

REPRODUCTION HORMONES IN THE DOG: FRIENDS OR FOES?

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In many countries surgical neutering of bitches and queens is often performed for the alleviation or prevention of pet overpopulation. In countries where pet overpopulation is not a major problem, owners may ask for an elective ovariectomy for their bitch or queen as a means of preventing diseases at an older age. Progesterone produced in the ovaries is an important causative factor for the development of endometritis, mammary tumors, and growth hormone (GH) excess. The latter may lead to diabetes mellitus and/or acromegaly in bitches. Prevention of progesterone influence for promoting better quality of life in later years is therefore a primary reason for ovariectomy.

The removal of the ovaries may, besides the risk of anesthesia and surgery, lead to problems such as urinary incontinence, especially in certain breeds and large dogs. Furthermore, there is a greater risk, just as after castration in the male dog, for the development of several other diseases such as bone cancer in large and giant breeds, haemangiosarcoma, transitional cell carcinoma, malignant lymphoma or other problems such as tearing of the cranial cruciate ligament, especially if the gonads are removed early in life. Additionally, obesity is more often seen in neutered female and male dogs, due to changes in the metabolism, but this can be prevented with dietary measures.

Because of the disadvantages of ovary removal it is debated whether hysterectomy, as opposed to ovario(-hyster)ectomy might be preferable, especially in breeds predisposed for the development of urinary incontinence, bone cancer, etc. Likewise, in the search for non-surgical neutering methods the question arises if a search for a method based on negating reproduction hormone influence is to be preferred.

If methods for surgical contraception are used that leave the ovaries *in situ*, for example hysterectomy, a major risk for the development of mammary tumors due to the recurrent progesterone influence remains. The risk for mammary tumor development in a Swedish epidemiological survey of 260000 intact bitches during the first 10 years of their life differed considerably between breeds, with an average of 13%, but increasing to >40% in some breeds including the Dobermann, Leonberger and Irish Wolfhound. The last two breeds are also sensitive for the development of bone cancer, but in a much lower incidence rate than the risk for developing mammary tumors. To make matters more confusing, studies concerning the health effects of gonadectomy as compared to health issues in intact animals are frequently difficult to interpret because of a lack of standard terminology. For example, the Swedish study only included intact bitches <10 years of age, thus underestimating the incidence of endometritis and mammary tumors in breeds with a considerable higher life expectancy.

Some other studies are using the term “early age gonadectomy” if the surgery has been performed before the age of 12 months, and in other studies the term is used only if surgery is performed before the age of 3 months. There is most likely a difference in the chance for development of problems other than mammary tumors in bitches ovariectomized in the first months of life when compared to ovariectomy

after the first estrus. If hysterectomy instead of ovariectomy is advised it has been stated that diagnosing mammary nodules early in their development is important, but in practice this appears to be insufficient: every mammary tumor (in bitches about 50% are malignant) leads to an invasive surgery. Furthermore, other problems can be expected after a hysterectomy leaving ovaries or remnant ovarian tissue (ROT) in situ: periods of attractiveness to male dogs, estrous behavior and periodic or even continuous vaginal discharge and pseudopregnancy symptoms may be expected. In one study the hypothalamic-pituitary-ovarian axis (HPO) was examined in bitches with ROT after incomplete ovario-hysterectomy or ovariectomy; the histopathologically examined ovarian tissue was cystic in 2/3 of the bitches. The HPO axis appeared to be affected, with a significantly higher plasma LH concentration in the bitches with ROT than in the control bitches in anestrus despite the fact that the mean basal plasma estradiol concentration was higher in the bitches with ROT than those in anestrus. In addition, the basal plasma LH concentration was higher in bitches in which the interval between incomplete ovariectomy and the first appearance of estrus symptoms was more than 3 years. This may be due to changes in the HPO axis, induced by (temporary) ovarian hormone deficiency due to a disruption or change of the blood supply to the remnant ovarian tissue, leading to changes in and multiplication of the gonadotropic hormone-producing cells of the pituitary. This phenomenon is probably also of importance in cases involving the development of a granulosa cell tumor (GCT) in ROT. Ovarian tumors are rare in mammals, but among domestic animals they appear to be most common in the cow and bitch. In a study of 7 large dogs of different breeds with GCT 4 bitches had developed GCT in ROT. Similar results, i.e., development of GCT in ROT, have also been described by other researchers. In unpublished observations GCTs were observed in two Boxers when ovaries were placed in the proximity of the spleen to prevent urinary incontinence. The basal plasma LH concentrations were also higher in the GCT bitches, mainly due to the significantly higher plasma LH concentrations in the GCT-ROT bitches, compared to the anestrus bitches despite higher basal plasma estradiol concentrations in the GCT-ROT bitches. This once more indicates a loss of sensitivity to the negative feedback of estradiol due to changes in the HPO axis in those GCT bitches as described for the ROT bitches. It may be hypothesized that the elevated plasma gonadotropin concentration plays a role in tumorigenesis. In women, exposure to high gonadotropin levels, as seen after menopause or due to infertility treatments, is proposed to be a risk factor for developing ovarian tumors. Although this comparison is useful, one must, however, be careful when comparing species. In women, for example, many side effects are seen after ovariectomy which are not seen in dogs and cats.

