Background: Recent developments in assisted reproductive technology focus on potential advances to improve its success rate. Atosiban, a combined oxytocin/vasopressin V1a receptor antagonist, is a novel class of drug involved in basic priming of the uterus for successful implantation during embryo transfer (ET).

Objectives: The objective of this study is to evaluate the efficacy of atosiban (study group) in ET patients in comparison to placebo (control group) regarding implantation rate (IR), clinical pregnancy rate (CPR), and ongoing pregnancy rate and to assess the safety profile of atosiban.

Materials and Methods: A total of 320 women undergoing in vitro fertilization-ET at a tertiary care hospital were enrolled in the study. In the study group, atosiban was given as initial intravenous (IV) bolus injection 0.9 ml (6.75 mg), 30 min before ET followed by continuous IV infusion of atosiban. In the control group, placebo (normal saline) was infused at the same rate and dose. Pregnancy was confirmed 14 days after ET by β-human chronic gonadotropin level. IR and CPR were determined by doing transvaginal sonography 3 weeks and 6 weeks postET, respectively.

Results: In women with atosiban treatment, the positive pregnancy rate and CPRs were 41.25% and 36.25%, respectively. The IR per embryo transferred was 17.5%. No major side effects of atosiban were noted among enlisted patients. The miscarriage rate and ectopic pregnancy rate were low (12.12% and 4.54%, respectively). Forty-two women had singleton gestation, while twin and triplet pregnancies were encountered in 13 and 3 women, respectively. No congenital anomalies were observed during an antenatal scan at 18–20 weeks in ongoing pregnancies. The positive pregnancy rate, the CPR, and the IR in the control group was 35%, 30%, and 16.5%, respectively, which was significantly lower than the atosiban group.

Conclusion: Atosiban reduces uterine contractions and increases endomyometrial perfusion, both of which have potential benefits regarding improved IRs, CPR, and ongoing pregnancy rates. Atosiban has a good embryonic safety profile.

Keywords: Atosiban, clinical pregnancy rate, embryo transfer, implantation rate, placebo, positive pregnancy rate

INTRODUCTION

Assisted reproductive technology (ART) is advancement in the field of infertility, which helps to achieve the live birth of a healthy child to an infertile couple. In vitro fertilization (IVF) has now replaced the term ART which includes a spectrum of techniques of assisted conception. The effectiveness of ART is...
commonly reported regarding implantation rate (IR), clinical pregnancy rate (CPR), and live birth rate. Successful embryo implantation during IVF-embryo transfer (IVF-ET) depends on embryonic and uterine factors. Repeated implantation failure (RIF), in spite of good-quality embryo transferred, is frustrating for the clinician, distressing for the couple and also increases the financial burden on the society.[1] The various causes attributing to RIF are embryonic and uterine causes, hematological, immunological, and genetic causes.[2]

Over many decades, various advances have been made in the field of assisted conception; however, the overall effectiveness of IVF remains limited. Recent studies have shown a beneficiary role of atosiban in basic priming of the uterus for successful implantation during ET. Atosiban is a mixed oxytocin/vasopressin V1a receptor antagonist. Its combined oxytocin vasopressor antagonism function reduces uterine contractility with simultaneous reduction in prostaglandin F2 alpha (PGF2α) production and improved endo-myometrial perfusion, both of which are beneficial in preterm labor as well as in increased IRs after IVF-ET cycles.[3] Its mechanism of action during ET is based on the inverse correlation between the IR and the rate of uterine contractions. Steinwall et al. showed that oxytocin is synthesized in glandular epithelial cells of the endometrium of nonpregnant women.[4] This oxytocin triggers the production of PGF2α which, in turn, has a paracrine action on the uterus, leading to contractions.

Atosiban competes with oxytocin at oxytocin receptors in endometrial cells and inhibits oxytocin-induced PGF2α release, thus inhibiting uterine contractions and increasing chances of embryo implantation.[4] Through vasopressin V1a antagonism, atosiban causes relaxation of uterine arteries and thus improves perfusion of endometrium and myometrium leading to improved pregnancy rate and decreased miscarriage rate.[5] Atosiban also has a good embryonic safety profile.

Recent developments in ART focus on potential advances to improve its success rate. Reducing uterine contractions and better myometrial perfusion during IVF-ET have been promising regarding increased IVF success rates. The study is conducted to evaluate the efficacy and safety of atosiban in IVF-ET program.

