# Administration of atosiban in patients with endometriosis undergoing frozen–thawed embryo transfer: a prospective, randomized study

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**Objective:** To examine the effects of atosiban, given before transfer of frozen–thawed embryo to women with endometriosis (EMs).
**Design:** A randomized, controlled clinical trial.
**Setting:** University hospital and IVF center.
**Patient(s):** One hundred twenty women with endometriosis undergoing frozen–thawed embryo transfer were randomly allocated into the atosiban treatment and the control groups. Another 120 women with infertility due to tubal factor were enrolled into a tubal factor group, to compare serum oxytocin (OT) and prostaglandin (PG)$F_{2\alpha}$ levels and uterine contractions with the endometriosis group.
**Intervention(s):** In the endometriosis treatment group, a single bolus (6.75 mg, 0.9 mL per vial) of atosiban was administrated before ET.
**Main Outcome Measure(s):** Implantation rate and pregnancy rate.
**Result(s):** Serum OT level (1.89 ± 0.33 vs. 1.66 ± 0.32 ng/L), $PGF_{2\alpha}$ (2.83 ± 0.34 vs. 2.36 ± 0.35 ng/L) level, and uterine contractions (2.5 ± 1.2 vs. 1.8 ± 1.0 waves per minute) in the endometriosis group were all significantly higher than in the tubal factor group. The clinical pregnancy rate per cycle and implantation rate per transfer were 58.3% and 41.0%, respectively, in the atosiban treatment group, significantly higher than in the control group (38.3% and 23.4%, respectively).
**Conclusion(s):** Women with endometriosis showed higher serum OT level, $PGF_{2\alpha}$ level, and uterine contractions. Atosiban treatment before ET in endometriosis is effective in the priming of the uterus, suitable for embryo implantation. This is the first study to evaluate the effect of atosiban treatment in patients with endometriosis.
**Clinical Trial Registration Number:** ChiCTR-IOQ-14005715. (Fertil Steril® 2016;106:416–22. ©2016 by American Society for Reproductive Medicine.)
**Key Words:** Atosiban, clinical pregnancy rate, endometriosis, oxytocin, uterine contractility

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Endometriosis is a benign gynecologic disorder characterized by the presence of endometrial tissue outside the uterus and is accompanied by pain and infertility (1). The disease affects approximately 10% of women of reproductive age and 20%–50% of infertile women (2, 3). In vitro fertilization is currently the most effective treatment for endometriosis-associated infertility (4), especially for those who have experienced surgical treatment but are still infertile. Although the issue of whether the presence of endometriosis has a negative impact on the outcome of IVF has not been resolved (5), previous studies have shown that the pregnancy rate is reduced in infertile women with endometriosis undergoing IVF when compared with tubal factor infertility (6). The changed receptivity of the endometrium may account for this reduced performance.

Ideal intrauterine conditions that enable implantation include appropriate endometrial states, sufficient endometrial perfusion, and absence of excessive uterine contractions (7). A significantly higher uterine contraction

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frequency was found in women with endometriosis than in women without endometriosis (8), which may contribute to the development of endometriosis as well as to the reduced IVF success rate in women with endometriosis.

Oxytocin (OT), a nonapeptide synthesized by neurons of the supraoptic nucleus and released from the posterior pituitary gland, has diverse effects on the female reproductive system (9). It is known to be a factor causing uterine contractions. It has also been shown in animal models that endometrial cells contain oxytocin receptors (OTRs) and that OT has the capacity to trigger the production of prostaglandin (PG)$F_{2\alpha}$ from these cells (10, 11). Steinwall et al. (12) demonstrated that OT may be synthesized in the endometrium of nonpregnant women, particularly in the glandular epithelial cells. Hormone released from these sources may have a paracrine action on the uterus. Furthermore, Mechsner et al. (13) reported that OTRs are expressed in smooth muscle cells and in the epithelial cells of peritoneal endometriotic lesions and ovarian endometriotic cysts of premenopausal women, suggesting that OT might participate in the pathogenesis of endometriosis and contribute to infertility.

It is well known that an increase of plasma OT levels in pregnant women stimulates uterine contractions (14). Thus, we speculate that a hyperactivated autocrine/paracrine OT/OTR system in endometriosis may result in uterine hyperperistalsis and poor endometrial receptivity.

