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The use of oxytocin to cause cervical dilation for transcervical insemination in nulliparous goats: Improving pregnancy and kidding rates

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Abstract

To evaluate the effect of oxytocin as a cervical dilator, a study was carried out on nulliparous goats inseminated transcervically at the beginning of the breeding season. One hundred sixteen nulliparous goats with a mean live weight of 33.4 ± 0.68 kg and an age of 13.7 ± 0.37 months were used. The goats were exposed to active bucks of proven fertility for a period of 14 d in order to induce oestrus. One week later, the Ovsynch protocol was applied, which consisted of the application of 20 mg of gonadorelin (Day Zero), 0.075 mg of cloprostenol (Day 7) and of a second dose of 20 mg of gonadorelin applied on Day 9. Artificial insemination (AI) was performed 16 hr later. Three treatments were evaluated: T1 = 50 IU saline, T2 = 25 IU oxytocin; T3 = 50 IU of oxytocin, intravenously applied 10–15 min before AI. The time required to inseminate each treated goat from groups T2 and T3 was 49.56 and 56.25 s, respectively, versus 85.78 s needed for the goats from group T1 ($p < .0001$). In the T1 group of goats, the insemination catheter was inserted 2.1 cm into the cervical canal and in goats from groups T2 and T3 it reached 3.41 and 3.77 cm into the cervical canal, respectively ($p = .02$). Pregnancy rates and prolificacy (kids/doe) were higher ($p = .02$) for groups T2 (82.93%; 1.16) and T3 (76.92%; 1.21) respectively than for control goats (61.11%; 0.69). In conclusion, the intravenous administration of oxytocin led to greater dilation and depth of cervical penetration, obtaining higher pregnancy rates and prolificacy.

KEYWORDS
cervix dilation, depth of cervical penetration, prolificacy, reproductive performance, timed AI

1 | INTRODUCTION

Artificial insemination (AI) is an essential method for the introduction of genes of high genetic merit into a population of animals (Candappa & Bartlewski, 2011; Parkinson & Morrell, 2019). The most common routes of insemination in small ruminants are transcervical and intrauterine, but in nulliparous animals, the use of AI is of limited value for three major reasons. First, penetration with an insemination pipette may be difficult due to the anatomy of the cervix (Gibbons et al., 2019; Robinson et al., 2011). There is a great variation among species and breeds in the gross morphology of the cervices. The cervical canal may either be straight or tortuous and

contains mucosal annular rings which change with the reproductive cycle and age (Abiaezute et al., 2021; Robinson et al., 2011). In sheep, the cervix is a long, fibrous and tubular structure containing five rings (Halbert et al., 1990; Kershaw et al., 2005). Similarly, in goats, the cervix is also very long. Bazer (2020) reported a length of 5.7 cm, which is longer than that of bovine heifers, divided by 5–8 transverse folds that prevented passage of a catheter more than 0.5 mm, and furthermore, the reproductive tract of nulliparous goats was much smaller than that of multiparous goats. This makes it more difficult to pass the cervical canal with the insemination gun, and furthermore, a narrow vagina impairs insertion of the speculum, visualization of the entrance of the cervical canal and the deposition of the semen (Batista et al., 2009; Fonseca et al., 2017). Stage of the cycle affects the anatomy and penetrability of the cervix. In nulliparous Thai goats, the cervices during the follicular phase were smaller than those of multiparous goats resulting in shorter penetration with the inseminating pipette, but such differences were not seen in the cervices during the luteal phase (Bazer, 2020).

Second, pregnancy rates obtained in goats and sheep by AI with frozen semen are generally lower than those resulting from fresh semen. Luo et al. (2019) reported 75%–85% pregnancy rate in goats inseminated with fresh semen and 60%–65% with frozen-thawed semen. Similarly, in sheep, Gibbons et al. (2019) reported 50%–70% pregnancy rate with fresh semen via all routes of artificial insemination and 45% with intrauterine frozen-thawed semen. Third, the higher costs, time taken and the specialized equipment needed, in addition to animal welfare implications for laparoscopic intrauterine AI (Jamadi et al., 2017; Carneiro et al., 2019) limit the use of this technique in goats despite the greater reproductive success compared with the cervical route.

