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DESLORELIN (SUPRELORIN®) USE IN NORTH AMERICAN AND EUROPEAN ZOOS AND AQUARIUMS: TAXONOMIC SCOPE, DOSING, AND EFFICACY

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Abstract: The Association of Zoos and Aquariums Reproductive Management Center (RMC) in the US and the European Association of Zoos and Aquaria Reproductive Management Group (RMG) in Europe monitor efficacy of contraceptive products in participating institutions and use those results to inform contraceptive recommendations. This study used the joint RMC-RMG Contraception Database to analyze efficacy of deslorelin implants (Suprelorin®), a contraceptive used in a wide range of mammalian taxa. More recently its use has increased in birds and in some reptiles and fish. Deslorelin, a gonadotropin-releasing hormone (GnRH) agonist, stimulates the reproductive system before downregulating receptors on pituitary cells that produce hormones that stimulate gonadal steroids in both males (testosterone) and females (estradiol and progesterone), interrupting sperm production and ovulation, respectively. Nevertheless, it has been used mostly in females. Efficacy has been high in mammals, with failures resulting in offspring in only 1.3% of treated individuals and 0.5% of treatment bouts. The failure rate has been higher in birds, with 14.7% of individuals in 7.2% of bouts producing eggs, perhaps reflecting differences in avian GnRH molecules. Too few reptiles and fish have been treated for meaningful analysis. Although deslorelin appears very safe, a possible exception exists in carnivores, because the stimulatory phase can result in ovulation and subsequent sustained progesterone secretion that may cause endometrial pathology. However, the stimulatory phase can be prevented by treatment with megestrol acetate for 7 d before and 7 d after implant insertion. The two current formulations of Suprelorin are effective for minimums of 6 (4.7 mg) or 12 mo (9.4 mg). The data indicate that Suprelorin is an effective and safe contraceptive option for female mammals, although it may not be effective in males of some mammalian species. Further research is needed to ascertain its usefulness in nonmammalian taxa.

INTRODUCTION

Contraception is an essential tool in managing reproduction of animal populations in professional zoological institutions around the world. Because breeding is recommended in only a subset of individuals each year, reproduction must be prevented in the rest until they receive a breeding recommendation. Thus, it is crucial that contraceptives available to zoos be effective, safe, and reversible when an alternative to separation or permanent sterilization is desired. Since 1989, when the Association of Zoos and Aquariums (AZA) Contraception Task Force was formed, the AZA Wildlife Contraception Center, now the AZA Reproductive Management Center (RMC), has monitored the use of contraceptives in zoo animals through its annual survey. The counterpart to this program in Europe, the European Association of Zoos and Aquaria (EAZA) Reproductive Management Group (RMG, originally the European Group for Zoo Animal Contraception) was formed in 2008. With more than 48,000 records, the joint RMC-RMG Contraception Database is used to generate and refine recommendations, identify problems, serve as the basis of research projects, and answer day-to-day queries from the zoo community. The RMC and RMG also cooperate with the Reproductive Health Surveillance Program at Michigan State University on contraceptive safety.

In the 1970s, silastic implants containing the synthetic progestin melengestrol acetate (MGA) became the first contraceptive used in zoos.[52] They have since been shown effective in all major mammalian taxa except perissodactyls (RMC-RMG Contraception Database). However, research in the 1990s showed that long-term use was associated with a significantly higher risk of endometrial hyperplasia and mammary cancer in felids[40,41] and endometrial lesions and pyometra in canids.[1,39] Thus, a safer contraceptive option was needed for carnivores.

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Fortunately, a new type of contraceptive that showed promise as a safer alternative became available for research purposes in the United States. Deslorelin acetate implants, developed by Peptech Animal Health (Milperra, New South Wales 2214, Australia) for use in domestic dogs,[56,57] were first provided to the RMC in the late 1990s through Feracon LLC (Denville, NJ 07834, USA) as an investigational new animal drug. Then in 2002, the RMC was given responsibility for importing the product for AZA institutions.

The original implants contained either 3 or 6 mg of the gonadotropin-releasing hormone (GnRH) agonist deslorelin in a biolipid slow-release matrix. The new implant formulations, branded as Suprelorin® and containing either 4.7 or 9.4 mg of deslorelin (2.3 × 12.5 mm and 2.3 × 24 mm, respectively), became available to the RMC in 2005. Suprelorin was first approved for commercial sale in Europe in 2007, although some zoos there had acquired it directly from Peptech Animal Health as early as 2003.

