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# Evaluation of aglepristone and oxytocin on induction of parturition in guinea pig

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## Abstract

**Background:** Induction of parturition in guinea pigs appears to be essential because these animals have a higher rate of reproductive problems than rabbits and small rodents.

**Objectives:** Since aglepristone (AGL) is a competitive progesterone antagonist acting through binding to progesterone receptors while oxytocin (OT) is a powerful constituent of uterine smooth muscle, the aim of this study was to evaluate the clinical and ultrasonographic impacts of AGL and OT on guinea pig parturition induction.

**Methods:** In this study, guinea pigs were allocated into five groups; each included five animals on the 61st day of pregnancy. In the aglepristone group (Agle), AGL was administrated subcutaneously (SC) once daily on 2 consecutive days (Days 61 and 62 post mating). Oxytocin (OT) was administered subcutaneously once and twice at 4-h intervals on Day 62 post mating in oxytocin 1 (Oxy1) and oxytocin 2 (Oxy2) groups, respectively. The animals in the aglepristone-oxytocin group (Agle-Oxy) received AGL subcutaneously once daily on 2 consecutive days (Days 61 and 62 post mating) and OT on Day 62 post mating. The remaining sows received saline solution (0.9% NaCl) in the control group.

**Results:** According to the results, fetal heart rate, temperature, neonatal and maternal survival rates were not significantly different between the treatment and control groups ($p > 0.05$). Biparietal diameter of head and body weight of neonates in the Agle, Oxy2 and Agle-Oxy groups showed a significant decline, compared to the control group ($p < 0.05$). The time interval between injection and delivery and the duration of pregnancy was significantly reduced in Agle, Oxy2, Agl-Oxy groups, compared to the control and Oxy1 groups.

**Conclusions:** In conclusion, it seems that treatment Oxy2 can induce parturition in guinea pigs without side effects and lower pain during induction of parturition.

KEYWORDS
aglperistone, oxytocin, induction of parturition, guinea pig

## 1 | INTRODUCTION

Aglepristone (AGL) is a synthetic steroid that acts as an anti-progesterone and is widely used in small animal medicine in most European, Latin American and Pacific countries (Gogny & Fiéni, 2016; Özalp et al., 2013). However, the fact that this drug is used in cats and dogs, several side effects have been reported, including anorexia, necrosis, itching at injection sites and a decrease in body temperature (Özalp et al., 2013).

AGL is a competitive progesterone antagonist, which binds to progesterone receptors without triggering the progesterone-induced molecular cascade. Its affinity to these receptors is higher than progesterone (3.12, 3.8 and 9.26 times more significant than the bitch, doe rabbit and queen, respectively). This drug can treat various progesterone-dependent physiological and pathologic diseases, including terminating pregnancy in most animals such as bitches, cows and goats, treating pyometra and feline fibroadenomatosis (Gogny & Fiéni, 2016).

Guinea pigs have a long gestation period (69–71 days) and deliver precocial young. Guinea pigs, like humans, have a haemochorionic placenta, and the fetus accumulates large adipose storage throughout late pregnancy. In addition, their cardiovascular and metabolic characteristics are well understood, and their rapid maturation allows for life-course and intergenerational studies. Preterm surgical delivery and short-term survival are also conceivable. They have been utilized to investigate some of the short-term adaptive responses to preterm birth at the margins of viability (Berry et al., 2015).

Guinea pigs do not reproduce as easily or as prolifically as small rodents and rabbits. Although dystocia is uncommon in small rodents and rabbits, guinea pigs have a higher rate of parturition complications. Possible causes include narrow pelvic canals and the large size of guinea pig pups (Lopate, 2012).

Induction is one of the most effective treatments for preventing dystocia in guinea pigs due to the intolerance of even modest amounts of blood loss, heightened hypothermia concerns as a result of small body mass, and the possibility of gastrointestinal difficulties after surgery. However, surgery is sometimes the only option and is recommended for induction (Lopate, 2012).

Because uterotonic (or ecbolic) agents like oxytocin (OT) and progesterone receptor inhibitor agents like AGL are commonly used to treat dystocia in humans and animals, the aim of this study is to evaluate the clinical and ultrasonographic effects of AGL and OT on parturition induction in guinea pigs.

