COURSE OF UTERINE INVOLUTION AND THE LEVEL OF PROGESTERONE IN BITCHES WITH ENDOMETRITIS-PYOMETRA COMPLEX TREATED WITH AGLEPRISTONE

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Abstract

The aim of the study was to estimate the uterus involution and progesterone level after antigestagene therapy in 12 bitches with a closed form of endometritis-pyometra complex (EPC). The bitches were of pure and mixed breeds, between 2 and 13 years of age. All the animals were treated with the same pattern: aglepristone was administrated at the dose of 0.33 mL/kg, s.c. on days 1, 2, 7, and 14. Additionally, amoxycyline was given at the dose of 1 mL/10kg, s.c. every 48 h for 10 d. Complete elimination of pus masses and uterus involution were observed after 7-14 d of the treatment. Progesterone concentration was highly increased at the beginning of the treatment and was decreasing to low values during the first week of the therapy. Detectable uterus changes in the USG examination and physiological health status are not the only recovery criteria, but, most importantly, lack of recurrence of the EPC and the ability to deliver healthy progeny.

Key words: bitches, endometritis-pyometra complex, aglepristone, uterine involution, progesterone.

Conservative treatment of endometritis-pyometra complex (EPC) with aglepristone is becoming more and more the widespread therapeutic method (4, 5, 7, 9, 10, 13, 14, 17-19). However, in spite of the growing number of reports on that subject, the exact working mechanisms of that substance are still not fully explained. What makes an important mechanism of recovering is the contraction process of the uterus, which includes opening the cervix and evacuation of its content. A significant percentage of EPC cases occurs during the metoestrus phase of the oestrus cycle in bitches, during which progesterone becomes the dominant hormone (3, 4, 6, 8, 11). That hormone causes the block of uterine contraction activity, closing the cervix and intensifying secretion from endometrial glands (1, 6, 8, 11, 15). Such progesterone activity, combined with bacterial infections, make a crucial element of aetiopathogenesis in that disease (1, 2, 6, 7, 11, 15). The conservative treatment of EPC with antigestagens consists mainly of the eradication of the biological effects caused by progesterone. Data on the level of that hormone and the course of uterine involution process during therapy are rare and partially contradictory (4, 5, 8, 14, 18).

The aim of the study was to identify the course of uterine involution and the level of progesterone in the aglepristone therapy of bitches with EPC in its closed form confirmed during an ultrasound examination.

Material and Methods

The research material consisted of 12 bitches of various breeds, as well as cross-breeds, weighing from 6 to 32 kg, and aged 2 to 13 years. Based on their medical history (disorders in general health status, apathy, low appetite, polydypsia, enlargement of abdominal cavity, temporary small purulent-haemorrhagic vaginal discharge in some cases), general clinical examination, and laboratory findings (leukocytosis and increase in hepatic index - alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase) as well as ultrasound examination, the animals were diagnosed with a closed form of EPC. In the ultrasound examination, a closed form of pyometra was confirmed when significantly-enlarged uterine horns filled with liquid content occurred. Eleven animals were in the phase of 3-6 weeks after their last oestrus and one - a 13-year-old bitch - was in her last oestrus about 48 weeks before symptoms of EPC occurred. None of the animals had been administered hormonal therapy before.

All the bitches were subjected to the same treatment procedure, including administration of aglepristone (Alizine, Virbac®) in a dosage of 0.33 mL/kg. b.w., s.c., on days 1 and 2 in a 24-h interval, and then on days 7 and 14. Moreover, amoxicillin (Clamoxyl, Pfizer) was applied systemically in a dosage of 1 mL/10 kg. b.w. s.c., every 48 h for 10 d.
During aglepristone administration, all the animals were subjected to general clinical examination, ultrasound examination of their uteruses, and measurement of levels of progesterone.

For the ultrasound examinations, Pie Medical (Maastricht, Holland) with a 5.0 MHz sector probe, was used. The examinations were performed through abdominal integuments in the linea alba, on the standing animal. The ultrasound examination performed in the following days of the therapy made it possible to observe the contraction process of the uterus until the total loss of its lumen. Sections of the uterine horns were measured in centimetres.

