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ARTICLE

Atosiban improves implantation and pregnancy rates in patients with repeated implantation failure

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Abstract This prospective cohort study examined the effects of atosiban on uterine contraction, implantation rate (IR) and clinical pregnancy rate (CPR) in women undergoing IVF/embryo transfer. The study enrolled 71 women with repeated implantation failure (RIF; no pregnancies from an average of 4.8 previous embryo transfers with a mean of 12 top-quality embryos) undergoing IVF/embryo transfer using cryopreserved embryos. The total atosiban dose was 36.75 mg. The IR per transfer and CPR per cycle were 13.9% and 43.7%, respectively. Before atosiban, 14% of subjects had a high frequency of uterine contractions ($\geq$16 in 4 min). The frequency of uterine contractions was reduced after atosiban. This reduction of uterine contractions in all cycles was significant overall (from 6.0 to 2.6/4 min; $P < 0.01$), in cycles with $\geq$16 uterine contractions/4 min at baseline (from 18.8 to 5.1; $P < 0.01$) and in cycles with $<$16 uterine contractions/4 min (from 3.9 to 2.2; $P < 0.01$). IR and CPR improved in all subjects, irrespective of baseline uterine contraction frequency. This is the first prospective study showing that atosiban may benefit subjects with RIF undergoing IVF/embryo transfer with cryopreserved embryos. One potential mechanism is the reduction in uterine contractility, but others may also contribute.

KEYWORDS: atosiban, clinical pregnancy, implantation rate, IVF/embryo transfer, uterine contractility

Introduction

Implantation failure is the main factor affecting the success rate of IVF procedures. Excessive uterine contractions have been described as a potential mechanism for reduced implantation rates in IVF cycles (Fanchin et al., 1998; Lesny et al., 1999a). A smooth process of embryo transfer is important for the success of IVF (Mansour et al., 1990;

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Tomas et al., 1998; Visser et al., 1993; Wood et al., 1985), particularly with respect to minimizing the release of oxytocin, which stimulates uterine contractions (Lesny et al., 1999a,b). In addition, uterine contraction may be triggered by the ovarian stimulation procedure (Ayoubi et al., 2003; Fanchin et al., 1998; Lesny et al., 1998, 1999a). Increased frequency of uterine contraction during ovarian stimulation cycles compared with the corresponding phase of natural menstrual cycles has been documented in a number of studies (Abramowicz and Archer, 1990; Fanchin et al., 2000; Lyons et al., 1991). Contractile activity of the uterus could move the implanted embryo towards the Fallopian tubes or cervix/vagina (Knutzen et al., 1992) or the embryo might even be expelled out of the uterus (Fanchin et al., 1998; Lesny et al., 1999a).

Mechanical measures to reduce uterine contractions at the time of embryo transfer include the utilization of a soft catheter without touching the uterine fundus (Lesny et al., 1998) and the use of ultrasound to guide embryo transfer (Frydman, 2004). From a pharmacological perspective, the ability of a number of agents to reduce uterine contractions has been assessed, with variable results (Bernabeu et al., 2006; Fanchin et al., 2001; Moon et al., 2004; Pinheiro et al., 2003; Tsirigotis et al., 2000).

Atosiban is a combined oxytocin/vasopressin V_{1A} receptor antagonist, which is indicated for the delay of imminent preterm labour. It has been shown to be effective and well tolerated in this indication (European Atosiban Study Group, 2001; French/Australian Atosiban Investigators Group, 2001; Goodwin et al., 1996; Husslein et al., 2007; Moutquin et al., 2000; Romero et al., 2000; Worldwide Atosiban versus Beta-agonists Study Group, 2001). Furthermore, the embryonic safety of atosiban has been confirmed in an animal model (Pierzynski et al., 2007a).

Combined antagonism at oxytocin and vasopressin V_{1A} receptors reduces uterine contractile activity with a corresponding reduction in intrauterine prostaglandin $F_{2\alpha}$ production and improvement of uterine blood supply (Pierzynski, 2011). These effects are of potential benefit not only in preterm labour but also for implantation support during IVF/embryo transfer cycles. The first report of the use of atosiban in a woman with repeated implantation failure (RIF) to achieve live birth was documented in 2007 (Pierzynski et al., 2007b).

Based on the published data, atosiban can reduce uterine contractility and improve uterine blood supply (Pierzynski, 2011) and it has been used successfully in IVF/embryo transfer in two case reports (Pierzynski et al., 2007b; Liang et al., 2009). Atosiban has been used for embryo transfer in An Sinh Hospital (Ho Chi Minh City, Vietnam) since the beginning of 2011. This prospective open-label study examined the effect of atosiban on uterine contractile activity, implantation and clinical pregnancy in a series of patients with RIF undergoing IVF/embryo transfer.

