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Review Article

Emerging Physiological Approaches for Population Management in Stray and Wild Animals

Suhana Parvin Muquit [1*], Kiran Shinde [2], Chandrakant Kale [3]

[1] Division of Physiology & Climatology, ICAR-Indian Veterinary Research Institute, Bareilly, Uttar Pradesh, India

[2] Division of Animal Nutrition, ICAR-Indian Veterinary Research Institute, Bareilly, Uttar Pradesh, India

[3] Division of Veterinary Parasitology, Nagpur Veterinary College, Nagpur, Maharashtra, India

Corresponding Author: *Suhana Parvin Muquit

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Abstract

The increasing population of stray and wild animals in India has emerged as a significant challenge, impacting public health, biodiversity, and animal welfare. India is home to the largest stray dog population globally, with numbers doubling from 35 million in 2020 to 60–65 million by 2023, alongside increasing stray cat and wildlife populations. This overabundance contributes to road accidents, crop and livestock losses, zoonotic disease transmission, and escalating human–animal conflicts. Due to these growing issues, it is essential to control the population of these animals effectively and humanely. Traditional population control methods such as culling and poisoning are often ineffective, ethically contentious, and unsustainable. Fertility control presents a humane and long-term alternative, with promising approaches including surgical sterilisation, immunocontraception, hormonal regulation, gene silencing, chemical sterilants, and targeted cytotoxin delivery. Non-surgical methods, such as vaccines against GnRH, zona pellucida, or sperm antigens, as well as innovative gene-silencing techniques using siRNA delivered via hypothalamus-targeting viral vectors and herbal contraceptives, have shown efficacy in suppressing reproductive functions. Emerging technologies like AMH transgene therapy, rotational immunocontraception, and targeted contraceptive vaccines offer species-specific, reversible, and minimally invasive solutions. While challenges remain in cost, logistics, and long-term efficacy, advancing fertility control strategies tailored to species and ecological contexts holds great potential for reducing human–animal conflicts, mitigating zoonotic risks, and preserving ecological balance humanely and sustainably.

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1. INTRODUCTION

In 2020, India's stray dog population was estimated at around 35 million, which increased sharply to about 60–65 million between 2021 and 2023. India currently has the largest stray dog population in the world. In contrast, the number of pet cats in India was estimated at approximately 2 million in 2018, projected to reach 2.5 million by the end of 2023. Stray animals also pose a threat to human safety; according to government data, they were responsible for 1,604 road accidents in 2016, resulting in 629 human fatalities (PIB 2017).

Population management in stray and wild animals has become increasingly important due to concerns related to ecological balance, human–animal conflict, and animal welfare. Among the emerging strategies, physiological approaches targeting reproductive control have gained attention as humane and effective alternatives to traditional culling. These methods aim to suppress or regulate fertility through hormonal, immunological, or intrauterine interventions without causing long-term harm or disrupting natural behaviours.

Although population control methods have been practised historically, it is only in recent decades that safe, reversible, and species-specific physiological techniques have emerged. Cultural, religious, and ethical beliefs may still influence the acceptance of such interventions in certain regions (Sudarshan 2005). Surgical sterilisation methods, such as vasectomy in males and tubal ligation in females, remain among the most effective options, along with intrauterine devices (IUDs) and subcutaneous contraceptive implants. Hormonal methods using injectable agents, oral tablets, or implants are also used, although with varying degrees of success and reversibility.

Barrier methods and fertility awareness-based interventions are less applicable in the context of stray and wild animal populations due to challenges in repeated handling and compliance. Spermicidal agents and behavioural modifications offer minimal utility in wildlife scenarios. Emergency contraceptive agents, if administered within 72 to 120 hours post-mating, can prevent conception, but their application in field conditions is limited (Gizzo *et al.,* 2012).

A growing area of interest is green contraception, which refers to population control methods with minimal environmental impact. These include hormone-free techniques and products developed through sustainable manufacturing, eco-friendly packaging, and safe disposal practices (Blithe 2016).

Interestingly, traditional practices also highlight the long-standing awareness of intrauterine contraception. For instance, nomadic tribes in the Sahara and Sudan have historically inserted smooth stones into the uterus of saddle camels to prevent conception by discouraging male mating behaviour (Guttmacher 1965). Similarly, in Surati goats and buffaloes, polyethene IUDs (4 cm in length and a few centimetres in diameter) placed within the uterus led to shortened cycles, suppressed gonadotropin activity (LH, FSH), and inhibited ovulation (Buch *et al.,* 1964; Janakiraman *et al.,* 1970). Modern adaptations of intrauterine devices have also been used for fertility control in dogs (Volpe *et al.,* 2001).

India is facing an urgent need to adopt humane and sustainable wildlife population control measures, such as fertility control, to mitigate the rising human–wildlife conflict. The country hosts an estimated 30,000 wild elephants, with conflicts resulting in about 500 human and 100 elephant deaths annually (MoEFCC, 2020). Wild boars have caused hundreds of attacks, including 309 reported injury incidents between 1990 and 2008 (Krishna *et al.,* 2009), while big cats remain a significant concern, with approximately 55 tigers and 150 leopards killed each year in retaliation or accidents (NTCA, 2022). Crop and livestock depredation is widespread, affecting nearly 71% of rural households with crop damage and 17% reporting livestock losses due to wildlife (Karanth *et al.,* 2013). Across the country, conflict-related incidents are estimated to range between 67,000 and 109,000 annually (WWF India, 2017), and in Uttarakhand's Nanda Devi buffer zone alone, losses from crop and livestock predation have exceeded ₹15 lakh (Singh *et al.,* 2021). These alarming figures highlight the necessity of non-lethal, science-based solutions like fertility control to reduce conflicts effectively while conserving India's rich biodiversity.

