

## The role of oxytocin antagonists in repeated implantation failure

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### Abstract

A prospective cohort study has been performed to find out if the administration of an oxytocin antagonist (Atosiban) at the occasion of embryo transfer has an effect on the pregnancy rate in patients with repeated failure of implantation. A total of 52 women with repeated failure of implantation after IVF/ICSI were included in this study. The ongoing pregnancy rate (OPR) in the total group of patients was 12 out of 52 (23.1%). Based on embryo quality all cases were categorized in two groups. One with good embryo quality (Group A) and one with poor quality embryos (Group B). Of all patients who became pregnant, 11 belonged to the group of 26 patients with good quality embryos (OPR 42.3 %) and only one to the group of 26 patients with poor quality embryos (OPR 3.8 %). Our results indicate that when good quality embryos can be obtained, the use of Atosiban at the occasion of embryo transfer might offer a significant better implantation rate in women with repeated implantation failure after IVF/ICSI.

**Key words:** IVF-embryo transfer, Atosiban, uterine contractibility, ongoing pregnancy rate, implantation rate, embryo quality.

### Introduction

Although many efforts have been made to improve the results of assisted reproduction (ART) over the last decades, the overall effectiveness of IVF and ICSI techniques still remains limited. (Nyboe Andersen et al., 2009). A variety of factors can influence success rates after IVF. Among them the embryo transfer is an important factor influencing the outcome of the fertility treatment (Tomas et al., 2002). Apart from the technique of transferring embryos, the embryo quality and uterine receptivity are *the* most important predictive factors (Kyrou et al., 2009).

Recent studies have demonstrated a beneficial effect of Atosiban (Ferring, Denmark) treatment before and during embryo transfer in priming the uterus for implantation (Moraloglu et al., 2010; Pierzynski, 2011; Lan, 2012). Atibosan is a combined oxytocin/ Vasopressin V1A receptor antagonist which is mostly used for the delay of imminent

premature labour. The effect of Atisoban on embryo implantation is based on the reverse correlation between the frequency of uterine contractions and implantation rate, which had already been described more than a decade ago by Fanchin et al. (1998). Also, the Vasopressin 1A antagonist function of the medication could exert a beneficial effect through an improved perfusion of the endometrium and the muscular wall of the uterus via relaxation of the uterine arteries (Vedernikov et al., 2006). Additionally V1A vasopressin receptors are also found to intermediate platelet aggregation (Tsukada et al., 2005). The embryonic safety of Atisoban has been confirmed in previous animal studies (Pierzynski et al., 2007).

The hypothesis has been that patients with repeated failure of implantation – defined as failure of implantation in at least three consecutive IVF attempts with transfer of one or two embryos (Simon and Laufer, 2012) – would benefit from the administration of Atosiban at the occasion of the embryo transfer (ET).

A prospective cohort study in patients with repeated implantation failure after IVF/ICSI has been performed, using Atosiban at ET. In this study the clinical pregnancy rates are described in relation to embryonic development (Baczkowski et al., 2004).

## Materials and methods

A total of 52 women with repeated failure after IVF/ICSI were informed about the working mechanisms of Atosiban. After giving an informed consent, they were included in the study. The treatment period started from the 1/12/2011 till 31/05/2012. The study has been performed in the IVF center of the hospital A.Z. Jan Palfijn in Gent.

Different ovarian stimulation protocols have been used: a combination of GnRH agonist (Decapeptyl® (Ferring), Suprefact® (Sanofi-aventis)) and FSH (Puregon® (Organon N.V.), Gonal F® (Merck Serono), Menopur® (Ferring), Elonva® (Organon N.V.)) or GnRH antagonist (Orgalutran® (Organon N.V.), Cetrotide® (Merck Serono)) plus FSH.

The ongoing pregnancy rate (at least one viable foetus beyond week 20 of pregnancy on ultrasound) has been analyzed. Subsequently embryonic morphology has also been evaluated at the moment of embryo transfer. Two different groups were categorized i.e. a group with good embryo quality (group A) and a group with impaired embryo quality (group B). Group A consisted of those patients showing good embryo quality (blastomeres grade A or B, fragmentation less than 10%, 7-8 cell stage on day 3), whereas the embryos of patients of group B had a rather poor embryo quality (6 cell stage or less on day 3, grade C blastomeres, fragmentation 10% or more). All patients received intravenous Atosiban 60 minutes before the embryo transfer procedure with a bolus of 6,75 mg, followed by an infusion at rate 18 mg/h for three hours (European Medicines Agency, 2009). Two hours after transfer, the infusion was stopped, patient was mobilized and discharged. All embryo transfers were performed on day 3 after oocyte retrieval. 13 days after transfer the results were evaluated through HCG measurement in a blood sample, followed by an ultrasound examination about ten days later with visualization of a gestational sac with fetal parts (Strom et al., 2012).