Unlike the earlier implants that contained different doses but in the same matrix with equivalent release rates, the new matrix formulations were designed to have either a minimum 6-mo (4.7 mg) or 12-mo (9.4 mg) duration of efficacy. The 9.4-mg implants contain twice the amount of deslorelin, but the altered matrix allows a slower release rate to achieve an extended period of fertility control.[22]

Although both formulations have been approved for use in domestic dogs in Europe, the only formulation commercially available in the United States is Suprelorin F®, but its use is limited specifically to ferrets for adrenal disease[22] and cannot be used off-label in other species. To be compliant with US Food and Drug Administration regulations for investigational drugs, the RMC is responsible for tracking usage of Suprelorin in US zoos and compiling data on efficacy and safety. Because Suprelorin is approved by regulatory agencies in Europe for commercial sale, the RMG does not have a regulatory responsibility. However, the primary objective of both the RMC and RMG is to collect data on contraceptive use in AZA and EAZA institutions to expand their joint database to provide evidence-based advice and recommendations to animal managers on the choice and application of contraceptives for the broad range of species in their care (www.stlzoo.org/contraception, https://egzac.org/Documents).

Suprelorin has a two-phase effect: an acute stimulatory phase followed by a chronic suppressive (contraceptive) phase when the hypothalamic-pituitary-gonadal (HPG) axis is downregulated. Specifically, Suprelorin stimulates the release of the gonadotropins, follicle stimulating hormone (FSH), and luteinizing hormone (LH), which in turn temporarily enhance spermatogenesis and testosterone production in males and can induce estrus and ovulation in females during the stimulation phase.[4,24,35] This stimulation phase is followed by downregulation of GnRH receptors on the pituitary gonadotropes[29] so that production of gonadotropins and gonadal steroid hormones is not supported. In contrast to the continual exposure to progestin from MGA implants, Suprelorin should be a safer alternative for female carnivores, because endogenous estrogen and progesterone has no proliferative effect on the endometrium and mammary tissue. Additionally, Suprelorin offers a male-directed method, either as a contraceptive or a means to mitigate aggression that is supported by testosterone.

The stimulation phase is a drawback to using Suprelorin. On the basis of data from domestic dogs,[23,24] treated females should be separated for 2–3 wk after implantation, and males require an even longer period of separation. Although testosterone concentrations may reach basal levels after 6-25 d in dogs,[49,56] death of sperm and disappearance of sperm from the ejaculate can take much longer.[49] For females, the stimulation phase can be prevented by giving an oral progestin like megestrol acetate (MA) for 1 wk before and 1 wk after implant placement.[61] Not only does this protocol eliminate the need to separate pair-bonded individuals, it is also protective of reproductive health, especially in female carnivores. During nonconceptive cycles in most carnivores, ovulation is followed by a prolonged period of elevated progesterone, which increases the risk for uterine and mammary pathology,[1] which makes Suprelorin plus MA a safer long-term contraceptive option for carnivores and provides an alternative for other mammalian taxa as well.

Reports on Suprelorin (referred to as deslorelin in earlier studies) use in wildlife have shown both positive and negative results, but because different dosages were used, results among studies are not directly comparable. Not surprisingly, the focus has mostly been on carnivores.[5–9,11,32–34,54] Fewer reports have been published for deslorelin use in other mammalian taxa (e.g., ungulates,[44,45] primates,[12,50] and bats[37,38]). A number of reports have been published for marsupials,[14,21,26–28,60] like-

ly because Suprelorin was developed in Australia and has been available there longer. Deslorelin also has been reported to reduce aggression successfully in male leopards[18,25] and hyrax.[48] Some avian species have been treated successfully for reproductive conditions and feather-plucking, but the cases reviewed all involved domestic, laboratory, or pet species.[36] Reports on treatment of reptiles have also been uncommon.[13,51]

Three taxon-focused reviews of contraceptive use have included coverage of Suprelorin in canids,[9] canids and felids,[2] and primates,[59] as well as a review of Suprelorin use in European zoos.[16] Given the limited scope of these reviews and especially considering the inconsistent results of other published reports, this comprehensive analysis of the combined RMC-RMG Contraception Database provides up-to-date information on the taxonomic scope of animals treated and the outcomes, focusing on efficacy, especially dosages and other possible reasons for failure.

