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Original Research Article

Efficacy, safety and interval from end of treatment to estrus in cats treated with an ultra-low dose megestrol acetate protocol for suppression of reproductive activity

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ABSTRACT

Cat breeders need safe, predictable and fully reversible temporary control of reproduction in queens. Megestrol acetate (MA), a short-acting progestogen was investigated in this study designed to determine whether low-dose treatment is both effective and safe in cats for periods up to 6 months. Twenty-eight queens were treated orally with 11.5 μg/kg/day of MA for one to six months. A physical examination, vaginal cytology, and reproductive ultrasound were performed before, during and after treatment, whilst urinalysis and hematological/biochemical tests, including progesterone assay, were performed before and after treatment. MA suppressed reproductive function effectively in 27/28 queens. Transient mammary and uterine hyperplasia were detected in four (14 %) and three (11 %) queens, respectively, treated for more than four months, without associated clinical signs. Pyometra was observed in only one queen following her first estrus cycle post-treatment. Significant but reversible weight gain was observed in 85 % of the animals. The resumption of cyclicity occurred on average 6 weeks after the end of treatment but was influenced by the duration of treatment and seasonality. An ultra-low dose MA treatment was effective in suppressing estrus in queens treated up to 6 months. Close monitoring should be paid to queens treated for longer than 4 months as the incidence of side effects, albeit minor and manageable, increases thereafter. Mammary gland assessment and progesterone assay are indispensable before treatment. Fertility is preserved, making MA a valuable option for temporary control of reproductive activity in queens, who otherwise cycle continuously leading to both unwanted behavior and pregnancies.

1. Introduction

Within the cat breeder fraternity there is a need for safe, predictable and fully reversible temporary control of reproduction in breeding queens. Cat breeders have to control breeding to comply with the regulation to limit the number of litters for each queen to three litters in two years. Compliance to this regulation by the international feline breeding organization is a prerequisite for registering the litter and the issuance of pedigree certificates [1]. During the breeding season, queens persistently cycle if not mated leading to unwanted estrus behavior such as vocalization and urine spraying [2]. Furthermore, such queens usually lose condition and for these reasons cat breeders seek safe options for temporary estrus control. Lastly, reversible estrus control allows few select undecided owners of intact queens to postpone the decision of permanent surgical sterilization [3]. For all other cats not intended for breeding where permanent sterility is desired, surgical sterilization (gonadectomy) should still be considered the primary approach because of the difficulty in keeping intact female cats in a home setting. This is despite strong evidence of obesity (which should be controlled by calorie restriction) and some evidence of potential long-term other health detriments associated with gonadectomy in queens such as orthopedic diseases and increase of overall risk of tumor

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development [4,5].

Temporary sterility and or estrus control in queens can be achieved by pharmacological methods and can be short term or long term, depending on duration of efficacy and the dosage regimens for the various pharmacological options. For cat breeders, the ideal estrus control method is one that can control estrus for a period of choice and has a predictable time to return to estrus with normal fertility following cessation of the estrus suppression. Currently, the only safe and proven reversible pharmacological option for long term reproduction control in queens is deslorelin, a GnRH agonist which is highly effective and has no non-reproductive adverse effects. The duration of efficacy of deslorelin averages 22 months but is highly variable and unpredictable (range 16–37 months) [6]. Ovulation and fertility are restored once the implant has outlasted its efficacy or the implant is removed with queens producing normal litter sizes afterwards [6,7]. When the implant is removed before its efficacy has been outlasted, time to return to estrus is short albeit variable (3–7 weeks) [8]. Furthermore, the removal of the implant requires anesthesia, prompting many breeders to opt for less invasive options of estrus suppression. Deslorelin is only registered for male cats and the use in queens is off-label [9]. Some immuno-contraceptives such as vaccines against GnRH, luteinizing hormone (LH), zona pellucida proteins and sperm antigens are interesting future prospects for long term reproductive control in queens but currently their efficacy is limited and they are not yet available for clinical use [9–11]. Another future prospect under investigation is a feline Anti-Mullerian hormone transgene delivered by a viral vector [12].

The short term medical options include melatonin and a variety of progestogens [9–11]. Melatonin is a neurohormone secreted in a circadian rhythm with the highest concentrations during periods of darkness [13]. Decreasing photoperiod results in high endogenous melatonin concentrations, suppressing estrous cyclicity in female cats. Therefore melatonin, either orally or in the form of a subcutaneous implant, can induce anestrus in queens. The duration is shorter compared to deslorelin, highly variable [14] and characterized by a significant frequency of ovulation induction [15]. Estrous cyclicity returns to normal about 21–40 days after the end of treatment [16]. However, a huge drawback of melatonin in queens is that it is not effective in all queens [17].

