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# COMPARISON BETWEEN THE EFFECT OF ATOSIBAN AND PIROXICAM ADMINISTRATION BEFORE EMBRYO TRANSFER ON *IN VITRO* FERTILIZATION OUTCOME

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**Abstract**

Embryo implantation is the most critical step in assisted reproduction treatment and is influenced by multiple factors, including the age of the patient, embryo quality, and endometrial receptivity. Uterine contraction induced by the embryo transfer (ET) process may have an adverse effect on embryo implantation.

To compare the effect atosiban and piroxicam administration at day of embryo transfer on implantation rate, clinical pregnancy rate, miscarriage rate and live birth rate.

The study included 60 patients diagnosed with primary or secondary infertility caused by a male or tubal-related factor, mild endometriosis or unexplained factors. The patients were divided randomly into two groups. First group were administered bullous dose of atosiban (6.75 mg) intravenously 30 minutes before ET, the second group received piroxicam suppositories 20 mg 1-2 hrs. before ET. Pregnancy outcome analyzed and compared between the two groups.

Atosiban demonstrated higher pregnancy, implantation, live birth rates than piroxicam group (60 % versus 53.3 %), (37.8 % versus 23.9 %) and (94.4 % versus 81.25) respectively, and lower miscarriage rate compared to piroxicam (5.6 % versus18.75 %), however there was no significant differences between the two groups regarding the ICSI outcome with *p* value greater than 0.05.

**Keywords**: atosiban, piroxicam, embryo transfer

## Introduction

Uterine contraction induced by the embryo transfer (ET) process may have an adverse effect on embryo implantation. Supraphysiological serum estradiol (E2) concentrations following an ovarian stimulation cycle may induce the endometrial production of oxytocin and the expression of oxytocin receptors, as well as the synthesis and release of prostaglandin F2α indirectly [1].

Approximately 30% of patients who undergo ET have excessive uterine contractions (> 5 per minute), which have been significantly associated with worse in vitro fertilization (IVF) outcomes [2].

Exaggerated uterine contractions before embryo transfer are observed in one third of women undergoing controlled ovarian stimulation. Detection of such patients could enable their qualification for pharmacologic treatment [3].

**Atosiban** (Tractocile; Ferring Arzneimittel, Kiel, Germany), a mixed vasopressin V1a and oxytocin receptor antagonist, has been registered for the treatment of imminent premature birth with minimal side effects. While the nanopeptide hormone oxytocin plays an important role in many reproductive functions, it was believed to have significance for uterine contractility in the non-pregnant uterus [4].

**Piroxicam**

Prostaglandin, which is synthesized from arachidonic acid by cyclooxygenase (COX), stimulates uterine contraction. Nonsteroidal anti-inflammatory drugs (NSAIDs) block the action of COX and inhibit the production of prostaglandin. Piroxicam is the most effective of all NSAIDs in the clinical relief of dysmenorrhea. It has been used before embryo transfer in various studies with different results. Its mechanism of action, although being similar to other NSAIDS, is not completely understood, but may be related to prevention of prostaglandin synthesis by a reversible inhibition of the cyclo-oxygenase enzyme [5].

**Aim of the study**

To compare effect of atosibam and piroxicam given at day of embryo transfer on:

- Implantation rate
- Clinical pregnancy rate
- Miscarriage rate
- Live birth rate

## Methods

The study involved 60 patients aged between 18 and 40 years old, diagnosed with primary or secondary infertility caused by a male or tubal-related factor, mild endometriosis or unexplained factors.

Antagonist protocol had been chosen for each patient according to her age, history and hormonal assay. Follow up of patients done with serial vaginal ultrasound and serum level of estradiol, then accordingly ovum pick up done.

Trans vaginal ultrasound guided Oocyte retrieval done after triggering of ovulation with HCG about 34-36 hrs.

At the day of embryo transfer, usually 2or 3 days (according to the number and grading of oocytes), the patients were divided randomly into two groups. First group were administered bullous dose of atosiban (6.75 mg) intravenously 30 minutes before ET, the second group receive piroxicam suppositories 20 mg 1-2 hrs. before ET. Serum ß-HCG assay was done on day 14 after the embryo transfer. A woman with the positive result was indicated by an ultrasound examination later in order to objectify the existence of 1 or 2 gestational sacs, indicative of clinical pregnancy [6], and fellow up of the pregnancy till live birth.