Improved methods of transcervical AI have been developed in small ruminants in order to counteract the limitations described above, in particular the use of cervical traction as described by Salamon and Maxwell (2000), and the Guelph equipment and insemination technique as described by Robinson et al. (2011). Deeper penetration of the cervix improves reproductive success of artificial insemination in goats (Viudes-de-Castro et al., 2009) and sheep (Robinson et al., 2011). Viudes-de-Castro et al. (2009) reported 74% kidding rate when does were inseminated with semen deposited in the uterine body, 49% kidding rate when semen deposited in the cervical canal, and 33% kidding rate when semen was deposited deeply in the vagina. To improve cervical penetration, in the last 20 years, exogenous dilating hormones have been used to improve the efficacy of AI in adult sheep and goats, as well as to carry out uterine flushing protocols of donor females through non-surgical methods (Fonseca et al., 2018); for example, the use of oxytocin (Lu et al., 2021; Viudes-de-Castro et al., 2009), misoprostol (15-desoxy-16-hydroxy-16-methyl PGE1) which is a stable synthetic analogue form of prostaglandin E1 (DeRossi et al., 2009) and dinoprostone (prostaglandin E2 [PGE2]) by means of vaginal devices. Also, local α1 adrenergic blockers (Padilha-Nakaghi et al., 2020) and the combination of oxytocin and oestradiol (E2) are used both in AI (Jamadi et al., 2017) and in uterine flushing, generally without adversely affecting luteal function (Dias et al., 2020; dos Santos et al., 2020) and lambing rates in ewes (King et al., 2004). However, in vitro studies of bovine luteal cells showed that high concentrations of oxytocin impaired progesterone production whilst low concentrations enhanced it (Tan et al., 1982).

Exogenous oxytocin has shown its effectiveness as a cervical dilator in enabling semen deposition in the uterine body in sheep and goats (Sayre & Lewis, 1996; Ijaz & Aleem, 2006; Viudes-de-Castro et al., 2009), as well as in cattle (Fuchs et al., 2002). Sayre and Lewis (1996) showed that oxytocin administration to ewes facilitated cervical dilation without impairing the transport of semen to the uterine tubes. Oxytocin provokes the release of prostaglandins such as PGE2, which acts on the adjacent connective tissue of the endometrium and smooth muscle cells, thus inducing dilation of the cervix and facilitating sperm transport upon insemination (Falchi & Scaramuzzi, 2015; Stellflug et al., 2001). Nevertheless, contradictory fertility results have been reported regarding the use of cervical dilators. In nulliparous animals, Leethongdee et al. (2020) reported a pregnancy rate of 65% and 56% with the use of hyaluronidase and Flunixin-Meglumine and forceps, enabling cervical traction, to facilitate deposition of the semen within the uterine body (Fonseca et al., 2017). In sheep, the application of oxytocin stimulated contractile activity of the cervix and uterus in vivo and in vitro, dilated the cervix and improved sperm transport after mating but not after insemination with frozen-thawed semen, in which case lambing rate was also depressed (Salamon & Maxwell, 2000).

The objective of the present work was to determine the effect of oxytocin as a cervical dilator on reproductive efficacy in nulliparous goats, 13–14 months of age, at the beginning of the breeding season.

2 | MATERIALS AND METHODS

2.1 | Location of the experiment site

This research was carried out at the Laboratorio de Reproducción Animal, Unidad Academica Marin de la Facultad de Agronomia de la Universidad Autonoma de Nuevo León (25° 23' N, 100° 02' W). The average annual temperature is 22°C, with a maximum temperature of 40°C and a minimum of 4°C.

2.2 | Relevant ethics and animal care documents

The study was carried out under the Mexican government's official criteria on animal health (NOM-059-ZOO-1997 on animal health, use of chemical, pharmaceutical, biological and hormonal products and NOM-062-ZOO-1999 concerning the technical specifications for the care and use of laboratory animals).

