Oxytocin Antagonist for Repeated Implantation Failure and Delay of Delivery

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Arginine vasopressin V1 receptors are present on human myometrial specimens obtained at cesarean section from women at the end of pregnancy (from 32 weeks to term). Oxytocin receptors increase in human parturition and are significantly correlated with the frequency of uterine contractions [1]. Oxytocin and vasopressin receptors may play a role in the regulation of labor, although increased oxytocin release primarily initiates labor contractions. The mixed V1 arginine vasopressin and oxytocin receptor antagonist, atosiban, is uterine-specific, decreasing uterine contractions in pregnant women, and is indicated for tocolysis in imminent premature birth [2]. Atosiban was developed specifically to treat preterm labor and is widely used in many countries. A single bolus of atosiban is indicated for acute tocolysis in term labor, such as in fetal distress, and arrest of contractions prior to emergency cesarean section. Atosiban has little effect on maternal and fetal heart beats compared with the significant effects of ritodrine, but appears to have an immediate and profound effect on uterine activity, comparable to that of ritodrine [3]. However, a Cochrane review suggested that atosiban shows no difference from placebo or other tocolytics in preventing preterm labor or improving infant outcome [4]. Maternal drug reactions with atosiban are increased compared with placebo, but these side effects are reduced when compared with beta-mimetics. Herein, we report a couple with recurrent implantation failure (RIF) who finally conceived successfully after an *in vitro* fertilization (IVF)–embryo transfer (ET) cycle in which atosiban was administered intravenously during embryo transfer, and delivery of the second and third triplet was delayed with the aid of atosiban infusion which inhibits contractility in both the nonpregnant and pregnant uterus.

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Accepted: September 10, 2008

This study was approved by the institutional review board of National Cheng Kung University Hospital. We report a 31-year-old patient, who experienced repeated failure of IVF-ET, and underwent a seventh course of controlled ovarian hyperstimulation. Informed consent was obtained from the patient. At the first visit, a male factor in infertility was suspected because of oligospermia (semen analysis revealed sperm concentration of 7×10^5/mL and 57% motile sperm at grade 3+4). No endocrine or genital structural abnormality was identified before infertility treatment. The couple had experienced two courses of intrauterine insemination failure, then four courses of IVF-ET with gonadotropin-releasing hormone agonist or antagonist during gonadotropin stimulation, and one course of frozen ET with good embryo grading, but without success.

From counseling and in-depth interview, interpersonal stress (especially the marital factor) as a result of the RIF was possibly the main reason for lack of success. In the seventh controlled ovarian hyperstimulation cycle, the patient was given a short gonadotropin-releasing hormone agonist protocol which began with daily buserelin nasal spray (Supremon; Hoechst, Frankfurt, Germany) from day 2 of the menstrual cycle, and recombinant gonadotropin (Gonal-F; Serono, Bari, Italy) was administered from day 3 for 8 days with 1,500 IU in total. When two follicles reached 18 mm, 250 μg of recombinant human chorionic gonadotropin (Ovitrelle; Serono) was injected, and transvaginal oocyte retrieval was performed 34 hours later with 14 oocytes collected, of which eight were fertilized normally. Three embryos with good embryo grading (all four-cell grade 1) were placed into the uterine cavity under transabdominal ultrasound guiding with fully distended bladder on day 2 after fertilization while two of the remaining embryos were stored for cryopreservation. After counseling for the anxiety related to ET, the patient received atosiban (Tractocile; Ferring AB, Limhamn, Sweden) infusion to reduce uterine activity with a bolus dose of 6.75 mg followed by infusion at 18 mg/hr for 3 hours immediately after ET, resulting in a successful triplet pregnancy.

The pregnancy continued smoothly with regular prenatal examinations. However, premature preterm rupture of the membranes associated with uterine contraction and cervical dilatation was found at a gestational age of 29 weeks, and a premature male baby (the first triplet) was delivered vaginally as labor progressed after intravenous ritodrine administration. Successful tocolysis was achieved by atosiban infusion (6.75 mg initial dose, 300 μg/min loading dose for 3 hours, 100 μg/min maintenance dose for 48–96 hours) after delivery of the first triplet, whose umbilical cord was clamped and packed back into vagina. The tocolysis was continued until the patient could not tolerate the persistent discomfort of full cervical dilation, and two premature babies (the second and third triplet) were delivered vaginally 7 days later.