Progestogens are analogs of progesterone that mimic their biological effect due to their affinity for progesterone receptors in the target organs, which reversibly block the hypothalamic gonadal axis and suppress the estrous cycle, securing subsequent fertility [18]. These drugs offer the possibility for cat breeders to respect breeding regulations, suppress unwanted estrus behavior during periods they wish not to breed, avoid undesired matings and better plan upcoming breedings, which in turn raises health standards for breeding queens. Progesterone-based drugs were approved in many countries across the world for temporary reproductive control in queens. The products on which comprehensive data regarding dosages, side effects and duration of therapy are available were MA, medroxyprogesterone acetate, proligestone, levonorgestrel and chlormadinone acetate [18]. Unfortunately, in many countries, progestogens have been withdrawn from the market and veterinarians wishing to use them need to have products compounded and use them off-label. The withdrawal of progestogens by the pharmaceutical industry may have been spurred by many reports of the adverse effects of endocrine nature such as adrenocortical suppression, hyperglycemia and finally diabetes mellitus due to stimulation of glucocorticoid receptors and growth hormone secretion [19–21]. Particularly, the diabetogenic properties of progestogens in dogs and cats may have aided in engendering negative publicity regarding use of progestogens within the veterinary fraternity. The severe and potentially life-threatening adverse effects of progestogens, when used incorrectly at very high doses, require discussion. Reports on the extra label uses of progestogens made veterinarians across the world aware of their glucocorticoid properties and their efficacy in some integumentary conditions in cats such as flea-allergy dermatitis, miliary eczema, perineal hair loss, neurodermatitis and eosinophilic granuloma or rodent ulcer [22,23] and anecdotally, for inflammatory bowel disease. This, together with reports on good results of progestogen treatment in cats for unwanted behaviors such as spraying, roaming and fighting, led to an era of the extensive use of progestogens in both male and female cats, intact or neutered [24]. The dosages used in practice were in most instances extraordinary high, constituting misuse [18]. Another contributing factor that led to negative reflection on the uses of progestogens in general was that they were often used in combination with long acting corticosteroids leading to a substantially increased risk of developing diabetes mellitus in treated dogs [25,26] and cats [27]. From the above it is clear that a substantial proportion of subjects treated with progestogens, and in many cases concomitantly also with corticosteroids, were extra label misuses such for integumentary, behavioral or inflammatory conditions that have nothing to do with reproductive control for which the progestogens are actually intended and labelled. All these factors combined, aided in causing a disproportionate fear against the use of progestogens.

MA is a short-acting synthetic progestogen that binds more effectively than any other in the progestogen family to progesterone receptors albeit its lower affinity for androgen and glucocorticoid receptors [14,18]. Different protocols have been used in the past, but unfortunately most with excessively high doses [18]. However, when administered in appropriate doses and restricting the duration of treatment to select patients, it can provide effective contraception in queens with only minor side effects (increased appetite and weight gain) [28,29]. When used at high doses the development of conditions such as cystic-endometrial hyperplasia (CEH), pyometra and adenomyosis [30–33] and mammary hyperplasia (benign mammary enlargement) and neoplasia may all be increased [34–37]. For the purposes of the current study, Estropill™ (MSD) was identified as the best suited MA containing product. This is because it is an oral veterinary MA formulation marketed for controlling reproduction in queens at a low dose of 11.5 μg/kg once a day. Furthermore, its ultra low concentration of MA in liquid form, allows for accurate dosing (1 drop per 200 g body weight).

The objectives of this study were a) confirming the efficacy and short-term safety of low-dose MA for reproduction control in queens, b) estimating the time required for queens to resume estrus after treatment cessation and c) assessing fertility after treatment.

2. Materials and methods

The study was conducted on a population of adult queens presented to the Veterinary Teaching Hospital of the University of Padova, Italy, and to the Small Animal Clinic of the Veterinary Faculty of the University of Ljubljana, Slovenia by private owners and cat breeders for short-term reproduction control.

The inclusion criteria were: a) post-pubertal, b) intact, c) not in estrus or diestrus based on vaginal cytology and serum progesterone concentration below 2.0 ng/ml, d) in good general and reproductive health based on clinical exam, hematology, biochemistry and reproductive ultrasound and e) no history of reproductive or endocrine diseases.

A clinical (A) and reproductive (B) examination were performed, the latter involved assessing the external genitalia, palpating the mammary glands and the uterus and a vaginal smear. The estrous cycle stage was determined by considering the results of vaginal cytology and serum progesterone assay. The ratio between keratinized (superficial and anucleated) and non-keratinized (intermediate and parabasal) cells was used to classify the estrous cycle of each queen. Detection of >70 % of cornified cells in a slide with moderate to high cellularity was considered indicative of estrus. Conversely, a predominance of intermediate and parabasal cells and low cellularity was considered indicative of anestrus. Interestrus was defined cytologically by a mixed population of cornified and non-cornified (intermediate and parabasal) cells [38]. Blood was collected (C) from the jugular vein to perform hematology

(ADVIA 120™, Siemens, Munich and Scil Vet abc Plus + ™, GmbH, Germany), biochemistry (BT 1500™; Biotecnica, Rome and RX Daytona Plus™, Randox Laboratories Ltd, UK) and serum progesterone assay (Automated Immunoassay Analyser-360TM, Tosoh, Tokyo and Mini Vidas™, Biomèrieux, France). A reproductive ultrasound (Affinity 50™, Philips, Amsterdam and GE Logiq S7 Pro™, GE Health Care, Chicago) (D) was then performed to identify any pathological changes in the uterus and ovaries. Urine was collected (E) by ultrasound guided cystocentesis or at home from a non-absorbable cat litter, if the bladder was empty during the ultrasound examination. In the case of combative or excessively stressed queens, they were sedated using a combination of butorphanol (0.1–0.2 mg/kg), dexmedetomidine (7 μg/kg) and ketamine (1 mg/kg) administered intramuscularly. The examinations performed at each moment are represented in Table 1.

If procedures A to E did not reveal any clinically significant changes and the findings met the inclusion criteria a) to f), the cat was included in the study. If a female was clinically examined for the first time while in estrus, treatment was not initiated until all signs of estrus had disappeared, according to owners' reports. If the serum progesterone level was above 2.0 ng/ml, indicating ovulation and the queen being in the luteal phase [39,40], initiation of treatment was delayed to rule out pregnancy and prevent progesterone overexposure, (ranging from 20 to 40 days, depending on the initial progesterone level and the date of the last estrus) [40].