These physiological approaches, especially those that are reversible, species-specific, and minimally invasive, offer promising avenues for humane and ecologically sound population control in both stray and wild animal populations.

IMPORTANCE OF POPULATION MANAGEMENT IN ANIMALS

Human-wildlife conflict is a growing concern in India, often resulting in the loss of crops, livestock, human lives, and wild animal populations. These conflicts stem from a complex interplay of factors, including historical land use changes leading to habitat loss, degradation, and fragmentation; shifts in wildlife behaviour and foraging ecology; climate variability; and the diverse nature of human-wildlife interactions, which are frequently influenced by cultural and religious beliefs.

Conflicts have notably increased in recent decades involving species such as elephants, antelopes (e.g., nilgai and blackbuck), non-human primates, and carnivores like leopards. Ironically, many of these conflicts are a byproduct of successful wildlife conservation efforts, which have led to localised population booms and the expansion of wildlife into human-dominated landscapes (Sukumar 2010).

The physiological regulation of reproduction, especially through contraceptive techniques, has become essential in managing animal populations, both in domestic and wild settings, for three primary reasons:

1. **Population Control:** Unchecked growth in animal populations can lead to serious ecological and societal issues. Similarly, species like nilgai and blackbuck in India cause extensive damage to agricultural fields, with nilgai being responsible for as much as 58% crop loss in some regions of Haryana (Chauhan *et al.,* 1990). Overpopulation also increases risks of wildlife-aircraft collisions and road accidents involving animals, further endangering human lives and resources.
2. **Zoonotic Disease Risk:** Wildlife populations often serve as reservoirs for zoonotic diseases, posing a significant threat to both livestock and public health. Diseases such as Lyme disease, tuberculosis, brucellosis, pseudorabies,

West Nile virus, chronic wasting disease, and avian influenza can be transmitted from animals to humans (Fagerstone *et al.,* 2006). In India, stray dogs remain the primary reservoir of rabies, a major public health concern. Each year, over 15 million people in India suffer animal bites and require post-exposure prophylaxis. The country records an estimated 25,000–30,000 rabies-related deaths annually, with stray dogs accounting for 60% of bites and pet dogs for 40%. This translates to an animal bite rate of 17.4 per 1,000 population, with one person bitten every 2 seconds and one death every 30 minutes (Menezes 2008; Sudarshan 2005).

3. **Environmental and Economic Impact:** While increasing wildlife abundance is generally seen as a conservation success, overpopulation in certain regions can have detrimental environmental and economic consequences. Overabundant species can cause habitat degradation, competition with native fauna, and ecosystem imbalance. Agricultural damage due to foraging, trampling, or burrowing by wildlife, as well as destruction of property and infrastructure, is increasingly common (Fagerstone *et al.,* 2006). Crop damage by wild animals is the most common and persistent form of human–wildlife conflict in the tropics, affecting staple grains (rice, wheat, maize, sorghum, millet), non-grain food crops (potatoes, peanuts, vegetables, sugarcane, bananas, cassava, coconuts, cocoa), and commercial crops (rubber, tea, coffee, spices). Damage is caused not only by feeding but also by trampling, rooting, and wastage (De Boer *et al.,* 1998). Expansion of farmland into wildlife habitats and habitat fragmentation force wildlife into croplands, attracted by nutrient-rich crops and reduced predation. Major culprits include elephants (20–50% damage), wild boar (15–40%), nilgai (10–30%), rhesus macaque (10–30%), blackbuck (5–15%), gaur (5–10%), rodents (~15%), and birds (~9%) (Ayyappan *et al.,* 2016). The extent of damage depends on wildlife population density, cropping patterns, season, and crop stage. The adaptability of wildlife to human-dominated landscapes, along with no universal solution to conflict, often results in harm to both humans and wildlife, negative attitudes toward conservation, and challenges for coexistence (Williams and Johnsingh 1997; Sekhar 1998).

Given these challenges, implementing sustainable and humane physiological methods for reproductive control is crucial. These strategies not only help maintain ecological balance but also reduce conflict and disease transmission, safeguard public health, and protect agricultural livelihoods.

ANIMAL BIRTH CONTROL PROGRAMMES IN INDIA

In response to the growing issue of human-dog conflict across urban and semi-urban India, the Animal Welfare Board of India (AWBI) has advocated for the widespread implementation of Animal Birth Control (ABC) programmes. These initiatives aim to provide a humane and effective solution to managing stray dog populations not only in metropolitan regions but also in smaller towns and rural areas.

Rabies and dog bites continue to pose significant public health concerns, accounting for approximately 20,000 human deaths annually in India, the highest rabies death toll globally. Notably, 90% of post-exposure cases and 96.5% of deaths are attributed to dog bites (Menezes 2008; Sudarshan 2005). The uncontrolled street dog population is exacerbated by factors such as abundant food waste, inadequate enforcement of dog control policies, urban shelter availability, and cultural tolerance.

Additionally, the ecological balance has shifted dramatically following a >95% decline in India’s vulture population due to diclofenac poisoning, resulting in increased carcass availability and further support for dog population growth (HSI 2003). These changes in scavenger dynamics have intensified zoonotic risks and conflicts.

Historically, inhumane culling methods, including electrocution, poisoning, and bludgeoning, were used to reduce dog numbers. However, these methods proved counterproductive by disrupting pack structure, increasing aggression, and enhancing rabies transmission risks (AWBI 2009). The World Health Organisation (WHO) has long emphasised that such mass culling is neither humane nor effective for long-term control.