## 2 | MATERIAL AND METHOD

### 2.1 | Animals

Twenty-five, 3- to 4-month-old, English short hair guinea pig sows were selected. They were housed together in plastic cages with wood-shaving bedding. No more than five females and one male were housed in each cage. The animals were fed guinea pig/rabbit pellets (Behparvar rabbit stud). Ascorbic acid (vitakim; 200 mg/L) was added daily to fresh drinking water. The animals were kept at a controlled temperature of 18–22°C, with a relative humidity of 50% to 60%. A 12-h light cycle wasinduced (Vitakim is the generic name of Ascorbic acid manufactured by Hakim Pharmaceutical Company, Iran).

### 2.2 | Determination of mating and mating procedure

The oestrous cycle of the guinea pig lasts around 16 days. The term lasts around 69 days. The presence of spermatozoa in a vaginal swab sample is usually a sign of successful mating. The anogenital region of a confined guinea pig was cleansed and moistened with sterile normal saline to obtain a vaginal swab specimen. Smears were obtained from the proximal third of the vaginal epithelium by gently inserting a wet, sterile swab 2 cm into the vagina and forcefully spinning it two times against the vaginal wall. After rolling the swab onto a glass microscope slide, the cells were fixed with methanol. Finally, Giemsa was used to stain glass microscopes (Blanco et al., 2016).

The date of conception, Day 0, was considered the first day of pregnancy. Pregnancy was confirmed through ultrasonographic detection of gestational sacs and embryonic structures 15 days after mating. Pregnant guinea pigs were divided randomly into five equal groups on Day 61 of pregnancy in different groups. AGL (Virbac) was administrated subcutaneously once daily on 2 consecutive days, 10 mg/kg (Days 61 and 62 post mating) in the Agl group. OT was administered 1 IU/kg subcutaneously once ($n = 5$) and twice with 4-h intervals ($n = 5$) on Day 62 post mating in Oxy1 and Oxy2 groups, respectively. AGL was administrated subcutaneously (10 mg/kg), once daily on 2 consecutive days (Days 61 and 62 post mating), and OT was injected subcutaneously (1 IU/kg) once on Day 62 post mating ($n = 5$) in the Agl-Oxy group. The remaining sows were treated with a saline solution (0.9% NaCl; $n = 5$) in the control group (Figure 1). Ultrasonographic and clinical assessments were performed before and after injections.

### 2.3 | Ultrasound procedure

The guinea pig sow was gently restrained on a padded board and positioned on its back.

Because the procedure was quick and painless, no anaesthesia was required. A small amount of contact jelly was applied after the hair on the abdomen was shaved. After that, the ultrasound transducer was placed on the maternal abdomen. The measurements were taken with an EMP V9 ultrasonography machine (Emperor). The fetal guinea pig was imaged, and the biparietal diameter (BPD) and fetal heart rate (FHR) were measured using a 10 MHz linear ultrasound transducer probe (GEM). All BPD measurements were made 'leading edge to leading edge' from the outer margin of the nearest skull line to the inner margin of the far skull line (Turner & Trudinger, 2000).

