CASE REPORT

Oxytocin antagonists may improve infertility treatment

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Objective: To confirm the improvement of uterine receptivity following administration of oxytocin and vasopressin V_{1A} antagonist atosiban.
Design: Case report.
Setting: Private reproductive medicine center.
Patient(s): A 42-year-old woman with a history of 15 years' infertility and seven failed in vitro fertilization/embryo transfer (IVF-ET) attempts.
Intervention(s): Atosiban (mixed vasopressin V_{1A}/oxytocin antagonist registered for the treatment of imminent premature birth) was administered on the 14th day of endometrial synchronization for oocyte donation.
Main Outcome Measure(s): Uterine contractile activity (component of uterine receptivity) and success of treatment of infertility.
Result(s): Intense spontaneous uterine contractility was visualized by transvaginal sonography. After 1 hour of intravenous infusion of atosiban, a repeated scan showed a significant decrease in contractile activity (11 vs 7 contractions per 4 minutes, respectively). The ET was performed immediately after, and the infusion of atosiban continued for the next 2 hours. The treatment decreased the uterine contractile activity and resulted in successful embryo implantation and a normal twin diamniotic pregnancy.
Conclusion(s): Atosiban may improve uterine receptivity during ET and may increase success rates of advanced infertility treatment procedures. (Fertil Steril® 2007;88:213.e19–22. ©2007 by American Society for Reproductive Medicine.)

Key Words: Oxytocin antagonists, vasopressin antagonists, IVF-ET, uterine contractility, atosiban, clinical pregnancy

The effectiveness of in vitro fertilization–embryo transfer (IVF-ET) usually does not exceed 30% per treatment cycle (1), and is further reduced in women older than 36 years (2). Good quality of embryos and optimal intrauterine environment are the basic determinants of success for ET, and the whole IVF-ET procedure. Ideal intrauterine conditions that enable implantation include appropriate endometrial status, sufficient endometrial perfusion and absence of excessive uterine contractions. In particular, increased uterine contractile activity may expel embryos from the uterus (3, 4).

Implantation and pregnancy rates are inversely correlated with the frequency of uterine contractions. High uterine contractile activity at ET (five or more contractions per minute) is found in about one-third of patients, and in these women clinical pregnancy rates reach 13% per cycle, in contrast to the 53% of successful pregnancies in women with lower uterine activity (three or less contractions per minute) (5). Moreover, irritation of the uterine cervix by the ET catheter is likely to induce additional contractile reflexes and further decrease the chances of successful embryo implantation (6).

However, uterine contractile activity, an important component of uterine receptivity, is currently not a subject of specific diagnosis or treatment in ET recipients. Progesterone supplementation, even when acting on uterine receptivity, improving endometrial status, and decreasing uterine contractions, shows no benefit for pregnancy rates after IVF-ET (7). Studies assessing the effectiveness of piroxicam (cyclooxygenase inhibitor) and ritodrine (β_2-adrenoreceptor agonist) have shown a positive effect on pregnancy rates (8, 9), but these drugs have failed to enter routine clinical use because of safety concerns.

Oxytocin antagonists constitute a new class of drugs introduced for the tocolytic treatment of preterm labor. Atosiban (TRACTOCILE; Ferring Pharmaceuticals A/S, Copenhagen, Denmark), a mixed vasopressin V_{1A}/oxytocin antagonist registered in Europe for the treatment of imminent premature birth, is more uterine selective and has minimal side effects compared with β_2-adrenoreceptor agonists (10). Inhibition of oxytocin or vasopressin V_{1A} receptors effectively stops uterine contractility in nonpregnant patients (11). Oxytocin/vasopressin V_{1A} receptor blockade may constitute a safe

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and effective treatment for improving uterine receptivity in women undergoing ET, providing a decrease in uterine contractile activity, an increase in endometrial perfusion, and improvement in endometrial status.

We report a case of application of atosiban during IVF-ET treatment that decreased contractions of the nonpregnant uterus, supported embryo implantation, and led to successful pregnancy after seven previous negative treatment cycles. This is the first case of successful pregnancy and delivery after atosiban treatment in an IVF-ET patient.