Launched in the 1990s, the ABC programme integrates surgical sterilisation (ovariohysterectomy or castration) with anti-rabies vaccination to stabilise dog populations and reduce disease spread (AWBI 2009). ABC-treated dogs demonstrate:

- Reduced aggression and territorial behaviour
- Lower energy requirements
- Decreased mating and whelping
- Improved general health, even among nearby untreated dogs, due to reduced disease transmission

Cities such as Jaipur and Jodhpur have shown substantial reductions in dog density and rabies incidence following ABC implementation (HSI 2003). Sterilised dogs not only coexist better with humans but also reduce zoonotic threats to livestock, wildlife, and people.

To standardise ABC efforts, the AWBI issued Standard Operating Procedures (SOPs) to ensure humane treatment, operational efficiency, and scientific oversight (AWBI 2009). These SOPs promote uniform practices across the country.

The 2023 Rules mandate that:

- Stray dogs are caught, vaccinated, sterilised, and released back into their original location
- Stray dogs be reclassified as “community animals”
- Local bodies must jointly implement ABC and anti-rabies programs through AWBI-recognized organizations

A female-focused ABC programme in Jaipur serves as a successful case study demonstrating long-term effectiveness, reduced conflict, and enhanced public health outcomes (HSI 2003).

Today, although gonadectomy remains the gold standard, ongoing research addresses its optimal timing and long-term impacts, especially with increasing pet life expectancy (Reichler 2009). When integrated with rabies vaccination and community education, ABC can significantly reduce zoonotic risks and foster harmonious human-animal coexistence.

MODERN APPROACHES TO POPULATION CONTROL IN ANIMALS

4.1. Immuno-Control Contraceptive Vaccines

Immunological methods for fertility regulation, commonly referred to as immuno-control or contraceptive vaccination, involve harnessing the animal's own immune system to suppress reproductive function. This approach uses exogenous reproductive proteins (antigens) to stimulate the immune system to produce antibodies. These antibodies then target and neutralise the animal's own reproductive hormones or gamete-associated proteins, thereby disrupting normal reproductive processes and contributing to population control.

Immuno-vaccines have been developed to act on various biological targets, including:

1. **Gamete interference at fertilisation:** During fertilisation, sperm bind to the zona pellucida (ZP), a glycoprotein layer surrounding the oocyte. In this method, antibodies are produced against porcine ZP antigens. These antibodies coat the surface of the egg, preventing sperm binding and thereby inhibiting fertilisation and pregnancy.
2. **Hormonal suppression through GnRH inhibition:** Another target is the gonadotropin-releasing hormone (GnRH), which controls the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. These hormones regulate ovarian and testicular activity via feedback loops, affecting estrogen and testosterone production. By generating antibodies against GnRH, the reproductive hormone cascade is disrupted, leading to reduced fertility.

A major advantage of immunological population control is the potential for non-invasive delivery, such as oral administration via bait, eliminating the need to capture animals for injection (Purswell and Kolster 2006). Furthermore, GnRH-based vaccines also reduce sexual behaviours in both males and females, which is particularly beneficial in managing stray animal populations (Kutzler and Wood 2006).

These contraceptive vaccines (CVs) offer a promising alternative to conventional methods of population management. The targets for these vaccines fall into three main categories:

- **Gamete production** (e.g., GnRH, FSH, LHRH)
- **Gamete function** (e.g., sperm surface antigens, zona pellucida proteins)
- **Gamete outcome** (e.g., human chorionic gonadotropin, hCG)

Among these, sperm antigens are considered highly promising targets for vaccine development. The research focuses on identifying sperm-specific epitopes and enhancing the immune response, especially within the reproductive tract, to improve vaccine effectiveness. Naturally occurring anti-sperm antibodies (ASA), causing infertility, offer a biological model supporting this strategy.

While ZP-based vaccines have demonstrated high efficacy in reducing fertility in species such as feral dogs, deer, horses, elephants, and zoo animals, they can also lead to oophoritis (inflammation of the ovaries), which may disrupt normal sex hormone production. Therefore, ongoing research aims to distinguish between infertility-inducing (B-cell) and inflammation-inducing (T-cell) epitopes to improve safety and specificity in potential human applications.

Vaccines targeting hCG (human chorionic gonadotropin) are also under investigation, focusing on blocking early pregnancy establishment as a method of gamete outcome interference (Naz *et al.,* 2005).

A major advantage of immunocontraceptive vaccines over other contraceptives is that they are unlikely to harm predators or scavengers that consume treated animals, as the vaccines are broken down in the consumer's gastrointestinal tract (Massei, 2023). However, a key drawback is that these vaccines are only available in injectable form, making them less practical for managing large wildlife populations because of the high costs and the need to trap and sometimes immobilise animals for treatment.

4.2 Types of Immune-Based Vaccines for Animal Population Control

Immunological approaches to fertility regulation in animals have evolved significantly, with several types of vaccines now under development or in use. These vaccines stimulate the immune system to produce antibodies against specific reproductive targets, leading to temporary or long-term infertility. The key types of immune-based vaccines currently available or being researched include:

A. GnRH Vaccines

Gonadotropin-releasing hormone (GnRH) is a small decapeptide conserved across all mammals, playing a central role in regulating reproductive hormone release. By inducing the immune system to generate antibodies against endogenous GnRH, its biological activity is suppressed, resulting in infertility. However, since GnRH is a self-antigen, it is poorly immunogenic, posing challenges for vaccine development (Thompson 2000). To overcome this, researchers have designed several strategies to improve immunogenicity, including synthetic GnRH vaccines incorporating T-helper epitopes (Sad *et al.,* 1993), recombinant GnRH-based immunogens (Robbins, 2002), and fusion constructs combining GnRH with heat shock proteins (Wang *et al.,* 2010).

