ORIGINAL ARTICLE
https://doi.org/10.5653/cerm.2016.43.4.233
pISSN 2233-8233 · eISSN 2233-8241
Clin Exp Reprod Med 2016;43(4):233-239

CERM

Efficacy of oxytocin antagonist infusion in improving *in vitro* fertilization outcomes on the day of embryo transfer: A meta-analysis

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Objective: Uterine contraction induced by the embryo transfer (ET) process has an adverse effect on embryo implantation. The aim of this study was to determine the effect of oxytocin antagonist supplementation on the day of ET on *in vitro* fertilization outcomes via a meta-analysis.
Methods: We performed a meta-analysis of randomized controlled trials (RCTs). Four online databases (Embase, Medline, PubMed, and Cochrane Library) were searched through May 2015 for RCTs that investigated oxytocin antagonist supplementation on the day of ET. Studies were selected according to predefined inclusion criteria and meta-analyzed using RevMan 5.3. Only RCTs were included in this study. The main outcome measures were the clinical pregnancy rate, the implantation rate, and the miscarriage rate.
Results: A total of 123 studies were reviewed and assessed for eligibility. Three RCTs, which included 1,020 patients, met the selection criteria. The implantation rate was significantly better in patients who underwent oxytocin antagonist infusion (19.8%) than in the control group (11.3%) (n = 681; odds ratio [OR], 1.92; 95% confidence interval [CI], 1.25–2.96). No significant difference was found between the two groups in the clinical pregnancy rate (n = 1,020; OR, 1.57; 95% CI, 0.92–2.67) or the miscarriage rate (n = 456; OR, 0.76; 95% CI, 0.44–1.33).
Conclusion: The results of this meta-analysis of the currently available literature suggest that the administration of an oxytocin antagonist on the day of ET improves the implantation rate but not the clinical pregnancy rate or miscarriage rate. Additional, large-scale, prospective, randomized studies are necessary to confirm these findings.

Keywords: Atosiban; Embryo transfer; Implantation; Oxytocin; Uterine contraction

Introduction

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. Supraphysiological serum estradiol (E_2) 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 [1,2]. 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 [3]. Mansour et al. [4] investigated the expulsion of methylene blue dye following a dummy ET and concluded that the dye was extruded at the external os in more than 25% of the cases. It has also been demonstrated that < 50% of the transferred embryos remained in the uterus 1 hour after transfer [5], and that approximately 15% of embryos were present in the vagina following ET [6]. These findings suggest that excessive uterine contractions at the time of ET may expel embryos from the uterus. Therefore, in addition

Received: Jul 20, 2016 · Revised: Sep 23, 2016 · Accepted: Sep 23, 2016
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to a gentle approach during the ET procedure, the effectiveness of using a soft catheter under ultrasound guidance to avoid touching the uterine fundus [7,8], as well as administering agents (e.g., progesterone, cyclooxygenase inhibitors, and β2-adrenergic agonists) in order to reduce uterine contractions has been assessed, with variable results [9-11].

Atosiban (Tractocile, Ferring Arzneimittel, Kiel, Germany) is a combined oxytocin/vasopressin V1a receptor antagonist, which is indicated for the delay of imminent preterm labor. It has been demonstrated to be effective for this indication [12,13]. The first study that used atosiban in stimulated IVF cycles was published in 2007 [14]. Other studies have subsequently analyzed the effect of oxytocin antagonist (OA) supplementation on the day of ET on IVF outcomes. The results of these studies have been inconsistent and controversial [15-18].

Therefore, there is a clear need for a meta-analysis to compare the IVF outcomes in women who were treated with an OA or a placebo at the time of ET.

Methods

1. Search strategy

We searched PubMed, Embase, Medline, and the Cochrane Library for all relevant articles under the following Medical Subject Heading terms to generate subsets of studies: (1) 'atosiban' or 'oxytocin antagonist' or 'oxytocin receptor antagonist,' (2) '*in vitro* fertilization' or 'IVF' or 'assisted reproductive techniques' or 'ART,' and (3) 'pregnancy' or 'pregnancy rate' or 'implantation' or 'live birth' or 'embryo transfer' (subset 1 with either 2 or 3) with 'AND' to identify citations appropriate for evaluating the effect of OA supplementation on the day of ET on IVF outcomes. Furthermore, the bibliographies of all primary papers were reviewed to identify cited publications that had not been identified in the computerized search. Databases were searched through May 2015 without restriction by country of origin, blinding, sample size, or publication status. The searches were independently conducted by two reviewers (EJH and SKK).

