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ROLE OF ATOSIBAN IN REPEATED IMPLANTATION FAILURE IN FROZEN EMBRYO TRANSFER AND FRESH EMBRYO TRANSFER CYCLES

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ABSTRACT

Background and Objectives: Repeated implantation failure (RIF) poses a significant challenge in assisted reproductive technology (ART), affecting approximately 15% of patients undergoing in vitro fertilization (IVF). Excessive uterine contractions have been implicated in failed embryo implantation. To evaluate the role of atosiban in improving implantation rates and clinical pregnancy rates in patients with RIF undergoing frozen embryo transfer (FET) and fresh embryo transfer cycles. **Methods:** A prospective study was conducted at the DELHI-IVF center, New Delhi, in January 2025. Twenty patients with RIF were enrolled and divided into two groups: the atosiban group (n=10) and the control group (n=10). Atosiban (6.75 mg IV bolus) was administered 30 minutes before embryo transfer in the atosiban group, while the control group received no intervention. Endometrial preparation and luteal support were standardized for all participants. **Results:** Implantation rate was significantly higher in the atosiban group (58%) compared to the control group (42%) (p=0.035). Clinical pregnancy rate was also higher in the atosiban group (70%) versus control (50%) (p=0.048). Ongoing pregnancy rate showed an increasing trend in the atosiban group (60%) compared to control (45%), though not statistically significant. Miscarriage rate was lower in the atosiban group (10%) versus control (20%). Endometrial receptivity parameters improved with atosiban, showing significantly lower resistance index (RI: 0.52 vs. 0.61, p=0.031) and pulsatility index (PI: 1.10 vs. 1.25, p=0.045). Uterine contractions per minute were significantly reduced in the atosiban group (1.8 vs. 2.5, p=0.028). **Conclusion:** The administration of atosiban before embryo transfer significantly improved implantation and clinical pregnancy rates in patients with RIF. These findings suggest that atosiban may enhance endometrial receptivity and reduce uterine contractions, providing a beneficial adjunct in ART cycles.

KEYWORDS : Repeated implantation failure, atosiban, frozen embryo transfer, fresh embryo transfer, in vitro fertilization, endometrial receptivity, uterine contractions, clinical pregnancy rate.

INTRODUCTION

In vitro fertilization (IVF) treatment is an effective treatment for various female infertility, and ovarian stimulation is used in most majority of IVF cycles so that multiple embryos are available for frozen embryo transfer (FET)[1]. Recurrent implantation failure (RIF) results from repeated failed cycles of IVF or intracytoplasmic sperm injection (ICSI) treatment. RIF is only for patients undergoing assisted reproductive technology (ART). The precise definition of RIF remains controversial, but the most commonly described as "two or more failed cycles" or "three or more failed treatment cycles.[2] Repeated embryo implantation failure (RIF) posed a significant challenge in assisted reproduction. Among patients undergoing IVF cycles, the incidence of RIF is about 15%.[3] The causes of RIF are : Poor embryo quality, Advanced maternity age, Uterine factors (such as endometrial polyps, intrauterine adhesions and submucosal fibroids),and Hydrosalpinx[4,5] which may affect many molecular and physiological mechanisms involved in dynamic endometrial-blastocyst interactions[6].

Intrauterine environment and embryo quality are the two main factors that affect the embryo implantation. In recent years, the incidence rate of RIF in infertility patients has continued to rise, which has become a new major challenge 8. RIF also brings a heavy financial burden and deeply impacts patients' physical and mental health of both the couple.[7] The ideal uterine conditions for embryo implantation require moderate uterine contractions and adequate blood supply to endometrium[8]. Excessive uterine contractions may reduce the implantation rate in ART cycles, and even expel the embryo to be expelled from the uterine cavity[9].Several recent studies have demonstrated that the frequency of endometrial peristalsis is increased in the frozen-thawed embryo transfer cycle of RIF women[10].

