humans, livestock, luteinizing hormone, breed differences, sex differences, body size, gonadal hormones

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EARLY PRACTICES OF NEUTERING AND SPAYING ANIMALS AND CASTRATING HUMANS

Having dogs as companions to humans dates back to prehistoric times: recent archeological studies of dental microwear of canine skeletons suggest that early protocols differed in their diets from wolves, were behaviorally and morphologically distinct, and already were companions to humans in the Paleolithic age, over 28,000 years ago (1).

As farming by early humans came to include husbandry of cattle, horses, sheep, and goats, castration of male livestock animals became commonplace, and was practiced at least 8,000 years ago (2). Gonadectomized male livestock were strong enough for doing work and easier to manage than unaltered bulls; these oxen, being castrated, were the favored draft working animals. Interestingly, the ancient Sumerians passed laws around 2400 BC protecting the welfare and affirming the value of their oxen, specifying penalties for injuries to oxen when they were rented (3). An injury to the oxen's horn had a penalty of one-third of the oxen's value, to the eye was

one-half the value, and if drowned, the full value or a replacement ox was to be paid. Similarly, King Hammurabi of Babylon around 1750 BC passed 29 law codes concerning crimes against oxen and specifying rules regarding payments by someone hiring oxen or for veterinary bills (4). Breaking off a horn, cutting of a tail, or hurting its muzzle required paying one-fourth of its value in money to the owner. A veterinarian performing a serious operation on an ox and killing it, was required to pay the owner one-fourth of its value. Someone stealing an ox needed to pay back thirty times its value (5).

Castrating male livestock, a relatively easy procedure, was commonly practiced in Egypt (6). Ancient Egyptians maintained huge herds of cattle, sheep, and goats; for example, over 400,000 livestock were maintained for the temple at Thebes (1, p. 43). The cattle selected for use in special religious ceremonies there invariably were castrated bulls (6).

In ancient Greece, most cattle, sheep, goats, and pigs were castrated, except for a few males needed for breeding (7). As well-known then, the castration reduced problems with aggression in groups of animals, and the castrated males yielded more and fattier meat. Galen explained that oxen were castrated for usefulness in farming, and pigs to yield more tasty meat (6). With swine, the meat of a castrated male tasted better than that from intact males and thus provided a way to avoid the "boar taint." Neutering of animals in ancient Greece is also depicted in engravings on urns and jugs (7). During wars, oxen, mules, and asses marched with the army, carrying heavy loads (8). Large flocks of sheep, primarily castrated males, were raised for wool (9). Aristotle advocated that all authors should possess knowledge on a variety of topics, including the castration of a boar (8). Although many male animals were castrated, ancient documents from Greece around 200 BC provide evidence that at the same time, the uncastrated male animals represented a cultural ideal that was preferred for sacrifice and rituals (7).

In Asia Minor, castration sometimes was incorporated into religious or sacrifice ceremonies. Around the world and throughout ages, people were making decisions on specifically which males to neuter and which method to use, while also choosing not to castrate certain individuals. Spaying females, or ovariohysterectomy, did not come into practice until much later, undoubtedly because of the greater surgical complexity and risks of infections. Even now, spaying females is not common in the husbandry of livestock or horses.

The prevalent practice in major ancient cultures of castrating boys and men was a practice that produced eunuchs who had special roles in several ancient societies; awareness of the methods, purposes, and effects of human castration was inevitable. Studies of eunuchs in Late Antiquity and the court cultures of Byzantium, Islam, and China are available, outlining their important integrated roles in society; less is known about the worldwide slave trade in eunuchs in the Afro-Euro-Asian world (10, 11). Also, the Bible contains numerous references to eunuchs (12). Some men castrated themselves for religious reasons to acquire improved status in the church (13). Others were castrated for a variety of reasons, with different outcomes. Well known is the castration of young boys as Roman castrati singers from third century BC through sixth century AD (14). Considering the ubiquity of human castration in the ancient world, a somewhat sophisticated awareness of castration must have resulted. The methods and employment of castration of humans, as with animals, involved specific decisions in each situation.

In recent times, castrated cattle were selected to be the special display bulls of the Dinka people, as was done in ancient Egypt, and they also would be the ones selected for sacrifice (15). The Dinka often delayed the castration of bulls and rams until the animals were a bit older, presumably to allow the conformation and characteristics of the animal to be manifest before making a decision on whether to castrate. Most bulls were castrated for important cultural and esthetic reasons, to reduce fighting, for easier control, and to prevent indiscriminate breeding of estrous cows. Little is known about castration of dogs and cats during the Renaissance, though a wall painting depicted castration of a cat in 1531–1532 (16).

In the twentieth century, when many animals were living on farms, people still were well aware of options of neutering livestock animals. Pet dogs were typically living outside of homes, often in their dog houses. Gradually there was a movement toward having the dogs inside homes where they came to be considered members of the family (17). As closer contact increased between humans and their dogs, more people began to neuter and spay their dogs. This prevented those dogs from reproducing, and somewhat reduced some of the problematic behaviors of male dogs, especially roaming (18), but some research has found more aggressive problems among neutered dogs (19). Spayed females also have been found to be more aggressive than intact females (19). Anesthetic and surgical techniques for removing the ovaries and uterus of females were sufficiently developed by then that these procedures also were commonplace. Spaying of female dogs became more common in the U.S. than neutering males (20), as is generally the case in many countries today. Spaying the females avoided unplanned or unwanted puppies and eliminated estrous behavior, and the proestrous bleeding of the females which attracted males.

THE BROAD PHYSIOLOGICAL EFFECTS OF NEUTERING FROM HORMONAL WITHDRAWAL

Although neutering is thought of as a means of rendering the male or female infertile by removing the source of sperm and ova, neutering also removes the primary source of testosterone (T) or estrogen (E) which acts on the basal brain hypothalamus and suprachiasmatic nucleus to facilitate some behaviors. People often believe that after neutering, males will no longer have an interest in mating and will be less aggressive toward other male dogs and people. However, these behaviors are mediated by a neural circuitry, and testosterone simply facilitates the neural circuitry. Even with little T available, the male-like behaviors can still be activated in many male dogs (21). In females, the behavioral aspects of estrus are closely tied to E as part of mating coordination, and

TABLE 1 | Receptor sites for the luteinizing hormone in male and female dogs possibly related to non-cancerous and cancerous diseases (22).

LH receptor sites and possible non-cancerous diseases related to neutering
Gastrointestinal tract—possible increase in appetite
Urinary tract, especially in females—urinary incontinence, urinary calculi
Pancreas—diabetes mellitus, obesity
Thyroid gland— hypothyroidism
Head of femur—ligaments and cartilage—hip dysplasia
Cranial cruciate ligament—cranial cruciate ligament rupture or tear
Hippocampus and hypothalamus—behavioral changes seen with neutering
Central nervous system—cognitive decline
LH receptor sites and possible cancerous diseases related to neutering
Prostate gland—prostate cancer
Bladder and urethra—transitional cell carcinoma
Vascular endothelial and smooth muscle in heart and spleen—hemangiosarcoma
Skin—mast cell tumors
Lymphoid tissue and lymphocytes—lymphoma

neutering females largely removes any further display of estrous behavior permanently.

What is less well known is that production of the gonadal hormones is under the control of gonadotropic hormones produced by the pituitary, the luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In intact males, T levels are controlled by means of a feedback mechanism which maintains T at a consistent level. The T production acts on the hypothalamus which produces the gonadotropin releasing hormone (GnRH); if T levels are low, GnRH induces the pituitary to produce more LH until T levels return to normal. The rising LH in an intact male causes more T to be produced, and then LH drops. Following removal of the gonads in males, the production of LH is not suppressed by T working on the feedback loop. LH levels rise—and remain permanently high. A similar process occurs in females; removal of the ovaries results in low estrogen and this causes consistently high levels of LH.

If there are physiological effects of high levels of LH, these could occur wherever there are receptors for LH. Until recently, little was known about this topic. The various LH receptor sites are now better understood, although what functions might be affected remain to be clarified (22). Several LH receptor sites have been identified where possibly LH may activate these sites and cause physiological effects, especially when with high LH levels. The tissue receptor sites are categorized in **Table 1**, showing potentially associated non-cancerous and cancerous diseases that could be associated with very high levels of LH.

A perusal of the diseases associated with neutering in some breeds or sexes reveals that the diseases listed in **Table 1** can be associated with the tissues which have been identified as receptor sites for LH. This does not mean that LH is causing the disease, but the fact that LH levels reach and sustain very high levels suggests that this factor should be explored. Breeds may differ with regard to specific receptor sites—a point that also could be investigated.

IMPLICATIONS OF NEUTERING'S EFFECTS ON JOINT DISORDERS AND CANCERS FOR SOME DOGS

The data-based findings on 35-breeds of dogs reveal wide differences among breeds with regard to increased risks of joint disorders and/or cancers (23). Given the huge differences in breed sizes and shapes, the differences in vulnerability to joint disorders or cancers associated with ages of neutering are not surprising.

Knowing about increased risks of disabling joint disorders with neutering, and avoiding the increased risks, is important not just in companion canines but also in working dogs used in police and military work, service dogs working in assisting people in wheelchairs, and dogs used in hunting, herding and agility trials. This emphasizes that the age of neutering should be chosen to avoid the vulnerable period which in some breeds is up to 2 years of age. Avoiding increasing the risk of cancer is important for every role that companion dogs have. There is a range of vulnerabilities to cancers associated with neutering, differing among various breeds, just as is true with joint disorders.