2. Study selection

The target population was infertile patients undergoing ovarian stimulation as well as IVF or intracytoplasmic sperm injection. OA was supplemented on the ET day in the study group, whereas no such compound was used in the control group. The primary outcome was the clinical pregnancy rate (CPR), and the secondary outcomes were the implantation rate (IR) and miscarriage rate (MR). All full manuscripts were independently reviewed for the selection and exclusion of publications according to predefined inclusion criteria by two reviewers (EJH and SKK). The extraction of data from each study (e.g., information such as the study design, inclusion/exclusion criteria, population characteristics, and outcomes) was also independently conducted by two of the authors (EJH and SKK) using predetermined tables and forms. Disagreements regarding article selection or data extraction were resolved by consensus or arbitration by a third reviewer (JRL). The risk of bias was assessed using the guidelines of the Cochrane Collaboration, with the findings illustrated as a risk-of-bias graph. The evidence was summarized using a tool provided by the Cochrane Collaboration.

3. Statistical analysis

We used the RevMan 5.3 software package (Cochrane Collaboration, Oxford, UK), provided by the Cochrane Collaboration, for statistical analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method for binary data variables. Statistical heterogeneity was assessed using the I^2 statistic and was considered absent if I^2 was $<50\%$. The heterogeneity of treatment effects was graphically assessed using forest plots and statistically assessed using the chi-square heterogeneity test. Publication bias was assessed via a funnel plot analysis using the Egger test. The meta-analysis results are displayed as forest plots.

Results

1. Study selection

The electronic search yielded 133 publications, of which 116 publications were excluded by screening of the titles and abstracts. Full manuscripts were retrieved for the remaining 17 articles, including

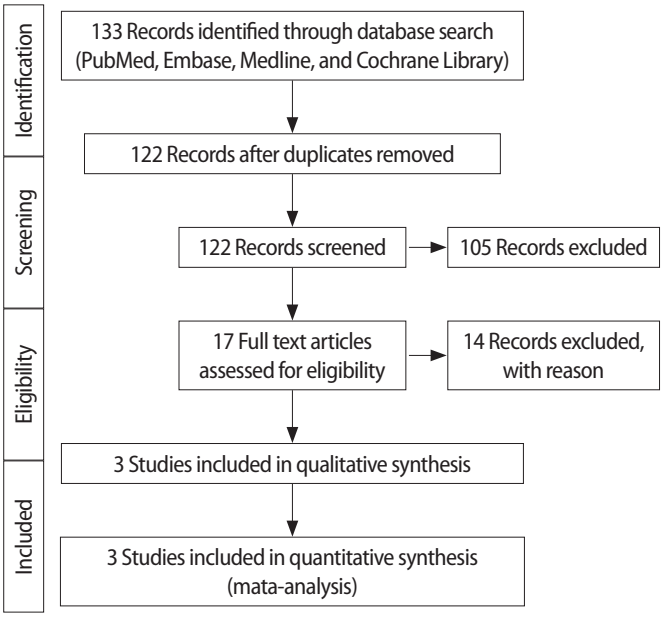

Figure 1. Flow diagram of the selected studies.

https://doi.org/10.5653/cerm.2016.43.4.233

two case series [19,20], three prospective cohort studies [18,21,22], one retrospective cohort study [17], seven randomized controlled trials (RCTs) [15,16,23-27], and four reviews [28-31]. Only RCTs were included in this study. Four RCTs were excluded [23,25-27]; three [25-27] because they did not include the CPR or IR, and one [23] because it was written in Chinese. The Preferred Reporting Items for Systematic Reviews and meta-analyses flow chart explaining the RCT selection is shown in Figure 1.

