Atosiban improves the outcome of embryo transfer. A systematic review and meta-analysis of randomized and non-randomized trials

Juan Enrique Schwarze1,2, Javier Crosby1, Antonio Mackenna1

1Reproductive Medicine at Clínica Las Condes, Santiago, Chile
2Obstetrics and Gynecology Department, Universidad de Santiago, Chile

ABSTRACT

Objective: To estimate the effectiveness of Atosiban in improving the outcome after embryo transfer. The effectiveness of embryo transfer per cycle is still relatively low. One possible explanation might be uterine contractility that expels the transferred embryos. Atosiban improved the outcome of embryo transfer by reducing uterine contractility.

Methods: Data sources: A systematic review of papers in English using MEDLINE and EMBASE (1990-2019). Search terms included Atosiban, embryo transfer. Study selection: We included studies that compared the outcomes of embryo transfer with Atosiban and a control group. Data Extracting: Independent extraction of papers by two authors, using predefined data fields, including study quality indicators.

Results: All pooled analyses were based on a fixed-effect model. Four randomised controlled trials, including 1,025 women, and two non-randomised trials, including 686 patients, met our inclusion criteria. In both studies, the heterogeneity was moderate. Atosiban increased clinical pregnancy rates regardless of the indication for ART or type of embryo transferred. Pooled OR in randomized controlled trials reached 1.47 (1.18-1.82), and in non-randomized controlled trials it reached 1.50 (95% CI 1.10-2.05).

Conclusion: Atosiban appears to increase the clinical pregnancy rates in women undergoing embryo transfer.

Keywords: atosiban, in vitro, pregnancy rate

INTRODUCTION

In spite of advanced progress in assisted reproduction technology (ART) over the past 20 years, the effectiveness of embryo transfer (ET) per cycle is still relatively low. In 2015, the delivery rate (DR) per ET in Latin America reached 25.6% in fresh autologous ET, and 36.8% when using donated eggs (Zegers-Hochschild et al., 2017a;b). After ET the effectiveness of embryo implantation depends on embryo quality, endometrial receptivity and adequate dialogue between them (Achache & Revel, 2006). Traditionally, an abnormal chromosomal complement has been considered as the main cause for implantation failure and, in clinical practice, considerably little effort has been devoted to improve uterine receptivity. Generally, appropriate endometrial status, sufficient endometrial perfusion and absence of excessive uterine contractions are necessary for ideal endometrial receptivity and to facilitate embryo implantation (Pierzynski & Reinheimer, 2007). Although increased contractions have been found in approximately 30% of patients undergoing ET, to date uterine contractility is not included in any diagnostic measures, and the therapies to reduce uterine contractions before ET such as beta agonists, non-steroid anti-inflammatory drugs (NSAIDs) or progesterone had not shown definite benefits (Bernabeu et al., 2006; Fanchin et al., 2001).

Theoretically, uterine contractions can expel the embryos after transfer, as per indicated by a study of mock embryo transfer processes (Fanchin et al., 1998a). As such, a stepwise decrease in implantation rates and clinical ongoing pregnancy rates occurred from the lowest to the highest uterine contraction frequencies (Fanchin et al., 1998b).

Atosiban was administered to inhibit uterine contractions (He et al., 2016a; Hebisha et al., 2016). Atosiban is a uterine-specific, mixed vasopressin V1-a and oxytocin-receptor antagonist, that is registered for tocolysis in imminent premature birth. It also inhibits uterine contractility in nonpregnant women. Thus, Atosiban may decrease uterine contractions and promote uterine receptivity in patients undergoing embryo transfer.

We conducted this systematic review and meta-analysis to investigate whether Atosiban improves pregnancy outcomes in the women undergoing ET.

MATERIALS AND METHODS

Literature search and study selection

We searched the computerised databases Medline and Embase from January 1990 to July 2019. We explored the following terms as free text terms and MeSH terms (shown in italics): (embryo transfer; atosiban) and (fertilization in vitro; atosiban). Additionally, the citation lists of all relevant publications and review papers were hand-searched.