The data also reveal that for most breeds, there is no increased risk of joint disorders or cancers associated with neutering. Thus, from the standpoint of these two disease categories there is no generally recommended age for neutering across all breeds where these diseases were not associated with age of neutering. The caregiver and/or veterinarian can make a personal choice after assessing their own context and situation without adversely increasing risks of these diseases. Veterinarians may wish to provide their own guidelines.

For female dogs, the occurrence of mammary cancer is a concern. Some evident differences were found among the 35 breeds in the proportion of females left intact that developed mammary cancer; in some breeds, as many as 6 percent of intact female dogs had mammary cancer, while other breeds were at 0 percent (22). In one study, the median age of onset of this cancer in intact females was 10 years (24), an age which is considerably older than the median age of dogs in the records of cases in the study of 35 breeds, which was 5–6 years. Thus, one would expect the number of cases with mammary cancer to increase as dogs age further. As mentioned in the paper on 35-breeds, when only cases were counted in which the record went beyond 8 years of age, the differences in proportions of intact females with the cancer did not change. The dangers of mammary cancers in females may be overrated. This view is also supported by a published meta-analysis which concluded that the occurrence of mammary cancer was only weakly related to leaving females intact (25).

Two large studies have examined the relationship between neutering and lifespan. One was based on the Veterinary Medical Database of over 40,000 dogs, and another involved over 20,000 dogs from three separate veterinary hospitals in the US. Both studies found that neutered dogs lived significantly longer than

those left intact (26, 27). The studies did not analyze the data with respect to age of neutering. Both studies revealed that neutered dogs were much more likely to die of a cancer [especially those cancers subsequently analyzed in the 35-breed paper: (23)]. The intact dogs were more likely than the neutered dogs to die of trauma, such as automobile accidents or infectious disease. Confounding factors to consider include the variability in size of the dogs, since small dogs live longer. If one wants a long-lived dog, one could be drawn toward a small-dog breed. To reduce the risks of a cancer killing the dog prematurely, one could consider selecting a breed with no cancer vulnerability related to neutering. Additionally, one could choose not to neuter the dog, or at least time the age of neutering beyond the period of vulnerability.

An extensive literature documents the relationship between a decline of gonadal hormones with aging in humans and the increased risk of Alzheimer's disease (28–31). These studies on humans raise the issue of the relationship between the standard of early neutering in dogs and later cognitive decline which results in a relatively longer absence of gonadal hormones in the brain than in the human studies. One study, based on the predictable progression of behavioral changes involved in canine cognitive decline in older dogs, found that neutering of males was associated with an accelerated cognitive decline compared with that in intact males (32). The effect of lifetime absence of gonadal hormones, be it testosterone or estrogen, on cognitive activities, is an area that has scarcely been explored for dogs, especially the possibility of breed differences and the degree of lifetime absence of gonadal hormones.

DEALING WITH DOGS THAT HAVE NOT BEEN NEUTERED

Although the authors do not necessarily recommend that caregivers completely avoid neutering their male or female dogs, in many cases this is the choice of the caregivers. This may or may not present problems to work out. For those with dogs of large body size the pursuit of females in estrus may present challenges. With large females, managing the proestrus bleeding may require doggy diapers and housing management. These are issues of less concern in small dogs.

The behavior issues for intact males, such as roaming, urine marking in the house or aggression to another family dog or human family member, sometimes can be reduced by neutering. However, research has revealed that neutering may resolve these behaviors only in a minority of neutered dogs (roaming and urine marking, 40 percent; aggression to another family dog or human, 20 percent) (21). Recent studies point to the complexity of aggressive behavior of male dogs and its triggers, showing that aggression can be increased by neutering. Neutered dogs are more likely to be sniffed in their anal region by intact males and were more anxious and insecure (33); they perhaps present a confusing stimulus that leads to aggressive conflict. Another study found that dogs with a lower percentage of lifetime exposure to gonadal hormones were reported to have 8 fearful and 7 aggressive behaviors reported more frequently by their owners (34). The aggressive problem behaviors dealt were directed at strangers, except for one behavior of being approached by an unfamiliar female dog.

For dogs used in service or assistance roles it may not be acceptable to have an intact dog because of the discipline required and the risk of an intact dog being attracted to, or attracting, dogs of the opposite sex. This is usually not an issue with police or military dogs, and intact German Shepherd males and females were found to be more trainable than neutered dogs for police dog narcotics olfaction performance and behavior; males performed better than females (35). For these various working roles, there could have been extensive training involved. The importance of not neutering too early so as to not unnecessarily increase the risk of a disabling joint disorder has been covered. What may be on the horizon is whether in some breeds, early neutering could advance cognitive impairment as the dog ages, impairing the role in service work or police or military work.

THE PARADIGM SHIFT TO PERSONAL CHOICE IN THE TIMING OF NEUTERING

In general, the idea is to replace the long-standing practice of expecting that the puppy should be spayed or neutered before or at 6 months, or in the case of some females, before the first estrus. Others also raise questions about this across-the-board timing that has been favored the past few decades (36). Instead, the new paradigm is for the veterinarian and pet owner, or the pet owner alone, to use the available data-based information to decide on the best age for neutering. As mentioned, the data suggest that for most of the 35 breeds, there is no increased risk of a joint disorder or cancer with neutering at any age. Thus, the decision with these breeds is up to the owner as to the best time for their circumstances.

The above background is intended to provide the veterinarian or the caregiver of the puppy some information with which to decide on the best age for neutering on a case-by-case basis. Generally, one would focus on the breed and sex of the puppy. If the breed is one of the 35 breeds covered in our study (23), this is straight forward. If the breed is not covered, one could look at closely related breeds. Or, using the paper on mixed breeds (37), one could then see if a mixed-breed puppy in question is expected to mature into one of the weight categories with an increased risk of a joint disorder with neutering at an early age. Finally, data available in supplementary files of the 35-breed and mixed breed papers give the actual estimated risks and percentages for each joint disorder and type of cancer with neutering at each age interval. In some instances, the risk may appear low, even if significant, compared with the other factors being considered, and one should choose not to be guided by the risk alone.

Since ancient times, humans have altered the hormonal status of animals and men with castration, making choices as to which individuals would have these procedures. Emphasizing the concept of personal choice, the idea inherent in the paradigm shift is to take each puppy as a separate case and consider all the relevant factors of the living context when deciding upon the age for neutering. As we learn more about some

aspects of neutering such as age-related cognitive decline, there may be some additional considerations that may impact some breeds. The idea of a paradigm shift is that additional relevant information may come about and influence decisions made by puppy owners and their veterinarians.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

LH and BH: concept, draft, and edits shared equally. Both authors contributed to the article and approved the submitted version.

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REVIEW
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A Review of the Impact of Neuter Status on Expression of Inherited Conditions in Dogs

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Gonadectomy is an important reproductive management tool employed in many countries, and is highly prevalent in the US with an estimated 85% of dogs being neutered. Despite the societal benefits in pet population control, negative associations between neuter status, and health conditions have been reported in recent years. Most particularly observed are the consequences of early age neutering. Knowing that different physiological systems rely upon gonadal steroids during development and physiological maintenance, studies have been undertaken to assess the impact of neuter status on multiple body and organ systems. For some inherited conditions, neutering is associated with an increased risk of expression. Neutering has also been associated with altered metabolism and a predisposition for weight gain in dogs, which may confound the detected risk association between neutering and disease expression. This review summarizes the effects of neutering on cancer, orthopedic, and immune disorders in the dog and also explores the potentially exacerbating factor of body weight.

Keywords: neuter, dog, spay, inherited disease, immune disease

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INTRODUCTION

Gonadectomy, or more generally referred to as "neutering," is a common procedure in many countries as a means to control reproduction in companion dogs and promoted extensively as a means to reduce dogs relinquished to shelters (1). It is also employed to alter undesirable behavioral characteristics such as aggression and roaming (2–4) although within the literature are disparate reports of aggressive dog behavior being greater among neutered dogs of both sexes (5–9) whereas other literature suggests that neutering decreases aggressive behavior (10, 11). Neutering has been associated with reduced relinquishment (12) and increased lifespans (13, 14). Additional advantages of neutering are the reduced incidence of reproductive disorders (15–18) and elimination of the behavioral and physical changes that occur during estrus in the female. However, with respect to neutering for convenience, ethical considerations have been raised (19, 20).

With neutering of dogs widespread within the United States, much published literature has been devoted to ascertaining the optimal age of neutering and assessing any health consequences associated with early or late neutering (21). For example, a report in 2004 evaluated dogs neutered at early or later ages and the authors found an association between health conditions such as hip dysplasia, urinary incontinence, and cystitis with early neutering (22). Such findings resulted in a greater scrutiny of the potential adverse effects of neutering on health conditions, especially since it is well-known that different physiological systems and behavioral responses rely upon gonadal steroids during development. Beyond the

timing of neutering, research has targeted the impact of neuter status on physiology (23). In particular, cancer and orthopedic conditions have been evaluated because of the known association of gonadal steroid hormones on normal development in the case of the latter (24, 25) and on cancer progression in the case of the former (15, 26, 27). Recent studies have looked at the potential effects of neutering on multiple organ systems (28, 29).