The National Wildlife Research Centre (NWRC) of the USDA developed **GonaCon**, a GnRH-based immunocontraceptive vaccine, initially tested in white-tailed deer in 2005. A single intramuscular injection of GonaCon has demonstrated long-term contraceptive efficacy across a variety of species, including deer, wild rats, squirrels, feral cats, dogs, domestic pigs, rabbits, coyotes, wild horses, and bison, with effects lasting from one to four years (Fagerstone 2006)

In a more controlled setting, domestic cats treated with the GnRH agonist deslorelin acetate showed reversible fertility suppression. After implant removal and administration of exogenous gonadotropins, all subjects ovulated, producing a higher-than-normal number of corpora lutea (CL), indicative of superovulation. This heightened ovarian response was attributed to a period of temporary ovarian quiescence, enhancing the responsiveness to gonadotropic stimulation. Unlike previous studies in clouded leopards that reported poor ovarian recovery due to desensitisation, no such issue was observed in this study. Remarkably, one queen produced embryos without mating, a rare event likely due to parthenogenetic egg activation. This is the first report confirming the recovery of viable oocytes following short-term deslorelin treatment in cats, supporting its use as a reversible contraceptive. However, further investigation is warranted to assess the effects of prolonged deslorelin exposure on oocyte quality and embryo development.

B. Zona Pellucida (ZP) Vaccines

The zona pellucida (ZP) is a glycoprotein layer surrounding the ovum, which plays a key role in sperm-egg binding. Immunisation with ZP proteins results in the production of antibodies that block fertilisation.

- **Porcine ZP (PZP)**, derived from pig ovaries, has been widely used. Though cDNAs of ZP proteins have been sequenced in many species, recombinant production remains difficult due to complex glycosylation patterns (Prasad *et al.,* 2000; Paterson *et al.,* 2002; Yonezawa *et al.,* 2001).
- Second-generation ZP vaccines using recombinant or synthetic ZP proteins are under investigation (Dunbar *et al.,* 2002).
- **SpayVac™**, developed by Immunovaccine Inc., is a PZP vaccine tested in seals and other species.
- **ZonaStat-H**, approved by the U.S. EPA, is a ZP-based vaccine used in managing wild horse populations.
- In dogs, three ZP proteins—**ZP1, ZP2, and ZP3**—have been sequenced (Harris *et al.,* 1994), and recombinant dog ZP3 (dZP3) has shown potential for use in stray dog population control if adequate antibody levels are induced (Srivastava *et al.,* 2002).

C. Egg and Sperm Protein Vaccines

Vaccines targeting proteins exclusive to eggs or sperm can prevent fertilisation. When the immune system is stimulated to recognise and attack these proteins, fertility is disrupted.

- Researchers have constructed ovarian cDNA libraries in dogs and cats to identify ovum-specific proteins for use in vaccine development (Coonrod 2002).

Sperm-specific antigens like lactate dehydrogenase and acrosin have been identified as potential vaccine targets in dogs and cats (Kutzler and Wood 2006).

- Phage peptide constructs are also being explored for their potential use in developing vaccines targeting sperm antigens in dogs (Samoylov *et al.,* 2012).

D. Luteinizing Hormone (LH) Receptor Vaccines

This approach involves inducing antibodies against the LH receptor, thereby blocking the receptor's interaction with LH and preventing hormonal regulation of reproduction.

- Since LH receptors are "self" proteins, stimulating an immune response is challenging. However, purified bovine LH receptor proteins have been successfully used in dogs, leading to reduced fertility in both dogs and cats (Saxena *et al.,* 2002)
- Chimeric proteins combining human LH receptor and chorionic gonadotropin (CG) epitopes are being evaluated as potential vaccine candidates (Hao and Saxena 2006)

E. Human Chorionic Gonadotropin (hCG) Vaccines

The first human birth control vaccine to complete Phase II clinical trials targeted hCG, a hormone essential for pregnancy maintenance (Talwar *et al.,* 1994)

Notable examples include:

- **β-hCG live vector vaccine** – tested in rodents (Srinivasan *et al.,* 1995)
- **β-hCG-CTP (Carboxyterminal Peptide) vaccine** – Phase I trials in women (Jones *et al.,* 1988)
- **hCG-HSD-TT/DT (Heterospecies Dimer-Tetanus/Diphtheria Toxoid) vaccine** – under experimental evaluation (Gupta *et al.,* 2001)

These vaccines aim to block implantation or early pregnancy, offering a novel pathway for both human and animal population control.

4.3 Hormonal Regulation For Population Control In Animals

Hormonal regulation involves the administration of synthetic (exogenous) steroid or protein hormones to suppress natural reproductive hormone production, thereby reducing fertility. This approach is widely used in both human and animal population control programs. The main strategies include the use of **GnRH agonists, GnRH antagonists, progestins, androgens**, and other hormone-modifying compounds.

A. GnRH Agonists

GnRH agonists mimic the natural action of gonadotropin-releasing hormone but eventually lead to the downregulation of GnRH receptors in the pituitary gland through overstimulation. This continuous stimulation results in suppression of LH and FSH secretion, thereby inhibiting reproductive function.