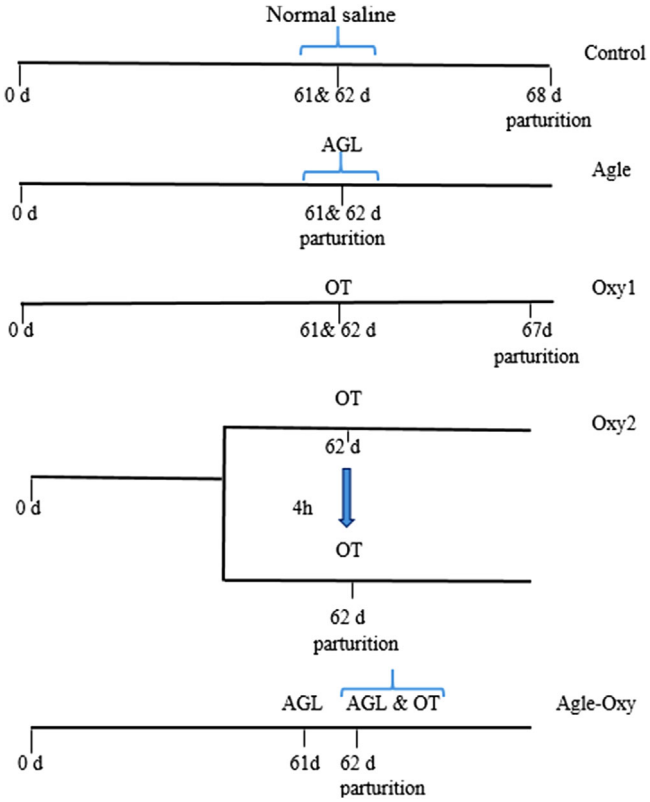


**FIGURE 1** Diagrammatic representation of four treatment and control groups. Twenty-five pregnant guinea pigs were divided into five groups on the 61st day. The Control group received 10 mg/kg normal saline on the 61st and 62nd days post mating. Agle group: AGL 10 mg/kg once on the 61st day and once on the 62nd day was injected. Oxy1 group, OT 1 IU/kg once on Day 62, Oxy2 group, OT twice on Day 62 with 4-h intervals and Agle-Oxy group, AGL once daily on 61st and 62nd days, 10 mg/kg and OT, 1 IU/kg once on Day 62, received. The day on which the observation of vaginal plaque or spermatozoa was found in the vaginal smear was designated as embryonic Day 0 (0 d). AGL: aglepristone, OT: oxytocin. Oxytocin group with one dose OT: Oxy1, oxytocin group with two doses OT: Oxy2, aglepristone with oxytocin group: Agle-Oxy, aglepristone group: Agle

## 2.4 | Clinical evaluation

Pup and mother survival rate and pain, mean birthweight, body temperature, the time between the last administration and first pup expulsion and duration of parturition and gestation length were all measured. Wolfensohn and Lloyd's criteria were used to rate parturition pain. In brief, the pain was classified into four judgment groups: Group 1 (0–4): standard; Group 2 (5–9) monitor carefully, consider analgesics or other treatments; Group 3 (10–14) suffering, provide relief, observe regularly and Group 4 (15–20) severe distress (Wolfensohn & Lloyd, 2008).

# 3 | RESULTS

There was no significant difference in pup number between groups ($p > 0.05$). Post-injection FHR was similar in the treatment groups and control group ($p = 0.29$); moreover, there was not any significant difference in all treatment and control groups between pre and post injection ($p < 0.05$; Table 1). The results presented a relationship between fetal guinea pig BPD and the gestational age of the fetus; BPD in Agle, Oxy2 and Agle-Oxy groups was significantly lower than the control group ($p < 0.05$). Nevertheless, there was not any significant difference between Oxy1 and the control group (Table 1, $p > 0.05$). The mean birthweights of pups in the control and Oxy1 were significantly higher than in the other groups ($p < 0.05$). OT did not significantly affect the mean number of live-born pups per litter.

Before and after drug injections, there was no significant difference between groups in the body temperatures of the sows (Table 1). The mean interval from the last injection to the onset of parturition in all treatment groups was shorter than the control and Oxy1 groups ($p < 0.05$). A significant interval between the last injection and first pup expulsion was detected in Oxy2 and Agle groups ($p < 0.05$). The present study demonstrated that the mean interval from injection to the onset of parturition was 153.6 ± 6.4 h in the control group, 126 ± 3.92 h, 1.41 ± 2.7 h, 0.61 ± 0.11 h and 1.87 ± 0.49 h in Oxy1, Agle, Oxy2 and Agle-Oxy groups, respectively (Figure 2). Duration of parturition in Agle, Oxy2 and Agle-Oxy groups was significantly longer than the control and Oxy1 ($p < 0.05$). The sows in the parturition-induced groups, except in the Oxy1 group, had a significantly shorter gestation length, compared with the sows with spontaneous parturition (Figure 3; $p < 0.05$). The number of dead puppies born was similar between the groups ($p < 0.05$). There was no adverse maternal morbidity or mortality following preterm induction of labour in comparison with the control group. In this study, the pain in the Oxy2 group was significantly lower than in other groups.