The majority of studies assessing the impact of neutering are retrospective, and look at correlations between conditions and the neuter status of a dog. Retrospective studies only reveal associations some of which may be spurious. For example, in early onset conditions it is possible that neutering may have been a consequence of disease diagnosis rather than causal of the disease or the disease itself may have precluded neuter surgery; such nuances will not be revealed in a retrospective study. Nevertheless, retrospective studies can be instructive and reveal meaningful associations. Together the reports present a complicated picture of the health impacts of neutering and reinforce the need for a thorough consultation between veterinarians and their clients when considering elective neuter surgery. This review will focus on the risk associated with neutering for diseases considered to be heritable.

BACKGROUND

For diseases that involve the reproductive system, such as mammary, or testicular cancer, neutering has a profound effect on reducing and/or eliminating the incidence. For other disorders, there have been few reports investigating the relationship of neutering and disease expression, and all have been retrospective epidemiological studies. Studies that have included neuter status as an explanatory variable for disease expression often have concluded that neuter status was not associated with disease diagnosis or that being neutered was associated with improved health of the dog. Evaluating the studies together suggest that the association of neuter status and expression of many inherited disorders is minimal or equivocal across published studies, although as will be discussed below, for cancer, orthopedic, and immune-mediated diseases, neuter status has frequently been associated with increased risk. Inherited diseases of physiological systems that do not rely upon gonadal steroids appear to not be influenced by neuter status in the expression of those diseases.

EPILEPSY, GASTRIC VOLVULUS, AND EYE DISORDERS

Idiopathic epilepsy has been reported to have no association (30, 31) or significant but modest positive associations (29, 32) across all breeds. In contrast, another all breed study reported a reduction of cluster seizures with neutering (33) although another study reported the exact opposite (34). Several breed specific studies did not report an association between neutering and idiopathic epilepsy although the data in some suggest that neutering might have a role in improving welfare by decreasing seizure frequency, duration, or euthanasia (35–38). The conflicting reports in the published literature have led researchers to conclude that no definitive sex or neuter effect can be determined at this time (39). Consistent with this view is that although sex steroids have been implicated in modulating seizure thresholds, their role in epilepsy remains unclear (40).

Similarly, being neutered has not been reported to alter the risk for canine gastric volvulus (41, 42) though in some reports, neutering is associated with reduced risk (29, 43, 44). The disagreement of whether neutering has an impact on gastric volvulus needs further, prospective exploration. In contrast, for inherited eye disorders, neutering has been reported to have no significant impact on expression though there are typically higher numbers of cases seen in neutered animals reflecting a general higher representation of neutered animals in the study population (29, 45, 46).

CANCER

For cancers having an inherited component, there is a generalized trend for an increase in risk associated with neutering across breeds and sexes. The physiological mechanism underlying that breed specific susceptibility for cancer is unknown although it may be related to breed-specific genetic signatures of the major histocompatibility complex (47, 48), a component of the immune surveillance that can detect developing tumor cells (49) as well as other ancestry related susceptibility.

Health disorders seen among dog breeds often reflects their genetic heritage. For instance, the breeds of dogs selected for use in hunting and retrieving, the sporting breeds, cluster together in tightly related ancestral clades (50) suggesting that within breeds of those clades, there may be shared genetic susceptibility that underlies the association of risk for certain diseases. This risk may be enhanced with neutering. It is likely that the actual genetic susceptibility may differ between the breed groupings because, for example, the sporting group breeds are genetically distinct from the working group breeds. However, in some cases, though breeds may be unrelated, they are phenotypically similar due to the genetic selection employed to meet breed standards. Convergent selection may have resulted in similar biological pathways being altered in unrelated breeds that predisposes to common diseases. The risk observed in mixed breeds may reflect the amalgamation of diverse genetic susceptibilities from many different breeds.

For many cancers exhibiting a genetic predisposition, being neutered increases risk (26, 27, 29, 51–53). In contrast, the incidence of cancers associated with the reproductive tract are reduced. For instance, the risk of mammary tumors, known to have a genetic component (54, 55), is greatly reduced with neutering (56). Neutering also reduces the risk of testicular cancer and perianal adenomas (57).

When aggregated data for all dogs across multiple breeds are analyzed, neutering increases the overall risk of hemangiosarcoma, lymphoma, mast cell tumors, and osteosarcoma in both sexes although females exhibit a greater risk when neutered than seen for neutered males across all these

cancers (29). Another broadly based retrospective study reported an increased risk associated for lymphoma and mast cell tumors across both sexes and only increased risk for hemangiosarcoma in females and osteosarcoma in males associated with neutering (58). An increase in lymphoma risk associated with neutering was reported for a study across more than 1 million dogs of multiple breeds (59, 60) and a multibreed study in South Africa found that neutered males were at a lower risk for lymphoma than intact dogs but neutered females were at a greater risk (61). In contrast, Modiano et al. (62) did not find a neuter effect on lymphoma in more than 1,200 dogs of many different breeds. Another published study using a smaller population reported that when compared to intact counterparts, the risk of mast cell tumors was 4 times greater in neutered females and only 1.3 times greater in neutered males (63). Likewise, osteosarcoma and hemangiosarcoma exhibit an elevated risk associated with neutering that is greater in neutered females than neutered males (51, 52, 64). A similar sex effect has been reported in studies that evaluated specific breeds and cancers (53, 65, 66). On the whole, there appears to be a generalized risk associated with neutering and expression of these cancers although there are variabilities which may reflect breed predisposition and which breeds comprised the populations under study.

For lymphosarcoma, hemangiosarcoma, and mast cell tumors, certain breeds have a higher proportion of neutered dogs presenting with cancer. Such a finding strongly indicates a genetic basis underlying cancer susceptibility. When three popular breeds, the Labrador and Golden retriever and the German shepherd dog, were compared (65–67), the risk for lymphosarcoma, hemangiosarcoma, and mast cell tumors was increased with neutering in Golden retrievers, most particularly for females, but not for either Labrador retrievers or German shepherd dogs. Across breed differences in cancer risk associated with neutering were also revealed when the published data reported in the supplemental figures of Belanger et al., were explored (29). Specifically, there are interesting cancer trends when breeds are grouped on functionality.

The American Kennel Club (AKC) assorts the different registered dog breeds into categories representing functionality. The breed groupings also often reflect similar genetic backgrounds that can provide insight into shared genetic susceptibility for various traits. For example, the "working breed" group is comprised of large breed dogs bred for particular jobs to assist humans; pulling sleds, guarding, and water rescue. Many breeds within the working group are genetically similar (50). The herding group likewise consists of breeds with similar function and often common ancestral breed contributions. For breeds categorized as "sporting" or "working" by the AKC, the risk of lymphosarcoma, hemangiosarcoma, mast cell tumors, and osteosarcoma tends to be much greater in neutered females than neutered males. Similar trends were seen for mixed breeds and for pit bull type dogs (29). Yet for some breeds and some cancers, there is equivalent risk across the sexes or reduced risk associated with neutering (29). Osteosarcoma is more frequently diagnosed in large breed dogs presumably as a result of disruption of osteoblast maturation (64, 68). For example, within the herding group, both neutered males and females of German shepherd dogs and Australian shepherds are at elevated risk for osteosarcoma. Ru et al. (64) also reported an elevated risk for osterosarcoma in German Shepherd dogs as well as large and giant breeds corroborating the association in the working and sporting groups seen in the Belanger et al., study. Another study reported the risk in female Rottweilers was greatly elevated (risk reported as a one in four chance) if dogs were neutered early (26) although an effect of neutering on Rottweilers was not detected in a smaller study (69). Interestingly, for breeds noted as being predisposed to osteosarcoma [reviewed in (69)] neutering in females was associated with an increased risk across all predisposed breeds whereas in males, the effect of neutering was nominal. Neutered males for breeds within the hound group, such as Afghan Hound, Basset Hound, Bloodhound, and Borzoi, were at a reduced risk for osteosarcoma than their intact counterparts. In contrast, neutering of females from this breed grouping, and for breeds generally predisposed for osteosarcoma, increased the risk for this cancer.

The variability along with sex and breed specificity noted in the literature suggests caution is needed when evaluating the potential impact of neutering on cancer expression. For example, osteosarcoma is associated with rapid bone growth and estrogens play a role in normal osteoblast differentiation (70). The removal of estrogens through ovariectomy stimulates the production and therefore activity of osteoblasts (71) and this osteoblastic expansion could possibly account for the elevated risk reported in neutered females, especially in breeds selected for large size which typically experience rapid growth and highly active osteoblasts.

When considering the effect of neutering on cancers, the mechanism of action is likely to be complex involving many factors including breed ancestry (phylogenetic relationships) as noted above, developmental stage at time of neuter, and physiological interactions of gonadal steroids with other physiological systems. For example, low circulating 25-hydroxycholecalciferol, a molecule in the Vitamin D synthetic pathway, is also associated with elevated risk for many human cancers (72). Studies have shown that vitamin D plays a critical role in modulating immune function, including the regulation of proteins involved in apoptosis, cell proliferation, and immune surveillance (73), the latter being particularly relevant in cancer detection by the body. Importantly for this discussion, plasma concentrations of 25-hydroxycholecalciferol are positively associated with gonadal hormones in humans (74, 75) and in dogs (76), although for the latter, dietary intake may have confounded the observed association. When gonadal hormones are removed with neutering, circulating plasma 25-hydroxycholecalciferol may be reduced thereby increasing susceptibility to cancer development as is seen for human cancers [e.g., (77, 78)] and reported for dogs (79). Additional evidence of the direct association between plasma 25-hydroxycholecalciferol and gonadal hormones was seen in the small study by Weidner et al. (80). The authors reported that the 25-hydroxycholecalciferol status subsumed the impact of sex/neuter status as a factor in cancer prevalence; that is, the impact of sex/neuter status was reflected completely in the plasma 25-hydroxycholecalciferol levels which might be expected if gonadal hormones had a role in regulating that molecule.