Estropill™ (MSD Animal Health) was administered by the owner, according to the manufacturer's instructions [41]: 5 drops per kg (1 drop per 200 g) which corresponds to 11.5 μg/kg PO SID in the morning for a duration of one to six months. The owners were instructed to administer the drops directly into the cat's mouth; if the animal did not cooperate, the owner would administer the drops along with food (a piece of bread or a few spoons of moist pâté), attempting to make sure that the animal would ingest the full portion. In case the owner could not assure daily administration of the drug approximately every 24 h due to any reason, the queen was excluded from the study. The duration of treatment for each queen was decided upon by the owner in increments of one month. Periods of treatment longer than six months were not proposed to the owners, despite the 1-year maximum duration of treatment claim by the manufacturer (Estropill™ (MSD) medical leaflet). The six months maximum duration of treatment limitation was adhered to in the current study, due to the lack of published evidence supporting the safety and efficacy of treatment even for shorter periods.

Monthly follow-up appointments and one appointment at the end of the treatment were carried out, repeating clinical and reproductive examination steps (A, B, and D), and full diagnostic procedures (A–E) at the end of treatment, respectively, to confirm the efficacy and short-term safety of the treatment. A final clinical appointment took place when the owner first noticed the resumption of signs of estrus, at which time vaginal cytology was performed to confirm the resumption of ovarian activity. At the end of the trial, owners could decide whether or not to perform surgical sterilization on their queens, in which case histology would be performed. The results of potential influences the low-dosage MA may have had in the current study on histopathology of uteruses and ovaries of the queens, will be published separately.

Sample size was calculated for obtaining ethical approval using the variable *interval of time from implant's removal and resumption of testosterone secretion* in Ferrè-Dolcet, 2020 [42], establishing a minimum of 6 individuals per group. The normality of quantitative variables, including age, body weight and time to resumption of ovarian activity (measured in days between the end of treatment and the first observed estrous signs), was tested using the Shapiro-Wilk. Variables following normal distribution (body weight and time to resumption of ovarian activity) were expressed as mean ± standard deviation (SD), whereas variables that did not follow normal distribution (age) were expressed as median ± interquartile range (IQR). The age of the queens from each university was analyzed with a Mann-Whitney test. A paired samples T-test was performed to compare body weight at different time points of the study, and an unbalanced two-way ANOVA type II was used to test the influence of seasonality and treatment duration on time to resumption of cyclicity.

The study was approved by the University of Padova Ethics Committee (Project n ° 57/2024).

3. Results

3.1. Animals

A total of 28 queens were enrolled in the study, 17 queens from the University of Padova and 11 from the University of Ljubljana (Table 2). The queens belonged to ten different breeds including European Shorthair Cats. The majority of the study population (18/28) were pure-bred queens, and this tendency was also observed within each country group (9/17 for Italy and 9/11 for Slovenia). The median age of the queens was 1.35 ± 1.4 years. Queens from Padova (1.00 ± 0.7 years) were significantly younger (p-value = 0.038) than queens from Ljubljana (1.90 ± 1.25 years). Nevertheless, the overall population was composed of young-adult queens, with 23 cats being 2 years-old or younger. Regarding living conditions, 23/28 queens were exclusively indoors, whereas the remaining 5 had outdoor access. Nevertheless, daily administration of the drug was assured by the owners. Twelve queens were part of a breeding cattery or were housed with other intact female and male cats. Six females lived with other sterilized conspecifics, whereas seven queens had no contact with other cats. Living and housing conditions could not be retrieved for 3/28 cats. Queens were treated throughout different seasons with queens initiating treatment in all months of the year except for September, November and December. Fifteen/28 queens ended treatment during the reproductive season (January to September), whereas the remaining 13 ended treatment between the months of October to December. Queen P12 received a melatonin implant five years prior to enrollment in this trial; queen P16 was treated with MA (Estropill™ 11.5 μg/kg PO SID) for a period of 30 days, 2 years before being enrolled and queen L11 was treated with 4.7 mg deslorelin acetate at 1 year of age and its contraceptive effect lasted eight months.

Seven out of 28 queens presented serum progesterone above 2.0 ng/ml at their initial appointment, therefore, treatment onset was postponed. Progesterone values before and after the end of treatment are available on Table 4 in supplementary material.

Table 1
Exams and procedures conducted for each cat during the several appointments planned in the study protocol.

Appointments	Pre-treatment	Monthly Controls	End of Treatment	Return to Estrus
Exams/Procedures Conducted	A Physical examination B Reproductive examination C Blood analysis D Reproductive ultrasound E Urinalysis	A Physical examination B Reproductive examination D Reproductive ultrasound	A Physical examination B Reproductive examination C Blood analysis D Reproductive ultrasound E Urinalysis	A Physical examination B Reproductive examination

Note: Reproductive examination included vaginal cytology and mammary gland palpation, and blood analysis comprised hematology, biochemistry and progesterone assay. Treatment would be started after the pre-treatment appointment if all the exams conducted indicated that the queen was in good health and not in estrus or diestrus. If serum progesterone overcame 2 ng/ml, treatment onset was postponed.

Table 2
Demographic data (sex, age, breed, megestrol acetate treatment duration and month of end of treatment) of the 28 queens enrolled in the study.