Three RCTs [15,16,24] that evaluated 1,020 women allocated to experimental or control groups to analyze the efficacy of ET-day OA infusion in improving IVF outcomes were included in the meta-analysis. The combined experimental group contained 510 women and the control group contained 510 women. The characteristics of the included trials are shown in Table 1. The quality assessment of the included trials is presented in Table 2. Three RCTs [15,16,24] reported the CPR as an outcome, and two RCTs [15,24] reported the IR as an

Table 1. Characteristics of the included studies

Study	No. of participants	Inclusion criteria	Intervention group	Control group	Age (yr)	Outcome
Ahn et al., 2009 [15]	40 (20 in study group, 20 controls)	At least 2 failures of IVF/ICSI	1 hour prior to ET, started with a bolus dose of 6.75 mg intravenously and continued at an infusion rate of 18 mg/hr Following ET, reduced to 6 mg/hr and continued for 2 hours	No atosiban administration/no placebo	Study group: 34.7±4.0 Control group: 35.0±3.3	CPR, IR
Moraloglu et al., 2010 [24]	180 (90 in study group, 90 controls)	(1) Basal FSH hormone concentration less than 10 IU/L, (2) age between 20 and 39 years, (3) first IVF cycle, (4) long protocol with gonadotropin-releasing hormone agonist and recombinant FSH, and (5) at least 2 top-quality embryos after ICSI	30 minutes prior to ET, started with a bolus dose of 6.75 mg intravenously and continued at an infusion rate of 18 mg/hr Following ET, reduced to 6 mg/hr and continued for 2 hours	Placebo-controlled: saline infusion for the same duration	Study group: 30.4±6.1 Control group: 30.6±4.4	CPR, IR, MR
Ng et al., 2014 [16]	800 (400 in study group, 400 controls); multi-center (250 in China, 250 in Hong Kong, and 300 in Vietnam)	(1) age <43 years, (2) normal uterine cavity indicated via ultrasound scanning	30 minutes prior to ET, started with a bolus dose of 6.75 mg intravenously and continued at an infusion rate of 18 mg/hr Following ET, reduced to 6 mg/hr and continued for 2 hours	Placebo-controlled: Saline infusion for the same duration	Study group: 32.0±4.0 Control group: 33.0±4.0	CPR, MR, EPR, LBR, IR per woman

Values are presented as mean±standard deviation.
IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; ET, embryo transfer; CPR, clinical pregnancy rate; IR, implantation rate; FSH, follicle-stimulating hormone; MR, miscarriage rate; EPR, ectopic pregnancy rate; LBR, live birth rate.

Table 2. Quality assessment of the included studies

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Ahn et al., 2009 [15]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk
Moraloglu et al., 2010 [24]	High risk	Unclear	Unclear	Unclear	Low risk	Low risk
Ng et al., 2014 [16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Bias risk was determined using the Cochrane risk of bias tool.

Study or subgroup	Atosiban Events	Atosiban Total	Control Events	Control Total	Weight (%)	Odds ratio M-H, Random, 95% CI
Ahn et al., 2009 [15]	8	20	4	20	11.5	2.67 [0.65, 10.97]
Moraloglu et al., 2010 [24]	42	90	26	90	34.3	2.15 [1.16, 3.99]
Ng et al., 2014 [16]	201	400	187	400	54.2	1.15 [0.87, 1.52]
Total (95% CI)		510		510	100.0	1.57 [0.87, 2.67]
Total events	251		217			

Heterogeneity: $Tau^2 = 0.12$; $\chi^2 = 4.32$, df = 2 ($p = 0.12$); $I^2 = 54\%$.
Test for overall effect: Z = 1.67 ($p = 0.10$).

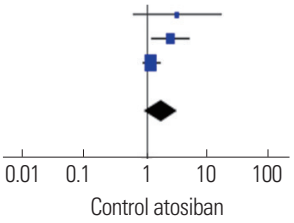

Figure 2. Meta-analysis of the clinical pregnancy rate. M-H, Mantel-Haenszel; CI, confidence interval.

Study or subgroup	Atosiban Events	Atosiban Total	Control Events	Control Total	Weight (%)	Odds ratio M-H, Random, 95% CI
Ahn et al., 2009 [15]	11	65	4	67	12.9	3.21 [0.97, 10.66]
Moraloglu et al., 2010 [24]	57	279	34	270	87.1	1.78 [1.12, 2.83]
Total (95% CI)		344		337	100.0	1.92 [1.25, 2.96]
Total events	68		38			

Heterogeneity: $Tau^2 = 0.00$; $\chi^2 = 0.80$, df = 1 ($p = 0.37$); $I^2 = 0\%$.
Test for overall effect: Z = 2.97 ($p = 0.003$).