Another potential mechanism underlying elevated cancer risk associated with neutering relates to components of the body's immune surveillance. Neutering of male cattle, rabbits, and guinea pigs (81), and both male and female mice (82, 83) causes an enlargement of the thymus gland and a decrease in thymocytes programmed with a suppressor or cytotoxic phenotype (83). Suppressor and cytotoxic T cells are important in eliminating cancer cells. Perhaps the removal of the gonadal steroids might disrupt the ability to recognize and destroy precancerous cells thus creating a physiological tolerance for the proliferation of cancer cells.

ORTHOPEDIC DISORDERS

Given the interaction of gonadal steroids and normal musculoskeletal development (24, 84), it is unsurprising that neutering impacts bone elongation in the dog (23) and thus, inherited conditions related to bone maturation. In one large study across many dog breeds, neutered males were at risk for hip dysplasia and neutered females for cruciate ligament damage with dogs of large and giant breeds at the greatest risk (85).

Certain categories of breeds, such as working, herding, and sporting breeds, show greater susceptibility to orthopedic disorders in general; specifically, dogs having large stature or great substance are at greater risk for hip and elbow dysplasia (86, 87). Within those breed groupings, some breeds prone to the orthopedic disorders did not show elevated risk for disease with neutering. For example, neutering did not worsen a risk for hip dysplasia for German shepherd dogs or Rottweilers, and in some breeds (e.g., Labrador retriever, Old English sheepdog) neutering was associated with reduced risk (29, 67). However, for other large breed dogs known to be predisposed for hip and elbow dysplasia, neutering was associated with an increased risk (e.g., Newfoundlands, Saint Bernards, Samoyeds). Terriers and toy breeds are not prone to hip and elbow dysplasia and neutering did not change that low risk. Taken together, there does not appear to be generalizable trends across breeds.

Small breed dogs, while being prone to patella luxation (86), were not at increased risk as a consequence of neutering in a study based upon records from the United States (29). Breeds for which patella luxation is not typically associated though did show an increased risk associated with being neutered (29). In contrast, in a United Kingdom retrospective study, the risk of patellar luxation increased more than 2-fold in neutered small dogs for both sexes (88).

In an all breed analysis, neutered males had elevated risk for intervertebral disk disease (IVDD). Certain breed morphology was especially linked to an elevated risk when neuter status was evaluated (29). Dachshunds are particularly noted for IVDD diagnosis with being neutered described as a risk factor for the condition (89); a recently published retrospective analyses demonstrated a correlation between early neutering (<12 months of age) and risk of intervertebral disc herniation in dachshunds of both sexes (90). For ruptured anterior cruciate ligament, neutering was associated with risk across all breed groupings although the working and large breed dogs appear to be overrepresented (29, 91, 92).

For inherited orthopedic conditions, such as hip and elbow dysplasia, removing the gonadal hormones that regulate the duration of bone elongation would be expected to alter growth patterns and subsequent joint alignment exacerbating any preexisting propensity for disease. Interestingly, horses, another athletic quadruped in which the vast majority of males are neutered early in life, exhibit disproportionate bone growth (93) and yet, do not appear to exhibit orthopedic deficits. The risks of orthopedic disorders associated with neutering seen in dogs may be a reflection of different stages of development at birth with horses being precocial whereas dogs are altricial and therefore more reliant on postnatal hormones for musculoskeletal development. Alternatively, extensive genetic selection applied in breed formation of the dog may play a role especially as a greater risk associated with neutering appears to be breed and ancestral lineage specific in some orthopedic diseases.

Taken together, despite some variability, for dogs of breeds in which a susceptibility to a particular orthopedic disorder exists, neutering may worsen that risk. It is quite likely that any orthopedic risk associated with neutering reflects the age of neutering. Linear bone growth represents an interplay of gonadal hormones, pituitary hormones, and growth factors (94) with gonadal steroids playing a prominent role in growth plate closure (95). The removal of the sex hormones prior to initiation of growth plate closure would promote the continued proliferation of cells within the growth plate thus permitting bone elongation that exceeds the normal growth period. Growth cessation differs for different bones within the body and the closure and growth is tightly orchestrated to optimize joint configuration. Neutering prior to cessation of bone growth would impact bone elongation and joint formation. Large breed dogs have a longer growth period than smaller stature dogs and thus bone/joint articulation may be more susceptible to environmental and exogenous perturbations in the large breeds. Recommending neutering based upon a standardized age would not take into account the growth stage of a particular dog; an early age of neuter recommendation might impact larger breed dogs disproportionately. Current perspectives argue for more individualized decision making as to the optimal time to neuter (96).

IMMUNE-MEDIATED DISORDERS

Female dogs, as also seen in humans and mice, are more prone to immune-mediated disorders (97, 98) and neutering appears to exacerbate that risk. The risk of certain immune diseases is elevated with neutering in both males and females: atopic dermatitis, autoimmune hemolytic anemia, hypoadrenocorticism, hypothyroidism, immune-mediated thrombocytopenia, inflammatory bowel disease, and systemic lupus erythematosus (14, 28, 99–102). For dogs diagnosed with hypoadrenocorticism, the relative risk of death is 2-fold higher than that seen for other dogs and in a large retrospective study in Sweden, breed by sex interactions were detected with some

breeds exhibiting a female predisposition although in other breeds, both sexes were equally affected (103).

Even though neutered males have a greater, albeit moderate, risk for atopic dermatitis, hypothyroidism, immune-mediated thrombocytopenia, and inflammatory bowel disease when compared to intact males, the elevated risk seen in neutered females is much greater than that seen for neutered males; for some conditions, such as hypothyroidism and immune-mediated thrombocytopenia, the risk is 3-fold greater in neutered females than the elevated risk in males (28). Some studies have reported that neutering in both sexes was associated with increased risk of hypothyroidism (99, 100) although in smaller studies no relationship between neuter status and hypothyroidism was recorded (104, 105). In a study of American Eskimo dogs, neutering, especially for females, was a significant factor in diabetes mellitus expression (106) whereas other studies found that neutered males were more at risk for diabetes mellitus across many different breeds and females were at no greater risk if neutered (107, 108) and another multibreed study found neutering in both males and females increased risk of diabetes mellitus (109). Across studies, neutering was consistently associated with elevated risk of diabetes mellitus although various authors have suggested that the male gonadal hormones may be protective and age of neutering may not have been accounted for sufficiently in the studies (108). In a recent review, Niaz et al., reported that neutering females at ∼1 year of age, prevented the development of diabetes mellitus in the dog by removing the ovary and the uterus and thereby hormones that activate diabetes (110). There is need however, for caution in interpreting retrospective studies centering on diabetes: potential alterations of body weight as a consequence of neutering may confound the risk of diabetes being attributed to neutering.

A sex effect on risk for immune disorders related to neutering is consistent with the risk noted above for cancers as impaired immune function is also associated with cancer progression (111). Gonadal steroids exhibit differential effects on the immune system and are believed to account for the sex specific susceptibility to immune and autoimmune disorders (112). Estrogens, acting through their cognate receptors, are critical modulators of both innate, and adaptive immune function (113). Estrogens increase the production of immunoglobulins, thereby enhancing the humoral immune response (114) as exemplified by females exhibiting a greater antibody response to vaccines (115). Estrogens can enhance the production of autoantibodies (116, 117) and preferentially stimulate IgM production (97), the immunoglobulin form most predominant in autoimmune disease (118). Thus, immunoglobulin production induced by estrogen has been implicated in mediating autoimmune pathologies (119) especially as estrogens impair the body's process of removing autoreactive B cells (115). In contrast, testosterone reduces humoral immunity, reducing immunocompetence, as seen in birds (120), lizards (121), fish (122), mice (123), and humans (124). Within mice, the impact of gonadal steroids on immune response has been shown to be genetically linked: the sexes of different mouse strains exhibit differential immune and antibody response (123). An influence of genetic background on the relationship between gonadal steroids and immune response may play a role in breed and sex specific immune-mediated diseases seen in the dog.

An altered immune response by neutering could be permissive for destruction of self-tissue, by failing to remove autoreactive antibodies, as in the case of autoimmune disorders. Neutered male mice show a slight increase in autoreactive antibodies (125) and neutered female mice exhibit depressed immune function (126). As noted above, in general, females produce higher numbers of autoreactive antibodies than males (97). Neutering female mice prone to severe autoimmune disease greatly accelerates the disease process and increases the T cells that are permissive for autoantibody production (127) and female mice prone to systemic lupus erythematosus also increase autoantibody production when neutered (128). Although similar studies of autoantibody production in response to neutering have not been undertaken in the dog, the findings in mice and other species may offer insight into the mechanism for the observed elevated risk of immune conditions with neutering and potential approaches to mitigate that risk.

