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Research Article

The Efficacy of Alone or Combined Treatment of Aglepristone and Cabergoline on Termination of Mid-term Pregnancy in Cats [1][2]

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Abstract

This study determined the efficacy of a combination of aglepristone and cabergoline on termination of mid-term cat pregnancies. Twenty cats with unwanted pregnancies between 30-40 days were included in the study. Aglepristone (10 mg/kg, sc) was given to the AGL group (n=6) twice in a 24-h interval. Cabergoline (5 µg/kg, peros) was administered to the CBG group (n=7) once daily until abortion started or for 8 days. AGL+CBG (n=7) received a combined treatment with both drugs. Abortion occurred in 50% of cats in the AGL group, 71.4% in the CBG group, and 100% in the AGL+CBG. However, the completion of pregnancy termination rate was 85.7% because of fetal retention in one cat from the AGL+CBG group. The interval between treatment-start of abortion (T-SA) was shorter in the AGL+CBG group (3.6±0.3 days) than in the AGL (6.5±0.0) and CBG (6.2±0.2) groups (P<0.01). Similarly, the interval between treatment-end of abortion (T-EA) was shorter in the combined group (4.3±0.5 days) than the others (7.3±0.3 and 6.9±0.9 days, respectively) (P<0.01). Decreasing in progesterone concentration was non-significant in the AGL group from the start of treatment to abortion completion day (dA/d8), but significant in the others (P<0.001). On dA/d8, it was significantly lower in the CBG group (P<0.01) and combined group (P<0.01) than in the AGL group. Only slight diarrhea was observed in 15.4% of the AGL+CBG group. In conclusion, the AGL+CBG combination increased the rate of abortion induction and significantly shortened T-SA and T-EA with negligible side effects.

Keywords: *Aglepristone, Dopamine agonist, Pregnancy termination, Queen*

Kedilerde Orta Dönem Gebeliklerin Sonlandırılmasında Aglepriston ve Cabergolinin Tek Başlarına veya Birlikte Uygulanmasının Etkinliği

Öz

Bu çalışmada kedilerde orta dönem gebeliklerin sonlandırılmasında aglepriston ve cabergolin kombinasyonunun etkinliği belirlendi. Çalışmada istenmeyen gebeliği olan ve gebeliğin 30-40. günleri arasında olan 20 kedi kullanıldı. AGL grubuna (n=6) aglepriston (10 mg/kg, sc) 24 saat arayla iki defa uygulandı. CBG grubuna (n=7) cabergolin (5 µg/kg, peros) abortuslar başlayana kadar veya 8 gün süreyle günlük olarak uygulandı. AGL+CBG (n=7) grubuna ise her iki ilaç birlikte verildi. AGL grubunda kedilerin %50'sinde, CBG grubunda %71.4'ünde ve AGL+CBG grubunda ise %100'ünde abortuslar şekillendi. Bununla birlikte AGL+CBG grubundaki bir kedide fetal retensiyondan dolayı gebelik sonlanma oranı %85.7 olarak şekillendi. Tedavi-abortus başlama aralığı (T-SA) AGL+CBG grubunda (3.6±0.3 gün) AGL (6.5±0.0) ve CBG (6.2±0.2) gruplarından daha kısa bulundu (P<0.01). Benzer şekilde, tedavi-abortus tamamlanma aralığı (T-EA) kombine grupta (4.3±0.5 gün) diğer gruplardan (sırasıyla, 7.3±0.3 ve 6.9±0.9 gün) daha kısa olarak belirlendi (P<0.01). Tedavi başlangıcından abortus tamamlanma gününe (dA/d8) arasında progesterone konsantrasyonundaki azalma AGL grubunda önemsizken CBG ve kombine grupta önemliydi (P<0.001). Progesteron düzeyi dA/d8 gününde CBG ve kombine grupta AGL'den önemli derecede düşüktü (P<0.01). AGL+CBG grubunda 15.4% oranında sadece hafif derecede ishal görüldü. Sonuç olarak, AGL+CBG kombinasyonun abortusları uyarma oranını artırdığı, T-SA ve T-EA'yı göz ardı edilebilecek düzeyde yan etki ile önemli oranda kısalttığı belirlendi.