Unfortunately, early postpartum hemorrhage and transient low blood pressure were noted after extrusion of the three placentae but improved after uterine massage and vaginal gauze packing. Late postpartum hemorrhage occurred 1 week after delivery, and ultrasound revealed an intrauterine mass. Pathologic investigation confirmed retained placental tissue after the procedure of dilation and curettage. The follow-up period was subsequently uneventful.

Pierzynski et al [5] first reported that atosiban reduced intense spontaneous uterine contractility as visualized by transvaginal sonography, allowing improved uterine receptivity resulting in successful embryo implantation during ET after endometrial synchronization with the donated oocyte recipient. We presented a woman who was first treated with atosiban for RIF and successfully conceived, then delivery of her second and third triplet in preterm labor was delayed with the aid of atosiban infusion. Thus, atosiban inhibited contractility in both the nonpregnant and pregnant uterus.

Good correlations between oxytocin receptor concentrations and uterine contractility have been observed in both the pregnant and nonpregnant states [6]. Therefore, atosiban, a selective oxytocin receptor antagonist capable of inhibiting uterine contractility, has been proposed for clinical evaluation in dysmenorrhea and preterm labor. It has been found to be comparable in clinical tocolytic effectiveness to conventional β-agonist therapy, but with less maternal side effects in preterm labor patients with intact membranes [7]. In this report, it was reasonably effective in the inhibition of oxytocin-induced contractions of the myometrium after delivery of the first baby of the triplet, allowing the delayed delivery of the two remaining fetuses which had intact membranes. Delayed delivery is recommended in some cases of multiple pregnancy after the first delivery, especially if this occurs early. Delayed delivery of the remaining fetus(es) under 30 weeks' gestation for 2 or more days, with careful observation of the fetal and maternal condition, improves survival and decreases morbidity among latter-born siblings [8]. The tocolytic effect of atosiban helped to prevent delivery of the remaining fetuses contemporaneously which improved infant survival.

In spite of a high pregnancy rate following IVF-ET, some couples, as in our case, have repeated failure of ET after reasonably good embryos have been transferred. Further investigation should be initiated, such as into psychologic factors. It is stressful during the course of infertility treatment, especially when women are undergoing IVF-ET. The emotional distress in infertile women is often underestimated. More than 40% of infertile women who visited for a new course of assisted reproductive technology treatment had a psychiatric disorder, including anxiety and/or depression [9]. This high prevalence of psychiatric morbidities is not affected by demographic features (including age, education level, income, or years of infertility), or a history of previous assisted conception treatment. The negative impact of the psychologic factors may contribute to implantation failure which reduces IVF success. However, the effect of psychologic treatments for infertile individuals lacks proof of efficacy in improving pregnancy rate [10].

As psychologic stressors are associated with preterm labor [11], the elevated uterine contractile activity (component of uterine receptivity) may also be related to the increase in stress or anxiety during ET. Atosiban may increase the success rates of infertility treatment with the possibility that a reduction in stress responses may help to increase uterine receptivity during ET, especially in women with RIF. A significant decrease in uterine contractility activity visualized by transvaginal sonography was found after 1 hour of intravenous infusion of atosiban [5]. Although we did not use ultrasonography, a biologically plausible explanation for the benefit of atosiban during ET in our case may be a decrease in the uterine contractile activity induced by psychologic stressors, resulting in successful embryo implantation and a normal triplet pregnancy. However, it is equally plausible that the patient may have conceived if she had received no treatment at all. Further prospective well-designed, randomized, controlled trials are needed to compare atosiban with placebo infusion during ET in women with RIF, after appropriate institutional review board approval and informed consent.