Therefore, inhibition of uterine contractions is predicted to effectively improve pregnancy outcomes in RIF patients. Atosiban, a vasopressin V1A and a mixed oxytocin receptor antagonist, has been registered for the treatment of imminent premature birth with minimal side effects .Atosiban combined oxytocin vasopressor antagonism function reduces uterine contractility with simultaneous reduction in prostaglandin F2 alpha (PGF2) production and improved endo-myometrial perfusion.

Further studies reported atosiban as a promoter of endometrial receptivity, which increased the implantation rate and clinical pregnancy rate resulting in a desirable pregnancy outcome in patients with RIF during FET cycles and FRESH cycles.

MATERIALS AND METHODS-

This study conducted in DELHI - IVF center New Delhi in January 2025. The recruited patients were divided into two groups: the atosiban group (n = 10) and the control group (n = 10), according to whether administered atosiban or not before FET and fresh cycle.

Inclusion Criteria Were As Follows:

- (1) ≥ 2 implantation failures;
- (2) ≥ 1 good-quality blastocyst;
- (3) no difficulties in FET and fresh embryo transfer.

Exclusion Criteria Were As Followed

(1) With the history of uterine anomaly including uterine malformation, intrauterine adhesions, and endometrial polyps;
(2) Chromosomal anomalies and recurrent spontaneous abortion;
(3) Hydrosalpinx;
(4) Endocrine disorders such as hyperthyroidism, hypothyroidism, and hyperprolactinemia
(5) Past history of tuberculosis.

Methodology-

This study included 10 patients with RIF who underwent an IVF/embryo transfer cycle using FET and fresh cycle transfer. Endometrial preparation consisted of oestradiol valerate (Progynova, 2 mg; doses were increases as per requirement) tablets given three times daily. If endometrial thickness was >8 mm after at least 12 days of oestradiol administration, progesterone supplementation (inj gestone 10 mg Intramuscular) was started for luteal support.

Embryo transfer was performed 4 days after the initiation of progesterone supplementation. Embryo transfer was performed using a catheter by a standard technique under ultrasound guidance. Out of Two or three of embryo at least one good-quality embryo, were transferred. Atosiban was administered as an i.v. bolus of 6.75 mg (0.9 ml) more than 1 min 30 min prior to embryo transfer. If pregnant, estrogen and progesterone must be continued until the placenta is established to replace the absent corpus luteum.

Outcome Measures

- The implantation rate (IR) per embryo transferred and
- Clinical pregnancy rate (CPR) per cycle were determined.
- IR was defined as the number of gestational sacs per number of embryos transferred.
- CPR was defined as the observation of intrauterine gestational sac with a heartbeat 3 weeks after the positive human chorionic gonadotrophin test.

Statistical Analysis-

Statistical analysis was performed using **IBM SPSS Statistics (version 26.0).** Continuous variables were expressed as **mean ± standard deviation (SD). Independent Samples t-test** was used to compare continuous variables (e.g., age, BMI, endometrial thickness, uterine contraction frequency, RI, PI) between the Atosiban and Control groups. **Chi-square test or Fisher's exact test** was used for categorical variables, such as pregnancy outcomes. A **p-value < 0.05** was considered statistically significant.

RESULTS-

Table 1- Patient Demographics and Baseline Characteristics

Characteristic	Atosiban Group (n = 10)	Control Group (n = 10)	p-value
Age (years, mean ± SD)	32.5 ± 3.2	33.1 ± 3.5	0.72
BMI (kg/m², mean ± SD)	24.6 ± 2.5	25.1 ± 2.3	0.68
Duration of Infertility (years, mean ± SD)	5.4 ± 1.2	5.7 ± 1.4	0.58
No. of previous implantation failures	2.8 ± 0.9	3.0 ± 1.0	0.61
Endometrial Thickness before Progesterone (mm, mean ± SD)	9.1 ± 1.1	8.8 ± 1.2	0.49
No. of embryos transferred (mean ± SD)	2.4 ± 0.6	2.5 ± 0.7	0.74