Anahtar sözcükler: *Aglepriston, Dopamin agonisti, Gebelik sonlandırma, Dişi kedi*

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INTRODUCTION

Corpora lutea are the main progesterone source in cats like most other domestic species. However, as in dogs, after 25 to 30 days of gestation, prolactin is secreted as a luteotrophic hormone [1,2] and its plasma concentration reaches a plateau around 50 days of gestation [1]. Thus, corpora lutea may continue to produce progesterone. At the same time, placental progesterone begins to appear during the second half of pregnancy in cats. Recently two studies at the molecular level by Braun et al.[3] and Siemieniuch et al.[4] demonstrated that the feline placenta is capable of progesterone secretion. Therefore, high plasma progesterone concentrations are maintained, which is of vital importance for the continuation of pregnancy after 30 days of gestation. Thus, difficulties could be encountered in termination of mid-term pregnancies in cats.

Because of the critical changes to support progesterone secretion in mid-term pregnancy, the hormones $PGF_2\alpha$, dopamine agonists, and progesterone receptor blockers or their combinations could be used for pregnancy termination in cats. Frequent and repetitive applications of $PGF_2\alpha$ as a luteolytic causes serious side effects: vomiting, diarrhea, hyperpnea, hypersalivation, etc.[5]. Therefore, it is not preferable to use it alone. In addition, $PGF_2\alpha$ is ineffective after the 38^{th}-40^{th} days of gestation [6,7].

Prolactin is secreted from the pituitary by simultaneously increasing plasma serotonin and decreasing dopamine concentrations. Therefore, the dopamine agonists bromocriptine and cabergoline (CBG) act as prolactin inhibitors. Thus, luteotrophic concentrations of prolactin decrease or disappear [2,8,9]. Both agents act as strong dopamine D2-receptor agonists and stimulate the chemoreceptive trigger zone. However, CBG is preferred in clinical practice because it has a more specific D2-receptor activity, which induces less severe side effects than bromocriptine [10]. Although its abortifacient feature is known [2], CBG has not been studied in cats as much as dogs. A drawback of CBG use is prolonged fetal expulsion arising from insufficient uterine smooth muscle contraction [9]. It is also more effective after 40 days of gestation [8]. In addition, the duration of pregnancy termination in CBG treatment is quite wide [11].

Aglepristone (AGL) is licensed as a progesterone receptor blocker in veterinary practice and its use in cats [7,12-14] with 9.26-times higher affinity than native progesterone. It prevents pregnancy in bitches when applied early diestrus even at the lower than standard doses [15]. After binding to the progesterone receptor, it abolishes the biological effects of progesterone [16,17] and leads to fetal death and fetal expulsion [17]. Data from studies with AGL show the abortifacient effect varies between 66.7% and 100%, depending on gestational age [12,14,18]. The abortifacient effect of AGL decreases as the gestational age increases [16].

Combined hormone treatments for termination of pregnancy such as AGL+PGE1 [19], AGL+$PGF_2\alpha$ [20], or CBG+$PGF_2\alpha$ [8] have been used with satisfying results in dogs. Although reports of combined hormone treatments in cats are not as prevalent as in dogs, a few studies use combined treatments to terminate the pregnancy in cats. In these studies, CBG was combined with $PGF_2\alpha$ analogs [11,21,22]. Unfortunately, in these regimens, the disadvantages of $PGF_2\alpha$ remain. Therefore, new methods or combinations are needed for termination of mid-term pregnancies in cats with a higher abortion induction rate and lower side-effect ratio in parallel with clinical rationales for combination therapy. To the best of our knowledge, there is no study using a combination of a progesterone receptor blocker and dopamine agonist to terminate the pregnancy in cats. Therefore we designed an AGL and CBG combination as a new, effective, and reliable method for termination of mid-term pregnancies in cats.

MATERIAL and METHODS

Twenty healthy mix breed cats with unwanted pregnancies between 30 and 40 days (mean 35.8±3.6 days), mean aged 17.5±6.3 months (range 9 to 30 months), and body weight 3.4±0.2 kg (range 2.4 to 4.7 kg) were used in a randomized design. Animals were hospitalized indoors, fed a commercial dry cat food once daily, and given water *ad-libitum* during the study. The study was approved by the animal experiments local committee of Kafkas University, Turkey (KAÜ-HADYEK/2017-052).

