Contraception and pregnancy termination in canines - a review

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Bitches are generally kept as pets. Since the occurrence of oestrus curtails normal exercise patterns of these pets and unwanted litters contribute only to the already considerable stray dog population, contraception and pregnancy termination has gained importance in recent times. The most effective, safest, least controversial and practical method of birth control in the bitch is surgical sterilization. It is permanent, has beneficial side effects, and is the most approved method. However, for many purebred animals there is a perceived if not real need for a temporary, safe, reversible method of contraception during periods of work, performance, or exhibition. Moreover, veterinarians are routinely contacted to prevent or terminate pregnancy following an unwanted breeding, although no method that is both entirely safe and fully effective has been approved for this purpose. Before contraception is instituted it is very important to furnish the owner with relevant information regarding the nature of proposed method, whether permanent or reversible, and the possible complications that may ensue.

I. Surgical contraception

This can be achieved by ovariectomy, hysterectomy, tubal ligation, salpingectomy, or ovariohysterectomy. Of these, the recommended approach to surgical sterilization in the bitch is ovariohysterectomy. Removal of the uterus, and cervix when feasible, along with the ovaries precludes any subsequent development of ovarian, uterine or cervical diseases.

Earlier authors do not recommend ovariohysterectomy prior to the first oestrous period of a bitch because of its reported association with infantile vulva and urinary incontinance[5]. However, this association is yet to be proved. Spaying of young prepubertal bitches has been proposed for several reasons including economy of time, effort and expense[1]. Since endogenous oestrogen production plays a role in the aetiology of spontaneous mammary tumours, ovariohysterectomy before the first oestrus provides a definitive protective factor against such tumours[7]. Moreover, anaesthetics pose little risk to young animals. Care should be taken to ensure that a bitch is not spayed during false pregnancy[4]. When ovariectomy is performed during luteal phase, a transient pseudopregnancy marked by extensive mammary development, lactation, and altered behavious may occur. This is probably caused by the rapid decline in serum progesterone concentrations, which initiates increased prolactin activity and lactation, as normally occurs at parturition[6].

The most common side-effect of ovariohysterectomy is subsequent obesity. Therefore, owners of bitches should be advised to weigh the dog periodically and reduce food intake and increase exercise at signs of increased body weight. Urinary incontinence is another complication. It can be controlled by administration of diethyl stilboestrol, oestradiol valerate, or medroxy progesterone acetate.

II. Medical contraception

A. Prevention and suppression of oestrus

1. Steroidal contraception

A variety of steroids has been tried to inhibit normal cyclical activity. These can be administered during anoestrus to prevent the occurrence of oestrus (prevention) or during pro-oestrus or oestrus to abolish the signs of that particular oestrus (suppression). These steroids include naturally occurring steroids, progesterone and testosterone, and a variety of synthetic steroids (progestins - medroxy progesterone acetate, clormadinone acetate, megestrol acetate, dalmadinone acetate, melengestrol acetate, proligestone, norethisterone acetate and the androgen - mibolerone). Some of these are marketed in the United States and Europe as canine contraceptives. For example, megestrol acetate (Ovaban tablets - 5mg, 20mg, Scherring corp., Kenilworth, NJ) and mibolerone (Cheque Drops, the Upjohn Co., Kalamazoo, MI). Neither is approved for use in cats.

The mechanism of action of these steroids is suppression of gonadotrophin secretion. Administration of progestins may sometimes

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promote the development of cystic endometrial hyperplasia and subsequent uterine infection, mammary development, and post therapy lactation in dogs. Androgens may induce mild to severe external masculinization. Prolonged periods of administration of progestins can result in acromegaly, insulin resistance, diabetes mellitus, liver enlargement, gall bladder disease, and mammary tumours[6]. Attention must therefore be given to appropriate pharmacological preparation, dose, stage of cycle when initiating administration, and duration of treatment.

(i) Megestrol acetate oral contraception

Doses and duration of treatment depends on the stage of oestrous cycle of the bitch when treatment is initiated. When used in anoestrous bitches for cycle postponement the dose recommended is 0.5 mg/kg per day for 32 days. The treatment should be initiated at least 1 to 2 weeks prior to next expected pro-oestrus. If pro-oestrus had already begun a higher dose of 2.2 mg/kg per day for 8 days is required. The treatment should be initiated during first 3 days of pro-oestrus confirmed by vaginal smears (with fewer than 50 per cent of epithelial cells being cornified superficial cells). This assumes that pro-oestrus is detected early and has an average duration of 9 days[7]. Suppression of pro-oestrus occurs 3 to 8 days after the onset of treatment. Subsequent pro-oestrus in both the above treatment schedules is usually expected 4 to 6 months later. Among indications for this kind of treament are participation in dog shows and during the hunting and racing seasons. The practitioner must be aware that more difficulties can arise with the administration of progestins for suppression of oestrus than for its prevention[5].