Selection criteria, data extraction and quality assessment

We established the criteria for inclusion/exclusion of studies prior to the literature search. We selected randomised controlled trials and observational studies that compared Atosiban at the time of ET with placebo or no treatment. Trials that included intracytoplasmic injection of sperm as well as in vitro fertilization were eligible, as were studies using fresh and frozen/thawed ET. We excluded trials that evaluated other intervention in conjunction with Atosiban. We imposed no restrictions on publication type (that is, either full article or abstract), and restricted language to English. Two authors (JES and JC) independently selected articles and extracted data, with disagreements resolved by discussion.
RESULTS

Search results

The extensive literature search performed between the years 1990-2018 on Medline, EMBASE, yielded 13 publications. Of these, two were excluded based on the title and abstract. We then obtained the full text of the remaining 11 papers. See flow diagram in Figure 1.

Included studies

Seven studies were considered in the synthesis, including 3 observational studies (Chou et al., 2011; He et al., 2016b; Lan et al., 2012) and 4 randomized controlled trials (He et al., 2016a; Hebisha et al., 2016; Moraloglu et al., 2010; Ng et al., 2014). The characteristics of the included trials are shown in Table 1.

Methods in the included studies

The study population included patients undergoing ICSI with the transfer of top-quality embryos (Moraloglu et al., 2010), regular IVF (Ng et al., 2014), women with repeated implantation failure (Chou et al., 2011; Lan et al., 2012), transfer of frozen/thawed embryos (He et al., 2016b), and transfer of frozen/thawed embryos in women with endometriosis (He et al., 2016a).

The intervention included the administration of a single bolus dose (Chou et al., 2011; Hebisha et al., 2016; He et al., 2016a;b) prior to the embryo transfer, or the administration of a bolus doses plus maintaining a continuous dose (Lan et al., 2012; Moraloglu et al., 2010; Ng et al., 2014).

The outcomes evaluated included implantation rate (Chou et al., 2011; He et al., 2016a; Lan et al., 2012; Moraloglu et al., 2010), clinical pregnancy rate (He et al., 2016b; Lan et al., 2012; Moralognu et al., 2010; Chou et al., 2011; Hebisha et al., 2016) and delivery rate (Chou et al., 2011; Ng et al., 2014).

Methodological quality of included studies

According to the guidelines suggested by the Cochrane Collaboration, the quality of most of the included studies was low to moderate due to unclear selection, performance and detection bias. Table 2 depicts the quality assessment of the included trials.

Result of the outcome measures

In total, 1,025 women were allocated to Atosiban and 953 were allocated to a control group. Overall, we analysed four randomized controlled trials, including 1,292 patients, and two observational studies, including 686 patients.

In both, observational and randomized controlled studies, Atosiban was associated with an increased risk of clinical pregnancy. In the case of observational studies, the OR (95% CI) was 1.50 (1.10-2.05), with a moderate level of heterogeneity (I² 68%, p=0.08). In the case of randomized controlled trials, the OR (95% CI) of clinical pregnancy was 1.47 (1.18-1.82), with moderate heterogeneity (I² 62%, p=0.05). Figure 2 shows a forest plot with subgroup analyses for randomized and non-randomised controlled trials. To explore the heterogeneity, a funnel plot was drawn. The funnel plot (Figure 3) shows evidence of considerable symmetry.
Figure 1. Flow diagram
Table 1. Characteristics of the studies included