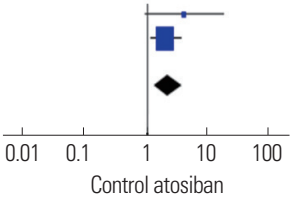

Figure 3. Meta-analysis of the implantation rate. M-H, Mantel-Haenszel; CI, confidence interval.

Study or subgroup	Atosiban Events	Atosiban Total	Control Events	Control Total	Weight (%)	Odds ratio M-H, Random, 95% CI
Moraloglu et al., 2010 [24]	7	42	6	26	20.6	0.67 [0.20, 2.26]
Ng et al., 2014 [16]	21	201	24	187	79.4	0.79 [0.43, 1.48]
Total (95% CI)		243		213	100.0	0.76 [0.44, 1.33]
Total events	28		30			

Heterogeneity: $Tau^2 = 0.12$; $\chi^2 = 4.32$, df = 2 ($p = 0.12$); $I^2 = 54\%$.
Test for overall effect: Z = 1.67 ($p = 0.10$).

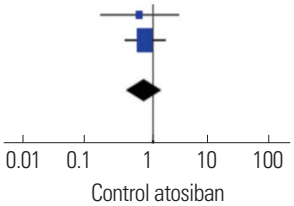

Figure 4. Meta-analysis of the miscarriage rate. M-H, Mantel-Haenszel; CI, confidence interval.

outcome; thus, these outcomes were independently analyzed.

2. Methodological quality of the 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 bias, performance bias, and detection bias.

3. Outcome measures

1) Clinical pregnancy rate

Three published RCTs [20,22,24], which included 1,020 patients, reported the CPR. Only one study [22] demonstrated a statistically significant improvement in the CPR. The combined CPR was 49.2% in the OA infusion group and 42.5% in the control group. Substantial statistical heterogeneity was found ($\chi^2 = 4.32$, df = 2, $p = 0.12$, $I^2 = 54\%$). Pooling the data using a random effect model indicated no difference in the CPR (n = 1,020; OR, 1.57; 95% CI, 0.92–2.67) (Figure 2).

2) Implantation rate

The IR was reported in two studies [15,24], which included 681 patients. The combined IR was 19.8% in the OA infusion group and 11.3% in the control group. Pooling the data together indicated that a significant difference was present in the IR between the women pretreated with an OA compared with the women without OA pretreatment (n = 681; OR, 1.92; 95% CI, 1.25–2.96) (Figure 3). Homogeneity ($\chi^2 = 0.80$, df = 1, $p = 0.37$, $I^2 = 0\%$) was found between the two studies [15,24] that reported the IR.

3) Miscarriage rate

For the MR, we combined the outcomes of two trials [16,24], which included 243 women in the OA infusion group and 213 women in

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the control group. The combined MR was 11.5% in the OA infusion group and 14.1% in the control group. Pooling the data together indicated the MR was not significantly different between the OA infusion group and the control group (n = 456; OR, 0.76; 95% CI, 0.44–1.33) (Figure 4). No indication of statistical heterogeneity was found ($\chi^2 = 0.06$, df = 1, $p = 0.80$, $I^2 = 0\%$).

Discussion

In this study, we examined the effect of OA supplementation on the day of ET on IVF outcomes. It is well known that the synthesis of oxytocin, which causes uterine contractions, is strongly influenced by E_2 [32]. In pregnant women, increased E_2 concentrations induce the expression of oxytocin receptors in the myometrium prior to labor, and this process is involved in labor induction [33]. A high E_2 concentration also promotes the effects of oxytocin by increasing oxytocin receptor gene expression in the uterus even in the absence of pregnancy [1]. The excessive uterine contraction in IVF patients may be a consequence of the induction of oxytocin synthesis and expression of oxytocin receptors, as well as indirectly of the formation and release of prostaglandin F2α caused by supraphysiological serum E_2 concentrations following an ovarian stimulation cycle [1,2]. Considering the causative effect of oxytocin on uterine contraction, oxytocin/vasopressin V1a receptor blockade may improve uterine receptivity, thereby decreasing uterine contractions and increasing uterine perfusion. The results of this meta-analysis confirmed this possibility by demonstrating an improved IR associated with OA treatment.

Several agents have been assessed to determine their effects on reducing uterine contractions (e.g., β2-adrenergic agonists, progesterone, and cyclooxygenase inhibitors). Atosiban is more selective for the uterus than other tocolytic agents [34]. Furthermore, atosiban is well tolerated, and its embryonic safety has been confirmed [14,35]. In a preclinical trial of atosiban, no toxic effects were identified at concentrations up to 50-fold the blood levels associated with therapeutic doses. Atosiban did not affect the survival rate of 1-cell rabbit embryos or hatched rabbit blastocysts. A human sperm motility bioassay also failed to demonstrate adverse effects [14].