Cat	Age (years)	Breed	Treatment duration (months)	Month of end of treatment
P1	1	Thai	1.5	November
P2	0.6	European Shorthair	2.5	June
P3	0.6	European Shorthair	2	March
P4	1	European Shorthair	1.5	March
P5	0.7	European Shorthair	1	April
P6	1.2	British Shorthair	1	May
P7	0.8	British Shorthair	1	May
P8	0.8	European Shorthair	1	May
P9	1.5	British Shorthair	1	June
P10	1.4	European Shorthair	1.5	July
P11	1	European Shorthair	4	August
P12	6	Persian	4	November
P13	0.8	European Shorthair	4	June
P14	0.9	Bengal	5	August
P15	5.6	Norwegian Forest	4	August
P16	3.2	British Shorthair	6	February
P17	2.4	British Shorthair	6	February
L1	2.3	British Shorthair	6	October
L2	1.3	Maine Coon	6	October
L3	1.8	Maine Coon	6	October
L4	1.9	Siamese	6	November
L5	1.5	Sphynx	6	November
L6	6	Sphynx	6	November
L7	3	British Shorthair	6	November
L8	1	European Shorthair	6	November
L9	1	European Shorthair	6	November
L10	4	Ragdoll	5	November
L11	2.1	Maine Coon	5	November

3.2. Efficacy

MA was effective in 27 out of 28 queens, which exhibited behavioral and cytological signs of anestrus (Fig. 1) throughout the treatment. One queen (P14) showed typical estrous behavior (lordosis, rubbing and vocalizations) during the first month following the initiation of treatment presumably due to significant weight gain resulting in underdosage. After correcting the dosage, the queen reverted to anestrus. In general, owners reported that administering the product was straightforward, both in measuring the dose (counting drops) and delivering it to the animal (the majority of owners resorted to food). No owner reported that the animal rejected the product or the food containing it.

3.3. Safety

3.3.1. General health

All animals remained healthy throughout the treatment. The hematological and biochemical values, as well as urinalysis, were clinically unremarkable both before and after treatment. Only two queens showed hyperglycemia in the hematology before treatment, with one exhibiting also glycosuria. However, fructosamine values of this queen were within normal limits suggesting the hyperglycemia was temporary and likely a stress response. Post-treatment blood analysis was not conducted for this queen due to owner non-compliance, but the queen remained clinically healthy during and after treatment. One or more liver enzymes, including alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT), were marginally above the upper limit range in seven subjects before and in four after treatment, without any clinical significance. Creatinine kinase (CK) was expressed at high concentrations pre- (N = 4) and post-treatment (N = 3), with only one queen exhibiting high CK values at both times. The authors deemed these laboratory deviations, alongside the animals' clinical status, to be clinically insignificant.

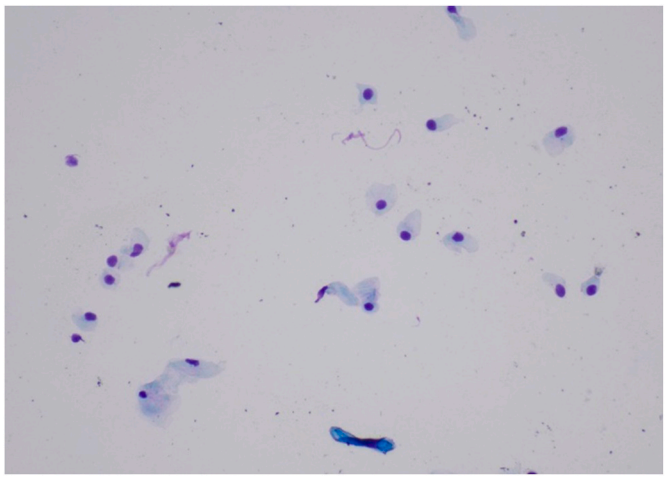

Fig. 1. Vaginal cytology of queen P13 one month after the beginning of treatment, indicative of anestrus. The cytology is characterized predominantly by non-keratinized (parabasal and small intermediate) cells in a background with presence of debris at 200x magnification.

Weight measurements were recorded at three intervals: during treatment, between the end of treatment and the first estrus, and between the end of treatment and 4–6 months later in 20/28, 10/28 and 14/28 cats, respectively and illustrated in Fig. 2. All treated cats showed an increased appetite resulting in significant weight gain in 17 out of 20 cats, with a mean increase of 0.50 ± 0.47 kg (p-value <0.001). The weight gained during treatment was gradually lost during the following 4–6 months post-treatment. Weight loss averaged 0.14 ± 0.33 kg (not statistically significant) at the first post-treatment estrus (n = 7/10), and 0.40 ± 0.38 kg (p-value <0.001) by 4–6 months after the end of treatment (n = 13/14). No statistical difference was observed between pre-treatment weight and weight 4–6 months after the end of treatment (Supplementary material - Table 3). Queens treated for 1–2.5 months were excluded from the body weight analysis and are not represented in Fig. 2 due to insufficient data availability.

