ORIGINAL PAPER

Drugs used during embryo transfer to improve pregnancy rate

August, 2025

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ABSTRACT

The results in embryo transfer (ET) have been very varied and not very encouraging, recognizing embryo implantation as the most important step to achieve pregnancy. This failure is due to multiple factors, which is why various methods have been implemented to mitigate this negative effect and increase the pregnancy rate. Hormones, oligoelements, oxytocin inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) have been used, with very diverse results, which depend mainly on the species in which they are used, the dose, site and time of application. This document compiles a variety of information on the different drugs and treatments used in various species at the time of ET and their results.

Keywords: embryo transfer, pregnancy rate, hormones, oligoelements, oxytocin inhibitors, NSAIDs.

RESUMEN

Los resultados en la transferencia de embriones (TE) han sido muy variados y no muy alentadores, reconociendo a la implantación del embrión, como el paso de mayor importancia para lograr la gestación. Esta falla se debe a múltiples factores, es por ello que se han implementado diversos métodos para mitigar este efecto negativo e incrementar la tasa de gestación. Se han empleado hormonas, oligoelementos, inhibidores de oxitocina y antiinflamatorios no esteroideos (AINES), con resultados muy diversos, los cuales dependen de la especie en la que se emplean, la dosis, sitio y momento de aplicación, principalmente. Este documento recopila información variada sobre los diferentes medicamentos y tratamientos utilizados en diversas especies al momento de realizar la TE y sus resultados.

Palabras clave: *transferencia de embriones, tasa de gestación, hormonas, oligoelementos, inhibidores de oxitocina, AINES.*

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https://doi.org/10.58149/aq0m-gs34

INTRODUCTION

The optimization of assisted reproduction techniques is necessary to maintain profitable cattle breeding (Ribeiro *et al*., 2012); among these techniques is embryo transfer (ET), which has been used in veterinary practice for the last five decades, and its efficacy depends on several conditions, including individual, environmental, technical and technological (Hasler, 2014). In the bovine industry, ET is the extraction of one or more embryos from the reproductive tract of a donor cow, to later transfer them to the lumen of the oviduct or uterus of one or more recipient cows. It is used to obtain a maximum number of embryos from a genetically superior sire in the shortest possible time and thus maximize the genetic potential in a herd, obtaining females or sires with outstanding productive characteristics; however, ET is limited by the critical implantation process (Hasler, 1992; Elli *et al*., 2001; Bó y Mapletoft, 2014).

There are many factors that prevent the embryo from implanting, such as stage of development, the quality of the embryo transferred, types of transfer (fresh or thawed), synchrony between donor and recipient, physiological state or age of the recipient, and the functioning of the corpora lutea (CL) (Purcell *et al*., 2005). Another undoubtedly important factor is the skill of the technician in charge of performing the ET and the time taken to carry it out, since excessive manipulation of the uterus or the passage of the transfer pipette causes an inflammatory response to be unleashed and the spontaneous rupture of the uterus (Van Gestel *et al*., 2003).

Due to the above, various treatments have been implemented with the objective of increasing the concentration of progesterone (P4) post-ET and decreasing the harmful effects of PGF2α on embryo implantation, such as the case of non-steroidal anti-inflammatory drugs known as NSAIDs (Elli *et al*., 2001; Jaśkowski *et al*., 2021), which, according to a meta-analysis, manage to increase the rate of gestation after ET by at least 15% (Besbaci *et al*., 2021). In addition to the use of oxitocin inhibitors that decrease uterine contractions at the time of ET, and thus increase implantation in women (Huang *et al*., 2017). In addition to this, several hormones such as human chorionic gonadotropin (hCG) and gonadotropin releasing hormone (GnRH) have been administered with the purpose of increasing endogenous P4 before or after ET with contrasting results (Purcell *et al*., 2005). Likewise, the application of P4 via intramuscular (IM) or intravaginal devices, have not been shown to improve the post-ET gestation rate ET (Tribulo *et al*., 1997; Purcell *et al*., 2005; Chagas e Silva *et al*., 2008) or five days after artificial insemination (Roque *et al*., 2016).

On the other hand, various trace elements have been evaluated in ET, either to improve the quality and production of embryos in vitro, where they have been shown to have a beneficial effect (Van Emon *et al*., 2020); however, when used in donors, this effect has not been clearly established (Da Silva *et al*., 2018). However, in recipients, they have been shown to improve the luteal response and increase embryo survival (Sales *et al*., 2011).