Assessment for gestational age was made using the internal dimensions of the gestational sac, fetal occipital-sacral length, fetal parietal diameter, and thoracic diameter with ultrasound (5-7.5 MHz probe; MyLab™Five VET, Esaote) described by Zambelli [23]. Those between 30-40 days were included in the study and assigned to three groups. Aglepristone (10 mg/kg, subcutaneously, Alizin®, Virbac) was administered twice in 24 h intervals in the AGL group (n=6). Cabergoline (5 µg/kg, peros, Galastop®, Ceva) was administered to the CBG group (n=7) once daily until abortion started. The last group, AGL+CBG (n=7), was treated with an AGL and CBG combination using the same dose and route as the single treatments. After treatments, monitoring occurred every 12 h using clinical and ultrasonographic examinations. The start of abortion was marked with the start of bloody-dark vaginal discharge. A total absence of any fetal structures in ultrasonographic examination marked the end of abortion. Animals were followed-up for 8 days and those that did not start abortions during this period were considered abortion negative. At the request of a patient's owner, one animal in the CBG group was followed-up for a longer period.

Blood samples were collected at the start of treatment (d0), 4 days later (d4), and when abortion was completed or at the end of treatment day 8 (dA/d8). Sera were stored at -20°C until analyzed. Concentrations of progesterone

were measured using an electrochemiluminescence immunoassay with Cobas Modular E170 Analyzer (Roche Diagnostics, Germany) by an accredited laboratory (Düzen Laboratories Group, Ankara, Turkey: TÜRKAK, TS EN ISO/IEC 17025:2005).

Generalized linear models (PROC GENMOD) for T-SA, T-EA, and D-A were analyzed according to functions corrected as normal probability functions. Intergroup comparisons were made by analyzing the contrast structure in orthogonal polynomials. The comparisons were completed by chi square test in accordance with nxc contingency table with one sided hypothesis for the abortion rates. Progesterone analyses were made by Kruskal-Wallis test. Differences were considered significant at P<0.05.

RESULTS

There were no significant differences in age, body weight, and gestational age between the groups at the beginning of the study (P>0.05).

Abortions were successfully induced in all animals (100%, 7/7) administered the AGL and CBG combination, whereas only 3 of 6 (50%) cats treated with AGL (P<0.05) and 5 of 7 cats (71.4%) treated with CBG were successfully induced. Fetal death was observed in one cat treated with the AGL and CBG combination 4 days after treatment started. Ovariohysterectomy was performed in this cat since there was no evidence of fetal expulsion 24 h after detected fetal death (at day 45 of gestation). Therefore, abortion was successfully induced, but not completed, in this cat. During statistical evaluation of the interval between treatment-end to abortion interval and duration of abortion, parameters were analyzed without the values from this cat. Thus, while all animals that started abortions in AGL and CBG group terminated pregnancies, in the combined group this rate was decreased to 85.7% (6/7) (P>0.05).

The interval between treatment-start of abortion (T-SA), the interval between treatment-end of abortion (T-EA), and duration of abortion (D-A) are presented in *Table 1*. The combined treatment reduced the T-SA (3.6±0.3 days) approximately 44.6% and 41.9% compared with the AGL (6.5±0 days) and CBG (6.2±0.2 days) groups, respectively *(Table 1, Fig. 1)*. Similarly, the T-EA value (4.3±0.5 days) in the combined group was approximately 41% and 37.6% shorter than in the AGL (7.3±0.3 days) and CBG (6.9±0.9 days) groups, respectively (P<0.01) *(Table 1, Fig. 2)*. No significant difference (P>0.05) was detected in the duration of abortion (interval between T-SA and T-EA) between groups *(Table 1)*.