MATERIALS AND METHODS

Data on deslorelin (Suprelorin) use were gathered from the combined RMC-RMG Contraception Database, which contains information from the historic Annual Survey plus direct online entry. Data reported through 24 August 2020 were included in the summaries, representing 306 institutions worldwide. Only bouts (times treated) containing start dates were used.

Although the RMC-RMG Contraception Database contains information to the subspecies level, summaries present data by species on the assumption that subspecies are sufficiently similar in reproductive physiology to respond similarly to contraceptive treatment. Because many individuals were treated more than once, both the number of individuals and total number of contraceptive bouts were calculated for each species. The summaries of deslorelin usage include treatment for contraception, medical conditions, behavioral modification (e.g., aggression reduction, feather-plucking), and other unspecified reasons. However, only administration for the purpose of contraception was included in calculating contraception failure rates. Additional information for all four implant formulations (3, 6, 4.7, and 9.4 mg) can be found in a series of supplemental tables in the on-line version of this manuscript (doi: 10.1638/2020-0127).

Contraceptive failure was defined as a bout in which a female gave birth or a male sired offspring after the initial stimulation phase (1 mo for females and 2 mo for males) but before the expected minimum period of efficacy ended (i.e., 6 mo for the 3, 6, and 4.7-mg formulations and 12 mo for the 9.4-mg formulation). Failure rates were only calculated for bouts where contraception was the indicated reason for treatment. Some reports to the Contraception Database included information about other measures of efficacy by secondary measures (e.g., sperm in semen samples or failure to suppress testosterone in males or estrogen in females). Unfortunately, these methods were not standardized across institutions, so no consistent criteria were reported. However, because this information is still pertinent to understanding contraceptive efficacy, they are summarized and presented separately from contraceptive failures. The same time frame was used as for failures that resulted in birth; that is, these other measures of efficacy only included those failures documented after the stimulation phase but before the expected minimum period of efficacy ended. No behavioral signs of estrus as failures were included.

RESULTS

At the time of analysis, the RMC-RMG Contraception Database contained 8,141 bouts for 3,473 individual animals treated with at least one formulation of deslorelin (Table 1). The vast majority of individuals treated were mammals (94%), followed by birds (4.8%), reptiles (0.8%), and fish (0.3%). Among taxonomic groups, carnivores represented 45.4% of mammals treated (Table 1); primates were second (34%) and ungulates a distant third (8.8%). Other mammalian taxa represented even lower percentages.

As was the case for number of individuals treated, most bouts represented mammalian taxa (94.9%). However, across all taxonomic groups, the number of bouts per individual (B/I, a measure of repeated treatments) was roughly similar (mammals 2.36, birds 2.17, reptiles 1.48, and fish 1.09 B/I). However, variability was considerable among avian families, with individuals in six families treated only once, but in others up to 11 times (Gruidae 4.1, Bucerotidae 7, and Cracidae 11 B/I). The number of individual birds in each family was typically very small, though, indicating that only a few individuals contributed to those rates. Even fewer individual reptiles and fish were treated, and bouts per individual typically were low.

Overall, deslorelin was used much more commonly in females (78.3%) than males (21.7%). That gender bias was most pronounced in carnivores (83% females). In contrast, more

Table 1. Total number of species, individuals, females, and males treated with deslorelin (Suprelorin) contraceptive implants, and total number of treatment bouts reported to the joint Reproductive Management Center and Reproductive Management Group Contraception Database.