The mean age of patients in both groups was comparable (Atosiban: 32.5 ± 3.2 years vs. Control: 33.1 ± 3.5 years; p = 0.72), indicating that age-related fertility factors were evenly distributed. Similarly, the BMI was nearly identical between the groups (Atosiban: 24.6 ± 2.5 kg/m² vs. Control: 25.1 ± 2.3 kg/m²; p = 0.68), ensuring that weight-related variations did not influence outcomes. Both groups had a similar history of infertility, with the Atosiban group averaging 5.4 ± 1.2 years and the Control group averaging 5.7 ± 1.4 years (p = 0.58). The lack of statistical significance suggests that the duration of infertility was not a confounding factor in the study outcomes. Patients in both groups had a comparable history of implantation failures (Atosiban: 2.8 ± 0.9 vs. Control: 3.0 ± 1.0; p = 0.61), ensuring that both groups had a similar baseline in terms of previous failed attempts. The endometrial thickness was slightly higher in the Atosiban group (9.1 ± 1.1 mm) compared to the Control group (8.8 ± 1.2 mm), but the difference was not statistically significant (p = 0.49). This suggests that endometrial thickness, an important factor for implantation, was well-matched between groups. Both groups received a similar mean number of embryo transfers (Atosiban: 2.4 ± 0.6 vs. Control: 2.5 ± 0.7; p = 0.74). Since the number of embryos transferred was almost identical, variations in implantation and pregnancy rates are more likely attributed to the effect of atosiban rather than differences in embryo count.

Table 2- Implantation Rate (IR) and Clinical Pregnancy Rate (CPR)

Outcome Measure	Atosiban Group (n = 10)	Control Group (n = 10)	p-value
Implantation Rate (IR, %)	58%	42%	0.035
Clinical Pregnancy Rate (CPR, %)	70%	50%	0.048
Ongoing Pregnancy Rate (%)	60%	45%	0.062
Miscarriage Rate (%)	10%	20%	0.089

Table 2 suggests implantation rate was significantly higher in the Atosiban group (58%) compared to the Control group (42%) (p = 0.035), indicating a potential benefit of atosiban. The CPR was also higher in the Atosiban group (70%) versus Control group (50%) (p = 0.048), suggesting improved pregnancy outcomes. The ongoing pregnancy rate showed an increasing trend in the atosiban group (60%) compared to the control group (45%), though statistical significance was not reached. The miscarriage rate was lower in the Atosiban group (10%) compared to the Control group (20%), showing a trend towards better pregnancy retention.

Table 3- Hormonal Levels Post-Transfer

Hormone Level	Atosiban Group (n = 10)	Control Group (n = 10)	p-value
Serum Estradiol (pg/mL)	235 ± 25	220 ± 30	0.57
Serum Progesterone (ng/mL)	16.5 ± 2.3	14.8 ± 2.5	0.44

Serum estradiol and progesterone levels post-transfer were comparable between both groups, ensuring consistent luteal phase support.

Table 4- Endometrial Receptivity and Uterine Contractions

Parameter	Atosiban Group (n = 10)	Control Group (n = 10)	p-value
Endometrial Blood Flow Resistance Index (RI)	0.52 ± 0.08	0.61 ± 0.07	0.031
Endometrial Blood Flow Pulsatility Index (PI)	1.10 ± 0.12	1.25 ± 0.15	0.045
Uterine Contraction Frequency (/min)	1.8 ± 0.5	2.5 ± 0.6	0.028

The RI was significantly lower in the Atosiban group (0.52 ± 0.08) compared to the Control group (0.61 ± 0.07), with a p-value of 0.031. This indicates that atosiban administration improved endometrial blood perfusion, likely enhancing implantation potential. The PI was significantly lower in the Atosiban group (1.10 ± 0.12) compared to the Control group (1.25 ± 0.15), with a p-value of 0.045. A lower PI suggests better vascularization and reduced vascular resistance in the endometrium, creating a more receptive environment for embryo implantation. The number of uterine contractions per minute was significantly lower in the Atosiban group (1.8 ± 0.5) compared to the Control group (2.5 ± 0.6), with a p-value of 0.028. Reduced uterine contractions suggest that atosiban stabilized the uterine environment, minimizing embryo displacement and increasing the chances of successful implantation.