Failures in the establishment of gestation and embryo mortality

In general, embryo implantation is the most critical step to obtain a pregnancy in embryo transfer, which is why nowadays there is a lot of research directed to try to facilitate this step (Elli *et al*., 2001). Currently, it has been possible to increase fertilization rates in cattle to values of 80 to 95%; however, there are still deficiencies in the establishment of gestation, being embryonic mortality (EM) the one that stands out as the greatest source of reproductive loss (20-40%) (Hanzen *et al*., 1999). There are a variety of potential causes of EM including chromosomal abnormalities, failure of maternal gestational recognition (MGR), environmental stress factors such as heat, toxins, and infectious diseases (Hansen, 2002). In 40% of cases, the EM occurs before the MGR (between day 8 and 17) (Thatcher *et al*., 1994) and increased early endometrial secretion of PGF2α (Thatcher *et al*., 2001). Another important factor is the type of embryo transferred; Siqueira et al. (2009) achieved a post- ET gestation rate of 58.8% vs. 31.0% for embryos obtained in vivo and in vitro, respectively.

Okada *et al*. (2016) state that the low percentage of pregnancy in recipients may be due to the contamination of the uterus that could occur at the moment of performing ET, as well as the manipulation of the genital tract during the maneuver, which would cause the release of PGF2α, enough to cause luteolysis and embryonic death (Ferguson's reflex) (Ferguson, 1941). When difficulty in ET occurs or when the technician in charge is inexperienced, the uterus can be manipulated to great excess. Schrick *et al*. (2003) mention that there is a significant decrease in the gestation rate when difficulty in ET is encountered; they attribute this to PGF2α secretion. Another possible cause of PGF2α release at the time of ET is when the catheter passes through the cervix into the uterus, which could cause irritation of the reproductive tract and subsequent inflammation (Odensvik *et al*., 1993); such PGF2α release was demonstrated when Scenna et al. (2005) performed serum profiles of this hormone after ET, and found that such manipulation of the reproductive tract during ET was followed by increased PGF2α release from the uterine endometrium.

Gordon (1976) demonstrated that when ET took longer than 3 minutes, it reduced the gestation rate; likewise, Tervit *et al*. (1980) asserted that pregnancy was affected by the time used to perform ET, which varied between 0.7 to 6.3 minutes with a mean of 1.8 minutes. In addition, when the maneuver is performed clumsily, it causes irritation of the endometrium, which can lead to a decrease in the implantation rate.

The experience of the technician in charge of performing ET is important, since the time that elapses in crossing the cervix and depositing the embryo is fundamental to achieve pregnancy; for which, the embryo must be placed in the uterine horn ipsilateral to the corpus luteum to help the maternal recognition of gestation (Cutini *et al*., 2000). This site has been the subject of study; however, if the embryo was of quality I, there is no influence on the deposit site on the pregnancy percentage (Hasler, 2010).

Difficulty in ET causes premature regression of the CL by secretion of PGF2α and decrease in P4, also causing release of OT and with it contractions of the myometrium, thus inducing embryonic death and reabsorption (Echeverría, 2006). In addition, it has been shown that bovine epithelial cells secrete PGF2α consequently in response to OT secretion causing luteolysis (Takahashi *et al*., 2001). PGF2α may have a direct effect on the embryo, reducing the rate of gestation (Purcell *et al*., 2005; Cardoso, 2009; Kim *et al*., 2014). In several in vitro embryo production studies, PGF2α was added to the culture medium, which inhibited development to the morula and expanded blastocyst stage (Breuel *et al*., 1993) and decreased the rate of hatched blastocysts (Schrick *et al*., 2003) in several species

(Kim *et al*., 2014). This decrease could be due to an alteration in Na^+ transport (MacPhee et al., 2000).

Stocco *et al*. (2007) indicate that PGF2α alters steroidogenesis by decreasing cholesterol transport into the mitochondrial membrane, negatively affecting P4 production. In addition, PGF2α has been implicated in the production of Endothelin-1 in the CL, which in turn decreases blood flow, inhibiting P4 production in steroidogenic luteal cells (Ohtani *et al*., 1998).

Antiluteolytic strategies to improve gestation rate

Any improvement in gestation rate or decrease in EM will lead to better productive numbers in cattle (Purcell *et al*., 2005). Binelli *et al*. (2001) identified 6 antiluteolytic strategies to improve gestation rate including: 1) an increase in the size of the preovulatory follicle to generate a larger CL, 2) increase the growth rate of the CL, 3) increase the luteal phase and thus P4, 4) decrease the effect of a dominant follicle on the critical period, 5) increase antiluteolytic stimulation by the conceptus and 6) decrease maternal luteolysis.