| Study, year | Design | Inclusion Criteria | Outcomes | Atosiban dose |
|-------------|--------|--------------------|----------|---------------|
| Moraloglu et al., 2010 | Prospective, randomized, placebo-controlled clinical study | Women undergoing intracytoplasmic sperm injection who had top-quality embryos | Clinical pregnancy rate per cycle and implantation rate | Intravenous atosiban 30 min before the embryo transfer with a bolus dose of 6.75 mg, and the infusion was continued with an infusion rate of 18 mg/h. After performing embryo transfer, the dose of atosiban was reduced to 6 mg/h and the infusion was continued for 2 h (total administered dose: 37.5 mg). |
| Chou et al., 2011 | Retrospective cohort study | Repeated implantation failure (RIF) | Implantation rate, clinical pregnancy rate, live birth rate | Forty patients received a single bolus dose (6.75 mg, 0.9 mL/vial) of atosiban before ET (Group 2), and 30 patients received a bolus dose of 6.75 mg atosiban followed by infusion at 18 mg/hr. for 3 hours immediately after ET (Group 3). |
| Lan et al., 2012 | Prospective cohort study | Women with repeated implantation failure | Uterine contraction, implantation rate (IR) and clinical pregnancy rate (CPR) | I.V. bolus of 6.75 mg at 30 min prior to embryo transfer followed by i.v. infusion at a rate of 18 mg/h for 1 h and 6 mg/h for the subsequent 2 h. The total dose administered was 36.75 mg. |
| Ng et al., 2014 | Multi-center randomized double blind study | Consecutive subfertile women undergoing IVF treatment | The primary outcome measure was the live birth rate and the secondary outcome measures including positive pregnancy test, clinical pregnancy, ongoing pregnancy, miscarriage, multiple pregnancy and ectopic pregnancy rates. | I.V. Atosiban 30 min before the transfer with a bolus dose of 6.75 mg, and the infusion was continued at a rate of 18 mg/h for 1 h. The dose of Atosiban was then reduced to 6 mg/h after embryo transfer and the infusion was continued for another 2 h. Therefore, the total administered dose was 37.5 mg. |
| He et al., 2016a | Randomized, controlled clinical trial. | Women with endometriosis undergoing frozen-thawed embryo transfer | Implantation rate and pregnancy rate. | IV bolus of 6.75 mg at approximately 30 min before ET. |
| He et al., 2016b | Prospective cohort study | Patients undergoing IVF/ET using cryopreserved embryos | Uterine contraction, clinical pregnancy rate | I.V. bolus of 6.75 mg at about 30 min prior before ET. |
| Hebisha et al., 2016 | Randomized controlled trial. | One hundred and eighty two women, prepared for intracytoplasmic sperm injection for male or tubal factor infertility, using long agonist protocol | Pregnancy rate, implantation rate. | 7.5 mg Atosiban by slow IV injection |

DISCUSSION

Atosiban was associated with an increase in the chance of clinical pregnancy. This increased probability was seen in both observational and randomized controlled studies, using different doses. ET is one of the crucial steps in ART, and the use of high-quality embryos together with the presence of an optimal intrauterine environment are the basic determinants of ET success (Dessolle et al., 2009). Fanchin et al. (1998a) demonstrated that uterine contractions occur during the course of ET. They reported that excessive uterine contractions can expel embryos from
Table 2. Bias risks of the included RCT

| Study, year          | Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | Domain 7 |
|----------------------|----------|----------|----------|----------|----------|----------|----------|
| Moraloglu et al., 2010 | High     | High     | Low      | unknown  | Low      | Low      | unknown  |
| Nget et al., 2014     | Unknown  | Low      | Low      | unknown  | Low      | Low      | Low      |
| He et al., 2016a      | Low      | Low      | unknown  | unknown  | Low      | Low      | Low      |
| Hebishet al., 2016    | Unknown  | unknown  | unknown  | unknown  | Low      | Low      | unknown  |

1: Random sequence generation (selection bias)
2: Allocation concealment (selection bias)
3: Blinding of participants and personnel (performance bias)
4: Blinding of outcome assessment (detection bias) (patient-reported outcome)
5: Blinding of outcome assessment (detection bias) (all-cause main outcome)
6: Incomplete outcome data (attrition data)
7: Selective outcome data (reporting bias)

In summary, we found that Atosiban was associated to an improvement in ART cycle outcomes, which might be of clinical significance, although, its administration requires a peripheral venous catheterization, longer hospitalization, and makes ET more expensive. Perhaps, the development of Nolasibam, an oral oxytocin receptor antagonist with the potential to decrease uterine contractions, will overrule these disadvantages in the near future.

CONFLICT OF INTERESTS
There is no conflict of interest.

Corresponding author:
Juan Enrique Schwarze
Reproductive Medicine
Clinica Las Condes
Santiago, Chile.
E-mail: jschwarze@clc.cl
REFERENCES

Achache H, Revel A. Endometrial receptivity markers, the journey to successful embryo implantation. Hum Reprod Update. 2006;12:731-46. PMID: 16982667 DOI: 10.1093/humupd/dml004

Bernabeu R, Roca M, Torres A, Ten J. Indomethacin effect on implantation rates in oocyte recipients. Hum Reprod. 2006;21:364-9. PMID: 16284067 DOI: 10.1093/humrep/dei343

Chou PY, Wu MH, Pan HA, Hung KH, Chang FM. Use of an oxytocin antagonist in in vitro fertilization-embryo transfer for women with repeated implantation failure: a retrospective study. Taiwan J Obstet Gynecol. 2011;50:136-40. PMID: 21791296 DOI: 10.1016/j.tjog.2011.04.003

