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Impact of the oxytocin receptor antagonist atosiban administered shortly before embryo transfer on pregnancy rates after ICSI

S.A. Hebisha, Hisham M. Adel

Department of Gynecology, Faculty of Medicine Alexandria University, Alexandria (Egypt)

Summary

Objective: To evaluate the impact of the oxytocin receptor antagonist atosiban on implantation and pregnancy rates after first ICSI trial in good prognosis cases. *Design:* Randomised controlled trial. *Materials and Methods:* The study included 182 women, prepared for first trial of ICSI for male or tubal factor infertility, using long agonist protocol, were randomized to receive 7.5 mg atosiban or placebo IV 20 minutes before embryo transfer (ET). *Results:* Fifty-eight (63.7%) cases had ongoing pregnancy in the study group while 44 (48.4%) cases had ongoing pregnancy in control group and this was statistically significant ($p = 0.037$). Implantation rates were 45.20%, and 34.69%, respectively, which was also statistically significant ($p = 0.045$). All of the intermediate cycle parameters were also comparable. *Conclusion:* Atosiban in the given dose and regimen improved both implantation and on going pregnancy rates in good prognosis cases undergoing first ICSI trial and blastocyst stage embryo transfer.

Key words: Atosiban; Embryo transfer; ICSI; Clinical pregnancy rate.

Introduction

Embryo implantation remains the bottle neck of assisted reproduction with fewer improvements and little deeper understanding than the old days of IVF. Notwithstanding the vast number of trials including reasonable and non-reasonable interventions performed at time of embryo transfer (ET) to improve implantation rates, little if any progress is achieved. Uterine cavity perfusion with hCG, irrigation with embryo culture supernatant, or cultured cumulus cells, or administration of granulocyte colony stimulating factor were claimed at first to be of value, but did not withstand rigorous evaluation [1-6]. Other interventions like mechanical pressure to close the cervical canal following ET, the use of fibrin sealants added to the ET fluid, and longer recumbence following ET were not any better [7, 8].

It has long been known that uterine quiescence is a prerequisite for implantation. Under physiological conditions, uterine quiescence is achieved in parallel with endometrial preparation in response to progesterone [9, 10]. In the earlier part of the cycle, estrogen stimulates uterine waves which are thought to be required for gamete and embryo transport. In stimulated IVF cycles, supraphysiological serum estradiol (E2) concentrations may induce endometrial production of oxytocin, formation of oxytocin receptors, and indirectly the synthesis/release of prostaglandin (PG F2a) [10,11]. and consequently inducing uterine contractions. It was found that around 30% of patients undergoing ET have frequent uterine contractions (> 5 per minute) which were associated with significantly lower pregnancy rates. Uterine contractions in stimulated IVF cycles measured by ultrasound scanning were increased by six-fold when compared with that in the natural cycle [12]. So far, administration of beta mimetics or non-steroid anti-inflammatory drugs has not been associated with any progress.

Oxytocin receptor system in the myometrium and the endometrium is a potential target for new class of medications aiming to improve implantation rates [10]. Few observational studies suggested that the use of the oxytocin receptor antagonist (OTRa), atosiban (tractocile) a mixed vasopressin V1a and oxytocin receptor antagonist, around ET resulted in higher pregnancy rates in IVF cycles [13]. Furthermore, other studies reported improvement in implantation and pregnancy rates after the use of atosiban in women with repeated implantation failure (RIF), which represents one of the main challenges to IVF [14].

Materials and Methods

The study included 182 women recruited among patients prepared for ICSI in a private centre in Alexandria, Egypt between January 2013, and December 2014. The study was explained to them and written informed consent for participation was obtained.

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Table 1. — *Comparison between the two studied groups according to demographic data.*

	Group A (n = 91)	Group B (n = 91)	*t*	*p*
Age (years)				
Min – max	21.0 – 40.0	19.0 – 39.0	1.182	0.239
Mean ± SD	29.57 ± 4.38	30.40 ± 5.0		
BMI (kg/m^2)				
Min – max	23.0 – 29.0	22.0 – 29.0	0.327	0.744
Mean ± SD	26.65 ± 1.44	26.72 ± 1.50		

t: Student t-test

Table 2. — *Comparison between the two studied groups according to serum E2, P4, AMH levels, and number of oocyte retrieved.*

