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ARTICLE

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

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Dr Vuong Thi Ngoc Lan received her MD in 1996 and her Master's in clinical embryology at the National University of Singapore in 1999. She was a member of the first IVF team in Vietnam in 1997. Since then, she has taken part in more than 15,000 IVF cycles. Currently, she works in the Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Ho Chi Minh City, where she is a PhD fellow in reproductive medicine. Her primary interests are luteal-phase support, use of antagonists in IVF, ovulation induction in patients with polycystic ovary syndrome and in-vitro maturation.

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