3.3.2. Reproductive health

On ultrasound examination, all subjects showed normal echogenicity of the uterus and ovaries before treatment, except for queen P12, which had bilateral ovarian cysts (approximately 0.7 cm). Based on ultrasonography, ovariectomy was discussed but the owner rejected the idea as the queen had never shown any clinical abnormality and had cycled regularly until then. During treatment, the cysts remained unchanged with no clinical evidence of hyperestrogenism during the first estrus post-treatment. The queen was subsequently sterilized and histopathological examination revealed *rete ovarii* cysts. In three queens (P12, P13 and P16) treated for four or more months, ultrasound examination revealed mild uterine wall hyperplasia, evidenced by an increase in uterine diameter without fluid content or associated clinical signs. Endometrial cyst-like structures were observed exclusively in queen P16 after five months of treatment (Fig. 3). An additional ultrasound was

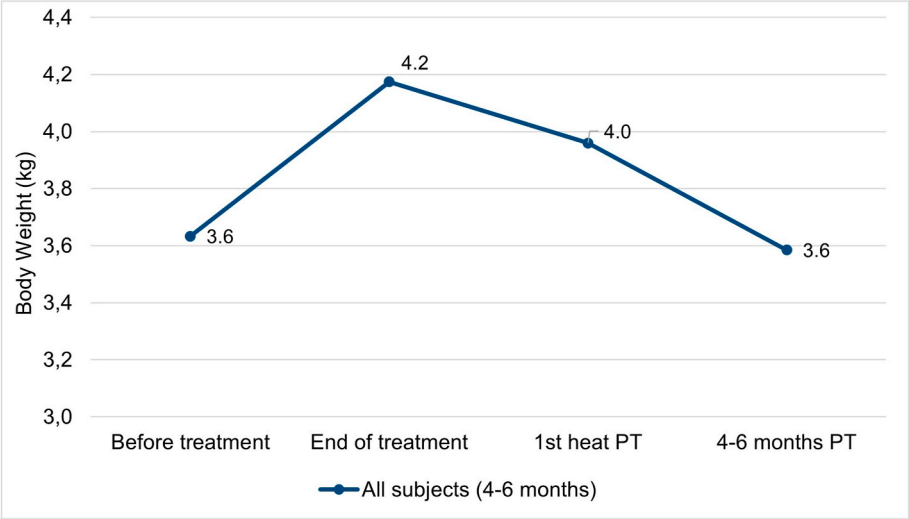

Fig. 2. Mean body weights values of 18 cats treated with megestrol acetate over a period of 4–6 months, before and at the end of treatment (N = 18), at the time first estrus/heat (N = 10) and 4–6 months after treatment (PT) (N = 13). Individual values are shown in Table 3 in the ''Supplementary material'' section.

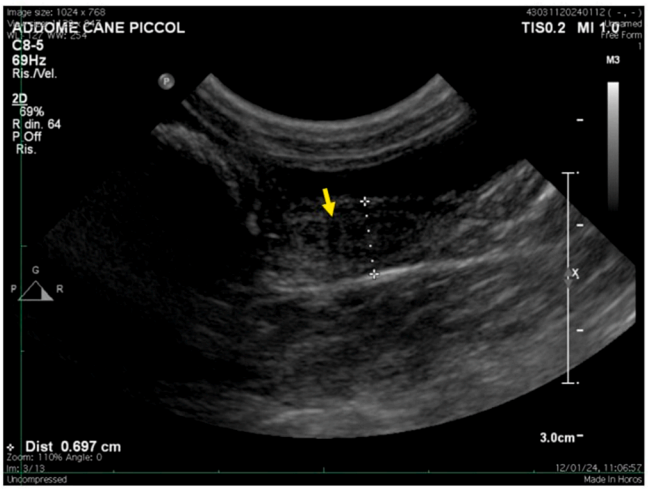

Fig. 3. Uterus of queen P16 at five months of treatment in longitudinal section. The uterine diameter is 0.697 cm. Anechoic circular structures (arrow) can be observed in the internal layer of the uterus (presumably endometrium). The uterine diameter during the first month of treatment was 0.508 cm.

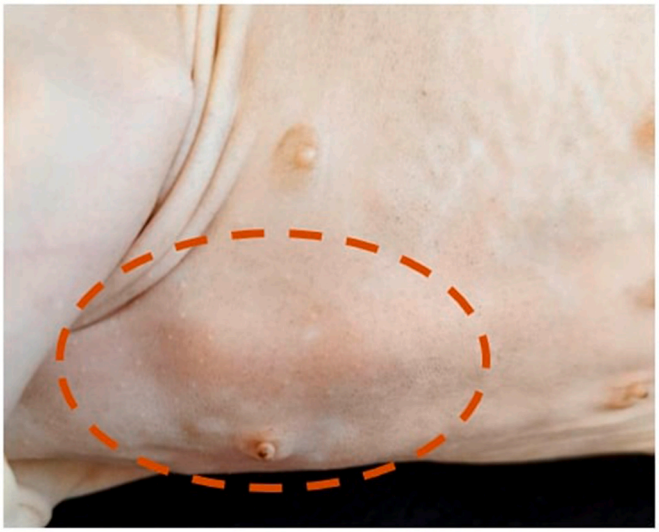

Fig. 4. Mammary enlargement in queen L5 noticed 1 month after the beginning of treatment, more evident in this figure on the left inguinal mammary gland, but present in all four pairs of glands.

performed ten days later in this queen. The cysts were no longer visible. The queen continued the treatment without any complication. In queen L4, an ovarian cyst (2.5 cm in diameter) was detected during the first estrus after treatment. Surgical sterilization was refused by the owner of this queen. Estrous behavior persisted for 34 days along with a keratinized vaginal cytology. Estrous manifestations ceased seven days after administration of hCG (500 IU IM) [43]. Estrus recurred 35 days later, at which point the queen was successfully mated. Five healthy kittens were delivered via elective C-section, after which the queen was surgically sterilized.