	Group A (n = 91)	Group B (n = 91)	Test of sig.	*p*
E2				
Min – max	1100.0 – 4300.0	800.0 – 9000.0	Z=1.840	0.066
Mean ± SD	2568.8 ± 719.0	2418.7 ± 1289.7		
P4				
Min – max	0.50 – 1.50	0.30 – 1.50	t=1.358	0.176
Mean ± SD	1.04 ± 0.18	1.08 ± 0.20		
AMH				
Min – max	0.90 – 4.70	0.90 – 4.40	Z=0.313	0.754
Mean ± SD	2.16 ± 0.91	2.20 ± 0.90		
M2				
Min – max	3.0 – 26.0	1.0 – 26.0	Z=1.368	0.171
Mean ± SD	12.53 ± 4.26	11.53 ± 5.77		

t: Student t-test
Z: Z for Mann Whitney test

Table 3. — *Comparison between the two studied groups according to total number of transferred embryos and implantation rate.*

	Group A (n = 91)	Group B (n = 91)
ET		
Min – Max	1.0 – 2.0	1.0 – 2.0
Mean ± SD	1.60 ± 0.49	1.62 ± 0.49
Total no. of ETs	146.0	147.0
Implantation		
Min – max	0.0 – 2.0	0.0 – 2.0
Mean ± SD	0.74 ± 0.66	0.55 ± 0.58
t (*p*)	2.018 (0.045)	
Total no. of implantations	67.0	50.0
Implantation rate	45.20%	34.69%

t: Student t-test

Table 4. — *Comparison between the two studied groups according to pregnancy rate.*

	Group A (n = 91)	Group B (n = 91)	c^2	*p*
Pregnant cases	58	44	4.372	0.037
Pregnancy rate	63.7%	48.4%		

χ^2: Chi square test

Inclusion criteria were: age between 25 and 35 years, BMI not greater than 35 kg/m^2, and tubal or male factor infertility doing ICSI using fresh semen sample. Exclusion criteria were: PCOS, endometriosis, AMH less than 1.5ng/ml, and thin pre-ovulatory endometrium (≤ 6 mm) on previous cycle.

All cases were stimulated using the long agonist protocol starting from mid-luteal phase of previous cycle using decapeptyl 0.1 mg subcutaneously. Stimulation commenced using 300IU of hMG starting from second day of menses with suppression confirmed by E2 < 50 pg/ml. All cases were monitored as usual using sonographic examination and hormonal evaluation including E2 and progesterone (P4) values.

Ovum pick-up was performed 34-36 hours after 10,000 IU hCG. ICSI procedure was completed as usual and blastocyst stage embryo transfer (BET) was done on day 5 with cryopreservation of surplus embryos.

Participants were randomized to receive 7.5 mg atosiban by slow IV injection (tractocile) or placebo (sodium chloride 0.9% solution) also by IV injection 20 minutes before ET.

The study group was designated group A (atosiban group) and the control group as group B (placebo group). Serum B-hCG was measured two weeks after ET and clinical pregnancy was confirmed by the presence of a fetal heartbeat identified on transvaginal ultrasound 28 days after ET. Statistical analysis was done using SPSS software version 20.

Results

Base line data of the include women were comparable regarding age and body weight (Table 1). Serum E2 and P4 on day of hCG were measured and compared using independent samples *t*-test. No significant difference was found. Serum AMH level and number of oocytes retrieved were comparable (Table 2).

There was a significant increase in the implantation rate in atosiban group (group A) compared to placebo group (group B); (45.20% *vs.* 34.69%, $p = 0.045$ (Table 3, Figures 1 and 2). The pregnancy rate was also significantly higher in group A compared to group B (63.7% *vs*. 48.4%, $p = 0.037$), (Table 4, Figures 3 and 4).

Discussion

When top quality embryos transferred to normal uterus with sonographically excellent endometrium fail to implant, there are namely two possibilities, that embryos remain there for enough time but embryo-endometrial dialogue fails or that they are expelled outside the uterine cavity by a wave of myometrial contraction. It might be speculated that cases of sporadic implantation failure represent a combination of the two possibilities in varying proportion, while each case of repeated implantation failure has a consistent problem in either of them. Therefore, it is unlikely that single intervention would improve implantation in all of these cases as they represent heterogeneous mix with several underlying causes that should be tackled individually in every case.