WEIGHT AS A CO-FACTOR

Although there exists conflicting information as to whether neutering alters metabolism thereby causing weight gain in dogs (129), neutering is viewed as a common predisposing risk factor for obesity, most especially for cats but also for dogs (130–137). Neutering associated with increased body weight is speculated to reflect energetic metabolic changes (138), dysregulated feeding behavior (139), and the removal of estrogen, a known regulator of food intake in cats (140). Obesity is a risk factor for many disorders and that risk between disease and obesity is overrepresented in females (141). This suggests a role for gonadal steroids across many inherited diseases and an interaction with body weight. Many inherited diseases do in fact show greater risk with neutering although that risk does not appear associated with weight gain. The risk of obesity associated with neutering is influenced by breed and sex of the dog (142). In turn, obese dogs are at an increased risk for numerous health conditions including those of genetic origin such as ruptured cruciate ligament, hip dysplasia, and hypothyroidism (137, 141, 143). Some cancers are also associated with obesity and a study by Weeth et al., found that the association in dogs between obesity and cancer varied by cancer type (144). Two small studies reported an association between excess weight and diabetes mellitus (145, 146) however in those studies the body weight was owner-reported and may reflect preconceived biases because the body condition information was collected after the dog was diagnosed with diabetes.

To account for increased body weight as a potential aggravating factor in the correlation between neuter status and disease expression, we analyzed the published data for 31 inherited conditions from our previous studies (29, 147) by weight category for the different breeds. For each breed, the distribution of recorded body weights was simply divided into thirds forming tertiles of low, medium, and high weight categories. The odds ratio (OR) of disease risk in neutered animals relative to disease risk in intact animals was then calculated by sex and by weight tertile within breed using the

TABLE 1 | The number of observations across all breeds and all diseases (29) in which weight affected the risk for disease in neutered animals across three evenly-spaced, within breed, weight groups.

	Males			Females		
	Weight					
	Low	Medium	High	Low	Medium	High
Disease risk						
Strongly lowers	50	86	103	98	126	146
Moderately lowers	42	81	134	110	190	245
No impact	1,954	1,916	1,836	1,885	1,807	1,751
Moderately increased	32	7	13	25	11	0
Strongly Increased	20	8	12	25	9	1

methodology previously detailed (29). From the published data, only breeds with at least 75 observations and one case for a given disease were used. With the extensive number of comparisons, the analyses are presented as heat maps to aid in visualization of the association of weight, disease risk, and neuter status (**Supplemental Figure 1**). For the heat maps, five risk categories were generated: neutering strongly lowered disease risk (depicted as green), neutering moderately lowered disease risk (depicted as light green), neutering had no decisive impact on disease risk (depicted as blue), neutering moderately increased disease risk (depicted as peach), and neutering strongly increased disease risk (depicted as red); white squares indicate insufficient data for analysis. Inspection of the heat maps depicting the risk associated with neutering for different AKC breeds categorized by weight, revealed an absence of substantive impact of weight on the disease risk associated with neuter status. There was however a notable exception to this generalization: underweight, neutered male Newfoundland dogs were at greater risk for the majority of inherited conditions evaluated in that study. Also of interest, being within the upper tertile of body weight reduced the disease risk associated with neutering for females of most breeds.

Additionally, we were interested in assessing if, for a given breed and disease combination, there was a trend in disease risk as animals progressed from the low to high weight tertiles. Such a trend would also provide evidence of weight being an additional risk factor for disease. Specifically, we counted the number of instances in which a breed/disease combination increased in disease risk (or decreased in disease risk, or remained in the same disease risk group) when comparing the low weight tertile group to the medium weight tertile group. Similarly, we counted the change in risk when comparing a breed/disease combination in the medium weight tertile with that of the high weight tertile. As seen in **Table 1**, across body weights the majority of instances related to disease risk associated with neutering and weight across all dog breeds indicated that there was no decisive impact of weight on risk. That is, weight did not exacerbate nor ameliorate the risk associated with neutering for a particular disease. This finding corroborates a retrospective study report in which weight was not found to be a risk factor for osteosarcoma (64).

As for any retrospective approach, there are limitations to associating body weight with the disease risk associated with neutering in that the recorded body weight may or may not be temporally relevant to the original disease diagnosis. Despite this limitation, the data do not provide compelling evidence that any weight gain that may be associated with neutering increases the risk of inherited disease expression as a consequence of neutering. Therefore, the association of the risk of neutering on the expression of the conditions appears to be a direct effect of the neutering and not a secondary association due to altered weight metabolism.

SUMMARY

In many cases, neutering is promoted as the means to reduce the number of dogs euthanized in shelters, although one study (148) reported that "no clear results were found demonstrating the impact of total spay/neuter procedures on shelter intake." With 85% of the dogs in the United States neutered (149) and yet ∼3.3 million dogs enter a shelter annually in the United States (150), there are reasons beyond a failure to neuter that account for the number of dogs relinquished to shelters. With that backdrop, neutering is not the sole answer to reduce shelter euthanasia. However, there are definite advantages to neutering beyond preventing unwanted pregnancies including offering substantial convenience for owners and a reduction or elimination of some reproductive disorders.

When evaluating the risks of neutering, the economic impact should be part of the equation. The advantages and costs of surgical neutering should be weighed against potential welfare impacts on the dog. For instance neutering is a relatively low cost solution to unintended litters, reproductive disorders such as pyometra, dystocia, mammary tumors, testicular cancer, and perianal cancers. Should a dog be diagnosed with one of the aforementioned conditions, remediation can run thousands of US dollars. Studies summarized here demonstrate that neutering is associated with increased risk for some inherited diseases. Financial costs of treatments for hip surgery, diabetes control, cancer chemotherapy, and hormonal replacement vary by region, severity of the condition, and the duration or follow up but typically run thousands of dollars. Costs to repair a cranial cruciate ligament injury was estimated to range from $1,000 to $3,500 US dollars (151, 152). However, those individual costs must be balanced against the societal costs of pet relinquishment, abandonment, and overpopulation. A study in 2004 summarized the societal costs of dog overpopulation in the US including those from shelter management, animal control, dog bites, and vehicular accidents; the overall impact greatly exceeded $1.5 billion (153). A more recent study estimates $2.4 billion just on the shelter costs alone (154). Furthermore, it is important to assess the relative risk of a disorder associated with neutering and whether the elevated risk warrants undue concern. For example, a modest 1.3-fold increase in risk of a disorder being expressed may be statistically significant but not of substantial biological concern when contrasted with the risk of remaining intact [e.g.,

risk of testicular cancer having a prevalence exceeding 25% in the dog population (17)].

Reviewing multiple studies that have encompassed multiple breeds with respect to the effects of neutering on risk of disease expression may provide insight to the underlying susceptibility between neutering and a disorder. In the formation of breeds, specific phenotypic traits may be genetically linked to other genes that predispose some breeds to health disorders on their own or when selection practices lead to an exaggeration of those traits such as in the case of intervertebral disc disease and brachycephalic obstructive airway syndrome (155). Selection for phenotypic traits may have also inadvertently been permissive for the presence of deleterious alleles that may predispose certain breeds to diseases whose expression pathways interact with gonadal steroids, thereby making a breed more vulnerable to the expression of inherited disorders with neutering. This information may aid in decision making as to if, and when, to neuter an individual dog.

The studies reviewed here are retrospective studies. Despite the limitations of retrospective analyses with the limited numbers of disease cases, breed, and sex category, and most importantly, the timing of the neuter, the findings provide substantial information on the association of neutering with the development of genetic diseases. Breeds predisposed to a disorder may be more susceptible to the risks associated with neutering. The elevated risk reported in neutered dogs, most especially females, for many of the diseases underscores the need for deep consultation with animal care providers on timing of the neuter procedure and consideration of the potential positive and negative consequences that may be associated with the removal of gonadal steroids on overall health.

AUTHOR CONTRIBUTIONS

JB: data extraction and collation, interpretation, and edited manuscript. TF: informed data collection, determined and executed optimal design analysis, and edited the manuscript. AO: project conception, design, analysis, and manuscript preparation. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2019.00397/full#supplementary-material

Supplemental Figure 1 | Heat maps of risk associated with neutering in males and females by dog breed, assembled into AKC breed groupings, by body weight tertiles for inherited disorders. Five risk categories generated: neutering strongly lowered disease risk (depicted as green), neutering moderately lowered disease risk (depicted as light green), neutering had no decisive impact on disease risk (depicted as blue), neutering moderately increased disease risk (depicted as peach), neutering strongly increased disease risk (depicted as red), and white squares indicate insufficient data for analysis. **Supplemental Tables 1**, **2** provide the codes for the breeds and diseases evaluated.

Supplemental Table 1 | Breed codes.

Supplemental Table 2 | Disease abbreviations.