Mild mammary gland enlargement was observed in four queens (L5, L6, L10, and P2) during or after treatment. In queens L5 (Fig. 4), L6 and L10, a modest and painless increase in the thickness of the mammary tissue in all four pairs of glands was noted at the first follow-up examination (one month after the beginning of treatment). It persisted in all three queens, without further development, until the end of treatment and regressed after treatment was discontinued. No reproductive side effects occurred in subject P2 during treatment. However, a slight increase in the volume and consistency of the caudal abdominal and inguinal mammary pairs was noted ten days after the first estrus (39 days after the end of treatment), with no signs of pain, edema, changes in skin color, nodules or ulcers. The queen was surgically sterilized the same day without complications, and three months later all mammary glands had returned to normal.

Queen P13 was treated for four months, showing slight uterine hyperplasia on ultrasound in the last appointment during treatment. The queen came into estrus 27 days after the end of treatment, with normal estrus behavior lasting 6 days. Two weeks after the end of estrus, the queen showed purulent and bloody vaginal discharge. Pyometra was diagnosed based on clinical presentation and diagnostic imaging. An ovariohysterectomy was performed and subsequent histopathologic examination revealed cystic and atypical endometrial hyperplasia and endometritis. Corpora lutea were present in both ovaries.

3.4. Resumption of reproductive cyclicity

All queens returned to estrus, confirmed through vaginal cytology

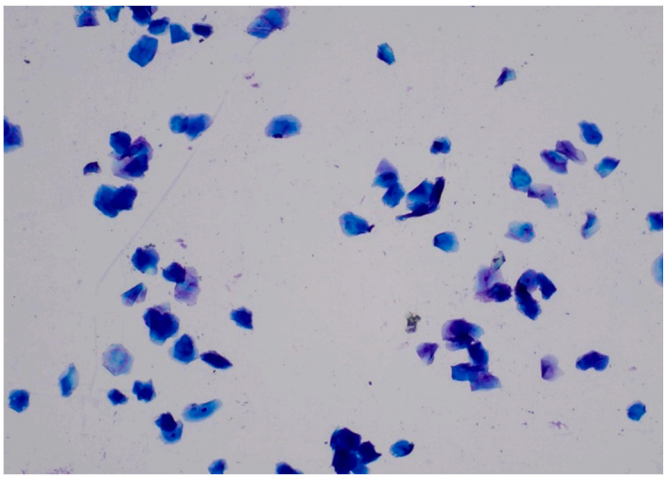

Fig. 5. Vaginal cytology of queen P13 during the first post-treatment estrus. The cytology is characterized by keratinized (superficial and anucleate) cells in a clear background. Left - 100x magnification; Right - 200x magnification.

(Fig. 5), after an average of 40 ± 20 days. Queen P15 took 184 days to show the first signs of estrus and was considered an outlier, and therefore not included in this particular calculation. The number of days between the end of treatment and the first estrus increased significantly (p-value = 0.027) with the duration of treatment: under 3 months: 22 ± 10 days (N = 10); 4–5 months: 46 ± 21 days (N = 6); and 6 months: 53 ± 16 days (N = 11) (Fig. 6).

The time until ovarian resumption tended to be shorter, 27.9 ± 17.0 days, in the queens whose treatment ended during the reproductive season (January to September) than during the seasonal anestrous period (October to December), 56.18 ± 12.3 days, (p-value = 0.072). The interaction between the two variables (treatment duration and seasonality) was not significant.

Estrus behavior, duration and cytological patterns were normal in all queens, except for L4 (duration of estrus due to ovarian cyst). Follow up examination after treatment was possible in 14 queens. Twelve queens (P2, P3, P4, P5, P10, P11, P12, P13, L4, L6, L10 and L11) were surgically sterilized. Nine queens (one treated for 1.5 months and eight treated for 6 months), were mated and produced litters. P1 was mated during her second estrus after treatment and gave birth to four kittens without complications. P16 became pregnant on her first estrus after treatment, while P17 only became pregnant on her second estrus after treatment. In both cases, five live healthy kittens were born naturally. L4 delivered five kittens and subsequently underwent ovariohysterectomy. Queens L1, L7 and L9 were mated during their second estrus, giving birth to five, three and two kittens, respectively, whereas queens L2 and L8 queened four and three kittens, respectively, after being mated during their first post-treatment estrus. Only queen L11 did not become pregnant after having been mated only on the second estrous cycle following treatment. She was subsequently spayed and no macroscopic ovarian or uterine pathology could be observed.

4. Discussion

This study aimed to evaluate the efficacy and safety of an ultra-low dose MA protocol for short term (≤6 months) reversible reproduction control in queens. The results in the current study demonstrate that MA can be used both safely and effectively for periods up to six months at doses approximately ten times lower than those previously reported [18].

The minor laboratory deviations found in some cats are not attributed to the drug as they were observed both pre and post-treatment but are likely the result of acute stress (hyperglycemia), physical constraint [44] and intramuscular injection [45] for sedation (CK). The drugs used for sedation, specifically dexmedetomidine, may exert an effect on glucose homeostasis, but in the present study this was not responsible for the hypoglycemia in the two queens. Blood sugar levels increase 60 min after intramuscular injection of dexmedetomidine [46], yet the blood was collected within half an hour from the sedatives' administration.

When administered at the appropriate dosage, the physiological side effects of progestogens in healthy cats are generally transient and clinically insignificant. These include endometrial and mammary parenchymal hyperplasia, a slight decrease in adrenocorticosteroid secretion, increased prolactin and growth hormone secretion, mild anti-insulinic effect [27], increased appetite and weight gain [29]. In our study, MA caused significant weight gain in 85 % (17/20) of the treated queens for which body weight values were available. All animals returned to their original weight within four to six months after treatment. No clinical or laboratory abnormalities were associated with the weight gain. Increased appetite and weight gain are a consistent feature of progestogen treatment and therefore owners should be informed accordingly and advised on the necessity of restricting the queen's calory intake.