Dessolle L, Daraï E, Cornet D, Rouzier R, Coutant C, Mandelbaum J, Antoine JM. Determinants of pregnancy rate in the donor oocyte model: a multivariate analysis of 450 frozen-thawed embryo transfers. Hum Reprod. 2009;24:3082-9. PMID: 19726449 DOI: 10.1093/humrep/dep303

Fanchin R, Righini C, Ayoubi JM, Olivennes F, de Ziegler D, Frydman R. Uterine contractions at the time of embryo transfer: a hindrance to implantation? Contracept Fertil Sex. 1998a;26:498-505. PMID: 9810121

Fanchin R, Righini C, Olivennes F, Taylor S, de Ziegler D, Frydman R. Uterine contractions at the time of embryo transfer alter pregnancy rates after in-vitro fertilization. Hum Reprod. 1998b;13:1968-74. PMID: 9740459 DOI: 10.1093/humrep/13.7.1968

Fanchin R, Righini C, de Ziegler D, Olivennes F, Ledée N, Frydman R. Effects of vaginal progesterone administration on uterine contractility at the time of embryo transfer. Fertil Steril. 2001;75:1136-40. PMID: 11384639 DOI: 10.1016/s0015-0282(01)01787-3

Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med. 2006;25:3443-57. PMID: 16345038 DOI: 10.1002/sim.2380

Hebisha SA, Aboelazm BA, Adel HM, Ahmed AI. Impact of the oxytocin receptor antagonist (ATOSIBAN) administered shortly before embryo transfer on pregnancy outcome after intracytoplasmic sperm injection (ICSI). Fertil Steril. 2016;106:e88-9. DOI: 10.1016/j.fertnstert.2016.07.260

He Y, Wu H, He X, Xing Q, Zhou P, Cao Y, Wei Z. Administration of atosiban in patients with endometriosis undergoing frozen-thawed embryo transfer: a prospective, randomized study. Fertil Steril. 2016a;106:416-22. PMID: 27143518 DOI: 10.1016/j.fertnstert.2016.04.019
He Y, Wu H, He X, Xing Q, Zhou P, Cao Y, Wei Z. Application of atosiban in frozen-thawed cycle patients with different times of embryo transfers. Gynecol Endocrinol. 2016b;32:811-5. PMID: 27147474 DOI: 10.1080/09513590.2016.1180680

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60. PMID: 12958120 DOI: 10.1136/bmj.327.7414.557

Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. PMID: 22008217 DOI: 10.1136/bmj.d5928

Lan VT, Khang VN, Nhu GH, Tuong HM. Atosiban improves implantation and pregnancy rates in patients with repeated implantation failure. Reprod Biomed Online. 2012;25:254-60. PMID: 22818095 DOI: 10.1016/j.rbmo.2012.05.014

Moraloglu O, Tonguc E, Var T, Zeyrek T, Batioglu S. Treatment with oxytocin antagonists before embryo transfer may increase implantation rates after IVF. Reprod Biomed Online. 2010;21:338-43. PMID: 20638340 DOI: 10.1016/j.rbmo.2010.04.009

Ng EH, Li RH, Chen L, Lan VT, Tuong HM, Quan S. A randomized double blind comparison of atosiban in patients undergoing IVF treatment. Hum Reprod. 2014;29:2687-94. PMID: 25336707 DOI: 10.1093/humrep/deu263

Pierzynski P, Reinheimer TM, Kuczynski W. Oxytocin antagonists may improve infertility treatment. Fertil Steril. 2007;88:213.e19-22. PMID: 17481622 DOI: 10.1016/j.fertnstert.2006.09.017

Pierzynski P. Oxytocin and vasopressin V(1A) receptors as new therapeutic targets in assisted reproduction. Reprod Biomed Online. 2011;22:9-16. PMID: 21130036 DOI: 10.1016/j.rbmo.2010.09.015

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. PMID: 27733354 DOI: 10.1136/bmj.i4919

Zegers-Hochschild F, Schwarze JE, Crosby J, Musri C, Urbina MT; Latin American Network of Assisted Reproduction (REDLARA). Assisted reproduction techniques in Latin America: the Latin American Registry, 2014. Reprod Biomed Online. 2017a;35:287-95. PMID: 28837023 DOI: 10.5935/1518-0557.20170034

Zegers-Hochschild F, Schwarze JE, Crosby J, Musri C, Urbina MT. Assisted reproductive techniques in Latin America: The Latin American Registry, 2014. JBRA Assist Reprod. 2017b;21:164-75. PMID: 28837023 DOI: 10.5935/1518-0557.20170034