## 3.1 | Pain

In this study, pain in Oxy2 group was significantly lower than in other groups ($p < 0.05$). There was no any significant difference between Agl and control groups.

# 4 | DISCUSSION

Dystocia can be managed medically with uterotonic (or ecbolic) drugs such as OT or calcium and aided fetal evacuation or surgically with a caesarean section. OT is one of the most potent uterotonic drugs used to induce labour in clinical practice. As an ecbolic substance, it is commonly used to treat dystocia in humans and animals (Narver, 2012). AGL is a synthetic steroid with an anti-progesterone activity that is extensively used in small animal practice in most European, Latin American and Pacific countries (Özalp et al., 2013). Furthermore, AGL is a safe abortifacient drug in cats, dogs and rabbits, with no notable side effects (Özalp et al., 2013).

The simplest way to determine fetal viability is to detect the heartbeat. Fetal stress is indicated by a decrease in FHR, which can be caused by hypoxia. The average FHR is approximately twice that of

**TABLE 1** Comparison of biparietal diameter (BPD), mean birthweight, body temperature of pup and mother survival percentage and heartbeat of fetuses in pre and post administration in treatment and control groups.

| Groups | BPD (mm) | Mean birthweight (g) | Body Before | After Temperature (°C) | Pup and mother survival percentage | | Pre administration | Post administration |
|---|---|---|---|---|---|---|---|---|
| | | | | | Pup | Mom | | |
| Control | [a]1.84 ± 0.01 | [a]3.76 ± 92.03 | 37.2 ± 0.18 | 35.74 | 90.9 | 100 | 273.75 ± 22.98 | 285 ± 8.66 |
| Agle | [bc]1.74 ± 0.02 | [b]3.42 ± 69.0 | 37.4 ± 0.2 | 36.66 ± 0.84 | 70 | 70 | 253.33 ± 8.81 | 247.5 ± 25.82 |
| Oxy1 | [ac]1.77 ± 0.02 | [ac]5.09 ± 85.2 | | 37 | 75 | 100 | 307.5 ± 4.9 | 280 ± 10 |
| Oxy2 | [bc]1.75 ± 0.02 | [bc]4.16 ± 75.66 | 36.55 ± 0.16 | 36.8 ± 1 | 91.66 | 100 | 270 ± 13.22 | 285 ± 8.66 |
| Agle-oxy | [bc]1.75 ± 0.02 | [bc]3.73 ± 71.66 | 37.2 ± 0.14 | 37.6 ± 0.2 | 66.66 | 100 | 249 ± 6.4 | 255 ± 15 |
| Index | 0.005 | 0.001 | 0.13 | 0.13 | 0.12 | 100 | 200-250 | 200-250 |
| *p*-value | | | | | | | 0.18 | 0.29 |

Abbreviations: Agl, aglepristone; Agle-oxy, aglepristone-oxytocin; Oxy1, oxytocin 1; Oxy2, oxytocin 2.
a, b and cDifferent letters indicate significant differences between groups (P<0.05).