Blood samples for the measurement of progesterone concentration were collected from the cephalic vein and centrifuged immediately for 20 min at 3,000 rpm. The obtained plasma was moved to sterile tubes and stored in -20°C until the analysis. The level of progesterone was measured by radioimmunoassay (RIA) by extraction (2).

Results and Discussion

The progesterone concentration before treatment was significantly raised (34.47 ±9.54 ng/mL on average) in all the bitches, after which it gradually decreased to low values as the treatment progressed. However, concentrations below 2 ng/mL were obtained no sooner than between the 7th and 14th d of the therapy (Fig. 1). The process of cervix opening was connected with occurrence of vaginal discharge and, on average, happened after 38.0 ±6.92 h from the beginning of the therapy (Fig. 2). The highest intensity of the outflow from the reproductive tract was observed during the first 24 h from the moment of its occurrence. In the following days, the vaginal discharge kept decreasing significantly; however it continued for the next 5 to 7 d.

The size of the uterine horns before the therapy and the contraction process of the uterus during the therapy were documented by ultrasound scans (Fig. 3). An average section of the uterus lumen before the treatment was 3.83 ±0.98 cm and decreased gradually until its total loss after 7-14 d (Fig. 2). Usually, in the majority of the animals (nine bitches), the lumen loss took place up to the 7th d of the treatment. In three animals only, the end of the uterus contraction process was observed no sooner than on day 14. In those animals, the cross-section of their uterine horns was much larger before the therapy and measured from 4.5 to 5.5 cm. The described contraction process of the uterus was accompanied by a visible improvement of the animals’ general condition, particularly noticeable even in the first week of the treatment.

The time of cervix opening in the own study was similar to the results of other authors, who also observed this phenomenon during 24 to 48 h from the first administration of aglepristone (4, 9, 10, 12, 16, 19). Fieni (10) was the only one who found the cervix opening process as early as after 4 h from the first administration of aglepristone; however, the full opening took place after 42 h. In the own study, the size of the puss-filled uterine horns did not affect the time of cervix opening.

As it has been mentioned in the introduction, progesterone is an incredibly important hormone in the developing of the endometritis-pyometra complex. It is dominant in the metoestrus phase and thus many authors stress the fact of spontaneous occurrence of this disease in that phase. This phenomenon was demonstrated by Lemmer (16) in up to 71% of animals with EPC in their metoestrus phase and by Fieni et al. (9) in all 54 examined bitches. Blendinger (4) also observed the occurrence of EPC in the majority of bitches in the middle of luteal phase when progesterone reached its highest values (>30 ng/mL). Generally, 60%-70% of the EPC cases are detected in the metoestrus phase (2, 5, 7, 10, 11, 14, 18, 20). Progesterone regulates the activity of the myometrium and has a suppressive effect on the local uterine defence mechanisms (1, 7, 15). In this study, the treated animals suffered from the closed form of pyometra, which was accompanied by a high concentration of progesterone. The applied treatment made it possible to eliminate the effect of that hormone on the uterus by blocking its receptors (16). That process was manifested with ongoing cervix opening and contraction of the uterus in spite of the still high level of progesterone, which makes it quite interesting (Fig. 2).

A similar profile of that hormone during the aglepristone therapy has also been observed by Blendinger (4). In his research, the excretion of puss and uterine involution took place in most of his patients at still-high values of progesterone. That phenomenon is most probably connected with the influence pattern of aglepristone - mainly on progesterone receptors in the myometrium and then, secondarily, on the corpus luteum, which is connected with its incomplete and very slow luteolysis (19). This also resulted in the research by Martin et al. (19), who demonstrated different effects of aglepristone and cloprostenol on the corpus luteum and uterus in bitches between the 30th and 34th d of pregnancy. It should be added that regulation of the corpus luteum function in pregnancy and in the oestrus cycle in bitches is similar in principle. The influence of antigestagens directly on the uterine tissues, and indirectly on the corpus luteum, has also been shown by Gerres and Hoffmann (12). They found an undisturbed function of the corpus luteum after antigestagen therapy in bitches after hysterectomy. It has been suggested that the effect of antigestagens depends on the level of progesterone and expression of its receptors, the administered dosage, and also on the changing, endo or paracrine, role of progesterone in various phases of the oestrus cycle in bitches (16).