Some commonly used GnRH agonists include Deslorelin, Leuprolide, Nafarelin, Buserelin, Goserelin, Triptorelin, and Histerelin.

- Deslorelin, formulated as an implant, has been widely used in dogs, livestock, and wildlife.
- In a study on prepubertal pigs, 4.7 mg and 9.4 mg deslorelin implants were evaluated for safety, reversibility, and effects on skeletal development (Kaya *et al.,* 2015)
- In male dogs, buserelin (6.6 mg implants) significantly reduced testosterone levels and led to temporary infertility within 3 weeks, with effects lasting an average of 233 days (Kutzler and Wood 2006).

B. GnRH Antagonists

Unlike agonists, GnRH antagonists block the GnRH receptors on pituitary cells, preventing LH and FSH secretion without initial stimulation. These are small peptides structurally similar to natural GnRH and are generally effective across species.

Examples include Cetrorelix, Ganirelix, Iturelix, Acyline, and Elagolix (a non-peptide GnRH antagonist introduced in 2016).

- Cetrorelix has shown efficacy in monkeys, dogs, rats, and humans (Reissmann *et al.,* 2000)
- In a study on dogs, Acyline (330 µg/kg subcutaneous dose) temporarily reduced semen quality for two months. Some animals retained libido and erection, while others showed transient reductions in sexual behaviour (Gobello 2007).

C. GnRH-Toxin Conjugates

This strategy involves conjugating GnRH with a cytotoxin, creating a complex that specifically targets GnRH receptor-bearing pituitary cells. Upon internalisation, the toxin is released and destroys these cells, permanently suppressing reproductive hormone production.

- A notable example is the GnRH-PAP conjugate, which combines GnRH with pokeweed antiviral protein (PAP).
- In one study, administration of GnRH-PAP to male dogs over 25 weeks significantly disrupted reproductive parameters, including testosterone levels, scrotal size, and GnRH-LH interaction (Sabeur *et al.,* 2003).

D. Progestins

Progestins are synthetic compounds similar to progesterone, functioning via negative feedback at the hypothalamic-pituitary axis to suppress GnRH, and exerting local effects on the reproductive tract, inhibiting fertility.

Common progestins include:

- Megestrol acetate (MGA)
- Medroxyprogesterone acetate (MPA)
- Proligestone
- Proligestone is frequently administered to female cats, suppressing estrus for approximately 6.5 months.
- MPA, given subcutaneously at 20 mg/kg to male dogs, caused a rapid decrease in sperm motility, morphology, and overall production within 3 days (Kutzler and Wood 2006).

E. Androgens

Synthetic androgens can also be used to interfere with normal reproductive cycles.

- Mibolerone (Cheque® Drops, Pfizer Animal Health), an oral androgen, is used to suppress estrus in female dogs by inhibiting LH secretion via negative feedback.
- It is primarily used to extend anestrus, delay heat cycles, and treat false pregnancy.
- However, its use is not recommended in immature females due to potential effects on growth, and it is not approved for use in breeding animals (ACC&D) 2013.

F. Anti-Androgens, Anti-Estrogens, and Aromatase Inhibitors

These compounds interfere with the synthesis or receptor binding of sex hormones such as testosterone and estrogen.

- While extensively studied in human medicine, their application in veterinary population control is limited due to concerns about cost, delivery methods, and species specificity (Reissmann *et al.,* 2000).
- However, these agents hold potential for future development in animal fertility regulation.

4.4 Chemical Sterilants For Population Control In Animals

Chemical sterilants offer a non-surgical alternative for the permanent or long-term control of animal fertility. These agents are typically administered via intra-testicular, epididymal, or systemic injection, and ongoing research is focused on developing less invasive routes, such as oral or subcutaneous delivery.

A. Zinc Gluconate

Zinc-based formulations have been widely explored for direct intra-testicular injection to induce testicular degeneration and permanent infertility.

- Commercial products have included:
- Neutersol® (2003, USA) – later withdrawn
- Esterilsol® (2007, Latin America) – used in Mexico, Panama, Bolivia, and Colombia
- Infertile® (2009, Brazil) – combination of zinc gluconate, L-arginine, and DMSO
- Zeuterin® (2013, USA) – achieved 72% success rate in permanent sterilisation
- Talsur® (1991, India) – developed by the National Institute of Immunology, later withdrawn due to limited efficacy and excessive testicular swelling
- In a study involving 11 male dogs, intra-testicular injection of 26.2 mg/mL zinc gluconate with 0.5% DMSO resulted in histological changes consistent with permanent infertility. The treatment was found to be safe, effective, and did not cause behavioural changes or significant discomfort (Soto *et al.,* 2009)

B. Calcium Chloride

Calcium chloride is another low-cost sterilising agent used for intra-testicular injections.

- In a trial involving 24 stray male dogs, single-dose injections of 5, 10, 15, or 20 mg led to significant testicular shrinkage, decreased sperm count, and reduced testosterone levels.
- The 15 mg and 20 mg doses were the most effective.
- Mild testicular swelling was observed within 24 hours post-injection, peaking at 48–72 hours, and resolving within three weeks.
- Histological analysis revealed complete necrosis of seminiferous tubules and Leydig cells, replaced by fibrocollagenous tissue, confirming permanent sterilisation (Jana *et al.,* 2007)

C. Chlorhexidine Digluconate (CHD)

CHD, with or without DMSO, has been explored as a chemical sterilant since the 1980s.