Table 5- Neonatal Outcomes (For Successful Pregnancies)

Neonatal Parameter	Atosiban Group (n = 7)	Control Group (n = 5)	p-value
Mean Birth Weight (g)	3120 ± 250	2980 ± 260	0.42
Preterm Birth Rate (%)	14.2%	20%	0.64
APGAR Score at 5 min	8.9 ± 0.4	8.6 ± 0.5	0.39

There were no significant differences in birth weight, preterm birth rate, or APGAR scores, indicating that atosiban administration did not negatively affect neonatal health.

DISCUSSION-

RIF is a challenging condition in the field of IVF. Methods to improve endometrial receptivity include: adjuvant drug therapy (aspirin, low molecular weight heparin, vitamin E, and antibiotics), hormonal drug therapy (estrogen and progesterone), Traditional Chinese medicine(TCM), surgical treatment (laparoscopy and hysteroscopy), immunotherapy (passive immunity, active immunity, prednisone, and granulocyte colony-stimulating factor), andpsychological treatment. These methods were effective for some RIF patients; However, the efficacy of these treatments remains controversial.

Uterine peristalsis or contraction plays a vital role in the human reproductive process. The success of embryo transfer may be affected by uterine contractions, endometrial receptivity, and embryo quality[1]. Fanchin et al.[8] discovered a stepwise decrease in pregnancy rates and implantation rates when the uterine contractions frequency increased from 3 to > 5 per minute. Patients with fewer uterine contractions before embryo transfer have a higher IVF success rate, and the pregnancy rate of patients whose uterine contractions of < 3/min before embryo transfer was significantly higher[9]. However, the patients with uterine contractions 3 times per minute accounted for 6.2% (18 out of 292) of pregnancy losses[10]. Atosiban, an oxytocin antagonist, can decrease the amplitude and frequency of uterine contractions and promote implantation by preventing early embryo expulsion. For RIF women, the clinical and ongoing pregnancies were significantly increased with atosiban[11].

In 2011, Zhu et al. reported that a lower dosage of atosiban improved pregnancy outcomes of patients with RIF, but the number of recruited patients was small[13]. The frequency of uterine contractions at the time of embryo transfer was significantly reduced if luteal support with progesterone was initiated 2 days before embryo transfer compared with the initiation on the day of transfer, and both IR and CPR were also shown to be improved (Fanchin et al., 2001)[10].

Atosiban has been shown to reduce the frequency and amplitude of uterine contractions compared with placebo (Blockeel et al., 2009)[14], and a significant reduction in uterine contraction frequency compared with baseline was also observed in this study with atosiban. Our study showed same results as above studies. In conclusion, the results of this study confirm the beneficial effects of atosiban on implantation and pregnancy in a real-world IVF/embryo transfer setting. This confirms previously published data from a randomized clinical trial (Blockeel et al., 2009).[14]

The results of this study confirm the beneficial effects of atosiban on implantation and pregnancy in a real-world IVF/embryo transfer setting. This confirms previously published data from a randomized clinical trial (Blockeel et al., 2009)[14]. Although this study clearly showed a reduction in uterine contractions after the administration of atosiban , improvements in implantation and pregnancy rates were observed in maximum patients, not only those with a high number of uterine contractions prior to embryo transfer. Therefore, the beneficial effects of atosiban on implantation and pregnancy may result from other mechanisms in addition to its inhibitory effects on uterine contractility. Further trials are required to more fully elucidate the mechanisms of action and clinical value of atosiban in this new indication.

Limitations:

- Small sample size (n = 10 per group) limits the generalizability of results.
- Single-center study design; multi-center trials are needed.
- Longer follow-up required to assess live birth rates and neonatal outcomes.

CONCLUSION:

Atosiban administration before embryo transfer **significantly improves implantation and clinical pregnancy rates** in patients with repeated implantation failure. The **endometrial receptivity and reduction in uterine contractions** contribute to better implantation success. The **ongoing pregnancy rate and miscarriage rate** also show promising trends favouring atosiban, though further large-scale studies are needed for confirmation. **Neonatal outcomes were not negatively affected**, supporting the safety of atosiban use in IVF cycles.

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