Materials and methods

Study population

This prospective open-label cohort study (NCT01493440) included 71 patients with RIF who underwent an IVF/embryo transfer cycle using cryopreserved embryos at the ART unit, An Sinh Hospital, Ho Chi Minh City, Vietnam from March to August 2011. There are several definitions of RIF in the clinical setting (Stephenson and Fluker, 2000). In this study, RIF was defined as the failure to conceive after at least three embryo transfers with eight top-quality embryos or more. Patients with RIF fulfilling the following inclusion criteria were prospectively recruited: (i) age 18–40 years; (ii) baseline FSH $<$10 IU/l; (iii) menstrual cycle of 25–34 days; (iv) clear information about previous IVF/embryo transfer cycles (including number of embryos transferred, embryo quality, endometrial thickness); (v) one or more good-quality embryo after warming on the day of embryo transfer. Exclusion criteria were: (i) adenomyosis; (ii) uterine anomaly; (iii) uterine fibroids; and (iv) hydrosalpinges.

Written consent was obtained for the participation in the study. The study protocol was approved on 10 January 2011 by the IVFAS Research and Ethics Board, An Sinh Hospital, Ho Chi Minh City, Vietnam (approval reference number IVFAS1103).

IVF/embryo transfer protocol

Cryopreserved embryos were used in all embryo transfer cycles. Stimulation protocols for egg retrieval and embryo cryopreservation were the standard procedures at An Sinh Hospital. Vitrification was used. Vitrifying and warming of embryos was also performed according to a standard protocol. Embryo quality after warming was defined using existing criteria (Veeck, 1999); embryos were assigned a score according to the number and regularity of blastomeres and the degree of fragmentation.

Endometrial preparation consisted of oestradiol valerate (Progynova, 2 mg; Bayer HealthCare Pharmaceuticals) tablets given four times daily. If endometrial thickness was $>$8 mm after at least 12 days of oestradiol administration, progesterone supplementation (Crinone, 8% 90 mg; Merck Serono) was started with two doses of 90 mg daily. Cryopreserved embryo transfer was performed 2 days after the initiation of progesterone supplementation. Embryo transfer was performed using a catheter (Tulip set; Gynetics) by a standard technique under ultrasound guidance. Two or three embryos were cryopreserved in each straw and usual practice was to warm one straw. If this contained at least one good-quality embryo, no further straws were warmed and all warmed embryos were transferred. If there was no good-quality embryo in the first straw and the patient had other cryopreserved straws available, another straw was warmed and, as long as there was at least one good-quality embryo, embryos from both warmed straws were transferred. If the first straw did not have any good-quality embryos or if, after warming the second straw, there was still not at least one good-quality embryo, the available embryos were transferred but the patient was excluded from the study. Cryopreserved embryos were warmed on the day of embryo transfer.

Atosiban treatment

Atosiban (Tractocile; Ferring Pharmaceuticals) was administered as an 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. Atosiban was supplied in 5 ml vials of 7.5 mg/ml.

Measurement of uterine contractions

The frequency of uterine contractions was measured using transvaginal ultrasound (SSD 1700 with 7.5 MHz transvaginal convex probe; Aloka Holding) 30 min before and 3 h after embryo transfer (corresponding to the time immediately before the bolus dose of atosiban and after completion of atosiban infusion). Measurement of uterine contractions was performed using the method documented by Fanchin et al. (1998, 2000). To minimize bias, all ultrasound examinations were performed with the same single sonographer. The probe was placed on a pillow to avoid pressure to the uterus. A camera recorder was connected to the ultrasound machine to document the measurements for 4 min. Recordings were then analysed to count the number of uterine contractions.

Outcome measures

The implantation rate (IR) per embryo transferred and clinical pregnancy rate (CPR) per cycle were determined. IR was defined as the number of gestational sacs per number of embryos transferred. CPR was defined as the observation of intrauterine gestational sac with a heartbeat 3 weeks after the positive human chorionic gonadotrophin test. The ongoing pregnancy rate was defined as pregnancy persisting for $\geq$12 weeks. The frequency of uterine contractions before and after atosiban administration is reported.

Statistical analysis

Statistical Package for Social Sciences version 19 (SPSS, USA) was used for data analysis. Mean values were compared using Student's *t*-test. A *P*-value <0.05 was defined as statistically significant.