		Females		Males			
Taxonomic group	Total no. of species	No. of individuals	No. of bouts	No. of individuals	No. of bouts	Total no. of individuals	Total no. of bouts
Mammals	290	2,542	6,039	724	1,684	3,266	7,723
Carnivores	70	1,226	3,047	258	626	1,484	3,673
Marine mammals	9	38	105	28	77	66	182
Cetaceans	1	20	68	4	4	24	72
Pinnipeds	8	18	37	24	73	42	110
Primates	103	810	1,907	301	587	1,111	2,494
Apes	9	41	79	8	9	49	88
NW monkeys	39	378	932	81	205	459	1,137
OW monkeys	39	212	426	168	312	380	738
Prosimians	16	179	470	44	61	223	531
Rodents	22	80	178	26	54	106	232
Ungulates	57	263	558	23	36	286	594
Artiodactyls	53	254	540	19	32	273	572
Perissodactyls	4	9	18	4	4	13	22
Chiroptera	4	20	32	32	160	52	192
Hyrax	1	1	1	46	130	47	131
Lagomorphs	1	1	1	0	0	1	1
Marsupials	14	81	148	4	4	85	152
Scandentia	1	0	0	1	3	1	3
Tubulidentata	1	4	6	1	3	5	9
Xenarthra	7	18	56	4	4	22	60
Birds	57	125	299	42	64	167	363
Accipitriformes	3	8	32	1	3	9	35
Anseriformes	5	9	31	3	5	12	36
Bucerotiformes	1	1	7	0	0	1	7
Casuariiformes	1	1	4	0	0	1	4
Charadriiformes	4	10	31	4	15	14	46
Columbiformes	4	3	3	1	1	4	4
Cuculiformes	2	3	3	0	0	3	3
Galliformes	7	42	87	10	15	52	102
Gruiformes	3	5	27	2	2	7	29
Pelecaniformes	4	7	10	1	1	8	11
Psittaciformes	14	21	42	16	17	37	59
Sphenisciformes	3	5	5	0	0	5	5
Strigiformes	4	4	6	1	1	5	7
Struthioniformes	2	6	11	3	4	9	15
Reptiles	16	21	28	8	15	29	43
Crocodilia	1	4	6	0	0	4	6
Squamata	6	9	14	3	3	12	17
Testudines	9	8	8	5	12	13	20
Fish	5	8	9	3	3	11	12
Elasmobranchs	3	7	8	2	2	9	10
Osteichthyes	2	1	1	1	1	2	2
Grand total	368	2,696	6,375	777	1,766	3,473	8,141

[a] NW indicates New World; OW, Old World.

males were treated in some mammalian families: Phocidae (73%), Sciuridae (79.5%), Pteropodidae (83.3%), and, in particular, Procaviidae (99.2%). Notably, in two Prosimian families (Cheirogaleidae and Indriidae), only males were treated, but the total numbers were quite low. Although fewer birds, reptiles, and fish have been treated, the bias also has been toward treating females (Table 1).

Although long-term data for most avian species are lacking, a pattern of apparent desensitization was seen with successive treatment in some (e.g.,

Table 2. Suprelorin contraception failures resulting in offspring in mammals or egg-laying in birds, reptiles, and fish.

Taxonomic group[a]	Females	Males	Total failures	% failures in total no. of individuals
Mammals	22	13	35	1.3
Prosimians	2	1	3	1.6
NW monkeys	4	6	10	2.4
Apes	1	0	1	2.9
Canids	2	1	3	1.2
Ursids	0	1	1	2.5
Small carnivores[b]	4	3	7	1.6
Artiodactyls	3	0	3	1.3
Rodents	6	1	7	7.9
Birds	11	0	11	14.7

[a] NW indicates New World.
[b] Includes Ailuridae, Herpestidae, Mustelidae, Procyonidae, and Viveridae.

tufted puffins, *Fratercula cirrhata*, Charadriiformes; yellow-knobbed curassow, *Crax daubentoni*, Galliformes), in which shorter treatment intervals or higher doses were required to maintain suppression. Yet in others (red-sided eclectus, *Eclectus roratus*, Psittaciformes; bald eagle, *Haliaeetus leucocephalus*, Accipitriformes), females were treated repeatedly with no apparent desensitization.

Efficacy

Deslorelin implants were very effective at achieving contraception across mammalian species, with very low failure rates (Table 2). Defining failure for mammals as production of offspring, only 1.3% of the total number of individuals treated and 0.5% of total treatment bouts resulted in offspring. The highest mammalian failure rate was seen in rodents (7.9%) and the lowest in carnivores (0.8%). For birds, the failure rate, defined as egg laying, although higher than for mammals was still relatively low, with 14.7% of total number of females treated, representing 7.2% of total treatment bouts (Table 2). Although records showed that offspring were produced by one turtle and one stingray, they were treated for medical reasons, not for contraception.