Table 1. *The interval between treatment-start/end of abortion (day, mean± stderr)*

Groups	n	T-SA	T-EA	D-A
AGL	6	6.5±0.0[a]	7.3±0.3[a]	0.8±0.3
CBG	7	6.2±0.2[a]	6.9±0.9[a]	0.7±0.1
AGL+CBG	7	3.6±0.3[b]	4.3±0.5[b]	0.7±0.1
P value		P<0.01	P<0.01	P>0.05

Different superscripts [a,b] in the same colon means statistically different
T-SA: The interval between treatment-start of abortion; T-EA: The interval between treatment-end of abortion; D-A: The interval between T-SA and T-EA

All pregnancies (100%, 6/6) were terminated on the 5th days post-treatment in the combined group and 66.67% (4/6) of these pregnancies were terminated on the 4th day post-treatment. In the AGL group, none of the pregnancies were terminated during the first 5 days post-treatment (6/6 vs 0/3, P<0.01). In the AGL group, pregnancies were terminated on the 7th (2/3, 66.67%) and 8th (1/3, 33.33%) days post-treatment. Pregnancies were terminated in a wide range between day 4 and 9 post-treatment in the CBG group *(Fig. 3)*.

In the AGL group, a non-significant decrease in progesterone concentration was found from d0 to dA/d8 (P>0.05). In both the CBG and combined groups, a significant difference was found in the progesterone concentration from d0 to d4 and from d4 to dA/d8 (P<0.001) *(Fig. 4)*.