(ii) Mibolerone oral contraception

Mibolerone, an adrogenic anabolic steroid, is effective and apparently reliable for oestrus prevention. Mibolerone acts by specifically blocking the ovulatory release of LH[5]. It is effective in preventing oestrous cycles for up to 5 years of continuous treatment, although the recommended maximum duration is 2 years[6]. Administration should begin at least 30 days prior to the next expected oestrus. Dosage is dependant on body weight and breed (Table 1).

Table 1. Dosage of Mibolerone*6

Body Weight range (Kg)	Mibolerone dosage (/ug / kg)
1-11 kg	30
12-23 kg	60
24-45 kg	120
>46 kg	180
Any Alsatian or Alsatian* derived mixed breed	180

** The reason for the higher dosage requirement in purebred or mixedbreed bitches of Alsatian is unknown*

Many side effects have been reported for mibolerone[7]. Vaginal discharge and/or varying degrees of clitoral enlargement may be expected in 15 to 20 per cent treated bitches. Overdosage can result in anal gland inspissation and associated odours. Prolonged treatment for more than 9 years can result in ovarian fibromas[15]. In pregnant animals it may cause masculinization of female foetuses and in lactating animals it may interefere with lactation[16]. It is not recommended for use in Bedlington terriers.

(iii) Non-approved and experimental contraceptive steroids

(a) Depot injectable progestins

A single intramuscular injection of depot form of medroxy progesterone acetate (MPA) maintains effective circulating levels of MPA for 3 to 6 months[7]. A suspension form of MPA was marketed as a canine contraceptive in the US until 1969, but was removed from market because of a high incidence of cystic endometrial hyperplasia (pyometra) in treated bitches. High doses of MPA in the dog may also cause mammary tumours, adrenal suppression, acromegaly and diabetes. An aqueous form of MPA may be used with fewer complications[13]. This should be given subcutaneously every 5-6 months. The minimum effective contraceptive dose of MAP is 2-3 mg/kg. Extreme care should be taken never to exceed such doses and to

limit use to one or two times as a short-term contraceptive.

MPA can also be used for suppression of oestrus. When administered orally starting 5 days before the effect is required, MPA is effective, and the treatment should continue as long as suppression is desired. Treatment is safe if it does not exceed 1 month[17].

(b) Injection of proligestone

The progestin proligestone as a depot injectable canine contraceptive at a dose rate of 10 to 30 mg/kg should be injected subutaneously. Subsequent injections are given at 5 month intervals. Many of the problems associated with other progestins are also seen with proligestone. When administered in pro-oestrus this results in the disappearence of heat signs within 5 days. Retreatment after 3 months maintains oestrus prevention in most bitches[18].

(c) Testosterone injections

Weekly administration of testosterone propionate (110 mg/week) has been tried in greyhounds to prevent oestrus. Anabolic effects of testosterone may account for the high rate of use as a contraceptive in racing greyhounds. Oral testosterone has also been used (25 mg methyl testosterone, weekly) for 5 years. Virilizing side effects are common.

(d) Steroid hormone implants

Silastic capsules filled with either testosterone or progesterone, when placed subcutaneously, release hormone for long periods of time resulting in persistent anoestrus. Such implants are unlikely to be made available commercially because they are not biodegradable and are relatively large and their insertion and removal requires minor surgery.

(e) Induction of asexuality

Efforts to produce sterile female puppies by injection of androgens and progestogens within 48 h of birth have not been successful[19].

2. Nonsteroidal contraception

(i) Irradiation

There is at present insufficient knowledge of the value of single dose irradiation as a method of treatment of prepubertal puppies but this may provide a practical procedure for controlling fertility in the future

(ii) Devices

Vaginal devices developed as blocks to copulation are unacceptable due to problems with fitting, retention, perforation, and inflammatory reactions. Intrauterine devices are not practical in dogs owing to the difficulty in cannulating the canine cervix per vagina.

(iii) Immunization

Immunization against GnRH or LH can have a contraceptive effect in dogs. Immunization with zona pellucida protein prepared from porcine oocytes has been reported to have limited efficacy. To date, no contraceptive immunization protocol for bitches has warranted large-scale clinical trials.

(iv) Long-term GnRH agonist administration

Constant administration of high doses of a GnRH agonist results in down regulation of pituitary GnRH receptors and causes suppression LH and FSH secretion. Field trials have not been reported.

B. PREVENTION OF IMPLANTATION

Following an undesirable mating (misalliance), conception may be prevented in the bitch by administration of high doses of oestrogen. Oestrogens are useful because they affect the Ovum's (Zygote's) passage through the oviducts and they alter the endometrium. The effect of oestrogen on ovum transportation is dose dependent. Lower doses enhance passage and the normal ampullary-isthmic delay is abolished. Higher doses delay the passage of ovum into the uterus and result in degeneration of embryos. In addition, they tend to prevent the normal endometrial glandular changes for nidation[1].

Many bitches given oestrogen to prevent pregnancy subsequently develop cystic endometrial hyperplasia and pyometra. It can also result in bone marrow suppression, aplastic anaemia, thrombocytopenia, internal haemorrhage and death. Therefore, if preservation of the animal's reproductive function is important, the owner should be

counselled to allow the unwanted litter to

be born. It should be pointed out that having a mongrel litter will not affect the pedigree of future litters by the involved bitch. We should also consider the fact that more than 50 per cent of bitches presented for misalliance are not pregnant.