Offspring conceived during the GnRH agonist–induced stimulation phase were not counted as failures. However, production of offspring conceived during the last quarter (>4.5 or >9 mo, respectively) of the expected 6- and 12-mo minimum periods of efficacy for the two Suprelorin formulations was counted as failure. Only 7 of the 35 failures fell into this category.

Table 3. Cases of Suprelorin failure to suppress gonadal hormones or sperm production.[a]

Taxonomic group	Female	Male	Total
Primates	2	4	6
Carnivores	10	3	13
Artiodactyls	1	3	4
Marine mammals	0	1	1
Mammal total	13	11	24
Fish	4	0	4

[a] Only individuals treated for the purpose of contraception are included.

For mammals, failure rates were three times higher in males than in females, at 3.2% and 1.0%, respectively. A trend for males to require higher doses than conspecific females to achieve suppression was seen, particularly in male primates, such as mandrills (*Mandrillus sphinx*), drills (*Mandrillus leucophaeus*), baboons (*Papio* spp.), and lion-tailed macaques (*Macaca silenus*).

Body weight was not a consistently accurate predictor of effective dose. Some canid species were notable for the number of implants needed to suppress reproduction; for example, failures were reported in bush dogs, *Speothos venaticus* (one implant); red wolves, *Canis rufus* (two implants); painted dogs, *Lycaon pictus* (two implants); and gray wolves, *Canis lupus* (three implants). In contrast, much larger felids, such as lions (*Panthera leo*) and tigers (*Panthera tigris*), were successfully contracepted, with between one and three implants.

Failure to suppress gonadal hormones in males or females or to suppress sperm production in males despite adequate contraception was reported and tabulated separately (Table 3). Because the total number of individuals monitored by hormone assay or semen collection is unknown, the proportions in which these parameters were not suppressed cannot be calculated. The reports did not include thresholds for hormone or sperm concentrations used to determine failure of suppression.

DISCUSSION

Since deslorelin, later branded as Suprelorin, became available for use in US zoos in 1998 and in Europe in 2003, it has become a popular method of contraception for mammals, especially carnivores. Because long-term use of MGA implants had been associated with uterine pathology in felids and canids,[1,39–41] the Reproductive

Health Surveillance Program cautioned against use of progestin contraceptives for all carnivores. According to the RMC-RMG Contraception Database, zoos have followed that recommendation, with more carnivores being treated with Suprelorin than any other taxonomic group, both in the number of individuals treated and the number of bouts. The initial interest in Suprelorin for carnivores then expanded to include most mammalian taxa represented in zoos. Additionally, an increasing number of avian species have been implanted with Suprelorin in recent years, as well as some reptiles and even fish.

In addition to its contraceptive effects, deslorelin has been used in zoos and aquariums to reduce aggression in both males and females. In birds, it has also been used to inhibit egg laying and to treat egg binding and feather plucking. Similarly, some reptiles have been treated to prevent egg laying. Unfortunately, the RMC-RMG Contraception Database does not at present contain sufficient information to evaluate efficacy for these other applications.

In general, more females have been contracepted than males, with some notable exceptions among seals, squirrels, bats, hyrax, and prosimians. The bias to treating females may reflect population objectives, such as managing multifemale social groups, in which all females do not have current breeding recommendations. Longer separation is needed when males are treated: 2 mo compared with only 1 mo for female treatment. Efficacy is also simpler to confirm in treated females through absence of estrous behaviors, male interest, or other external signs of estrus, such as genital swellings. In contrast, confirmation of efficacy in males typically involves semen collection, which requires capture, anesthesia, and specialized equipment and training. A clear cutoff for sperm numbers or quality, below which a male can be considered infertile, has not been established, which further complicates evaluating efficacy in males. Furthermore, males of some species seem resistant to GnRH agonist suppression, notably some male bovids[19,45] and marsupials.[14,21,27] This historical bias away from treating males means that more is known about effective dose and reversibility in females, which tends to perpetuate the trend.