At the start of treatment (d0), progesterone concentrations

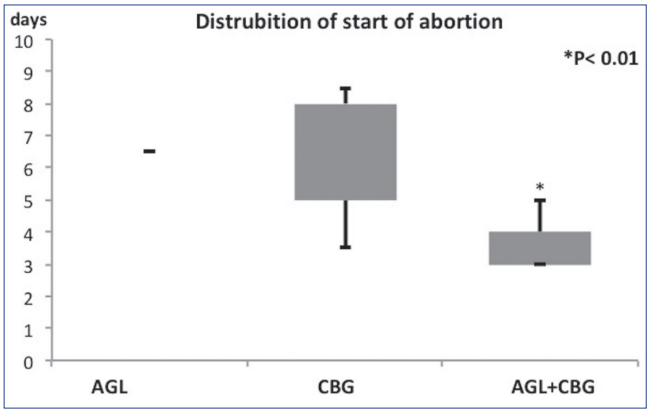

Fig 1. Distribution of interval between treatment-start of abortion

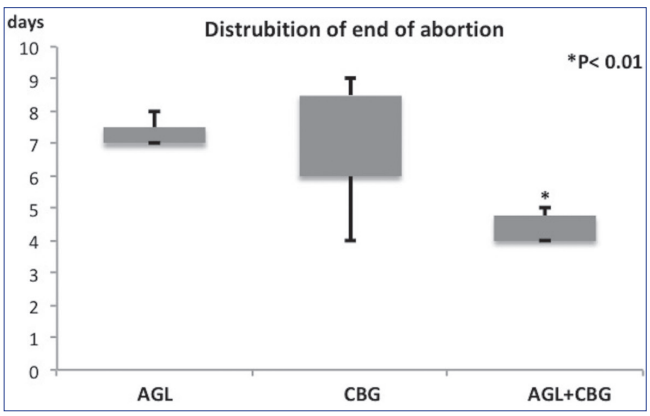

Fig 2. Distribution of interval between treatment-end of abortion

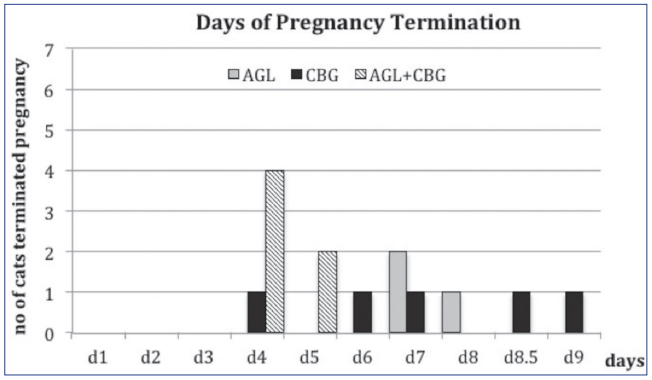

Fig 3. The number of cats terminated pregnancies

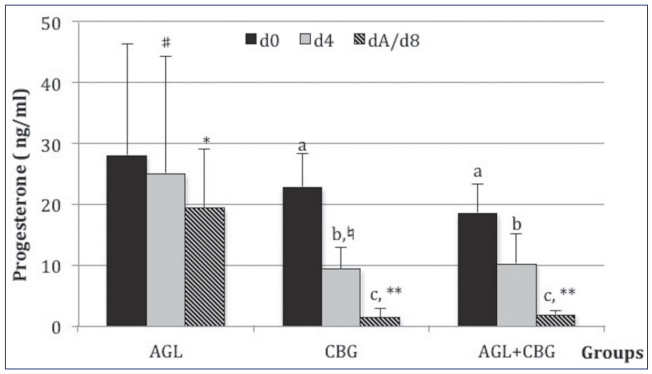

Fig 4. Progesterone concentrations in groups (day, mean± stderr)
In same groups, different superscripts [a,b,c] are significantly different (a,b and b,c: < 0.01, a,c <0.001). In different groups asterix (#, ǂ,*,**) are significantly different (#, ǂ <0.05 and *, ** <0.01)

in all groups were not different (P>0.05). However, progesterone concentrations in the CBG group were significantly lower on d4 compared with the AGL group (P<0.05) and continually increased to the dA/d8 (P<0.01). In the combined group, progesterone concentrations on dA/d8 were significantly lower than in the AGL group (P<0.01) *(Fig. 4)*.

Only diarrhea was observed in 4 of 26 applications (15.4%) in the AGL+CBG group during the study. No other side effects were seen in all groups. Observed diarrhea was slight and lasted for 1 or 2 days.

DISCUSSION

In the present study, the most satisfactory results were obtained in the combination of AGL and CBG group in accordance with our hypothesis. Contributing factors in achieving this result may be hormone doses, gestational age of cats, and duration of follow-up

Fienni et al.[14] reported that 88.5% of pregnancies are terminated using a dose of 15 mg/kg AGL at approximately 31 d of gestation with 90% success [24]. In addition, 10 mg/kg AGL terminated the pregnancies in 87% of cats at 25-26 days of gestation [18]. Verstegen et al.[21] terminated 80% of pregnancies in cats at 30 days of gestation using the dose 1.65 µg/kg CBG orally. Erünal-Maral et al.[11] achieved 100% pregnancy termination on 34-42 days of gestation using 15 µg/kg CBG.

In this study, the doses of AGL and CBG were determined according to manufacturer recommendations and the literature. The results obtained from the AGL and CBG studies are satisfactory. Based on the above data, we can speculate that satisfactory results will be obtained even if both AGL and CBG are administered at different doses than those found in the literature. Therefore, we postulate that our results are related to the gestational ages of cats and duration of follow-up, not the dose used in the study.

In the cat, the mid-term of pregnancy is a physiological transition period due to the reasons mentioned in the introduction. After this stage, AGL becomes less effective and CBG more effective (>40 days) [8] for pregnancy termination in cats. These data may explain why we obtained lower pregnancy termination rates in the AGL and CBG groups than previous studies.

Abortifacient results of the CBG+$PGF_2\alpha$ combinations in previous cat studies were satisfactory, but side effects from $PGF_2\alpha$ were very intense. Using these combinations, pregnancies were terminated within 8-10 days [22] and 3-10 days [11] from the beginning of treatment.

In our study, abortions were successfully induced (7 of 7 cats) in all animals in the combined group. Although the rate of terminated pregnancies was 87.7% due to fetal retention in one cat (1 of 7 cats), the result is consistent with previous studies in cats and dogs using combined applications.

After a successful abortion attempt, pregnancies are terminated by the way of fetal expulsion (in late-term pregnancy) or embryonic/fetal resorption. In accordance with this study, Erünal-Maral et al.[11] observed embryonic/fetal resorption or fetal expulsion between 25 to 35 days of gestation and fetal expulsion higher than 35 days of gestation in cats administered CBG for pregnancy termination. Verstegen et al.[21] reported 75% of pregnancies treated with CBG induced fetal resorption without any clinical symptoms except vaginal discharge. However, there is always the possibility of treatment failure (viable birth of kittens/puppies) and fetal retention during termination of pregnancies following treatment with AGL [14,18,25,26] or CBG [11] in dogs and cats.

In the literature, AGL treatment failures have been reported. Partial abortion resulted in physiologic parturition at mid-term in 2 of 69 dogs [26] and 1 of 21 cats [18], fetal retention in 4 of 61 cats [14], endometritis in two cats [25], physiologic parturition with viable kittens in 1 of 21 cats, and fetal maceration in 1 of 21 cats [18]. Similarly, three cats had CBG treatment failure in the Erünal-Maral et al.[11] study, resulting

in physiologic parturition for two cats and premature birth for one cat. Therefore, follow-up of the pregnancy termination process with ultrasonography is important for early intervention and protection of maternal health.