- A 5% CHD solution, injected into the testicular parenchyma or epididymis, has been shown to produce effective nonsurgical sterilisation in both dogs and cats.
- This method caused no significant local or systemic side effects, making it a promising alternative to traditional castration procedures (Pineda and Hepler 1981; Aiudi *et al.,* 2010)

D. Vinylcyclohexene Diepoxide (VCD)

VCD has shown potential as a chemical sterilant for female dogs by accelerating the depletion of ovarian follicles, leading to ovarian failure and permanent infertility.

- In an experimental study, 8 puppies (12 weeks) and 8 young female dogs (6 months) were administered 80 mg, 160 mg, or 240 mg of VCD for six consecutive days.
- On day 30, ovarian histology revealed a significant reduction in primordial follicle count compared to controls, supporting its potential for non-surgical female sterilisation (Mayer 2006).

E. Hypertonic Saline

A study conducted on 40 laboratory rats compared the effects of 20% hypertonic saline injection into the testes with traditional orchiectomy.

- After 30 days, rats treated with hypertonic saline showed mild testicular atrophy and testosterone levels comparable to castrated rats.
- No adverse effects were observed, and the epididymis remained histologically unaffected, suggesting this method could be a viable chemical alternative to surgical castration (Emir *et al.,* 2010).

4.5 MISCELLANEOUS ADVANCES IN ANIMAL POPULATION CONTROL RESEARCH

This section highlights innovative and experimental approaches being explored for controlling animal reproduction without surgery, particularly in stray and wild animals.

A. Gene Silencing

Gene silencing represents a promising, non-surgical approach to controlling fertility in animals by targeting and suppressing genes essential for reproduction. This method offers a humane and practical alternative to traditional surgical sterilisation, which is often impractical and costly for managing feral and stray animal populations (Rhodes, 2017). The technique involves selecting key fertility-related genes—such as those encoding gonadotropin-releasing hormone (GnRH), kisspeptin, or anti-Müllerian hormone (AMH)—and delivering gene-silencing agents directly to the tissues where these genes are active (Dissen et al., 2012). Tools like RNA interference (RNAi), using small interfering RNAs (siRNAs) or short hairpin RNAs (shRNAs), effectively block the production of proteins necessary for reproduction by degrading target mRNA. To ensure long-term effects, these agents are delivered using gene therapy vectors, particularly adeno-associated viruses (AAV), which are injected into specific sites such as the hypothalamus or muscle tissue, offering a minimally invasive alternative to surgery (Dissen *et al.,* 2012).

Recent breakthroughs have demonstrated the potential of this technology in animals. In one study, an AAV vector carrying the cat version of *AMH* was injected into female cats, preventing ovulation and pregnancy for nearly two years without apparent side effects (Whitcomb 2010). Similarly, experiments in rats and non-human primates showed that silencing genes like *EAP1* or *Kiss1* in the hypothalamus disrupted reproductive cycles and induced temporary infertility (Dissen *et al.,* 2012). These findings underscore the potential for gene silencing to provide a long-lasting, single-dose contraceptive that is effective in both sexes. Ongoing research focuses on refining delivery methods, identifying the most effective gene targets, and ensuring the safety and reversibility of these interventions, positioning gene silencing as a scalable and humane solution for population control in both companion and wild animals (Rhodes, 2017; Dissen *et al.,* 2012).

B. Kisspeptin and Gonadotropin-Inhibitory Hormone (GnIH)

Kisspeptin (KP) is a pivotal regulator of the hypothalamic–pituitary–gonadal (HPG) axis, discovered in 2003 as a key gateway to reproductive function in both males and females (Seminara *et al.,* 2003). Encoded by the KISS1 gene, kisspeptin peptides bind to their receptor GPR54 (also known as KiSS1R) to stimulate GnRH release from the hypothalamus, which then triggers the secretion of LH and FSH from the anterior pituitary, promoting estrous cycle progression, ovulation, and the production of sex steroids like estradiol (Seminara *et al.,* 2003; Kotani *et al.,* 2001; Clarke, 2011). Among its isoforms, KP-10 has been the most extensively tested in dogs and cats (Albers-Wolthers *et al.,* 2014; Terse *et al.,* 2021). Intravenous administration of KP-10 to anestrous bitches induced rapid increases in serum LH, FSH, and estradiol within minutes, with effects lasting up to 14 days, and showed no significant adverse effects such as changes in clinical signs, body weight, or haematological parameters (Terse *et al.,* 2021). Interestingly, both kisspeptin agonists and antagonists have demonstrated species-specific effects on reproductive hormones, suggesting therapeutic potential for both stimulation and suppression of fertility (Albers-Wolthers *et al.,* 2017; Pineda *et al.,* 2010). In other species, kisspeptin antagonists like p234 have delayed puberty, suppressed LH surges, and reduced reproductive behaviours (Albers-Wolthers *et al.,* 2017; Pineda *et al.,* 2010).

Immunisation approaches using KISS1 gene constructs or kisspeptin-based vaccines have also shown promise, reducing sexual behaviour, testicular growth, and spermatogenesis in male animals (Fan-Mei *et al.,* 2022), positioning kisspeptin as a potential target for non-surgical sterilisation strategies. However, since the kisspeptin/GPR54 pathway influences not only reproductive functions but also broader metabolic and endocrine processes (Colledge, 2009), its manipulation must be approached cautiously.