Both controlled ovarian hyperstimulation (COH) and ET

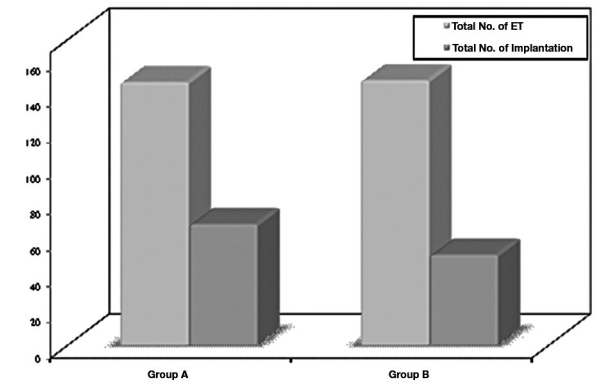

Figure 1. — Comparison between the two studied groups according to total number of ETs and total number of implantations.

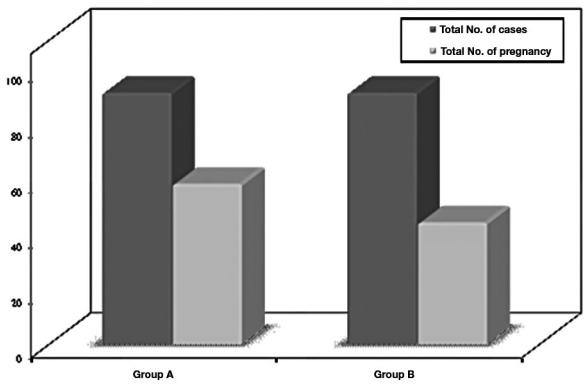

Figure 3. — Comparison between the two studied groups according to pregnancy outcomes.

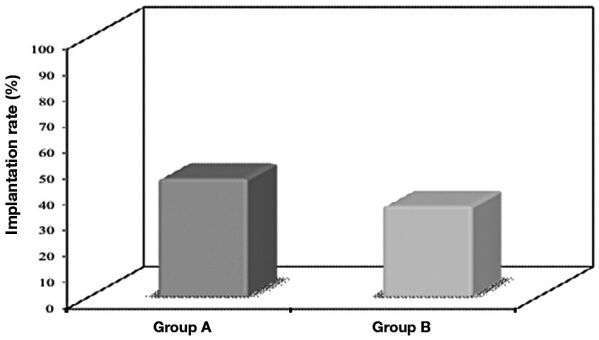

Figure 2. — Comparison between the two studied groups according to Implantation rate.

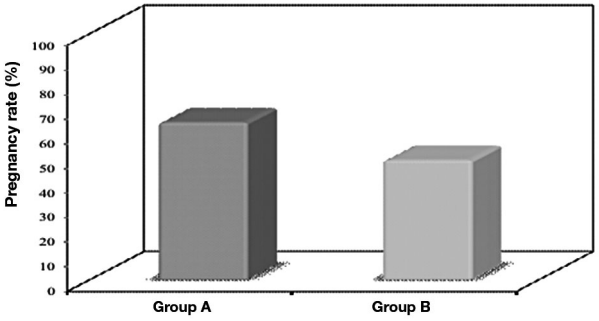

Figure 4. — Comparison between the two studied groups according to pregnancy rate.

procedure itself were found to increase uterine irritability in terms of myometrial peristaltic activity [15, 16]. In view of this, the current study was conducted to examine the effect of the OTRa in restoring uterine quiescence and minimizing embryo expulsion, hoping to find an impact on implantation rates.

The current study reported significant improvement in the implantation and pregnancy rates in the study group where atosiban was used. Implantation rates were nearly 45.20% and ongoing pregnancy rates were nearly 63.7%, while in the control group implantation rates were 34.69% and ongoing pregnancy rates were 48.4%.

In agreement with the present results, Lan *et al.* [14] conducted a study on frozen embryo transfer (FET) cycles in women with previous RIF in both fresh and FET cycles, and atosiban significantly improved implantation and pregnancy rates. Furthermore, the beneficial effect of the drug was not restricted to patients who had a high frequency of uterine contractions at baseline but also in those who had a low frequency. Several recent reports suggested that atosiban might have other benefits in addition to its effect on myometrial activity, as it also showed to involve the endometrium as well as sub-endometrial blood flow in both human and animal uteri [17-20].

Conclusion

Atosiban increases the implantation and pregnancy rates. Because it is uterine specific and embryo safe, atosiban may constitute a new treatment opportunity in ET procedures.

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Corresponding Author:
S.A. HEBISHA, M.D.
Faculty of Medicine Alexandria University
661 horria rd, janakles
Alexandria (Egypt)
sherifanies@gmail.com