MATERIALS AND METHODS

In the referred cycle, the patient was treated according to the standard procedures of endometrial synchronization for donated oocyte recipients (12). Increasing doses of estradiol valerate (Progynova; Schering AG, Berlin, Germany) were administered at 2–8 mg/day for 14 days and micronized progesterone (Utrogestan, Laboratories Besins International, Paris, France) at 600 mg/day; IVF with intracytoplasmic sperm injection (ICSI) for two donated oocytes was performed, with embryo culture, ET, and luteal support after ET (Utrogestan, 600 mg per day for 12 weeks). Oocytes used in this cycle had been donated by a healthy, 27-year-old woman with a good response to ovarian stimulation, who had presented to the IVF-ET treatment program for male factor infertility.

The patient's previous treatment cycles had involved pituitary desensitization, controlled ovarian hyperstimulation, oocyte collection, IVF-ICSI, embryo culture, and ET for three cycles, then the donated oocyte scheme previously described for four consecutive cycles.

In the referred cycle, ET was performed on the 14th day of synchronization using a soft transfer catheter (Labotect GmbH, Goettingen, Germany). A transvaginal sonography scan with 4-minute digital recording of a sagittal transsection of the uterus (SSD 1700 with 7.5 MHz transvaginal convex probe; Aloka Holding, Zug, Switzerland) with a digital camcorder (DCR PC100E, Sony Corporation, Tokyo, Japan) was performed before the start of atosiban infusion and then repeated directly before the ET. Assessment of uterine contractions was performed with digital 4× speed sonography film sequences, using Direct X software (Microsoft, Redmond, WA) that visualized time-compressed vertical displacements of an image segment that covered the endometrial–myometrial interface.

CASE PRESENTATION

A 42-year-old, otherwise healthy woman was referred for treatment after a 15-year history of infertility. Following an initial diagnosis of intramural uterine myomata and left simple ovarian cyst, surgical treatment that included laparotomy, myomectomy with reconstruction of the uterus, and left cystectomy was performed with no complications. The patient was unsuccessfully treated in three consecutive IVF-ET programs (cycles one to three) with a total number of four transferred embryos (A and B class). Normal appearance of the uterine cavity was hysteroscopically confirmed before the continuation of infertility treatment. Taking into consideration her poor ovarian response to controlled hyperstimulation, further treatment plans employed donated oocytes. In the following 7 months, four consecutive ET cycles (cycles four through seven) that used a total of eight top-quality embryos resulted in negative outcomes. Four otherwise healthy women who had been included within the IVF programs for male factor infertility had donated the oocytes used in these cycles.

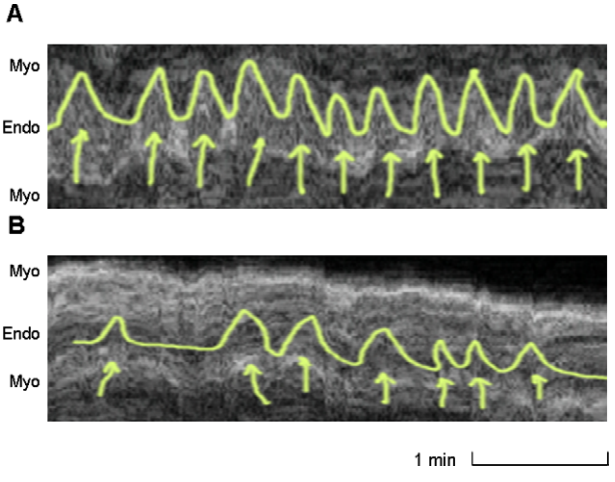
For the 8th cycle, after obtaining approval of a local ethics committee and receipt of the patient's written informed consent, we decided to administer atosiban.

RESULTS

One hour before ET, analysis of the digital transvaginal sonography (TVS) recording demonstrated high spontaneous uterine contractile activity (11 contractions within 4 minutes; Fig 1A). Intravenous administration of atosiban started with a bolus dose of 6.75 mg and continued thereafter at an infusion rate of 18 mg/hour. Directly before ET, a marked decrease in uterine contractility with decreased intensity of contractions was demonstrated (seven contractions within 4 minutes; Fig 1B). All of the visualized contractions were of fundocervical

FIGURE 1

Ultrasonography of endometrial–myometrial interface movements on the sagittal section of the uterine fundus. (Endo: endometrium; Myo: myometrium.) The interface is marked with bright color for better visualization; arrows represent uterine contractions. (**A**) High spontaneous uterine contractile activity before the treatment (control). (**B**) Reduced uterine activity during atosiban infusion (directly before embryo transfer).



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