TABLE 1 Effect of oxytocin (thexitocin) applied intravenously 10–15 min prior to transcervical artificial insemination in nulliparous goats (13–14 months of age) on time required to inseminate each doe (AI time), depth of penetration into the cervix (PEN), pregnancy and kidding rates and prolificacy (Mean ± *SEM*)

Treatment	Age (months)	Live weight (kg)	Per cent of females in oestrus (%)	Pregnancy rate (%)	Kidding rate (%)	AI time (s)	PEN (cm)	Prolificacy (kids/doe)
Control (saline)	13.28 ± 0.30	32.88 ± 0.57	94.44 (34/36)	61.11 (22/36)	52.78^{b} (19/36)	85.78 ± 4.02^{a}	2.10 ± 0.38^{b}	0.69 ± 0.12^{b}
25 IU Thexitocin	13.77 ± 0.40	33.65 ± 0.77	95.12 (39/41)	82.93 (34/41)	78.05^{a} (32/41)	49.56 ± 5.38^{b}	3.41 ± 0.52^{a}	1.12 ± 0.16^{a}
50 IU Thexitocin	14.07 ± 0.41	33.71 ± 0.79	82.05 (32/39)	76.92^{a} (30/39)	76.92 (30/39)	56.25 ± 5.55^{b}	3.77 ± 0.53^{a}	1.21 ± 0.17^{a}
p value	.27	.60	.08	.02	.08	<.0001	.02	.02

Note: Means within columns with different superscripts are significantly different ($p < .05$). Kidding rate is the number of does kidding/number of does inseminated.

2.3 | Animal handling

The experiment was carried out during the onset of the breeding season (June 2019). One-hundred-and-sixteen nulliparous goats of Alpine ($n = 50$) and Nubian ($n = 66$) breeds, with an average age of 13.7 ± 0.37 months and a body weight of 33.4 ± 0.68 kg, were used.

Fifteen days before the study commenced the goats were treated with anthelmintic (oral administration of 10 ml/kg Closantel 5%; Chinoin) and provided with vitamin supplementation (vitamin A, D and E: 500.000, 75.000 and 50 IU/ml, respectively; Internacional Prode; 2 ml per animal).

2.4 | Reproductive management and oestrus synchronization

All goats reached puberty before the trial began as determined by twice-daily visual observation of the oestrus of each female. All the goats were exposed to a group of four sexually active bucks of proven fertility for a period of 14 d in order to induce sexual activity. The bucks were fitted with an apron tied around their abdomen in order to prevent mating. One week after the bucks were removed, all the does were submitted to the Ovsynch synchronization protocol described by Holtz (2005). Four groups of 20 goats and one of 16 goats were formed to start the Ovsynch protocol with a difference of 2 hr to avoid inseminating too late after the recommended 16 hr. The protocol consisted of 20 mg gonadorelin (Laboratorios Grimaan) applied on day zero, 0.075 mg of cloprostenol (Internacional Prode) on day 7 and finally, a second dose of 20 mg of gonadorelin applied on day 9.

2.5 | Experimental treatments

The goats were divided into three experimental groups. The goats in group 1 (T1; $n = 36$) received 2 ml of 0.9% sodium chloride, as control; group 2 (T2; $n = 41$) and group 3 (T3; $n = 39$) treatments consisted of 25 and 50 IU of oxytocin, respectively (Provena, Laboratorio Internacional Prode). All treatments were injected via the jugular vein 10–15 min prior to the transcervical artificial insemination (AI) taking place. The AI was carried out 16 hr after the second application of GnRH. Oestrus was observed from the second application of GnRH for 40 hr and recorded using a sexually active buck three times a day.

2.6 | Transcervical artificial insemination

Fresh semen, collected using an artificial vagina, from two fertile bucks of Alpine and Nubian breeds was used for transcervical AI. Two consecutive collections of semen from each buck were performed on the day of insemination, with an interval of 1 hr between collections. Immediately after being collected, the samples were placed in a 37°C

water bath to evaluate the following values: mass motility, progressive motility and sperm concentration.

Subsequently, the diluent Andromed (Minitube, Mexico) was used in order to obtain a total of 60 straws of 0.25 ml from each buck, with a concentration of 100 million sperm cells per straw.

The semen was allowed to stabilize at 5°C for at least 2 hr. All inseminations were performed by the same technician at a rate of four goats per batch, with no delay so that the transcervical AI was performed as close as possible to 16 hr after the second application of gonadorelin (Holtz et al., 2008). The hind limbs of the goats were lifted, then the lubricated speculum with a light source was introduced into the vagina to visualize the cervical opening. The insemination gun with a semen straw was introduced into the cervix (Holtz, 2005), and the depth of the cervical penetration of the insemination catheter and time required to inseminate each goat were recorded. Pregnancy diagnosis was carried out 45 days after insemination, using transrectal ultrasound (Sonoscape E2. USA).