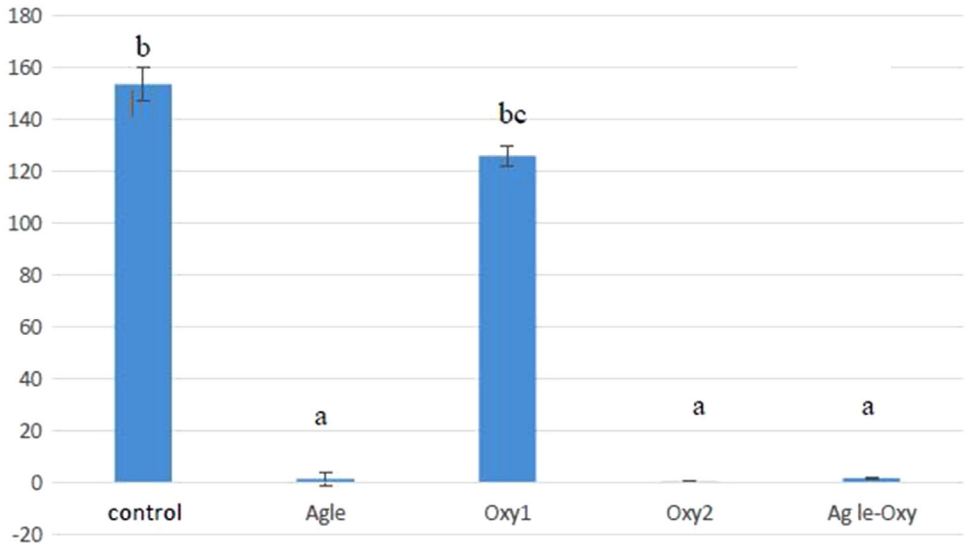


**FIGURE 2** Effect of AGL and OT on time between last administration and first pup expulsion in the guinea pig. Control group saline solution (0.9% NaCl) 10 mg/kg SC was injected on 61st and 62nd days post mating. Agle group, AGL 10 mg/kg once on the 61st day and once on the 62nd day, oxy1 group, OT 1 IU/kg once on Day 62, Oxy2 group, OT twice on Day 62 and Agle-Oxy group, AGL once daily on 2 days, 61st and 62nd, 10 mg/kg and OT, 1 IU/kg once on Day 62 was received SC. There are significant differences between the control and Agle, Oxy1, Oxy2 and Agle-Oxy groups. Also, there are not any significant differences between Agle, Oxy1 and Oxy2 ($p < 0.05$). The Control group had the longest duration between injection and expulsion of the first pup in different groups. AGL: aglepristone, OT: oxytocin. Oxytocin group one dose: Oxy1, oxytocin two doses: Oxy2, aglepristone with oxytocin group: Agle-Oxy, aglepristone group: Agle. Subcutaneously: SC

the mother. An elevated or reduced heart rate can indicate fetal stress and has been used clinically in human medicine (Nyland & Mattoon, 2002). In this study, the treatment and control groups had the same post-administration FHR. It has been seen that inducing parturition has no adverse effects on the FHR (Table 1). This result is comparable to the results by Akinaga (2016) and Verspyck & Sentilhes (2008), who showed that using OT to induce parturition did not result in any abnormal changes in FHR (Akinaga et al., 2016; Verspyck & Sentilhes, 2008). Breukelman in 2012 discovered that using AGL to induce abortion in the cow resulted in no changes in the fetus's heartbeat until the moment of abortion (Breukelman et al. 2012). Blanco (2016), on the other hand, found that the heartbeat of feline fetuses whose mothers had received AGL was higher than the control group. This might explain why different animals have reacted differently to AGL (Blanco et al., 2016).

In this study, the mean of BPD in Oxy2, Agl and Oxy-Agl groups was lower than in Oxy1 and control groups. This result indicates a relationship exists between fetal guinea pig BPD and the fetus's gestational age. Therefore, lower BPD in the mature fetus can facilitate the parturition process and reduces the dystocia probability. These results are consistent with Turner and Trudinger's findings. This can be due to the shorter time of pregnancy in Agl, Oxy2 and Agl-Oxy groups than two other groups (Turner & Trudinger, 2009). Our results showed significant differences in pup birthweight between the control and Oxy1