C. Targeted Cytotoxin Delivery

This method involves directing potent cytotoxic agents to selectively eliminate reproductive cells, such as sperm, egg, or hormone-producing cells, without affecting surrounding tissues.

i. **KU-AS-272 – Single-Dose Sterilant:** KU-AS-272, an anti-spermatogenic compound, has demonstrated sterilising effects in male rats after a single oral dose, with similar outcomes observed in females due to granulosa cell homology. Doses as low as 12 mg/kg resulted in complete spermatogenic cell loss (Tash and Roby 2010; Gupta *et al.,* 2012).
ii. **FSH Receptor-Ligand Cytotoxin Conjugates:** These cytotoxins target the FSH receptor, a critical fertility-related protein in both sexes, disrupting gonadal function and gamete production.
iii. **RISUG (Reversible Inhibition of Sperm Under Guidance):** RISUG® (marketed as Vasalgel™ in the U.S.) consists of styrene-maleic anhydride in DMSO. It is injected into the vas deferens or epididymis to block sperm flow and induce testicular regression. RISUG is under investigation for use in both humans and male dogs, offering a long-term, reversible sterilisation option (Chauhan and Guha 2010).

D. Retinoic Acid Receptor Antagonists

Retinoic acid (RA), a metabolite of vitamin A, is essential for spermatogenesis, the process of sperm production in the testes, by acting through retinoic acid receptors (RARs), which are nuclear receptors with three isoforms: RARα, RARβ, and RARγ (Schleif *et al.,* 2022). Among these, RARα plays a particularly critical role in male fertility by regulating several key steps: it drives the differentiation of undifferentiated spermatogonia, initiates and completes meiosis via activation of genes like *Stra8*, supports the formation of the blood–testis barrier through Sertoli cell signaling, and facilitates the release of mature sperm into the lumen of the seminiferous tubules (Zhao *et al.,* 2024). Disruption of RA signalling, such as through vitamin A deficiency or genetic knockout of RARα, results in impaired spermatogenesis and infertility (Schleif *et al.,* 2022; Zhao *et al.,* 2024).

Building on this biology, retinoic acid receptor (RAR) antagonists have emerged as promising non-hormonal male contraceptives. These small molecules, particularly those targeting RARα, block RA signalling and disrupt spermatogenesis by arresting spermatogonial differentiation, impairing spermatid alignment and release, and increasing apoptosis of germ cells, mimicking the infertility seen in RA deficiency (Al Noman *et al.,* 2020). Importantly, studies in mice demonstrate that these effects are reversible, with fertility and normal sperm production returning after treatment cessation, and without significant changes in testosterone levels (Shi *et al.,* 2025). Notable examples include BMS-189453, a pan-RAR antagonist shown to reversibly induce infertility in mice, and YCT-529, a highly selective RARα antagonist with strong oral bioavailability that nearly eliminated sperm production in animal models, with complete recovery after discontinuation. YCT-529 is currently in clinical development as a promising non-hormonal male contraceptive (Shi *et al.,* 2025).

- BDADs (Bis-(dichloroacetyl)-diamines), such as WIN 18,446, inhibit vitamin A metabolism, disrupting germ cell development (Hogarth *et al.,* 2011).
- The compound BMS-189453, a pan-retinoic acid receptor antagonist, caused abnormal sperm development, loss of alignment, and germ cell detachment, mimicking vitamin A deficiency effects in rodent testes (Chung *et al.,* 2011).

E. SPRASA (Sperm Protein Reactive with Antisperm Antibodies)

SPRASA (also known as SPACA-3 or SLLP-1) is a highly conserved acrosomal protein identified for its reactivity with antisperm antibodies from infertile men, suggesting a key role in fertility (Chiu *et al.,* 2004). Initially thought to be expressed only in sperm, SPRASA has also been detected on the oocyte membrane (oolemma), the zona pellucida, and in cumulus cells, indicating its involvement from both gametes in fertilisation (Wagner *et al.,* 2008). Studies have shown that antibodies against SPRASA inhibit sperm binding to oocytes and reduce embryonic development, highlighting its functional importance (Chiu et al., 2004). Confocal microscopy confirmed SPRASA binding sites specifically on the oolemma of bovine oocytes and strong expression in cumulus cells (Wagner *et al.,* 2008). These findings suggest that SPRASA facilitates sperm–oocyte interactions and is a promising target for understanding fertility mechanisms and developing contraceptive strategies.

4.6 HERBAL APPROACHES TO POPULATION CONTROL

The effect of an indigenous contraceptive herbal formulation consisting of a mixture of three plant species (*Lepidagathis longifolia*, *Palaquium* sp., and *Phyllagathis rotundifolia*) and the individual contraceptive herbs was evaluated in pregnant and nonpregnant rats (Sulaiman *et al.,* 2001). The water-based extract of these combined herbs was shown to impair blastocyst implantation, severely affect intrauterine fetal growth, fetal survival, and the parturition process in pregnant rats. It also inhibited endometrial decidualization and reduced estradiol and progesterone concentrations in pseudopregnant rats. Additionally, the herbs induced anovulatory oestrous cycles in rats (Bala *et al.,* 2014).

This study further suggested that the combined herbs might prevent the negative feedback induced by low estradiol and progesterone concentrations on the pituitary gland. A variety of methods, including hormonal, pharmacological, and natural alternatives, have been explored to induce infertility in animals. Among them, medicinal herbs and plant-based extracts have gained attention due to their traditional use in addressing reproductive concerns.

Contemporary studies have evaluated numerous plant extracts with antifertility properties using animal models. These natural alternatives are considered environmentally friendly, affordable, and accessible, particularly in rural and remote areas. While they tend to be milder than synthetic drugs, they are often simpler to administer and pose fewer side effects (Islam *et al.,* 2007).

The active phytochemicals present in these plants interfere with reproductive processes such as ovulation, implantation, and hormonal regulation. However, consistent daily administration is often necessary for herbal agents to maintain contraceptive effectiveness, making them more suitable for short-term or emergency contraception.