Results

A total of 71 subjects with RIF were recruited into this study. Patient characteristics and demographic data are summarized in **Table 1**.

The subjects were allocated to one of the two groups according to the baseline uterine contraction frequency: $\geq$16 contractions per 4 min (high) or $<$16 contractions per 4 min (low). Ten subjects (14%) had a high frequency of uterine contractions before embryo transfer (**Table 2**). The administration of atosiban significantly reduced the mean frequency of uterine contractions during and immediately after embryo transfer (**Table 2**). This statistically significant reduction was documented in the combined patient group, in cycles with $\geq$16 uterine contractions in the initial 4-min recording period, and in those with $<$16 uterine contractions (**Table 2**).

Details of pregnancy outcomes in the 71 cycles in which atosiban was administered are shown in **Table 3**.

The number of previously failed cycles of IVF/embryo transfer was three in 22 patients, four in 16 patients, five in seven patients, six in 10 patients, seven in 14 patients and nine and twelve in one patient each. The CPR stratified by the number of previous cycle failures is shown in **Figure 1**. None of the 71 subjects had previously achieved a clinical pregnancy despite an average number of 4.8 embryo transfers with a mean of 12 top-quality embryos, and therefore the CPR in these patients prior to this study was zero.

Discussion

The results of this study suggest that atosiban administration during embryo transfer may potentially improve the IR and CPR in patients with RIF undergoing IVF/embryo transfer. A significant reduction in the number of uterine contractions after drug administration was also observed.

In IVF/intracytoplasmic sperm injection cycles, some patients fail to conceive after a number of cycles despite

Table 1 Patient characteristics and demographic data.

Characteristic	*Sample population (n = 71)*
Age (years)	34.2 ± 5.2 (24–40)
Infertility duration (years)	6.2 ± 4.0 (1–19)
Indications for IVF	
Tubal factor	35 (49.3)
Male factor	20 (28.2)
Endometriosis	8 (11.3)
Unexplained infertility	5 (7.0)
Other	3 (4.2)
Endometrial thickness (mm)	10.7 ± 1.6 (8–14)
No. of previous failed embryo transfers	4.8 ± 1.8 (3–12)
No. of top-quality embryos transferred in previous failed cycles	12.4 ± 5.3 (8–32)

Values are mean ± SD (range) or *n*/total (%).

Table 2 Uterine contractions.

Parameter	*Sample population*
Frequency of uterine contractions	
≥16 contractions per 4 min	10/71 (14.1)
<16 contractions per 4 min	61/71 (85.9)
No. of contractions per 4 min	
Total	
Before atosiban	6.0 ± 5.7 (0–20)
After atosiban	2.6 ± 2.1 (0–9)[a]
Cycles with ≥16 uterine contractions per 4 min	
Before atosiban	18.8 ± 1.6 (16–20)
After atosiban	5.1 ± 2.6 (2–9)[a]
Cycles with <16 uterine contractions per 4 min	
Before atosiban	3.9 ± 2.4 (0–8)
After atosiban	2.2 ± 1.7 (0–6)[a]

Values are *n*/total (%) or mean ± SD (range).
[a]$P < 0.01$ compared with atosiban administration.

Table 3 Pregnancy outcomes of IVF/embryo transfer cycles after atosiban administration.

Outcome	*Sample population*
No. of embryos transferred	3.4 ± 0.7 (2–5)
Clinical pregnancy per cycle	31/71 (43.7)
Type of pregnancy	
Singleton	29/31 (93.5)
Twins	1/31 (3.2)
Triplets	1/31 (3.2)
Implantation per embryo transferred	34/245 (13.9)
Miscarriage per cycle	3/71 (4.2)
Ectopic pregnancy per cycle	1/71 (<1.0)
Ongoing pregnancy per cycle[a]	26/70 (37.1)

[a]Data could not be determined for one patient, who moved overseas.

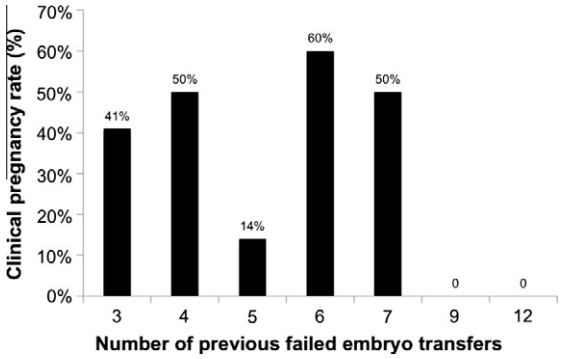

Figure 1 Clinical pregnancy rates stratified by the number of previous failed embryo transfers.

the transfer of top-quality embryos, good endometrial quality and the use of excellent technique by the physicians.