Embryonic/fetal deaths start one day after the first AGL application and end 4-7 days later (range 3.6-14 days) [16]. In our case, fetal deaths were determined on day 44 of gestation after 4 days of treatment (40 days of gestation) in accordance with the literature. Our expectation was fetal expulsion in all cats. However, one cat was ovario-hysterectomized in the request of its owner day 45 of gestation because fetal expulsion was not achieved within 24 h after the kittens died.

According to previous studies, pregnancies are terminated within 1 to 7 days [14] or 5-9 days [18] after AGL treatment and in these studies, the follow-up period was 14 and 20 days, respectively. Cabergoline applications terminate pregnancies within 3-10 days [11]. In CBG and $PGF_2\alpha$ combined applications, pregnancies are terminated within 3-10 days. Our follow-up period (8 days) was shorter than in previous studies and this could explain our low pregnancy termination rate in the AGL and CBG groups. However, our data show that abortions were started earlier in the combined group than AGL and CBG ($P<0.01$). This reduction is also reflected in T-SA and abortions were ended 41% and 37.6% earlier in the combined group than in the AGL and CBG groups, respectively ($P<0.01$). In our opinion, this data is the most important result of the study. Up to now, only a few studies were performed to reduce side effects, increase the abortifacient effect of hormones [8], and reduce the treatment period [19] in dogs. According to our results, the AGL+CBG combination does not reduce the duration of abortion, similar to Agaoglu et al.[19] Two studies demonstrated that the combination of AGL and PGE1 reduces the completion to abortion interval [19,27] during mid-term dog pregnancies, but not the combinations of AGL+$PGF_2\alpha$ (cloprostenol) and AGL+CBG+PGE1. As clearly seen in this study, the combined treatment of AGL and CBG significantly reduced the T-SA and T-EA intervals. To the best of our knowledge, this is the first study reporting the combined treatment caused an approximately 40% reduction in the treatment period in cats.

The efficiency of abortifacient treatment can be monitored by blood serum progesterone measurements. In cats, blood serum progesterone concentrations should drop under 2 mg/mL within 24 h to provide normal parturition [28]. On the other hand, parturition and abortion could be induced by AGL without any significant effect on serum progesterone concentration as opposed to other methods ($PGF_2\alpha$ or CBG). In previous studies of abortion induced with AGL, serum progesterone concentrations are higher than basal levels in dogs [19,27] and cats [18]. In this study, the progesterone concentration in the AGL group did not significantly decrease throughout the study, similar to previous studies.

However, CBG caused significant decreases in progesterone concentration in both CBG groups, similar to other studies. Onclin et al.[29] reported under 2 ng/mL progesterone concentration five days after the start of CBG treatment is an indicator of successful pregnancy termination in dogs. CBG and $PGF_2\alpha$ (alphaprostol, cloprostenol) treatment on day 30 of gestation cause progesterone concentration to drop under 1 ng/mL within 8 days in cats [21,22].

While AGL has genotoxic and cytotoxic effects on bone marrow when used to terminate mid-term pregnancies in rabbits [30], there is no evidence of such side effects in cats or dogs; both AGL and CBG have been reported to be safe in dogs and cats aside from some mild side effects (diarrhea, anorexia/depression, inflammation at injection site, lethargy for AGL) [13,14,20] and (vomiting for CBG) [1]. The side effects from combined use were related to $PGF_2\alpha$ [11]. In this study, no side effects were observed in the AGL and CBG groups. In the combined group, observed diarrheas were so mild that we considered that stress from the abortion process, hospital environment, or feed changes may have caused diarrhea.

Pregnancy termination in cats is not as well studied as in dogs. Safe methods are still needed that have a high abortion induction rate and induce a quick-response. Our results clearly show that combined treatment with aglepristone and cabergoline is capable of meeting these requirements and supports our hypothesis. As expected from the combined treatment, aglepristone and cabergoline synergistically increase the rate of abortion induction and significantly shorten interval between treatment-start of abortion and interval between treatment-end of abortion with negligible side effects.

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