In addition to the above, another tactic widely used with success in ET is the use of nonsteroidal anti-inflammatory drugs (NSAIDs), among which there are selective NSAIDs to inhibit cyclooxygenase-2 (COX-2), an enzyme that participates in the synthesis of PGF2α, helping improve implantation and pregnancy rates in different species (Elli *et al*., 2001; Moon *et al*., 2004; Scenna *et al*., 2005; Paksoy y Daş, 2013; Schlapp *et al*., 2015; Jaśkowski *et al*., 2021). Besbaci *et al*. (2021) in a meta-analysis report relevant results in the establishment of gestation using NSAIDs in ET when applied in cows with difficulty in passing the catheter through the cervix during ET, resulting in up to 15% more probabilities of achieving implantation after treatment with some NSAID in comparison with the control group.

Prevention of the synthesis of PGF2α

Pinto *et al*. (2008) point out that one of the mechanisms of maternal recognition consists in the inhibition of PGF2α synthesis; as a consequence, the metabolism of arachidonic acid is stopped, and PGF2α is not formed; the CL is preserved and therefore the concentration of P4 is maintained at an optimal level to allow the establishment of pregnancy.

PGF2α acts very actively on the CL, promoting vasoconstriction of the vessels that irrigate the luteal cells and consequently luteolysis occurs (Pinto *et al*., 2008), which is characterized by a rapid decrease in P4 after 8 to 12 hours after the release of PGF2α began (Kim *et al*., 2014); that is to say, the premature secretion of PGF2α will produce a short luteal phase (Schrick et al., 1993).

The availability of arachidonic acid and endoperoxidase synthases (COX-1 and COX-2) is the two limiting factors of PGF2α secretion (Thatcher *et al*., 1997). COX-2 mRNA expression is significantly decreased during days 1 - 12 of the estrous cycle, increasing at the end of the estrous cycle (days 13 - 21), near the time of luteolysis (days 16 - 18), when PGF2α secretion from the uterine endometrium is increased (Arosh *et al*., 2002). During gestation, COX-2 mRNA expression was significantly higher in the bovine uterus and fetal membrane during early (<50 d) and late (>250 d) pregnancy than at mid-pregnancy, whereas COX-1 mRNA was expressed at low levels throughout gestation (Arosh *et al*., 2004).

Certain compounds could inhibit the action of cyclooxygenases. Some polyunsaturated fatty acids prevent prostaglandin synthesis by inhibiting cyclooxygenases activity and competing with arachidonic acid for processing by enzymes, such as linoleic acid (Thatcher *et al*., 1994), eicosapentaenoic, and docosahexaenoic acid (Thatcher *et al*., 2001).

Another method that inhibits PGF2α release is through the use of NSAIDs, whose main actions are antipyretic, anti-inflammatory, and analgesic; these actions prevent PGF2α synthesis through the inhibition of COX-1 and COX-2 enzymes; competing with arachidonic acid (released in the inflammatory response) for the active sites in the enzymatic channels (González *et al*., 2002).

- **Flunixin meglumine (FM).** FM injected at the time of ET can improve the gestation rate of embryo recipient females during uterine manipulation, which can cause PGF2α release from the endometrium and subsequent gestation loss (Ferguson, 1941; Purcell *et al*., 2005; Schrick *et al*., 2003; Farias *et al*., 2013). In a study by Schrick *et al*. (2001), a total of 737 cows were injected with 10 mL of FM immediately after fresh and thawed embryo transfer. The gestation rate was higher in FM-administered cows than in the control group (63.8 and 51.1%, respectively). In another similar experiment conducted by Scenna *et al*. (2005), where they also used FM after ET in 1300 cows and 797 as a control group, the result was that pregnancy rates were higher in those cows treated with FM (65%) vs. (60%) of the control group.

  Purcell *et al*. (2005) conducted a study with beef cattle, applying a 500 mg dose of FM 2-12 minutes before ET or inserted CIDR shortly after ET. The first of the four groups was designated as the control group, CIDR to the second group, FM to the third group, and the combination of FM with CIDR to the fourth group. The gestation rates were 65%, 60.7%, 74.7% and 69.8%, respectively. Thus, they concluded that FM aids pregnancy establishment in the ET of cattle. In addition, Merrill *et al*. (2007) demonstrated that IM administration of FM decreased serum PGF2α concentration and increased the percentage of gestation in cattle. These results agree with Yoon *et al*. (2011) who increased the pregnancy rate for in vitro produced embryos (IVP) after ET after FM administration compared to the control group (76.7% vs. 70.0%, respectively) in heifers.