Mammary and uterine hyperplasia were observed in some queens in this study. Mammary gland hyperplasia was also observed in another study in all queens treated with progestogens [47], compared to 14 % of

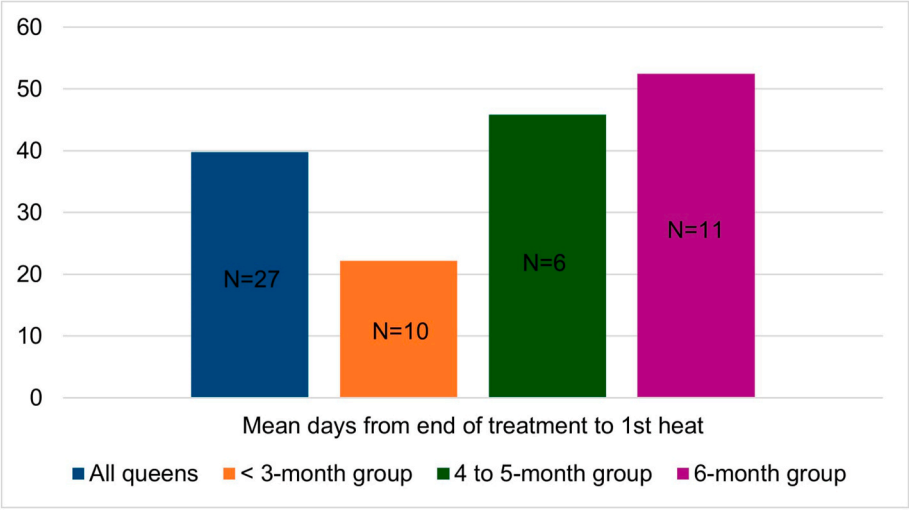

Fig. 6. Interval from the end of treatment until ovarian resumption, in days, in queens treated with megestrol acetate for less than 3 months–6 months.

queens in the current study. The progestogen used was medroxyprogesterone acetate which has a long-acting effect being administered subcutaneously in a single treatment at 50 mg/cat. Mammary gland hyperplasia was noticed 30 days after treatment and at 90 days had regressed. Similarly, in the current study, the queens in which mammary gland hyperplasia developed, resolved shortly after treatment cessation. Queen P2 did not exhibit mammary gland hyperplasia until after the first post-treatment estrus. Although a serum progesterone assay was not conducted at this stage, it is evident that this queen had ovulated, whether spontaneous or induced. When bound to their ligand, progesterone receptors in the mammary gland stimulate the local synthesis of growth hormone and insulin-like growth factors in epithelial cells, resulting in pronounced anti-apoptotic, mitogenic, and proliferative effects (Mol et al., 2012; Payan-Carreira, 2013). Mammary parenchymal enlargement in queen P2 may have been due to a delayed effect of the progestogen treatment, endogenous progesterone secretion following ovulation, or a combination of both factors. After ovariectomy, the hyperplasia resolved, further supporting the probable contribution of endogenous progesterone to this condition rather than MA. The mammary hyperplasia noticed in the 4 queens was clinically different from feline mammary hypertrophy [48,49] being very slight. It rather resembled the mammary enlargement characteristic of pseudopregnant dogs, even though symptomatologic pseudopregnancy is not recognized in cats. Yet, progesterone (endogenous or exogenous) seems to have been the trigger for mammary hyperplasia as it occurs with mammary hypertrophy. The management of these conditions depend on the removal of the progesterone stimulus and, as observed, hyperplasia waned off after the end of treatment. No evidence suggests that mammary hypertrophy increases the risk of mammary neoplasia [48,49]. Uterine hyperplasia was noted in 3 out of 18 queens treated for four months or longer. The increase in uterine wall thickness was not clinically significant. Uterine hyperplasia, specifically cystic endometrial hyperplasia facilitates pyometra [50]. Although in 3/4 cases uterine hyperplasia regressed spontaneously, one queen (P13) developed pyometra after MA treatment had stopped and the queen had completed her first estrus post-treatment. This queen ovulated spontaneously pre- and post-treatment and would likely continue to do so if an ovariohysterectomy had not been performed. Three additional queens also ovulated spontaneously prior to treatment, with no complications observed during treatment or afterwards. Although, the combined effect of exogenous and endogenous progesterone may increase the risk of reproductive side effects associated with progestogen treatment on the uterus, it remains speculative whether queen P13 would have developed a pyometra even in the absence of exogenous progesterone. Notwithstanding, it is known that spontaneous ovulation expedites the insurgence of pyometra, increasing the number of occasions of exposure to progesterone [39,51]. Thus, in case the queen was a consistent spontaneous ovulator, it is likely that pyometra would have occurred even without the progestogen stimulus. Queen P13 lived exclusively indoors and had no animal cohabitants. Since the incidence of spontaneous ovulation seems to exceed one-third of the intact female cat population [39], it is crucial to assess serum progesterone levels before administering MA, so that treatment is not started in queens who are already subject to the effects of endogenous progesterone. This is particularly important in breeding catteries, since the presence of tomcats and other non-copulatory stimuli even from females can increase the incidence of spontaneous ovulation [52]. It may therefore be of benefit to isolate queens destined for MA treatment from olfactory, auditory and visual contact with intact toms some time beforeand after treatment if practical. Prior to initiating treatment, apart from progesterone assay, history collection and thorough physical examination including mammary gland palpation are crucial. If there are no financial constraints, a reproductive ultrasound is advised particularly in older queens or in case of repeated treatments. Hematology and serum biochemistry were performed in this study to assess the safety of the protocol but are not strictly necessarily before treatment if the queen is deemed clinically healthy. The price of the product along with the necessary examinations to ensure its safety, was deemed affordable by most owners.