The possible embryo toxicity of atosiban during implantation in IVF-ET programs may be of concern. The gene expressions of oxytocin and its receptor are detected in human cumulus cells surrounding the

oocytes [12]. The effect of oxytocin may enhance blastocyst formation and play a physiologic role on embryogenesis in fertilized mouse oocytes. The messenger RNA expressions of oxytocin receptor have been demonstrated in mouse oocytes and embryos up to the blastocyst stage [13]. Its expression is increased immediately after fertilization which is compatible with a possible role of oxytocin in this process, then oxytocin receptor messenger RNA gradually decreases after the four-cell stage of pre-embryonic development. The expression of the oxytocin receptor has also been shown in the mouse uterus, suggesting that oxytocin may play a potential role in the implantation process [13]. It is possible that any drug utilized in IVF-ET programs, which involves the interaction with the oxytocin receptor, will affect the receptivity/quality of the implanting endometrium. However, clinical application of atosiban is considered for the novel indication of improvement of uterine receptivity in ET recipients from an *in vitro* animal study [14]. Preimplantation rabbit embryo development is not affected by atosiban in concentrations 50-fold higher than the mean plasma concentration reached during regular therapy. A clinical case report [5] and this case supported this hypothesis.

In conclusion, we suggest that the use of oxytocin antagonist may be of benefit for IVF with RIF and for delaying delivery in a multi-fetal pregnancy after IVF as in this present report. The potential use of atosiban will inhibit uterine contractility, which may be a good intervention to help minimize the psychologic burdens in women undergoing IVF, in the 2-week waiting period prior to the pregnancy test. However, further randomized, controlled trials are required to investigate the indication of oxytocin antagonist for ET in infertility treatment, especially in cases of anxiety with RIF.

References

1. Maggi M, Del Carlo P, Fantoni G, et al. Human myometrium during pregnancy contains and responds to V1 vasopressin receptors as well as oxytocin receptors. *J Clin Endocrinol Metab* 1990;70:1142–54.
2. Bossmar T, Akerlund M, Fantoni G, Szamatowicz J, Melin P, Maggi M. Receptors for and myometrial responses to oxytocin and vasopressin in preterm and term human pregnancy: effects of the oxytocin antagonist atosiban. *Am J Obstet Gynecol* 1994;171:1634–42.
3. de Heus R, Mulder EJ, Derks JB, Kurver PH, van Wolfswinkel L, Visser GH. A prospective randomized trial of acute tocolysis in term labour with atosiban or ritodrine. *Eur J Obstet Gynecol Reprod Biol* 2008;139:139–45.
4. Papatsonis D, Flenady V, Cole S, Liley H. Oxytocin receptor antagonists for inhibiting preterm labour. *Cochrane Database Syst Rev* 2005;(3):CD004452.
5. Pierzynski P, Reinheimer TM, Kuczynski W. Oxytocin antagonists may improve infertility treatment. *Fertil Steril* 2007; 88:213:e219–22.
6. Akerlund M, Melin P, Maggi M. Potential use of oxytocin and vasopressin V1a antagonists in the treatment of preterm labour and primary dysmenorrhoea. *Adv Exp Med Biol* 1995; 395:595–600.
7. Lamont RF. Evidence-based labour ward guidelines for the diagnosis, management and treatment of spontaneous preterm labour. *J Obstet Gynaecol* 2003;23:469–78.
8. Zhang J, Hamilton B, Martin J, Trumble A. Delayed interval delivery and infant survival: a population-based study. *Am J Obstet Gynecol* 2004;191:470–6.
9. Chen TH, Chang SP, Tsai CF, Juang KD. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. *Hum Reprod* 2004;19:2313–8.
10. Boivin J. A review of psychosocial interventions in infertility. *Soc Sci Med* 2003;57:2325–41.
11. Field T, Diego M, Hernandez-Reif M. Prematurity and potential predictors. *Int J Neurosci* 2008;118:277–89.
12. Furuya K, Mizumoto Y, Makimura N, et al. A novel biological aspect of ovarian oxytocin: gene expression of oxytocin and oxytocin receptor in cumulus/luteal cells and the effect of oxytocin on embryogenesis in fertilized oocytes. *Adv Exp Med Biol* 1995;395:523–8.
13. Beretsos P, Loutradis D, Koussoulakos S, et al. Oxytocin receptor is differentially expressed in mouse endometrium and embryo during blastocyst implantation. *Ann N Y Acad Sci* 2006;1092:466–79.
14. Pierzynski P, Gajda B, Smorag Z, Rasmussen AD, Kuczynski W. Effect of atosiban on rabbit embryo development and human sperm motility. *Fertil Steril* 2007;87:1147–52.