## Results

Atosiban demonstrated higher pregnancy, implantation, live birth rates than piroxicam group (60 % versus 53.3 %), (37.8 % versus 23.9 %) and (94.4 % versus 81.25) respectively, and lower miscarriage rate compared to piroxicam (5.6 % versus18.75 %), however there was no significant differences between the two groups regarding the ICSI outcome with *p* value greater than 0.05, as illustrated in table 1.

## Discussion

Embryo transfer is a critical step of an IVF cycle which merits great attention. Its success depends on the frequency of uterine contractions, the endometrial receptivity and the quality of embryos transferred. Excessive contractions may decrease the implantation potential of embryos by expelling the embryos from the uterus. Studies have revealed a six-fold increase in uterine contractility in IVF

cycles when measured before ET as compared to the condition before ovulation in natural cycles [7].

Excessive manipulation of cervix such as the use of tenaculum during difficult ET can also trigger uterine contractions, consequently leading to failure of embryo implantation. Studies showed that <50% of embryos transferred remained in utero 1 h after transfer and about 15% were found in the vagina after ET [1].

Schwarze *et al*, found that Atosiban was associated to an improvement in ART cycle outcomes, which might be of clinical significance [8]. Atosiban acts mainly via blocking the oxytocin and vasopressin V1a receptors and this blockade may constitute a safe and effective treatment for improving uterine receptivity in women undergoing embryo transfer, providing a decrease in uterine contractile activity, an increase in endometrial perfusion and improvement in endometrial status [9].

Piroxicam is an NSAID which has been used before embryo transfer (30 minutes to 2 hours before embryo transfer) in various studies with controversial results. Its mechanism of action is not completely understood, but may be related to prevention of prostaglandin synthesis by a reversible inhibition of the cyclooxygenase enzyme [10].

Among available NSAIDs, piroxicam was used in this trial, mainly due to the findings of previous studies evaluating the effect on various NSAIDs on fresh embryo transfer. It has been shown that piroxicam has superior efficacy when compared to other NSAIDs such as indomethacin or diclofenac in increasing the chance of successful clinical pregnancy rate [5].

However, a recent study suggests that piroxicam administration before ET has no beneficial effects on pregnancy rate among women undergoing IVF and frozen-thawed ET [11].

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**References**

1. Decleer, W., Osmanagaoglu, K. and Devroey, P., 2012. The role of oxytocin antagonists in repeated implantation failure. Facts, views & vision in ObGyn, 4(4), p.227.
2. Ng, E.H.Y., Li, R.H.W., Chen, L., Lan, V.T.N., Tuong, H.M. and Quan, S., 2014. A randomized double blind comparison of atosiban in patients undergoing IVF treatment. Human reproduction, 29(12), pp.2687-2694.
3. Pierzyński, P. and ZbuckaYKrętowska, M., 2014. Uterine contractile activity before embryo transfer as a new target of pharmacotherapy in the treatment of infertility.
4. Chou, P.Y., Wu, M.H., Pan, H.A., Hung, K.H. and Chang, F.M., 2011. Use of an oxytocin antagonist in in vitro fertilization–embryo transfer for women with repeated implantation failure: A retrospective study. Taiwanese Journal of Obstetrics and Gynecology, 50(2), pp.136-140.
5. Nyachieo, A., Siristatidis, C.S. and Vaidakis, D., 2019. Nonsteroidal anti-inflammatory drugs for assisted reproductive technology. Cochrane Database of Systematic Reviews, (10).
6. Pandey, S., Shetty, A., Hamilton, M., Bhattacharya, S. and Maheshwari, A., 2012. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. Human reproduction update, 18(5), pp.485-503.
7. Mishra, V., Agarwal, H., Goel, S., Roy, P., Choudhary, S. and Lamba, S., 2018. A prospective case–control trial to evaluate and compare the efficacy and safety of atosiban versus placebo in in vitro Fertilization-embryo transfer program. Journal of human reproductive sciences, 11(2), p.155.
8. Schwarze, J.E., Crosby, J. and Mackenna, A., 2020. Atosiban improves the outcome of embryo transfer. A systematic review and meta-analysis of randomized and non-randomized trials. JBRA Assisted Reproduction, 24(4), p.421.