Such a scenario of RIF is a significant problem for those undergoing IVF/embryo transfer, and it is the main cause of infertility in women with no other explanation for infertility (Margalioth et al., 2006). Suboptimal uterine receptivity accounts for around two-thirds of implantation failure; embryo quality contributes to the remaining one-third (Lédée-Bataille et al., 2002). Treatment options for RIF are limited. Those that have been previously evaluated include preimplantation genetic screening (Gianaroli et al., 1997; Mastenbroek et al., 2011; Twisk et al., 2006) and the use of antithrombotic or anticoagulant agents, with variable success (Qublan et al., 2008; Sher et al., 1998; Stern et al., 2003).

Of the 71 subjects with RIF included in this study, no clinical pregnancies had been previously achieved despite an average of 4.8 previous embryo transfers with a mean of 12 top-quality embryos. The CPR can therefore be said to have improved from zero to an average of 43.7% when atosiban was added during the embryo transfer procedure. The 43.7% CPR achieved using atosiban in this study is almost identical to the overall average CPR of IVF/embryo transfer at An Sinh Hospital (45%). Furthermore, the IVF/embryo transfer cycles included in this study were carried out using cryopreserved rather than fresh embryos. This is the first report of atosiban administration during IVF/embryo transfer cycles using cryopreserved embryos.

Uterine contractile activity has been indirectly shown to be important in establishing appropriate conditions for embryo implantation (Ijland et al., 1997; Knutzen et al., 1992). In addition, it has been suggested that excessive uterine contraction is a cause of implantation failure during IVF/embryo transfer (Fanchin et al., 1998; Lesny et al., 1999a). For example, the success rate of IVF/embryo transfer is up to 3-fold lower in the subgroup of patients who have pronounced uterine contractions (Fanchin et al., 1998). In this study, the cut off of ≥16 uterine contractions during the 4-min recording period was chosen on the basis of

previous data, which shows that the CPR was 50% lower in patients with ≥4 versus <4 uterine contractions per 1 min. The 4-min recording period was selected because a period of 2 min was considered too short to achieve stable measurement conditions and excessive discomfort for the patient occurs if the measurement is longer than 4 min. No data on the direction of uterine contractions were gathered as there is no evidence to show that contraction direction has an impact on the implantation process (Fanchin et al., 1998; Narayan and Goswamy, 1994).

Pharmacological interventions to reduce uterine contractility during IVF/embryo transfer have been associated with variable results. The frequency of uterine contractions at the time of embryo transfer was significantly reduced if luteal support with progesterone was initiated 2 days before embryo transfer compared with the initiation on the day of transfer, and both IR and CPR were also shown to be improved (Fanchin et al., 2001).

A single 10-mg oral dose of the nonsteroidal anti-inflammatory drug piroxicam improved the IR and CPR after IVF/embryo transfer in both fresh and frozen–thawed cycles (Moon et al., 2004). It was postulated that piroxicam administered just prior to embryo transfer primes the uterus to be suitable for implantation. However, uterine contractions and uterine blood flow were not assessed in this study. In contrast, another type of NSAID (indomethacin) did not improve the IR in a similar study setting (Bernabeu et al., 2006). Conflicting results have also been reported with the use of beta-blockers during the peri-implantation period of assisted reproduction cycles, with improving pregnancy and implantation rates documented in one study (Tsirigotis et al., 2000) but no effect shown in another (Pinheiro et al., 2003).

These inconsistent results lend support to the suggestion that uterine contractility is not the only important factor in determining the implantation and pregnancy rate. In the first case report of the use of atosiban during IVF/embryo transfer, Pierzynski et al. (2007b) suggested that the mechanism by which atosiban improved the success rate of assisted reproductive procedures was via a reduction in uterine contractions. The subject in this case report had undergone eight unsuccessful embryo transfers, and transvaginal sonography scan data confirmed a reduction in uterine contractions over 1 h after the initiation of atosiban infusion. Embryo transfer was carried out at the same time and was associated with clinical pregnancy and delivery of healthy twins 8 months later. Similar results were subsequently reported in another case report (Liang et al., 2009).