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Incidence of Health and Behavior Problems in Service Dog Candidates Neutered at Various Ages

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Saint Francis Service Dogs (SFSD) trains dogs to aid people with multiple sclerosis, brain injury, and many other conditions. Organizations like SFSD must carefully consider when to neuter dogs to give them the best chance at successfully completing lengthy and expensive training. The objective of this retrospective cohort study was to assess differences in the incidence of health or behavior problems leading to dismissal between dogs neutered at different ages. Data on 245 dogs—including birth date, sex, neuter date, dismissal or successful completion of training, and (where applicable) reason for dismissal—were collected from SFSD records. Age-at-neuter was grouped (<7 months; 7–11 months; >11 months) and compared for dogs who successfully completed training and dogs who were dismissed. Dogs neutered from 7 to 11 months of age were dismissed at a significantly lower overall rate than dogs neutered at an older or younger age. There were no differences between males and females. Labrador and golden retrievers were less likely to be dismissed than other breeds. This pattern was the same for dismissals for behavioral reasons. Dogs neutered at <7 months had more than twice the risk for health-related dismissals as dogs neutered at any older age and this pattern held for orthopedic dismissals. Labradors were at higher risk for orthopedic-related dismissal than golden retrievers and all other breeds. This study suggests that there is a relationship between dogs' age at neuter and the incidence of health and behavioral problems that can lead to dismissal from service dog training.

Keywords: gonadectomy, spay, neuter, service dogs, dogs, orthopedics, behavior

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INTRODUCTION

In general, pet owners are encouraged to spay or neuter their dogs in order to reduce the incidence of accidental litters and improve some aspects of pet health. Reported risks and benefits of gonadectomy may include effects on musculoskeletal problems, neoplasia, behavior, urinary incontinence, weight, or lifespan (1–7). However, questions remain about the safety and long-term effects of the gonadectomy procedure (spay/neuter) for animals at a young age, despite considerable literature on the subject, some of which is contradictory. In addition to many pet dogs in the U.S., dogs who act as service animals are often gonadectomized; Assistance Dogs International, an accreditation organization, requires that service dogs be spayed or neutered in its training standards (8).

Examinations of the effects of gonadectomy in service dog training programs are rare. Unlike pet dogs, service dogs are judged on their ability to successfully complete training requirements, in addition to meeting standards of health and behavior. Kustritz has stated that age at gonadectomy did not alter trainability of working dogs (9), but more detailed examinations of service dogs-in-training are critical to our understanding of the needs of future service animals.

Saint Francis Service Dogs (SFSD) is a non-profit organization in Roanoke, Virginia, USA, which trains service dogs for children and adults with disabilities. Founded in 1996, SFSD has placed dogs with people with disabilities and in locations such as courtrooms and healthcare facilities since 1998. Puppies of about 8 weeks of age, typically donated by private breeders, are placed with a puppy-raiser—usually in a private home—and taught basic manners and commands until ∼15 months of age, at which time they are transferred to a trainer to begin 9 to 12 months of formal training as a service dog.

Until 2013, most puppies in the SFSD program were spayed/neutered at ∼4 to 6 months of age. Gonadectomy at this early age has commonly been recommended to prevent accidental litters and reduce the risks of cancers of the reproductive organs, and in large-breed dogs, puberty has not yet occurred at this time. For example, golden retrievers typically experience puberty between 9 and 11 months of age (10). However, concerns have developed about the long-term effects of early-age neutering, including increased risks of cystitis, hip dysplasia, and urinary incontinence (11). Beginning in ∼2014, due to a change in SFSD policy at the suggestion of breeders, dogs in the program were spayed/neutered at ∼1 year of age, after most of the dogs had reached puberty. This situation provided an opportunity in a group of similarly-managed animals to assess differences in the incidence of health or behavior problems between dogs neutered at different ages, as well as the animals' ability to complete service dog training.

MATERIALS AND METHODS

Information from the files of all dogs who participated in the SFSD training program between 1996 and 2017 were examined for this study. Whelp date, date of neuter (including castrations and spays), sex, breed, the cause of dismissal for each of the dogs, and details about the dog's dismissal—such as a behavior trigger or medical test performed—were abstracted into a spreadsheet [Excel]. Dogs were excluded from the study if less than 3 months had elapsed between their date of neuter and their dismissal or graduation from the training program, or if dogs were not neutered until after either completion of training or dismissal. This was an effort to eliminate any dogs who might have already had signs of hip dysplasia at the time of neuter. Dogs were also excluded if records were missing crucial variables needed for analysis.

Two general categories for dismissal were established: behavior problems (including behaviors that caused training difficulties) and health problems. Health reasons for dismissal were diagnosed by a veterinarian. Determinations of behavioral and training-related difficulties were made by a trainer. Some dogs were dismissed from the SFSD training program for reasons that included both a health and a behavior problem. This group was reported separately in descriptive analyses but included in each dismissal group when compared separately to dogs that graduated. For the purposes of this study, the terms "graduation" or "successful" dog referred to a dog that completed the SFSD training program.

Labrador retrievers and golden retrievers included in the analysis were considered their own groups. All other breeds and mixed-breed dogs were grouped into an "Other" breed group due to limited numbers.

Dogs were divided into three groups to compare the age-at-neuter periods most often used by SFSD (<7 months and >11 months), as well as the time period that covered the ages between the target neuter ages (7–11 months). These age-at-neuter groups also align with some current recommendations for early neutering (12) and with physiological milestones, such as the onset of puberty and closure of growth plates in the long bones (13) at about 12 months of age. Delays in closure may result in increased long bone length and possible alterations to a dog's normal conformation.

The proportion of dogs that graduated or were dismissed for behavioral, orthopedic, or other health reasons was determined for the three age-at-neuter groups and also for other variables (sex and breed) that were potential confounders. To further characterize the relationship of age-at-neuter with each outcome, the median and inter-quartile range were also determined (because age-at-neuter was not normally distributed).

Confounding and effect modification were first assessed by stratifying the analysis of age-at-neuter and dismissal by sex and breed [(14); SAS 9.4®, PROC FREQ] and presented graphically. Multivariable log-binomial regression was used to estimate the risk for dismissal by age-at-neuter group, while examining potential for confounding or effect modification by sex and breed. This type of regression was used because the dichotomous outcome of interest was not rare [(15); SAS 9.4®, PROC GENMOD]. Statistical significance was set at $p \leq 0.05$. Because this was a retrospective study, and no dogs were handled or manipulated in the execution of this study, no IACUC approval was required.

RESULTS

Of the 357 dogs who had training records during this period, 21 dogs were excluded because they were neutered less than 3 months before dismissal. An additional 91 dogs were excluded from analysis because their records lacked sufficient information on key variables, most commonly about the cause of their dismissal, whelp date, and/or date of neuter. Of the 245 dogs in the study, 110 (45%) were neutered at less than 7 months of age, 58 (24%) between 7 and 11 months of age, and 77 (31%) when older than 11 months of age. The median age-at-neuter was 244 days (8.1 months) of age (range: 107 to 1,319 days). Two dogs neutered after 3 years of age joined the SFSD program as

adults and were in training during and after their gonadectomy. Most dogs were male, and Labrador and golden retrievers were the predominant breed types, although there were other breeds, including purebred dogs (6 Australian Shepherds, 3 Standard Poodles, 2 Smooth Coated Collies, 1 German Shorthair Pointer, 1 Belgium Traverne, 1 Border Collie, and 1 Portuguese Water Dog) as well as 24 mixed-breed dogs (**Table 1**). Less than half of dogs successfully completed the training program and there were no significant differences in graduation rates between males and females or between breeds (**Table 1**). Most dismissals were for behavior-related reasons (**Table 1**, 75% of all dismissals), while 20.5% of all dismissals were for health-related reasons and 4.1% of all dismissals were for simultaneous health and behavior problems.

Behavior problems resulting in dismissal included aggression, dominance, snapping/biting, growling, resource guarding, being confrontational, being possessive, hyperactivity, reactive or alarm barking, high prey drive, fear, separation anxiety, weak human bond, or sensitivity to sound. This category also included behavioral problems related to barriers to training or reliable work as a service dog, such as poor focus, distractibility, unpredictability, inconsistency, lack of motivation, slowing down when trainer was in a hurry, poor retrieve drive, poor recall, hesitation or refusal to participate in new or familiar environments, and inability or unwillingness to perform required skills.

Orthopedic health problems that resulted in dismissal (17% of all dismissals) included abnormalities associated with the musculoskeletal system, such as hip dysplasia or poor score on PennHIP (16), elbow dysplasia, osteochondritis dissecans (OCD), cruciate ligament disease, degenerative joint disease (DJD), and/or related structural and functional problems. Non-orthopedic health problems that led to dismissal (7.5% of all dismissals) included cardiac disease, heart murmur, overbite, underbite, seizures, unexplained trembling or weakness, histiocytosis, inflammatory bowel disease (IBD), persistent urinary tract infection, allergies, compromised vision, and/or orthopedic problems.

Total dismissals and dismissal for behavioral problems followed similar patterns. Neither differed by sex or breed but both were significantly less common among dogs neutered between 7 and 11 months than among dogs neutered before 7 months or after 11 months (**Table 1**, **Figure 1**). This pattern of a lower proportion of dogs dismissed among those neutered between 7 and 11 months compared to dogs neutered at younger and older ages was seen among females and males when analyzed separately (**Figure 1**) and for golden and Labrador retrievers (**Figure 2**). Using multivariable log-binomial regression, total dismissals and behavioral dismissal were about 40% less likely in dogs neutered between 7 and 11 months than among dogs neutered before 7 months (RR = 0.6, 95% CI: 0.4, 0.8, $p < 0.01$ for both) and about 30% less likely than among dogs neutered after 11 months (RR = 0.7, 95% CI: 0.5, 1.00, $p = 0.05$ for both). Interestingly, when age-at-neuter was in the model, there was also a significant difference between breed groups, with both Labrador and golden retrievers at lower risk for total dismissals (RR = 0.7, 95% CI: 0.5, 0.95, $p = 0.02$ and RR = 0.8, 95% CI: 0.6, 0.9, $p = 0.01$, respectively) and behavioral dismissals (RR = 0.7, 95% CI: 0.5, 1.0, $p = 0.03$ and RR = 0.7, 95% CI: 0.5, 0.9, $p = 0.005$, respectively) than the pooled other breeds. Sex was still not a significant predictor of dismissal nor did it modify the effects of age-at-neuter and was not included in either model.