The much higher risk for mammary tumors in intact bitches compared to the risk for other afflictions as previously described after ovariectomy, an increased GH secretion which may lead to diabetes mellitus and acromegaly, and also the chance of developing cystic structures and GCT in the ovarian tissue makes leaving ovaries in a neutering procedure ethically questionable, as estrus prevention alone can also be achieved by less invasive medical treatment without increasing the risk for problems such as endometritis and mammary tumor development compared to the intact cyclic bitch. In bitches from owners more worried about the risk for e.g. bone cancer than mammary tumors, a weak progestagen, e.g. proligestone, appears to offer a solution until a long-term non-surgical estrus prevention method has been found. In the search for a non-surgical permanent method of neutering, a method which prevents progesterone influence seems, in light of the gained health benefits, to be preferable to a method whereby the ovaries remain active.

For healthy male dogs the situation is different. Castration of male dogs may be helpful in decreasing the number of unwanted pups in countries in which pet overpopulation is a problem. In other countries, however, it is questionable if an invasive surgery such as castration with hardly any advantages resulting in a healthier and longer life is ethically justifiable. An advantage of castration is the prevention of benign prostate hyperplasia and prostatitis. However, prostate cancer, although seldom, is seen about twice as often in castrated dogs as in the intact dog. In addition, as previously mentioned, there is an increased risk of bone cancer in castrated male dogs, especially when this procedure is performed at an early age. Additionally, if sterility is wanted because of pet overpopulation it is important to keep in mind that testosterone influences inter-male behavior. For this last reason the intratesticular injection of zinc gluconate neutralized by arginine frequently “painlessly” administered without anesthesia may be a treatment of preference for males in the prevention of pet overpopulation, since dogs treated with zinc gluconate and arginine are no longer fertile but the serum testosterone concentration is not as seriously decreased as in castrated dogs. Early data describe a general decrease in the serum testosterone concentration after a zinc gluconate and arginine injection. The decrease varies between different dogs but levels are comparable to levels in intact male dogs after two years. A disadvantage of the administration of zinc gluconate and arginine are the complications that arise if it is not properly injected, which may lead to extensive surgery such as orchiectomy, extensive surgical debridement, including scrotal ablation.

Another method for achieving male sterility is the placing of a GnRH agonist implant. This procedure is less invasive and reversible; sterility is not achieved until 4-12 weeks after implantation. Circulating testosterone levels decrease to levels similar to surgically castrated dogs. This procedure may be performed instead of castration or zinc gluconate and arginine administration in countries in which there is no problem with free roaming dogs and pet overpopulation, but “male sexual dimorphic behavior” of the dog is a problem for the owner. In one study effects of surgical castration were compared to the use of a GnRH implant in pet dogs. Eighteen dogs underwent surgical castration and 24 dogs received the GnRH implant (Suprelorin® 4.7). Endocrinological parameters and aggression, fear/insecurity, play behavior and sexual behavior were assessed and questionnaires were completed prior to and 4-5 months post-procedure. No significant difference was found between the two approaches in terms of plasma testosterone concentration and behavioral parameters. The perceived effect of surgical castration on male sexual behavior in the presence of bitches in estrus was greater than that of the implant and despite the similarly low basal plasma testosterone concentrations in both groups the pituitary testicular axis was not completely down-regulated in all implanted dogs. A GnRH implant may therefore be considered if the owner has a problem with “male sexual dimorphic behavior”, or if diseases due to the influence of testosterone are present. In the last situation it is good to realize that the testosterone concentration will initially increase after implanting the GnRH agonist, which may lead to a temporary exacerbation of the primary problem.

Abbreviated reference list:

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