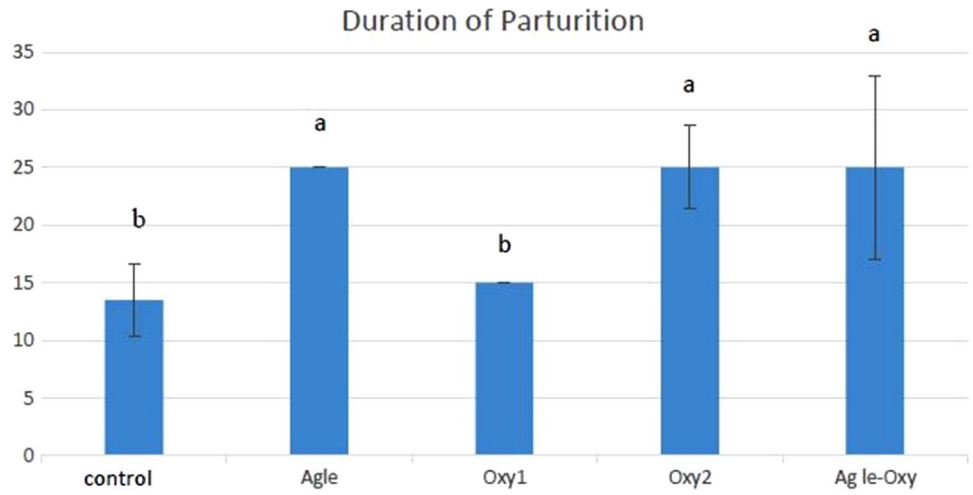


**FIGURE 3** Diagram of gestation length. Control group saline solution (0.9% NaCl) 10 mg/kg SC was injected on the 61st and 62nd days post mating. Agle group, AGL 10 mg/kg once on the 61st day and once on the 62nd day, Oxy1 group, OT 1 IU/kg once on Day 62, Oxy2 group, OT twice on Day 62 and Agle-oxy group, AGL once daily on 2 days, 61st and 62nd, 10 mg/kg and OT, 1 IU/kg once on Day 62 were received SC. Agle, Oxy2 and Agle-Oxy groups had significantly shorter gestation lengths than Oxy1 and control groups. AGL: aglepristone, OT: oxytocin. Oxytocin group one dose: Oxy1, oxytocin two doses: Oxy2, Aglepristone with oxytocin group: Agle-Oxy, Aglepristone group: Agle. Subcutaneously: SC

groups with other treatment groups and were similar to Özalp and Berry's findings in parturition induction in ewes and guinea pigs by AGL (Berry et al., 2015; Özalp et al., 2017). However, the findings contradict those of Fontbonne, who found that the mean weight at parturition was not substantially different in the AGL group. The interval between induction and parturition might be one explanation for this disparity (Fontbonne et al., 2009).

According to the results, there was no significant difference in guinea pig body temperature between treatment groups. This is comparable to Özalp's findings, which revealed that after administering AGL to induce parturition in sheep and rabbits, body temperature did not change considerably (Özalp et al., 2013, 2017). Furthermore, the study by Nagel (2017) showed that treatment with OT after foaling did not effect on skin temperature in mares (Nagel et al., 2017). Nonetheless, following treatment with AGL, bitch body temperature fell, and the authors believed that AGL had hypothalamic effects on bitches (Özalp et al., 2013). Similarly, cows tended to have lower body temperatures 20 to 30 h following AGL treatment. Some changes recorded 84 h after administration could be accepted as individual or seasonal fluctuations because they were unrelated to treatment effects (Özalp et al., 2017).

In our study, parturition in all treatment groups except the Oxy1 group was induced sooner than the control group. Similar to our results, Gogny and Fiéni (2016) claimed that AGL induces effective labour in 100% of bitches and reduces gestation length in treated dams. Özalp in 2017 also showed that parturition induction with two different doses of AGL shortened the gestation length significantly, compared with the control group in ewes. The use of OT and AGL as uterotonic agents have been proven effective in parturition induction (Fieni & Gogny, 2009). In the present study, the duration between injection and initiation of parturition (DIIP) was significantly decreased in all treatment groups except the Oxy1 and control group. Therefore, OT in Oxy1 cannot induce the parturition. Treatment with AGL in cattle resulted in the expulsion of live calves within 48.5 ± 7.3 h after injection (Gogny & Fiéni, 2016).

In ewe, Özalp et al. (2017) showed that all pregnancies were induced 24 to 48 h after the first AGL injection.