2.7 | Statistical analysis

The experimental groups were balanced for age, body weight and percentage of goats in which oestrus was induced by a vasectomized adult male. Statistical analyses were performed using SAS version 9.0 (SAS Institute Inc.).

The time required to inseminate each goat (TIA), the depth of the cervical penetration of the insemination catheter (PEN) and prolificacy, were analysed with a linear model, using the GLM procedure. The model included the fixed effect of oxytocin treatment and residual error. Least-squares means for each treatment were obtained and used for multiple mean comparison using the Tukey test. Pregnancy and kidding rates were analysed through a contingency table with chi-square tests using the FREQ procedure. Kidding rate is defined as the proportion of does that kidded. Prolificacy is the number of kids per does that kidded.

3 | RESULTS

Table 1 presents the main effects of the application of oxytocin in nulliparous goats. A shorter time ($p < .0001$) was required to perform AI and a greater cervical depth of penetration ($p = .02$) was achieved in goats treated with oxytocin than in control (saline-treated) goats. The mean times required to inseminate goats treated with 25 and 50 IU of oxytocin were 49.56 and 56.25 s, respectively, whilst in the control group of goats, the mean time was 85.78 s. The depths of cervical penetration in goats treated with 25 and 50 IU of oxytocin were 3.41 and 3.77 cm, respectively, which were deeper ($p = .02$) than in the case of the T1 group. Pregnancy rate was greater ($p = .02$) for goats treated with oxytocin than for the T1 group of goats. The prolificacy of the T1 group goats was 0.69 ± 0.12, which was less ($p = .02$) than the prolificacy of the T2 and T3 groups. The proportion of goats in oestrus tended ($p < .08$) to be less in does that received the highest dose of oxytocin than in the other two groups.

4 | DISCUSSION

The objective of this study was to evaluate the application of exogenous oxytocin as a cervical dilator in nulliparous goats 13–14 months of age at the beginning of the breeding season. The application of OT induced cervical dilation and improved the semen deposition depth in young nulliparous goats as it did in adult goats in the trial of Viudes de Castro et al. (2009). Oxytocin promotes the release of arachidonic acid to be converted by cyclooxygenase 2 into prostaglandin H, which is the precursor of PGE2 (Falchi & Scaramuzzi, 2015) and subsequently acts on the adjacent connective tissue and smooth muscle cells (Fuchs et al., 2002). In sheep also, the administration of oxytocin stimulated both cervical dilation and uterine/oviductal contractility (Lu et al., 2021).

Most inseminators report both having difficulties passing the cervical canal in nulliparous goats and a negative effect of increased genital stimulation at the time of AI on the first-service conception rate. Given that each cervical canal is anatomically different, the depth of cervical penetration depends on the inseminator's abilities. Therefore, if oxytocin in not used as a cervical dilator, few cervical canals of nulliparous goats can successfully be penetrated (Houdeau et al., 2008). In our study, the insemination was carried out by a single expert inseminator in order to prevent undesired cervical lesions, which in both sheep (Seifi-Jamadi et al., 2017) and goats (Houdeau et al., 2008), have a negative effect on pregnancy rates. The application of oxytocin dilated the cervix and enabled a deeper penetration of the cervical canal (1.3 and 1.7 cm for goats treated with 25 IU and 50 IU of oxytocin, respectively) compared with the control group of goats.

There was a trend that goats that received the highest dose of oxytocin (50 IU Oxytocin) presented a lower incidence of oestrus (13% less), resulting in a 6% lower kidding rate, which may be due to other factors unrelated to the effect of the application of oxytocin. Similarly, King et al. (2004) reported in ewes, that administration of 10 IU oxytocin resulted in a 10% reduction in the number of ewes lambing. However, in the present study, oxytocin increased the prolificacy whilst King et al. (2004) found no effect on litter size. This may be because high doses of oxytocin increase uterine contractions and may have a negative effect since they can evacuate the uterine contents before optimal colonization of the oviductal isthmus with spermatozoa, causing a decrease in fertility (Ijaz & Aleem, 2006; Lu et al., 2021). The luteolytic effects of oxytocin up to now could be limited, since it has been found that when applied intramuscularly in ewes, the concentrations levels in the peripheral plasma decrease from 90 min after its application (King et al., 2004). However, in ewes, 15% and 20% higher pregnancy and lambing were found rate when applying 100 and 150 IU of oxytocin via intramuscular and intravenous routes (Seifi-Jamadi et al., 2017).