Atosiban has been shown to reduce the frequency and amplitude of uterine contractions compared with placebo (Blockeel et al., 2009), and a significant reduction in uterine contraction frequency compared with baseline was also observed in this study with atosiban. In a recent randomized, placebo-controlled study, treatment with atosiban (using a dosing regimen identical to the current study) significantly improved both the IR and CPR, but uterine contraction was not assessed (Moraloglu et al., 2010). The current study measured uterine contraction in all subjects. There was an interesting finding when subjects were arbitrarily sorted into those with either high or low uterine contraction frequency; the benefits of atosiban therapy, in terms of increased IR and CPR, were not restricted to the 14% of subjects with frequent uterine contractions prior to embryo transfer but were instead documented in all atosiban recipients.

Reducing uterine contractility is certainly one way to improve uterine receptivity. The inhibition of oxytocin and vasopressin V_{1A} receptors would be expected to improve uterine receptivity, but other possible beneficial mechanisms may also contribute to the effect. These include interference with prostaglandin $F_{2\alpha}$/oxytocin systems and probably also the improvement of endometrial perfusion (Vedernikov et al., 2006). Blocking both oxytocin and vasopressin V_{1A} receptors is an optimal approach because oxytocin exerts a relatively strong effect on the V_{1A} receptor (Akerlund et al., 1999). Certainly, the results of the current study, where the beneficial effects of atosiban on IR and CPR were not restricted to those with frequent uterine contractions prior to embryo transfer, support the idea that atosiban has multiple mechanisms of action, which work together to improve uterine receptivity after embryo transfer. This is in line with hypotheses proposed by other researchers (Moraloglu et al., 2010; Pierzynski et al., 2007a,b) who suggested increased endometrial perfusion and improved endometrial status as additional potential mechanisms for the beneficial effects of atosiban in the setting of IVF/embryo transfer.

Although there are a limited number of published reports on the use of atosiban in the potential indication of IVF/embryo transfer, there is a good body of evidence documenting its safety and tolerability in its registered indication, of delaying preterm labour (European Atosiban Study Group, 2001; French/Australian Atosiban Investigators Group, 2001; Goodwin et al., 1996; Husslein et al., 2007; Moutquin et al., 2000; Romero et al., 2000; Worldwide Atosiban versus Beta-agonists Study Group, 2001). Atosiban has high specificity for the uterus and is not associated with systemic adverse effects (De Heus et al., 2008). In addition and of particular relevance to the use of atosiban in infertility treatment, atosiban appears to have a good embryonic safety profile (Pierzynski et al., 2007a) and has no effect on the endocrine profile at the time of implantation (Visnova et al., 2009).

This study was conducted in patients with RIF undergoing IVF/embryo transfer with cryopreserved embryos. However, atosiban has also been shown to have beneficial effects on implantation, pregnancy and miscarriage rates in a more conventional group of women undergoing IVF (Moraloglu et al., 2010). Therefore, adding atosiban therapy may be a suitable approach for improving outcomes in all women undergoing IVF/embryo transfer. However, additional research is needed before this recommendation can be made.

The number of embryos transferred per patient in this study was relatively high (range 2–5, mean 3.4). This was because the expectation of achieving pregnancy was low based on previous outcomes of IVF/embryo transfer in these patients with RIF. However, looking at the successful results reported here, atosiban could potentially facilitate a reduction in the number of embryos transferred per IVF cycle because the IR went from zero to 13.9% when atosiban was given and there were even some multiple pregnancies.

The main limitation of this study was its non-randomized design. However, getting enough patients with RIF at a single centre to conduct an adequately powered randomized

controlled trial is difficult. Therefore, multicentre trials may be more appropriate in the future. Non-randomized trials, such as the current study, have provided good proof-of-concept data. Despite the above limitation, this study was able to access a full set of treatment data on previous IVF/embryo transfer cycles for every patient recruited, which means that each patient was able to act as their own control.

In conclusion, the results of this study confirm the beneficial effects of atosiban on implantation and pregnancy in a real-world IVF/embryo transfer setting. This confirms previously published data from a randomized clinical trial (Blockeel et al., 2009). In addition, this is the first study to utilize cryopreserved embryos with the aid of atosiban in embryo transfer. There are a number of potential mechanisms by which atosiban may improve outcomes in IVF/embryo transfer cycles. These include interference with prostaglandin $F_{2\alpha}$/oxytocin systems, improved uterine perfusion and reduced uterine contractions. Although this study clearly documented a reduction in uterine contractions after the administration of atosiban, improvements in implantation and pregnancy rates were observed in all patients, not only those with a high number of uterine contractions prior to embryo transfer. Therefore, the beneficial effects of atosiban on implantation and pregnancy may result from other mechanisms in addition to its inhibitory effects on uterine contractility. Further trials are required to more fully elucidate the mechanisms of action and clinical value of atosiban in this new indication.

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