Antiprogestins, also known as progesterone antagonists, are synthetic steroids that bind to progesterone receptors with high affinity, displacing endogenous progesterone and therefore preventing progesterone from exerting its biological effects. As a result, they could hasten parturition. Furthermore, these medications can hasten parturition by increasing myometrial response to OT and prostaglandins, as well as by activating mechanical stimulation receptors (Chwalisz et al., 1997; Oguejiofor & Ochiogu, 2018). Our results showed that two OT injections could accelerate the parturition via myometrium contraction, whereas one OT, on Day 62, could not induce it. In Chwalisz's (1997) study, there was an increase in uterine tone and sustained contractions of low amplitude after treatment with increasing doses of OT, and there was an increase in uterine tone and sustained contractions of low amplitude (Chwalisz et al., 1997). In the guinea pig, however, OT receptor concentrations were maximal for at least 1 week before the end of gestation. The concentration of OT receptors in the uterus of a guinea pig dictates the sensitivity of the uterus to OT; however, it does not appear in itself to account for the initiation of labour contractions. It is conceivable that, unlike rats, the guinea pig requires a periparturient rise in OT and/or prostaglandin levels in the blood to initiate labour (Alexandrova & Soloff, 1980). In this study, expulsion phase length (EPL) in Agl, Oxy2 and AGL-Oxy groups were significantly longer than in control and Oxy1 groups (Figure 4 ). Fontbonne (2009) showed that a protocol combining AGL and OT successfully induced parturition in all the bitches, irrespective of their size or breed (Fontbonne et al., 2009). The mean duration of parturition was 9.6 ± 5.4 h vs. 8.0 ± 4.8 h in the control group. Fieni and Gogny (2009) showed that total

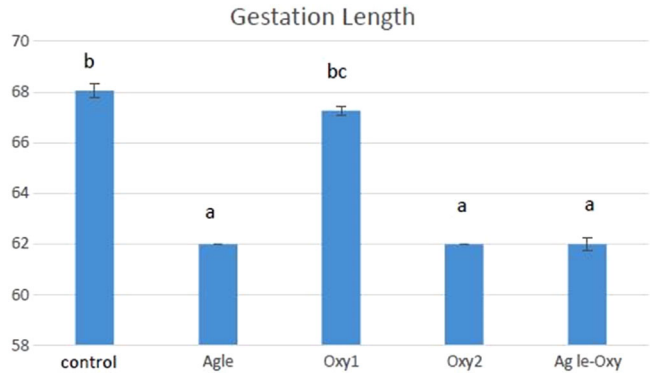


**FIGURE 4** Diagram of the length of the expulsion phase. Control group saline solution (0.9% NaCl) 10 mg/kg SC was injected on 61st and 62nd days post mating. Agle group, AGL 10 mg/kg once on the 61st day and once on the 62nd day, Oxy1 group, OT 1 IU/Kg once on Day 62, Oxy2 group, OT twice on Day 62 and Agle-Oxy group, AGL once daily on 2 days, 61st and 62nd, 10 mg/kg and OT, 1 IU/kg once on Day 62 was received SC. duration of parturition in Agle, Oxy2 and Agle-Oxy was longer significantly than in control and Oxy1 groups. AGL: aglepristone, OT: oxytocin. Oxytocin group one dose: Oxy1, oxytocin two doses: Oxy2, aglepristone with oxytocin group: Agle-Oxy, aglepristone group: Agle. Subcutaneously: SC

expulsion time in the spontaneous whelping group was shorter than the induced group (Fieni & Gogny, 2009). EPL and inter-pup interval were comparable to those of spontaneous parturitions in our results. However, Fontbonne reported conflicting results regarding the inter-pup interval, which was longer in induced parturition than in spontaneous whelping (Fontbonne et al., 2009; Gogny & Fiéni, 2016). In the studies on dogs, the EPL, the inter-pup interval, the number of pups born dead and the number of therapeutic interventions required during parturition did not differ significantly between the spontaneously whelping and the induced groups (Baan et al., 2008).