Establishing dosages

When the RMC first began distributing Suprelorin, dosages were only available for domestic dogs: 3 mg for small breeds and 6 mg for large breeds.[30] RMC-RMG have extrapolated from dogs, based on body weight, to arrive at dosages for wild species; for example, lions were given 12 mg (2 × 6 mg), and smaller animals such as painted dogs were given a single implant.[5–7] Later research with the Suprelorin formulation (4.7 mg) showed that a single implant was sufficient to suppress testosterone in male domestic dogs regardless of bodyweight (BW), although small males (<10 kg) were suppressed longer, on average, than medium (10–25 kg) and large (>25 kg) dogs.[57]

However, according to reports to the RMC-RMG Contraception Database, wild canids, in the same family (Canidae) as domestic dogs, appear to require higher doses relative to body size. Despite their relationship to domestic dogs, bush dogs, red wolves, gray wolves, and painted dogs all require more than one 4.7-mg implant for adequate contraception. Female gray wolves given three implants were seen mating (RMC-RMG Contraception Database), so the recommendation is now four implants, comparable to a dose for giraffe (*Giraffa camelopardalis*), despite the average body weight for the wolves being 27–38 kg. Establishing proper dosages for each species and gender depends not only on formal research studies but on information in reports to the RMC-RMG Contraception Database from the zoo and aquarium community.

A further challenge with establishing minimum effective doses is that many managers prefer having overt confirmation of suppression (i.e., absence of estrous-type behaviors in female mammals or sperm production in males). However, ovarian follicles may produce sufficient estrogen to support estrous behavior and stimulate male interest or even copulation without being followed by ovulation and conception. Thus, suppressing follicle growth may require a higher dose than necessary for effective contraception.

For males, a threshold for number and quality of sperm necessary for fertilization has not been established for any wildlife species, so, in general, azoospermia is preferred to ensure infertility. However, completely eliminating sperm production likely requires a higher dose than may be needed to achieve effective contraception. Fortunately, at present no known side effects are associated with these higher doses, except perhaps longer duration of efficacy, which can affect time to reversal when breeding is recommended.

Efficacy

Failure rates have been very low. Among mammals, only 1.3% of individual animals treated

have produced offspring during the expected minimum period of efficacy, representing only 0.5% of treatment bouts, which reflects the number of times treated. The percentage of failures per individual was higher in birds, though, at 14.7%, representing 7.2% of bouts. Reptiles and fish have each had only one failure, although very few individuals have been treated.

Calculation of failures excluded conceptions or egg laying during the first month after implant placement in females and fertilization during the first 2 mo for males. Deslorelin, like other GnRH agonists, first stimulates the HPG axis, which can result in ovulation in females and temporarily enhanced sperm production and aggression in males. For this reason, the recommendation is to separate males from females during this period or to prevent ovulation in female mammals by administering oral megestrol acetate for 7 d before and 7 d after implant placement.[61] A method for preventing the stimulation phase in males has not been developed. GnRH agonist stimulation of ovulation typically occurs within the first month after implant insertion, but in males, 2 mo should be allowed for sperm to disappear from the ejaculate after downregulation occurs.

Failure rates were higher for males, perhaps because they may require higher doses than females. This phenomenon has been most apparent in males of some primate species, for example, mandrills, drills, baboons, and lion-tailed macaques, in which dosages (kg^{-1} BW) that suppress conspecific females have been insufficient in males. However, too few males have been treated in most taxa to draw more general conclusions. This phenomenon may also be influenced by difficulty in completely suppressing sperm production. In addition to questions of dosage, spermatogenesis may be supported in at least some species by FSH alone,[58] and FSH may not be completely suppressed by downregulation of GnRH receptors on pituitary gonadotrophs.[43]

Also of interest, hormone monitoring in some males and females showed that dosages sufficient for contraception did not suppress gonadal hormones to baseline in all individuals. As for spermatogenesis, sustained gonadal hormone production may be supported by FSH secretion that is not affected by GnRH agonist downregulation[43].