In this study, we attempted to determine whether the use of atosiban in stimulated IVF cycles had a beneficial effect on IVF outcomes via a meta-analysis. The current meta-analysis indicated that the IR was significantly higher in the OA infusion group than in the control group (19.8% vs. 11.3%, respectively; OR, 1.92; 95% CI, 1.25–2.96). In contrast, no significant beneficial effects were found on the CPR or the MR. In contrast to the present meta-analysis, several non-RCTs have demonstrated that the use of atosiban administered at the time of ET improved the CPR as well as the IR. One potential explanation for this discrepancy may be differences in the characteristics of the study subjects and the lack of homogeneity in the regimen of atosiban supplementation. In one prospective study, Lan et al. [18] reported that atosiban improved the CPR (from 0% to an average of 43.7%) and the IR (from 0% to an average of 13.9%) in patients with repeated implantation failure (RIF) undergoing IVF/ET with cryopreserved embryos. In that study, atosiban was administered as an intravenous bolus of 6.75 mg 30 minutes prior to ET, followed by an intravenous infusion at a rate of 18 mg/hr for 1 hour and 6 mg/hr for the subsequent 2 hours. Another prospective study demonstrated that the ongoing pregnancy rate was improved from 0% to an average of 23.1% when atosiban was administered during the ET procedure in patients with RIF [21]. All patients received intravenous atosiban 60 minutes prior to the ET procedure with a bolus of 6.75 mg, followed by an infusion rate of 18 mg/hr for 3 hours. In another retrospective study [17], the patients received a single bolus of 6.75 mg of atosiban prior to ET with an infusion time of more than 1 minute or a bolus dose of 6.75 mg of atosiban, followed by an infusion of 18 mg/hr for 3 hours immediately after ET. The CPR (37.5%) and IR (30.21%) in the patients who received a single bolus dose of atosiban were significantly higher than those of patients who only received infusion treatment (CPR, 20%; IR, 15.9%) and the control group (CPR, 12.5%; IR, 11.8%) ($p < 0.05$). In summary, non-RCT studies have been conducted in patients with RIF; however, only one [15] of the studies included in the present meta-analysis was performed in patients with RIF. Another difference was the regimen of atosiban supplementation. Although no significant difference was found in this study, improvements in the CPR and MR are expected. Additional large-scale RCTs are required to confirm this conclusion.

Our study has both strengths and limitations. To our knowledge, this is the first meta-analysis regarding the use of atosiban in IVF. We suggest that the study selection was unbiased because two reviewers independently performed the selection. Furthermore, only randomized controlled studies were included to ensure quality. However, the quality of the included trials was moderate due to limitations of allocation concealment and blinding in two studies, which used weekdays [23] or provided insufficient information regarding randomization [15]. Another limitation was the heterogeneity of the study protocols and inclusion criteria. The patients in two studies received intravenous atosiban 30 minutes prior to the ET with a bolus dose of 6.75 mg, and the infusion was continued with an infusion rate of 18 mg/hr. Following ET, the dose of atosiban was reduced to 6 mg/hr, and the infusion was continued for 2 hours [16,24]. In the other study, the administration of atosiban was initiated 1 hour prior to ET [15]. Moreover, among the included studies, only Ahn et al. [15] evaluated patients with RIF, and the other two studies were conducted in a conventional group of subjects. Therefore, our findings should not be extended to women with RIF, uterine myomas, or adenomyo-

sis, who may have more uterine contractions. These points may be further clarified by updating the meta-analysis with future studies that recruit adequately powered sample sizes, consider various intervention groups (e.g., RIF, uterine myomas, or adenomyosis), and measure uterine contractions to explain the mechanism of the potentially improved outcomes in the intervention group.

In conclusion, the combined data presented in the present meta-analysis suggest the possibility that atosiban may improve IVF outcomes. However, due to the lack of relevant RCTs and the heterogeneity of the included studies, firm recommendations cannot be made regarding its clinical applicability at this time. Additional, large-scale, multicenter RCTs are required to clarify the benefits of OA supplementation therapy in routine clinical management.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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