  On the other hand, McNaughtan (2004), who injected 10 ml of 2.5 mg/kg FM to heifers just before ET, identified during pregnancy diagnosis at 90 d after ET, that there was no difference between the treatment and the control group (50% vs. 45%). In another similar study, Bülbül *et al*. (2010) administered 500 mg of FM IM five min before ET to 39 Swiss cows; pregnancy diagnosis was performed at 30 d post-ET, resulting in a 50% pregnancy rate for the FM-treated group vs. 52.6% for the control group. This can be associated with the study by Schlapp *et al*. (2015) who assert that FM improves the birth rate but not the gestation rate, suggesting that its effect is mainly associated with embryo survival rather than luteal maintenance.

  Although the use of FM does not influence the increase in P4 concentration during the luteal phase, it allows the fall in P4 concentration to be progressive in the treated animals and not abrupt as occurred in the control group, thus allowing early luteolysis not to occur (Pinto *et al*., 2008). Several authors (Aké-López, 2002; Aké-López *et al*., 2011; Geary *et al*., 2010) assert that the application of FM allowed a lengthening of the luteal phase and consequently delayed luteolysis, suppressing the synthesis of PGF2α and providing more time for maternal recognition of gestation and its success.

Recent studies (Kasimanickam *et al*., 2018) report that recipient cows with a calm temperament had a higher pregnancy rate compared to those with an excited temperament (59.4 vs. 51.7%). Subsequently, they obtained a lower pregnancy rate in excited cows without FM (46.3%) than that achieved in those excited cows that received FM (56.8%) and calm cows that received FM (59.3%) or not (59.4%), respectively. In addition, Kasimanickam *et al*. (2019) were able to increase gestation rate by 62.8% for FM vs. 51.2% of the control group respectively after application of 1.1 mg/kg of FM via IM.

- **Meloxicam (MEL).** Another NSAID widely used as a selective COX-2 inhibitor is MEL, which has anti-inflammatory, analgesic and antipyretic effects. It has a half-life of 13 h in cows. It is used IM, IV and SC in single doses of 0.5 mg/kg (Radostits *et al*., 2006; Plumb, 2011). In heifers that received Nelore embryos, it had a positive effect on the pregnancy rate when they were treated with MEL (200 mg per head) before ET, which reduced the serum level of PG, which in turn, was produced in lower quantity after uterine manipulation and thus, a lower influence on the possible destruction of the CL (Lopes *et al*., 2015); the gestation rate obtained in recipients where there was a short period of time in passing the cervix (<80 s) and performing ET, was significantly higher (90.48%) compared to the control group (47.62%) when quality I embryos were transferred. No differences were found with the use of quality II embryos (54.54% vs. 42.86%, respectively, for the MEL and control groups). Aguiar *et al*. (2013) obtained similar results using IVP embryos, where the recipients treated with MEL had a higher implantation rate (66.7% vs. 49%, respectively, for MEL and control). Even clearer differences were observed when there was difficulty in passing the pipette through the cervix (> 80 s), where 78.84% of gestations were achieved in recipients with MEL, compared to the control group (21.15%).
- **Ibuprofen.** In a study carried out by Elli *et al*. (2001) the application of ibuprofen was investigated on the implantation rate during ET in cattle, for which they administered 5 mg/kg of ibuprofen IM 1 h before ET; obtaining a gestation rate for the ibuprofen group of 82% vs. 56% of the control group, managing to demonstrate that the application of ibuprofen in ET significantly increases the percentage of pregnancy. In addition, Narvaez et al. (2010) asserted that Ibuprofen administered IM (5 mg/kg) had a significant effect in increasing pregnancy in Nelore recipients with embryos of grade I quality and the administration of the anti-inflammatory 1 h before ET (43.3% vs. 14.4% for the ibuprofen and control group, respectively).
- **Tolfenamic acid.** Tolfenamic acid has recently been used in recipient females subjected to ET, improving pregnancy maintenance and embryo survival in mice (Schlapp *et al*., 2015). Singh *et al*. (2020) assert that combined therapies of buserelin acetate, progesterone and tolfenamic acid may be beneficial in AI in cattle crossbreds.
- **Aspirin.** Aspirin has the potential to be both antithrombotic and thrombogenic, thus, the use of low-dose aspirin treatment in ET programs increased uterine and ovarian blood flow velocity, improving the ovarian responsiveness and gestation rate when PIV embryos patients were transferred (Rubinstein *et al*., 1999).