Deslorelin has been used in only a small percentage of avian species, but the range of orders has been rather broad, with the notable exception of Passeriformes. Failure rates have been higher than for mammals, which may reflect taxon-specific differences in response to this particular GnRH agonist. One difference may be duration of inhibition. Egg production was reported to be inhibited in chickens (*Gallus gallus domesticus*) for 180 d (4.7-mg formulation) and 319 d (9.4 mg)[42] and in cockatiels (*Nymphicus hollandicus*) for 180 d (4.7 mg).[55] Yet in another study with chickens, egg laying was suppressed for only 8–14 wk.[20] Similarly, in pigeons (*Columba livia*) the period of efficacy was less than 6 mo,[15] and in Japanese quail (*Coturnix coturnix japonica*) only 70% of females laid fewer eggs and for a shorter period of time.[46,47] Another variation reported to the Contraception Database for some avian species was an apparent desensitization to repeated treatment, requiring a higher dose or more frequent treatment to maintain efficacy, a response not yet seen in mammals, reptiles, or fish. However, very few reptiles and fish have been treated, so trends have yet to emerge.

Differences in the structure of the GnRH molecule may explain some of the variability in response in these nonmammalian taxa. The GnRH molecule is identical across all mammalian species but can vary among other vertebrate classes.[53] Birds have three GnRH forms, but it is not clear what role each plays in regulating reproductive processes.[3] Also unknown is whether differences in GnRH forms or in expression of GnRH receptors account for the inconsistent responses to GnRH agonists in birds or other nonmammalian taxa. Data reported to the RMC-RMG Contraception Database have reflected those sometimes contradictory results.

Nevertheless, the results here are consistent with those of others[36] that Suprelorin can be used successfully in some avian species as therapy for reproductive problems (e.g., excessive egg laying and repeated egg binding), as well as managing behaviors such as feather plucking. However, treatment may not be successful in all species or individuals or may only be effective initially but less so with repeated treatment.

Apparently contraceptive doses of Suprelorin (i.e., no offspring produced) failed to suppress estrogen production in some female mammals. Early follicle growth depends primarily on FSH stimulation, whereas final follicular growth and ovulation depend on an LH surge. There is evidence that FSH secretion is partially independent of GnRH support,[43] so even complete downregulation of GnRH receptors might still allow some FSH production and subsequent follicle growth to support estradiol production and secretion, while blocking the LH surge. Something similar has been seen with MGA

treatment, which also may be accompanied by estrous behavior that is not followed by production of offspring. In a study of ovaries from MGA-treated felids, almost all had tertiary follicles, the stage capable of secreting estradiol,[31] and some even had evidence of recent ovulation. Although not known for GnRH agonists, progestins can prevent pregnancy at multiple points in the reproductive process,[10] and higher doses are typically needed to block ovulation.[17] More study is needed to determine whether higher deslorelin doses can more effectively suppress follicle growth and estradiol production.

Although implant loss might be a reason for contraceptive failure, reports of Suprelorin implant loss have been rare. However, the small size of the implants complicates confirming their presence. Original instructions were for interscapular placement, but alternative sites such as inner thigh, forelimb, flipper, or base of ear can make it easier to confirm that implants remain in place and facilitate removal when reversal is desired. Removal is also made easier by careful insertion, which entails creating a tunnel ahead of the implant with the insertion trocar, then depositing the implant in that space as the trocar is withdrawn.

Contraceptive failure late in the expected period of efficacy could be considered early reversal. However, because of its complexity, Suprelorin contraceptive reversal will be the subject of future analyses and publications. That complexity highlights the importance of data submission by participating institutions and these collaborations with regional breeding program managers. First, not all individuals previously contracepted receive a breeding recommendation in their lifetimes, and breeding recommendations may come many years after contraceptive treatment, creating a lag time between initial data on treatment and any information on potential reversal. Additionally, of course, many factors other than contraception can affect fertility and reproductive success, with the most obvious being general health, age, and reproductive history. Some of the most difficult information to acquire involves mate access and pair compatibility (i.e., acceptance of mating). Some recommended pairs are never actually introduced and others may not mate. Even when reproduction is successful, institutions must also remember to report births. Proper statistical analyses of reversal dynamics require a sufficient sample size of noncontracepted individuals (to establish species reproductive norms) as well as those receiving the contraceptive. Lions and small-clawed otters are anticipated to be the first species with enough data for analysis.

In conclusion, Suprelorin appears to be an effective and safe contraceptive option for female mammals, although it may not be effective in males of some mammalian species. Further research is needed to ascertain its usefulness in nonmammalian taxa.

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