**Materials And Methods**

**Study objectives**

- **Primary objective** – To evaluate the efficacy of atosiban (study group) and placebo– Normal saline (control group) in increasing the IR, CPR and ongoing pregnancy rate after ET in IVF cycles
- **Secondary objective** – To evaluate the safety profile of atosiban in the enlisted patients

- **Study design** – Prospective case–control study
- **Study period** – June 2016 to November 2016
- **Sample size** – The study was conducted on 320 women undergoing IVF-ET in our department. After fulfilling eligibility criteria and obtaining written informed consent, 160 enrolled women received atosiban (study group) and another 160 women received placebo (control group). Thereafter, observations were made at specified time intervals. The study was carried out on a patient undergoing IVF for the first time as well as repeated embryo transferred in both groups. Considering the current success rate of IVF treatments and the mean number of embryos transferred in each cycle, we recommend defining RIF as a failure of implantation in at least three consecutive IVF attempts, in which 1–2 embryos of high-grade quality are transferred in each cycle.

**Inclusion criteria**

1. Women ≥20 years age
2. Body mass index– 18.5–30 kg/m²
3. The normal uterine cavity on ultrasound scan
4. At least one good quality embryo present for transfer
5. Basal FSH hormone level <10 IU/l
6. Women willing to comply with the clinical study protocol
7. Endometrium thickness ≥7 mm with endometrial volume 2–2.5 ml and good endometrial and subendometrial vascularity.

**Exclusion criteria**

1. Women ≥ 45 years age
2. Uterine abnormalities that can compromise the IRs (e.g., endometrial polyp, fibroids, hydrosalpinx, and adenomyosis)
3. Patients at risk of ovarian hyperstimulation syndrome
4. Patients with a history of hypersensitivity to atosiban
5. Endocrine dysfunction
6. Major organ dysfunction such as liver or kidney failure.

**Study medication**

- **Strength** – Atosiban is available in injection form, in the strength of 7.5 mg/mL
- **Dosage and administration regimen** – Before drug administration, the vials were checked visually for any particulate matter or any discoloration. Then, atosiban was administered in three stages as follows:
  - **Step 1:** Initial intravenous injection (bolus) 0.9 ml of atosiban (6.75 mg) intravenous (IV) bolus dose was given using 1 ml syringe, 30 min before ET under adequate medical supervision
  - **Steps 2 and 3:** Followed by intravenous infusion
Immediately followed by continuous intravenous infusion of atosiban 5 ml (37.5 mg) in 100 ml normal saline as shown in Table 1.

**Placebo (normal saline)**
In the other 160 women, placebo, i.e., 0.9 ml of normal saline was given 30 min before ET immediately followed by 100 ml infusion at the rate of 18 mg/h and 6 mg/h for 1 h after ET and for remaining time until infusion bag was empty, respectively.

**Study assessments**

**Positive pregnancy rate**
Pregnancy was confirmed 14 days after embryo transfer (ET) by serum $\beta$-hCG level.

**Implantation rate**
Implantation is defined as a number of gestational sacs per number of embryos transferred.[6] It was determined by doing transvaginal sonography 3 weeks after ET.

**Clinical pregnancy rate**
Clinical pregnancy is defined as observation of intrauterine gestational sac, fetal pole, and cardiac activity on transvaginal sonography, 6 weeks after ET.[3]

**Ongoing pregnancy rate**
Ongoing pregnancy was defined as the presence of at least one fetus with heart pulsation on ultrasound beyond 8 weeks.[6]

**Safety assessments**
- Vital signs (temperature, pulse, blood pressure, and respiratory rate) were measured at baseline and at specific time intervals
- Adverse events – The type of adverse event and its severity was assessed during the study period. The events were enlisted in case report form and graded as mild, moderate, or severe.

**RESULTS**
The study was conducted on 320 women who underwent IVF-ET in our department. Among them, 160 enrolled women received atosiban and placebo (normal saline) was administered to the other 160 women. Data of all the women were collected and formulated in the data entry sheet. There were no women, who were enrolled in the study and were lost to follow-up.

The mean age of women in the study group and in the control group, it was 31 years and 33 years, respectively. The most common cause of infertility in both the groups was unexplained factor followed successively by an ovarian factor, male factor, tubal factor, and mixed causes [Table 2]. Since, our institute is a referral center, patients diagnosed with infertility in the vicinity and other surrounding states are sent to our hospital for advanced IVF care. Hence, the number of patients with unexplained infertility is quite high in our center.

In women who underwent treatment with atosiban before and during ET, the positive pregnancy rate and CPR were 41.25% and 36.25%, respectively. The IR per embryo transferred was 17.5%. The miscarriage
rate and ectopic pregnancy rate were low (12.12% and 4.54%, respectively) in these enrolled women. The positive pregnancy rate, the CPR, and the IR in the control group was 35%, 30%, and 16.5%, respectively, which was significantly lower than the atosiban group [Table 3 and Graph 1].

A total of 42 women had singleton gestation while 13 had twin conception and only 3 women had triplet pregnancy [Graph 2]. No congenital anomalies were encountered during antenatal scan at 18–20 weeks in ongoing pregnancies. No major side effects of atosiban were observed in patients except for mild nausea and itching at injection site in one patient each which were self limiting.