(i) Oestradiol cypionate

In canines, oocytes remain in the uterine tubes until 1 to 3 days after the onset of cytologic dioestrus as determined by vaginal smears. Thus, the oocytes remain susceptible to a transport-delaying effect of oestrogen until this period. Therefore, only if a vaginal smear suggests that the bitch is truly in oestrus or early dioestrus should oestradiol cypionate be considered[6]. Oestradiol cypionate administration should be performed during oestrus and after ovulation to be most effective and not during pro-oestrus. Administration should be avoided after the end of cytologic oestrus in order to reduce the incidence of iatrogenic uterine disease[5]. No more than a single injection should ever be considered[1]. It should be given IM at a dose of 0.02-0.04 mg/kg to a maximum of 1.0 mg per bitch. The client should be informed of potential side effects, the likelihood of prolonged drug induced oestrus, the danger of a second injection, and the need to bring the dog after 4 weeks for pregnancy diagnosis and uterine evaluation.

(ii) Diethylstilboestrol (DES)

Successful use of oral therapy with stilboestrol given on a daily basis at a rate of 5 mg, commencing during oestrus and continuing for 21 days or until recommencement of vaginal bleeding has been suggested[8]. This ensures almost 100 per cent effect but the high dose could result in complications of hyper-oestrogenism. The advisable dosage of oral silboestrol is 0.1 mg/kg daily for 5 days begining within 48 h of mating[1].

(iii) Oestradiol benzoate or valerate

Oestradiol benzoate or valerate is recommended at a dosage of 0.1 mg/kg IM (not to exceed a total dosage of 3.0 mg).

C. TERIMINATION OF PREGNANCY

1. Use of prostaglandin $F_{2\mu}$

(i) $PGF_{2\mu}$ for pregnancy termination

The 'natural' prostaglandin can be luteolytic in the bitch if administered repeatedly[10]. PGF also acts directly on the myometrium to cause uterine contractions. PGF in doses of 50 to 100 µg/kg, given twice daily until abortion occurred routinely aborted mid - to late - pregnant bitches. Efficacy also depends on injecting more frequently than once a day, because of rapid half-life of PGF. Cessation of treatment at the initiation of resorption or abortion can result with the remainder of the litter going to term.

(ii) $PGF_{2\mu}$ for mismating

Higher doses are needed to cause complete luteolysis in early pregnancy than in late pregnancy. Doses of 250 µg/kg, given subcutaneously twice a day for 4 days, terminated pregnancy in 80 per cent of mated bitches when initiated at about day 13 of pregnancy, but not if initiated earlier[11].

PGF should be used judiciously because of possible side effects. To judge the potential side effects, the first injection should be limited to a lower dose of 50 to 100 µg/kg. The transient side effects increase in severity with dosage. These can include excessive salivation, vomiting, diarrhoea, defecation, hyperpnoea, ataxia, urination, anxiety and pupil dilatation followed by constriction. Such reactions are usually seen within 5 to 30 minutes and last for less than one hour[10]. Atropine has been reported to reduce these symptoms when administered at a dose of 50 mg/kg, IM, either at the time of PGF injection or at the onset of symptoms[7]. Next oestrus is likely to occur earlier than normal. PGF 'analogs' should not be used in small animals because of the severity of their side effects and paucity of information on appropriate doses.

2. Use of corticosteroids

Daily IM administration of dexamethasone (5 mg) for 10 days from day 30 of pregnancy

resulted in intrauterine death and resorption of foetuses; an identical treatment from day 15 resulted in birth of dead foetuses on days 55 to 59 of pregnancy[2]. However, the use of glucocorticoids is not justified as a means of termination of pregnancy in small animals because of lack of more information.

3. Prolactin suppression

Bromocriptine is an ergot alkaloid and dopamine agonist that reduces prolactin secretion in the dog. Bromocriptine administered orally or parenterally is luteolytic and thus abortifacient following multiple administrations after day 30 of pregnancy[7]. Treatment with 100 µg/kg twice daily after day 35 is likely to be effective if administered until pregnancy termination is confirmed. Bromocriptine administration results in emesis, lethargy, and inappetence.

Cabergoline, a more potent dopamine agonist marketed for veterinary use in Europe is reported to have fewer side effects than bromocriptine and can be used for termination of pregnancy in bitches[12].

4. Other agents

Oral or parenteral administration of epostane results in a decrease in the production of progesterone, when given orally (50 mg/dog/day) for 7 days, starting on the first day of dioestrus as determined by vaginal cytology[9]. It will also terminate pregnancy when administered later in gestation without any adverse side effects. However, additional trials on safety, efficacy, and dose requirements in dogs of various sizes and breeds are still needed.

GnRH antagonists and anti-progestins (eg: mifepristone; Ru-486) can be used for pregnancy termination[6]. The commercial availability of these for veterinary use is unlikely in the near future perhaps due to the controversy surrounding the potential use of such compounds for human fertility regulation.

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