Queen P14 displayed estrous manifestations during MA administration, confirmed through vaginal cytology. This queen gained 1.9 kg during treatment. The drug's reduced efficacy may be attributed to underdosage caused by the weight increase after commencement of treatment regimen. After the dosage was adjusted to account for the new weight, the queen returned to anestrus. Inconsistent dosing, particularly underdosing, can impact the drug's efficacy. This underdosing case suggests that the dosage employed is close to the minimum effective dose. Likewise, lack of owner compliance in daily administration of the drug can be detrimental for treatment's efficacy. The drug has a high absorption rate and daily administration is necessary to maintain effective pharmacological activity.

For a variety of practical constraints (inability to control food intake, exposure to other species) MA has no role to play in controlling free roaming cat populations although it has been used with some success in managing cat colonies [18]. However, in breeding programs of select wildlife species, reversible suppression of estrus using MA deserves investigation.

The time it took for estrus to resume after MA treatment was significantly influenced by the treatment duration, with longer duration of treatments determining longer intervals until the resumption of reproductive activity. Additionally, queens tended to return to estrus more quickly when treatment ended between January and September, coinciding with the seasonally reproductive period in the northern hemisphere. The relationship between seasonality and the interval until return to estrus might reach statistical significance with a larger sample size. Post-treatment fertility does not appear to be influenced by treatment duration, as queens treated for both shorter and longer periods (one to six months) successfully mated and conceived during their first post-treatment estrus cycles.

Queen P15 was considered an outlier regarding the time to resume reproductive activity. This queen ended treatment in August 2023, but the first signs of estrus were only observed in February 2024, over six months later. However, subject P15 was housed in an outside enclosure and not checked frequently or thoroughly by the owner, which may have hindered proper heat detection.

Of the 28 queens studied, eight developed reproductive side effects. Most (7/8) were reported in queens treated for periods of four or more months: mild uterine hyperplasia in three queens (one developed pyometra more than one month after the end of treatment); prolonged estrus caused by ovarian cysts (successfully treated with hCG) in one queen and mild mammary hyperplasia in three queens, although it was detected after the first month of treatment. Queens treated for up to four months did not develop any side effects correlated with MA treatment, confirming that low-dose treatments of four months or less are not associated with side effects [18]. Clinical follow-ups with mammary gland assessment and ideally reproductive ultrasound every two to three months in the first 6 months post-treatment are optimal for queens treated for 4 months or more, in order to predict or early diagnose any additional side effects. Despite the moderate incidence of the above side effects, from which 6 out of 8 resolved spontaneously, further studies are needed to establish the safety of a four to six-month treatment duration and whether a lower dosage or longer durations of treatment can be considered. The same applies to repeated use of the ultra-low dose MA protocol. Although the manufacturer states that the treatment can be repeated given that the break between treatments lasts at least as long as the duration of treatment, no safety studies are available to backup this claim. As the incidence of side effects increases with the duration of treatment, it is likely that the same trend is observed with several treatments. Further research is necessary to demonstrate the safety of extended and repeated use of MA before advocating for it. Regarding queens treated for periods longer than four months, it is of great importance to closely monitor them after the fourth month of treatment and in the following year for possible signs of pyometra or mammary

gland changes and to perform scrupulous examination before initiating another hormonal treatment.

5. Conclusion

Ultra-low dose MA treatment was effective and safe in suppressing cyclicity in all ten queens treated for up to four months of duration. Apart from a single case that developed pyometra at her first estrus cycle following treatment, side effects observed in the other seven queens (uterine hyperplasia, mammary gland enlargement and a case of ovarian cysts) were mild, short-lasting and did not hinder post-treatment fertility. The remaining 10 queens treated for 4 months or longer did not develop reproductive side effects A clinical and reproductive examination, including palpation of the mammary glands, and a progesterone assay should be performed prior to treating a queen with an 11.5 μg/kg dose of MA. Previous or current endocrine or reproductive problems must be ruled out. Weight gain should be expected during treatment and should be controlled by adjusting the food intake during treatment in cat breeding establishments. For those cases in which weight gain is not controlled, MA dosage should be adjusted accordingly. Cyclicity resumes on average about 6 weeks after the end of treatment but is dependent on the duration of treatment and might be influenced to some extent by the season in which treatment is discontinued. Queens are fertile from the first estrus after treatment and queening of healthy kittens proves the complete reversibility of the drug even after 6-month duration. Medical contraception with a dose of 11.5 μg/kg dose of MA offers an interesting possibility for reversible and short-term suppression of reproductive activity in queens, provided that patients are carefully selected and monitored. The current study proves that the judicious use of MA at a low dose of 11.5 μg/kg in queens to suppress estrus for four months is effective, safe with a predictable interval from end of treatment to return to estrus and normal fertility is maintained post treatment.

CRediT authorship contribution statement

Maria Pereira: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Anna Grassi:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Maja Zakošek Pipan:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Data curation. **Giulia Contato:** Writing – review & editing, Methodology. **Giada Dal Ponte:** Writing – review & editing, Methodology, Data curation. **Anna Ghezzo:** Writing – review & editing, Methodology, Data curation. **Kurt.G.M. De Cramer:** Writing – review & editing, Writing – original draft. **Stefano Romagnoli:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Ethical approval

This study was approved by the University of Padova Ethics Committee (Project n ° 57/2024).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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