In the study group, i.e., in women receiving atosiban before and during ET, the positive pregnancy rate in women undergoing IVF for the first time and in women undergoing IVF after recurrent implantation failure was 38.88% and 44.28%, respectively. The positive pregnancy rate of our center in patients undergoing IVF for the first time and in patients with repeated IVF failure without atosiban is 33.34% and 35.54%, respectively. However, the CPR of our center in patients undergoing IVF for the first time and in patient with repeated IVF failure without atosiban is 29.34% and 33.89%, respectively. The CPR for the above two groups was 33.33% and 40%, respectively. Similarly, the ongoing pregnancy rate in the aforementioned groups was 27.77% and 35.71%, respectively [Table 4]. As per the statistical analysis, the $P$ value is not significant in all the groups.

### Table 2: Demographic variables, causes of infertility, stimulation protocol and ovarian response and embryos transferred in the study and control population ($n=320$)

| Parameters                                      | Study group ($n=160$) | Control group ($n=160$) |
|-------------------------------------------------|-----------------------|-------------------------|
| Age of women (years)                            | 31 (29-35)            | 33 (29-42)              |
| BMI (kg/m²)                                     | 21.8 (20.1-23.8)      | 20.9 (18.4-23.2)        |
| Type of infertility, n (%)                      |                       |                         |
| Primary infertility                              | 118 (73.8)            | 132 (82.5)              |
| Secondary infertility                            | 42 (26.3)             | 28 (17.5)               |
| Duration of infertility, a                       | 7 (5-10)              | 4 (2-7)                 |
| Cause of infertility, b, n (%)                  |                       |                         |
| Unexplained                                      | 61 (38.1)             | 58 (36.2)               |
| Ovarian                                          | 41 (25.6)             | 37 (23.1)               |
| Male                                             | 27 (16.9)             | 36 (22.5)               |
| Tubal                                            | 26 (16.3)             | 25 (15.6)               |
| Mixed                                            | 5 (3.1)               | 4 (2.5)                 |
| Cycle number, n (%)                             |                       |                         |
| First cycle                                      | 90 (56.3)             | 133 (83.1)              |
| Repeat cycle                                     | 70 (43.8)             | 27 (16.8)               |
| Stimulation protocol and ovarian response        |                       |                         |
| Antral follicle count                            | 14.5 (10-23.5)        | 14.8 (10-26.4)          |
| FSH/HMG dosage (IU)                             | 2150 (1575-2775)      | 2250 (1650-2900)        |
| FSH/HMG duration (days)                         | 9 (8-10)              | 9 (8-10)                |
| Endometrial thickness (mm)                      | 7.5 (7.1-8.2)         | 7.0 (6.8-7.8)           |
| Number of oocytes obtained                      | 9 (6-14)              | 10 (7-15)               |
| Number of oocytes fertilized                    | 5 (3-7)               | 6 (4-8)                 |
| Number of embryos transferred, a, n (%)          | 457                   | 489                     |
| One                                             | 12 (7.5)              | 14 (8.7)                |
| Two                                             | 35 (21.9)             | 42 (26.2)               |
| Three                                            | 77 (48.1)             | 85 (53.1)               |
| Four                                            | 36 (22.5)             | 34 (21.2)               |

Data are median (25th and 75th percentile), a Data are n (%).

BMI=Body mass index, FSH: Follicle stimulating hormone, HMG=Human menopausal gonadotropin

### Table 3: Pregnancy outcomes ($n=320$)

| Parameters                              | Study group ($n=160$) | Control group ($n=160$) | $P$ |
|-----------------------------------------|-----------------------|-------------------------|-----|
| Mean embryos transferred                | 2.86±0.85             | 2.94±0.76               |     |
| Positive pregnancy rate, a              | 41.25 (66.160)        | 35.00 (56.160)          | <0.001 |
| Clinical pregnancy rate, a              | 36.25 (58.160)        | 30.00 (48.160)          | <0.001 |
| Ongoing pregnancy rate, a              | 31.25 (50.160)        | 26.25 (42.160)          | <0.01 |
| Miscarriage rate, a                     | 12.12 (8.66)          | 10.71 (6.56)            | NS  |
| Ectopic pregnancy rate, a              | 4.54 (3.66)           | 5.35 (3.56)             | NS  |
| Implantation rate per embryo transferred| 17.50 (80.457)        | 16.56 (81.489)          | NS  |

Data are (%). NS=Not significant

Graph 2: Types of pregnancy (n = 58)
Thus indicating the efficacy of atosiban in improving early pregnancy outcomes in both the groups, i.e., in women with first time IVF and in women with IVF after recurrent implantation failure.