OT antagonist (Atosiban)

Mann *et al*. (2003) used an OT antagonist (L-368,899) in sheep, reducing PGFM (PGF2α precursor) production during the period of luteolysis, lengthening the estrous cycle by a few days; in goats, it reduced CL regression between days 12 to 20 by suppressing PGFM concentration beyond day 20 (Homeida y Khalafalla, 1987). In addition, Skarzynski and Okuda (1999) reported a decrease in the secretion of PGFM in luteal cells using Atosiban (10-7 M), with no effect of OT on its production. All this suggests that the use of an inhibitor of OT secretion could improve the gestation rate after ET; there are no studies on this subject in cattle.

Progestogens: effect on gestation rate

An elevated P4 concentration in the immediate post-conception period has been associated with embryo growth, conceptus elongation, increased IFN-τ production and, in some cases, a higher gestation rate in cattle (Lonergan y Sánchez, 2020).

Increased P4 can be achieved either by formation of an accessory CL or by administration of exogenous P4 (Thatcher *et al*., 1997). Such hormone can be administered as a feed additive, as an ear implant, or an intravaginal P4-releasing implant; alternatively, endogenous P4 can be elevated if an accessory CL is formed, followed by administration of hormones such as hCG or GnRH since these hormones cause luteinization of the follicles (Purcell *et al*., 2005).

Roque *et al*. (2016) administered P4 IM (500 mg) at 5 days post-IA to increase the conception rate, however, there was no difference between treatments. On the contrary, when using exogenous P4 during ET, encouraging results have been obtained, especially when administered to asynchronous recipients (Randi *et al*., 2016), resulting in an acceleration of conceptus development, but not in a higher pregnancy rate.

Siqueira *et al*. (2009) assert that there is no correlation between CL size and P4 production and that this does not affect implantation. However, several treatments have been implemented to increase the level of P4 in the ET to help increase the implantation rate (Purcell *et al*., 2005; Wallace *et al*., 2011). Treatment with hCG in the ovulation period can promote an increase in P4 by stimulating luteal tissue, thus helping to prevent early embryonic losses, as well as positively influencing embryo development (Köhne *et al*., 2014). With the application of GnRH analogues, an increase in circulating LH was observed not only in the preovulatory period, but also in various stages of the estrous cycle (Castro *et al*., 2016; Brito *et al*., 2017).

Various P4 presentations have been applied during ET, such as melengestrol acetate (MGA), ear implants (Norgestomet) (Favero *et al*., 1993; Smith *et al*., 1996) and CID-R® (Pfizer; New York, NY) (Tribulo *et al*., 1997; Purcell *et al*., 2005; Chagas e Silva *et al*., 2008) all of them with discouraging results in increasing gestation. In addition, Kenyon *et al*. (2013) evaluated the effect of P4 needed to maintain gestation in Holstein cows in post-ET lactation, concluding that a faster increase in P4 concentration during metestrus and early diestrus is associated with the establishment of pregnancy after ET, inferring the modulation of the uterine environment, histotroph secretion, adhesion and placentation. Another study used in vitro embryos transferred to the oviduct on day 2. Thirty-four females were used as recipients, of which 17 belonged to the control group and 17 received the insertion of a P4 intravaginal releasing device (PRID) from d 3 until embryo retrieval; this resulted in a significant elevation of P4 concentration from d 3.5 to d 6, however, elevated P4 did not affect the proportion of embryos that developed to the blastocyst stage (Carter *et al*., 2010).

hCG to stimulate the luteal response

Lewis *et al*. (1990) evaluated hCG 6 h before AI and 6 h after AI. The pregnancy rate of cattle treated with hCG ranged from 10 to 25% higher than that of the control group. In another study, Wallace *et al*. (2011) evaluated the use of 1000 IU of hCG or 1 mL of saline solution (control) at the time of ET (day 5.5 to 8.5 after estrus). 69% of cows treated with hCG had multiple CL and the pregnancy rate ranged between 61.8 and 58.6% for hCG and 53.9 and 51.3% for the control group, in both experiments; thus, the use of hCG in ET increases the incidence of CL and the pregnancy rate.