9. Moraloglu, O., Tonguc, E., Var, T., Zeyrek, T. and Batıoglu, S., 2010. Treatment with oxytocin antagonists before embryo transfer may increase implantation rates after IVF. Reproductive biomedicine online, 21(3), pp.338-343.
10. Verma, S., 2020. Adjuvant therapy in assisted reproduction treatment (ART): Current evidence and recommendations for clinical practice. Fertility Science and Research, 7(1), p.7.
11. Zarei, A., Homayoon, N., Hessami, K., Hashemi, A., Davoodi, S., Razavi, B., Ghasempour, L. and Alamdarloo, S.M., 2021. Effect of piroxicam administration on outcome of frozen–thawed embryo transfer: A randomized, double-blinded, placebo-controlled trial. Journal of Obstetrics and Gynaecology Research, 47(1), pp.296-301.

**Table 1. Comparison of ICSI outcome between atosiban & piroxicam group**

| ICSI outcome | Atosiban group | Piroxicam group | *p* value |
|---|---|---|---|
| Pregnancy rate (n.)(%) | 18 (60 %) | 16 (53.3 %) | 0.602 |
| Implantation rate (%) | 37.8 % | 23.9 % | 0.089 |
| Miscarriage rate (n.)(%) | 1 (5.6 %) | 3 (18.75 %) | 0.233 |
| Live birth rate (n.)(%) | 17 (94.4 %) | 13 (81.25 %) | 0.233 |

**Figure 1. Pregnancy, miscarriage and live birth rates in atosiaban group**

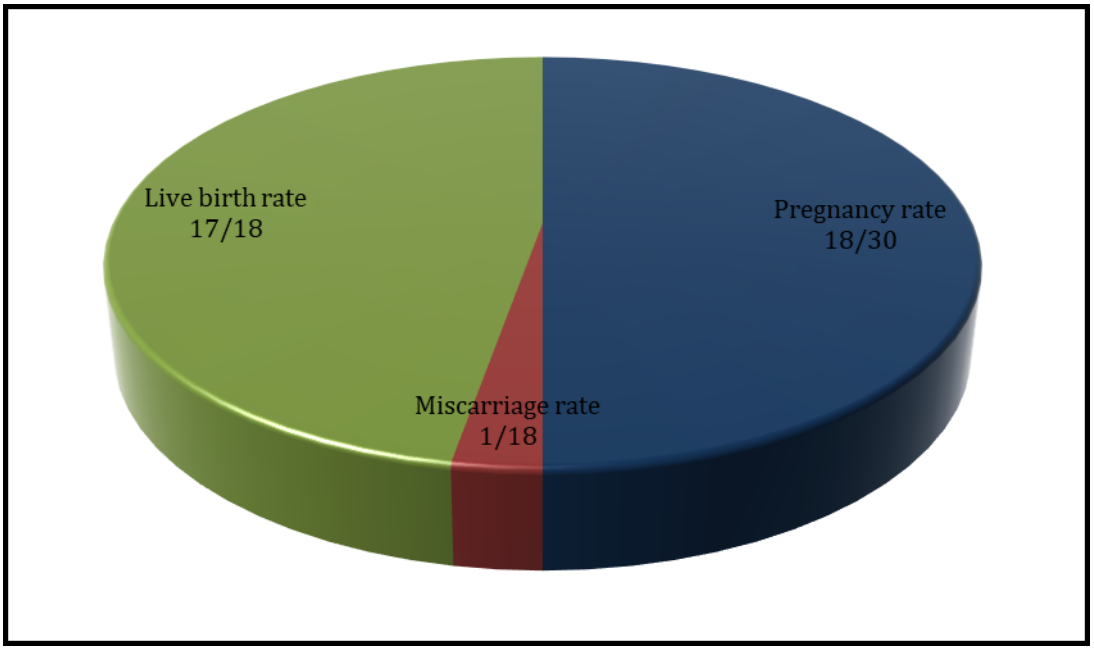

**Figure 2. Pregnancy, miscarriage and live birth rates in piroxicam group**