## Statistical analysis

All analyses were performed in SPSS 19.0 statistical software. Continuous variables were analysed using the independent sample T-test, while categorical variables (pregnancy rates) were analysed with the Fisher's exact test. All tests were two-tailed with a level of significance 0.05.

## Results

Fifty two subsequent patients have been included in the study, twelve ongoing pregnancies were noticed (23.1%). Analyzing embryonic morphology 26 patients fulfilled the criteria of good quality embryos and in 26 patients embryo quality turned out to be suboptimal or poor.

Overall the patients had undergone an average of 5.1 fresh embryo replacements. This means that for the entire cohort 265 failed cycles had been performed. Group A had an average of 4.8 failed treatment cycles, group B patients 5.4. Furthermore both groups were homogenous not only for age, but also for the causes of infertility, characteristics of ovarian stimulation. As far as the number of transferred embryos is concerned a mean of 2.4 embryos was transferred in group A and 2.0 in group B ( $P = 0.021$ ).

The number of pregnancies for the total group of patients ( $n = 52$ ) belonging to so called RFI patients (repeated failure of implantation) was 12 out of 52, or 23,1%. Of these 12 pregnancies, 11 belonged to group A (26 patients) and only 1 was allocated to group B (26 patients). This leads us to an ongoing pregnancy rate of 42.3% in the group with good embryos and only 3.8% in the poor embryo group. The difference in pregnancy outcome of these two groups was highly significant ( $P \leq 0.001$ ).

## Discussion

According to the literature, the definition of repeated implantation failure can be used when transferred embryos fail to implant after at least three treatment attempts (Simon and Laufer, 2012). Some authors suggest that the implantation rate from the fourth cycle onwards is unacceptably low, indicating that patients should begin to consider other options such as oocyte donation (Martin-Johnston et al., 2009). In our study of an overall RIF population we found an acceptable pregnancy rate of 81 pregnancies out of 325 patients or 24.9%. Our patient group had an average of more than 5 failed treatment cycles in the past which means that we were dealing with a real poor prognosis group, willing to find a solution to ameliorate their chances. The overall pregnancy rate of 23.1% in this group of "hopeless" people is very acceptable. The pregnancy rate of the A group (embryos of good quality) shows an extremely high number of 42.3% which is even higher than the overall pregnancy rate of our IVF center over the last year (37.8%). In the poor embryo group the administration of Atosiban doesn't seem to influence the implantation rate.

Our results seem to confirm the hypothesis that in patients with repeated failure of implantation, and

with good embryo quality, the cause of the unsuccessful therapy can be found in uterine factors such as the quality of the endometrium, perfusion and contractility of the myometrium (Fanchin et al., 1998; Vedernikov et al., 2006; Moraloglu et al., 2010). Perfusion and contractility can be influenced through the blockage of the V1A receptor (more relaxed arterioles and less thrombocyte aggregation) and the oxytocin receptor (less uterine contractions) by administration of Atosiban at the occasion of embryo transfer. If however, the embryo quality is poor, the most probable cause of RIF can be found at the level of the embryo itself and no benefit can be expected by offering relaxation and better perfusion of the uterine wall.

The beneficial effect of Atosiban to improve pregnancy rates is in agreement with previously published data (Moraloglu et al., 2010; Pierzynsky, 2011; Lan, 2012).

In order to further elaborate the data a randomized placebo controlled trial in patients with repeated implantation failure and good embryo quality is indicated.

## Conclusion

Atosiban infusion at the occasion of embryo transfer may improve implantation and pregnancy rates in patients with repeated implantation failure. In a prospective cohort study we found that a very acceptable ongoing pregnancy rate can be obtained with this treatment, at least if good quality embryos are available. If embryo quality is poor, Atosiban doesn't seem to increase the pregnancy rate. Our results confirm that the clinical application of oxytocin antagonists might improve results of IVF/ICSI in selected cases of RIP.

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