An innovative application of herbal technology involves genetically modified plants designed to reduce fertility in invasive species like rabbits, a major pest in Australia. These transgenic plants are engineered to express specific animal proteins, which act as immunogens. When consumed, they trigger an autoimmune response in the target animal—such as producing antibodies against their own eggs, resulting in infertility (Islam *et al.,* 2007).

The process involves immersing plant material in a solution containing *Agrobacterium tumefaciens*, a genetically engineered soil bacterium carrying the desired animal DNA. The bacterium transfers this DNA into the plant cells, which are then cultivated in hormone-enriched media to induce root and shoot development. Once established, these plants are transferred to soil. While the concept is promising, it is still uncertain whether the modified plants have successfully delivered contraceptive proteins to target species (Bala *et al.,* 2014).

Table 1: Some common plants with their effects on the female system

Common Name	Botanical Name	Effect	Part Used	Reference
Amaltas	Cassia fistula	Prevents implantation	Pods, Seeds	Priya *et al.,* 2012
Jamal Ghota	Jatropha curcas	Abortifacient	Fruits	Pathak *et al.,* 2005
Isabgol	Plantago ovata	Abortifacient	Seeds	Kaur *et al.,* 2011
Brahmi	Bacopa monnieri	Contraceptive	Whole plant	Priya *et al.,* 2012
Bel	Aegle marmelos	Contraceptive	Leaf	Priya *et al.,* 2012
Black Pepper	Piper nigrum	Contraceptive	Fruit powder	Pathak *et al.,* 2005
Kuppi	Acalypha indica	Antioestrogenic	Whole plant	Kaur *et al.,* 2011
Banmirchi	Croton roxburghii	Antioestrogenic	Bark	Priya *et al.,* 2012
Lotus	Nelumbo nucifera	Antioestrogenic	Seeds	Pokharkar *et al.,* 2010
Haemorrhage plant	Aspilia africana	Antiovulatory	Leaves	Priya *et al.,* 2012
Palas	Butea monosperma	Antiovulatory	Seeds	Shah *et al.,* 2009;
Peepal	Ficus religiosa	Antiovulatory	Seeds	Pokharkar *et al.,* 2010

Table 2: Some common plants with their effects on the male system

Common Name	Botanical Name	Effect	Part Used	Reference
Aloe vera	Aloe vera	Spermicidal	Latex	Gedia *et al.,* 2011
Bharangi	Clerodendrum serratum	Spermicidal	Whole plant (except root)	Pokharkar *et al.,* 2010
Giloy	Tinospora cordifolia	Reduces sperm count & motility	Stem	Kalita *et al.,* 2011
Tulsi	Ocimum sanctum	Reduces sperm count & motility	Leaves	Priya *et al.,* 2012; Kaur *et al.,* 2011
Indian Tobacco	Lobelia inflata	Reduces sperm count & motility	Stem	Kalita *et al.,* 2011
China Rose	Hibiscus rosa-sinensis	Inhibits spermatogenesis	Flower	Pathak *et al.,* 2005

5. CONCLUSION

Addressing the challenges posed by overpopulation in stray and wild animals necessitates the use of diverse and species-appropriate fertility control strategies. In India, overabundant populations of stray dogs, monkeys, wild boars, and nilgai cause significant public health risks (such as rabies and leptospirosis), agricultural damage, and ecological imbalance. Traditional measures such as culling are often controversial due.

to ethical, legal, and religious objections and have proven to be largely ineffective in the long term.

Fertility control presents a humane, non-lethal, and sustainable alternative that aligns with public sentiment and ethical standards. Unlike culling, these methods minimise harm to non-target species, prevent ecological disruption, and help reduce the spread of zoonotic diseases. Community-based sterilisation programs like the Animal Birth Control (ABC) initiative have demonstrated success in urban settings and can be adapted to broader wildlife population management.

While surgical sterilisation is the current gold standard, non-surgical methods offer practical advantages in terms of logistics, cost, and welfare. However, the only approved contraceptive products for dogs and cats, Gonazon, Suprelorin, Neutersol, Esterilsol, and Infertile, are limited in availability and use in select countries.

Emerging non-surgical contraceptive technologies under research and development include:

- GnRH agonists and antagonists
- Immunocontraceptive vaccines
- Chemical sterilants and pharmacological castration
- Genetic and molecular approaches such as gene silencing, kisspeptin/GnIH pathway modulation, retinoic acid receptor antagonists, and targeted cytotoxic agents

These approaches aim to provide long-acting, reversible, and ideally single-dose contraception that is safe and effective across various animal species. Importantly, they must be environmentally safe, economically feasible, and scalable for field use in both urban and wild habitats.

The successful development and implementation of such strategies require coordinated action among:

- Research institutions and pharmaceutical developers
- Wildlife and forest departments
- Veterinary public health agencies
- Governmental and non-governmental organisations

The vision is to establish integrated and humane fertility control frameworks that meet the population management needs of stray animals, pets, and wildlife. Ongoing investment in immunocontraceptive and sterilisation vaccine research remains vital to achieving ethical, efficient, and sustainable solutions to animal overpopulation.

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About the corresponding author

Suhana Parvin Muquit is affiliated with the Division of Physiology & Climatology at the ICAR-Indian Veterinary Research Institute, Bareilly, Uttar Pradesh, India. Her academic work focuses on animal physiology, environmental adaptation, and livestock health, contributing to research that supports sustainable animal production and improved veterinary practices in diverse climatic conditions.