The shorter insemination time in the goats treated with oxytocin could also favour prolificacy, as the time that the semen remained in the insemination catheter was shorter in the present study, but the time needed to perform the AI was longer (52.91 s) compared with that reported by Houdeau et al. (2008), who also inseminated nulliparous goats (39.0 s).

In addition, higher pregnancy and kidding rates obtained after applying the oxytocin protocol could be primarily due to the accomplished deeper cervical penetration, in contrast to results reported in adult goats by Viudes-de Castro et al. (2009) who applied higher oxytocin doses (100 IU and 200 IU) and in sheep where the oxytocin was administered intramuscularly prior to transcervical AI (King et al., 2004). However, Prellwitz et al. (2019) found no difference in the embryo recovery rate after the administration of exogenous oxytocin by different routes.

In the present study, the effect of low doses of oxytocin applied intravenously was assessed. The short oxytocin impulse created this way improved the measured reproductive parameters. In contrast, in a previous study conducted in sheep, the intramuscular application of 10 IU of oxytocin resulted in the highest concentration 15–45 min after application and resulted in a decreased lambing percentage (King et al., 2004).

The use of oxytocin and its impact on the prolificacy rate, at least in sheep, has been contradictory. For example, in a study carried out in adult ewes using 10 IU of oxytocin to perform transcervical insemination, litter size was not affected, compared to those that were not treated (King et al., 2004). In our study, the higher prolificacy achieved in the goats treated with oxytocin could be due to a direct effect of oxytocin on the ovulation rate, as found in sheep (King et al., 2004). This may be due to the fact that at some point oxytocin can modulate the selection of premature follicles in the last phase before ovulation, increasing the release of plasma leptin, as reported by Bobowiec et al. (2003), who found that the ovulation rate increased 0.3 per ewe when oxytocin was administered intravenously for a period of 24 hr every 30 min after the onset of oestrus. In contrast to our results, administration of 100 IU oxytocin to Iranian Zel ewes, improved pregnancy and lambing rates but had no effect on prolificacy (Seifi-Jamadi et al., 2017) but the very large difference in oxytocin dose prevents a valid comparison.

Oxytocin seems to improve sperm transport from the cervix, thus increasing the number of sperm reaching the fertilization site and the number of fertilizations (Viudes-de-Castro, 2009). This can be seen in the effect of a short impulse of oxytocin, achieved after intravenous application that simulates clitoral stimulation by males during natural mating in goats, which contracts the smooth muscle of the genital tract and improves sperm transport towards the place of fertilization (Sayre & Lewis, 1996). Nevertheless, injection or 1 IU of oxytocin failed to alter reproductive performance of Saanen goats (Kandemir et al., 2017), but again the dose, in this case very low, and applied intramuscularly, prevented any conclusion.

The results from the present study suggest that oxytocin can be used in nulliparous goats to be artificially inseminated with semen of bucks of high genetic merit creating opportunities to increase genetic progress of the flock through higher selection intensity of bucks and does and reduction in the generation interval. Therefore, even though oxytocin has been studied for more than two decades as a cervical dilator for artificial insemination and in recent years in the transcervical lavage of embryos, more research is required in goats regarding the dose, route and frequency of oxytocin application to find the optimal dose that dilates the cervix without affecting the fertility of transcervically inseminated goats.

5 | CONCLUSIONS

Overall, we concluded that the intravenous administration of oxytocin at the beginning of the breeding season in nulliparous goats induced cervical dilation allowing deeper cervical penetration and deposition of semen; this resulted in higher pregnancy and kidding rates and prolificacy.

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CONFLICT OF INTEREST

There are no conflicts of interest between the authors involved in the present study.

AUTHOR CONTRIBUTIONS

F. Sánchez-Dávila involved in conceptualization, writing, validation, review and formal analysis. V. Alvarado-Gutierrez and R.A. Ledezma-Torres involved writing, review, investigation and methodology. C. Luna-Palomera involved writing, investigation and methodology. Sam Peterson, José Fernando Vázquez-Armijo, Nicolás López-Villalobos, E. Garza-Brenner and Juraj Grizelj involved writing and review.

DATA AVAILABILITY

The database is available upon request from the reader from the author by correspondence.

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