On the other hand, Santos *et al*. (2001) conducted a study where 406 high producing dairy cows were synchronized and treated by AI, then injected with saline (n=203) or 3,300 IU hCG (n=203) on d 5 post-estrus. Accessory CL were formed in 86.2% (n=175) of the cows treated with hCG. The plasma concentration of P4 from day 11 to 16 after AI increased on average 5 ng/mL while the conception rate at day 28 was 38.7% for the control group and 45.8% for hCG. Similar results were obtained after AI by administering hCG on day 7 post-AI, increasing the pregnancy rate (Rajamahendran y Sianangama, 1992). However, Walton *et al*. (1990) did not observe differences in the pregnancy rate of cows treated with 1500 IU of hCG 5 d after AI. Lewis *et al*. (1990) conducted a study in which they included GnRH and hCG after AI, in which, although the hCG treatment significantly increased the concentration of P4 in milk, there were no significant differences observed in the pregnancy rate between treatments. Similar results were obtained by Alonso *et al*. (2017) in mares.

Recently, a meta-analysis (Chen *et al*., 2023) has been carried out in which it is asserted that the use of GnRH and hCG only influences those females with poor fertility (<40%), increasing the conception rate, while in cows with good fertility (>40%), this rate is not affected. Treatment with GnRH or hCG also significantly improves pregnancy rate in multiparous lactating cows compared to nulliparous ones.

Oligoelements in ET

There are various trace elements that are essential for proper cellular functioning in various physiological states, both in the mother and offspring, however it is unknown which ones and in what quantities they are needed (Van Emon *et al*., 2020). Due to the above, various trace minerals have proven their value in in vitro embryo culture, improving the production and quality of embryos, such as: Cu (Rosa *et al*., 2016), Fe (Gao *et al*., 2007), Mn (Anchordoquy *et al*., 2016), Se (Lizarraga *et al*., 2019) and Zn (Wooldridge *et al*., 2019). In the same way, its effect on chromosomal stability has been evaluated, which depends significantly on the level of vitamin B9 (folic acid) in the blood, since as its content increases, the level of damage to the DNA decreases. For Zn, Ca and vitamin B12 there was no significant difference (Wójcik *et al*., 2023).

Lamb *et al*. (2008) conducted a study in which embryo donor cows were supplemented with organic, inorganic and non-supplementation minerals (control) to assess embryonic production and quality. They found no significant difference between treatments; therefore, the source of minerals does not influence the quality or number of embryos. Similarly, da Silva *et al*. (2018) supplemented donor cows with 90 mg Cu, 60 mg Mn, 30 mg Se and 360 mg Zn (Multimin® 90) as treatment 1 and treatment 2 (control). The results they obtained were increased concentration of Se in the liver; however, there was no effect on embryo production or gestation rate in the recipients of these embryos.

In another study by Marquezini *et al*. (2010), embryo donor cows were supplemented with Nutrition Horizons Grade OneTM bioactive peptides and oligosaccharides; Brookville, OH), group NHG1 (n = 35) and without them, control group (n = 37). The number of embryos collected did not differ between treatments, however, the quality of transferrable embryos (quality 1) improved after donor cows received NHG1 prior to embryo collection. In addition to this, the oocyte appears to be susceptible to maternal dietary supplementation of trace elements (amino acid complexes of Zn, Cu and Mn, as well as glucoheptonate of Co; Availa Plus; Zinpro Corp.), as the pre-oocyte collection supplementation by Ovum Pick-Up (OPU) increased the number of cumulus-oocyte complexes (COC) collected and increased oocyte maturation rates during in vitro culture (Dantas *et al*., 2019).

Understanding the cow's productive cycle and manipulating the diet will improve the ability of receiving cows to conceive with the transferred embryo (Mapletoft *et al*., 1986; Beal, 1999). Supplementation with injectable trace elements 11 days before AI tended to decrease the diameter and volume of LC, although progesterone concentration was not affected (Vedovatto *et al*., 2019). This suggests that luteal cells can produce P4 more efficiently after supplementation with injectable trace minerals improving oocyte quality and LC function (Van Emon *et al*., 2020). In addition, subcutaneous administration of Multimin® 90 (100 mg Zn, 100 mg Mn, 50 mg Cu and 25 mg Se) 17 days before ET did not increase the number of successfully synchronized heifers, although it did increase the rate of conception (embryonic survival) 23 and 48 days after TE in crossed heifers Bos indicus x Bos taurus (Sales *et al*., 2011).

CONCLUSIONS

Understanding the various drugs applied during ET, as well as knowledge of the diversity of failures in establishing pregnancy, are of great importance to increase the pregnancy rate during ET programs and achieve elite animals by reducing the generation interval.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare in regard to this publication.

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