Health-related dismissals did not differ by sex or breed but were significantly less common for dogs neutered at 7–11 months than for dogs who were neutered before 7 months (**Table 1**). There was no significant difference between dogs neutered between 7 and 11 months and those neutered after 11 months. This pattern was the same for the subset of health dismissals due to orthopedic problems (**Table 1**). Based on multivariable log-binomial modeling, dogs neutered before 7 months were more than twice as likely to be dismissed for health reasons than dogs neutered at any older age (RR = 2.4, 95% CI: 1.3, 4.2, $p = 0.005$), with no other significant predictors. Dogs neutered before 7 months were more than twice as likely to be dismissed for orthopedic problems than dogs neutered at any older age (RR = 2.2, 95% CI: 1.1, 4.3, $p = 0.03$). Labrador retrievers were at also higher risk for orthopedic-related dismissal than golden retrievers and all other breeds (RR = 3.3, 95% CI: 1.1, 10.2, $p = 0.04$).

DISCUSSION

Although pet owners are usually encouraged to spay or neuter their household animals, the effects of gonadectomy and the best time at which to perform this procedure are still being explored. Previous research has encompassed a range of age groups, breeds, and health problems, and the results of those studies have been varied, making definitive generalized conclusions challenging. The American Veterinary Medical Association (AVMA)[1] supports the concept of pediatric/pre-pubertal gonadectomy in order to reduce the population of unwanted dogs and cats, but the AVMA has also acknowledged that veterinarians must consider each animal's case individually and the best information on spay/neuter available at that time (AVMA). For the service dog community, effects of timing of gonadectomy on health and behavior that can result in the dismissal of an animal from training are particularly relevant. We found that the short-term, behavioral and health effects of age-at-neuter differed. The 7 to 11 month age-at-neuter group had the fewest behavioral dismissals while dogs neutered before 7 months had the most health-related dismissals. This was true for both sexes and our breed groups. Breed was associated with dismissal when adjusted for age-at-neuter.

Successful graduation rates ranged from 7 to 70% when dogs were grouped by different age-at-neuter, sex, and breed combinations. Other studies have also found graduation rates between 30 and 50% with behavioral problems as the major reason for dismissal of service dogs during training (17). Most of our dismissals were due to behavioral problems in all groups. A prospective study of neutering before puberty also found

[1] American Veterinary Medical Association website, *Pediatric Spay/Neuter of Dogs and Cats*. Available online at: https://www.avma.org/KB/Policies/Pages/Pediatric-Spay-Neuter-Dogs-And-Cats.aspx (accessed August 3, 2019).

TABLE 1 | Characteristics of dogs that graduated or were dismissed from training from 1996 through 2017 among a cohort of SFSD dogs.

Demographic characteristics[a]	Graduated ($n = 99$)	Dismissed for behavior ($n = 110$)[#]	Dismissed for orthopedic problems ($n = 25$)[#]	Dismissed for other health problems ($n = 11$)[#]	Dismissed for behavior and health problems ($n = 6$)
SEX					
Female ($n = 77$)	29 (37.7%)	40 (51.9%)	8 (10.4%)	0 (0%)	3 (3.9%) [3 O, 0 H]
Male ($n = 168$)	70 (41.7%)	70 (41.7%)	17 (10.1%)	11 (6.5%)	3 (1.8%) [2 O, 1 H]
BREED					
Labrador Retriever ($n = 149$)	63 (42.3%)	58 (38.9%)	22 (14.8%)	6 (4.0%)	5 (3.4%) [4 O, 1 H]
Golden Retriever ($n = 57$)	25 (43.9%)	27 (47.4%)	3 (5.3%)	2 (3.5%)	1 (1.8%) [1 O, 0 H]
Mixed or Other Breed ($n = 39$)	11 (28.2%)	25 (64.1%)	0 (0%)	3 (7.7%)	0 (0%)
AGE-AT-NEUTER					
< 7 months of age ($n = 110$)	35 (31.8%)	52 (47.2%)	15 (13.6%)	8 (7.3%)	4 (3.6%) [3 O, 1 H]
7-11 months of age ($n = 58$)	34 (58.6%)	20 (34.5%)	4 (6.9%)	0 (0%)	0 (0%)
> 11 months of age ($n = 77$)	30 (39.0%)	38 (49.4%)	6 (7.8%)	3 (3.9%)	2 (2.6%) [2 O, 0 H]
Continuous (days)	284 (115–1,070)	238 (109–644)	254 (101–1,319)	194 (115–478)	236 (120–459)

[a]*Actual numbers and row percentages are reported for categorical data. Continuous variables are indicated by reporting median and range for non-normally distributed variables.*
[#]*Dogs that had both behavioral and orthopedic (O) or other health (H) reasons for dismissal are included in totals for these columns.*

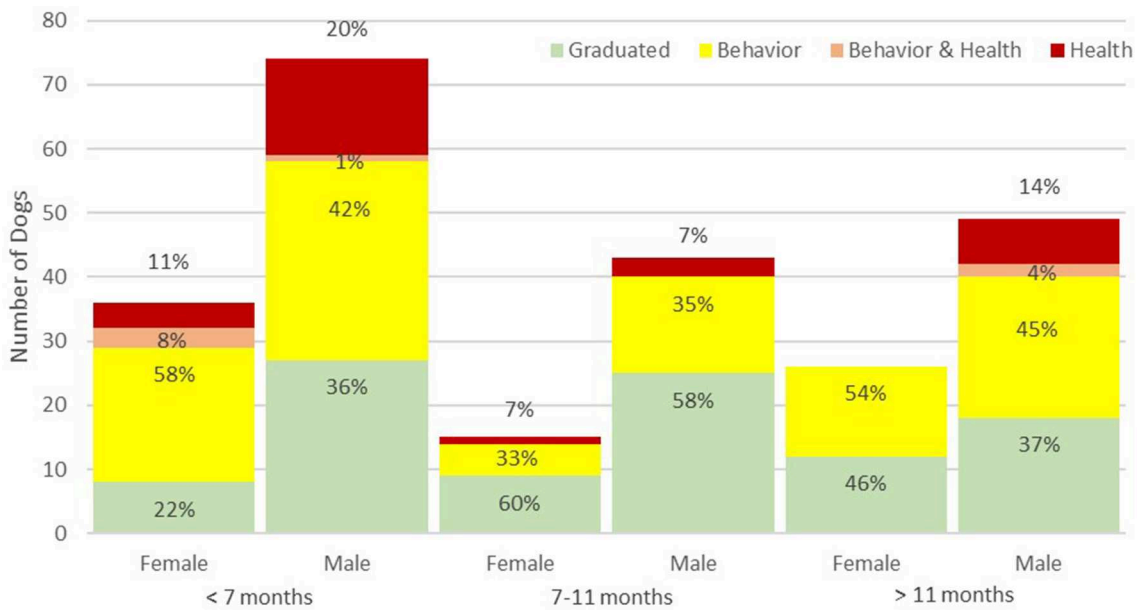

FIGURE 1 | Percent of each training outcome for females and males by age at neutering. Health dismissals are red, behavior dismissals are yellow, simultaneous health and behavior dismissals are orange, and graduations are in green.

behavior as the leading cause of dismissal [reported in Zink et al. (18)]. For behavior, the age-at-neuter group with the least dismissals was 7 to 11 months of age for both sexes. Associations between behavioral problems and age-at-neuter have varied. A study of dogs adopted from a shelter in NY found that barking in males, noise phobias and sexual behaviors decreased linearly with increasing age-at-neuter while escaping from the home increased with age-at-neuter. Dogs with an age-at-neuter less than 5.5 months of age had less separation anxiety but more aggression toward household members than those neutered at an older age (11). Another study of more than 13,000 dogs also found that dogs neutered before 6 months had more aggression to family members and that aggression toward family and strangers was less in dogs neutered after 12 months (19). Some studies have not found differences in behavior problems between the age-at-neuter groups we studied (18, 20). Our findings support effects of age-at-neuter on the development and training success of service dogs. This likely extends beyond service dogs, since more than 80% of owners, across cultures, report that their dogs have behavioral problems and this is the most common reason for relinquishing dogs (21). Studies that measure behavior longitudinally over time and that look at specific rather than