As our study is a pioneer study and also atosiban is known to improve IR and CPR in IVF patients, hence, we gave atosiban to all enrolled women undergoing IVF-ET including women who had first time IVF as well as those who had IVF after recurrent implantation failure. Considering the current success rate of IVF treatments and the mean number of embryos transferred in each cycle, we recommend defining RIF as a failure of implantation in at least three consecutive IVF attempts, in which 1–2 embryos of high-grade quality are transferred in each cycle.

**DISCUSSION**

ET is a critical step of an IVF cycle which merits utmost attention. Its success depends on the frequency of uterine contractions, the endometrial receptivity and the quality of embryos transferred.

Uterine contractions are the most fundamental constituents of the uterine receptivity. Excessive contractions may decrease the implantation potential of embryos by expelling the embryos from the uterus.\(^7\) Studies have revealed a six-fold increase in uterine contractility in IVF cycles when measured before ET as compared to the condition before ovulation in natural cycles.\(^8\) Fanchin *et al.* revealed increased uterine contractility in about 30% of women who underwent ET. Excessive manipulation of cervix such as the use of tenaculum during difficult ET can also trigger uterine contractions, consequently leading to failure of embryo implantation.\(^7\)

IVF success rates have been potentially improved by the use of drugs which inhibit pronounced uterine contractions at the time of ET. Treatment strategies such as the use of beta-agonists or nonsteroidal anti-inflammatory agents for tocolysis have not been beneficial in IVF-ET procedures.\(^9\)

Recently published studies showed that atosiban inhibits oxytocin-induced PGF2α and uterine contractility, consequently leading to improved IRs. Studies have shown a considerable reduction in the frequency of uterine contractions from 16/4 min to 6–2.6/4 min before and after administration of atosiban in women undergoing ET. Study on pregnant baboons demonstrated the role of atosiban regarding significant inhibition of myometrial contractility and simultaneously minimizing the maternal cardiovascular system changes.\(^10\)

In a randomized control trial, atosiban has been proved to reduce the amplitude and frequency of uterine contractions in oocyte donors as compared to placebo.\(^11\) In our study, among 160 enrolled women, the rate of implantation per embryo transferred was 17.5% and the CPR was 36.25%. These results are comparable to the study done by Moraloglu *et al.*, in 2010. Moraloglu *et al.* performed a randomized controlled trial with placebo versus atosiban in about 160 women undergoing ET (37.5 mg total dose of atosiban infused IV before and until 2 h after the ET). A significant increase in rates of both implantation as well as clinical pregnancy was noted. The rate of implantation per embryo transferred was 20.4% versus 12.6% while the CPR per cycle was 46.7% versus 28.9% (atosiban versus placebo).\(^12\) The ongoing pregnancy rate in our study was 31.25%. In a randomized double-blind study, documented ongoing pregnancy rate was 42.8%.\(^6\) Lower rates in our study may be attributed to significantly increased number of women with longer duration of infertility and with RIF at various centers previously. Through vasopressor antagonism, atosiban causes relaxation of uterine arteries, thus leading to improved endometrial and myometrial perfusion.

Studies showed that <50% of embryos transferred remained *in utero* 1 h after transfer and about
15% were found in the vagina after ET. Three-D power Doppler studies during IVF program have revealed an endometrium with better receptivity and characteristics more predictive of implantation in women who received atosiban before and during ET.

In a preclinical study, atosiban had a good embryonic safety profile and has no effect on endocrine profile up to 50 fold therapeutic blood concentrations. It neither affected the survival of 1-cell rabbit embryo nor affected the hatched rabbit blastocysts percentage. It had no adverse influence on human spermatozoa during sperm motility bioassays.

The most common side effect of atosiban reported is nausea and the most common reason for stopping the treatment is injection site reaction. Other adverse events include tachycardia, hypotension, dizziness, headache, vomiting, hot flushes, and hyperglycemia. In a retrospective study involving 75 women, the efficacy and safety of nifedipine versus atosiban was compared. Both the drugs were devoid of any major adverse effects. A statistically significant difference was seen in the occurrence of palpitation, hypotension, and flushing in nifedipine group. In our study, atosiban proved to have a good safety profile. One patient had nausea, whereas the other patient had itching at injection site localized to arms which was self limiting and resolved in few minutes. A few studies have reported cases of atosiban overdosing without any specific signs and symptoms and for which no specific treatment was needed.

**Conclusion**

ET is the final stage of IVF which independently influences the treatment outcome. Successful embryo implantation is dependent on uterine receptivity. Atosiban is a novel class of drug which is effective in priming the uterus for implantation. It reduces uterine contractions and increases endomyometrial perfusion, both of which have potential benefits regarding improved IRs, CPR, and ongoing pregnancy rates. Atosiban has a good embryonic safety profile. It has no systemic toxicity, no mutagenic effects, and no carcinogenic effects.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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