There are not many studies describing the contraction process of the uterus in the literature, including the one after antigestagen administration in the EPC treatment. This also refers to physiological phenomena such as labour, where ultrasonography is the most frequently-used method to the evaluation of the uterine involution in bitches (2). Electromyography, which was a previous invasive method, has been used by van der Weyden et al. (20) in examination of uterine contraction activity in the perinatal period.
**Fig. 1.** The average progesterone plasma concentration (ng/mL) in treating animals (n=12) on days 1, 2, 7, and 14.

**Fig. 2.** The transverse cross-section (cm) of uterine horns in treating animals (n=12) on days 1, 2, 7, and 14.
Fig. 3. Ultrasound image of uterine horns in following days of the treatment.

With it, they observed that the myometrium is capable of partial contracting as early as in the time of progesterone dominance, starting from around the 50th d of pregnancy, and an increasing activity of the uterus was noticed even from the 7th d before the labour. However, the full contractibility of that organ occurred in the time of 24-13 h before whelping a first pup, which correlated with a rapid decrease in progesterone concentration (21). That research, although referring to the late pregnancy period, due to its unique documentation of the uterine contractibility process in relation to progesterone in bitches, may also be partially considered to show the phenomena described in this study.

In the own study, full uterine involution was found in all the treated animals until the 14th d of treatment; however individual differences were observed in the course of that process connected with the length of the disorder and the level of puss-filled uterine horns before treatment. The greatest dynamics of that process was observed in those animals, in which the morbidity was short and the diameter of puss-filled uterine horns was small. The uterine involution after the aglepristone treatment has not been a subject of intensive studies so far; only Blendinger et al. (4) have referred precisely to that process. In other studies, the process of uterine involution was confirmed by ultrasound examination and usually it ended after 7-14 d; however no details of that phenomenon have been provided (9, 10, 13, 18, 20). In the study by Blendinger et al. (4), in some of the treated animals, the loss of the uterine lumen was noticed as early as after 6 d of the therapy. Moreover, in three bitches, in which the initial cross-section of their uterine horns was small and ranged from 23 to 36 mm, the total loss of the uterine lumen took place even on the 4th d of the therapy (4). In two other animals, the time of full uterine involution was a few days longer, which may have been connected with a large section of the uterine lumen at the beginning of the treatment.

It should be added that in the own study, the measurements of the cross-sections of the uterine lumen were taken relatively infrequently, i.e. only on the days of aglepristone administration. It resulted from the fact that more frequent visits to the clinic were not possible for most of the owners of the treated animals. Apart from progesterone, other factors crucial for myometrium contractibility are also known (e.g.: levels of glucose and Ca++ ions) (2, 21) yet they were not investigated in this study. However, relatively quick uterine involution after eliminating the progesterone influence on that organ proves their physiological levels.

Fieni et al. (9, 10) as well as Gobello et al. (13) have applied cloprostenol, together with aglepristone, in the conservative EPC therapy. Fieni (10) has observed there that the speed of uterine lumen loss and uterine involution may depend on the combined administration of aglepristone and prostaglandins. Prostaglandin treatment, together with antigestagens, seems reasonable, due to their uterotonic properties and the possibility of accelerating the dynamics of uterine involution. Additionally, their direct effect on the corpus luteum and the creation of an additional mechanism for progesterone elimination is of some importance (10, 13,
However, some side-effects that accompany administration of PGF$_2\alpha$ must be considered in bitches. It should be added that clinical recovery, which is evaluated by stopping the discharge from the reproductive tract, a totally contracted-uterus in an ultrasound scan, and a general physiological condition in the animal, is not the final criterion for effective recovery but is the first stage only. Most important are the lack of recurring morbidity and the fertility of bitches that condition their capabilities of becoming pregnant and this should be considered as the final recovery (10, 18, 19, 20).

References