Our study illustrates that the survival rate in treatment groups was not significantly different from the control group. Berry has developed a viable guinea pig model of preterm birth that emulates the human clinical condition. There was no adverse maternal morbidity or mortality following preterm labour induction with AGL. AGL treatment had no significant influence on pup survival (Berry et al., 2015). Parturition induction with AGL at Days 270 and 271 of pregnancy resulted in the expulsion of live calves within 48.5 h after the initial injection in cattle (Gogny & Fiéni, 2016). Although lamb birthweight was lower after lambing induction, no adverse effects were detected in lamb survival and growth (Özalp et al., 2017). Survival rates at birth and 48 h after birth was similar in treated bitches with AGL and spontaneous whelping bitches (Fontbonne et al., 2009). Using exogenous OT to induce parturition of newborn rabbits was found to be very simple, reliable and highly safe for both mother and offspring in comparison with caesarean section (Morgan, 1974). In 2006, Mota-Rojas demonstrated that giving OT to farrowing sows reduced newborn viability due to increased myometrial contractions' quantity, intensity and frequency. Changes in the variables were determined by the OT application route and time of action (Mota-Rojas et al., 2006). OT was used subcutaneously (SC) in our study, and its administration did not affect viability.

Clearly, we illustrated that the expected labour pain in all groups was similar to other species (Mainau & Manteca, 2011). Guinea pigs are wary and alert creatures who attempt to escape being caught and confined. Any unusual sign of acceptance indicates the animal is unwell. Loud vocalisation accompanies even minor and transient pain. When they have a sense of pain often, they appear sleepy and rarely show aggression. Even mild and transitory discomfort is accompanied by loud vocalisation.

When they are in discomfort, they generally seem lethargic and display less aggressiveness. Because they are sociable creatures, determining whether they are in pain with a single glance can be challenging. Therefore, a carefully used pain scoring assessment method should be employed (Wolfensohn & Lloyd, 2008). We demonstrated that guinea pigs in the Oxy2 group showed the lowest pain. Mainau and Manteca discovered that labour pain is acute pain, and OT can act as an analgesic for acute pain in animals (Mainau & Manteca, 2011). There are at least two potential biologically plausible mechanisms connecting OT and pain reduction. The first involves a direct pathway in which OT projections to the dorsal horn and activation of presynaptic OT receptors located superficially there (lamina I and II) and subsequently excite inhibitory GABAergic (Gama Amino Butyric Acid (GABA)) interneurons (Rash et al., 2014). An indirect pathway through the endogenous opioid system is the second potential mechanism linking OT and pain. The fact that an opioid antagonist may block OT's analgesic effects suggests that OT binds to opioid receptors. Furthermore, OT may cause endogenous opioids to be released in the brain (Rash et al., 2014). Antiprogestins enhance myometrial responsiveness to uterotonics, including OT and prostaglandins, according to several in vitro and in vivo investigations. An increase in gap junction might be the primary mechanism of increased responsiveness to OT following antigestagen therapy. Antiprogestins promote cervix remodelling, which can lead to the induction of parturition, by the increase intracellular Ca entry, decreasing nitric oxide and enhancing collagen lysis, as seen in our Agl-Oxy and Agl groups (Wolfensohn & Lloyd, 2008). As mentioned above, the duration of parturition for Agl-Oxy, Agl and Oxy2 groups was longer than others; since the duration of parturition is one of the important affecting factors on labour pain, it is probable that this can be the reason for the increase in labour pain in Agl-Oxy and Agl groups (Mainau & Manteca, 2011). Likewise, the reason for the drop in labour pain in Oxy2 despite the long parturition duration could be the analgesic effect of pain (Rash et al., 2014).

According to the result of our study, treatment OT 2 can successfully induce parturition in guinea pigs without side effects and lower pain during induction of parturition.

## AUTHOR CONTRIBUTIONS

*Methodology, software, writing—original draft preparation*: Sara Tayeban. *Project administration, conceptualisation, investigation*: Reza Narenji Sani. *Supervision, writing—review and editing*: Morteza Keywanloo. *Ultrasound work, preparing drugs, methodology, writing—review and editing*: Yasamin

Vali. *Ultrasound work*: Sarang Soroori. *Formal analysis, investigation, methodology*: Ebrahim Shahroozian.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

## DATA AVAILABILITY STATEMENT

No

## ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as mentioned in the author guidelines page of the journal, have been followed and the approval of the Research Ethics Committee of the Faculty of Veterinary Medicine of Semnan University has been received. US National Research Council guidelines for the care and use of laboratory animals were followed.

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## PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/vms3.1078

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