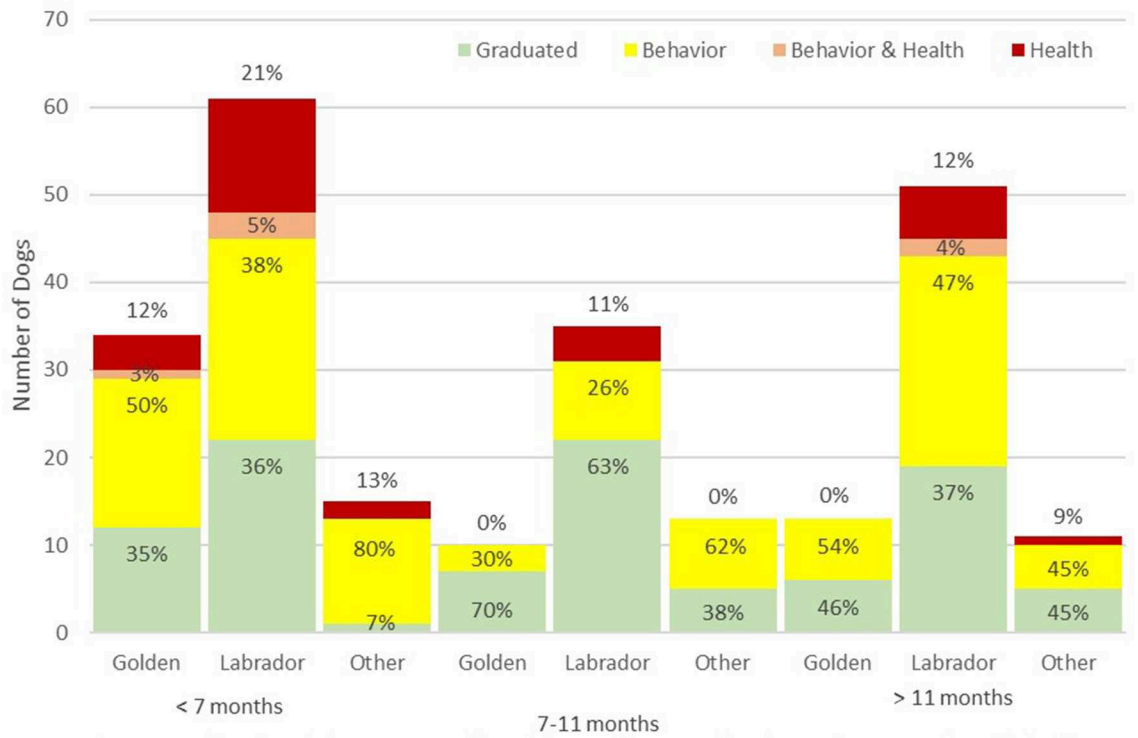

FIGURE 2 | Percent of each training outcome for golden retrievers, Labrador retrievers, and pooled other breeds by age at neutering. Health dismissals are red, behavior dismissals are yellow, simultaneous health and behavior dismissals are orange, and graduations are in green.

overall behavioral concerns are needed to better understand the dynamics of neutering, behavioral development, and specific problems and potential corrections.

Our finding of a significantly higher rate of dismissal for health problems, mainly orthopedic, among dogs neutered before 7 months is similar to findings in a number of studies. A higher risk for dogs neutered earlier than 6 months, compared to older groups, was reported for hip dysplasia and cranial cruciate ligament tears among golden retrievers (22) and German shepherds (12). Dogs adopted from a shelter in New York who were gonadectomized prior to 5.5 months of age were more likely to demonstrate hip dysplasia when compared with dogs gonadectomized at a later age (11). Golden retrievers neutered before 12 months were also significantly more likely to experience cranial cruciate ligament tears than those neutered after 12 months and early-neutered male golden retrievers were significantly more likely to have hip dysplasia than late-neutered males (23). In contrast, this pattern was less clear for a study of Labrador retrievers (22), and another study found no significant increase in musculoskeletal disorders or hip dysplasia in prepubertal (<24 weeks old) gonadectomized dogs when compared to dogs gonadectomized after 24 weeks of age (20). Overall, the present study adds evidence to others who have shown a greater risk of orthopedic disease in dogs neutered at <7 months of age, despite the short-term follow-up until dismissal during training. Factors in the development of orthopedic disease may include changes in the production of sex hormones and therefore growth in young animals, as well as a possible delay in the closure of growth plates, resulting in orthopedic changes.

Other health problems were noted more frequently in the youngest SFSD age group when compared with the older age-at-neuter groups, although these were a very uncommon reason for dismissal in our study. Most health concerns that have been studied for an association with neutering occur much later in life than during the early training period that we studied (11, 24). It would be ideal to follow these dogs over their lifetimes to gain a more complete picture of health risks. However, dogs are currently not traced after they leave the SFSD program.

On the subject of breeds, our results suggested that Labrador and golden retrievers were less likely than other pooled breeds to be dismissed for behavior problems. This was not surprising, as these two retrievers have commonly and successfully been used as service animals in the past, due in part to their behavior. Within each age-at-neuter group, Labrador retrievers had a greater risk for dismissal for orthopedic disease than golden retrievers or other breeds. This was unexpected, particularly as the Orthopedic Foundation for Animals[2] reports both hip dysplasia and elbow dysplasia to be more common in golden retrievers than in Labrador retrievers (OFA). Given the absence of substantial genetic history of the dogs in the SFSD study group, it is difficult to determine how much of this finding might be attributed

[2]Orthopedic Foundation for Animals website. Available online https://www.ofa.org/diseases/breed-statistics#detail (accessed July 28, 2019).

to heritable factors which are well recognized to predispose to a number of orthopedic problems. It is unlikely, though, that breeders would have utilized animals with a history of orthopedic problems for breeding purposes, and other health and environmental factors, such as diet, exercise, and hormones, are important contributors to the development of hip dysplasia (25).

This study had several limitations. Because this study's population was primarily made up of the two retriever breeds, generalization to the dog population as a whole may be challenging. Both breeds are popular as pets, though, making the consequences of neutering relevant to many pet owners and private practice veterinarians. Differences between the necessary qualities of a service dog and qualities of a pet may also affect the generalization of the results here to other, non-service dogs. For example, the owner of a household pet may find a dog's health problem (e.g., overbite) negligible but a behavior problem (e.g., strong prey drive) more challenging.

Dogs did not enter the program at the same age and were not randomly assigned to the time of neutering. Their experiences outside the SFSD program could have affected their behavior or overall health. Any characteristics predictive of training success, that also led to choice of neutering time, could have biased results. For example, puppies demonstrating health or behavior problems prior to their neutering could have been dismissed, leaving more successful dogs in the older age groups. However, most neutering times resulted from overall policies in place at certain times and so this was less likely. Dogs neutered later may not have been checked for hip dysplasia or completed training until later in their lives, providing them a longer period during which to develop health or behavior problems compared to dogs neutered at an earlier age. However, we found the opposite; a greater incidence of orthopedic and health dismissals among younger dogs. The effects of neutering before 7 months may be even larger than our estimates.

Misclassification bias was a concern for the behavior dismissal group, where trainer subjectivity may have affected the decision to classify each dog as having behavioral problems. Additionally, misclassification bias may have been introduced when the authors interpreted the recorded data for each dog, as in when a reason for dismissal had to be determined. The elimination of more than 90 dogs—more than a quarter of the initial study population—from analysis due to missing information may also have affected the results. The data may also have been affected by unmeasured confounders, potentially including genetics, environment, and the type of training during the dog's puppy-raising period.

Future studies could expand upon these findings by randomly assigned age-at-neuter and using standardized methods to measure behavioral problems. Also, if study population sizes were larger, it would also be helpful to subdivide the behavior group so that specific behaviors (i.e., fear, aggression, unwillingness to perform tasks) might be analyzed separately. Similar studies considering multiple cohorts of service dog candidates at different training organizations would also be valuable in drawing conclusions applicable to a wider range of animals, potentially including more breeds, under a variety of different living and training conditions.

CONCLUSION

This study suggests that there is a relationship between dogs' age-at-neuter and their subsequent behavior and health. Neutering between 7 and 11 months of age may represent a desirable window for service dogs in training. Orthopedic problems may be more pronounced in dogs neutered at less than 7 months of age, and this may be particularly true of Labrador retrievers.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

MZ collected data, performed data analysis, and composed parts of the manuscript. VC initiated the study along with MA and helped with data analysis and manuscript editing. MA and EG collected data. LH performed data analysis, composed parts of the manuscript, and helped with study design and manuscript editing.

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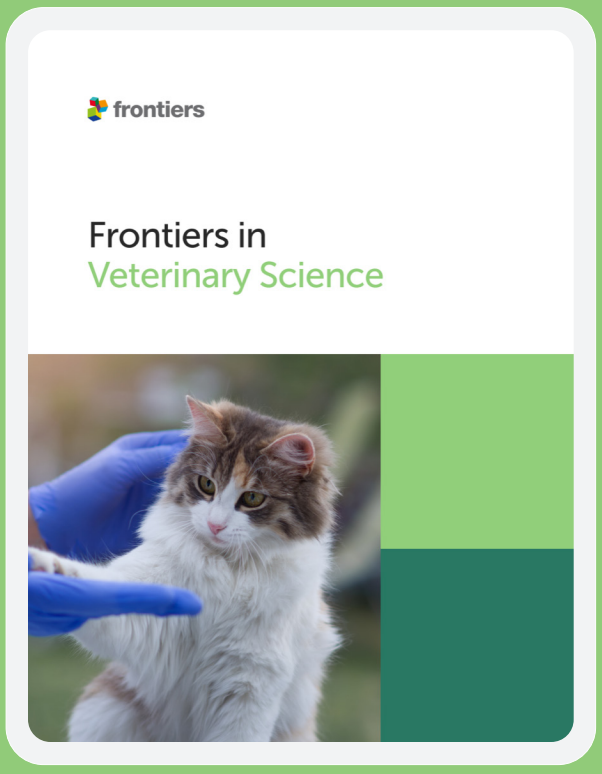

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