The therapeutic efficiency of atosiban, an OTR antagonist, was confirmed in a report using endometriotic rat models in which the volumes of endometriotic implants and proliferating cell nuclear antigen expression levels were significantly reduced in the atosiban treatment group (15).

On the basis of this background, we designed the present study to investigate the effect of atosiban used before ET in patients with endometriosis and analyze serum OT and $PGF_{2\alpha}$ levels and uterine contractions in patients with endometriosis.

## MATERIALS AND METHODS

This was a randomized clinical trial for the first part described. The part comparing endometriosis patients with tubal factor patients was a prospective cohort study. The study was performed from December 2014 to July 2015. A total of 120 patients with endometriosis undergoing IVF/ET using cryopreserved embryos in the reproductive center of the First Affiliated Hospital of Anhui Medical University were randomized into treatment (n = 60) and control (n = 60) groups. Clinical pregnancy rate (PR) and implantation rate (IR) were compared between the treatment and control groups.

Uterine peristalsis frequency and serum OT and $PGF_{2\alpha}$ levels of another group of 120 patients without endometriosis but with tubal factor infertility were compared with those of the endometriosis group.

Written informed consent was obtained from each patient before inclusion. The study was approved by the institutional review board (Clinical Trial Registration Number: ChiCTR-IOQ-14005715). There is no conflict of interest with any product used in this study.

### Study Population

Patients meeting the following inclusion criteria were prospectively recruited into the endometriosis group: [1] aged 20–45 years; [2] with baseline FSH <10 IU/L; [3] having endometriosis, as demonstrated by laparoscopy; [4] normal serum CA-125 level (<35 IU/L); [5] one or more day-5 good-quality embryo(s) available for transfer; and [6] fewer than three previous ET cycle failures.

Most of these patients had minimal or mild endometriosis (n = 82), and the rest had moderate or severe endometriosis (n = 28), according to the revised classification of the American Society of Reproductive Medicine (formerly the American Fertility Society) (16). A total of 120 matched women without endometriosis but with tubal factor infertility were assigned to the tubal factor group. They were matched as follows: [1] women aged 20–45 years, with regular cycles (25–35 days); [2] to enter IVF/intracytoplasmic sperm injection cycles of down-regulation with the long GnRH agonist protocol; [3] basic FSH level <10 IU/L; [4] basic antral follicle count level >5; [5] body mass index (BMI) ≤28 kg/$m^2$; and [6] normal features of uterus and bilateral ovaries.

The exclusion criteria for the endometriosis and tubal factor groups were as follows: [1] uterine anomaly; [2] uterine fibroids; [3] presence of hydrosalpinges; [4] fresh embryo transfer cycle; [5] patients received GnRH agonists or antagonists (GnRH analogous) treatment before frozen–thawed embryo transfer (FET) (if they received GnRH agonists or antagonists within 3 months or their ovaries were still suppressed with no regular menstruation); [6] endometrial thickness <8 mm; [7] day-3 ET; and [8] endocrine disorders (hyperthyroidism or hypothyroidism, hyperprolactinemia, premature ovarian failure, and polycystic ovary syndrome).

### Cryopreservation Cycles

The entire cohort of good-quality embryos was cryopreserved on day 5 and vitrified using an open system.

In our center we use the Gardner blastocysts score. Blastocysts were given a numerical score from 1 to 6 on the basis of their degree of expansion and hatching status, as follows: 1, an early blastocyst with a blastocoel that is less than half of the volume of the embryo; 2, a blastocyst with a blastocoel that is half of or greater than half of the volume of the embryo; 3, a full blastocyst with a blastocoel completely filling the embryo; 4, an expanded blastocyst with a blastocoel volume larger than that of the early embryo, with a thinning zona; 5, a hatching blastocyst with the trophectoderm starting to herniate though the zona; and 6, a hatched blastocyst, in which the blastocyst has completely escaped from the zona.

For blastocysts graded as 3–6 (i.e., full blastocysts onward), the development of the inner cell mass was assessed as follows: A, tightly packed, many cells; B, loosely grouped, several cells; or C, very few cells. The trophectoderm was assessed as follows: A, many cells forming a cohesive epithelium; B, few cells forming a loose epithelium; or C, very few large cells.

By using this scoring system, good-quality embryo (≥3BB) was selected for transfer.